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# Sudden death in patients receiving drugs tending to prolong the QT interval

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drugs slowing electocardiographic QT conduction can cause tachyarrhythmias, torsades de pointes (TdP) and cardiac arrest.
- Associated risks of sudden death have been consistently found for older, typical, antipsychotic drugs, but epidemiological evidence of risks for other drugs are poorly defined.

## WHAT THIS STUDY ADDS

- In a population-based study risk of sudden death with noncardiac drug treatment was mainly posed by antipsychotics both typical and atypical, and by antidepressants, particularly selective serotonin reuptake inhibitors.
- Results could not be accounted for by confounding.
- No significant risk was associated with use of other noncardiac or psychiatric drugs.
- A published general categorization of risk of drug-induced TdP corresponded poorly with these findings.

## AIMS

To examine risks of sudden death in the community associated with drugs grouped by their risk of causing torsades de pointes (TdP) and to explore the risks for individual drugs.

## METHODS

Case–control study comparing prior drug intakes and morbidities, using the Arizona classification of drugs causing TdP. Participants included 1010 patients dying suddenly where post-mortem examination did not identify a clear cause of death, and 3030 matched living controls from primary care.

## RESULTS

Noncardiac drug risk was posed by antipsychotics and antidepressants. Significantly raised odds ratios (ORs) were found for takers of typical and atypical antipsychotics, ORs [95% confidence interval] 3.94 (2.05, 7.55) and 4.36 (2.54, 7.51), and of selective serotonin reuptake inhibitors [SSRIs] rather than tricyclic antidepressants, ORs 2.21 (1.61, 3.05) and 1.44 (0.96, 2.13). No significant risk was associated with other, noncardiac or psychiatric drugs, OR 1.09 (0.85, 1.41). Arizona classified drugs considered to raise risk of TdP were associated with raised risk of sudden death, as were those only weakly associated with TdP and not considered to pose a risk in normal use, ORs 2.08 (1.45, 3.00) and 1.74 (1.33, 2.28), respectively.

## CONCLUSIONS

Atypical and typical antipsychotic drug use were both strongly associated with raised risks, as were SSRIs. Tricyclic antidepressants were not associated with raised risks. The Arizona classification of risk of TdP was a poor predictor of likelihood of noncardiac drug-associated sudden death.

## Introduction

Prior cardiac disease, pre-existing arrhythmia and the use of drugs that tend to prolong cardiac repolarization and hence increase the electrocardiographic QT interval, are associated with the occurrence of torsades de pointes (TdP) [1–3]. Limited evidence confirms consequent risk of sudden death. Almost a threefold increase in the chances of sudden death was found in a Dutch practice database [4], where any noncardiac QT-prolonging drug was in use, and significantly raised risk with the use of typical antipsychotics, particularly thioridazine [4–7], and also in takers of erythromycin [8].

The International Registry for Drug-induced Arrhythmias Arizona classification lists 34 drugs as likely to pose risks of causing TdP, 41 drugs are associated with TdP or QT prolongation, but lack substantive evidence, while 21 others, many from the same therapeutic classes, are considered, on the basis of combined consideration of available pharmacological, clinical and epidemiological information, to be unlikely to cause such risk when used in recommended doses and in patients without other risk factors. We therefore compared prior drug use of all types in individuals dying suddenly in the community where coroner's post-mortem examination had failed to identify a clear cause for their deaths. We also systematically collected information on past medical histories of those dying suddenly and their controls to allow exploration of potential confounders.

We hypothesized that use of any drug with the potential to prolong cardiac repolarization would be associated with an increased chance of sudden death in the community, independent of pre-existing risk factors or underlying cardiac disease, and risk should be concentrated on drugs identified by the Arizona classification as predisposing to such death [9].

## Methods

### Cases

We undertook a population-based case–control study. Cases were adults aged 20–85 years who had died in the community in the Midlands of England in Birmingham, Solihull, Coventry and Nottingham (estimated population 2.1 million) in the period September 2003 to February 2007. To maximize the chances of identifying likely arrhythmic deaths [10], we searched the Public Health Mortality files for suitable cases by selecting those who had been referred to HM Coroner because death had occurred suddenly in the community and the cause was unclear. All cases then had to have had a post-mortem examination where a clear cause of death could not be identified, apart from descriptions of coronary atherosclerosis with no evidence of plaque rupture, nor of current or recent myocardial infarction, and evidence to suggest drug overdosage was lacking.

In the UK, deaths are referred to a coroner if death follows an accident or injury, industrial disease, occurs during an operation or before recovery from an anaesthetic, or if the cause of death is unknown, or was violent or unnatural or sudden and unexplained, or if the deceased was not seen by the doctor issuing the medical certificate after they died, or during the 14 days before death. In 2002, 38% of all deaths in England and Wales were reported to a coroner, 60% of which had a post-mortem examination [11].

### Controls

Three controls were identified per case, with matching for age (being the nearest three patients in age registered in the same general practice as the case) and for sex. Where cases had been found to have cardiovascular disease (CVD) (based on clinical features and treatment of at least one of previous myocardial infarction, angina, history of coronary revascularization, heart failure, hypertension, bradycardia, heart block, or atrial fibrillation), controls were selected with CVD as indicated by the presence of any one of these features.

### Exposure definition

Details were noted of all drugs prescribed in the 90 days prior to death of the case (name, dose, frequency, route of administration), and of diagnosed disease of the cardiovascular, respiratory, renal, alimentary and neurological systems. The timings and quantities prescribed were used to estimate whether the drugs were prescribed to be taken during the 7 days, 8–30 days or 31–90 days prior to the date of death of the case. Information was transcribed from general practice computerized and paper records both for cases and matched controls.

### Covariates and risk factors

To explore pre-existing risk of sudden cardiac death, aspects of past medical history were identified. These included the above cardiovascular features and syncope, dizziness, epilepsy, renal dysfunction (case note reported or biochemical results outside normal range), biochemical evidence of episodes of low serum potassium, high serum potassium, low serum calcium or low serum magnesium, abnormal liver function, drug (substance) misuse, and alcohol abuse.

### Analyses

Data were examined by conditional logistic regression to take account of the matching with calculation of odds ratios (ORs) and their 95% confidence intervals (CIs), with and without adjustment for the presence of prior disease and/or for concurrent drug use. Initial subdivision by Arizona classes used the groupings currently advised [9]. This classification defines as: Group 1, drugs generally

accepted to have a risk of TdP; Group 2, drugs with a possible risk of TdP but lacking substantial evidence; Group 4, drugs weakly associated with TdP but unlikely to pose risks in normal use. Group 3, drugs to be avoided by congenital long QT syndrome patients, largely summates from other groups and only those not covered in Groups 1, 2 and 4 are included here.

Drug groupings were obtained using the hierarchy employed in the British National Formulary (BNF) [12], which for example allows separation of typical and atypical antipsychotics, and tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressants. All potential covariates associated with sudden death that we collected were included in a backwards stepwise regression analysis using $P > 0.1$ for removal from the model. Remaining covariates were used in the adjusted analyses. To evaluate a possible dose-effect, a test for trend was undertaken.

Data were then considered by therapeutic groups, and for patients with and without a prior diagnosis of CVD. Categorization of the dose of antipsychotic and antidepressant drugs was undertaken by one of the authors (M.J.S.L.), who was blinded to case or control status. This was based on the recommended therapeutic ranges in the BNF with drugs prescribed in doses less than these as low dose.

### *Ethics*

The study was approved by the West Midlands Multicentre Research Ethics Committee, and the National Health Service Patient Information Advisory Group for use of patient-identifiable information.

### *Role of the funding source*

The sponsors of the study had no role in study design, the collection, analysis or interpretation of data, the writing of the report or the decision to submit the paper for publication.

## Results

We identified 1137 potential cases, but medical records were not obtainable in 127 (11.2%) due to refusal to allow access by their general practices. The remaining 1010 cases were successfully matched with 3030 controls for age and sex. The 436 cases without histories of CVD were largely successfully matched with controls without such disease, but cases were significantly more likely to have a history of hypokalaemia, epilepsy, dizziness, liver disease, or history of drug or alcohol abuse, which were considered as potential covariates for the adjusted analysis. Although the 574 cases with CVD were matched with controls with CVD, cases were significantly more likely to have prior histories of myocardial infarction, heart failure, heart block, atrial fibrillation and syncope, and also of epilepsy, renal dysfunction, low serum potassium, abnormal liver function, drug (substance) misuse, and alcohol abuse (Table 1).

**Table 1**

Characteristics of cases and controls

| | Cases *n* = 1010 | % | Controls *n* = 3030 | % | OR | 95% CI |
|---|---|---|---|---|---|---|
| **Age (mean, SD)** | 67.60 | 12.40 | 67.60 | 12.37 | | |
| **Males** | 681 | 67.4 | 2043 | 67.4 | | |
| **No history of cardiovascular disease** | 436 | 43.2 | 1308 | 43.2 | | |
| **Past medical history:** | | | | | | |
| **Myocardial infarction** | 110 | 10.9 | 214 | 7.1 | 1.72* | 1.32, 2.23 |
| **Angina** | 142 | 14.1 | 385 | 12.7 | 1.14 | 0.92, 1.44 |
| **Coronary revascularization** | 37 | 3.7 | 124 | 4.1 | 0.88 | 0.60, 1.30 |
| **Heart failure** | 101 | 10.0 | 113 | 3.7 | 3.52 | 2.57, 4.83 |
| **Hypertension** | 522 | 51.7 | 1606 | 53.0 | 0.76 | 0.56, 1.04 |
| **Low serum potassium** | 29 | 2.9 | 31 | 1.0 | 3.00 | 1.77, 5.09 |
| **Low serum calcium** | 6 | 0.6 | 9 | 0.3 | 2.00 | 0.71, 5.62 |
| **Low serum magnesium** | 0 | 0 | 1 | 0.03 | – | – |
| **Bradycardia** | 10 | 1.0 | 18 | 0.6 | 1.69 | 0.77, 3.70 |
| **Heart block** | 10 | 1.0 | 10 | 0.3 | 3.36 | 1.31, 8.62 |
| **Atrial fibrillation** | 74 | 7.3 | 125 | 4.1 | 1.98 | 1.44, 2.72 |
| **Epilepsy** | 56 | 5.5 | 54 | 1.8 | 3.20 | 2.19, 4.69 |
| **Syncope** | 20 | 2.0 | 31 | 1.0 | 2.05 | 1.13, 3.70 |
| **Dizziness** | 47 | 4.7 | 119 | 3.9 | 1.20 | 0.85, 1.71 |
| **Renal dysfunction** | 62 | 6.1 | 127 | 4.2 | 1.58 | 1.13, 2.20 |
| **Abnormal liver function** | 30 | 3.0 | 28 | 0.9 | 3.34 | 1.97, 5.66 |
| **High serum potassium** | 33 | 3.3 | 75 | 2.5 | 1.35 | 0.88, 2.07 |
| **Drug misuse** | 8 | 0.8 | 2 | 0.1 | 12.00 | 2.55, 56.50 |
| **Alcohol abuse** | 117 | 11.6 | 55 | 1.8 | 8.53 | 5.90, 12.32 |

### *Arizona classification*

Table 2 shows ORs for sudden death, unadjusted and adjusted, for all drugs falling within Arizona Groups 1, 2 or 4, and for the subset of Group 3 not already included in Groups 1, 2 and 4, which had been prescribed for use in the 30 days prior to death or the equivalent period in the controls. Unadjusted overall risks were doubled for Group 1 (drugs generally accepted as posing risks), OR (95% CI) 2.08 (1.45, 3.00), but with considerable variation, being raised sixfold in takers of haloperidol, but not raised in takers of sotalol. Raised risk was also found for erythromycin prescribed during the prior 7 days, OR 4.50 (1.27, 15.94), but not during the previous 8–31 days (OR 0.82, 95% CI 0.29, 2.93), nor for amoxicillin during 0–7 days (OR 1.2, 95% CI

## Table 2

Drugs prescribed (used) within the 30 days prior to death of the case

| | Cases *n* | Controls *n* | OR | 95% CI | | Adjusted OR | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| **Arizona Group 1** | | | | | | | | |
| **Amiodarone** | 17 | 17 | 3.0 | 1.53 | 5.88 | 1.99 | 0.93 | 4.28 |
| **Chlorpromazine** | 4 | 8 | 1.5 | 0.45 | 4.98 | 1.28 | 0.34 | 4.86 |
| **Clarithromycin** | 2 | 6 | 1.0 | 0.20 | 4.95 | 0.94 | 0.18 | 5.07 |
| **Disopyramide** | 0 | 1 | – | – | – | – | – | – |
| **Domperidone** | 6 | 12 | 1.5 | 0.56 | 4.00 | 1.60 | 0.59 | 4.36 |
| **Erythromycin** | 8 | 12 | 2.0 | 0.82 | 4.89 | 2.07 | 0.82 | 5.24 |
| **Haloperidol** | 6 | 3 | 6.0 | 1.50 | 23.99 | 3.63 | 0.84 | 14.64 |
| **Methadone** | 1 | 1 | 3.0 | 0.19 | 47.96 | 3.78 | 0.23 | 61.43 |
| **Sotalol** | 5 | 14 | 1.07 | 0.39 | 2.97 | 1.03 | 0.36 | 2.99 |
| **Thioridazine** | 2 | 0 | – | – | – | – | – | – |
| **Any type I drug** | 50 [51] | 74 [74] | 2.08 | 1.45 | 3.00 | 1.76 | 1.19 | 2.62 |
| **Arizona Group 2** | | | | | | | | |
| **Alfuzosin** | 5 | 31 | 0.48 | 0.18 | 1.24 | 0.60 | 0.22 | 1.55 |
| **Amantadine** | 2 | 1 | 6.0 | 0.54 | 66.17 | 11.18 | 0.94 | 132.68 |
| **Chloral hydrate** | 2 | 1 | 6.0 | 0.54 | 66.17 | 5.48 | 0.48 | 62.34 |
| **Clozapine** | 1 | 0 | – | – | – | – | – | – |
| **Flecainide** | 1 | 4 | 0.75 | 0.08 | 6.71 | 0.70 | 0.07 | 6.82 |
| **Indapamide** | 15 | 67 | 0.65 | 0.37 | 1.16 | 0.77 | 0.42 | 1.42 |
| **Levofloxacin** | 0 | 2 | – | – | – | – | – | – |
| **Lithium** | 6 | 10 | 1.8 | 0.65 | 4.95 | 1.75 | 0.62 | 4.95 |
| **Nicardipine** | 1 | 2 | 1.5 | 0.14 | 16.5 | 2.74 | 0.24 | 31.34 |
| **Quetiapine** | 3 | 4 | 2.25 | 0.50 | 10.05 | 3.49 | 0.71 | 17.15 |
| **Risperidone** | 15 | 10 | 4.5 | 2.02 | 10.02 | 4.22 | 1.82 | 9.79 |
| **Tamoxifen** | 1 | 11 | 0.27 | 0.04 | 2.11 | 0.28 | 0.04 | 2.20 |
| **Vardenafil** | 0 | 6 | – | – | – | – | – | – |
| **Venlafaxine** | 10 | 14 | 2.14 | 0.95 | 4.82 | 2.24 | 0.93 | 5.38 |
| **All Group 2** | 50 [66] | 138 [159] | 1.09 | 0.78 | 1.53 | 1.30 | 0.93 | 1.80 |
| **Arizona Group 3 (not in 1, 2 or 4)** | | | | | | | | |
| **Ephedrine** | 1 | 1 | 3.0 | 0.19 | 47.96 | 1.05 | 0.04 | 24.97 |
| **Pseudoephedrine** | 1 | 7 | 0.42 | 0.05 | 3.48 | 0.36 | 0.04 | 3.19 |
| **Salmeterol** | 43 | 110 | 1.18 | 0.82 | 1.70 | 1.13 | 0.77 | 1.66 |
| **Sibutramine** | 0 | 1 | – | – | – | – | – | – |
| **Terbutaline** | 9 | 23 | 1.18 | 0.54 | 2.56 | 1.30 | 0.57 | 2.94 |
| **Tolterodine** | 5 | 16 | 0.94 | 0.34 | 2.56 | 1.03 | 0.35 | 3.03 |
| **Any group 3** | 59 [59] | 154 [158] | 0.94 | 0.34 | 2.56 | 1.12 | 0.81 | 1.57 |
| **Arizona Group 4** | | | | | | | | |
| **Amitriptyline** | 16 | 41 | 1.17 | 0.66 | 2.09 | 1.17 | 0.64 | 2.12 |
| **Ciprofloxacin** | 4 | 12 | 1.0 | 0.32 | 3.10 | 0.78 | 0.25 | 2.50 |
| **Citalopram** | 19 | 25 | 2.28 | 1.25 | 4.14 | 1.83 | 0.97 | 3.56 |
| **Clomipramine** | 2 | 4 | 1.5 | 0.27 | 8.19 | 1.63 | 0.28 | 9.35 |
| **Fluconazole** | 0 | 1 | – | – | – | – | – | – |
| **Fluoxetine** | 18 | 24 | 2.29 | 1.23 | 4.24 | 2.11 | 1.08 | 4.20 |
| **Imipramine** | 1 | 5 | 0.6 | 0.07 | 5.14 | 0.63 | 0.07 | 5.36 |
| **Nortriptyline** | 0 | 1 | – | – | – | – | – | – |
| **Paroxetine** | 10 | 19 | 1.60 | 0.73 | 3.48 | 0.93 | 0.44 | 2.23 |
| **Sertraline** | 9 | 9 | 3.0 | 1.19 | 7.55 | 2.90 | 1.07 | 7.99 |
| **Solifenacin** | 1 | 3 | 1.0 | 0.10 | 9.61 | 1.21 | 0.11 | 12.18 |
| **Trimethoprim** | 11 | 17 | 1.94 | 0.91 | 4.14 | 1.73 | 0.75 | 3.87 |
| **Trimipramine** | 1 | 0 | – | – | – | – | – | – |
| **Any Group 4** | 88 [92] | 157 [161] | 1.74 | 1.33 | 2.28 | 1.49 | 1.13 | 1.99 |

Adjusted for heart failure, MI, atrial fibrillation, revascularization, hypokalaemia, bradycardia, syncope, epilepsy, renal dysfunction, history of alcohol abuse.

**Table 3**

Odds ratio (OR) (crude and adjusted) for categories of psychiatric drugs 0–30 days

| | Crude OR | 95% CI | | Adjusted OR* | 95% CI | |
|---|---|---|---|---|---|---|
| **All antipsychotics** | 4.27 | 2.78 | 6.59 | 4.29 | 2.68 | 6.88 |
| **High dose** | 5.59 | 2.84 | 10.98 | 5.64 | 2.66 | 11.98 |
| **Low dose** | 4.02 | 2.11 | 7.68 | 4.65 | 2.36 | 9.19 |
| **Injected/depot** | 2.17 | 0.61 | 7.77 | 1.31 | 0.34 | 6.58 |
| **Typical antipsychotics†** | 3.94 | 2.05 | 7.55 | 3.35 | 1.64 | 6.83 |
| **Atypical antipsychotics‡** | 4.36 | 2.54 | 7.51 | 4.97 | 2.78 | 8.90 |
| **Tricyclic antidepressants§** | 1.44 | 0.96 | 2.13 | 1.41 | 0.93 | 2.13 |
| **High dose** | 2.10 | 0.74 | 3.45 | 2.11 | 1.10 | 4.22 |
| **Moderate dose** | 0.90 | 0.45 | 1.79 | 0.85 | 0.42 | 1.73 |
| **Low dose** | 1.61 | 1.07 | 4.08 | 1.60 | 0.72 | 3.56 |
| **SSRIs¶** | 2.21 | 1.61 | 3.05 | 1.89 | 1.34 | 2.69 |
| **High dose** | 3.29 | 1.62 | 6.65 | 2.78 | 1.24 | 6.24 |
| **Moderate dose** | 1.95 | 1.27 | 2.99 | 1.55 | 0.96 | 2.49 |
| **Low dose** | 1.75 | 0.69 | 4.44 | 1.83 | 0.70 | 4.78 |

Includes for cases and controls: †chlorpromazine 4 and 8, flupentixol (4 mg plus) 3 and 3, fluphenazine 1 and 2, haloperidol 6 and 3, perphenazine 1 and 0, sulpiride 1 and 0, thioridazine 2 and 0, trifluoperazine 2 and 0, zuclopenthixol 1 and 2; ‡clozapine 1 and 0, olanzapine 14 and 8, quetiapine 3 and 4, risperidone 15 and 10; §amitriptylline 16 and 41, clomipramine 2 and 4, dosulepin 16 and 26, impramine 1 and 5, lofepramine 1 and 2, nortriptyline 0 and 1, trimipramine 1 and 0, mianserin 1 and 2; ¶citalopram 19 and 25, escitalopram 4 and 8, fluoxetine 18 and 24, paroxetine, 10 and 19, sertraline 9 and 9, venlafaxine 10 and 14. *Adjusted for heart failure, MI, atrial fibrillation, revascularization, hypokalaemia, bradycardia, syncope, epilepsy, renal dysfunction, history of alcohol abuse.

0.69, 2.09). The overall OR was only just above unity for drugs in Group 2 (with possible risk of TdP), OR 1.09 (0.78, 1.53), and not raised for the few drugs in Group 3 (to be avoided by patients with congenital long QT syndromes) not already included in Groups 1, 2 or 4, OR 0.94 (0.34, 2.56). By contrast, the overall OR was significantly raised for drugs in Group 4 (considered unlikely to cause TdP) prescribed in the prior 30 days, OR 1.74 (1.33, 2.28). Adjustment of figures to take account of the significant differences in patient characteristics noted in Table 1 had no substantial or consistent effects except for tending to reduce ORs for amiodarone and haloperidol.

## *Antipsychotic drugs*

Significant individual unadjusted raised risks were noted for the antipsychotic drugs risperidone (OR 4.5; 2.02, 10.02), olanzapine (OR 5.25; 2.2, 15.5) and haloperidol (OR 6.0; 1.50, 23.99), although falling slightly after adjustment to take account of covariates. Table 3 shows that unadjusted ORs appeared slightly greater, although not significantly so, in recipients of any atypical antipsychotic than in those receiving typical varieties (OR 4.36; 2.54, 7.51 and OR 3.94; 2.05, 7.55, respectively). Adjustment to take account of cardiovascular and other factors tended to reduce these calculated risks for typical antipsychotics, but to raise them for atypical agents, all differences from controls remaining significant. Takers of antipsychotics (of any type) who had started in the prior 30 days appeared to be at greatest risk (OR 9.00; 1.81, 44.59) compared with continuous users in the prior 90 days; or past users, prescribed prior to the past 30 days (OR 3.65; 2.29, 5.82, and OR 1.50; 0.14, 16.54, respectively). Data for prochlorperazine (OR 1.07; 0.52, 2.21) were excluded from these calculations as all use appeared to be at low doses where it has indications for nausea and vertigo. We explored dosage and route of administration of antipsychotics and found the highest risk to be in those taking a high dose (adjusted OR 5.54, 95% CI 2.60, 11.82) and lowest risk in those receiving depot injections (adjusted OR 1.5, 95% CI 0.34, 6.60) (Table 3). Examination of coincident use with other psychiatric drugs (such as lithium) identified no difference between cases and controls.

## *Antidepressants*

Significant unadjusted risks were found (Table 2) for the SSRIs citalopram (OR 2.28, 95% CI 1.25, 4.14), fluoxetine (OR 2.29, 95% CI 1.23, 4.24), and sertraline (OR 3.0, 95% CI 1.19, 7.55), with small reductions after adjustment to take account of significant risk factors, remaining significant except for citalopram.

ORs (Table 3) were significantly raised for recipients of any SSRI (OR 2.21, 95% CI 1.61, 3.05), but not for takers of tricyclic agents (OR 1.44, 95% CI 0.96, 2.13). When data were adjusted to take account of coincident risk factors the risk ratios tended to fall slightly for SSRIs to 1.89 (95% CI 1.34, 2.69), but were little changed for tricyclic antidepressants (OR 1.41, 95% CI 0.93, 2.13). Results similar to those for SSRIs were obtained for the combined SSRI and noradrenaline reuptake inhibitor venlafaxine, unadjusted and adjusted ORs 2.14 (95% CI 0.95, 4.82) and 2.24 (0.93, 5.38), respectively. A significant trend in SSRI dose–response relationship was seen in unadjusted results with the OR rising from low dose, 1.75 (0.69, 4.44) to moderate dose 1.95 (1.27–2.99), and high dose 3.29 (1.62, 6.65) ($P < 0.001$). This was not mirrored for tricyclic antidepressants, low dose 1.61 (1.07, 4.08), moderate dose 0.90 (0.45, 1.79) and high dose 2.10 (0.74, 3.45) ($P = 0.07$), but scrutiny of tricyclic antide-

## Table 4

Adjusted odds ratio (OR) for antipsychotic agents and selective serotonin reuptake inhibitors (SSRIs), in patients with and without prior diagnosed cardiovascular disease, and prescribed for use within 0–30 days of death of the case

| | With cardiovascular disease | | | | | Without cardiovascular disease | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Controls | Adjusted OR* | 95% CI | | Cases | Controls | Adjusted OR† | 95% CI | |
| **All antipsychotics** | 27 | 14 | 6.15 | 3.02 | 12.57 | 24 | 25 | 3.26 | 1.67 | 6.36 |
| **Haloperidol** | 4 | 1 | 7.83 | 0.84 | 72.80 | 2 | 2 | 2.63 | 0.14 | 48.30 |
| **Quetiapine** | 3 | 3 | 4.24 | 0.80 | 22.41 | 0 | 1 | – | – | – |
| **Risperidone** | 11 | 1 | 28.70 | 3.61 | 228.06 | 4 | 9 | 1.48 | 0.44 | 4.98 |
| **Olanzapine** | 5 | 4 | 4.25 | 0.95 | 19.01 | 9 | 4 | 7.40 | 1.94 | 28.23 |
| **All SSRI** | 45 | 64 | 2.04 | 1.33 | 3.13 | 24 | 34 | 1.63 | 0.86 | 3.10 |
| **Citalopram** | 12 | 17 | 1.81 | 0.81 | 4.03 | 7 | 8 | 1.70 | 0.50 | 5.99 |
| **Paroxetine** | 9 | 12 | 1.42 | 0.53 | 3.83 | 1 | 7 | 0.20 | 0.02 | 2.01 |
| **Sertraline** | 4 | 7 | 2.06 | 0.57 | 7.47 | 5 | 2 | 3.91 | 0.62 | 24.62 |
| **Venlafaxine** | 9 | 8 | 3.73 | 1.33 | 10.45 | 1 | 6 | 0.67 | 0.07 | 6.19 |
| **Fluoxetine** | 10 | 15 | 2.26 | 0.96 | 5.34 | 8 | 9 | 2.44 | 0.77 | 7.74 |
| **All tricyclics** | 24 | 52 | 1.34 | 0.79 | 2.28 | 14 | 29 | 1.61 | 0.83 | 3.13 |
| **Amitriptyline** | 9 | 25 | 1.07 | 0.48 | 2.40 | 7 | 16 | 1.34 | 0.54 | 3.43 |
| **Clomipramine** | 1 | 1 | 1.85 | 0.11 | 30.20 | 1 | 3 | 1.64 | 0.16 | 17.24 |
| **Dosulepin** | 12 | 18 | 2.11 | 0.92 | 4.84 | 4 | 8 | 1.65 | 0.49 | 5.54 |

*Adjusted for heart failure, MI, revascularization, hypertension, hypokalaemia, hyperkalaemia, epilepsy, syncopy, renal dysfunction, history of alcohol abuse. †Adjusted for epilepsy, dizziness, history of drug or alcohol abuse, hypokalaemia and renal dysfunction.

pressant dosage details showed that prescriptions tended to be well below recommended maintenance doses. Only five of 69 current users of SSRIs amongst those dying suddenly had started treatment within the prior 30 days (unadjusted OR 1.25; 0.44, 3.54) compared with 49 who had been treated for at least 90 days (unadjusted OR 1.98; 1.44, 2.85).

### *Other drugs*

Ninety cases and 249 controls were taking other psychiatric or noncardiac drugs listed as possibly posing risk of TdP in the Arizona classification. No significant risk was associated with their use, unadjusted and adjusted ORs 1.09 (0.85, 1.41) and 1.11 (0.85, 1.44), respectively.

### *Patients with and without prior cardiovascular disease*

Table 4 shows that in the 574 patients with diagnosed CVD the risk of sudden death in association with antipsychotic treatment was considerably higher than the risk in those without CVD (OR 6.15; 95% CI 3.02, 12.57; and OR 3.26; 1.67, 6.36, respectively), with risk appearing particularly high in takers of risperidone with prior CVD (OR 28.70, 95% CI 3.61, 228.06). Significant differences in the chances of sudden death also emerged for takers of SSRIs with, but not in those without diagnosed CVD (OR 2.04, 95% CI 1.33, 3.13, and OR 1.63, 95% CI 0.83, 3.10, respectively).

### *Coincident use of antipsychotics and antidepressants*

Nine (18%) of 51 case-takers of antipsychotics were also taking SSRIs, and three (6%) were takers of tricyclic antidepressants. Adjustment of risks of sudden death associated with the use of antipsychotic drugs to take account of prior diagnosed disease, and of antidepressant use, had no material effect on calculated ORs: adjusted OR for antipsychotics 4.12 (95% CI 2.57, 6.60); typical antipsychotics OR 3.14 (95% CI 1.53, 6.43); atypical antipsychotics OR 4.79 (95% CI 2.67, 8.59). Similar adjustment of risks to take account of prior diagnosed disease and concurrent antipsychotic use associated with SSRI use (OR 1.78, 95% CI 1.24, 2.55) and tricyclics (OR 1.28, 95% CI 0.84, 1.96) did not change the findings (Table 5).

## Table 5

Odds ratio (OR) for categories of psychiatric drug use within 0–30 days adjusted for coincident use of other drugs with a raised OR for sudden death

| | Adjusted OR | 95% CI | |
|---|---|---|---|
| **Tricyclics*** | 1.28 | 0.84 | 1.96 |
| **SSRIs*** | 1.78 | 1.24 | 2.55 |
| **All antipsychotics†** | 4.12 | 2.57 | 6.60 |
| **Typical antipsychotics†** | 3.14 | 1.53 | 6.43 |
| **Atypical antipsychotics†** | 4.79 | 2.67 | 8.59 |

*Adjusted for heart failure, MI, atrial fibrillation, revascularization, hypokalaemia, bradycardia, syncope, epilepsy, renal dysfunction, history of alcohol abuse and antipsychotic use. †Adjusted for heart failure, MI, atrial fibrillation, revascularization, hypokalaemia, bradycardia, syncope, epilepsy, renal dysfunction, history of alcohol abuse and SSRI use.

## Discussion

Risk of sudden death appeared little different for categories of noncardiac drugs considered by the International Registry for Drug-Induced Arrhythmias Arizona classifica-

tion [9] most likely (Group 1) or least likely (Group 4) to cause TdP. Our findings, based on observational data, could reflect true risk or be due to confounding, notably as a consequence of prescribing drugs perceived as less likely to be harmful to patients whose disease tended to cause death. However, analyses taking account of prior morbidities, including cardiovascular factors in view of the failure of full matching with controls, did not materially alter overall estimates of risk according to Arizona group classification.

We consistently found associations of antipsychotic and SSRI antidepressant treatment with sudden unexplained death, significantly raised risk ratios being found for typical and atypical antipsychotics, the latter including risperidone and olanzapine individually, and the SSRI antidepressants, including citalopram, fluoxetine and sertraline individually. When these were taken out of consideration no significant risk appeared to be associated with the use of other psychiatric or noncardiac drugs, although many feature in lists of drugs predisposing to TdP.

Results suggesting enhanced risk in takers of atypical antipsychotics and of SSRI antidepressants were unexpected because of much pharmacological and clinical evidence suggesting greater cardiac safety of a typical compared with typical antipsychotics [13–18], and particular risk for tricyclic antidepressants [19–21].

However, the atypical antipsychotic risperidone has been shown to retard cardiac repolarization and to exert cardiac electrophysiological effects at clinically relevant concentrations [22]. Olanzapine can also prolong repolarization [23], and another atypical antipsychotic, clozapine, has been found to block human ether-a go-go-related gene (HERG) human cardiac $K^+$ channels and the rapidly activating delayed rectifier $K^+$ current in ventricular myocytes [24]. A recent cohort study has also reported raised risk of sudden cardiac death in patients taking atypical antipsychotics [25].

Risks of sudden death associated with typical or atypical antipsychotic use found by us were some fourfold higher than noted previously for overall death rates [26–29]. The difference can be explained by our study population. Individuals in whom death certificates could not be signed after sudden death because the cause was unclear were likely to have enhanced risks of arrhythmic death [10]. Our findings for antipsychotic drugs may represent causal effects for the following reasons. Adjustment of ORs by logistic regression to take account of confounding diseases, though diminishing, did not abolish differences. Separate consideration of individuals who had no prior clinical evidence of heart disease reduced but did not remove risks. Those receiving higher daily oral doses of antipsychotic treatment, or who had recently started treatment, were at greatest risk.

We also found, in contradistinction to Ray *et al*. [21], that risk of sudden death may be at least as great with SSRI as with tricyclic agent treatment. The Nurses' Health Study [30] reported an association between antidepressants (of which 61% were SSRIs) and sudden cardiac death. SSRIs have often [31–34] but not always [35, 36] been claimed free of cardiotoxic effects. However, in the same way that blockade of the HERG channel has recently been shown for the tricyclic antidepressant doxepin [37], interference with intracardiac conduction has been found for the SSRIs fluvoxamine [38] and fluoxetine [39], adding to earlier evidence of HERG inhibition by citalopram [40]. By contrast, in another study 'physiologically relevant' inhibition of HERG was found only with very high concentrations of fluoxetine, citalopram and venlafaxine [41].

The general associations between sudden death and prior disease found by us and others [1, 2, 5, 6] leave suspicion that underlying CVD was important in augmenting antidepressant- and antipsychotic-associated drug risk. However, risk ratio adjustment to take account of significant general disease did not alter results materially. However, in the substantial group of our cases and their controls who were clinically free of CVD, the point estimate for SSRI risk was reduced and no longer statistically significantly raised. Risk in relation to treatment duration could not be examined, because almost all patients had been treated for at least 3 months, but a significant dose–response trend was found for maintenance doses of SSRIs, and not for tricyclic antidepressants. Prescribed doses of tricyclic drugs were almost all well below amounts normally recommended and patients with prior myocardial infarction were more likely to receive SSRIs rather than tricyclic agents. Advice in the BNF relating to the potential cardiotoxicity of tricyclic agents compared with SSRIs [12] may be relevant here. It is possible that the raised risk of sudden death with SSRIs and atypical antipsychotics could be confounded by the targeted prescribing of these drugs to individuals with underlying disease that predisposes to QT prolongation, rather than using the older drugs with known toxicity. This could inflate the risks associated with the SSRIs and atypical antipsychotics.

Bowker and colleagues [42] analysed findings at coroner's post-mortem examinations in England in individuals dying suddenly and unexpectedly. They estimated such deaths to occur in 11 per 100 000 apparently healthy adults aged 15–64 years each year, of whom some 40% had no evidence of coronary heart disease as a cause apart from coronary atheroma or myocardial scarring. Their definitions of cases for inclusion differed from ours, but their figure is reconcilable with our finding of 1137 cases, male or female of all ages, including individuals with clinically diagnosed heart disease, in approximately 7.35 million patient-years (2.1 million population $\times$ 3.5 years), or 15.5 per 100 000 who were apparently free of recent evidence of infarction or coronary occlusion at post mortem.

A strength of this study is the exploration of cause of death by post-mortem examination for all cases, which contrasts with previous studies investigating this hypothesis [4, 5, 6, 8, 29]. Two-thirds of such (post-mortem) exami-

nations were in men, and higher proportions of men have been found by others [42, 43], raising the possibility that single men who are prone to alcohol abuse may have been preferentially included. However, we were able to show that drug associations remained in adjusted analyses taking account of known or suspected alcohol abuse. Moreover, multivariate analyses in Oregon have shown separate significant independent relationships for sex and use of QTc-prolonging drugs [43].

Imperfect matching for CVD was addressed in the adjusted analyses and by the inclusion of a subgroup without CVD. The data being based upon practice records reduced our ability to explore the effects of other potential confounding variables, such as smoking. Although we have undertaken a large number of analyses, the primary analyses are for the Arizona and drug groupings, with exploratory analyses for individual drugs. In this situation we did not undertake multiple test adjustments [44]. Observational studies cannot control completely for confounders, and it remains possible that uncontrolled patient-related factors were important. Thus it is suggested that individuals with depression have diminished cardiac vagal control, and may be at risk of ventricular arrhythmias [45, 46].

## Conclusions

We conclude that out-of-hospital sudden cardiac deaths appear concentrated in takers of psychiatric agents, with antipsychotic use, whether typical or atypical, and SSRI treatment being associated with increased risks of sudden unexplained death. We have also confirmed previous findings [8] of raised risk with erythromycin treatment. Differences could not be accounted for by confounding factors.

## Competing interests

M.J.S.L. has received a fee for speaking from Bayer GmbH, and has received consulting fees from Galpharm, and from Procter and Gamble. Consulting fees from Merck and Co. Inc. have been paid to the University of Birmingham. M.J.S.L. is also an Honorary Consultant to the WHO Collaborating Centre for International Drug Monitoring in Uppsala. M.J.S.L.'s wife holds shares in GlaxoSmithKline.

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