USE OF VENLAFAXINE COMPARED WITH OTHER ANTIDEPRESSANTS AND THE RISK OF SUDDEN CARDIAC DEATH OR NEAR-DEATH: A NESTED CASE-CONTROL STUDY

Supplemental Table 1

Antidepressant use of cohort members in the year prior to cohort entry by the entry-defining antidepressant agent

	Venlafaxine (n = 19268)	Fluoxetine (n = 90924)	Citalopram (n = 53300)	Dosulepin (n = 43892)
Antidepressant use in the year prior to cohort entry				
Venlafaxine	0 (0.0)	288 (0.3)	370 (0.7)	150 (0.3)
Fluoxetine	1889 (9.8)	0 (0.0)	1591 (3.0)	1235 (2.8)
Citalopram	865 (4.5)	654 (0.7)	0 (0.0)	299 (0.7)
Dosulepin	813 (4.2)	2574 (2.8)	1224 (2.3)	0 (0.0)
Other SSRIs	6421 (33.3)	7587 (8.3)	6192 (11.6)	4526 (10.3)
Tricyclics	3502 (18.2)	10052 (11.1)	5929 (11.1)	5097 (11.6)
MAO inhibitors	146 (0.8)	127 (0.1)	87 (0.2)	42 (0.1)
Other antidepressants	1211 (6.3)	1225 (1.3)	1111 (2.1)	765 (1.7)
Number of antidepressants				
0	7478 (38.8)	71058 (78.2)	39053 (73.3)	33386 (76.1)
1	8793 (45.6)	16849 (18.5)	11883 (22.3)	8716 (19.9)
2	2420 (12.6)	2532 (2.8)	1959 (3.7)	1499 (3.4)
>2	577 (3.0)	485 (0.5)	405 (0.8)	291 (0.7)
Antidepressant prescribed on the day of cohort entry				
Venlafaxine	19268 (100.0)	6 (0.0)	7 (0.0)	12 (0.0)
Fluoxetine	44 (0.2)	90924 (100.0)	14 (0.0)	35 (0.1)
Citalopram	24 (0.1)	15 (0.0)	53300 (100.0)	11 (0.0)
Dosulepin	48 (0.2)	128 (0.1)	86 (0.2)	43892 (100.0)
Other SSRIs	154 (0.8)	100 (0.1)	71 (0.1)	188 (0.4)
Tricyclics	169 (0.9)	507 (0.6)	340 (0.6)	69 (0.2)
MAO inhibitors	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Other antidepressants	86 (0.4)	49 (0.1)	89 (0.2)	52 (0.1)

Results are expressed as Number (%) or Mean ± SD

Supplemental Table 2

Characteristics of cohort members at or prior to cohort entry by cohort entry-defining antidepressant agent

	Venlafaxine (n = 19268)	Fluoxetine (n = 90924)	Citalopram (n = 53300)	Dosulepin (n = 43892)
Enrollment duration at cohort entry (yrs)	7.8 ± 4.2	7.8 ± 3.7	8.4 ± 4.3	7.3 ± 3.3
Follow-up time (yrs)	2.7 ± 2.1	3.5 ± 2.6	2.3 ± 1.7	4.5 ± 2.7
Age at cohort entry	46.3 ± 16.8	43.5 ± 16.7	46.9 ± 18.3	48.7 ± 17.3
18 – 29 years	3124 (16.2)	19911 (21.9)	9887 (18.5)	6257 (14.3)
30 – 59 years	12107 (62.8)	55282 (60.8)	30337 (56.9)	25604 (58.3)
60+	4037 (21.0)	15731 (17.3)	13076 (24.5)	12031 (27.4)
Male sex (%)	6881 (35.7)	28098 (30.9)	16806 (31.5)	13202 (30.1)
Obesity prior to cohort entry				
Obese	2966 (15.4)	13418 (14.8)	7595 (14.2)	6378 (14.5)
Non-Obese	13791 (71.6)	66695 (73.4)	39189 (73.5)	32400 (73.8)
Missing	2511 (13.0)	10811 (11.9)	6516 (12.2)	5114 (11.7)
Smoking prior to cohort entry				
Ever Smoker	9016 (46.8)	41622 (45.8)	24565 (46.1)	19496 (44.4)
Never Smoker	7932 (41.2)	37826 (41.6)	22587 (42.4)	18912 (43.1)
Missing	2320 (12.0)	11476 (12.6)	6148 (11.5)	5484 (12.5)
Alcohol abuse prior to cohort entry	460 (2.4)	1181 (1.3)	929 (1.7)	549 (1.3)
Diagnosis at or prior to cohort entry				
Depression	14177 (73.6)	74975 (82.5)	36401 (68.3)	31021 (70.7)
Anxiety	3072 (15.9)	9283 (10.2)	10938 (20.5)	8768 (20.0)
Both	2019 (10.5)	6666 (7.3)	5961 (11.2)	4103 (9.3)
Record of depression/anxiety in the year prior to cohort entry				
Depression	126312 (60.9)	10490 (54.4)	29052 (54.5)	63082 (69.4)
Severe	8106 (3.9)	1269 (6.6)	2116 (4.0)	3161 (3.5)
Moderate	47375 (22.8)	4156 (21.6)	11684 (21.9)	23774 (26.1)
Mild	70831 (34.2)	5065 (26.3)	15252 (28.6)	36147 (39.8)
Anxiety	19379 (9.3)	1759 (9.1)	7498 (14.1)	5041 (5.5)
Both	29593 (14.3)	3848 (20.0)	8495 (15.9)	10916 (12.0)
None	32100 (15.5)	3171 (16.5)	8255 (15.5)	11885 (13.1)
Suicide attempt in year prior to entry	639 (3.3)	1156 (1.3)	706 (1.3)	351 (0.8)

Results are expressed as Number (%) or Mean ± SD

Supplemental Table 3

Cardiovascular co-morbidity of cohort members in the year prior to cohort entry by cohort entry-defining antidepressant agent

	Venlafaxine (n = 19268)	Fluoxetine (n = 90924)	Citalopram (n = 53300)	Dosulepin (n = 43892)
Acute myocardial infarction				
0 – 3 months	16 (0.1)	101 (0.1)	73 (0.1)	33 (0.1)
3 – 6 months	7 (0.0)	61 (0.1)	73 (0.1)	29 (0.1)
6 months – 1 year	19 (0.1)	112 (0.1)	75 (0.1)	48 (0.1)
Cardiac revascularization	34 (0.2)	154 (0.2)	118 (0.2)	50 (0.1)
Intraventricular conduction delay	2 (0.0)	4 (0.0)	11 (0.0)	3 (0.0)
Supraventricular arrhythmia	100 (0.5)	449 (0.5)	440 (0.8)	185 (0.4)
Left ventricular hypertrophy	5 (0.0)	22 (0.0)	21 (0.0)	6 (0.0)
Coronary artery disease and angina	237 (1.2)	1224 (1.3)	852 (1.6)	628 (1.4)
Congestive heart failure (CHF)	107 (0.6)	505 (0.6)	376 (0.7)	223 (0.5)
Severe CHF*	80 (0.4)	369 (0.4)	288 (0.5)	147 (0.3)
Ischemic stroke	120 (0.6)	484 (0.5)	337 (0.6)	215 (0.5)
Transient ischemic attack	82 (0.4)	351 (0.4)	274 (0.5)	207 (0.5)
Peripheral vascular disease	66 (0.3)	265 (0.3)	167 (0.3)	143 (0.3)
Diabetes	521 (2.7)	2133 (2.3)	1521 (2.9)	977 (2.2)
Hyperlipidemia	164 (0.9)	590 (0.6)	502 (0.9)	320 (0.7)
Hypertension	538 (2.8)	2157 (2.4)	1515 (2.8)	1365 (3.1)
Hypokalemia	23 (0.1)	86 (0.1)	56 (0.1)	43 (0.1)
Hypomagnesemia	0 (0.0)	2 (0.0)	0 (0.0)	1 (0.0)
Conduction disorder	2 (0.0)	10 (0.0)	6 (0.0)	2 (0.0)

Results are expressed as Number (%)
*Severe CHF is defined by the presence of a diagnosis for decompensated CHF or by any CHF diagnosis followed by a prescription of a loop diuretic within 3 months.

Supplemental Table 4

Non-cardiovascular co-morbidity and co-medication use in the year prior to cohort entry of cohort members by entry-defining antidepressant agent

	Venlafaxine (n = 19268)	Fluoxetine (n = 90924)	Citalopram (n = 53300)	Dosulepin (n = 43892)
Co-morbidity				
Rheumatoid Arthritis	46 (0.2)	274 (0.3)	149 (0.3)	147 (0.3)
Epilepsy	113 (0.6)	341 (0.4)	338 (0.6)	184 (0.4)
Schizophrenia	91 (0.5)	143 (0.2)	98 (0.2)	43 (0.1)
Other Medication use				
NSAID	5819 (30.2)	24334 (26.8)	15895 (29.8)	13859 (31.6)
Anti psychotic	2681 (13.9)	5967 (6.6)	4291 (8.1)	3748 (8.5)
Benzodiazepine	4201 (21.8)	11677 (12.8)	8502 (16.0)	7991 (18.2)
Mood stabilizer*	997 (5.2)	1575 (1.7)	1347 (2.5)	897 (2.0)
Anti arrhythmics	128 (0.7)	492 (0.5)	454 (0.9)	195 (0.4)
Lipid regulating drugs	886 (4.6)	2788 (3.1)	2858 (5.4)	1317 (3.0)
Loop diuretics	740 (3.8)	2894 (3.2)	2321 (4.4)	1479 (3.4)
Drugs with potential effect on QT-prolongation				
Strong evidence**	4665 (24.2)	16630 (18.3)	10041 (18.8)	9076 (20.7)
Soft evidence ***	1513 (7.9)	4504 (5.0)	3158 (5.9)	2718 (6.2)

Results are expressed as Number (%)
*Mood stabilizers include: carbamazepine, clonazepam, gabapentin, lamotrigine, lithium carbonate, lithium citrate, sodium valproate, topiramate, valproate semisodium, valproic acid

**Drugs with strong evidence of potential effect on QT prolongation include: amiodarone hydrochloride, amitriptyline hydrochloride, arsenic trioxide, chloroquine phosphate, chloroquine sulphate, chlorpromazine, chlorpromazine hydrochloride, cisapride monohydrate, clarithromycin, clozapine, desipramine hydrochloride, disopyramide, disopyramide phosphate, domperidone, domperidone maleate, doxepin hydrochloride, droperidol, erythromycin, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin stearate, flecainide acetate, halofantrine, haloperidol, haloperidol decanoate, hydroxychloroquine sulphate, imipramine hydrochloride, methadone hydrochloride, pentamidine isetionate, pimozide, procainamide hydrochloride, quetiapine fumarate, quinidine sulphate, risperidone, sotalol hydrochloride, sparfloxacin, terfenadine, thioridazine hydrochloride
***Drugs with soft evidence of potential effect on QT prolongation include: alfuzosin hydrochloride, amantadine hydrochloride, azithromycin dihydrate, chloral hydrate, ciprofloxacin, ciprofloxacin lactate, dolasetron mesilate, foscarnet, fosphenytoin sodium, granisetron, granisetron hydrochloride, indapamide, isradipine, levofloxacin, levofloxacin hemihydrate, lithium carbonate, lithium citrate, moexipril hydrochloride, moxifloxacin hydrochloride, nicardipine hydrochloride, octreotide, ofloxacin, ofloxacin hydrochloride, ondansetron, ondansetron hydrochloride dihydrate, quinine, quinine bisulphate, quinine dihydrochloride, quinine hydrochloride, quinine sulphate, tacrolimus, tamoxifen citrate, telithromycin,

tizanidine hydrochloride, vardenafil hydrochloride trihydrate, voriconazole

Supplemental Table 5

Crude and adjusted odds ratios of sudden cardiac death or near-death associated with current use of venlafaxine relative to current fluoxetine, citalopram and dosulepin use, using the restricted outcome definition of acute ventricular tachyarrhythmia and sudden cardiac death only

	Cases	Controls	Crude OR	Adjusted* OR
	(n=263)	(n=6995)		(95% CI)
Current use of				
Venlafaxine	10 (3.80)	276 (3.95)		
Versus fluoxetine	27 (10.27)	592 (8.46)	0.79	0.73 (0.34 to 1.58)
Versus citalopram	25 (9.51)	513 (7.33)	0.78	0.73 (0.34 to 1.58)
Versus dosulepin	12 (4.56)	425 (6.08)	1.39	1.05 (0.43 to 2.57)
Versus any of the three	64 (24.33)	1530 (21.87)	0.89	0.78 (0.39 to 1.59)

Past user and non-user are included in the model
*Adjusted for BMI≥ 30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, CABG & endosc CA procedures, supraventricular arrhythmias, Left ventricular hypertrophy, CAD and angina, CHF, severe CHF, ischaemic stroke, TIA, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalemia, rheumatoid arthritis, epilepsy, schizophrenia, use of anti psychotics, benzodiazepine, mood stabilizer, anti-arrhythmics, drugs with some evidence of prolonging QT, drugs with stronger evidence of prolonging QT, lipid regulating drugs, loop diuretics all in the year prior to the year before index date and AMI in the year prior index date

Supplemental Table 6

Crude and adjusted odds ratios of sudden cardiac death or near-death associated with current use of venlafaxine relative to current fluoxetine, citalopram, dosulepin use adding a grace period of 15 days to the duration of prescriptions

	Cases (n=568)	Controls (n=14812)	Crude OR	Adjusted* OR (95% CI)
Current use of				
Venlafaxine	24 (4.23)	622 (4.20)		
Versus fluoxetine	77 (13.56)	1532 (10.34)	0.72	0.69 (0.42 to 1.14)
Versus citalopram	48 (8.45)	1242 (8.39)	0.97	0.92 (0.55 to 1.55)
Versus dosulepin	44 (7.75)	1172 (7.91)	1.05	0.87 (0.51 to 1.49)
Versus any of the three	169 (29.75)	3946 (26.64)	0.88	0.81 (0.51 to 1.28)

Past user and non-user are included in the model
*Adjusted for BMI≥ 30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, CABG & endosc CA procedures, supraventricular arrhythmias, Left ventricular hypertrophy, CAD and angina, CHF, severe CHF, ischaemic stroke, TIA, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalemia, rheumatoid arthritis, epilepsy, schizophrenia, use of anti psychotics, benzodiazepine, mood stabilizer, anti-arrhythmics, drugs with some evidence of prolonging QT, drugs with stronger evidence of prolonging QT, lipid regulating drugs, loop diuretics all in the year prior to the year before index date and AMI in the year prior index date

Supplemental Table 7

Crude and adjusted odds ratios of sudden cardiac death or near-death associated with current use of venlafaxine relative to current fluoxetine, citalopram and dosulepin use using the criterion of a minimum 10% change in odds ratio to keep covariates for adjustment

	Cases	Controls	Crude OR	Adjusted* OR
	(n=568)	(n=14812)		(95% CI)
Current use of				
Venlafaxine	18 (3.17)	544 (3.67)		
Versus fluoxetine	63 (11.09)	1281 (8.65)	0.65	0.63 (0.36 to 1.09)
Versus citalopram	39 (6.87)	1079 (7.28)	0.90	0.88 (0.49 to 1.57)
Versus dosulepin	35 (6.16)	1012 (6.83)	0.99	0.84 (0.46 to 1.52)

Past user and non-user are included in the model
Covariates kept for adjustment: alcohol abuse, diabetes, benzodiazepine, drugs with stronger evidence of prolonging QT, loop diuretics, all in the year prior to the year before index date, AMI in the 3 months before index date.

Supplemental Table 8

Crude and adjusted odds ratios of sudden cardiac death or near-death associated with current use of venlafaxine relative to current fluoxetine, citalopram and dosulepin use restricted to patients with the diagnosis of depression

	Cases (n=481)	Controls (n=13218)	Crude OR	Adjusted* OR (95% CI)
Current use of				
Venlafaxine	16 (3.33)	508 (3.84)		
Versus fluoxetine	58 (12.06)	1179 (8.92)	0.61	0.62 (0.35 to 1.12)
Versus citalopram	33 (6.86)	972 (7.35)	0.92	0.92 (0.49 to 1.72)
Versus Dosulepin	28 (5.82)	861 (6.51)	0.96	0.83 (0.44 to 1.58)
Versus any of the three	119 (24.74)	3012 (22.79)	0.78	0.76 (0.44 to 1.31)

Past user and non-user are included in the model

*Adjusted for BMI$\geq$ 30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, CABG & endosc CA procedures, supraventricular arrhythmias, Left ventricular hypertrophy, CAD and angina, CHF, severe CHF, ischaemic stroke, TIA, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalemia, rheumatoid arthritis, epilepsy, schizophrenia, use of anti psychotics, benzodiazepine, mood stabilizer, anti-arrhythmics, drugs with some evidence of prolonging QT, drugs with stronger evidence of prolonging QT, lipid regulating drugs, loop diuretics all in the year prior to the year before index date and AMI in the year prior index date

Supplemental Table 9

Crude and adjusted odds ratios of sudden cardiac death or near-death associated with current use of venlafaxine relative to current

fluoxetine, citalopram and dosulepin use

restricted to patients with no acute myocardial infarction prior to the index date

	Cases	Controls	Crude OR	Adjusted* OR
	(n=530)	(n=13604)		(95% CI)
Current use of				
Venlafaxine	18 (3.40)	494 (3.63)		
Versus fluoxetine	57 (10.75)	1175 (8.64)	0.73	0.73 (0.42 to 1.27)
Versus citalopram	35 (6.60)	976 (7.17)	1.02	0.96 (0.53 to 1.74)
Versus Dosulepin	35 (6.60)	960 (7.06)	1.04	0.91 (0.50 to 1.66)
Versus any of the three	127 (23.96)	3111 (22.87)	0.90	0.85 (0.51 to 1.42)

Past user and non-user are included in the model
*Adjusted for BMI≥ 30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, CABG & endosc CA procedures, supraventricular arrhythmias, Left ventricular hypertrophy, CAD and angina, CHF, severe CHF, ischaemic stroke, TIA, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalemia, rheumatoid arthritis, epilepsy, schizophrenia, use of anti psychotics, benzodiazepine, mood stabilizer, anti-arrhythmics, drugs with some evidence of prolonging QT, drugs with stronger evidence of prolonging QT, lipid regulating drugs, loop diuretics all in the year prior to the year before index date.

Supplemental Table 10

Crude and adjusted odds ratios of sudden cardiac death or near-death associated with current use of venlafaxine, fluoxetine, citalopram and dosulepin, comparing switching to no switching from the cohort-entry defining antidepressant

	Cases (n=568)	Controls (n=14812)	Crude OR (95% CI)	Adjusted OR (95% CI)
Venlafaxine				
No switch	14 (2.46)	318 (2.15)	1.00 (Reference)	1.00 (Reference)
Switch	4 (0.70)	226 (1.53)	0.36 (0.12 to 1.13)	0.31 (0.10 to 0.99)
Fluoxetine				
No switch	51 (8.98)	1104 (7.45)	1.00 (Reference)	1.00 (Reference)
Switch	12 (2.11)	177 (1.19)	1.37 (0.71 to 2.66)	1.65 (0.83 to 3.28)
Citalopram				
No switch	33 (5.81)	852 (5.75)	1.00 (Reference)	1.00 (Reference)
Switch	6 (1.06)	227 (1.53)	0.58 (0.24 to 1.43)	0.63 (0.25 to 1.56)
Dosulepin				
No switch	30 (5.28)	853 (5.76)	1.00 (Reference)	1.00 (Reference)
Switch	5 (0.88)	159 (1.07)	0.88 (0.33 to 2.33)	0.85 (0.32 to 2.27)

Past user and non-user are included in the model

*Adjusted for BMI ≥ 30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, CABG & endosc CA procedures, supraventricular arrhythmias, Left ventricular hypertrophy, CAD and angina, CHF, severe CHF, ischaemic stroke, TIA, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalemia, hypokalaemia, rheumatoid arthritis, epilepsy, schizophrenia, use of anti psychotics, benzodiazepine, mood stabilizer, anti-arrhythmics, drugs with some evidence of prolonging QT, drugs with stronger evidence of prolonging QT, lipid regulating drugs, loop diuretics all in the year prior to the year before index date and AMI in the year prior index date.