# Thioridazine and sudden unexplained death in psychiatric in-patients[†]

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**Background** Sudden death has been linked to antipsychotic therapy, but the relative risk associated with specific drugs is unknown.

**Aims** To assess the risk of sudden unexplained death associated with antipsychotic drug therapy and its relation to drug dose and individual agents.

**Method** A case–control study of psychiatric in-patients dying suddenly in five hospitals in the north-east of England and surviving controls matched for age, gender and mental disorder. Logistic regression analysis was used to identify significant risk factors, and odds ratios were calculated.

**Results** Sixty-nine case–control clusters were identified. Probable sudden unexplained death was significantly associated with hypertension, ischaemic heart disease and current treatment with thioridazine (adjusted odds ratio=5.3, 95% CI 1.7–16.2, $P$=0.004). There was no significant association with other individual antipsychotic drugs.

**Conclusions** Thioridazine alone was associated with sudden unexplained death, the likely mechanism being drug-induced arrythmia.

**Declaration of interest** None.

[†]See editorial, pp. 483–484, this issue.

Psychiatric patients have a high death rate from cardiovascular causes (Harris & Barraclough, 1998). One contributory mechanism may be drug-induced arrhythmia, because some antipsychotic drugs delay ventricular repolarisation (Warner *et al*, 1996; Reilly *et al*, 2000) and this may result in a form of ventricular tachycardia, termed torsades de pointes, which may cause sudden death (Thomas, 1994). This retrospective matched case–control study investigated the hypotheses that the risk of sudden death is increased in psychiatric in-patients exposed to antipsychotic drugs, that this is a dose-related phenomenon and that the relative risk is greatest for those drugs shown to have the most marked effects on the QT interval. Additional risk factors studied were other psychotropic drug therapy, past medical history and psychiatric diagnosis.

## METHOD

The study was carried out in five large psychiatric hospitals in the north-east of England serving a total catchment population of 1.23 million. There was no direct patient contact and all information was obtained from medical records, following ethical approval.

### Cases

All in-patient deaths involving those aged 18–74 years (inclusive) from 1 January 1984 to 31 December 1995 were identified and medical notes were sought and screened. Death was classified as 'probable' sudden unexplained death provided that (a) the patient died within 1 h of being observed in their usual state of health (or was found dead more than 1 h after having last been seen, but having been seen in their usual state of health within the previous 24 h) and (b) there was no evidence of a non-cardiac cause, including choking or convulsions.

Patients could be included as cases if they had suffered recent symptoms potentially caused by prodromal cardiac arrhythmia (dizziness, palpitations, syncope, chest pain or breathlessness) provided that there was no clinical evidence of an alternative cause such as myocardial infarction, stroke or chest disease.

Post-mortem data were sought, including from the local coroner, for all cases of 'probable' sudden unexplained death. If an alternative cause of death was demonstrated, including myocardial infarction, the patient was excluded as a case. If no alternative cause for death was identified, the death was classified as 'confirmed' sudden unexplained death. Coronary artery disease did not exclude use as a case unless there was evidence of recent coronary thrombosis or recent myocardial infarction.

Notes of all cases were examined independently by a researcher who was blind to drug therapy, to confirm that study criteria for sudden unexplained death were met. Possible cases where there was disagreement were rejected.

### Controls

Two controls were sought for each case. Both were in-patients at the same hospital at the time of death of the case. They were each matched for age, gender and duration of in-patient stay and one was also matched for primary psychiatric diagnosis. The purpose of using two controls was to increase the statistical power of the study. The availability of a control unmatched for psychiatric diagnosis allows the investigation of diagnosis as a risk for sudden death, whereas the availability of a control matched for psychiatric diagnosis is helpful if diagnosis is found to be a significant factor for sudden cardiac death. The use of two types of controls also allows the consistency and robustness of associations with drug therapy to be determined in different models. Controls were identified by searching hospital databases for patients of the same gender who were within 5 years of the age of the case. For cases who had been in hospital less than 5 years, controls were sought from the age- and gender-matched controls admitted within 1 year of the death of the case. Close matching by year of admission was more difficult for cases who had been in hospital for more than 5 years. For these, age- and gender-matched controls who had also been in hospital for more than 5 years and who



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were in-patients at the time of death of the case were sought. For either group, the potential controls selected were those whose date of admission most closely matched that of the case. If no controls were identified, the process was repeated using a 10-year age band. The same process was used to select the second controls, who were also matched according to primary psychiatric diagnosis and classified according to ICD–10 (World Health Organization, 1992) in one of five categories (organic disorders, schizophrenia, affective disorders, alcohol dependence or misuse and 'other', including neuroses, eating disorders and personality disorders).

### Data collected

Psychiatric diagnoses, medical history, cardiac history and all drug therapy within the previous 6 months prior to death (cases) or the index date (controls) were recorded for both patients and controls. For controls of those cases who had died within 60 days of admission, the index date was defined as the same number of days after admission as death occurred in the case. If the interval was longer, the index date was taken as the date of death of the case. The index time was the time of death of the case. Exposure to drugs was defined as use, according to the hospital prescription chart, within 24 h of death or the index date and time. Antipsychotic drugs were put in three groups by dose using the following chlorpromazine equivalent dose ranges: zero (none), $\leqslant$1000 mg per day (low dose) and $>$1000 mg per day (high dose).

### Statistical analysis

Probable sudden death and confirmed sudden death were defined as the outcome variables for separate conditional logistic regression analyses. The statistical software packages SPSS version 10 and EGRET for Windows (1999, Cytel Software Corporation, Cambridge, Massachusetts, USA) were used.

The original design specified the matching of each case with two controls, one of which was matched for psychiatric disease group. Before performing this analysis, a 1:1 case–control analysis was to be performed using the single control unmatched for psychiatric disease to determine if there was an association between psychiatric disease group and sudden cardiac death. If this was found, the influence of psychiatric disease would be included in the final model. In the absence of a significant association, it was to be ignored.

For each analysis, unadjusted odds ratios for 'probable' sudden unexplained death were first calculated for a range of possible predictive variables, including specific drug therapy and cardiac disease. Adjusted odds ratios were then obtained via the conditional logistic regression model, incorporating those variables where $P<0.05$. The method of backward stepwise regression was also used to establish the most important predictive variables, for which adjusted odds ratios were calculated. Using this method, the least significant predictive factors are eliminated from the conditional logistic regression analysis in turn, until only those that are significantly associated with sudden death remain. Variables were retained in the model if their significance level was less than 15%. The unadjusted and adjusted odds ratios using 'confirmed' sudden death as the outcome variable were obtained using the same approach.

## RESULTS

There were 1350 deaths identified in the 5 hospitals over the 12-year period of study and 89% of case notes were available for review. Of these, 77 initially met the criteria for 'probable' sudden unexplained death. In 30, a post-mortem was available and 3 of these were excluded as cases because there was evidence of an alternative cause of death (three myocardial infarctions). Thus, 74 (5%) of all deaths met the study criteria for 'probable' and 27 met the criteria for 'confirmed' sudden unexplained death.

Of the 74 'probable' cases, 37 (50%) were female. The median age was 69 years. Seventeen cases were younger than 65 years but only one was less than 50 years old. No sudden deaths occurred during restraint or within 1 h of parenteral antipsychotic medication. Adequately matched controls could not be found for 5 (disease unmatched) and 11 (disease matched) 'probable' cases, leaving a total of 69 and 63 clusters for the respective case–control analyses. Demographic information and breakdown by principal psychiatric diagnosis, cardiovascular disorder and drug therapy are shown in Table 1. There was a particular lack of information on smoking and alcohol use in the medical notes.

Two initial analyses were performed using single controls, unmatched and matched for psychiatric diagnosis, respectively. Table 1 shows the unadjusted odds ratios for the 'probable' sudden death group ($n$=69) using the single control unmatched for diagnosis. Odds ratios adjusted using conditional logistic regression and backwards stepwise regression are shown in Table 2. In this analysis, the psychiatric conditions of mood disorder and schizophrenia were not significantly associated with sudden cardiac death. However, the presence of organic disorder was significantly associated after adjustment for confounding. Other factors significantly associated with probable sudden death in this analysis were the presence of a history of hypertension or myocardial infarction and current treatment with diuretics or thioridazine. There was a significant negative association with carbamazepine and sodium valproate therapy (Table 2).

Because of the significant association between organic disease and sudden death, a further case–control analysis was performed using the single control matched for psychiatric disorder. In this analysis (data not shown), factors significantly associated with sudden death after adjustment for confounding using backwards stepwise regression were the presence of ischaemic heart disease (odds ratio=17.0, 95% CI 2.3 to $>$100, $P$=0.005) or hypertension (odds ratio=13.6, 95% CI 1.6 to $>$100, $P$=0.018), and current therapy with thioridazine (odds ratio=15.4, 95% CI 2.6–89.5, $P$=0.002). In this analysis, there was no significant association with diuretic therapy.

The prespecified primary analysis for the study used both controls to optimise study power. Because the presence of organic disorder was shown to be significantly associated with sudden unexpected death, this was adjusted for in the model. In this analysis, sudden unexpected death was again significantly associated only with hypertension, ischaemic heart disease and thioridazine therapy (Table 3). The possibility was considered that differences in the duration of hospital stay between cases and controls might be an important confounding factor, leading to a spurious association between thioridazine therapy and sudden death. However, the use of thioridazine was not related to duration of hospital stay, and removing those clusters with the poorest matching by duration of



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**Table 1** Risk factors for 'probable' sudden death

| Risk factor | Cases included in analysis | Controls unmatched for diagnosis | Controls matched for diagnosis | Missing data (across all three groups) | Unadjusted odds ratios (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Total number | 69 | 69 | 63 | | – | |
| Age in years (mean and s.d.) | 66.7 (7.7) | 66.6 (8.7) | 66.9 (10.7) | | – | |
| Male | 33 | 31 | 33 | | – | |
| Median length of stay in days | 633 | 300 | 345 | | – | |
| *Psychiatric disorder* | | | | | | |
| Schizophrenia | 23 | 24 | 19 | | 0.92 (0.40–2.1) | 0.84 |
| Mood disorder | 27 | 22 | 17 | | 1.4 (0.68–2.7) | 0.38 |
| Organic disorder | 31 | 30 | 32 | | 1.1 (0.57–1.9) | 0.88 |
| *Physical illness* | | | | | | |
| Arrhythmia | 5 | 2 | 1 | 3 | N/A | |
| Chronic lung disease | 6 | 2 | 2 | 3 | 2.5 (0.49–12.9) | 0.27 |
| Heart failure | 7 | 3 | 1 | | N/A | |
| Hypertension | 9 | 3 | 3 | 3 | 4.0 (0.85–18.8) | 0.08 |
| Ischaemic heart disease | 17 | 6 | 3 | 3 | 3.5 (1.15–10.6) | 0.027 |
| Previous myocardial infarction[1] | 11 | 3 | 2 | | 3.7 (1.02–13.1) | 0.05 |
| Stroke | 8 | 8 | 8 | 3 | 1.0 (0.25–4.0) | 1.0 |
| Alcohol excess | 4 | 4 | 3 | 140 | N/A | |
| Smoking ever | 15 | 19 | 12 | 136 | N/A | |
| *Antipsychotic therapy* | | | | | | |
| Chlorpromazine | 5 | 6 | 7 | 1 | 0.75 (0.17–3.3) | 0.71 |
| Droperidol | 2 | 0 | 0 | | N/A | |
| Flupenthixol | 5 | 3 | 3 | 1 | 1.67 (0.40–7.0) | 0.48 |
| Fluphenazine | 3 | 6 | 5 | 1 | 0.40 (0.08–2.1) | 0.27 |
| Haloperidol | 7 | 13 | 6 | | 0.50 (0.19–1.3) | 0.16 |
| Risperidone | 0 | 1 | 1 | | N/A | |
| Sulpiride | 1 | 1 | 2 | | 1.0 (0.06–16.0) | 1.0 |
| Thioridazine | 24 | 19 | 9 | | 1.6 (0.67–3.9) | 0.28 |
| Trifluoperazine | 3 | 3 | 6 | | 1.0 (0.20–4.9) | 1.0 |
| Zuclopenthixol | 2 | 0 | 1 | | N/A | |
| High-dose antipsychotic | 4 | 4 | 1 | | 1.0 (0.25–4.0) | 1.0 |
| Low-dose antipsychotic | 38 | 38 | 30 | | 1.1 (0.56–2.3) | 0.72 |
| Any antipsychotic | 42 | 40 | 31 | | 1.1 (0.55–2.4) | 0.71 |
| *Other drug therapy* | | | | | | |
| Beta-blockers | 4 | 0 | 0 | | N/A | |
| Benzodiazepines | 12 | 13 | 14 | | 1.0 (0.35–2.8) | 1.0 |
| Carbamazepine | 5 | 10 | 4 | | 0.38 (0.10–1.4) | 0.15 |
| Chlormethiazole | 7 | 7 | 4 | | 1.0 (0.29–3.4) | 1.0 |
| Diuretics | 17 | 3 | 10 | | 8.0 (1.8–34.8) | 0.01 |
| Lithium | 2 | 4 | 3 | | 0.50 (0.09–2.7) | 0.42 |
| Other | 1 | 1 | 0 | | 1.0 (0.06–16.0) | 1.0 |
| Phenelzine | 2 | 0 | 0 | | N/A | |
| Procyclidine | 11 | 10 | 9 | | 1.1 (0.43–2.9) | 0.80 |
| Sodium valproate | 1 | 5 | 1 | | 0.2 (0.02–1.7) | 0.14 |
| SSRIs | 2 | 2 | 2 | | 1.0 (0.14–7.1) | 1.0 |
| Tricyclic antidepressants | 13 | 12 | 11 | | 1.11 (0.45–2.7) | 0.81 |

1. Unadjusted odds ratios calculated using one control (unmatched for psychiatric diagnosis) for each case.
SSRIs, selective serotonin reuptake inhibitors.

hospital stay from the analysis did not alter the size or statistical significance of the odds ratio linking thioridazine with sudden death.

To examine for the presence of a dose–response relationship with sudden death, further analyses were performed grouping antipsychotic drugs together, according to dose in chlorpromazine equivalents. When both controls were used in the analysis, a significant relationship between high-dose antipsychotic



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**Table 2** Risk factors for 'probable' sudden death

| Risk factor | Adjusted odds ratios[1] (full model) | | Adjusted odds ratios[1] (backwards stepwise regression) | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| *Psychiatric disorder* | | | | |
| Schizophrenia | 1.2 (0.12–11.2) | 0.90 | | |
| Mood disorder | 0.69 (0.09–5.5) | 0.72 | | |
| Organic disorder | 9.9 (1.2–83.6) | 0.035 | 5.2 (1.3–21.8) | 0.022 |
| *Physical illness* | | | | |
| Chronic lung disease | 22.4 (0.31–>100) | 0.16 | | |
| Hypertension | >100 (7.7–>100) | 0.011 | >100 (4.6–>100) | 0.008 |
| Ischaemic heart disease | 6.2 (0.47–81.0) | 0.17 | | |
| Previous myocardial infarction | 7.6 (0.47–>100) | 0.15 | 10.9 (1.7–69.7) | 0.012 |
| *Antipsychotic therapy* | | | | |
| Chlorpromazine | 7.6 (0.54–108.1) | 0.132 | 7.2 (0.52–>100) | 0.141 |
| Flupenthixol | 9.4 (0.21–>100) | 0.25 | | |
| Fluphenazine | 0.06 (0.00–6.0) | 0.23 | | |
| Haloperidol | 4.1 (0.39–42.1) | 0.24 | | |
| Thioridazine | 37.0 (2.1–>100) | 0.014 | 16.9 (2.0–>100) | 0.009 |
| *Other drug therapy* | | | | |
| Carbamazepine | 0.00 (0.00–0.19) | 0.006 | 0.02 (0.00–0.30) | 0.006 |
| Diuretics | >100 (24.3–>100) | 0.003 | >100 (14.8–>100) | 0.002 |
| Lithium | 0.42 (0.02–9.6) | 0.58 | | |
| Sodium valproate | 0.00 (0.00–9.1) | 0.13 | 0.00 (0.00–0.28) | 0.019 |

1. Odds ratios (OR) adjusted by conditional logistic regression (full model) and by backwards stepwise regression. One control (unmatched for psychiatric diagnosis) used for each case.

therapy and sudden death was obtained by conditional logistic regression (low-dose odds ratio=1.6, 95% CI 0.7–4.1, $P$=0.28; high-dose odds ratio=12.5, 95% CI 1.1–139.2, $P$=0.04). However, the odds ratio for high-dose therapy was not statistically significant at the 5% level after backwards stepwise regression (odds ratio=7.8, 95% CI 0.8–71.3, $P$=0.07) or if the single psychiatric disease-matched controls were used (adjusted odds ratio=19.7, 95% CI 0.72 to >100, $P$=0.08).

To study a potential dose–response in the relationship between thioridazine and sudden death, an analysis was performed examining the effects of low- and high-dose thioridazine exposure. No cases were prescribed thioridazine at doses above 1000 mg (the chlorpromazine equivalent threshold for high dose) or 800 mg per day (maximum recommended by the *British National Formulary* (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2000)). The median dose of 75 mg per day was chosen as a threshold for the high dose. Both low- (⩽75 mg/24 h) and high-dose (>75 mg/24 h) thioridazine exposure were each significantly associated with sudden death and these effects were consistent whether either or both controls were used (Table 4). However, no statistically significant dose–response effect could be demonstrated.

A case–control analysis was also performed using the same methods by restricting analysis to the subgroup of cases with 'confirmed' sudden death ($n$=27). Using both controls, only ischaemic heart disease was significantly associated with sudden death. Thioridazine was not a statistically significant predictor of 'confirmed' sudden death, but the odds ratio for the association was greater than unity and the power of this part of the study is low (Table 5).

## DISCUSSION

### Background

Many antipsychotic drugs affect cardiac repolarisation, but these effects appear more prominent for some antipsychotic drugs than for others (Fulop *et al*, 1987; Fritze & Bandelow, 1998), raising the concern that these drugs, in particular, may provoke arrythmias and sudden death. Regulatory action has previously been taken for pimozide and sertindole, and we recently demonstrated that prolongation of the QT interval is more common with thioridazine and droperidol than with other antipsychotic drugs (Reilly *et al*, 2000). However, the systematic evidence in support of a direct link between antipsychotic drug therapy and arrythmia or sudden cardiac death is sparse.

### Characteristics of sudden death patients

This study indicates that most patients who die suddenly without explanation in psychiatric hospitals are over 50 years old and many have pre-existing cardiovascular disease, in common with those at greatest risk in the wider community. No cases occurred in the aftermath of parenteral administration of antipsychotics or in the context of restraint, and this is consistent with the findings of other systematic research (Ungvari, 1980; Davis & Zhang,



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**Table 3** Risk factors for 'probable' sudden death

| Risk factor | Adjusted odds ratios[1] (full model) | | Adjusted odds ratios[1] (backwards stepwise regression) | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| *Psychiatric disorder* | | | | |
| Schizophrenia | 1.1 (0.18–6.1) | 0.95 | | |
| Mood disorder | 2.5 (0.57–10.9) | 0.22 | | |
| Organic disorder | 1.6 (0.43–6.4) | 0.47 | | |
| *Physical illness* | | | | |
| Arrhythmia | 11.9 (0.52–> 100) | 0.12 | 10.9 (0.61–> 100) | 0.10 |
| Chronic lung disease | 6.1 (0.82–44.8) | 0.077 | 4.1 (0.74–22.4) | 0.11 |
| Heart failure | 6.1 (0.45–83.8) | 0.17 | 10.5 (0.92–> 100) | 0.059 |
| Hypertension | 8.6 (1.4–52.2) | 0.020 | 7.4 (1.6–33.7) | 0.009 |
| Ischaemic heart disease | 6.0 (0.95–37.8) | 0.057 | 5.4 (1.1–25.4) | 0.034 |
| Previous myocardial infarction | 3.0 (0.47–18.8) | 0.24 | 4.5 (0.77–26.3) | 0.096 |
| *Antipsychotic therapy* | | | | |
| Chlorpromazine | 0.93 (0.19–4.5) | 0.93 | | |
| Flupenthixol | 0.87 (0.11–6.7) | 0.89 | | |
| Fluphenazine | 1.2 (0.21–7.2) | 0.82 | | |
| Haloperidol | 1.2 (0.33–4.3) | 0.79 | | |
| Thioridazine | 5.0 (1.4–17.5) | 0.012 | 5.3 (1.7–16.2) | 0.004 |
| Zuclopenthixol | 5.1 (0.11–> 100) | 0.41 | | |
| *Other drug therapy* | | | | |
| Carbamazepine | 0.34 (0.06–1.9) | 0.23 | | |
| Diuretics | 2.3 (0.61–8.8) | 0.22 | | |
| Lithium | 0.60 (0.06–6.1) | 0.67 | | |
| Sodium valproate | 0.10 (0.01–1.7) | 0.11 | 0.08 (0.01–1.0) | 0.052 |

Odds ratios (OR) calculated using two controls (one matched for psychiatric diagnosis) for each case and adjusted using conditional logistic regression (full model) and backwards stepwise regression.

**Table 4** Thioridazine dose and 'probable' sudden death

| Risk factor | Adjusted odds ratios[1] (full model) | | Adjusted odds ratios[1] (backwards stepwise regression) | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| *One control, unmatched for diagnosis* | | | | |
| Low-dose thioridazine | > 100 (2.7–> 100) | 0.018 | 42.9 (2.8–> 100) | 0.007 |
| High-dose thioridazine | 25.6 (0.81–> 100) | 0.066 | 7.6 (0.71–82.4) | 0.094 |
| Any thioridazine | 37.0 (2.1–> 100) | 0.014 | 16.9 (2.0–> 100) | 0.009 |
| *One control, matched for diagnosis* | | | | |
| Low-dose thioridazine | 18.8 (0.7–> 100) | 0.075 | 17.0 (1.7–> 100) | 0.015 |
| High-dose thioridazine | 54.2 (1.5–> 100) | 0.028 | 14.4 (2.0–> 100) | 0.009 |
| Any thioridazine | 32.5 (2.0–> 100) | 0.015 | 15.4 (2.6–89.5) | 0.002 |
| *Two controls* | | | | |
| Low-dose thioridazine | 5.4 (1.2–23.9) | 0.028 | 5.3 (1.4–20.5) | 0.016 |
| High-dose thioridazine | 4.5 (0.86–23.7) | 0.075 | 5.2 (1.2–23.3) | 0.030 |
| Any thioridazine | 5.0 (1.4–17.5) | 0.012 | 5.3 (1.7–16.2) | 0.004 |

1. Odds ratios (OR) adjusted by conditional logistic regression (full model) and by backwards stepwise regression, using one control (matched or unmatched for psychiatric disease) or both controls.

1988). The prominence of these factors in previous studies involving younger patients (Jusic & Lader, 1994; Lareya, 1995) may result from reporting bias. However, it is possible that antipsychotic drug-induced deaths that involve younger people occur more often in the community than in hospital and such deaths would not have been detected in this study. The low post-mortem rate suggests that many of the deaths in this study were not suspected by clinicians to be drug-related.



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**Table 5** Risk factors for 'confirmed' sudden death

| Risk factor | Adjusted odds ratios[1] (full model) | | Adjusted odds ratios[1] (backwards stepwise regression) | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| *Physical illness* | | | | |
| Arrhythmia | 1.4 (0.02–94.7) | 0.87 | | |
| Ischaemic heart disease | 4.2 (0.28–64.3) | 0.30 | 12.0 (1.6–89.7) | 0.015 |
| Previous myocardial infarction | 35.5 (0.07–> 100) | 0.26 | | |
| Hypertension | 2.9 (0.32–25.7) | 0.34 | | |
| Heart failure | 1.1 (0.01–> 100) | 0.96 | | |
| Chronic lung disease | 12.4 (0.26–> 100) | 0.20 | 7.3 (0.66–82.1) | 0.11 |
| *Drug therapy* | | | | |
| Thioridazine | 7.6 (0.47–> 100) | 0.15 | 2.9 (0.70–11.7) | 0.14 |
| Chlorpromazine | 5.5 (0.16–> 100) | 0.39 | | |
| Haloperidol | 0.18 (0.01–2.9) | 0.23 | | |
| Fluphenazine | 8.6 (0.47–> 100) | 0.15 | | |
| Zuclopenthixol | 1.9 (0.02–> 100) | 0.79 | | |
| Lithium | 16.4 (0.36–> 100) | 0.15 | | |
| Diuretics | 1.3 (0.14–12.0) | 0.82 | | |

1. Odds ratios (OR) calculated using two controls (one mismatched for psychiatric diagnosis) for each case and adjusted using conditional logistic regression (full model) and backwards stepwise regression.

## Study limitations and strengths

This matched case–control study has a number of limitations. The retrospective nature of the study and the reliance on descriptions of death recorded in medical notes are disadvantages. Records are often incomplete for important risk factors such as underlying cardiac disease, smoking or use of alcohol or illicit drugs. The low post-mortem rate raises the possibility that some of the deaths were from causes other than cardiac arrythmia, although these were only found in 3 out of 30 cases when a post-mortem had been done. Strengths of the study design and setting include the systematic method for collecting cases, which minimises potential recall or reporting bias, and the examination of hospital drug charts, which allows the collection of more detailed and accurate information about drug use than would be possible in a community setting.

## Factors associated with sudden death

In this study, sudden unexplained death in psychiatric in-patients was associated with ischaemic heart disease, previous arrythmia and hypertension. Diuretic therapy was a significant risk factor in one analysis but not others. This might be because it is a marker for underlying cardiovascular disease or because diuretic therapy itself increases the arrythmia risk by causing hypokalaemia, as reported previously (Siscovick *et al*, 1996).

Thioridazine was the only single antipsychotic drug therapy found to be an independent risk factor for sudden unexplained death. There was also a possible association with increasing total antipsychotic dose. Droperidol has previously been shown to be associated with repolarisation abnormalities (Reilly *et al*, 2000), but there were too few exposed cases in this study to perform a reliable analysis of the impact of this drug on sudden death. Tricyclic antidepressants prolong cardiac repolarisation and have been associated with sudden death (Coull *et al*, 1970; Ballinger & Ramsay, 1976). However, no association was found in this study. The apparent negative association between sudden unexpected death and the antiepileptic drugs carbamazepine and sodium valproate, may be due to diagnostic bias because deaths possibly caused by epilepsy were excluded as cases. However, we cannot exclude the possibility that these drugs may afford some protection by an unknown mechanism.

## Confounding factors

In spite of the small size of this study and its retrospective nature, we have shown a consistent association between thioridazine and 'probable' sudden death. The possibility should be considered that this association is not causal but results from confounding or bias. Age is unlikely to provide important confounding because cases and controls were matched for age, albeit in 5- or 10-year bands, and the mean ages of cases and controls were similar. It seems unlikely that thioridazine would be used preferentially in patients with cardiac disease and there is no evidence of this; indeed, adjustment for the influence of cardiovascular disease increases the strength of the association. A cohort effect on prescribing linked to length of stay in hospital is also unlikely because length of stay was matched for patients dying within 60 days. Although there were differences in the cases and controls for mean length of stay when the case died after more than 60 days, removal of those clusters with the poorest matching did not affect the strength of the association between sudden death and thioridazine. We cannot completely exclude the possibility that thioridazine use is a marker for a more debilitated population more prone to sudden death for other reasons. It has not been possible to correct for the possible confounding effects of smoking or use of alcohol or illicit drugs, because information on these factors was usually missing from the patient's notes. If these factors contribute to the increased risk of sudden death



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associated with thioridazine, this would mean that thioridazine must be prescribed preferentially to smokers, drinkers or illicit drug-takers, which seems implausible. Caution is also required because no significant association was found between post-mortem 'confirmed' sudden unexplained death and thioridazine therapy, and neither was a dose–response relationship demonstrated. However, the small numbers of cases and controls involved hinder both of these analyses.

## Mechanism of sudden death

Although other mechanisms of antipsychotic-induced sudden death have been suggested, including convulsions, hypotension, choking or asphyxia, myocarditis or pulmonary embolism, we believe that the most likely explanation for the association demonstrated here is that thioridazine causes arrythmias and sudden cardiac death. This finding is consistent with other evidence. Although most antipsychotic drugs show some propensity for cardiac adverse effects, thioridazine is cited most frequently. It appears more cardiotoxic than other antipsychotic drugs in overdose (Buckley *et al*, 1995) and prolongs the heart rate corrected QT interval to a greater extent (Reilly *et al*, 2000). Thioridazine is a potent blocker of the delayed rectifier potassium channel ($I_{kr}$), the main determinant of cardiac repolarisation (Drolet *et al*, 1999). This effect is likely to be independent of the drug's dopamine receptor blocking effect because it occurs with antipsychotic drugs such as sertindole that have low potency for dopamine receptors, as well as with a wide range of drugs that do not block dopamine receptors (Thomas, 1994). Torsades de pointes induced by thioridazine has been reported frequently in the context of both overdose (Kiriike *et al*, 1987) and therapeutic administration (Denvir *et al*, 1998). A previous study linked sudden death with thioridazine, although this did not adjust for age (Mehtonen *et al*, 1991).

## Clinical implications

Although rarely prescribed now as a first-line drug for schizophrenia, thioridazine is often perceived as having fewer adverse effects than more potent neuroleptics and, until recently, was commonly prescribed for anxiety, confusion and behavioural problems. Considering the risk of repolarisation abnormalities and the apparent association with sudden cardiac death, this widespread use of thioridazine can no longer be justified. If thioridazine is used at all, it should be given in the lowest possible dose because higher doses have been shown to cause more marked repolarisation abnormalities. However, we were unable to demonstrate a dose–response effect in this study and low doses are not free from risk. Based on accumulating evidence of cardiotoxicity, regulatory authorities in the USA and the UK have now recommended restriction of thioridazine prescribing to those with treatment-resistant schizophrenia. Caution is advised where thioridazine is prescribed to patients with cardiovascular diseases and is contraindicated in those most at risk of torsades de pointes. Electrocardiographic screening prior to initiation of drug therapy and monitoring during therapy are recommended. Co-prescription with inhibitors of CYP2D6 – a hepatic cytochrome P-450 isoform responsible for thioridazine metabolism – should be avoided, and patients should be monitored for hypokalaemia, which can also increase the risk of arrhythmia (Committee on Safety of Medicines, 2001).

The results of this study should be interpreted with caution. We cannot be reassured that significant risks do not exist with other antipsychotic drugs. Larger studies of sudden unexplained death in psychiatric in-patients are needed, such as the national study now underway (Appleby *et al*, 2000).

Sudden unexplained death in psychiatric patients is uncommon. A proportion may be related to antipsychotic drug therapy, particularly thioridazine, and a higher index of suspicion is required when deaths occur, whether in hospital or in the community. This is a rare adverse drug reaction that should be considered in the context of the major benefits offered to

### CLINICAL IMPLICATIONS

- Most patients who die suddenly without explanation in psychiatric hospitals are over 50 years old and many have pre-existing cardiovascular disease.
- A proportion of sudden deaths may be related to antipsychotic-induced torsades de pointes and thioridazine is particularly implicated.
- Both UK and US regulatory action to restrict the prescribing of thioridazine is further justified by this study.

### LIMITATIONS

- Data were collected via retrospective examination of case notes, leading to incomplete information on smoking, alcohol use and illicit drugs, all of which may influence the risk of sudden death.
- The small size of the study limits conclusions about risks posed by drugs that were infrequently prescribed in the sample.
- Although the association with thioridazine appears robust and consistent, there remains the possibility that it may be explained by confounding factors.

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patients by appropriate antipsychotic therapy.

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