

## Psychotropic drugs and fatal pulmonary embolism

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### SUMMARY

**Purpose** To examine the association between the use of psychotropic drugs and fatal pulmonary embolism.

**Methods** We conducted a national case-control study of fatal pulmonary embolism. Cases were 75 New Zealand men and women aged 15–59 years who died between 1 January 1990 and 31 December 1998, where the underlying cause of death was certified as codes 415.1, 451 or 453 of the International Classification of Diseases (9th Revision). Four controls, matched for sex and age, were selected from the general practice to which each case had belonged. Information was abstracted from the records of general practitioners, family planning clinics and psychiatric services. Odds ratios and 95% confidence intervals (95% CI) were estimated using conditional logistic regression. The key analyses were restricted to cases ( $n = 62$ ) and controls ( $n = 243$ ) without major risk factors for venous thromboembolism.

**Results** Compared to non-use, the adjusted odds ratio for current use of antipsychotic drugs was 13.3 (95% CI: 2.3–76.3). Low potency antipsychotics appeared to carry the highest risk (odds ratio: 20.8 [95% CI: 1.7–259.0]). The main drug involved was thioridazine. The odds ratio for current use of antidepressants was also increased, at 4.9 (95% CI: 1.1–22.5).

**Conclusions** Our results for conventional antipsychotics are consistent with previous studies of non-fatal venous thromboembolism. The finding for antidepressants needs to be replicated in other studies. Copyright © 2003 John Wiley & Sons, Ltd.

**KEY WORDS**—antipsychotics; antidepressants; psychotropics; venous thromboembolism; pulmonary embolism; case-control study

### INTRODUCTION

In the year 2000, Zornberg and Jick reported that current users of antipsychotic drugs have an increased risk of non-fatal idiopathic venous thromboembolism.<sup>1</sup> Their study, based on the United Kingdom General Practice Research Database (GPRD), estimated the relative risk at 7.1 (95% CI: 2.3–21.9) for all antipsychotics and at 24.1 (95% CI: 3.3–172.7) for low potency preparations. Re-analysis of a case-control study of deep vein thrombosis provided support for

the hypothesis that antipsychotic drugs may be a risk factor for this condition.<sup>2</sup>

The only study to examine formally the risk of fatal venous thromboembolic events in users of antipsychotics was confined to an atypical preparation (clozapine).<sup>3</sup> We expanded a national case-control study of fatal pulmonary embolism<sup>4</sup> to explore any associations with antipsychotics or other psychotropic drugs. The deaths occurred between 1990 and 1998, when conventional antipsychotic drugs accounted for the majority of prescriptions.

### METHODS

We identified all New Zealand men and women aged 15–59 years who died between 1 January 1990 and 31 December 1998, where the underlying cause was

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certified as codes 415.1, 451 or 453 of the International Classification of Diseases (9th revision). Clinical information and names of general practitioners were obtained from coroners' and police records, death certificates and hospital records; when necessary, we also wrote to next of kin to ask for the name of the general practitioner. Of the 122 potential cases identified, 8 did not normally live in New Zealand, 9 had insufficient evidence for a diagnosis of pulmonary embolism and for 13, the pulmonary embolism was not the underlying cause of death (5 had advanced cancer, 7 had post-operative pulmonary emboli and 1 had portal vein thrombosis). The general practitioners of 2 of the 92 eligible cases could not be identified. For the others, general practitioners were asked if one of us (Lianne Parkin) could visit their practice and examine the records of the case and 4 controls. No doctor refused, but for 15 patients, the medical records had been lost. For the remaining 75, the diagnosis of pulmonary embolism was confirmed by necropsy in 69, by ventilation-perfusion scans or angiography in 3 and by two specialist clinicians (using standard criteria<sup>5</sup> and blinded to exposure status) in 3. The date of onset of the fatal episode was taken as an index date.

For each case, 4 controls, matched for sex and year of birth (except for 14 controls who were born in adjacent years to the cases), were selected from the group medical practice to which the case had belonged on the index date. The controls were selected randomly from an age-sex register in 71 practices (computerised in all except 1), from patient registration slips in 1 practice and by random selection of medical records in 3 practices. Potential controls were excluded if they were not normally residing in New Zealand or did not belong to the practice on the index date. Information about medical histories and drug exposures before the index date was abstracted from the records of general practitioners, psychiatric services and family planning clinics, using an identical approach for cases and controls. The date on which each patient had joined their general practice was recorded and because the records of many patients included information from practices to which they had previously belonged, the date of the earliest information was also noted.

Users of psychotropic drugs were defined as those who had been prescribed medication for at least 1 month. Current use was defined as prescribed use at any time during the 3 months before the index date. Psychotropic drugs were divided into three groups: antipsychotics, antidepressants and other psychotropics (a group including benzodiazepines and other anxiolytics, lithium carbonate, carbamazepine, sodium valproate and zopiclone). Antipsychotic

agents were classified according to potency, that is, the dose of the drug required to achieve a therapeutic effect.<sup>6-9</sup> In matched analyses, using conditional logistic regression (STATA v7.0), we estimated relative risks by calculating odds ratios and 95% confidence intervals. We adjusted for weight (four categories, including missing values, for both sexes) and combined oral contraceptive use and hormone replacement therapy within 3 months of the index date. Because conditional logistic regression can give misleading estimates with small numbers, we checked the analyses with unconditional logistic regression, adjusting for the matching factors. The association between psychotropic drug use and fatal pulmonary embolism was examined for all subjects, although the key analyses were restricted to those without major risk factors for venous thromboembolism. The latter group is regarded as the most informative for studying adverse effects of medicines. Ethical approval for the study was granted by each of the regional ethics committees.

## RESULTS

Of the 75 cases, 51 were female (median age 43.0 years) and 24 were male (median age 49.5 years). The mean times that cases and controls had been members of their practices were 9.9 years (standard error [SE] = 1.0) and 8.7 (SE = 0.6) years, respectively. The difference was not statistically significant ( $p = 0.2$ ). The mean number of years of recorded medical information was 13.5 (SE = 1.2) for cases and 12.2 (SE = 0.6) for controls. Again the difference was not statistically significant ( $p = 0.2$ ).

Ten cases and 2 controls had a past history of venous thromboembolism. A further 3 cases had a severe injury or prolonged immobility in the 2 months before the index date; while 3 controls were pregnant and 1 had major surgery during the same period. All of these people were classified as having major risk factors for venous thromboembolism. The following presentation of results will focus on people without major risk factors, although the tables also include results for all subjects.

Of the 62 cases without major risk factors, 43 were female (median age 42.0 years) and 19 were male (median age 47.0 years). Eight cases and 2 controls were current users of antipsychotics (Table 1). Thioridazine, a low potency antipsychotic, was used by 6 cases and 1 control. High potency antipsychotics were used by 2 cases (haloperidol) and by 1 control (prochlorperazine). There were no users of atypical agents. All users, except for the control who was

Table 1. Current use of antipsychotics

	Cases (exposed/total)	Controls (exposed/total)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Any antipsychotic <sup>†</sup>				
All subjects	9/75	3/300	12.0 (3.2–44.3)	9.7 (2.3–40.9)
Subjects without major risk factors for VTE <sup>‡</sup>	8/62	2/243	16.0 (3.4–75.3)	13.3 (2.3–76.3)
Low potency antipsychotic <sup>†</sup>				
All subjects	7/75	1/300	28.0 (3.4–227.6)	29.3 (2.8–308.2)
Subjects without major risk factors for VTE <sup>‡</sup>	6/62	1/243	24.0 (2.9–199.3)	20.8 (1.7–259.0)

\*Adjusted for weight (four categories, including missing values, for both sexes), combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date.

<sup>†</sup>Non-users of antipsychotics (never and past-users combined) are the reference group.

<sup>‡</sup>No history of venous thromboembolism or of prolonged immobility, severe injury, major surgery or pregnancy during the 2 months before the index date.

prescribed prochlorperazine for labyrinthitis 6 weeks before the index date, had received antipsychotic medication either continuously or intermittently over many years. Four cases and 1 control had a diagnosis of schizophrenia noted in their records, while another case had a possible diagnosis of schizophrenia recorded. Of the remaining cases, 1 had a bipolar affective disorder, 1 had an intellectual disability and was prescribed thioridazine for behavioural control and 1 was taking thioridazine to treat insomnia. No user had an acute psychotic episode in the 3 months before the index date; 1 man was admitted to hospital following an overdose.

Taking non-users (never and past-users combined) as the reference group, the odds ratio (adjusted for weight, combined oral contraceptive use and hormone replacement therapy) for current use of antipsychotics was 13.3 (95% CI: 2.3–76.3). Low potency antipsychotics carried the highest risk, with an adjusted odds ratio of 20.8 (95% CI: 1.7–259.0). The increased risk of pulmonary embolism in users of any antipsychotic persisted when women who were current users of combined oral contraceptives or hormone replacement therapy were excluded from the analysis, with an odds ratio (adjusted for weight) of 8.3 (95% CI: 1.3–53.5). Although the odds ratio for past use of anti-

psychotics, compared with never use, was elevated, this was not statistically significant (adjusted odds ratio 5.3 [95% CI: 0.6–45.8]). The adjusted odds ratio for use of antipsychotic medication within 1 month of the index date was 11.2 (95% CI: 1.9–65.4). An unmatched analysis (adjusted for age, sex, weight, combined oral contraceptive use, hormone replacement therapy and clustered on practice) gave similar results to the matched analysis, with an odds ratio for antipsychotic use within 3 months of the index date of 14.1 (95% CI: 3.3–61.1).

When current users of antipsychotics were excluded, 6 cases and 7 controls without major risk factors for venous thromboembolism were current users of antidepressants (Table 2). Tricyclic antidepressants were used by 4 cases and 5 controls. One of these cases and 1 further case were taking a selective serotonin reuptake inhibitor; the other case was taking a monoamine oxidase inhibitor. Of the remaining controls, 1 was using a selective serotonin reuptake inhibitor, while the other was taking a monoamine oxidase inhibitor. None of the users had been admitted to hospital for depression during the 3 months before the index date, although 2 cases were diagnosed with acute depression and were prescribed tricyclics as outpatients about 2 months before the

Table 2. Current use of antidepressants

	Cases (exposed/total)	Controls (exposed/total)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Any antidepressant <sup>†</sup>				
All subjects	8/66	7/261	5.5 (1.8–17.1)	10.0 (2.4–41.2)
Subjects without major risk factors for VTE <sup>‡</sup>	6/54	7/209	3.7 (1.1–12.5)	4.9 (1.1–22.5)

\*Adjusted for weight (four categories, including missing values, for both sexes), combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date.

<sup>†</sup>Current users of antipsychotics are excluded. Non-users of antidepressants (never and past-users combined) are the reference group.

<sup>‡</sup>No history of venous thromboembolism or of prolonged immobility, severe injury, major surgery or pregnancy during the 2 months before the index date.

index date. Only 1 user, a control, was taking a tricyclic for a reason other than depression (migraine prophylaxis). Of the remaining users, 1 case first commenced treatment 9 months before the index date, while all the others had been taking antidepressants intermittently or continuously for years. With non-users as the reference group, the odds ratio (adjusted for weight, combined oral contraceptive use and hormone replacement therapy) for current use of antidepressants was 4.9 (95% CI: 1.1–22.5). The adjusted odds ratios for current and past use of antidepressants, compared to never use, were 6.3 (95% CI: 1.3–30.8) and 2.9 (95% CI: 0.7–11.5) respectively. An analysis including current users of antipsychotics, but adjusting for such use, also found an increased risk in current users of antidepressants (odds ratio 5.5 [95% CI: 1.3–23.8]).

There was no increased risk for current or past use of other psychotropic drugs as a group. When we excluded users of antipsychotics or antidepressants, the adjusted odds ratio for current use was 1.4 (95% CI: 0.3–7.7). Adjusting for antipsychotic and antidepressant use produced an identical point estimate (odds ratio 1.4 [95% CI: 0.3–5.8]).

## DISCUSSION

This case-control study found that current users of antipsychotic drugs had an increased risk of fatal pulmonary embolism, when compared with non-users. Low potency antipsychotics carried the highest risk, with thioridazine being the main drug involved. The odds ratio for current use of antidepressants was also increased. The odds ratios for past use of antipsychotics and antidepressants were not significantly increased.

The study was population-based and it was possible to identify all cases of idiopathic fatal pulmonary embolism that occurred in New Zealand during the study period. Diagnostic bias was unlikely because most people who die unexpectedly in New Zealand are referred for necropsy. Information about drugs prescribed and medical history was derived from medical records and hence was not subject to recall bias. Controls were selected from the same general practices as cases and there was no significant difference in the mean time that cases and controls had been members of their practices or in the number of years of recorded medical information. The date of onset of the fatal episode (rather than the date of death) was taken as the index date, so the prescription of antipsychotic or antidepressant drugs for unrecognised early symptoms of venous thromboembolism is an unlikely explanation

for our results. Moreover, most of the cases had been taking their medication for at least a year.

Confounding by sex, age, weight, concomitant drug use or underlying medical conditions is unlikely: controls were matched to cases for sex and year of birth; we adjusted for weight, use of combined oral contraceptives and hormone replacement therapy; and we excluded individuals with major risk factors from the key analyses. It was not possible to adjust for body mass index because the height of many patients was unrecorded, but it is unlikely that adjusting for weight instead of body mass index made a substantial difference to our results.

The number of cases was inevitably restricted by the size of the New Zealand population. This limited our capacity to examine a number of features—especially any association with classes of drugs other than antipsychotics and antidepressants. The general practice records of 15 cases could not be located, which might have biased our results. However, this was mostly due to practice-related reasons (such as doctors moving premises, retiring or dying) and it did not appear to be related to particular characteristics of cases.

Our finding of an increased risk of fatal pulmonary embolism in current users of conventional antipsychotics is consistent with previous studies of non-fatal venous thromboembolism.<sup>1,2</sup> Like Zornberg and Jick,<sup>1</sup> we found that users of low potency formulations carried the highest risk. The re-analysis of the Leiden Thrombophilia Study in the Netherlands found that 4 of the 474 cases with deep vein thrombosis and none of the matched controls, were current users of antipsychotics.<sup>2</sup> The findings of a Canadian cohort study were less consistent.<sup>10</sup> Using linked data from health care administrative records, Ray *et al.* compared the risk of venous thromboembolism in users of antipsychotic drugs and users of thyroid replacement hormone. An increased risk was found for users of butyrophenone antipsychotics only (adjusted relative risk 1.43 [95% CI: 1.18–1.74]). However, the study was confined to patients of age 65 years and more and diagnostic bias could not be ruled out since users of antipsychotics were older, were more likely to be living in long-term care facilities and may have been more cognitively impaired than the comparison group.

Information about antipsychotic use and fatal venous thromboembolism is limited. Thomassen *et al.* reviewed necropsy reports at the Leiden University Medical Centre in the Netherlands.<sup>2</sup> Ten of the 27 deaths from idiopathic pulmonary embolism occurred in psychiatric patients, 5 of whom were known users of antipsychotic drugs. In a case-control study of fatal

cardiovascular disease in women of childbearing age in England and Wales, Thorogood *et al.* unexpectedly found an increased risk of myocardial infarction in users of psychotropic drugs, particularly tricyclic antidepressants and benzodiazepines.<sup>11</sup> An almost three-fold increased risk of pulmonary embolism in current users of psychotropics was also observed, although no estimates were reported for individual drug groups. Walker *et al.* linked data from a national registry of clozapine users with death registrations in the United States.<sup>3</sup> Among those aged 10–54 years, the standardised mortality rate for pulmonary embolism in current users was five times that of past users (relative risk 5.2). This may be a conservative estimate since patients who were classified as past users of clozapine could have been taking other antipsychotics.

Antipsychotic drugs have also been implicated in sudden cardiac death<sup>12</sup> and it is possible that deaths from pulmonary embolism could be misclassified as due to myocardial infarction or arrhythmia when necropsies are not performed. For example, in a recent case-control study, thioridazine was identified as a risk factor for sudden unexplained death among psychiatric inpatients (adjusted odds ratio 5.3 [95% CI: 1.7–16.2]).<sup>13</sup> Drug-induced arrhythmia was thought to be the most likely cause. Since a necropsy was performed in only 36% of the cases, the possibility that some of the remaining patients died from pulmonary embolism cannot be ruled out. Interestingly when the analysis was confined to patients who had undergone a necropsy, a significant association between thioridazine and sudden unexplained death was not found (adjusted odds ratio 2.9 [95% CI: 0.7–11.7]).

The previous evidence of an increased risk of non-fatal venous thromboembolism in antipsychotic users tends to argue against differential survival as an alternative explanation for our results. Moreover, the absence of a significantly increased risk for past use in our study is consistent with the hypothesis that the drugs, rather than any underlying characteristics of the people who used them, were responsible for the increased risk among current users. Nevertheless, the estimate for past use was elevated, with a wide confidence interval, so the possibility that people who are considered to need these drugs carry some increased risk cannot be ruled out. Earlier studies that found significantly elevated risks for current users of conventional<sup>1</sup> and atypical<sup>3</sup> antipsychotics, took past users as the reference group. This provided some control for the underlying condition, but it did not permit the evaluation of a possible increased background risk in users of antipsychotic drugs.

There is no clear explanation for the increased risk of venous thrombosis in users of antipsychotics. Several hypotheses have been proposed, including enhanced aggregation of platelets,<sup>1</sup> anticardiolipin antibodies,<sup>1</sup> exacerbation of venous stasis during sedation,<sup>1</sup> increased adrenaline secretion in the acute psychotic phase<sup>2</sup> and hyperhomocysteinaemia.<sup>10</sup>

The observed association between current use of antidepressants and fatal pulmonary embolism was not expected, although it should be noted that tricyclic drugs closely resemble the phenothiazines chemically.<sup>14</sup> There have been isolated reports of venous thromboembolic events in users of antidepressants who were also immobilised<sup>15</sup> or concurrently using antipsychotics.<sup>16</sup> Zornberg and Jick found an odds ratio of 1.7 (95% CI: 0.8–3.7) for current use of antidepressants.<sup>1</sup> This result was based on only 3 exposed cases and 20 exposed controls, so it was not incompatible with our observation. In the re-analysis of the Leiden Thrombophilia Study, 9 cases and 4 controls were current users of antidepressants, giving an odds ratio for current use of 2.3 (95% CI: 0.6–10.2).<sup>2</sup> The adjusted relative risk for current use of antidepressants in the Canadian cohort study was 1.04 (95% CI: 0.94–1.15).<sup>10</sup>

If the association between antidepressant drugs and fatal pulmonary embolism is real, it needs to be established whether antidepressant drugs increase the risk of venous thromboembolism or whether the people with depression are more likely to die from the condition. Antidepressants are widely used and further studies are required to clarify the association between these drugs and venous thromboembolism.

#### KEY POINTS

- Compared to non-use, current use of conventional antipsychotics was associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio 13.3 [95% CI: 2.3–76.3]).
- Low potency antipsychotics carried the highest risk (adjusted odds ratio 20.8 [95% CI: 1.7–259.0]).
- The odds ratio for current use of antidepressants was also increased (adjusted odds ratio 4.9 [95% CI: 1.1–22.5]).
- Current use of other psychotropic drugs was not associated with an increased risk.
- The findings for antipsychotics were consistent with previous studies, but the association between use of antidepressants and fatal pulmonary embolism was not expected and needs to be replicated.

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