Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care

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Abstract

Objectives To determine whether antidepressants are a risk factor for ischaemic heart disease and to compare the risk for different subgroups of antidepressants and individual antidepressants.
Design Case-control study.
Setting Nine general practices recruited from the Trent Focus Collaborative Research Network.
Participants 933 men and women with ischaemic heart disease matched by age, sex, and practice to 5516 controls.
Main outcome measure Adjusted odds ratio for ischaemic heart disease calculated by logistic regression.
Results Odds ratios for ischaemic heart disease were significantly raised for patients who had ever received a prescription for tricyclic antidepressants even after diabetes, hypertension, smoking, body mass index, and use of selective serotonin reuptake inhibitors had been adjusted for (1.56; 95% confidence interval 1.18 to 2.05). Patients who had ever taken dosulepin (dothiepin) had a significantly raised odds ratio for ischaemic heart disease after adjustment for confounding factors and use of other antidepressants (1.67, 1.17 to 2.36). There was no significant increase in the odds ratios for amitriptyline, lofepramine, and selective serotonin reuptake inhibitors in multivariate analysis. Increasing maximum doses of dosulepin were associated with increasing odds ratios for ischaemic heart disease. Similarly, there was a significant positive trend associated with increasing numbers of prescriptions of dosulepin (adjusted odds ratio 1.52 for 1 prescription, 1.39 for 2-3, and 1.96 for ≥ 4, $P < 0.002$).
Conclusion There is good evidence for an association between dosulepin and subsequent ischaemic heart disease and for a dose-response relation.

Introduction

Major depression is the fourth most important contributor to disability adjusted life years worldwide.[1] Over 45% of patients in hospital after a myocardial infarction have depression,[2] and it is an independent risk factor for increased mortality[3] and morbidity[4] after myocardial infarction. In 1998, we reported evidence for depression as a risk factor for ischaemic heart disease in men from a study conducted in a single practice.[5] This association may have been related to use of antidepressant drugs, although our sample was too small to be certain.

Tricyclic antidepressants are not recommended in patients with known ischaemic heart disease,[6] mainly because of their arrhythmogenic activity.[7] However, their potential role in the aetiology of ischaemic heart disease is unclear.[8–10] A case-control study of fatal myocardial infarction in young women found an odds ratio of 16.9 for the use of psychotropic drugs.[8] Conversely, a cohort study found that the association between ischaemic heart disease and tricyclic antidepressants probably reflected a primary relation between depression and ischaemic heart disease.[9] Another study associated tricyclic antidepressants with increased risk of myocardial infarction, although it did not distinguish between drugs individually and those in combination, and it focused on myocardial infarction rather than on first presentation of ischaemic heart disease.[11] We aimed to determine whether antidepressants are a risk factor for ischaemic heart disease and compare the risk for different subgroups of antidepressants and individual antidepressants.

Participants and methods

We recruited nine general practices from the Trent Focus Collaborative Research Network, which has been shown to be representative of other practices in Trent (unpublished data). Practices met minimum criteria for data quality: these were minimum levels of recording of nine chronic diseases (for example, prevalences of 4.3% for ischaemic heart disease, 2.7% for diabetes, and 10.3% for hypertension)[12]; lifestyle data and blood pressure recorded in more than 50% of adults; and use of practice computer for prescribing. The study was approved by Trent multicentre research ethics committee and local research ethics committee.

This was a matched case-control study. We identified incident cases from the practice computer records for 1 January 1995 to 31 December 1999. Cases were men and women who had a recorded diagnosis of ischaemic heart disease (including angina, myocardial infarction, and coronary artery surgery) or were receiving repeat prescriptions for nitrates.[13] We included only cases who had been registered with the

practice for more than five years before ischaemic heart disease was diagnosed and whose first recorded diagnosis was at least five years after the date on which the practice had its current computer installed.

Controls were patients who had never had a recorded diagnosis of ischaemic heart disease. We identified four to six controls, matched for age and sex, for each case. Controls were selected by finding the patients closest in age (years) from an ordered list of patients currently registered with the same practice. Each control was allocated to only one case. Controls had to be alive and registered with the same practice on the date that their matched case was diagnosed with ischaemic heart disease and for the five years before this.

Data collection

We extracted computerised data for cases and controls before the date of diagnosis (or diagnosis of matched case) using MIQUEST.[14] The data comprised name, dose, frequency, and dates of issue of all antidepressant drugs; Read codes and dates of onset for depression, ischaemic heart disease, diabetes mellitus, and hypertension; age; sex; body mass index; most recently recorded smoking status (current smoker, former smoker, non-smoker, or not recorded); and registration date. We coded antidepressants according to the classification in the *British National Formulary* (March 2000). We determined the time (in years) between the last prescription for each antidepressant and the date of diagnosis of the case.

Statistical methods

We calculated odds ratios with 95% confidence intervals using conditional multiple logistic regression analysis for individually matched case-control studies (Stata, version 5). Our outcome variable was ischaemic heart disease. The main variable of interest was use of any antidepressant drug before diagnosis. We compared the odds ratios and 95% confidence intervals associated with each *British National Formulary* category of antidepressants singularly and in combination. We tested for an interaction between tricyclic antidepressants and selective serotonin reuptake inhibitors; between dosulepin (dothiepin) and amitriptyline, and between dosulepin and lofepramine.

We adjusted for the potential confounding effects of diabetes, hypertension, body mass index, and smoking status by multivariate analysis. We present the unadjusted and adjusted odds ratios associated with each dose and duration category. Dose-response relations were tested for trend. A case-control set was excluded if the information for either the case or all its controls was not known for the variable in question.

Table 1 Baseline characteristics of cases and controls. Values are numbers (percentages) unless stated otherwise

	Cases (n=933)	Controls (n=5516)
Men	516 (55)	3081 (56)
Age at diagnosis (years)*:		
<50	64 (7)	384 (7)
50-59	202 (22)	1213 (22)
60-69	291 (31)	1732 (31)
70-79	271 (29)	1591 (29)
80-89	88 (9)	533 (10)
≥90	17 (2)	63 (1)
Total	933 (100)	5516 (100)
Body mass index (kg/m^2):		
Valid data available	578 (62)	3052 (55)
Mean (SD)	27.9 (5.0)	26.6 (4.4)
Diabetes	121 (13)	314 (6)
Hypertension	354 (38)	1367 (25)
Last recorded smoking status:		
Non-smoker	376 (40)	2160 (39)
Former smoker	194 (21)	900 (16)
Current smoker	192 (21)	993 (18)
Total with recorded status	762 (82)	4053 (73)

*Age at diagnosis of matched case for controls.

Calculation of sample size

Assuming 10% use of tricyclic antidepressants within the preceding five years, we calculated that we needed 804 case-control sets (one case to four controls) to show an odds ratio of 1.5 for the use of antidepressants before the onset of ischaemic heart disease with a 95% power at 5% significance.[15] We estimated that we would need nine general practices with a total population of 70 000 to ensure that we could identify 800 incident cases during the specified five years.

Results

Characteristics of study population

Among the 74 948 registered patients, there were 933 incident cases of ischaemic heart disease which met our inclusion criteria. We matched 516 men with ischaemic heart disease to 3081 male controls and 417 women to 2435 female controls. We had a mean of 7.5 (SD 1.5) years of prescription data for cases and 7.4 (SD 1.7) years for controls before the date of diagnosis. In total, we had 47 551 person years of prescription and morbidity data. Table 1 shows the numbers of cases and controls and their baseline characteristics.

Table 2 shows the odds ratios for ischaemic heart disease associated with the use of antidepressant drugs. Patients with a Read code for depression but no recorded use of antidepressants and those who had ever received monoamine oxidase inhibitors or a drug from *British National Formulary* section 4.3.4 (other antidepressants) did not have significantly raised odds ratios for ischaemic heart disease on univariate analysis or multivariate analysis.

By contrast, the odds ratio was significantly raised in patients who had ever had a prescription for antidepressants before their diagnosis date (1.67, 95% confidence interval 1.41 to 1.99). This persisted despite adjustments for confounding by diabetes, hypertension, smoking, and body mass index (adjusted odds ratio 1.63, 1.28 to 2.08).

Patients who had been prescribed selective serotonin reuptake inhibitors had a significantly increased odds ratio for ischaemic heart disease on univariate analysis (1.55, 1.18 to 2.01). However, the odds ratio was not significantly raised when adjustments were made for confounders and use of tricyclic antidepressants (1.29, 0.89 to 1.87). There was no significant interaction between ever use of selective serotonin reuptake inhibitors and ever use of tricyclic antidepressants. The odds ratio was significantly raised for patients who had ever received a prescription for tricyclic antidepressants (1.67, 1.38 to 2.01). The increase in odds ratio persisted after adjustment for confounders and use of selective serotonin reuptake inhibitors (1.56, 1.18 to 2.05).

Table 2 Use of antidepressants and recording of depression in cases and controls before diagnosis of ischaemic heart disease in cases

	No (%) of cases (n=933)	No (%) of controls (n=5516)	Odds ratio (95% CI)	P value	Adjusted odds ratio* (95% CI)	P value
Code for depression but no antidepressants	41 (4)	191 (3)	1.28 (0.90 to 1.81)	0.17	1.41 (0.92 to 2.19)	0.12
Any antidepressant drug ever	217 (23)	871 (16)	1.67 (1.41 to 1.99)	<0.0001	1.63 (1.28 to 2.08)	<0.0001
Selective serotonin reuptake inhibitor ever	76 (8)	303 (5)	1.55 (1.18 to 2.01)	0.001	1.29† (0.89 to 1.87)	0.19
Selective serotonin reuptake inhibitor only	33 (4)	132 (2)	1.50 (1.01 to 2.21)	0.04	1.37 (0.81 to 2.31)	0.24
Others antidepressants (*BNF* 4.3.4)	3 (0)	34 (1)	0.53 (0.16 to 1.72)	0.29	0.68‡ (0.14 to 3.29)	0.63
Tricyclic antidepressant ever	183 (20)	730 (13)	1.67 (1.38 to 2.01)	<0.0001	1.56§ (1.18 to 2.05)	0.001
Tricyclic antidepressant only	140 (15)	339 (6)	1.59 (1.30 to 1.95)	<0.0001	1.53 (1.15 to 2.03)	0.004
Amitriptyline ever	78 (8)	322 (6)	1.49 (1.15 to 1.94)	0.003	1.07¶ (0.70 to 1.66)	0.75
Dosulepin (dothiepin) ever	79 (8)	288 (5)	1.73 (1.33 to 2.26)	<0.0001	1.67** (1.17 to 2.36)	0.005
Lofepramine ever	36 (4)	133 (2)	1.66 (1.13 to 2.44)	0.009	1.54†† (0.81 to 2.93)	0.18

*Adjusted for diabetes, hypertension, body mass index, and smoking status.
†Additionally adjusted for ever use of tricyclic and other antidepressants.
‡Additionally adjusted for ever use of tricyclic antidepressants and selective serotonin reuptake inhibitors.
§Additionally adjusted for ever use of selective serotonin reuptake inhibitors and other antidepressants.
¶Additionally adjusted for ever use of selective serotonin reuptake inhibitors, dosulepin, lofepramine, and other antidepressants.
**Additionally adjusted for ever use of selective serotonin reuptake inhibitors, amitriptyline, lofepramine, and other antidepressants.
††Additionally adjusted for ever use of selective serotonin reuptake inhibitors, amitriptyline, dosulepin, and other antidepressants.

To determine whether our findings were due to a specific drug or a class of drugs, we repeated the analysis for amitriptyline, dosulepin (dothiepin), and lofepramine since these were the three most commonly used tricyclic antidepressants. The odds ratios were raised for each of the three tricyclic antidepressants (table 2), but the increases for amitriptyline and lofepramine were not significant once adjustments had been made for confounders and ever use of dosulepin. The increased odds ratio for dosulepin, however, remained after potential confounding factors were adjusted for (1.67, 1.17 to 2.36).

Table 3 shows the dose-response relation for dosulepin. Patients whose maximum dose of tricyclic antidepressant was over 50 mg had increased odds of ischaemic heart disease compared with patients with lower maximum doses on univariate and multivariate analysis (unadjusted odds ratio 1.74, 1.26 to 2.41; adjusted odds ratio 1.72, 1.12 to 2.63). The test for trend was highly significant ($P<0.0001$), suggesting a dose-response relation.

There was a significant positive trend associated with increasing numbers of prescriptions of dosulepin ($P<0.0001$) on univariate and multivariate analysis. The effect was greatest for patients with four or more prescriptions compared with no prescriptions (adjusted odds ratio 1.96, 1.24 to 3.09). This is also consistent with a dose-response relation. There was no consistent picture concerning time from last prescription. There was no significant interaction between ever use of dosulepin and either age or sex.

We compared the characteristics of cases and controls by type of antidepressant ever prescribed and found no significant differences between the two groups.

Discussion

We found that patients with ischaemic heart disease were more likely to have taken an antidepressant before their diagnosis than matched controls. The association remained for tricyclic antidepressants, but not other antidepressants, after confounding factors had been taken into account.

Depression could lead to coronary events directly or indirectly through poorer health related behaviours such as smoking or decreased physical activity.[16] Our results suggest that the increased risk is due to dosulepin. After confounding factors (including ever having taken a selective serotonin reuptake inhibitor, amitriptyline, or lofepramine) were adjusted for, patients who had taken dosulepin were 67% more likely to develop ischaemic heart disease than matched

Table 3 Dose-response relation for dosulepin (dothiepin)

	No (%) of cases (n=933)	No (%) of controls (n=5516)	Odds ratio (95% CI)	P value	Adjusted odds ratio* (95% CI)	P value
Highest dose (mg):						
0	854 (92)	5228 (95)	1.00		1.00	
1 to 49	5 (1)	36 (1)	0.86 (0.37 to 2.20)	<0.0001†	1.40 (0.46 to 4.22)	0.003†
50 to 99	51 (5)	186 (3)	1.74 (1.26 to 2.41)		1.72 (1.12 to 2.63)	
⩾100	23 (2)	66 (1)	2.19 (1.35 to 3.55)		1.77 (0.97 to 3.23)	
No of prescripitions:						
0	854 (92)	5228 (95)	1.00		1.00	
1	19 (2)	72 (1)	1.69 (1.01 to 2.82)	<0.0001†	1.52 (0.78 to 2.94)	0.002†
2 or 3	18 (2)	69 (1)	1.63 (0.97 to 2.77)		1.39 (0.70 to 2.76)	
⩾4	28 (3)	81 (1)	2.22 (1.43 to 3.48)		1.96 (1.24 to 3.09)	
Years since last prescription:						
0	854 (92)	5228 (95)	1.00		1.00	
⩾5	20 (2)	63 (1)	2.03 (1.22 to 2.39)	0.006	2.05 (1.04 to 4.04)	0.04
1.01 to 4.95	28 (3)	114 (2)	1.55 (1.01 to 2.37)	0.05	1.63 (0.95 to 2.77)	0.07
⩽1	31 (3)	111 (2)	1.76 (1.17 to 2.64)	0.007	1.60 (0.95 to 2.70)	0.08

*Adjusted for hypertension, diabetes, body mass index, smoking status, and ever use of selective serotonin reuptake inhibitor, amitriptyline, lofepramine, and other antidepressants.
†Test for trend across categories.

controls. Fifty patients would need to be treated for one year in order for one to be harmed, assuming an incidence of ischaemic heart disease of 3% a year.

The risk of ischaemic heart disease rises with increasing highest dose and number of prescriptions. This is consistent with a dose-response effect (table 3). We found no pattern between time since last exposure and risk of heart disease, which suggests that the cardiotoxicity of dosulepin remains long after treatment is stopped.

In terms of biological plausibility, tricyclic antidepressants are class one antiarrhythmic drugs and can cause orthostatic hypotension.[17] Both of these effects can precipitate a myocardial infarction.[7] Also, tricyclic antidepressants increase insulin resistance in non-insulin dependent diabetes,[18] a factor associated with atheroma. There is some evidence that dosulepin is more toxic than other tricyclic antidepressants.[19] In contrast, there is little evidence that selective serotonin reuptake inhibitors have serious adverse cardiac effects,[6 20] although long term data are not yet available.

Choice of methods

We have examined up to 12 years' exposure for cases and controls, which is longer than other studies.[11] We matched cases and controls on age, sex, and practice to ensure comparable completeness of prescription data, which will tend to minimise misclassification of the exposure variable. Any misclassification bias would result in underestimation of the odds ratio and, by implication, the strength of the association.[15] We used a bias-free method for selecting controls to eliminate selection bias. Recall bias is unlikely as we used electronic data that had been collected before the start of our study.

We do not have a non-drug related measure of the severity of depression, which is a limitation. Patients with more severe depression may be more likely to take dosulepin. We have also not adjusted for the possible confounding effects of serum lipid concentrations, diet, or use of alcohol. These factors may be associated with depression and causally linked with ischaemic heart disease. However, we have no reason to believe that they would be preferentially associated with dosulepin rather than other antidepressants.

We cannot rule out an association between depression alone and ischaemic heart disease as there were too few untreated patients. However, a post hoc power calculation showed that the study had 90% power at the 5% significance level to detect an odds ratio of 1.80 in this group.

Conclusion

The five main criteria for causality are association, temporal relation, dose-response, specificity, and biological plausibility. We have found good evidence for an association between dosulepin and subsequent ischaemic heart disease and a dose-response. We also offer a biological explanation. Our findings suggest that dosulepin has deleterious effects.

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Contributors: JHC initiated and designed the study, did the literature review, manipulated the data, analysed and interpreted the data, and drafted the paper. MP contributed to the development of core ideas, study design, interpretation of data, and drafting of the paper. VH coordinated recruitment of the practices, wrote the MIQUEST searches, coordinated the data collection, and helped with the data manipulation and interpretation. NC processed the ethical approval, contributed to the MIQUEST queries, imported data, collected references, and did the case-control matching. AM joined the project team at the data collection stage and contributed to the MIQUEST searches and the interpretation of data. AW contributed to the discussions and the literature search. CC advised on the statistical analysis and interpretation of data.

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What is already known on this topic

Over 45% of patients in hospital after myocardial infarction have depression

Depression is an independent risk factor for increased mortality and morbidity after myocardial infarction

What this study adds

Patients who had ever taken dosulepin (dothiepin) had significantly increased risk of ischaemic heart disease after confounding factors had been adjusted for

The association followed a dose-response relation

The effect of other antidepressants was not significant after adjustment for confounders