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RESEARCH

Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study

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ABSTRACT

Objective To assess whether use of the antidepressant venlafaxine is associated with an increased risk of sudden cardiac death or near death compared with other commonly used antidepressants.

Design Population based observational study.

Setting We did a nested case-control analysis within a new user cohort formed using the United Kingdom General Practice Research Database.

Participants New users of venlafaxine, fluoxetine, citalopram, or dosulepin on or after 1 January 1995, aged 18 to 89 years, with a diagnosis of depression or anxiety. Participants were followed-up until February 2005, or the occurrence of sudden cardiac death or near death, identified from medical records indicating non-fatal acute ventricular tachyarrhythmia, sudden death due to cardiac causes, or out of hospital deaths from acute ischaemic cardiac events. For each case, 30 controls were selected matched for age, sex, calendar time, and indication. We used conditional logistic regression to calculate the adjusted odds ratio of sudden cardiac death or near death associated with current use of venlafaxine compared with current use of fluoxetine, citalopram or dosulepin.

Results 207 384 participants were followed-up for an average of 3.3 years. There were 568 cases of sudden cardiac death or near death, which were matched to 14 812 controls. The adjusted odds ratio of sudden cardiac death or near death associated with venlafaxine use was 0.66 (95% confidence interval 0.38 to 1.14) relative to fluoxetine use, whereas compared with citalopram it was 0.89 (0.50 to 1.60) and with dosulepin 0.83 (0.46 to 1.52).

Conclusions In this large, population based study, the use of venlafaxine was not associated with an excess risk of sudden cardiac death or near death compared with fluoxetine, dosulepin, or citalopram, in patients with depression or anxiety.

INTRODUCTION

The safety of antidepressant drugs, particularly the newer agents, has been the subject of much debate. The selective serotonin receptor inhibitors (SSRI), as well as more recent agents such as venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), have received special scrutiny from regulators. Although the greatest attention has focused on the suicide associated risks with these agents, three observational studies conducted in the United Kingdom reported a higher rate of fatal overdose with venlafaxine use compared with SSRIs.[1-3] While these studies suggested that venlafaxine is more toxic in overdose, their design could not measure or adjust for patient factors that could also account for this observation, if the drugs were selectively prescribed to patients with different underlying risks of suicide.[4 5]

The mechanism of death in patients who died from venlafaxine overdose has not been well established. One hypothesis is that venlafaxine promotes haemodynamically significant (herein referred to as malignant) ventricular tachyarrhythmias through ion channel effects that prolong the QRS and/or QT interval. One in vitro study found that venlafaxine inhibited the fast sodium channel in guinea pig myocytes, but the study was not conducted under physiological conditions.[6] In vivo, QRS prolongation has been reported in the overdose setting but not seen in randomised controlled trials.[7 8] Clinically important increases in the QTc interval were observed rarely during registration trials,[9] in uncontrolled prospective cohort studies,[10] and in the overdose setting.[11 12] No cases of malignant ventricular arrhythmias were reported in the pre-registration clinical trials of venlafaxine,[8] but the studies were not powered to detect such rare adverse events. Another possible mechanism through which venlafaxine could promote arrhythmias is by precipitating cardiac ischaemia, given that the drug can increase blood pressure and heart rate.[10 13 14]

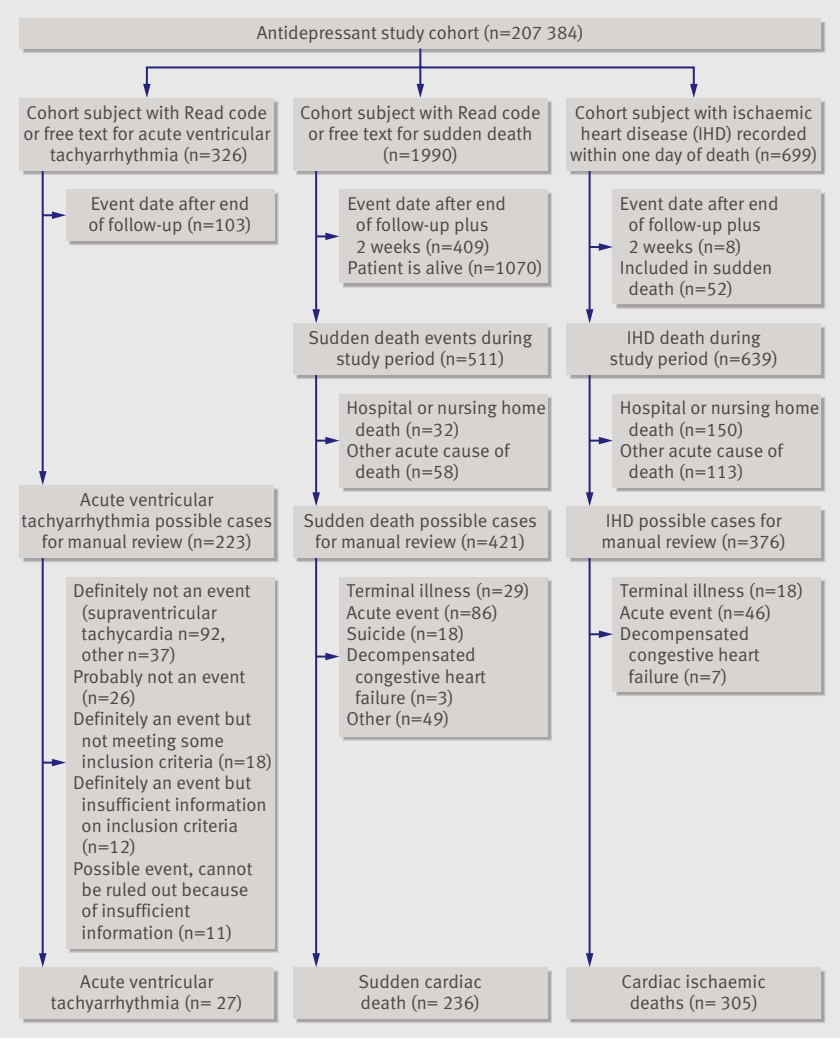
Concerns that venlafaxine was less safe than SSRIs in part due to cardiotoxicity led to regulatory action. In December 2004 the UK Medicines and Healthcare products Regulatory Agency (MHRA) restricted prescription of venlafaxine to specialists and contraindicated its use in patients with heart disease, electrolyte

imbalance, or in patients who are hypertensive.[15 16] After further review, in May 2006 the MHRA revised its regulatory position. The new prescribing information again allowed prescribing by non-specialists (except at very high doses) and updated the cardiac contraindications, advising now that only patients at very high risk of ventricular arrhythmia or with uncontrolled hypertension should not use venlafaxine.[9 17] However, we know of no systematic study that has assessed the risk of malignant arrhythmias or sudden cardiac death associated with the use of venlafaxine in usual clinical practice.

We therefore used a population based observational approach to assess the risk of out-of-hospital haemodynamically significant acute ventricular tachyarrhythmia or sudden cardiac death associated with venlafaxine use relative to the use of fluoxetine, citalopram, or dosulepin in patients treated for depression or anxiety.

METHODS

We did a cohort study with a nested case-control analysis using data obtained from the United Kingdom General Practice Research Database (GPRD). This database contains more than 35 million person years of data from patient records continuously collected since 1987. Participating general practices currently contribute data on more than 3 million patients, roughly 5% of the UK population. Data collected included demographics, medical diagnoses, all prescriptions, referrals to secondary care, and hospital discharge reports. Participating general practitioners (GPs) receive training in data entry, and once practices have met certain quality standards, they are deemed as "up-to-standard."[18] Diagnoses are recorded using OXMIS or Read codes.



Flowchart of case ascertainment

Study cohort and design

The study cohort has previously been used to assess the risk of suicide in patients treated with venlafaxine.[19] Briefly, it was formed from all new users of venlafaxine, fluoxetine, citalopram, or dosulepin on or after 1 January 1995. We defined new users as patients who had received no prescription of the study drug in the year before cohort entry. Patients were aged between 18 and 89 years on the date of the incident prescription, and only patients with a clinical record for depression or anxiety on the date of or at any time before the incident prescription were selected. Patients were included in the cohort if they had a permanent registration status with a participating general practice, had at least a one year longitudinal record before the incident prescription, had an acceptable patient status for data quality, and originated from a general practice which was up to standard for at least a year before the incident prescription.[20] Patients with a history of life threatening ventricular tachyarrhythmia, cardioversion, aborted cardiac arrest, or implantation of a cardiac defibrillator before cohort entry were excluded. Patients with a congenital conduction disorder or advanced cardiomyopathy (hypertrophic or dilated) before cohort entry or at any time during follow-up were also excluded.

Patients were followed-up over time from their incident prescription date (cohort entry) until the earliest of occurrence of the study outcome, death, transfer out of practice, or the practice's last collection date before February 2005, when data for this study were extracted. We used a case-control analysis nested within the cohort to deal with the complex time-varying nature of antidepressant use.[21 22]

Case definition

The unifying feature of our composite outcome of sudden cardiac death or near death was the occurrence of a malignant ventricular tachyarrhythmia, which typically occurs in the presence of coronary atherosclerosis, its complications, or other structural heart disease.[23] For near deaths, the occurrence of such a tachyarrhythmia was well documented and supported by the report of symptoms of presyncope or syncope before or during the event and/or the necessity of emergent cardioversion. For individuals who died, the tachyarrhythmia was often presumed because

Table 1 | Characteristics of cases and controls in the year before index date. Data are frequencies (percentages) unless otherwise stated. Percentages cannot be calculated directly from the corresponding frequencies as they are weighted by the number of controls matched to each case.

	Cases (n=568)	Controls (n=14 812)
Age at index date, mean (SD)*	72.9 (12.7)	72.9 (12.8)
Men (%)*	258 (45.4)	6404 (45.4)
Indication for cohort entry antidepressant*		
Depression	455 (80.1)	12893 (80.1)
Anxiety	87 (15.3)	1594 (15.3)
Both	26 (4.6)	325 (4.6)
Obesity status		
Obese (BMI ≥30)	86 (15.1)	2093 (13.4)
Non-obese (BMI <30)	372 (65.5)	10818 (73.3)
Missing information	110 (19.4)	1901 (13.3)
Smoking status		
Smoker	249 (43.8)	5565 (37.3)
Non-smoker	239 (42.1)	7429 (50.3)
Missing information	80 (14.1)	1818 (12.5)
Alcohol abuse	16 (2.8)	139 (1.0)
Depression/anxiety		
Depression	135 (23.8)	3751 (23.8)
Severe	11 (1.9)	333 (2.1)
Moderate	39 (6.9)	1372 (8.7)
Mild	85 (15.0)	2046 (13.0)
Anxiety	27 (4.8)	668 (5.3)
Both	35 (6.2)	771 (5.2)
None	371 (65.3)	9622 (65.7)
Suicide attempt	5 (0.9)	59 (0.4)

*Matching factors.

most deaths were not witnessed. Accordingly, three sources of out of hospital cases were identified: patients with non-fatal but haemodynamically significant acute ventricular tachyarrhythmia; patients with a record of sudden death due to cardiac causes ischaemic or otherwise; and patients seeming to have died out of hospital from an acute ischaemic cardiac event that was not necessarily labelled as sudden.

First, potential cases of acute ventricular tachyarrhythmia were identified from Read or OXMIS codes and word strings in the free text comments of GPs, in which case the complete de-identified free text was obtained from the GPRD. This text was reviewed by one of the authors (CM), blinded to exposure status, to assess whether additional chart information should be requested from the GP to clarify if the outcome of interest had occurred. The complete clinical profile of all these potential acute ventricular tachyarrhythmia cases was independently reviewed by two authors (CM and TA), who classified them as definite or not, and any discordance was resolved by consensus after further review and discussion. Then, sudden cardiac death cases were identified from Read/OXMIS code for "sudden death" or a word string in a free text comment that suggested the occurrence of a sudden death. Death certificates were obtained from the Office for National Statistics for England and Wales or the General Register Office for Scotland and Northern Ireland for the subset of those individuals who did not have a Read/OXMIS code or a free text comment that clearly stated a cause of death. Finally, people dying in the community from an acute cardiac ischaemic event that was not necessarily labelled as sudden formed the third group of potential cases, identified by scanning the Read/OXMIS codes for a code of ischaemic heart disease or myocardial infarction on the date of death (plus or minus one day). The complete profile of all potential sudden cardiac deaths and acute cardiac ischaemic deaths was subjected to a computer algorithm that identified and excluded deaths occurring either in hospital or in nursing homes and deaths apparently due to non-cardiac pathology. This algorithm was optimised after comparing the results of the initial run of the algorithm with the results of a manual review of a random set of 50 potential sudden death cases by two authors (CM and TA). All potential cases not excluded by the optimised computer algorithm then underwent a manual review by one of the authors (CM) to further exclude cases that did not meet all inclusion and exclusion criteria.

The definite acute ventricular tachyarrhythmia, sudden cardiac death, and acute ischaemic cardiac death cases were combined to form the series of cases of sudden cardiac death or near death. The date of occurrence was designated the index date of the case.

Control selection

For each case we randomly selected up to 30 controls from the cohort. These controls were matched on cohort entry date (date of incident prescription plus or minus 6 months), year of birth, sex, and indication (depression and/or anxiety). Additionally, controls had to be at risk of the event on the case's index date. Thus, the control's index date was defined as the date that corresponded to the same follow-up time as its matched case. When fewer than 30 controls were available for a given case, we relaxed the matching criteria for cohort entry to within one year. If after this step, a given case had fewer than 30 controls, all available individuals were used.

Antidepressant drug exposure

For each case and their matched controls, we extracted all prescription records for the study drugs and all other antidepressants before the index date. We calculated the duration of each prescription, starting with the last prescription prior to index date, from the number of tablets prescribed combined with the dosing instructions. When we were unable to derive duration of exposure from the available information we assumed a prescription length of 28 days. For unusually low or high values of prescription length, we assigned a minimum of seven days and a maximum of 90 days to the prescription length. These assumptions are based on current prescribing practices in the UK.

We defined current exposure to treatment by a prescription whose duration included the index date. As

Table 2 | Cardiovascular comorbidity of cases and controls before index date. Data are frequencies (percentages) unless otherwise stated. Percentages cannot be calculated directly from the corresponding frequencies as they are weighted by the number of controls matched to each case.

	Cases (n=568)	Controls (n=14 812)
In 2 years before index date		
Acute myocardial infarction before index date (%)		
0-3 months	14 (2.5)	28 (0.2)
3-6 months	7 (1.2)	27 (0.2)
6-12 months	10 (1.8)	57 (0.4)
12-15 months	6 (1.1)	29 (0.2)
15-18 months	1 (0.2)	28 (0.2)
18-24 months	2 (0.4)	62 (0.5)
In the year before the year before index date		
Cardiac revascularisation	1 (0.2)	47 (0.3)
Intraventricular conduction delay	0 (0.0)	0 (0.0)
Supraventricular arrhythmia	29 (5.1)	234 (1.6)
Left ventricular hypertrophy	2 (0.4)	8 (0.1)
Coronary artery disease and angina	39 (6.9)	628 (4.3)
Congestive heart failure (CHF)	51 (9.0)	368 (2.5)
Severe CHF*	37 (6.5)	256 (1.7)
Ischaemic stroke	9 (1.6)	199 (1.5)
Transient ischaemic attack	6 (1.1)	204 (1.5)
Diabetes	78 (13.7)	791 (5.0)
Peripheral vascular disease	11 (1.9)	166 (1.2)
Hyperlipidaemia	7 (1.2)	198 (1.4)
Hypertension	38 (6.7)	799 (5.4)
Hypokalaemia	4 (0.7)	39 (0.3)
Hypomagnesaemia	0 (0.0)	0 (0.0)
Conduction disorder	1 (0.2)	5 (0.03)

*Severe CHF defined by presence of a diagnosis for decompensated CHF or by any CHF diagnosis followed by a prescription of a loop diuretic within 3 months.

the focus of exposure was on current use, we defined as "no use" the absence of prescriptions of a given drug during the year prior to the index date. Patients with prescriptions for a given drug during the year before the index date, but not current users, were classified as past users.

Covariates

Risk factors for the outcome were identified from patients' records in the GPRD. In particular, we identified depression related factors (alcohol abuse, suicide attempt, depression severity),[24] cardiovascular risk factors (obesity, smoking, diabetes, left ventricular hypertrophy, hyperlipidaemia, hypertension, rheumatoid arthritis), cardiovascular diagnoses (acute myocardial infarction, coronary artery bypass graft and percutaneous coronary artery procedures, intraventricular conduction delay, supraventricular arrhythmia, atrial arrhythmia, coronary artery disease, angina, congestive heart failure, ischaemic stroke, transient ischaemic attack, peripheral vascular disease), other conditions that have been associated with an increased risk for sudden cardiac death (epilepsy and schizophrenia), and conditions or use of drugs that could prolong the QT interval, including hypokalaemia, hypomagnesaemia, and conduction disorders.[25,26] We also measured use of certain classes of drug including non-steroidal anti-inflammatory drugs (NSAIDs), antipsychotics, benzodiazepines, mood stabilisers, antiarrhythmic agents, lipid regulating drugs, and loop diuretics. Lastly, we identified individuals who had switched antidepressants between the time of cohort entry and the index date. Except for obesity, which we defined as a body mass index (BMI) of more than 30, covariates were ascertained from diagnoses, lifestyle factors, or prescriptions as they appeared in the medical record.

Data analysis

We used conditional logistic regression to compute the odds ratio of sudden cardiac death or near death, and its 95% confidence interval, associated with current exclusive use of venlafaxine compared with current exclusive use of each of the three other study drugs, as well as compared with the three drugs as one group. In a nested case-control study such as ours, the odds ratio provides an unbiased estimate of the rate ratio in the cohort.[27]

Because the number of controls matched to each case was variable and to allow unbiased comparisons between cases and controls, descriptive statistics for the characteristics of the controls were weighted by the inverse of the number of controls in each matched set, a procedure equivalent to standardising the number of controls to one control per case. After tabulating the data, we performed crude regression analyses. All analyses were then adjusted for comorbidity and other covariates measured 366-730 days before the index date, to avoid adjusting for factors affected by exposure during the year prior to the index date. We also assessed the effect of duration of exposure in patients currently exposed to the study drugs.

We performed several sensitivity analyses. We repeated the main analyses after restricting our outcome to the first two sources of cases (non-fatal acute ventricular tachyarrhythmia as well as sudden deaths due to any cardiac pathology). We repeated the main analyses adding a lag of 15 days to the end of the prescription duration, to allow for possible late exposures beyond the prescription duration. We repeated the main analyses using two alternative time periods in which covariates were measured. We first adjusted for comorbidities measured in the year beginning 415 days before the index date, instead of the year beginning 730 days before the index date, and then adjusted only for covariates ascertained prior to cohort entry, to address any concerns about adjusting for factors that were actually drug effects. We also restricted the covariates to those that affected the odds ratio by 10% or more. Finally, to assess effect modification, the estimates were stratified by the indication for the antidepressant, by the presence or absence of a diagnosis of myocardial infarction before the index date, and by the occurrence of switching among antidepressant classes

Table 3 | Comorbidity and drug use of cases and controls in the year before the year before index date. Data are frequencies (percentages) unless otherwise stated. Percentages cannot be calculated directly from the corresponding frequencies as they are weighted by the number of controls matched to each case

	Cases (n=568)	Controls (n=14 812)
Non-cardiovascular comorbidity		
Rheumatoid arthritis	4 (0.7)	72 (0.5)
Epilepsy	4 (0.7)	68 (0.5)
Schizophrenia	3 (0.5)	10 (0.1)
Drug use		
NSAIDs	273 (48.1)	6443 (43.7)
Antipsychotics	83 (14.6)	1840 (12.9)
Benzodiazepines	181 (31.9)	3582 (25.4)
Mood stabilisers	26 (4.6)	573 (3.8)
Antiarrhythmics	17 (3.0)	270 (1.8)
Lipid regulating drugs	65 (11.4)	1171 (7.8)
Loop diuretics	151 (26.6)	1860 (13.4)
Drugs with potential effect on QT prolongation*		
Strong evidence	172 (30.3)	3494 (23.6)
Soft evidence	87 (15.3)	1820 (12.3)

NSAID=non-steroidal anti-inflammatory drugs.
*Prescribed drugs associated with QT prolongation were stratified into two groups based on the strength of evidence supporting the drug's propensity to prolong the QT interval.[22,23]

as measured by a change of the current antidepressant from the cohort entry defining agent.

We used SAS v9.1. (Cary, NC, USA) statistical software for all analyses. The study protocol was approved by the Independent Scientific Advisory Committee for GPRD research, and this report includes all relevant STROBE elements.

RESULTS

The initial cohort included 269 084 individuals with an incident prescription of one of the study drugs after January 1995 and with at least a year of data prior to that prescription. We then excluded 2426 patients because they were younger than 18 years or older than 90 at the date of the incident prescription; 58 464 patients without a diagnosis of depression or anxiety before or concurrent with the incident prescription; 473 patients with congenital conduction disorder, cardiomyopathy, or history of acute ventricular tachyarrhythmia; 284 patients with cardioversion, cardiac arrest with resuscitation, or implantation of an internal cardiac defibrillator prior to cohort entry; and 53 patients with incomplete follow-up information. Thus, the final study cohort consisted of 207 384 first time users of venlafaxine (n=19 268), citalopram (n=53 300), fluoxetine (n=90 924), or dosulepin (n=43 892). Over the study period, 17 783 patients who entered the study taking one of the comparator antidepressants were subsequently prescribed venlafaxine, bringing the total number of individuals exposed to venlafaxine to 35 051.

The mean age at cohort entry was 46 years, with a mean of 7.8 years of available data in the practice between the time it was deemed up to standard for data collection purposes and cohort entry and a mean follow-up of 3.3 years. A third of cohort members were men. The diagnosis associated with antidepressant use was depression in 84% and anxiety in 16%. Almost half of the patients had never been prescribed any other antidepressant before the qualifying prescription. Compared with patients initiating fluoxetine, citalopram, or dosulepin, patients initiating venlafaxine were more likely to have previously used tricyclics, SSRIs, monamine oxidase inhibitors, or other antidepressants (supplemental table 1, see webextras). They also were more likely to have had more severe depression or attempted suicide (supplemental table 2). Patients initiating venlafaxine were no different in terms of their cardiovascular comorbidities at baseline but had greater use of antipsychotic drugs, benzodiazepines, and mood stabilisers, as well as somewhat higher use of drugs that may prolong the QT interval (supplemental tables 3-4).

The figure 1 describes the algorithm to identify the three sets of out of hospital cases. Using this algorithm, we identified 568 cases, including 27 acute ventricular tachyarrhythmias, 236 sudden cardiac deaths, and 305 out of hospital cardiac ischaemic deaths. The initial concordance rate regarding case status between the two authors after their manual review of all potential acute ventricular tachyarrhythmia and of the random set of 50 potential sudden death cases was 73%, and all disagreements were resolved after discussion.

The overall rate of sudden cardiac death or near death was 8.21 per 10 000 person-years. The 568 cases were matched to 14 812 controls, with a mean age of 73 years at the index date. Cases were more likely to be smokers, to abuse alcohol, and to have attempted suicide, despite no major differences in the severity of depression (table 1). In the year prior to the year before the index date, cases generally had a higher prevalence of cardiovascular related comorbidity, particularly diabetes, acute myocardial infarction, congestive heart failure, and atrial arrhythmia (table 2). Cases also had a higher prevalence of rheumatoid arthritis, epilepsy, and schizophrenia, as well as use of NSAIDs, benzodiazepines, lipid regulating agents, loop diuretics, and drugs that may prolong the QT interval (table 3). Although all patients were exposed to one of the study drugs at cohort entry, over time many did not continue on these treatments, as would be expected in clinical practice. On the index date only a subset of cases (n=155) and controls (n=3916) were currently exposed to a study drug.

Current venlafaxine use was not associated with an increased risk of sudden cardiac death or near death compared with current use of fluoxetine, citalopram, and dosulepin, with all point estimates of the adjusted odds ratio less than 1 (table 4, model 1). In an alternative model that included only covariates that were measured before cohort entry, results were essentially the same (table 4, model 2). Stratified analyses did not show any significant variations in risk by duration of

Table 4 | 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

	Cases (n=568)	Controls (n=14 812)	Crude odds ratio	Adjusted odds ratio Model 1* (95% CI)	Adjusted odds ratio Model 2† (95% CI)
Venlafaxine	18 (3.2)	544 (3. 7)			
Versus fluoxetine	63 (11.1)	1281 (8.6)	0.65	0.66 (0.38 to 1.14)	0.66 (0.38 to 1.14)
Versus citalopram	39 (6.9)	1079 (7.3)	0.90	0.89 (0.50 to 1.60)	0.88 (0.49 to 1.56)
Versus dosulepin	35 (6.2)	1012 (6.8)	0.99	0.83 (0.46 to 1.52)	0.86 (0.48 to 1.56).
Versus any of the three	137 (24.1)	3372 (22.8)	0.81	0.77 (0.46 to 1.30)	0.78 (0.47 to 1.29)

*Model 1 adjusted for BMI≥30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, coronary artery bypass graft and endoscopic cardiac procedures, supraventricular arrhythmias, left ventricular hypertrophy, coronary artery disease and angina, congestive heart failure, severe congestive heart failure, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalaemia, rheumatoid arthritis, epilepsy, schizophrenia, use of antipsychotics, benzodiazepine, mood stabilisers, antiarrhythmics, drugs with some evidence of prolonging QT, drugs with stronger evidence of prolonging QT, lipid regulating drugs, loop diuretics—all ascertained in the year prior to the year before index date and acute myocardial infarction in the year before index date.
†Adjusted for all factors listed for model 1 as ascertained before cohort entry. Models 1 and 2 included non-users and past users, in addition to current users. Because the contrasts here are limited to current users, drug specific counts of cases and controls do not add up to column totals.

use of any of the four antidepressants used to define the cohort (table 5).

Sensitivity analyses restricting our outcome to acute ventricular tachyarrhythmia and sudden cardiac death did not change the results, nor did adding a lag of 15 days to the end of the prescription duration (supplemental tables 5-6). Varying the time window to define covariates or adjusting only for covariates that changed the odds ratio by at least 10% also did not materially affect the results (supplemental table 7). Finally, results were similar in models restricted to patients with a diagnosis of depression as indication for the drugs or among patients with no diagnosis of acute myocardial infarction before the index date (supplemental tables 8-9). Switching from the antidepressant used at cohort entry to the one at index date was not associated with an increased risk of our composite outcome (odds ratio 0.83; 95% confidence interval 0.52 to 1.32). In an analysis of switching stratified by each study drug, the results did not change although the numbers were small (supplemental tables 10).

DISCUSSION

In this large population based cohort study of patients treated for depression or anxiety, we found no evidence that venlafaxine use was associated with a higher risk of out of hospital haemodynamically significant acute ventricular tachyarrhythmia or sudden cardiac death compared with the risk observed in fluoxetine, citalopram, or dosulepin users. While only 18 cases of sudden cardiac death or near death occurred in patients currently exposed to venlafaxine, the study allows us reasonably to exclude odds ratios higher than 1.14 compared with current fluoxetine use, 1.60 compared with current citalopram use, 1.52 compared with current dosulepin use, and 1.30 compared with current use of any of the three comparators, based on the upper bound of the 95% confidence interval for each of the four comparisons. We also found no compelling evidence that venlafaxine was preferentially prescribed to patients with lower risk for cardiac events, consistent with the observation that adjustment for potential confounders had minimal effect on results.

Comparison with other studies

The motivation for this investigation arose from three recent observational studies that reported a higher rate of fatal antidepressant overdose with venlafaxine use compared with SSRIs.[1-3] While one interpretation of these findings is that venlafaxine is relatively more toxic in overdose, patient factors rather than differential drug effects could also explain the phenomenon. None of these studies adjusted for potential confounding factors, and in fact a UK based utilisation study demonstrated that venlafaxine was preferentially prescribed to patients with a higher prevalence of risk factors for suicide.[28] The cause of venlafaxine overdose deaths has not been well characterised, although a cardiotoxic mechanism, mediated through malignant ventricular tachyarrhythmias, has been suggested.[6] The current study assessed the risk of malignant ventricular tachyarrhythmias and sudden cardiac death among patients receiving venlafaxine and comparator antidepressants at pharmacological doses, and found no such association.

While some studies compare current use of a drug to non-use to assess drug risk, we chose to compare current use of one drug to another drug. We believe that this approach is clinically sensible and minimises confounding by indication. We designed the study to address the following question a clinician might ask him or herself: "Given that I have chosen to treat my patient with an antidepressant, will the choice of venlafaxine instead of other antidepressants increase my patient's risk of unexpected cardiac death or life threatening ventricular tachyarrhythmia?" Alternatively, one could compare current use to distant past use, but such an approach could be vulnerable to confounding by indication. Several studies have suggested that depressed individuals are at increased risk for cardiac mortality compared with non-depressed individuals.[29-32] Less clear is whether depression associated risk of adverse cardiovascular outcomes attenuates when depression abates. If this is the case, an

Table 5 | Crude and adjusted rate ratios of sudden cardiac death or near death associated with current use of venlafaxine, fluoxetine, citalopram, and dosulepin, comparing longer with shorter duration of current use. Data are number (percentage) unless otherwise specified

	Cases (n=568)	Controls (n=14 812)	Crude odds ratio	Adjusted odds ratio* (95% CI)
Venlafaxine				
<90 days	2 (0.4)	70 (0.5)	1.00	1.32 (0.26 to 6.70)
≥90 days	16 (2.8)	474 (3.2)	1.00 (reference)	1.00 (reference)
Fluoxetine				
<90 days	8 (1.4)	261 (1.8)	0.61	0.70 (0.25 to 1.93)
≥90 days	55 (9.7)	1020 (6. 9)	1.00 (reference)	1.00 (reference)
Citalopram				
<90 days	8 (1.4)	153 (1.0)	1.94	1.81 (0.63 to 5.21)
≥90 days	31 (5.5)	926 (6. 3)	1.00 (reference)	1.00 (reference)
Dosulepin				
<90 days	8 (1.4)	207 (1.4)	1.27	1.44 (0.50 to 4.16)
≥90 days	27 (4.8)	805 (5.4)	1.00 (reference)	1.00 (reference)

*Adjusted for BMI≥30, smoking status, alcohol abuse, depression severity, suicide attempt, diabetes, coronary artery bypass graft and endoscopic coronary artery procedures, supraventricular arrhythmias, left ventricular hypertrophy, coronary artery disease and angina, congestive heart failure, severe congestive heart failure, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, hyperlipidaemia, hypertension, hypokalaemia, rheumatoid arthritis, epilepsy, schizophrenia, use of antipsychotics, benzodiazepine, mood stabilisers, antiarrhythmics, 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 acute myocardial infarction in the year prior index date. Because the contrasts here are limited to current users, drug specific counts of cases and controls do not sum to column totals.

association emerging from a comparison of current antidepressant use with distant past use could easily be a consequence of confounding by time dependent patient factors associated with depression itself. Thus, we selected three other antidepressant agents to define the comparison group, namely fluoxetine, citalopram, and dosulepin, as in a previous study of suicide risk associated with venlafaxine that used the same dataset.[19] Fluoxetine, an SSRI, and dosulepin, a tricyclic antidepressant, were selected because they were the most commonly prescribed drugs within their respective classes during the study period. As citalopram and venlafaxine were introduced in the same year, we assumed that doctors would preferentially prescribe both agents to patients who were unresponsive to previously available therapies.[5] To the degree that severity of depression could increase risk of cardiac events,[29] we believed that selecting citalopram as a comparator would minimise confounding by disease severity.

Like other antidepressants of the tricyclic class, dosulepin in the overdose setting can produce malignant arrhythmias, some fatal.[33 34] We identified only one population based study that evaluated the risk of sudden cardiac death involving tricyclic antidepressants at pharmacologic doses.[35] This study found that, compared with non-use of antidepressants, tricyclic antidepressants were not associated with an increased risk of sudden cardiac death at doses of less than 100 mg per day of amitriptyline equivalents. An increased risk, however, was observed at higher doses. Our GPRD study did not suggest an excess risk of sudden cardiac death or near death associated with dosulepin use. We suspect that the relatively infrequent use at higher doses may explain this finding. Among patients currently exposed to dosulepin on the index date for whom a daily dose could be measured, 87.6% (840/959) were prescribed less than 100 mg/day (we assume that amitriptyline and dosulepin are equivalent on a mg/mg basis).[36]

Limitations of study

Our study has some limitations, most of which involve the level of detail in the GPRD medical history and the challenge of determining the precise sequence of events in patients who died out of hospital. Firstly, we could not apply standardised definitions of sudden cardiac death such as those used in large clinical trials, since we lacked access to complete medical records and the ability to interview family members of deceased people. However, our definition of sudden cardiac death was largely consistent with the one used in a recent study of antipsychotic drug use and sudden cardiac death, although ours also included cases of life threatening but non-fatal ventricular arrhythmias.[37] Secondly, we cannot be certain that all of the fatal cases included in this study had a malignant ventricular tachyarrhythmia as the final cardiac event before death. In large part, this limitation is a consequence of most fatal cases both not being on an electrocardiograph at the time of haemodynamic collapse and not subsequently undergoing autopsy. Furthermore, we did not have access to medical records detailing the cardiac rhythm before death in the few cases whose arrest was witnessed and managed by paramedics or doctors. Community studies suggest that some patients who die shortly after haemodynamic collapse from a cardiac cause may not go through a phase of ventricular tachyarrhythmia or fibrillation before death.[38 39] Nevertheless, we suspect that among cases who did not have a malignant tachyarrhythmia, most died from some cardiac cause. To the degree that this occurred, it is reassuring that venlafaxine was not

WHAT IS ALREADY KNOWN ON THIS TOPIC

In recent reports from the UK, the antidepressant venlafaxine was associated with an increased rate of fatal overdose compared with several other SSRIs

The finding might be due to patient factors, as venlafaxine has been systematically prescribed to sicker patients who are at higher risk for suicide, or to inherent toxicity of venlafaxine, possibly because of a pro-arrhythmic mechanism

Whether use of venlafaxine at therapeutic doses is associated with an increased risk of sudden cardiac death or life threatening arrhythmia has not been studied

WHAT THIS STUDY ADDS

Using data from the General Practice Research Database, this observational study of more than 200 000 patients treated for depression or anxiety found no excess risk of sudden death or near death associated with use of venlafaxine compared with other commonly used antidepressants

associated with an increased risk of death from other cardiac causes. Our study reproduced several established risk factors of sudden cardiac death,[23] such as severe congestive heart failure (odds ratio 1.7), recent acute myocardial infarction (odds ratio 13.4), and left ventricular hypertrophy (odds ratio 5.9); and it found an incidence rate of sudden cardiac death or near death consistent with the rates of ventricular tachycardia observed in other cohorts.[40-44] These observations support the validity of our outcome measure despite incomplete clinical details for many of our cases.[45] Thirdly, although we adjusted our analysis for a comprehensive list of potential risk factors for the outcome based on the information available in the GPRD, this adjustment might be incomplete. Some traditional risk factors of coronary artery disease such as left ventricular hypertrophy, diabetes, hypertension, and hyperlipidaemia appeared to be incompletely captured by physician diagnoses given the lower than expected prevalence of these conditions. Furthermore, although we adjusted for coronary artery disease risk factors, coronary artery disease, myocardial infarction, or left ventricular dysfunction, we could not adjust for the age of onset and severity of coronary disease risk factors, burden and location of coronary atherosclerosis, location and size of previous myocardial infarction, or the left ventricular ejection function as measured on an echocardiogram. We cannot exclude the possibility that patients with more extensive cardiac disease and consequently a higher risk of malignant arrhythmias were less likely to have been prescribed venlafaxine. However, the distribution of cardiac comorbidities and coronary artery disease risk factors across the four groups of antidepressant users at study entry does not suggest that such channelling occurred (supplemental tables 2 and 3). Finally, we cannot exclude the possibility of exposure misclassification, which could have varied by study drug. Clinical trial data indicate that patients receiving venlafaxine discontinue therapy because of undesirable side effects more often than those receiving SSRIs.[46] Our GPRD study used prescription data as a proxy for antidepressant exposure and did not measure actual drug adherence.

Conclusion

In this large UK population based study in patients with depression or anxiety, venlafaxine was not associated with any excess risk of malignant ventricular tachyarrhythmia or sudden cardiac death when compared with fluoxetine, dosulepin, or citalopram.

Contributors: CM, DM, SS were responsible for the conception and design of the study. SD was responsible for the statistical analysis. CM and TA adjudicated cases of non-fatal ventricular arrhythmias. All authors contributed to the interpretation of results and manuscript preparation and granted final approval of this report. CM and SS are guarantors.
Funding: This study was sponsored by Wyeth, which produces and markets venlafaxine. The contract for this research specified that the non-company authors had ultimate control over all aspects of the study, including control over publication. During the course of the study, however, any differences about the presentation or interpretation of findings that arose between the company author and external investigators were resolved through honest scientific debate. All authors had access to the statistical reports and tables supporting the publication.
Competing interests: DM is a employee of Wyeth and owns company stock options. SS has participated in advisory board meetings and conferences, participated as a speaker in scientific meetings by various companies (AstraZeneca, Boehringer Ingelheim, Glaxo SmithKline, Pfizer, and Sepracor), and received research grants from AstraZeneca, Wyeth, and GlaxoSmithKline. TA, SD, and CM have nothing to declare.
Ethical approval: The study protocol was approved by the Independent Scientific Advisory Committee for GPRD studies (Protocol 06_054).
Data sharing: Read/OXMIS code lists used to identify outcomes are available from the corresponding author at samy.suissa@mcgill.ca.

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