Antipsychotics and the Risk of Sudden Cardiac Death

Sabine M. J. M. Straus, MD; Gysèle S. Bleumink, MD; Jeanne P. Dieleman, PhD;
Johan van der Lei, MD, PhD; Geert W. 't Jong, PhD; J. Herre Kingma, MD, PhD;
Miriam C. J. M. Sturkenboom, PhD; Bruno H. C. Stricker, PhD

Background: Antipsychotics have been associated with prolongation of the corrected QT interval and sudden cardiac death. Only a few epidemiological studies have investigated this association. We performed a case-control study to investigate the association between use of antipsychotics and sudden cardiac death in a well-defined community-dwelling population.

Methods: We performed a population-based case-control study in the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with complete medical records from 150 general practitioners. All instances of death between January 1, 1995, and April 1, 2001, were reviewed. Sudden cardiac death was classified based on time between onset of cardiovascular symptoms and death. For each case, up to 10 random controls were matched for age, sex, date of sudden death, and practice. Exposure at the index date was categorized as 3 mutually exclusive groups of current use, past use, and nonuse.

Results: The study population comprised 554 cases of sudden cardiac death. Current use of antipsychotics was associated with a 3-fold increase in risk of sudden cardiac death. The risk of sudden cardiac death was highest among those using butyrophenone antipsychotics, those with a defined daily dose equivalent of more than 0.5 and short-term (≤90 days) users. The association with current antipsychotic use was higher for witnessed cases (n=334) than for unwitnessed cases.

Conclusions: Current use of antipsychotics in a general population is associated with an increased risk of sudden cardiac death, even at a low dose and for indications other than schizophrenia. Risk of sudden cardiac death was highest among recent users but remained elevated during long-term use.

Arch Intern Med. 2004;164:1293-1297

I N DEVELOPED COUNTRIES, SUDden cardiac death is one of the major causes of cardiovascular mortality. According to the most recent definition, sudden cardiac death is a natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously with no evidence of a noncardiac cause.[1,2] Since the early 1960s, sudden cardiac death has been reported with antipsychotic use in case reports.[3-5] Although the precise mechanism remains uncertain, several have been suggested including peripheral vasodilatation leading to cardiovascular collapse, oral laryngeal-pharyngeal dystonia, acute myocarditis, and cardiomyopathy.[6] Particular attention has been paid to the ability of antipsychotics to prolong the corrected QT (QTc) interval, which may result in torsades de pointes and other cardiac arrhythmias.[6-8] Only a few epidemiological studies have addressed the issue of sudden cardiac death and antipsychotic use, finding an increased risk of sudden cardiac death with the use of antipsychotics, varying from 1.7 (rate ratio) to 5.3 (odds ratio).[8-10] These studies, however, were either small and performed in hospitalized psychiatric patients or were performed in administrative databases with little information on potential confounders. Moreover, because of the inability to validate the diagnosis of sudden cardiac death in medical records, most of these studies may have misclassified the outcome.

We performed a case-control study on the association between the use of antipsychotics and sudden cardiac death in a well-defined community-dwelling population with complete coverage of all relevant health care information.

Author affiliations are listed at the end of this article.

METHODS

SETTING

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database, containing data from computer-based medical patient records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP has a pivotal role by acting as a gatekeeper for all medical care. Details of the database have been described elsewhere.[11,12] Briefly, the database contains the complete medical records on approximately 500 000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care[13] and free text) from GPs and specialists, referrals, laboratory findings, hospitalizations, and drug prescriptions, including their indications and dose regimen. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research in several validation studies that evaluated the quality of the available information.[11] The Scientific and Ethical Advisory Board of the IPCI project approved this study.

SOURCE POPULATION

The source population comprised all subjects 18 years and older, who were registered with a GP participating in the IPCI project for at least 1 year. Subjects with a diagnosis of cancer were excluded from the source population, since in these patients the cause of death is often difficult to assess. The study period started on January 1, 1995, and ended on April 1, 2001. All subjects were followed up until death, transferral out of practice, date of last data collection, or end of the study period, whichever came first.

CASE AND CONTROL DEFINITION

The computerized medical and demographic data were screened for deaths that occurred during the study period. The medical records of identified cases of death were reviewed manually to assess whether death could be classified as sudden cardiac death. Validation was performed independently by 2 physicians blinded to exposure (S.M.J.M.S. and G.S.B.), and in case of discrepancy, a third expert (B.H.C.S.) arbitrated. Assessment was based on the most recent definition of sudden cardiac death.[1,2] Cases were classified as (probable) sudden cardiac death if the medical record indicated that death occurred within 1 hour after the onset of acute symptoms and if the following wording was found in the free text: "sudden cardiac death," "acute cardiac death," "mors subita," "sudden death," "died suddenly," "died unexpectedly," or if this was an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously and with no evidence of a noncardiac cause (eg, pneumonia, convulsion, choking, or stroke). Suicides were excluded. For each case of sudden cardiac death, up to 10 controls were randomly drawn from the source population matched for age (year of birth), sex, and practice. The index date was defined as the date on which sudden cardiac death occurred. This date was also the index date for matched controls.

EXPOSURE DEFINITION

To assess the use of antipsychotics at the index date, we calculated the duration of use for each antipsychotic as the total number of units (capsules/tablets) per prescription divided by the prescribed daily number of these units. Exposure at the index date was categorized into 3 mutually exclusive groups of current use, past use, and nonuse. Use of antipsychotics was defined as current if the index date fell within a period of use or within a maximum of 30 days after the end of the last prescription (to account for carryover effects). Past use was defined as discontinuation of an antipsychotic more than 30 days before the index date. If patients had no prescription for an antipsychotic prior to the index date, they were considered nonexposed. Among current users we evaluated the effect of duration (≤90 days and >90 days continuous use), type of antipsychotic (phenothiazines, butyrophenones, thioxanthenes, lithium, and other), indication for the antipsychotic prescription, and the daily dose in defined daily dose equivalents (DDD), as defined by the World Health Organization.[14] One DDD equivalent represents the recommended daily dose for an adult for the indication schizophrenia. To evaluate dose-response effects, the daily dose of antipsychotics was categorized into less than or equal to 0.5 DDD and more than 0.5 DDD.

COVARIATES AND RISK FACTORS

Known risk factors and other covariates for sudden cardiac death were gathered from the medical records through computerized searches and manual assessment. The covariates that were evaluated included cerebrovascular and cardiovascular ischemia (history of myocardial infarction, stroke, and angina pectoris), heart failure, hypertension, diabetes mellitus, arrhythmia, hypercholesterolemia, smoking, and alcohol abuse. Ischemia and heart failure were assessed based on the diagnoses provided by the GPs and specialists in the medical records. Hypertension was identified through the diagnoses in the medical records, the use of antihypertensive medication, and/or the assessment of blood pressure measurements according to the guidelines of the World Health Organization (a blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic).[15] Diabetes mellitus, arrhythmias, and hypercholesterolemia were identified through diagnoses from GPs and specialists in the medical records and/or the use of antidiabetic, antiarrhythmic, or lipid-lowering medication. Information on smoking and alcohol abuse was obtained from the medical records. We considered antidepressants, anxiolytics, hypnotics, and cardiovascular and known QTc-prolonging drugs as concomitant medication. Current use of these drugs was defined as use at the index date. The indication for the use of antipsychotics, classified according to the DSM-IV,[16] was obtained from the prescription records. We evaluated the effect of social economic status by including a variable on health care insurance, which is a proxy for income (those with an income <$25 000 a year, approximately, have sick fund insurance and those with an income >$25 000 a year have private insurance).

STATISTICAL ANALYSIS

The relative risk for sudden cardiac death associated with antipsychotics was estimated by calculation of the odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression analyses. Covariates that were univariately associated with sudden cardiac death ($P<.1$) were initially included in the regression analyses. Factors that changed the point estimate of the association between antipsychotic drug use and sudden cardiac death by more than 10%[17] were kept in the final model (diabetes mellitus, arrhythmias, hypertension, cerebrovascular and cardiovascular ischemia, use of diuretics, use of angiotensin-converting enzyme inhibitors, and use of anxiolytic or hypnotic medication). In addition, smoking and alcohol abuse were included in the model because these are known risk factors for sudden cardiac death. We investigated poten-

tial effect modification by age and sex and performed subanalyses to evaluate potential misclassification of sudden cardiac death by splitting the outcomes between witnessed and unwitnessed death. To evaluate a possible dose-effect relation, a trend test was performed. Furthermore, we evaluated potential confounding by indication by providing risk estimates for current antipsychotic use in patients with the indication schizophrenia and with current antipsychotic use for other indications.

RESULTS

In the source population (n=250000), 582 cases of sudden cardiac death were identified, representing an incidence rate of sudden cardiac death of almost 1 per 1000 person-years per year in the source population. No controls could be matched for 28 cases, and these cases were excluded from further analyses. Hence, the study population comprised 554 cases of sudden cardiac death and 4463 matched controls (approximate case-control ratio 1:8). There were 334 witnessed (60.3%) and 220 unwitnessed (39.7%) cases of sudden cardiac death. The median age of the study population was 71 years, and approximately 60% were male. Despite matching for year of birth, the median age of cases was higher than the median age of controls (74 years and 71 years, respectively), since more controls were available for younger cases than for elderly cases (**Table 1**). Autopsy had been performed in only 7 cases, but these were all compatible with a cardiac origin of sudden death. All known potential risk factors for sudden cardiac death were associated with an increased risk, notably ischemic cerebrovascular and cardiovascular disease, hypertension, arrhythmia, diabetes mellitus, heart failure, hypercholesterolemia, smoking, and alcohol abuse (Table 1). As expected, use of cardiovascular medication was associated with sudden cardiac death as well. There was no association between socioeconomic status and sudden cardiac death.

Current use of antipsychotics was associated with a 3-fold increased risk of sudden cardiac death (adjusted OR, 3.3; 95% CI, 1.8-6.2). Past use of antipsychotics was not associated with an increased risk of sudden cardiac death (**Table 2**). The risk of sudden cardiac death was highest among individuals using butyrophenone antipsychotics, predominantly pipamperone and haloperidol. Furthermore, the risk was highest among users of a DDD higher than 0.5 and among short-term (≤90 days) users. The risk of sudden cardiac death increased significantly with higher doses (P<.001). The risk of sudden cardiac death was also significantly increased in persons who used antipsychotics at a daily dose ≤0.5 DDD or continuously for more than 90 days. Most current users did not receive antipsychotics for schizophrenia. Twelve patients (5 cases and 7 controls) met the criteria for diagnoses of schizophrenia or schizoaffective disorders, whereas 44 patients (14 cases and 30 controls) received antipsychotics for other psychiatric diseases such as organic psychosis, dementia, stress, anxiety, or bipolar depression. The risk of sudden cardiac death in current users not meeting the criteria for the diagnosis of schizophrenia or schizoaffective disorders was significantly higher than in nonusers (OR, 3.3; 95% CI, 1.6-

Table 1. Demographics, Distribution of Covariates, and Use of Concomitant Medication in Cases and Controls

Characteristic	Cases, No. (%) (n = 554)	Controls, No. (%) (n = 4463)	Odds Ratio* (95% CI)
Sex, male	326 (59)	2657 (60)	
Age, yt			
≤55	67 (12.1)	736 (16.4)	
56-65	77 (13.9)	792 (17.7)	
66-75	175 (31.6)	1551 (34.8)	
>75	235 (42.4)	1390 (31.1)	
Sudden cardiac death, witnessed	334 (60.3)		
Comorbidities			
Ischemic cerebrovascular/ cardiovascular disease	203 (37)	780 (17)	2.6 (2.1-3.2)
Hypertension	359 (65)	2562 (57)	1.3 (1.0-1.6)
Arrhythmia	114 (21)	469 (11)	2.1 (2.1-3.2)
Diabetes mellitus	182 (33)	871 (20)	2.0 (1.6-2.5)
Smoking	92 (17)	469 (11)	2.2 (1.6-2.9)
Alcohol abuse	32 (6)	137 (3)	2.1 (1.4-3.3)
Heart failure	141 (25)	283 (6)	5.0 (3.9-6.4)
Hypercholesterolemia	47 (8)	266 (6)	1.7 (1.2-2.4)
Concomitant cardiovascular drugs			
β-Blocking agents	71 (13)	491 (11)	1.2 (0.9-1.6)
Diuretics	135 (24)	484 (11)	2.4 (1.9-3.1)
Ca-blocking agents	63 (11)	295 (7)	1.7 (1.3-2.3)
ACE inhibitors	100 (18)	378 (8)	2.4 (1.8-3.0)
ATII-blocking agents	19 (3)	66 (2)	2.5 (1.5-4.3)
Lipid-lowering agents	31 (6)	206 (5)	1.4 (1.0-2.1)
Cardiac glycosides	56 (10)	125 (3)	3.4 (2.4-4.9)
Antiarrhythmics	7 (1)	32 (1)	1.6 (0.7-3.9)

Abbreviations: ACE, angiotensin-converting enzyme; ATII, angiotensin II receptor antagonist; Ca, calcium; CI, confidence interval.
*All odds ratios are matched for age, sex, practice, and calendar time.
†The median age for cases was 74 years and for controls, 71 years.

6.6) and was not significantly different from those with the diagnosis schizophrenia (OR, 3.4; 95% CI, 0.9-12.8).

For witnessed cases of death, the association with current antipsychotic use was higher (OR, 4.7; 95% CI, 2.0-10.8) than for unwitnessed cases (OR, 2.4; 95% CI, 0.9-6.3). Stratified analyses showed that the risk of sudden cardiac death in users of antipsychotics tended to be higher in men (OR, 4.9; 95% CI, 1.7-13.0) than in women (OR, 2.9; 95% CI, 1.3-6.4) and higher in patients 65 years or younger (OR, 5.5; 95% CI, 1.0-31.1) than in patients older than 65 years (OR, 3.1; 95% CI, 1.6-6.1). None of these interactions, however, were statistically significant.

COMMENT

The results of our study indicate that current use of antipsychotics in a community-dwelling population is associated with an increased risk of sudden cardiac death, even at a low dose and in persons who use antipsychotics for indications other than schizophrenia. After adjustment for known confounding factors, current use of antipsychotics was associated with a more than tripled risk of sudden cardiac death. The risk was highest among users of butyrophenone antipsychotics but not significantly different from the other antipsychotics, possibly due to low numbers. Unlike some other studies, we did

Table 2. Risk of Sudden Cardiac Death and the Use of Antipsychotic Medication

Use of Antipsychotic Medication	Cases (n = 554)	Controls (n = 4463)	OR* (95% CI)	OR† (95% CI)
Nonuse	520	4352	1.0 (Reference)	1.0 (Reference)
Past use	15	74	1.4 (0.8-2.4)	1.1 (0.6-2.0)
Current use	19	37	3.7 (2.0-6.7)	3.3 (1.8-6.2)
Type of antipsychotic used‡§				
Nonuse	520	4352	1.0 (Reference)	1.0 (Reference)
Butyrophenones	12	13	6.1 (2.6-14.1)	7.3 (2.8-18.8)
Thioxanthenes	1	3	3.4 (0.5-32.6)	2.9 (0.3-32.9)
Other antipsychotics	2	7	2.6 (0.5-13.1)	1.9 (0.3-11.8)
Lithium	3	9	2.4 (0.6-9.3)	1.5 (0.3-8.3)
Phenothiazines	3	12	1.7 (0.4-7.7)	0.8 (0.2-3.8)
Daily dose				
Nonuse	520	4352	1.0 (Reference)	1.0 (Reference)
≤0.5 DDD	14	33	3.0 (1.6-5.8)	2.8 (1.4-5.6)
>0.5 DDD‖	5	4	8.8 (2.2-34.4)	9.8 (2.1-44.6)
Duration of use				
Nonuse	520	4352	1.0 (Reference)	1.0 (Reference)
≤90 d	10	15	4.4 (1.9-10.3)	5.0 (2.1-12.1)
>90 d	9	22	3.2 (1.4-7.1)	2.5 (1.1-6.0)

Abbreviations: CI, confidence interval; DDD, defined daily dose equivalent; OR, odds ratio.
*Odds ratios are matched for age, sex, practice, and calendar time.
†Odds ratios are matched for age, sex, practice, and calendar time, adjusted for (1) diabetes mellitus and arrhythmias; (2) use of diuretics, angiotensin-converting enzyme inhibitors, anxiolytics, or hypnotics; and (3) hypertension, smoking, alcohol abuse, and cerebrovascular/cardiovascular ischemia.
‡Antipsychotics included butyrophenones (haloperidol, pipamperone, bromperidol, and benperidol); phenothiazines (chlorpromazine, levomepromazine, triflupromazine, perphenazine, prochlorperazine, trifluoperazine, perazine, thioridazine, and periciazine); thioxanthenes (flupentixol and zuclopenthixol); and other (pimozide, clozapine, olanzapine, and risperidone).
§Since some patients used more than 1 antipsychotic, numbers do not add up.
‖Test for trend, P<.001.

not find an association with thioridazine, but this drug was hardly used in our study population.[9,10] The risk of sudden cardiac death was slightly but not significantly lower after prolonged use of antipsychotics, which might be the result of depletion of susceptibles.

A consistent finding in studies on the association between antipsychotic use and sudden cardiac death is that there seems to be a positive dose-response relationship.[6-10] A potential mechanism by which antipsychotic agents might induce sudden cardiac death relates to their capacity to prolong the QTc interval, which seems to be dose related.[18] However, the exact role of QTc prolongation in torsades de pointes, ventricular arrhythmias, and sudden cardiac death has not been resolved.[6,18-20] Antipsychotics seem to share the ability to antagonize the rapid component of the delayed rectifier potassium current, which leads to a variable lengthening of the action potential. Prolongation of QT is only a surrogate marker of cardiotoxicity, and there is no consensus on the degree of QT prolongation that becomes clinically relevant. In our study, low doses of antipsychotics were also associated with a significantly increased risk of sudden cardiac death. In the Tennessee Medicaid cohort study, the risk of sudden cardiac death was greater in women and in those 65 years or older.[8] In contrast, we found that the risk of sudden cardiac death tended to be higher in men and in those 65 years or younger. The fact that in our study elderly women predominantly used a low dose (≤0.5 DDD), while younger men mostly used a high dose, might explain this finding.

Our findings are consistent with earlier studies in which a higher rate of sudden cardiac death was found in patients taking antipsychotic drugs.[8-10] In 2 retrospective cohort studies among schizophrenic patients, the use of antipsychotics was associated with a significantly increased risk of sudden cardiac death. Reilly et al[9] found that thioridazine use was associated with a 5-fold increased risk of sudden cardiac death in psychiatric inpatients. Most of these studies, however, had limitations. First, patient populations in these studies included only cases with schizophrenia, either hospitalized[9] or in an outpatient setting.[8,10] Therefore, it was impossible to determine whether findings were due to the disease (confounding by indication) or to the antipsychotic drugs taken. Second, 2 studies used data from Medicaid programs. These data pertain to a skewed population of people from lower socioeconomic classes with a high cardiovascular risk profile, and these Medicaid databases have little or no information on important potential confounders. Third, for exposure assessment these studies used a fixed length of 30 days for a prescription since the exact dosing regimen was unknown. This may have caused exposure misclassification because under real-life circumstances dose variation will lead to different prescription lengths and consequently to varying exposure windows.[21] Finally, the outcome often cannot be assessed validly in such databases, since death and the reason for death are poorly registered and have to be proxied by assuming that not returning for health care consumptions means that the patient died.[10]

In our population, we were able to take advantage of the fact that in the Dutch health care system all medical information (including specialist and hospital care) is collected at practices that cover the general popula-

tion instead of selected socioeconomic groups. As a consequence, there was extensive information available on drug use, potential confounders, and the circumstances surrounding death. Moreover, data allowed for subanalysis of different indications, which confirmed that sudden cardiac death is associated with antipsychotic use rather than with schizophrenia itself.

Nevertheless, our study also has some limitations. First, we cannot exclude that some misclassification of outcome occurred. We may have missed some deaths, although this is minimal, since death is consistently registered by GPs. In contrast to other studies,[8,10] we could reduce misclassification by differentiating witnessed and unwitnessed cases. The percentage of unwitnessed deaths in our population was 39.2%, which is in line with earlier findings.[20,22] The risk of witnessed sudden cardiac death alone was more than quadrupled in current antipsychotic users, while the risk in the unwitnessed cases was lower. This is consistent with the fact that misclassification will occur more often in unwitnessed cases. In the latter group, some deaths might have been of noncardiac origin, and this could explain the lower risk estimates. Second, not all acute deaths may have been of cardiac origin. We had pathological autopsy information only for 7 cases, in which the cause of death was cardiac. Third, misclassification of exposure may have occurred since we used outpatient prescription data and had no information whether the prescription was actually filled and taken. It is likely, however, that such exposure misclassification will be random and evenly distributed among cases and controls. Therefore, the reported estimate is probably a conservative one. Fourth, the number of exposed cases in our study unfortunately prohibited us from comparing individual antipsychotic agents.

In conclusion, the results of our study indicate that current use of antipsychotics in a general population is associated with an increased risk of sudden cardiac death, even at a low dose and in persons who use antipsychotics for indications other than schizophrenia. The risk of sudden cardiac death seems to be highest among recent users but remained elevated during long-term use.

Corresponding author and reprints: Bruno H. C. Stricker, PhD, Pharmaco-epidemiology Unit, Department of Epidemiology & Biostatistics and Internal Medicine, Erasmus MC, PO Box 1738, 3000 DR Rotterdam, the Netherlands (e-mail: b.stricker@erasmusmc.nl).

REFERENCES

1. Myerburg RJ. Cardiac arrest and sudden cardiac death. In: Braunwald E, ed. *Heart Disease, A Text Book of Cardiovascular Medicine.* New York, NY: WB Saunders Publishing Co; 1997:742-779.
2. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J.* 2001;22:1374-450.
3. Granger ME. Phenothiazines and sudden death. *JAMA.* 1965;194:678-679.
4. Witton K. Phenothiazines and sudden death. *JAMA.* 1965;194:679.
5. Huston JR, Bell GE. The effect of thioridazine hydrochloride and chlorpromazine on the electrocardiogram. *JAMA.* 1966;198:134-138.
6. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs.* 2002;62:1649-1671.
7. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet.* 2000;355:1048-1052.
8. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry.* 2001;58:1161-1167.
9. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry.* 2002;180:515-522.
10. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ.* 2002;325:1070.
11. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med.* 1999;38:339-344.
12. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in the Netherlands. *Ann Intern Med.* 1993;119:1036-1041.
13. Lamberts H, Wood M, Hofmans-Okkes IM. International primary care classifications: the effect of fifteen years of evolution. *Fam Pract.* 1992;9:330-339.
14. *ATC Index With DDDs.* Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology; 2002.
15. 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension: Guidelines Subcommittee. *J Hypertens.* 1999;17:151-183.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association; 1994.
17. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health.* 1989;79:340-349.
18. De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of torsades de pointes with non-antiarrhythmic drugs: a call for consensus. *Eur J Clin Pharmacol.* 2001;57:185-209.
19. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry.* 2001;158:1774-1782.
20. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med.* 2001;345:1473-1482.
21. van Staa TP, Abenhaim L, Leufkens H. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. *J Clin Epidemiol.* 1994;47:183-189.
22. de Vreede-Swagemakers JJ, Gorgels AP, Weijenberg MP, et al. Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease. *J Clin Epidemiol.* 1999;52:601-607.