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ORIGINAL REPORT

Potential bias in pharmacoepidemiological studies due to the length of the drug free period: a study on antidepressant drug use in adults in the Netherlands†

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SUMMARY

Purpose The aim of this study was to evaluate the effect of the length of the drug free period on incidence measurements as well as on cohort characteristics in users of antidepressants.

Methods The study population consisted of patients aged 18 years or older who filled a prescription for an antidepressant drug in the Netherlands, between October 2001 and September 2002. One-year incidence of antidepressant drug use was estimated using drug free periods varying in length from 1 month to 9 years. In addition, we evaluated what effect the drug free period has on cohort characteristics by comparing a cohort of first time antidepressant drug users defined using a 9-year drug free period with cohorts using 6, 12 and 24 months drug free period.

Results When using a 6-month drug free period the measured incidence was about 32 per 1000 individuals (95%CI: 31.3, 32.6) while the measured incidence was 27.5 (95%CI: 26.9, 28.1), 23.5 (95%CI: 22.9, 24.0) and 17.2 (95%CI: 16.7, 17.7) per 1000 individuals when using a 12-month, 24 month respectively a 9-year drug free period. Furthermore, the prevalence of characteristics in inception cohort studies changes when using different drug free periods.

Conclusion Altering the drug free period from a short to a longer one results in decreased incidence. Furthermore, for inception cohorts where first time drug use is an inclusion criterion the drug free period can influence the prevalence of cohort characteristics and for short drug free periods give biased estimates. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — antidepressive agent; bias (epidemiology); cohort studies; databases; depression; incidence; methods; pharmacoepidemiology

INTRODUCTION

Depression is a common, chronic and recurrent mental illness affecting about 2–10% of the world population each year.[1–5] Due to the high prevalence and strong negative impact on functioning and well-being it is the fourth leading cause of disease burden in the world.[6] In the past decade, the incidence of depression has increased substantially and the use of antidepressants has risen even more pronounced.[7–10] The frequency of antidepressant drug use in large populations can nowadays quite easily be measured using prescription and insurance claims databases. Such databases are increasingly being used in pharmacoepidemiology and have shown to be strong research tools for providing information about the development of diseases, their treatment and outcomes in daily clinical practice, complementary to data retrieved from clinical trials.[11–16]

Studies into the incidence of drug use are useful for providing evidence about how many patients are starting drug treatment and what the characteristics of these patients are. For a valid measurement of the incidence of a specific drug exposure a certain 'drug

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free' period, that is a time period without use of the drug of interest, needs to be defined. Although incidence measurements are very commonly used in pharmacoepidemiological research, there is no consensus on the length of this drug free period. Drug free periods of 4 months,[17] 6 months,[1,18–20] 12 months,[5,9,21] 2 years[22] and up to 5 years[16,23–25] have been used in studies to measure first time use of an antidepressant drug. So far it is unclear what effect different lengths of the drug free period have on study results, thereby hampering comparison of estimates between populations.

In addition, the length of the drug free period could be of importance when designing inception cohort studies in which only incident drug users are to be included. Studies have shown that the risk of certain disease and treatment related outcomes differ for individuals experiencing their first depressive episode compared to recurrent users.[26–29] Therefore inclusion of recurrent cases, instead of incident cases, in an inception cohort might lead to biased risk estimates.

The aim of this study is to evaluate the effect of the length of the drug free period on incidence measurements as well as on cohort characteristics of antidepressant drug users.

METHODS

Prescription data were collected using the PHARMO record linkage system. This database has been described in detail elsewhere.[30] In brief, the PHARMO record linkage system includes pharmacy dispensing records from community pharmacies of all 950 000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1992 onwards. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are near complete with regard to prescription drugs.[31]

The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[32] Patient information per prescribed medicine includes gender and date of birth. Each patient is identified with an anonymous unique patient-identification code that allows for the observation of patient medication use in time. The database does not provide information concerning the indications for use of the medicines.

The source population included individuals, 18 years and older, registered in the PHARMO database for the entire period from 1992 until 2002 ($n = 268\,228$). The study population consisted of all patients from the source population who filled a prescription for an antidepressant drug in the Netherlands between October 2001 and September 2002 ($n = 21\,304$).

In the Netherlands, the following antidepressants were available and prescribed during the study period: tricyclic antidepressants (TCAs: amitriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, maprotiline, nortriptyline, trimipramine), selective serotonin reuptake inhibitors (SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and other (mianserin, mirtazapine, moclobemide, nefazodone, oxitriptan, phenelzine, trazodone, tranylcypromine, venlafaxine). Prescriptions of buproprion were excluded from our study, as in the Netherlands bupropion is not indicated for depression but for smoking cessation.

The 1-year incidence for antidepressant drug use in the Netherlands during October 2001 to September 2002 was determined using drug free periods of various lengths. The 1-year incidence was defined as the number of new users of an antidepressant drug per 1000 individuals, calculated with 95% confidence interval (95% CI).[33] The drug free period was defined as the time period, prior to the dispensing date of the first prescribed antidepressant drug during the study period, during which no antidepressant drug was received. The different drug free periods chosen for this study were 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 2 years, 3 years, 4 years, 5 years, 6 years and 9 years.

To evaluate what effect the drug free period has on inception cohort characteristics, we compared a cohort of first time antidepressant drug users identified using a 9-year drug free period with cohorts using time periods of 6, 12 and 24 months as a drug free period. The characteristics evaluated were gender, age group (18–30 years, 31–45 years, 46–60 years, >60 years), type of prescriber (general practitioner, psychiatrist, other) and type of antidepressant (SSRI, TCA, other). The difference in prevalence of these characteristics between the cohorts was presented as odds ratios (OR) with (95% CI). The OR represents relative frequency of misclassification in the 6, 12 respectively 24 month drug free period cohorts when compared to a 9 year drug free period cohort.

Table 1. Patient characteristics of the study population ($n = 21\,304$)

	N	%
Gender		
Male	6564	30.8
Female	14 740	69.2
Age (years)		
18–30	1973	9.2
31–45	5744	27.0
46–60	7157	33.6
>60	6430	30.2
Prescribed antidepressant		
SSRI	12 515	58.8
TCA	5797	27.2
Other*	2992	14.0
Prescriber		
General practitioner	17 839	83.7
Psychiatrist	1894	8.9
Other†	1571	7.4

*Other antidepressants; moclobemide, mianserin, trazodone, mirtazapine, venlafaxine.
†Other type of prescriber or information about prescriber not available.

RESULTS

Patient characteristics of the study population are presented in Table 1. The study population was predominantly female (69.2%) with a mean age of 52.6 years. The age distribution within our study population has a slight higher proportion of older individuals when compared to the age distribution in the general Dutch population.[34]

The overall incidence of antidepressant drug use, October 2001 to September 2002, when using drug free periods of different lengths, is shown graphically in Figure 1. The lengths of the drug free period have an effect on the measured incidence: when using a 6 month drug free period the measured incidence is about 32 per 1000 individuals (95% CI: 31.3, 32.6) while the measured incidence is 27.5 (95% CI: 26.9, 28.1), 23.5 (95% CI: 22.9, 24.0), 17.2 (95% CI: 16.7, 17.7) per 1000 individuals when using a 12 month, 24 month, or a 9 year drug free period, respectively. The proportion of individuals misclassified as incident antidepressant drug users when using a 6 months drug free period, given that the incident measurements for the 9 years drug free period represent true first time users, is about 46%. For the 12 and 24-month drug free period these proportions are 37 and 27%.

The proportion misclassified individuals for the different lengths in drug free period, stratified by age group and using the 9-year drug free period cohort as a reference, is shown in Figure 2. The figure shows that for each drug free period, the proportions of misclassified individuals are not equally distributed over age. When using a 6 months drug free period the proportion of misclassified individuals in age group 18–30 years is about 34%, while for the age group 46–60 years it is about 52%.

The difference in prevalence of characteristics between the reference incident user cohort (9 year) and cohorts formed by using drug free periods of 6, 12, and 24 months are presented as odds ratios in Table 2. Our measurements show that women are more likely ($p < 0.001$) to be misclassified in the 6, 12 and 24 months drug free period cohorts, with odds ratios ranging from 1.25 (95% CI: 1.14, 1.37) to 1.34 (95% CI: 1.19, 1.52). These cohorts are in addition more likely ($p < 0.001$) to represent older individuals. The odds ratios for age group 46–60 years range from 2.12 (95% CI: 1.82, 2.46) to 2.22 (95% CI: 1.79, 2.74), for the 6, 12 and 24 months drug free period settings. We did not see any significant

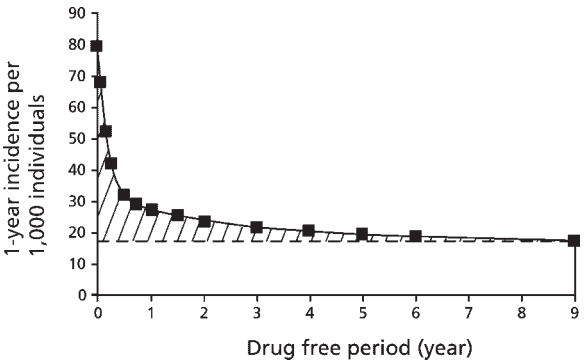

Figure 1. Overall incidence of antidepressant drug use in the Netherlands, October 2001 to September 2002, per 1000 individuals. The incidence was measured using drug free periods of different length. The striped area under curve represents misclassified individuals

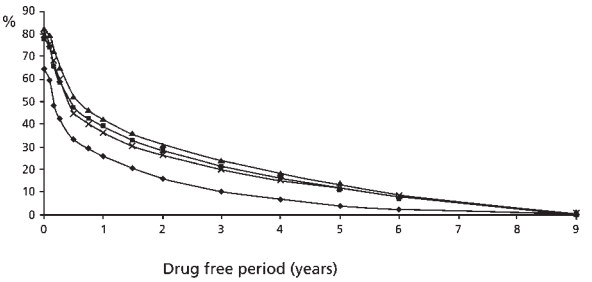

Figure 2. Amount (%) misclassified individuals in an incident users cohort, age groups 18–30 years, 31–45 years, 46–60 years and >60 years, when using drug free periods of different lengths. (Age groups: ◆ 18–30 years, ■ 31–45 years, ▲ 46–60 years, × >60 years)

Table 2. Odds ratios for cohort characteristics, of first time antidepressant drug users, in cohorts using 6, 12 and 24 months drug free periods when compared to a reference cohort

	6 months misclassified ($n = 3,970$)		12 months misclassified ($n = 2,767$)		24 months misclassified ($n = 1,690$)		9 years true ($n = 4,604$)
	%	OR	%	OR	%	OR	%
Gender							
Male	30.6	Reference	29.8	Reference	29.1	Reference	35.6
Female	69.4	1.25 (1.14, 1.37)	70.2	1.30 (1.17, 1.44)	70.9	1.34 (1.19, 1.52)	64.4
Age (years)							
18–30	9.0	Reference	8.9	Reference	8.2	Reference	15.3
31–45	28.8	1.77 (1.52, 2.06)	29.7	1.83 (1.54, 2.18)	29.9	2.02 (1.63, 2.50)	27.7
46–60	35.2	2.12 (1.82, 2.46)	34.4	2.08 (1.75, 2.46)	33.6	2.22 (1.79, 2.74)	28.4
>60	27.0	1.61 (1.38, 1.88)	27.0	1.60 (1.36, 1.91)	28.3	1.86 (1.50, 2.30)	28.6
Antidepressant							
TCA	27.5	Reference	27.5	Reference	28.4	Reference	28.9
SSRI	57.3	1.03 (0.93, 1.13)	57.4	1.03 (0.92, 1.15)	57.0	0.99 (0.87, 1.13)	58.7
Other*	15.2	1.29 (1.12, 1.49)	15.1	1.28 (1.09, 1.49)	14.6	1.20 (0.99, 1.44)	12.4
Prescriber							
General practitioner	82.6	Reference	82.4	Reference	83.7	Reference	82.8
Psychiatrist	8.0	1.49 (1.25, 1.77)	7.6	1.41 (1.16, 1.71)	6.2	1.14 (0.89, 1.45)	5.4
Other†	9.4	0.79 (0.69, 0.91)	10.0	0.85 (0.73, 0.99)	10.1	0.85 (0.70, 1.02)	11.8

The reference cohort, representing true first time users, was identified using a 9-year drug free period. Amount of misclassified individuals are identified for the 6, 12 and 24 months cohorts. Odds ratios are calculated with 95% CI.
*Other antidepressants; moclobemide, mianserin, trazodone, mirtazapine, venlafaxine.
†Other type of prescriber or information about prescriber not available.

difference in the use of SSRIs or TCAs between the cohorts, although the 6 and 12 months drug free period cohorts are more likely ($p < 0.05$) to include individuals using other types of antidepressants. There is a difference in type of prescriber for the reference cohort and the other cohorts, with psychiatrists being more likely to be the prescriber of the antidepressant drug when using a drug free period shorter than 24 months.

DISCUSSION

Our study has shown that the length of the drug free period has a clear effect on the measured incidence of antidepressant drug use. The difference when using a 6 or 12-month drug free period compared to the 9-years drug free period is substantial. When looking at the difference between the most commonly used drug free periods we see a 14% decrease in overall incidence if the drug free period is increased from 6 months to 12 months, and a 27% decrease in overall incidence when the drug free period is increased from 6 months to 2 years. These results support our theory that the comparison of incidence measurements between studies using drug free periods of different lengths should be done cautiously.

Furthermore, we compared characteristics of an incident user cohort using a 9-year drug free period with shorter drug free period cohorts to assess possible bias in inception cohort studies. This finding is of relevance to clinical epidemiological research, as first time drug use is often used as an inclusion criterion when designing inception cohort studies. Our results show that the characteristics of first time users change with different drug free periods. A short drug free period will result in a different age and gender distribution compared to when a long drug free period is used. When short drug free periods are used the cohort is more likely to include older individuals. This could, however, partly be due to the fact that older people have a higher chance of being misclassified, as younger individuals had less possibility of being exposed. For short drug free periods, the cohort is also more likely to include females and individuals receiving an antidepressant prescription from a psychiatrist when compared to using longer drug free periods. In addition, the relative risk of certain outcomes such as relapse, duration of depressive episode and time between depressive episodes is different for individuals experiencing their first depressive episode than for those individuals having a recurrent depressive episode.[27–29] Including those recurrent depressive individuals in an inception cohort of first time users could therefore influence outcome measurements and lead to biased results for certain study questions.

KEY POINTS

- The length of the drug free period has an effect on incidence measurements in pharmacoepidemiologic studies.
- For inception cohorts where first time use of a drug is an inclusion criteria the drug free period can influence the prevalence of cohort characteristics.

Limitations to our study are that in our measurements, we defined the true first time antidepressant drug users by using a 9-year drug free period. This definition does however not necessarily include only first time users and might still include some recurrent users that could only be identified when using an even longer drug free period.

The decreasing incidence when using longer drug free periods is not only evident when measuring first time use of an antidepressant drug but could be of importance when measuring first time drug use for other drug therapies. This is especially applicable for drug therapies of diseases that have a similar lifecycle as depression that can come in episodes, like types of allergy and migraine, where chronic constant medication is not always necessary. Our results are not likely to apply for chronic drug use due to diseases such as type I diabetes and asthma. However, our results could apply to preventive drug therapies such as hypertension and lipid lowering drug therapies. These therapies can be considered as chronic constant therapies but as immediate benefits are not always apparent to the patient, adherence is often low[35] and the medication use pattern can be similar to that for episodic diseases. In general, we consider further research needed to identify the most appropriate drug free period for the different groups of drugs.

In conclusion, the length of the drug free period has an effect on incidence measurements. Altering the drug free period from a short to a longer one will result in a decrease of measured incidence. For inception cohorts where first time use of a drug is an inclusion criteria the drug free period can influence the prevalence of characteristic in the cohort and for short drug free periods give biased estimates.

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