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Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study.Gwen L Zornberg and Hershel Jick. *The Lancet* 356.9237 (Oct 7, 2000): p1219. (4067 words)

Abstract:

In a study of 214 people, those who took anti-psychotic drugs were seven times more likely to develop venous thromboembolism. This condition occurs when a blood clot forms in veins and travels to other parts of the body. Chlorpromazine and thioridazine were more likely to cause this condition than haloperidol.

Summary

Background Antipsychotic drugs have been associated with an increased risk of adverse events such as venous thromboembolism. Our aim was to assess this risk in users of conventional antipsychotic drugs who had been diagnosed with first-time, idiopathic venous thromboembolism.

Methods From a baseline population of 29 952 recipients of conventional and atypical antipsychotic drugs aged younger than 60 years, we identified 42 individuals with idiopathic venous thromboembolism and 172 matched controls. We compared risk of current and recent use of antipsychotic drugs with non-use before the index date in cases and controls.

Findings Current exposure to conventional antipsychotic drugs was associated with a significantly increased risk of idiopathic venous thromboembolism compared with non-use (adjusted odds ratio 7.1 [95% CI 2.3-21.97]). Although we found no difference between phenothiazines, thioxanthenes, or other conventional antipsychotic drugs, low potency antipsychotic drugs drugs such as chlorpromazine and thioridazine were more strongly associated with venous thromboembolism (odds ratio 24.1 [3.3-172.7]) than were high potency antipsychotic drugs such as haloperidol (3.3 [0.8-13.2]). The risk for venous thrombosis was highest during the first few months of conventional antipsychotic drug use.

Interpretation Current exposure to conventional antipsychotic drugs significantly increases the risk of idiopathic venous thromboembolism in men and women younger than 60 years of age.

Lancet 2000; 356: 1219-23

Introduction

Antipsychotic drugs are widely used in medicine and psychiatry. Since their introduction, the newer atypical antipsychotic drugs have become more commonly prescribed, often replacing conventional drugs. Consequently, interest in their side-effect profiles has grown. Most attention has been paid to

adverse effects such as agranulocytosis, which has been associated with clozapine use, and more common adverse neurological reactions such as tardive dyskinesia.(1) Little attention has been focused on the potentially fatal adverse drug reaction of venous thromboembolism, which includes pulmonary embolism and deep-vein thrombosis.

In a mortality study of the atypical antipsychotic drug clozapine, Walker and colleagues(2) reported that pulmonary embolism occurred more frequently in present users than in past users. In addition to sporadic case reports of venous thromboembolism(3-5) and myocarditis-related pulmonary artery embolism reported in users of clozapine,(6) case reports(7,8) and observational studies(9,10) have documented positive associations with venous thromboembolism in recipients of conventional antipsychotic drugs, with a particular focus on the phenothiazine subclass.

After the introduction of phenothiazines, investigators reported that the frequency of thromboembolic complications associated with antipsychotic drug use was unrelated to psychiatric diagnosis and was greater than all other potentially fatal drug effects (ie, hepatotoxicity, agranulocytosis, or heart failure).(9) Pulmonary embolism is often misdiagnosed as sudden cardiac death. Of note, ten of 27 cases of idiopathic, fatal pulmonary embolism were diagnosed in psychiatric patients only at necropsy.(11) Spontaneous reports have described an association between sudden cardiac death and antipsychotic drug use.(12-15) However, the evidence for a causal link between antipsychotic drugs and risk of venous thromboembolism remains inconclusive.

In early studies of conventional antipsychotic drugs, patients were not free from cardiovascular and other thrombogenic risk factors,(10) and more recent spontaneous reports(7,8) lacked controls. Since antipsychotic drugs are common medications (particularly in psychiatric, chronically ill, and geriatric populations) and venous thromboembolism is a potentially fatal although treatable condition, there is a public-health need to further explore the findings of previous research on antipsychotic drug use. This led us to carry out a population-based, nested case-control analysis to explore the relation between antipsychotic drugs and the risk of developing first-episode, idiopathic venous thromboembolism in a large cohort of antipsychotic drug recipients by use of the UK-based General Practice Research Database (GPRD).

Methods

Study population and data source

The baseline population from which the GPRD data were derived has been described in detail elsewhere.(16-18) The GPRD database encompasses about 3 million residents of the UK who have been enrolled by selected general practitioners who use office computers originally provided by Value Added Medical Products and have agreed to provide data for research purposes to the GPRD. The information recorded in this database includes patients' demographics and characteristics (eg, height, weight, smoking status), symptoms, medical diagnoses, referrals, hospital admissions, drug prescriptions (including the specific preparation), route of administration, dose, and number of tablets for each prescription. All information is recorded by general practitioners on a daily basis (replacing paper charts), irrespective of future research hypotheses. On request, anonymised hospital discharge and referral letters are available for review and for validation of diagnoses recorded in the computer database. The GPRD has been the source for many epidemiological studies, and the accuracy and completeness of these data have been well documented and validated.(19,20)

The study population consisted of men and women who were younger than 60 years in 1998, and who had used at least one conventional (chlorpromazine, trifluoperazine, thioridazine, mesoridazine, fluphenazine, perphenazine, pericyazine, methotrimeprazine, pipothiazine, zuclopenthixol, flupenthixol, thiothixene, haloperidol, benperidol, sulpiride, pimozide, loxitane) or atypical (risperidone, olanzapine,

quetiapine, clozapine) antipsychotic medication at some time between Jan 1, 1990, and Oct 31, 1998. To be included, the individual had to have at least 6 months of information on drugs prescribed and medical diagnoses recorded on computer before the date of first prescription for an antipsychotic drug. Each prescription typically covered a period of 1 month.

Mean duration of observation was 6.8 years (SD 1.9). The baseline population was 29 952 men and women who had been prescribed at least one antipsychotic drug (total 293 646 prescriptions). Among antipsychotic drug users, 12 586 (42%) received one prescription, 8163 (27%) received two to four prescriptions, 3358 (11%) received five to nine prescriptions, and 5845 (20%) received ten or more prescriptions. In the baseline cohort, only 754 (3%) used an atypical antipsychotic drug (clozapine, risperidone, olanzapine, or quetiapine) within the study period. No individual included in the nested case-control study was exposed to an atypical antipsychotic medication; however, the proportion of atypical antipsychotic recipients in the baseline cohort during the study period was small.

No first-onset, idiopathic thromboembolic event was seen in any of the 16 clozapine users. Similarly, there was no evidence of thrombotic events in the individuals in the baseline cohort who were receiving risperidone (n=476), olanzapine (n=251), or quetiapine (n=11).

Identification of cases and controls

Individuals with a first-time diagnosis of venous thromboembolism between Jan 1, 1990, and Oct 31, 1998, were identified by computer-recorded medical diagnoses with a modification of the Oxford Medical Information System classification, which were mapped onto International Classification of Diseases (eighth revision) codes. Potential cases had to have been admitted and treated with anticoagulants for the venous thromboembolism. We sent for hospital discharge letters to verify the computer-recorded diagnosis, and for death certificates for those who died from venous thromboembolism. To be included, the diagnosis of venous thromboembolism had to be confirmed by impedance plethysmography, venogram, ultrasonography, or doppler test, and pulmonary embolism had to be confirmed by ventilation-perfusion scan, computed tomography, magnetic resonance imaging, or angiography. We defined idiopathic venous thromboembolism as occurring in the absence of important medical risk factors including conditions that predispose to immobilisation and recurrent hospital admission.

We restricted the study to case patients younger than 60 years of age on the date of diagnosis (index date) and those free of medical conditions potentially related to an increased risk of venous thromboembolism. Computer-recorded chronological records of medications received and clinical history of cases and controls were reviewed without knowledge of antipsychotic drug exposure. We excluded all individuals whose discharge summaries indicated that they had had a previous venous thromboembolism, and those with a history of trauma, pregnancy, or surgery in the previous 6 months, in addition to those whose discharge summaries indicated that before the index date they had conditions that are risk factors for thrombotic episodes, such as coagulopathies, congestive heart failure, myocardial infarction, cancer, renal failure, epilepsy, diabetes mellitus, cystic fibrosis, multiple sclerosis, an acute psychotic episode within 2 months of the index date, and alcohol and substance use disorders. 41 potential cases of venous thromboembolism were excluded on the basis of these criteria. The diagnosis of venous thromboembolism was not confirmed from the clinical record in six individuals.

From the baseline population, we randomly selected four controls matched to each case on age (year of birth), sex, general practice attended, years in GPRD, and index date. The same exclusion criteria for cases were applied to controls; no control was included if they were diagnosed with any of the conditions that may predispose them to thrombosis before the index date.

Exposure to antipsychotic drugs

Data on medication exposure were derived from the computerised prescriptions. For each case and control, we assessed the exposure history for antipsychotic drugs in three predefined time periods preceding the index date: current, recent, and non-exposed. Current antipsychotic drug use (with or without antidepressant use) was defined as receipt of a prescription 1-60 days before the index date. Recent antipsychotic drug use was defined as receipt of a prescription 61-120 days before the index date. Exposure was classified as non-use if no antipsychotic drugs were prescribed 1-120 days before the index date.

Conventional antipsychotic drugs were divided into three groups according to the relation between chemical structure and activity and into two groups according to potency (panel).

Data analysis

We did a matched analysis (conditional logistic regression) by use of SAS (version 6.12) to explore the association between the risk of idiopathic venous thromboembolism and conventional antipsychotic drugs (including potency, phenothiazines, thioxanthines, and other conventional agents), exposure timing (current use, recent use).

To control for age, sex, general practice, index date, and years of recorded history in the GPRD before the index date (by matching), we controlled the analysis for potential confounders such as smoking status (none, current, past, unknown), body-mass index ([less than] 24 kg/m2, 24-27.9 kg/m2, [greater than] 28 kg/m2), exposure to oestrogens (oral, transdermal, and parenteral contraception or oestrogen replacement therapy), antidepressant use (current use, recent use), and hypertension. Current oestrogen use was defined as having received the last prescription of systemic oestrogen formulations less than 180 days before the index date. Recent oestrogen use was defined as receipt 180-365 days before the index date. To assess whether these variables were modifiers of the effect measure associated with antipsychotic drug use, we stratified the analysis by age and sex. Odds ratios are presented with 95% CI, and p values are two-tailed.

Results

During follow-up, 42 (0.14%) individuals had a first-time diagnosis of venous thromboembolism between Jan 1, 1990, and Oct 31, 1998, in the absence of clinical risk factors. These cases were confirmed as idiopathic venous thromboembolism, and 168 matched controls were randomly selected. The distributions of age, sex, body-mass index, smoking status, use of oestrogens, hypertension, and hyperlipidaemia preceding the index date of the cases and their matched controls are shown in table 1. The mean age of the cases was 44.2 years (SD 10.1). The adjusted relative risk estimates of first-time venous thromboembolism associated with current and recent use of antipsychotics are shown in table 2.

Adjusted odds ratios did not differ between types of antipsychotic drugs. Among conventional antipsychotic drugs, phenothiazines were the most commonly used--by 19 (66%) of 29 patients. Odds ratios for current use were 6.1 (95% CI 1.9-19.7) for phenothiazines, 5.2 (0.7-39.1) for thioxanthines, and 4.1 (0.1-129.2) for other heterocyclic antipsychotic drugs such as butyrophenones. After adjustment for confounding, current use of low potency antipsychotic drugs accounted for a higher risk of venous thromboembolism than in non-users (table 2). The relation between antipsychotic drugs and venous thromboembolism seemed to be strongest during short-term use. In the cases, ten (67%) of 15 users of antipsychotic drugs were diagnosed with a venous thromboembolism within 3 months of the first prescription. There was no suggestion of a higher risk of venous thromboembolism among recipients of higher doses. No psychiatric or medical condition was independently associated with venous thromboembolism: schizophrenia and other psychoses, 1.2 (0.2-6.4); affective and anxiety disorders, 1.2 (0.5-3.1); and other medical conditions such as insomnia, fibromyalgia, premenstrual syndrome, back pain, 1.3 (0.4-4.0).

No association was found between antidepressant use alone and subsequent risk of venous thromboembolism when we controlled for antipsychotic drug exposure (table 1). The risk estimate for subsequent venous thromboembolism was associated independently with oestrogen use but did not confound the relation between antipsychotic drugs and venous thromboembolism in the multivariate model. We found no difference in the antipsychotic drug-related risk of venous thromboembolism between antipsychotic drug users who received oestrogens and those who had no current use of oestrogens.

Stratification by age, sex, and outcome (pulmonary embolism, deep-vein thrombosis) did not modify the findings. The risk of current antipsychotic drug use did not differ significantly between men [7.0 (1.6-29.9)] and women [6.7 (2.6-17.2)]. Hypertension was an independent risk factor for venous thromboembolism compared with normotensive individuals (table 1).

To assess fatal cardiovascular disorders that may have been masked cases of pulmonary embolism, we identified cases of sudden death among antipsychotic drug users in the baseline population, and found one case of sudden death in a current user of haloperidol from the baseline cohort. In the case-control study, two of the 42 cases of venous thromboembolism were fatal: one patient had been exposed to current use of flupenthixol; the other patient, who had not received antipsychotic drugs in the 120 days before the index date but had received oral contraception by depot injection, had deep-vein thrombosis followed by a pulmonary embolism.

Discussion

Our findings suggest that conventional antipsychotic drug use is associated with an increased risk of idiopathic venous thromboembolism. The risk seems to be an effect of current exposure to these drugs and is most pronounced during the first 3 months of exposure. The risk of venous thromboembolism was higher for low potency than for high potency conventional antipsychotic drugs. There was no evidence for effect modification by age, sex, or antidepressant or oestrogen use.

By restricting our analysis to idiopathic cases without a previous history of thromboembolism or other clinical risk factors for venous thromboembolism, and by matching controls to cases on age and sex, we compared recipients of antipsychotic drugs who were similar with respect to risk factors for venous thromboembolism other than exposure to the antipsychotic drug itself. The possible association between low-potency atypical antipsychotic drugs,(2-6) although not with high-potency drugs such as risperidone and olanzapine, are consistent with our findings of increased risk associated with low-potency conventional antipsychotic drugs.

Several biological mechanisms of action have been proposed to explain this relation. One plausible mechanism derives from research suggesting that conventional antipsychotic drugs are associated with enhanced aggregation of platelets.(21,22) A second possible explanation stems from the presence of anticardiolipin antibodies, which are associated with increased risk of venous or arterial thrombosis and are raised in some patients prescribed chlorpromazine. However, no link has been found between venous thromboembolism and antipsychotic drug use in those in whom anticardiolipin antibodies were detected.(23) A third hypothesis is that venous stasis exacerbated by sedation, commonly found in patients treated with low-potency antipsychotic drugs, may contribute to processes that increase the risk of thrombosis. Our findings, which were related to the risks of short-term use of antipsychotic drugs and the absence of a dose-response effect, suggest that certain individuals may be susceptible to antipsychotic drug-related venous thromboembolism.

Despite the fact that our findings indicate a causal role of antipsychotic drugs on the risk of venous thromboembolism, caution needs to be exercised in their interpretation. First, confounding might explain the findings if cases were more medically ill than controls, although only under the assumptions that the

clinical condition of the cases was associated both with being prescribed antipsychotic drugs and a higher likelihood of developing venous thromboembolism. Thus, our study is strengthened by the use of systematically collected drug exposure information and the fact that we restricted the analysis to fairly healthy individuals without a history of recurrent venous thromboembolism and with no apparent clinical risk factors for venous thromboembolism. Importantly, information about the clinical condition of patients available to us through the medical records and consultants' reports indicated that none of the cases was in poor health (neither partly nor completely bedridden) at the index date. Moreover, none of the cases were in an acute psychotic state in the 2 months before the index date.

Second, other medications taken concomitantly with antipsychotic drugs could account for the increased risk of venous thromboembolism. However, we found no association between antidepressant use and risk of venous thromboembolism. Moreover, the relation between oestrogen use and venous thromboembolism was independent of antipsychotic drug-related risk.

Third, antipsychotic drugs such as dopamine antagonists are used to palliate the symptoms of a wide range of disorders including psychoses, severe anxiety and mood disorders, behavioural disturbances, and dementia. A differential distribution of the underlying disorders for which antipsychotic drugs were prescribed might increase the risk of venous thromboembolism if cases were more likely than controls to be diagnosed with severe psychotic conditions that require immobilisation through chemical sedation or mechanical restraint. Restriction of the baseline cohort to outpatient users of antipsychotic drugs provided some control for the underlying disorder for which the drugs were prescribed and for intensity of surveillance by the physician. Moreover, the specific psychiatric diagnosis was unrelated to risk of venous thromboembolism.

Finally, although our findings of the relation between conventional antipsychotic drugs and venous thromboembolism are concordant with previous research,(8,9) our study provides little information on the relation between atypical antipsychotic drug use and risk of idiopathic venous thromboembolism. Further investigation is therefore warranted to assess this risk compared with that of conventional antipsychotic drugs.

Contributors

Both investigators contributed to the conception and design of the study, data collection, analysis, interpretation of the data and drafting and reviewing of all versions of the paper.

Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA 02421, USA (G L Zornberg MD, H Jick MD)

Correspondence to: Dr Gwen L Zornberg (e-mail: zornberg@bu.edu)

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Characteristic	Cases (n=42)	Controls (n=168)
Age (years)		
20-39	13 (31%)	51 (30%)
40-49	14 (33%)	59 (35%)
50-59	15 (36%)	58 (35%)
Sex		
Male	10 (24%)	40 (24%)
Female	32 (76%)	128 (76%)
Body-mass index (kg/m2)		
[less than] 24	8 (19%)	33 (19%)
24-27	6 (14%)	47 (28%)
f28	18 (43%)	31 (19%)
Unknown	10 (24%)	57 (34%)
Smoking		
None	10 (24%)	64 (38%)
Current	18 (43%)	49 (29%)
Former	5 (12%)	14 (8%)
Unknown	9 (21%)	41 (24%)
Medical history		
Hypertension	6 (14%)	7 (4%)
Hyperlipidaemia	2 (5%)	4 (2%)
Oestrogen use[*]		
None	28 (67%)	136 (81%)
Current use	10 (23%)	22 (13%)
Recent use	4 (10%)	10 (6%)
Antidepressant exposure		

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 without antipsychotic drug use
None                              29 (69%)        131 (78%)
Current use                        3 (11%)         20 (13%)
Recent use                         1 (4%)           5 (3%)
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Characteristic	Odds ratio (95% CI)
Age (years)	
20-39	. .
40-49	. .
50-59	. .
Sex	
Male	. .
Female	. .
Body-mass index (kg/m2)	
[less than] 24	1.0
24-27	0.5 (0.2-1.7)
f28	2.2 (0.9-5.5)
Unknown	0.6 (0.2-2.0)
Smoking	
None	1.0
Current	2.4 (1.0-5.6)
Former	2.4 (0.7-9.1)
Unknown	1.3 (0.4-4.1)
Medical history	
Hypertension	4.1 (1.2-13.6)
Hyperlipidaemia	2.0 (0.4-10.9)
Oestrogen use[*]	
None	1.0
Current use	2.4 (1.0-5.9)
Recent use	2.2 (0.6-8.2)
Antidepressant exposure without antipsychotic drug use	
None	1.0
Current use	1.7 (0.8-3.7)
Recent use	0.8 (0.1-7.4)

[*] All oestrogen use combined (with and without progestagens).

Table 1: Characteristics of cases and controls and risk of developing venous thromboembolism

Antipsychotic drug exposure	Cases (n=42)	Controls (n=168)
Exposure[]		
None	26 (62%)	150 (89%)
Current use (0-60 days)	14 (33%)	11 (7%)
Recent use (61-120 days)	2 (5%)	7 (4%)
Duration[]		
Never or past use	28 (67%)	157 (93%)
Current use		
0-11 months	12 (29%)	3 (2%)
f12 months	2 (5%)	8 (5%)

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Potency
None or past                28 (67%)           157 (94%)
Current use
   Low potency               7 (17%)             2 (1%)
   High potency              7 (17%)             9 (5%)

Daily dose
None or past                28 (67%)           157 (94%)
Current use
   0-99 mg                  11 (26%)             7 (4%)
   f100 mg                   3 (7%)              4 (2%)

Antipsychotic drug          Odds ratio[*]
exposure                    (95% CI)

Exposure[]
None                        1.0
Current use (0-60 days)     7.1 (2.3-21.9)
Recent use (61-120 days)    2.1 (0.4-11.8)

Duration[]
Never or past use           1.0
Current use
   0-11 months             28.7 (4.9-169.5)
   f12 months               1.0 (0.1-7.3)

Potency
None or past                1.0
Current use
   Low potency             24.1 (3.3-172.7)
   High potency             3.3 (0.8-13.2)

Daily dose
None or past                1.0
Current use
   0-99 mg                 12.4 (3.2-48.3)
   f100 mg                  2.3 (0.4-14.9)
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[*] Adjusted for smoking, body-mass index, hypertension, oestrogen use, and antidepressant use.

[] All antipsychotic drug classes, with or without antidepressant use.

Table 2: Odds ratios of developing venous thromboembolism associated with use of antipsychotic and antidepressant medications

RELATED ARTICLE: Categories of antipsychotic drugs

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Chemical structure and activity
Phenothiazines                    Chlorpromazine, trifluoperazine,
                                  thioridazine, mesoridazine,
                                  fluphenazine, perphenazine,
                                  pericyazine, methotrimeprazine,
                                  pipothiazine
Thioxanthines                     Zuclopenthixol, flupenthixol,
                                  thiothixene
Other heterocyclic                Haloperidol, benperidol, sulpiride,
agents                            pimozide, loxapine
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Potency
Low potency                          Chlorpromazine, thioridazine,
                                     mesoridazine, pericyazine,
                                     methotrimeprazine, pipothiazine,
                                     sulpiride
High potency                         Haloperidol, benperidol, pimozide,
                                     trifluoperazine, fluphenazine,
                                     perphenazine, zuclopenthixol,
                                     flupenthixol, thiothixene, loxapine
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Source Citation: Zornberg, Gwen L, and Hershel Jick. "Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study." The Lancet 356.9237 (Oct 7, 2000): 1219. Health Reference Center Academic. Gale. PIMA COUNTY PUBLIC LIBRARY. 31 July 2008 <http://0-find.galegroup.com.librarycatalog.pima.gov:80/itx/start.do?prodId=HRCA>.

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Antipsychotic drugs and venous thromboembolism.(Letter to the Editor).Hershel Jick, Gwen L Zornberg, E J Ferguson, J C R Hardwick, Stephen M Lawrie, Matira Taikato, Sara Kondracki, Elizabeth Hare and Rebecca Tipper. *The Lancet* 357.9253 (Feb 3, 2001): p391. (1173 words)

Sir—Gwen Zornberg and Hershel Jick (Oct 7, p 1219)(1) report that antipsychotic drugs can significantly increase the risk of idiopathic venous thromboembolism. This finding is potentially important and we appraised the paper in our evidence-based-medicine journal club. We are concerned that the finding represents an idiosyncratic drug reaction in a small number of patients, and could lead to people who would benefit from taking antipsychotic drugs not receiving them.

The cases described typically received less than 99 mg (we presume of chlorpromazine equivalents), generally for less than 4 months. Why patients would be prescribed such small doses and short-term courses is unclear, as is whether the patients actually took the drugs. We wonder whether patients had been prescribed antipsychotics at times of stress, when they might also have been drinking and smoking more than usual. Zornberg and Jicks' analyses control only for the presence or absence of smoking and hypertension, and did not specifically measure alcohol exposure, and there remains much scope for residual confounding.

The lack of a dose response between antipsychotic exposure and thromboembolism does not support the association and strongly argues against the possibility that dose-related side-effects such as sedation cause an increase in sedentary behaviour and explain the effect. Zornberg and Jick suggest that certain individuals are susceptible but the risk of venous thromboembolism is very low at 42 (0.14%) of 29 952 patients. Even if the odds are increased seven-fold, the rate of venous thromboembolism on antipsychotic drugs is still less than 1%. These figures should be contrasted with the beneficial effects antipsychotics have in patients with schizophrenia,(2) and certainly should not discourage doctors or patients from using antipsychotic drugs to treat the disorders they are licensed for.

Rebecca Tipper, Elizabeth Hare, Sara Kondracki, Matira Taikato,
[*]Stephen M Lawrie
Lothian Primary Care NHS Trust, Royal Edinburgh Hospital,
Edinburgh EH10 5HF, UK

(1) Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. Lancet 2000; 356: 1219-23.

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Sir—We are concerned that the risks of venous thromboembolism associated with phenothiazines reported by Gwen Zornberg and Hershel Jick1 also apply to the pregnant population.

Pregnancy is a thrombophilic state and venous thromboembolism is the most common cause of

maternal death.(2) Up to 50% of pregnant women are affected by vomiting in early pregnancy and antiemetics are effective in treating this disdorder.(3) The management of vomiting in pregnancy and hyperemesis frequently involves the use of phenothiazines, most commonly prochlorperazine.

Zornberg and Jick report that the group most at risk of a venous thrombosis were using a mild antipsychotic for a short time and that the link was not dose-dependent. Pregnant women who have been prescribed phenothiazines for vomiting in pregnancy (generally in primary care), or who are dehydrated with hyperemesis would be in this group. Dehydrated pregnant women are possibly at increased risk of venous thrombosis. A contributory factor might be pharmacological treatment. Pyridoxine can be as effective as other antiemetics in controlling nausea and vomiting in pregnancy.

If the increased risk of thromboembolism is true in pregnant women taking phenothiazines, further questions need to be addressed. Would thrombophilia testing be useful for women using long-term phenothiazines for psychiatric reasons? If the mechanism of action is via stimulation of anticardiolipin antibodies, would testing before treatment be beneficial? Should women using phenothiazines for any reason be offered antithrombotic prophylactic treatment?

There is much current interest in lowering morbidity and mortality from venous thrombosis in obstetrics. If this link is as strong as suggested by Zornberg and Jick, links in the obstetric population should be investigated.

[*] J C R Hardwick, E J Ferguson
Glasgow Royal Maternity Hospital, Glasgow G4 0NA, UK

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Authors' reply

Sir--The nature of our nested case-control study design suggests that thrombotic events occurred shortly after the start of treatment. This finding does not imply that affected individuals were intended by the prescribing physician to receive a short-term course of treatment. In fact, most of the patients continued to use these drugs after the first episode of venous thromboembolism, presumably because the attending physician did not think that the antipsychotic agent might be related to the occurrence of venous thrombosis. Moreover, to reduce confounding by drinking and smoking at the time of first use of antipsychotic drugs, we excluded individuals diagnosed with alcohol and substance-use disorders. The finding of an association between a medicine and thromboembolic events shortly after starting therapy is unusual and suggests that the effect is not cumulative and related directly to the pharmacological action of the drug.(1) Rather, there may be a group of users who are especially susceptible to these unpredictable thrombotic events and who experience the venous thrombosis early after starting the medicine, which is reminiscent of the type of association frequently seen for oral-contraceptive use and risk of venous thromboembolism.(2,3)

The low average doses (in chloropromazine equivalents) given to our outpatient population reflect

the prescribing patterns of family physicians designed for the treatment of a broad spectrum of medical disorders, including chronic psychotic disorders.

Our findings of an association between conventional antipsychotic drugs and raised risk of venous thromboembolism have been sug-gested in many previous reports since the introduction of phenothiazines.(4) We agree that the increased risk of venous thromboembolism is rare and should not discourage the use of antipsychotic drugs when indicated. Nevertheless, physicians and indi-viduals must be aware of this potentially fatal, though treatable, adverse drug reaction when starting treatment, especially in patients who have other risk factors for venous thromboembolism.

J Hardwick and E Ferguson point out correctly that pregnant women have a raised risk of venous thromboembolism.(5) We excluded pregnant women because of this increased risk. Therefore we can provide no information on the effect of these drugs in pregnancy.

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[*] Gwen L Zornberg, Hershel Jick
[*] Boston Collaborative Drug Surveillance Program, Boston University
School of Medicine, Lexington, MA 02421, USA; and
Department of Epidemiology, Harvard School of Public Health, Boston, MA
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Disclaimer: This information is not a tool for self-diagnosis or a substitute for professional care.