Eur J Clin Pharmacol (2007) 63:1069–1074
DOI 10.1007/s00228-007-0349-6

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

High concordance between self-reported medication and official prescription database information

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Received: 8 February 2007 / Accepted: 6 July 2007 / Published online: 22 August 2007

Abstract
Objective We set out to compare the agreement between self-reported psychotropic medication use and information obtained from the administrative prescription database of the Social Insurance Institution of Finland. We compared the point prevalence of psychotropic medication use, and self-reported vs. register-based information on antipsychotic medication dosage.
Methods The study population consisted of 905 participants from a population-based genetic study of schizophrenia, of whom 366 had schizophrenia spectrum disorder, 56 had bipolar spectrum disorder, and 483 were unaffected family members. Current medication use was obtained by interview and from the prescription reimbursement database. Agreement between data sources was compared using Cohen's kappa statistic and correlation coefficients.
Results The agreement between the two sources was generally good. Kappa values were best for lithium use (0.96; $p<0.0001$), followed by antipsychotics (0.87; $p<0.0001$) and antidepressants (0.77; $p<0.0001$). Agreement was lowest for benzodiazepines (0.42; $p<0.0001$). Correlation between antipsychotic medication dose estimates was 0.79 (95% CI 0.76–0.81).
Conclusion The concordance between self-reported psychotropic medication use and information obtained from an official prescription database was good for most psychotropic drugs. More studies are needed to replicate results with other forms of medication and patient groups.

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Introduction

Pharmacoepidemiology is the study of medication use and medication effects in populations. Pharmacoepidemiological studies often utilize data from official administrative individual-level prescription databases [1, 2, 11, 13, 14]. Because register-based observational studies are usually the only feasible study type in post-marketing surveillance, the validity of register data is very important when the quality of studies is being considered. Whether the focus of the study is drug use or drug effect, the quality of the findings is entirely dependent on the quality of the original data.

Individual-level prescription databases provide information on how each drug is utilized. However, even determining the point prevalence of the use of a drug from prescription data can be difficult [1]. For the determination of prevalence, a number of assumptions must be made, and the effects of assumptions are not usually carefully evaluated. One of the most important assumptions is that after purchase the drugs are utilized as prescribed. Usually, dose is assumed to be one international standard daily defined dose per day. Most methods entail assigning a period of usage to each prescription record [8]. The point prevalence on a given day is then estimated from the number of persons who have a prescription whose period of usage crosses this date. Usually, noncompliance or irregular patterns of periods on and off cannot be taken into account. To improve the quality of register-based pharmacoepidemiological studies, possible sources of bias and other factors that could distort information obtained from administrative registers should be carefully studied. One way to scrutinize such biases is to compare register-based data with data obtained from self-reports, or from plasma concentrations of medications.

When the utilization of medicines is estimated on the basis of an administrative register, there are several sources

of uncertainty. If the data are based on reimbursement, it is possible that low-price medicines have not been registered. This is the case in Finland, where reimbursement is paid only if the total purchase price exceeds a certain sum (8.41 Euros in 2002). This means that some older, generic medicines could be under-represented in reimbursement databases. On the other hand, individuals with severe chronic diseases are entitled to fully reimbursed medication for that disorder; thus, all their purchases will be registered. Because purchasing a drug does not guarantee that it will be taken, uncertainty always remains about the real exposure in register-based studies. Information about current drug use can be obtained by interviewing patients, or by using questionnaires. Comparing these two sources of information—register and self-reported utilization—could shed light on the validity of register-based data.

Only a few studies have compared the validity of self-reported medication use with prescription reimbursement data. In a Danish study of hormone replacement therapy carried out in 1999, both the sensitivity and specificity were high, being 74.8% and 98.0% respectively [7]. It was also observed that validity was not strongly associated with background factors such as age, alcohol intake, and smoking.

Information on all reimbursed medication prescriptions purchased from a pharmacy are registered by the Social Insurance Institution of Finland. The National Prescription Register covers all persons residing permanently in the country. This database has been used in pharmacoepidemiological studies, but no validation of register data against self-reported data has been carried out. The aim of our study was to compare the agreement between self-reported medicine utilization and information obtained from the administrative prescription database of the Social Insurance Institution of Finland. The point prevalence of psychotropic medication use and the dosage of antipsychotic drugs were the main focus of comparison.

Material and methods

Study population

Our study sample consisted of persons with schizophrenia and their siblings and parents who had participated in a genetic study. The study sample was formed as follows: from a cohort of all people born in Finland from 1940 to 1976 inclusive, we identified individuals with a diagnosis of schizophrenia using data derived from three nationwide computerized health care registers (the Hospital Discharge Register, the Medication Reimbursement Register, and the Pension Register) for 1969 to 1998 inclusive. Using the personal identification numbers of the affected individuals, we identified their first-degree relatives from the Population Register. Information from the health care registers was then requested for the relatives.

Two samples of families with at least one member with schizophrenia were invited to participate in a genetic study. The first sample consisted of families with at least two siblings with schizophrenia and their first-degree relatives from the whole of Finland (AF). The second sample comprised patients and their relatives from families with at least one member with schizophrenia from an isolated region in the northern part of the country (IS). The detailed construction of the study population is described elsewhere [3, 15]. In both samples, each affected individual was contacted only after permission had been received from the treating physician most familiar with the patient in order to begin the informed consent process. The study protocol was accepted by the Ethics Committee of the National Public Health Institute, and the study was approved by the Ministry of Social Affairs and Health. Only after the affected individual had given their written informed consent were the remaining family members contacted. Altogether, 905 persons participated in the clinical assessment, which consisted of the Structured Clinical Interview for DSM-IV (SCID) and neuropsychological testing. Three hundred and sixty-six individuals had schizophrenia spectrum disorder, 56 bipolar spectrum disorder, and 483 had no psychotic or bipolar disorder. Some members of the study population were living in nursing homes or within assisted living programs.

Information about medication

Information on medication was obtained from two sources. Current medication use was asked about in the interview, and to facilitate this, participants were requested to bring their prescriptions with them to the interview. Those individuals with schizophrenia living in supported housing or in institutions may also have had information on medication provided by the staff. Another source of medication information was the Finnish National Prescription Register of the National Social Insurance Institution (SII).

In Finland, the National Health Insurance is managed by SII, which also grants medication reimbursements. All official residents of Finland are entitled to medication reimbursement. Reimbursements of pharmaceuticals are based on the severity and duration of illness. Medications for severe conditions such as cancer, type 1 diabetes, and psychotic and bipolar I disorders are fully reimbursed. Medications for some other chronic conditions such as hypertension are 75% reimbursed. For all other physician-prescribed medications costing over 8.41 Euros (in 2002), the reimbursement is 50%. The Finnish National Prescription Register has been operating since 1996. It covers all pharmacies in Finland, and registers all drug purchases for which the SII has paid any

Table 1 Chlorpromazine equivalents of some antipsychotic drugs. *ATC* anatomic therapeutic chemical, *DDD* daily defined dose

ATC	Medication	DDD (mg)	Chlorpromazine equivalents (mg)
N05AA01	Chlorpromazine	300	100
N05AA02	Levomepromazine	300	100
N05AA03	Promazine	100	100
N05AB02	Fluphenazine	10	2
N05AB03	Perphenazine	30	10
N05AB04	Prochlorperazine	100	15
N05AC01	Periciazine	50	20
N05AC02	Thioridazine	300	100
N05AD01	Haloperidol	8	2
N05AD03	Melperone	300	100
N05AE02	Molindone	50	10
N05AE03	Sertindole	16	3
N05AF01	Flupentixol	6	2
N05AF03	Chlorprothixene	300	100
N05AF05	Zuclopenthixol	30	20
N05AH02	Clozapine	300	50
N05AH03	Olanzapine	10	3
N05AH04	Quetiapine	400	100
N05AL01	Sulpiride	800	250
N05AX08	Risperidone	5	1
N05AX12	Aripiprazole	15	3

reimbursement. For convenience, "medication use" refers to medication purchased from a pharmacy, although of course not all patients who have purchased medication actually take the medication as instructed. The available data contained information on the date of purchase and the dose, stated as the international standard daily defined dose (DDD). The medication was classified according to the Anatomic Therapeutic Chemical (ATC) classification system [12,16]. Prescription data were obtained for the period 1 January 1996 to 31 December 2005 inclusive.

Data analysis

From the register data we estimated the current medication on the interview date by using two methods: by accounting for all prescriptions made for the person less than half a year (180 days) before the interview, and by assuming that each medication period started on the purchase date and extended to 15 days after the imputed end of the prescription, based on the DDD multiplied by 1.1.

We estimated the individual daily dose based on the prescription register data using the following schema:

1. Individuals' medication periods ("in medication") were defined according to Mantel-Teeuwisse et al.'s method 4 [8]. We multiplied DDD by a factor of 1.1 and filled 15-day gaps between medication periods
2 The dose for each individual was estimated by dividing the sum of DDD from the whole follow-up period (10 years) for each medication, with the sum of days "in medication" defined as above

Table 2 Categories of drugs. ATC and name, mean amount (in DDD) purchased at a time, mean price of one DDD, and estimated mean price of purchase per time. Prices adjusted to 2005 levels [9]

Group	ATC (name)	Mean amount purchased in DDDs (SD)	Mean price per DDD (euro)	Mean price of purchase per time (euro)
Typical antipsychotics	N05AA01 (Chlorpromazine), N05AA02 (Levomepromazine), N05AB02 (Fluphenazine), N05AB03 (Perphenazine), N05AC02 (Thioridazine), N05AF01 (Flupentixol), N05AF03 (Chlorprothixene) , N05AD01 (Haloperidol), N05AD03 (Melperone), N05AF05 (Zuclopenthixol), N05AL01 (Sulpiride)	68 (63)	0.80	54.37
Atypical antipsychotics	N05AE03 (Sertindole), N05AH02 (Clozapine), N05AH03 (Olanzapine), N05AH04 (Quetiapine), N05AX08 (Risperidone), N05AX12 (Aripiprazole)	56 (44)	5.88	331.64
Antidepressive medication	Starting with N06A	75 (55)	1.17	87.45
Lithium	N05AN01	99 (43)	0.20	19.76
Benzodiazepines	Starting with N05BA	68 (54)	0.22	14.87
Mood stabilizers	N03AF01 (Carbamazepine), N03AF02 (Oxcarbazepine), N03AX09 (Lamotrigine), N03AX11 (Topiramate), N05AN01 (Lithium)	82 (46)	2.90	236.40
Biperiden	N04AA02	27 (15)	0.43	11.80
Other	N02AE01 (Buprenorphine), N05AB01 (Dixyrazine), N05BB01 (Hydroxyzine), N05BE01 (Buspirone), N06BA04 (Methylphenidate), N07BB01 (Disulfiram), N07BB04 (Naltrexone)	47 (37)	1.18	55.33

Table 3 Concordance between medication use reported by participants (columns), and data obtained from the prescription register. Medication purchased up to 6 months before the interview is taken into account

	Typical antipsychotics		Atypical antipsychotics		Antidepressive medication		Lithium		Benzodiazepines		Mood stabilizers		Biperiden		Other	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
No	606	12	767	7	760	21	876	1	688	13	842	4	835	10	890	5
Yes	37	250	19	112	28	96	1	27	132	72	21	38	18	42	8	2

In order to compare the utilization of antipsychotic drugs we converted the interview date doses into chlorpromazine equivalents. Table 1 contains information on the DDD and chlorpromazine equivalents used in the study for oral antipsychotic medications. The conversion was performed according to the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations [6]. For antipsychotics not mentioned in the PORT recommendations, we used the recommendations in the Finnish Psychiatric Association guidelines [4, 6] or, for some rarely used antipsychotics, conversion instructions obtained from the pharmaceutical industry.

To aid the comparison, psychotropic drugs were categorized into eight categories (Table 2), and comparison between self-reported and register-based information on medication use was carried out using Cohen's kappa statistic. Comparisons between estimated chlorpromazine equivalents were made using Pearson's correlation coefficient. The mean amount purchased at a time was calculated from prescription data, and approximate mean costs of purchases were estimated using data from 2005 [9]. The costs were calculated from the total price, without considering possible reimbursements.

Results

The amount purchased at a time was highest for lithium (99 DDD). Antipsychotics and benzodiazepines were purchased for about 2 months at a time. Benzodiazepines and lithium had the lowest mean price per purchase, 15 and 20 Euros, respectively. Atypical antipsychotics clearly had the highest cost per purchase, about 332 Euros.

The agreement between self-reported medication and medication data obtained from the prescription register was in general satisfactory (Tables 3, 4). The agreement was best for lithium and antipsychotic medication, and poorest for benzodiazepine use. Taking into account all prescriptions 6 months before interview slightly increased the agreement compared with defining the medication period using purchased DDD. We also calculated kappa statistics separately for diagnostic groups (schizophrenia vs. bipolar spectrum disorders vs. neither; data not shown). This analysis produced similar results to those of the pooled analysis, the only noticeable difference being the low kappa (0.17) for benzodiazepine use in the bipolar spectrum group.

The correlation between chlorpromazine equivalents from self-reported and register data was 0.79 (95% CI 0.76–0.81; Fig. 1). The mean for self-reported antipsychotic dosage, converted into chlorpromazine equivalents, was 191.1 mg (SD 395.3), while the respective value using register data was 202.7 mg (SD 273.9).

Discussion

We compared the reliability of register-based versus self-reported psychotropic medication use in a study sample that

Table 4 Comparison between self-reported medication and data obtained from the prescription register. Register data were used two different ways: medication purchased 6 months before the visit/interview taken into account, or medication period calculated assuming purchased DDD+10%+15d

	DDD + 10% + 15d			Six months before		
	Cohen's k	Z	*p*	Cohen's k	Z	*p*
Typical antipsychotics	0.6949	16.8809	<0.0001	0.8720	22.4613	<0.0001
Atypical antipsychotics	0.8604	14.1279	<0.0001	0.8794	14.7918	<0.0001
Antidepressive medication	0.7294	11.5324	<0.0001	0.7655	12.6166	<0.0001
Lithium	0.9631	7.3179	<0.0001	0.9631	7.3179	<0.000
Benzodiazepines	0.3728	6.7206	<0.0001	0.4216	7.8498	<0.0001
Mood stabilizers	0.7010	7.0212	<0.0001	0.7383	7.6296	<0.0001
Biperiden	0.5890	5.7104	<0.0001	0.7336	7.9998	<0.0001
Other	0.1269	0.4938	0.3107	0.2283	0.9457	0.1721

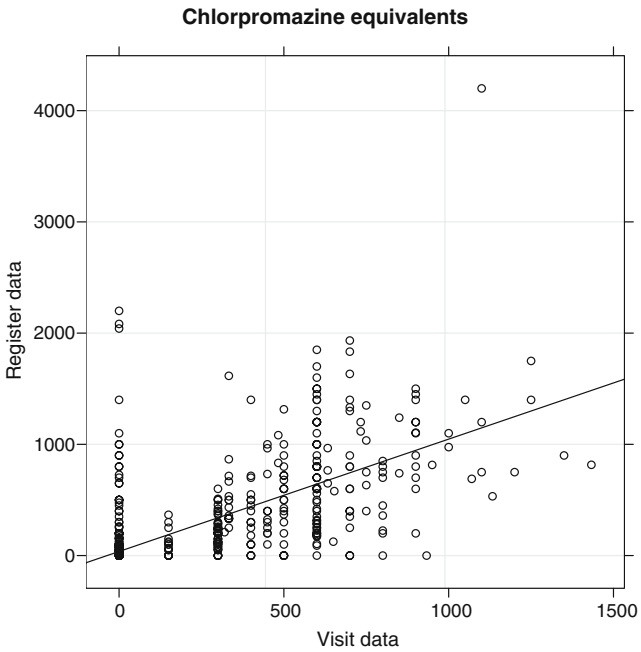

Fig. 1 Comparison of chlorpromazine equivalents from self-reported and register-based data with linear regression line

consisted of persons with schizophrenia or other psychotic disorder and their family members. We found that the agreement between the register of reimbursed prescriptions medication and data obtained by interview was generally good. In particular, current lithium and other antipsychotic exposure were reported similarly by both sources. Different definitions of register-based exposure did not materially change the result. Antidepressive medication and mood stabilizers also gave very concordant results. One reason for high concordance might be that participants were requested to bring their prescriptions with them to the interview.

The agreement in the utilization of benzodiazepines was lowest, Cohen's kappa being only about 0.4, and the kappa value for biperiden use was also modest. There may be several reasons for this. Antipsychotics, mood stabilizers, and antidepressants are fully reimbursed for persons with a psychotic disorder, while benzodiazepines are not. Benzodiazepines are often prescribed in small amounts, the cost of which is low and often below the minimum sum for drug reimbursement. Also, purchases that are not reimbursed are not registered. To prevent registration some people may also choose not to take the reimbursement. Therefore, information on the use of benzodiazepines in the register is less accurate than the information on other medication use. Although the price of lithium per DDD was low, the amount purchased at a time was the highest. This meant that the cost of a purchase usually exceeded the minimum reimbursement limit. On the other hand, lithium is dispensed free of charge if used as medication for chronic disease.

Our results are quite similar to those of the Danish study: the concordance between self-reported and reimbursement register-based data was good [7]. This is remarkable, considering the very different types of medications being investigated. Because of the medication reimbursement system, psychotropic medications that are fully reimbursed may be covered better by the prescription register. On the other hand, because of the possible stigma related to psychotropic medication use, some persons may choose not to take the reimbursement. It is important to demonstrate that information on psychotropic medication use in the National Prescription Register is accurate, since pharmacoepidemiologal studies are particularly common in psychiatric research. Prescription databases have been used to investigate medication effectiveness [13, 14], side effects [5] and the effect of drug use on mortality [10, 13]. For rare side effects pharmacoepidemiological studies may be the only method of revealing associations.

One limitation of our study is that some elderly participants were living in supported housing or institutions. However, persons living in all supported housing systems and also in some other institutions purchase their medications from pharmacies. This should not therefore have caused significant bias. The price information was inaccurate, because we had no data on the actual costs of purchases, but only an approximation based on country level mean prices. The register-based estimation of mean dose was based on the data for the whole follow-up period. This method gives a constant estimate of dose and does not capture time variations. One major limitation is that no measurements of serum levels of drugs were available. However, linking prescription data, self-reported usage, and serum level measurements would provide the most reliable information on the utilization of drugs.

To our knowledge, this is one of the first studies to evaluate the validity of register-based information on psychotropic drug utilization. Although several sources of uncertainty still remain, such as actual drug use after purchase, it can be concluded that register-based information is at least a satisfactory source for estimating the use of psychotropic drugs. Generalization of results to include other forms of medication or other patient groups is an open question. More studies are needed to confirm the results with other forms of medication and other patient groups.

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