Drug treatment episodes in pharmacoepidemiology

- antidepressant use as a model

Helga Garðarsdóttir

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DRUG TREATMENT EPISODES IN PHARMACOEPIDEMIOLOGY
Antidepressant use as a model

EPISODES VAN GENEESMIDDELENGEBRUIK IN FARMACOEPIDEMIOLOGISCH ONDERZOEK
Antidepressiva als model
(met een samenvatting in het Nederlands)

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ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 21 oktober 2009 des middags te 2.30 uur

door

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geboren op 12 augustus 1975 te Reykjavík, IJsland

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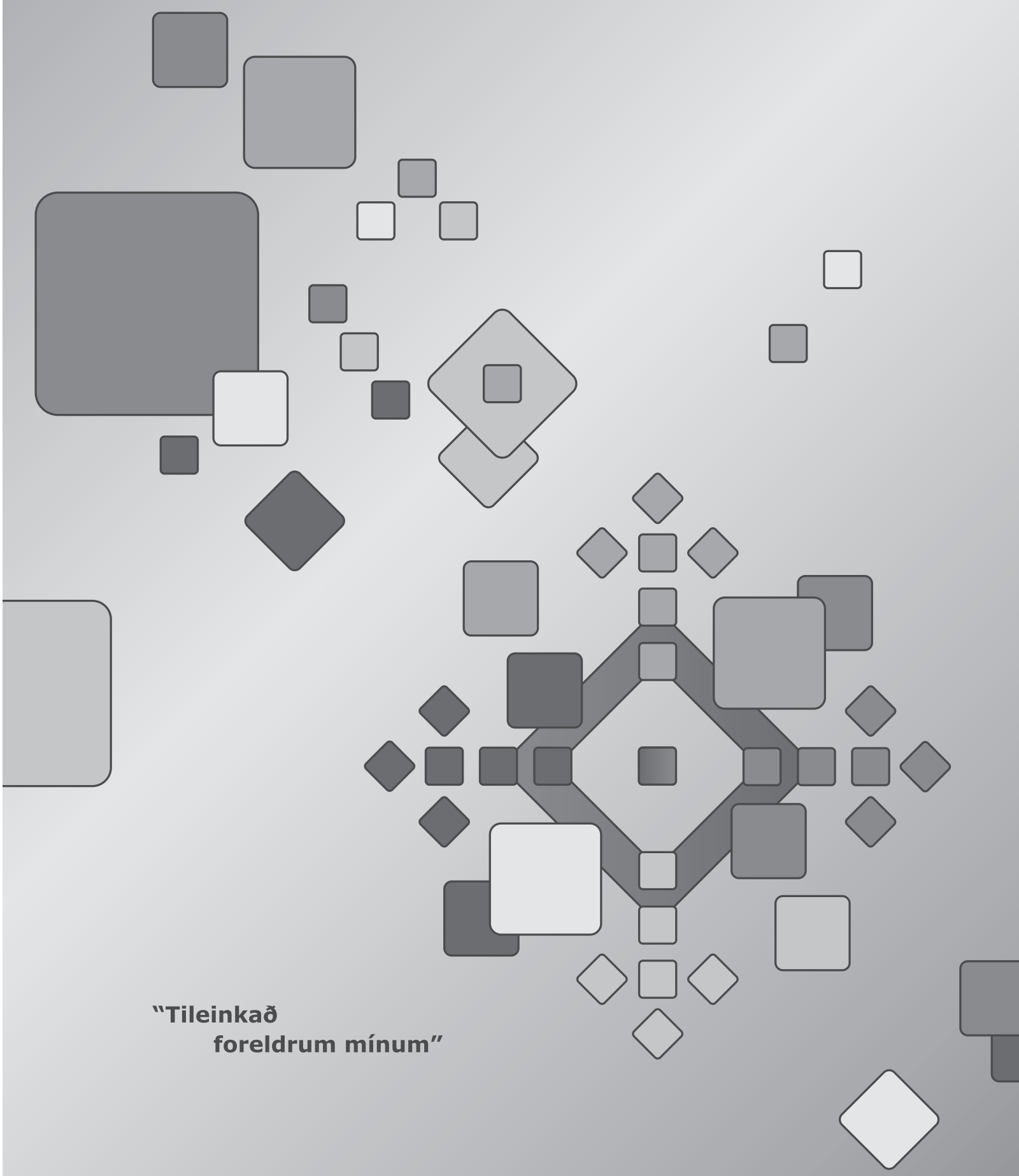

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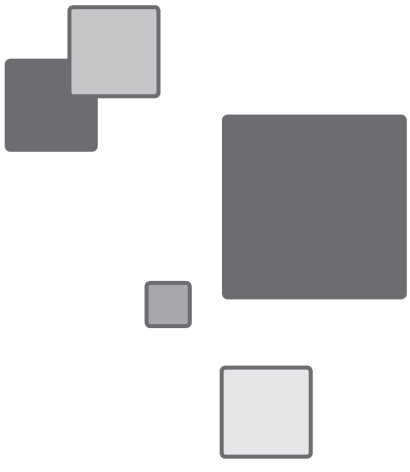
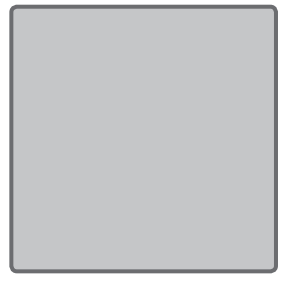
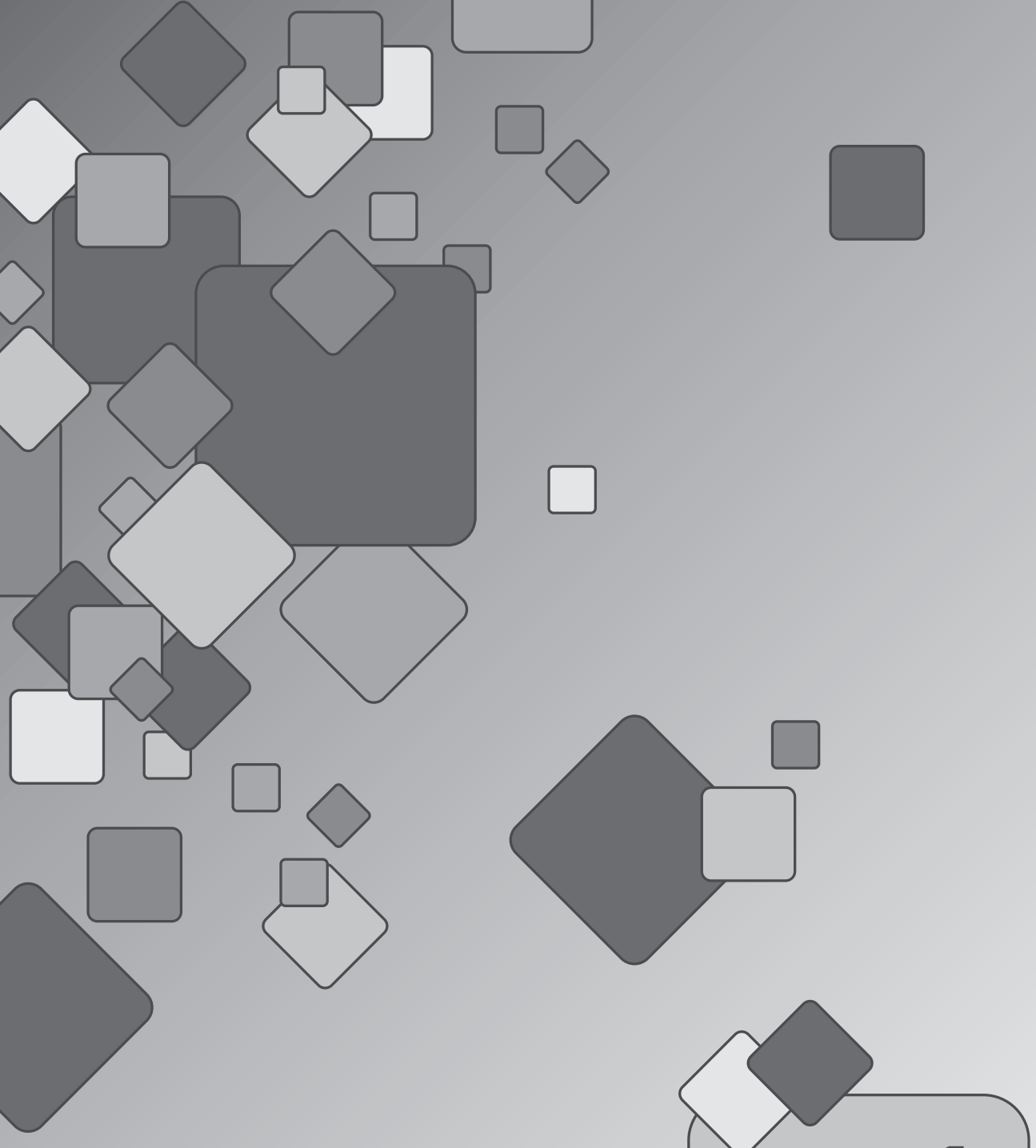






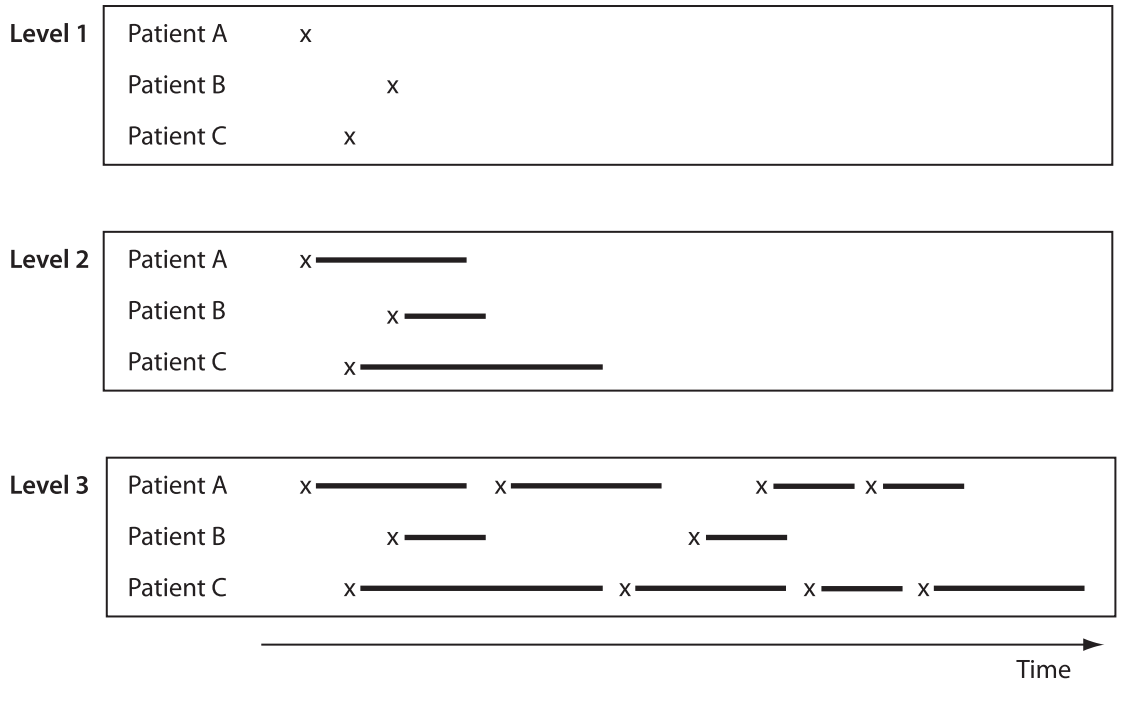
1

General introduction

DRUG EXPOSURE

In 1994, Leufkens and Urquhart organised drug exposure research into three levels evolving over time (Figure 1).[1] The first level focuses on a simple question – did/does the patient use 'drug x' – resulting in a dichotomous yes/no answer. First-level drug exposure data allows for estimation of (period) prevalence of drug use but is not sufficiently informative for estimation of events such as first initiation, drug discontinuation or switching between drug treatments. Each subsequent level of drug exposure measurement expands the time element, generating more opportunities for detailed research. The second level encompasses information on the dose and amount of drug prescribed or dispensed. By means of this extra information, the duration of a single prescription can be estimated which allows for measurement of point and period prevalence, as well as incidence. The third level further expands the time element by including multiple prescribing or dispensing moments. Drug exposure profiles can then be constructed for each individual patient by estimating their drug usage patterns over time. The drug exposure profile may entail numerous drug-taking moments, which can be composed of the same drug or a combination of different drugs.

Figure 1 **The three levels of classifying drug exposure**



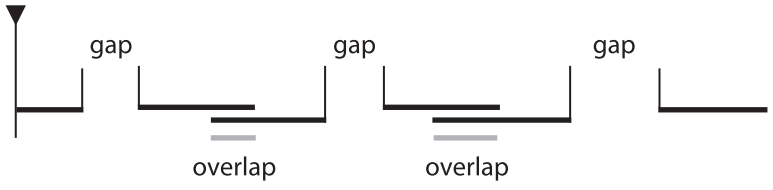
x = prescription/dispensing date; black lines = duration of a single prescription

Pharmacoepidemiological research often employs observational methods to explore drug exposure in relation to various outcomes. Commonly, a potential beneficial or adverse effect of drug exposure is studied in a defined sample of patients who suffer from a specific illness. Although many methods have been developed to measure drug exposure directly in patients, including electronic drug exposure monitors, blood/serum concentration measurements and self-reported drug use, most large-scale studies rely on information on drug exposure extracted from large databases originating from systematically collected administrative healthcare data.

Currently, pharmacoepidemiological research on drug exposure often focuses on classifying drug exposure according to the third level, where drug exposure patterns over time are estimated. Patient drug taking is a complicated process involving a sequence of individual drug taking moments which can be divided into acceptance, execution and discontinuation of drug therapy.[2] Patients' perspectives on drug use differ widely within these decisive drug taking moments [3-5] and as a result, a variety of drug exposure patterns occur. Therefore, the classification and description of drug exposure for the individual patient can be a convoluted task. Drug exposure over time can be measured in various ways such as by estimating the number of days that the patient is exposed to the drug during a given time period or as an individual drug-taking, or treatment, episode. The construction of drug treatment episodes is common practice in pharmacoepidemiology, as it offers an opportunity to investigate a variety of outcomes within a period in which the patient undergoes treatment.

The Cambridge dictionary defines an episode as "a single event or a group of related events".[6] Patient drug exposure can be defined as a single drug-taking event or as multiple drug-taking events over a period of time – a drug treatment episode. Drug treatment episodes can be constructed based on dispensing and/or prescribing moments extracted from administrative databases. The start of a drug treatment episode can be defined as the initiation of a certain drug, or combination of drugs, during a specific time period. It can be the first treatment episode, for patients with no prior use of the drug, or a new treatment episode, in case of prior use. Once the start of a treatment episode has been defined, the duration of use can be estimated for each prescription prescribed to the patient or dispensed at the pharmacy. The duration of a prescription can be estimated based on the amount of units prescribed or dispensed divided by the number of units prescribed to be taken daily. When information on the dosage regimen is missing, the duration can, on occasion, be based on the amount of defined daily dose or number of pills prescribed or dispensed.[7,8] The next step is to evaluate how many prescriptions belong to the treatment episode and when it ends. How the end of a treatment episode is defined is of consequence for the estimated duration of use and the number of prescriptions

Figure 2 **Patient drug exposure displaying overlaps and gaps in patient treatment pattern**



The black horizontal lines represent individual prescription durations and the grey horizontal lines overlapping prescription durations.

identified as belonging to a single drug treatment episode. As drug use is estimated over time, patients can experience multiple drug treatment episodes.

Patients who undergo drug treatment often do not collect their subsequent prescription on the exact day that they take the last dose from the previous prescription. Thus, administrative data on drug prescribing or dispensing moments usually do not represent the real life pattern of patient drug taking. Administrative databases often display an irregular drug 'pick up' pattern, which can lead to findings of an overlap of two prescriptions or a time gap between two consecutive prescriptions (Figure 2). Prescription overlap occurs when a patient collects a subsequent dispensing early, i.e. before the dispensed quantity from a prior dispensing has finished. Time gaps between prescriptions occur when the subsequent prescription is collected after the dispensed quantity from a prior dispensing has finished. To compensate for these irregular patterns of prescription collection, different methods are applied. In most cases, gaps of certain lengths are defined and as long as a subsequent prescription falls within a given amount of days after the estimated duration of a prescription, it is considered to belong to the same treatment episode. When drug taking events are used to construct drug treatment episodes, many methodological aspects need to be taken into account. The use of different definitions to define start and end of a drug treatment episode can lead to diversity in estimated results.

ANTIDEPRESSANTS

The perception of potential patterns of antidepressant drug exposure displayed among antidepressant drug users depends on the type of patient under investigation. If the research subject is mood disorders, antidepressant drug users are expected

to display a treatment pattern in line with the theoretical clinical pattern of depression. However, the treatment pattern that in theory represents the clinical course of depression is likely to diverge from the treatment patterns of patients included in randomized clinical trials and even more so from those displayed by antidepressant drug users in the general population. Antidepressant users represent a very heterogenic patient group having various co-morbidities and co-medication use. The dynamics in the characteristics of patients under investigation is likely to influence the observed antidepressant treatment patterns.

Figure 3 **The five possible outcomes of unipolar depression (response, remission, relapse, recovery and recurrence) during the three phases of depression treatment (acute, continuation and maintenance)**

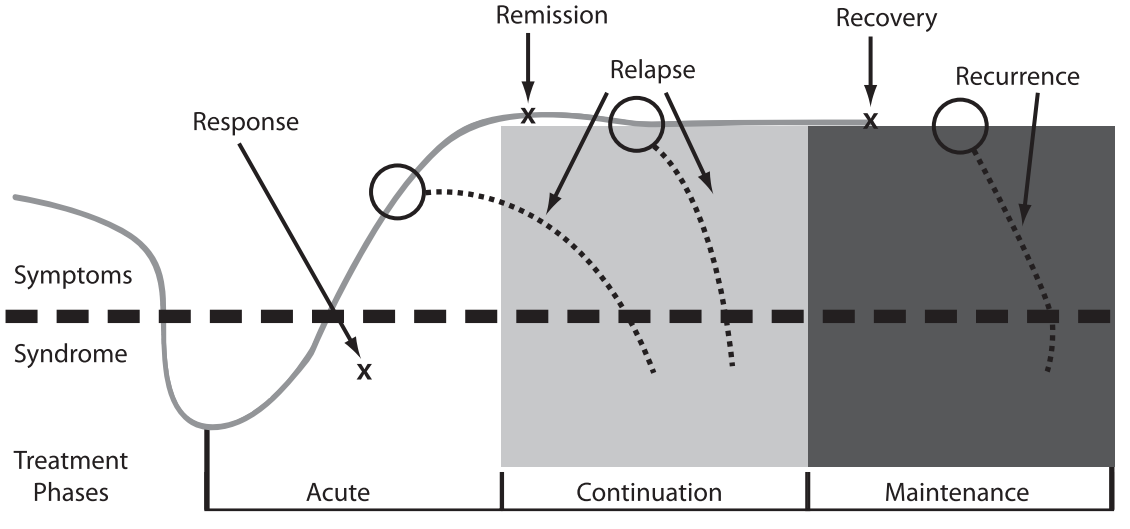


Figure after Kupfer, 1991.[9]

The theoretically expected pattern for antidepressant treatment in depressed patients follows the clinical course of depression as described by Kupfer.[9] Kupfer defined the natural clinical course of a depressive episode by dividing it into response, remission, relapse, recovery and recurrence (Figure 3). A large number of depressed patients are expected to show an episodic antidepressant treatment pattern, which includes acute treatment to resolve symptoms and gain remission, followed by 4-6 months of follow-up treatment to minimize relapse risk.[10-12] Randomized clinical trials have shown that patients with a history of depression may benefit from maintenance treatment for at least 1–5 years.[13,14] The antidepressant treatment pattern observed in these patients is likely to diverge from the theoretical episodic pattern into a

continuous chronic treatment pattern. When it comes to antidepressant use among the general population, the variety of treatment patterns expands even further, as antidepressants use expands beyond treating depression. Antidepressants are also indicated in the Netherlands for generalized anxiety disorders, obsessive-compulsive disorders, social phobia, panic disorders, eating disorders, neuropathic pain and nocturnal enuresis.[15] In addition, antidepressants are sometimes used for clinically accepted off-label indications such as sleeping disorders,[16] urinary incontinence,[17] and headache.[18] The diversity in the nature of these conditions is likely to result in a variety of antidepressant treatment patterns. These might deviate from the classic episodic or chronic treatment patterns observed when treating depression.
Antidepressant use has increased dramatically since the introduction of the selective serotonin reuptake inhibitors.[19] In the Netherlands in 2007, approximately 940 000 individuals were prescribed and dispensed, at least, a single antidepressant.[20] The common use of antidepressants in the general population, in addition to the fact that their treatment pattern does not always represent the traditional episodic nature of depression, makes this particular drug class a suitable model for methodological research on drug exposure.

OBJECTIVE OF THIS THESIS

One of the cornerstones of pharmacoepidemiological research is the study of drug exposure(s) in relation to specific outcome(s). Evidently, the accurate estimation of drug exposure plays a fundamental role. Drug exposure can be studied through the construction of drug treatment episodes. The objective of this thesis is to investigate methodological topics in observational research relevant to the construction of antidepressant treatment episode(s).

OUTLINE OF THIS THESIS

Chapter 2 focuses on investigating characteristics of patients who receive their antidepressants indicated to treat depression. *Chapter 2.1* explores the various indications registered by general practitioners when prescribing antidepressants. In *Chapter 2.2*, a specific algorithm is developed to identify patients with a diagnosis of depression amongst antidepressant users, using dispensing data.
In **Chapter 3**, the focus is on methodological definitions related to the start of an antidepressant treatment episode. In *Chapter 3.1* we investigated patients receiving a first antidepressant who do not get the antidepressant dispensed or who only

receive a single antidepressant prescription dispensed at the pharmacy. *Chapter 3.2* presents an assessment of the degree of bias resulting from the use of drug free periods of various lengths when defining new-user cohorts of antidepressant users. *Chapter 3.3* studies the seasonal pattern of initiation in antidepressant use and *Chapter 3.4* illustrates how different patterns of antidepressant treatment influence the risk of re-initiating antidepressant use.

Chapter 4 focuses on the end of an antidepressant treatment episode, where in *Chapter 4.1* we investigate the influence of gap-length between prescriptions on the construction of drug treatment episodes. The subject of gap-length is further explored in *Chapter 4.2* where the length of a gap or an overlap between prescriptions is associated with patient reported drug taking. Changes in antidepressant treatment patterns associated with the transition from general practice to specialist care (or vice versa) are explored in *Chapter 4.3*. In *Chapter 4.4* we describe how the use of different specifications, to define treatment episodes and to measure follow up time, leads to biased risk estimates.

Finally, **Chapter 5** provides a general discussion of the findings within a broader perspective.

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2

Indications for antidepressant treatment

2.1

Indications for antidepressant drug prescribing in general practice in the Netherlands

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Eibert R Heerdink
Liset van Dijk
Toine CG Egberts

J Affect Disord 2007;98:109-15

ABSTRACT

Objective

The intensity of the use of antidepressants in large populations can nowadays relatively easily be estimated using databases encompassing prescription data. There are shortcomings when using prescription databases as they contain no clinical data on patient illness. Antidepressants are prescribed for different illnesses, thus information on the indications could help when interpreting results from database studies on antidepressant drug use. The aim of this study is to investigate for which indications antidepressants are being prescribed in general practice in the Netherlands.

Methods

Data were obtained from the Second Dutch National Survey of General Practice, carried out by the Netherlands Institute for Health Services Research (NIVEL) (n = 385 461). Patients, 18 years and older, who received an antidepressant prescription from a general practitioner in 2001 were selected (n = 13 835). Indications for antidepressant drug prescribing were identified using time windows of different lengths.

Results

Antidepressants are most often being prescribed for depression (45.5%) and anxiety/panic disorders (17.2%). For these indications lengthening the time window around prescription date from 0 to 180 days resulted in an increase of 20-40% in antidepressant drug users identified with these indications.

Conclusion

General practitioners (GPs) prescribe antidepressants predominantly for treating depression. However, using antidepressant drug use as a proxy for identifying depressed patients in a prescription database should be done with caution and when possible in combination with clinical data.

INTRODUCTION

Antidepressant drug use has increased dramatically over the past decade.[1,2] Possible explanations for this increase are thought to be many, including the introduction of new antidepressants, increased depression awareness, acceptability of pharmacological treatment, better diagnosis, broadened indications and longer treatment periods.[3-7] The intensity and dynamics of the use of antidepressants in large populations can nowadays quite easily be estimated using databases encompassing prescription data.[8-10] There are, however, shortcomings when using these databases as they often only contain prescription data and no clinical data including information on the type of illness the treatment is intended for.

In the Netherlands antidepressants are approved not only for use in patients who suffer from depression but also for patients with nocturnal enuresis, social phobia, generalized anxiety disorders, obsessive-compulsive disorders, panic disorders and eating disorders.[11] In addition, the antidepressants are used for some clinically accepted off-label indications such as sleeping disorders,[12] urinary incontinence,[13] headache,[14] and neuropathic pain.[15] Previous studies have shown that use of antidepressants have even gone beyond the approved and clinically accepted off-label indications.[16] Given the different diseases and symptoms that the antidepressants can be prescribed for and the vast amount of research that has been done on antidepressant drug use,[6,7,17-22] it is of interest to investigate the indications for antidepressant drug prescribing. Information on how the antidepressants are being prescribed for the different symptoms and illnesses could help us in better understanding and interpreting results from prescription database studies done on antidepressant drug use e.g. where antidepressant drug use is set as a proxy for treatment of depression.

When identifying indication for antidepressant drug prescribing using general practice databases it is important that the indication is registered in the physician-patient contact file when a prescription is given. Not registering the indication for prescribing might occur in different situations, e.g., for new users where antidepressant drug therapy can be initiated before the general practitioner has come to a diagnosis. To try to overcome these problems time windows of different length around prescription date can be applied. By applying this method more physician-patient contact moments are used to identify the indication for prescribing.

The aim of this study is to investigate for which indications antidepressants are being prescribed in general practice in the Netherlands. In addition, we will investigate how using different time windows around prescription date will influence identifying indication for antidepressant drug prescribing in a general practice database.

METHODS

Setting and study population

Data of this study were obtained from the Second Dutch National Survey of General Practice (DNSGP-2) which was carried out in 2001 by the Netherlands Institute for Health Services Research (NIVEL) and has been described in detail elsewhere.[23] In short, 195 general practitioners (GPs) in 104 practices registered details of all physician-patient contacts during 12 months in a standardized way. GPs were trained during an intensive course on coding practices and problems by the LINH (Dutch Information Network GPs). The GPs registered all health problems presented within a consultation and diagnoses were coded using the International Classification of Primary Care, ICPC.[24]

In addition, all prescriptions made by the GPs were registered. The DNSGP-2 includes prescription data containing information on the dispensed drug, dispensing date, amount dispensed and prescribed dosage regimen. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[25] Each patient is identified with an anonymous unique patient-identification code.

The DNSPG-2 population consisted of patients from 104 general practices in the Netherlands (n = 385 461). Eight practices were excluded from the DNSGP-2 population for the present study due to insufficient contact and/or data collection. The source population included all individuals registered in the 96 general practices in the Netherlands in the year 2001 (n = 289 692). The study population consisted of patients, 18 years and older, from the 96 practices which received at least one antidepressant prescription from their GP in the year 2001 (n = 13 835). The 1-year prevalence of antidepressant drug use in the study population was 6.0% which is similar to the 1-year prevalence of antidepressant drug use in 2001 in the Netherlands.[26,27]

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, trazodone, tranylcypromine, venlafaxine).

Indications

The indications investigated in this study were based on officially approved indications for the antidepressants in the Netherlands.[11] In addition, some in clinical practice accepted off-label indications were selected such as sleeping disorders, migraine/headache prophylaxis and neuropathic pain. The indications for antidepressant prescribing investigated in this study were depression/feeling

depressed (ICPC codes: P03, P76), anxiety/panic disorder/feeling anxious (ICPC codes: P01, P74), obsessive-compulsive disorder/phobia (ICPC code: P79), sleeping disorders (ICPC code: P06), migraine/cluster headache (ICPC codes: N89, N90), neuropathic pain (ICPC codes: N03, N92, N94), eating disorders (ICPC code: T06) and enuresis/incontinence (ICPC codes: P12, U04).

Data analysis

The prescription date was defined as the date of first antidepressant prescription that the patient received from the GP in year 2001. An indication was considered as the GP's reason for prescribing an antidepressant when one of the ICPC codes could be identified in the physician-patient contact file. The registries in the physician-patient contact files were available from October 2000 until June 2002. It was possible for the antidepressant drug users to have more than one indication registered in the physician-patient contact file. The indications were identified by searching the physician-patient contact file using prescription date together with different time windows of 0, 28, 60, 120 and 180 days. Each time window extends for equal amount of days prior to and post prescription date, e.g., a time window of 28 days represents the time range of 14 days prior to 14 days post prescription date. The average duration of use for the first antidepressant prescription in our study population was 40 days. A time window of 180 days, 90 days prior to and 90 days post prescription date, was considered sufficiently wide to include at least two GP visits and was for that reason used as a reference to evaluate what effect the length of time windows has on identifying indications for antidepressant drug prescribing in the physician-patient contact file. The 180-day time window reference measurement was compared to the measurements where 0, 28, 60 and 120-day time windows were used to identify indication for antidepressant prescribing. The characteristics of patients identified with different indications where compared and odds ratios (OR) with 95% confidence intervals (95%CI) were calculated. A further analysis was done on the antidepressant drug users who had one of the selected indications, excluding those that did not have the selected indications registered in their physician-patient contact file. The cumulative change in amount of antidepressant users where an indication was identified in the physician-contact file was investigated over time. The time span investigated started at 90 days prior to prescription date and ended at 90 days post prescription date.

Table 1 **Patient characteristics of the study population, including information about the four most frequently prescribed antidepressants within the study population**

Characteristic	n=13 835 (100%)
Gender	
male	4 328 (31.3%)
female	9 507 (68.7%)
Age (years)	
18-30	1 618 (11.7%)
31-45	4 228 (30.6%)
46-60	4 168 (30.1%)
>60	3 821 (27.6%)
Prescribed antidepressant	
TCA	3 639 (26.3%)
SSRI	8 366 (60.5%)
other [a]	1 830 (13.2%)
Four most frequently prescribed antidepressants	
paroxetine	5 318 (38.4%)
amitriptyline	2 391 (17.3%)
fluoxetine	1 144 (8.3%)
mirtazapine	836 (6.0%)

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor
a) Other antidepressant: mianserin, mirtazapine, moclobemide, nefazodone, trazodone, tranylcypromine, venlafaxine.

RESULTS

General characteristics of the study population are presented in Table 1 along with the four most frequently prescribed antidepressants. The study population was mainly female (68.7%) with a mean age of 50.8 years. The four most frequently prescribed antidepressants within our study population were the same as the four most frequently used antidepressants in the general Dutch population.[28]

Indications for antidepressant prescribing in 2001 in general practice identified when using a 180-day time window around prescription date are presented in Table 2. In the study population (n = 13 835), depression (45.4%) and anxiety/ panic disorders (17.2%) represent the most common indications for antidepressant drug prescribing. About one third of the antidepressant drug users did not have any of the selected indications registered in the physician-patient contact file. When looking at the indications for antidepressant drug prescribing within each group of antidepressant drugs it was observed that more than half of the TCA users did not have the indications we investigated in their respective physician-patient contact file

in comparison to 30% of the SSRI users. In addition, the proportion of patients that did not have one of our selected indications registered in their physician-patient contact files was different for the antidepressant drug users who were receiving the specific antidepressant for the first time and those who had received the specific antidepressant before. About 40% of the antidepressant drug users who received the specific antidepressant for the first time had none of our selected indications in their physician-patient contact file, while for the antidepressant drug users that had registered prior use of the specific antidepressant this proportion was 28%.

We found that women were more likely than men to have the indications incontinence/enuresis (OR 3.3; 95%CI 2.0–5.3) and headache/migraine (OR 2.8; 95%CI 1.9–4.1) in their physician-patient contact file while men were more likely to have the indication neuropathic pain (OR 1.5; 95%CI 1.1–2.0). The 18- to 30-year-old antidepressant drug users were more likely than the > 60-year old to have the indications depression (OR 1.5; 95%CI 1.3–1.6), anxiety/panic disorders (OR 1.4; 95%CI 1.2–1.6) or obsessive-compulsive disorders/phobia (OR 5.3; 95%CI 3.1–8.9) registered in their physician-patient contact file while the > 60-year old antidepressant drug users where more likely to have the indications neuropathic pain (OR 3.7; 95%CI 1.7–8.2) or none of our selected indications registered

Table 2 **Indications for antidepressant prescribing in 2001 in general practice identified by using a 180-day time-window around prescription date (N_{total}=13 835)**

Indication	Total users [a] n (%)	TCA n (%)	SSRI n (%)	Other n (%)
Depression/feeling depressed	6 296 (45.5%)	899 (24.7%)	4 472 (53.5%)	925 (50.5%)
Anxiety/panic disorder/feeling anxious	2 380 (17.2%)	521 (14.3%)	1561 (18.7%)	298 (16.3%)
Obsessive-compulsive disorder/ phobia	200 (1.4%)	32 (0.9%)	145 (1.7%)	23 (1.3%)
Eating disorders	35 (0.3%)	1 (0.03%)	31 (0.4%)	3 (0.2%)
Enuresis/incontinence	170 (1.2%)	55 (1.5%)	96 (1.1%)	19 (1.0%)
Sleeping disorders	1 292 (9.3%)	427 (11.7%)	662 (7.9%)	203 (11.1%)
Headache/migraine	231 (1.7%)	78 (2.1%)	124 (1.5%)	29 (1.6%)
Neuropathic pain	161 (1.2%)	126 (3.5%)	30 (0.4%)	5 (0.3%)
None of above	4 956 (35.8%)	1 870 (51.4%)	2 461 (29.4%)	625 (34.2%)

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor

a) Total users exceed the total number of antidepressant drug users as the patients can have more than one indication registered in the physician-patient contact file.

Table 3 **Indications for antidepressant drug prescribing in general practice in the Netherlands identified using different time windows[a] around prescription date (N_{total} = 13 835)**

Indication	0 days n (%)	28 days n (%)	60 days n (%)	120 days n (%)	180 days n (%)
Depression/feeling depressed	4 861 (35.1%)	5 239 (37.9%)	5 541 (40.1%)	5 975 (43.2%)	6 296 (45.5%)
Anxiety/panic disorder/feeling anxious	1 398 (10.1%)	1 672 (12.1%)	1 909 (13.8%)	2 177 (15.7%)	2 380 (17.2%)
Obsessive-compulsive disorder/phobia	133 (1.0%)	154 (1.1%)	171 (1.2%)	191 (1.4%)	200 (1.4%)
Eating disorder	19 (0.1%)	21 (0.2%)	25 (0.2%)	32 (0.2%)	35 (0.3%)
Enuresis/incontinence	33 (0.2%)	65 (0.5%)	89 (0.6%)	134 (1.0%)	170 (1.2%)
Sleeping disorders	419 (3.0%)	657 (4.7%)	852 (6.2%)	1 102 (8.0%)	1 292 (9.3%)
Headache/migraine	58 (0.4%)	81 (0.6%)	127 (0.9%)	190 (1.4%)	231 (1.7%)
Neuropathic pain	79 (0.6%)	103 (0.7%)	117 (0.8%)	139 (1.0%)	161 (1.2%)
None of above	7 079 (51.3%)	6 480 (46.8%)	6 009 (43.4%)	5 406 (39.1%)	4 956 (35.8%)

a) Each time window extends for equal amount of days prior to and post prescription date, e.g., a time window of 28 days represents the time range from 14 days prior to 14 days post prescription date.

(OR 1.7; 95%CI 1.5–2.0). The antidepressant drug users who received a second antidepressant prescription within the 90 days following prescription date were more likely to have the indications depression (OR 1.6; 95%CI 1.4–1.7) and anxiety/panic disorder (OR 1.2; 95%CI 1.1–1.4) registered in the physician-patient contact file when compared to those who did not receive a second antidepressant within the 90 days following prescription date. Antidepressant users who did not receive a second antidepressant prescription within 90 days from prescription date were more likely to have the indications neuropathic pain (OR 1.6; 95%CI 1.1–2.1) or none of our selected indications (OR 1.4; 95%CI 1.3–1.5) registered in the physician-patient contact file.

The indications for antidepressant drug prescribing in general practice identified using time windows of different lengths around the prescription date are presented in Table 3. For the main indications (depression, anxiety/panic disorder, obsessive-compulsive disorder/phobia) lengthening the time window from 0 days to 180 days resulted in an increase of about 20-40% in antidepressant drug users identified with the indications. For the indications eating disorders and neuropathic pain the increase was about 50% and for the indications sleeping disorder, headache/migraine and enuresis/incontinence the increase was almost 70-80% when lengthening the time window from 0 days to 180 days. The total amount of antidepressant drug users with one of our selected indications registered and the amount where none of our selected indication was found in the physician-patient contact file are presented graphically for the different time windows in Figure 1. The figure displays that increasing the time window from 0 days to 180 days results in a 30% increase in the amount of antidepressant drug users for which an indication is identified. When investigating only the antidepressant drug users that had one of our selected indications in their physician-patient contact file (n = 8879) it appears that the indications are most often registered on prescription date. Figure 2 displays the cumulative changes in amount of antidepressant drug users identified, where any of our selected indications are registered in their physician-patient contact file, over a time window from 90 days prior to until 90 days post prescription date.

DISCUSSION

Our study shows that depression is the most common indication for antidepressant drug prescribing in general practice. About 45% of the antidepressant drug users got the antidepressant indicated for treating depression which is a bit lower proportion than what has been reported in earlier studies done in the Netherlands in 1994/95 [29] and in 1996.[30] In addition, our study shows that the proportion of antidepressant

Figure 1 **Proportion of total antidepressant drug users where the selected indications are identified and where none of selected indications are identified when using different time windows around prescription date**

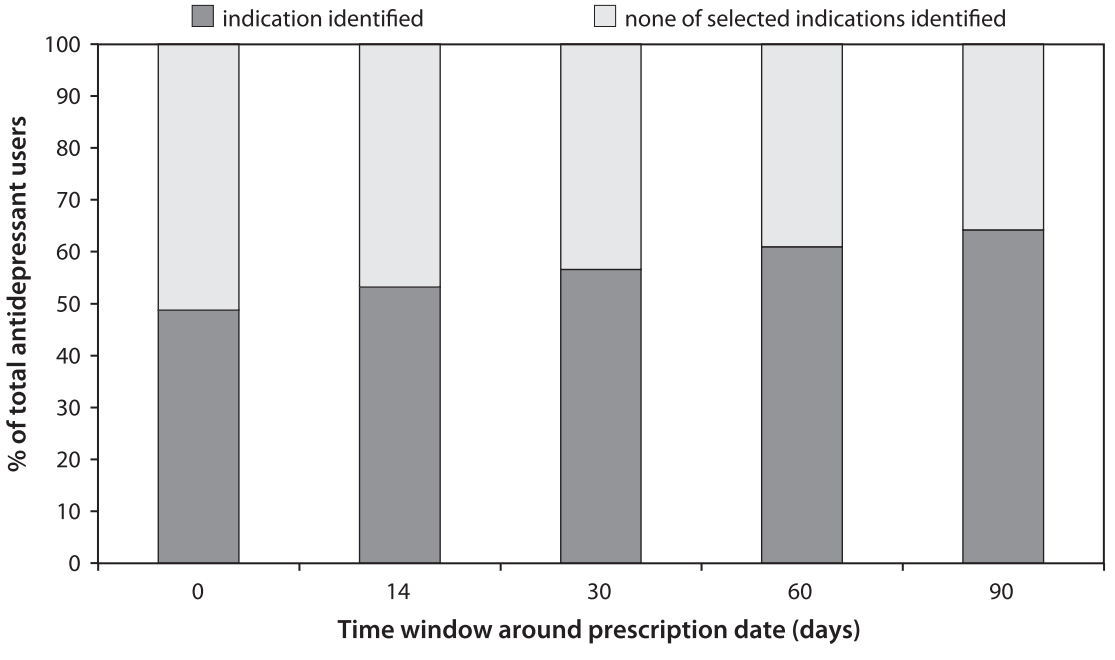
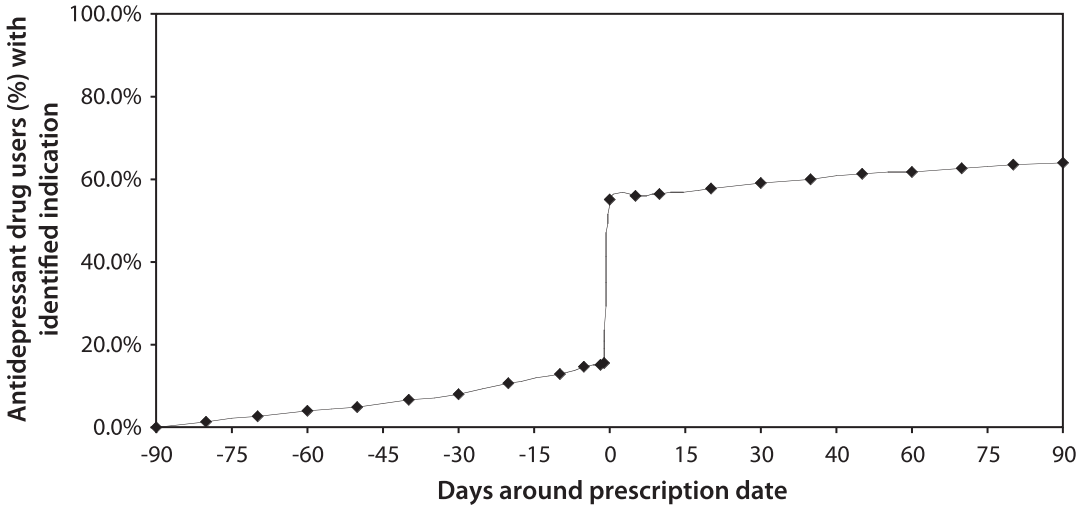


Figure 2 **Cumulative changes in amount of antidepressant drug users identified with one of the selected indications in their physician-patient contact files over time**



The time window ranges from 90 days prior to until 90 days post prescription date (0).

drug users with the indication depression registered in the physician-patient contact file is related to characteristics such as type of antidepressant, gender, age, time window and whether or not a second antidepressant prescription is prescribed in the 90 days following first prescription. The indications anxiety and sleeping disorders were quite frequently found registered in the physician-patient contact file of the antidepressant drug users as these disorders are known to be co-morbid with depression.[31,32]

Depression and anxiety are the most often registered indications for prescribing on prescription date (0 days time window) while the indications neuropathic pain, headache/migraine, sleeping disorders and enuresis/incontinence are less frequently registered on prescription date. With regard to depression expanding the time window did not result in a large increase in total amount of antidepressant drug users identified with depression. For other indications such as enuresis/incontinence, sleeping disorders and headache/migraine expanding the time window from 0 days to 180 days around prescription date had a large effect on the number of antidepressant drug users identified with the previously mentioned indications. Although most of the antidepressant drug users with the selected indications registered in their physician-patient contact file had the indication registered on prescription date about 14% got the indication registered post prescription date, suggesting that in some cases the GPs base the indication for prescribing on the effect of the therapy. This implies that when use of a specific medicine in combination with a diagnostic code(s) is used to identify patients with a specific disease the length of time windows applied can influence the outcome.

Many of the antidepressant drug users did not have any of our selected indications for prescribing registered in the physician-patient contact file. A possible explanation could be that the GPs did not register the indication for prescribing in the physician-patient contact register. This could happen when patients visit the GP due to a disease, unrelated to their antidepressant drug use, where they get a re-fill on their antidepressant drug prescription. When investigating the age of the antidepressant drug users who did not have any of our selected indications registered in the physician-patient contact file we found that these were mostly older users. Older patients are more likely to be in poor health, suffering from other co-morbid conditions, using more medication and having more frequent consultations with the GP, which would support previously mentioned explanation. Another reason could be that some of the patients pick up a prescription at the general practice without a consultation with the GP, resulting in a prescription without a registered indication for prescribing. This kind of situation would more likely apply to the younger patients who just 'drop by' to pick up a prescription. In addition, there is always the possibility that a diagnosis is not registered due to diagnostic uncertainty,

where the GP is still in the phase of evaluating the patient. When we investigated the antidepressant drug users who were receiving their antidepressant for the first time we found that about 40% of them had none of our selected indications registered in the physician-patient contact file. For the antidepressant drug users who had received their antidepressant drug before 2001 this proportion was about 28%. This supports our theory that the GP might not register the indication for antidepressant drug prescribing as he/she is still evaluating the patient. Finally, there is also the possibility that the GP prescribed the antidepressant for an indication other than those we selected to investigate in this study.

Limitations to our study are firstly the large amount of antidepressant drug users for whom none of our selected indications could be identified in the physician-patient contact file. We do not know the reasons for the indications not being registered in the physician-patient contact file and if this information were available it could influence the outcome of our study. Most of the antidepressant drug users had physician-patient file data information available from October 2000 until June 2002. An extra analysis was performed to specifically investigate if our results were being influenced by patients who received their antidepressants in the first three months of 2001 and did not have a full 90-day history prior to prescription date. The analysis verified that this limitation didn't influence our results.

Secondly, the study is performed in a general practice setting and did not include the antidepressant users who receive their antidepressants from a psychiatrist or those submitted to psychiatric wards. These patients would represent a more severely diseased group, which could influence how the antidepressant users are divided over the different indications for antidepressant drug prescribing.

As we have shown it is difficult to draw conclusion about depression in the general population based on prescription data only. Prescription data can be used in combination with clinical data to identify specific diseases.[33,34] This is a useful method when constructing patient cohorts of, e.g., type I diabetic patients, as insulin is only indicated for treatment of diabetes. However, when considering medicines that are indicated for treatment of more than one disease, like the antidepressants, it gets more complicated to construct these types of cohorts. From our study we see that although depression is the main indication for antidepressant drug prescribing it is not the only one. Using antidepressant drug use as a proxy for identifying depressed patients in a prescription database should therefore be done with caution and when constructing cohorts of depressed antidepressant drug users, prescription data should preferably be used in combination with clinical data. Not being able to identify why the antidepressant treatment is being initiated makes it difficult to study depression in databases without accepting some bias into

the study. It would be more proper for these types of research to use antidepressants as a name instead.

In conclusion, GPs prescribe antidepressants predominantly for treating depression and most of the time they register the indication for prescribing on prescription date. When use of a specific medicine in combination with a diagnostic code(s) is used to identify patients with a specific disease the length of time windows around prescription date applied can influence the outcome. A proportion of the antidepressant drug users receives the possible indication for prescribing prior to or post antidepressant drug prescription. Further research is recommended to investigate if and how these antidepressant drug users differ from those that receive indication for prescribing on prescription date.

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2.2

An algorithm to identify antidepressant users with a diagnosis of depression from prescription data

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ABSTRACT

Objective

Antidepressants are used for many indications besides depression. This makes investigating depression treatment outcomes in prescription databases problematic when the indication is unknown. The aim of our study is to develop an algorithm to identify antidepressant drug users from prescription data that suffer from depression.

Methods

Data for deriving the algorithm were obtained from the Second Dutch National Survey of General Practice, carried out in 2001 by The Netherlands Institute for Health Services Research (NIVEL), and for validation the Integrated Primary Care Information (IPCI) database was used. Both sets included adults receiving their first antidepressant drug in 2001 (n=1855 and n=3321, respectively). The outcome was a registered diagnosis of depression. Covariates investigated for developing the algorithm were patient and prescribing characteristics, and co-medication.

Results

The predictive algorithm included age, selective serotonin reuptake inhibitor (SSRI) prescribed on the index date, prescribed dose, general practitioner as prescriber and the number of antidepressant prescriptions prescribed plus medication for treating acid related disorders, laxatives, cardiac therapy or hypnotics/sedatives prescribed in the six months prior to index date. The probability that the algorithm correctly identified an antidepressant drug user as having a depression diagnosis was 79% with a sensitivity of 79.6% and a specificity of 66.9%.

Conclusion

In conclusion, we developed and validated an algorithm that can be used to compose cohorts of patients treated with antidepressants for depression from prescription databases.

INTRODUCTION

Many studies have been performed on antidepressant drug use investigating a multitude of outcomes such as efficacy and tolerability,[1] patterns of prescribing,[2-7] user characteristics,[8,9] and health utilization costs.[10] Studies on outcomes of antidepressant drug use have often been performed in prescription databases and consequently the results focus on the outcomes of antidepressant drug use rather than that of the diseases and symptoms that the antidepressants are intended to treat. Although the name 'antidepressant' correctly suggests that these medicines can be used to treat depression, nowadays the indications for antidepressant drug prescribing have broadened. Antidepressants are prescribed for a variety of psychiatric illnesses such as generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social phobia and bulimia nervosa. In addition, antidepressants are prescribed for somatic illnesses such as enuresis/incontinence, sleeping disorders, migraine prophylaxis, functional dyspepsia and neuropathic pain.[11-17] A recent study investigating the indications for which antidepressant drugs are prescribed in general practice revealed that general practitioners (GPs) prescribe antidepressants for various diseases and symptoms of which depression only contributed to around 45.0% while anxiety accounted for 17.0%, headache 2%, and obsessive-compulsive disorder and phobias for 1.5%.[18]

Unfortunately most prescription databases do not include information on the clinical reasons for prescribing. Researchers have tried to solve this problem by developing disease specific algorithms.[19-22] The development of such an algorithm is performed in databases where information on patient characteristics, medication use and diagnoses are available. The developed algorithm can subsequently be used in prescription databases to calculate the patient's probability of having a specific disorder based on a covariate profile including the patients' characteristics, prescriber information and medication use. Spettell et al.[23] investigated simple algorithms to identify patients with depression from administrative data, using both diagnostic and prescription data, but to our knowledge no such algorithm has been developed for use in prescription databases where diagnostic data is not readily available.

The aim of our study is to develop and validate an algorithm that can be used to compose cohorts of patients treated with antidepressants for depression from prescription databases.

METHODS

A diagnostic study was performed to develop an algorithm that identifies patients that use an antidepressant to treat depression from prescription database. The accuracy of the diagnostic algorithm was validated in a different population in the Netherlands.

Setting and study population

Data for the derivation set were obtained from the Second Dutch National Survey of General Practice (DNSGP-2) which was carried out in 2001 by the Netherlands Institute for Health Services Research (NIVEL) and has been described in detail elsewhere.[24] In short, 195 GPs in 104 practices registered all physician-patient contacts during 12 months. The GPs registered all health problems presented within a consultation in a standardized manner and diagnoses were coded using the ICPC scheme (International Classification of Primary Care).[25]

A part of the patients included in the DNSGP-2 have been linked to pharmacy dispensing data, which includes prescription data for the patients from 1999 until the end of 2003.[26] Thus, each patient had a complete prescription history spanning at least the 12 months prior to and 12 months post index date. The pharmacy dispensing data contains information on the dispensed drug, dispensing date, amount dispensed, prescribed dosage regimen and the estimated duration of use. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.[27] 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. 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.[28]

The source population included individuals registered in the DNSGP-2 who could be linked to pharmacy dispensing data (n=110 078). Patients, 18 years and older, from the source population who got an antidepressant prescription dispensed from a pharmacy in the year 2001 where selected (n=5140). The date of the first dispensed antidepressant prescription in year 2001 was set as index date. Only new starters of antidepressant drug therapy (n=1855) were selected thus those with any antidepressant drug use in the 12 months preceding the index date were excluded. 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).

Data for the validation set were obtained from the Integrated Primary Care Information (IPCI) database at the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam, the Netherlands. The IPCI database is a general practice research database with coded and anonymous electronic patient records of more than 800 000 patients from approximately 100 GPs. The database includes information on demographics, symptoms and diagnoses (ICPC and free text), clinical and laboratory findings, referrals, hospitalizations, and prescription information. Information on prescribed medicines includes drug name, ATC code, dose, dosage form, prescribed quantity and indication for prescribing.

The source population included individuals, 18 years and older, registered in the IPCI database in the year 2001 (n=341 498). The study population was composed of patients from the source population who got an antidepressant prescription from a GP in 2001 (n=7478). The date of the first dispensed antidepressant prescription in 2001 was set as index date. Only new starters of antidepressant drug therapy (n=3321) were selected thus those with any antidepressant drug use in the 12 months preceding the index date were excluded. Each patient had a complete prescription history spanning the 12 months prior to and 12 months post index date.

Development of diagnostic algorithm

The outcome was defined as depression diagnosed and registered by a GP. The antidepressant drug users who at any point during the 12 months of the DNSPG-2 study had the ICPC codes 'depression' or 'feeling depressed' (ICPC = P03, P76) registered in their medical file were defined as having a depression diagnosis. The antidepressant drug users that did not have a depression or feeling depressed diagnosis registered in their medical file had other diagnoses that could be associated with their antidepressant drug use such as anxiety disorder, obsessive-compulsive disorder, eating disorders, enuresis, incontinence, headache, migraine, sleeping disorder or neuropathic pain. For about a third of the study population no registered or clinically accepted indication for antidepressant drug prescribing was found in the medical file.[18]

The same method was used to define the outcome for the validation set as for the derivation set. Antidepressant drug users were defined as having a depression diagnosis if the ICPC codes 'depression' or 'feeling depressed' (ICPC = P03, P76) were found in their medical file as indication for prescribing or free text during the 12 months around the index date.

Covariates

The covariates that were investigated in this study were patient characteristics (age, gender), antidepressant characteristics (type of antidepressant prescribed at index date [TCA, SSRI, other], dose of the 2nd consequent antidepressant prescription following index date, if the first and second consequent antidepressant prescription differed [switch], number of antidepressant prescriptions received in 12 months following index date, type of prescriber at index date [GP, specialist/other/unknown]) and co-medication prescribed 6 months prior to and 6 months post index date. To investigate co-medication, all medicines were divided into groups according to second level ATC grouping, for example A01, A02. Each second level ATC group was investigated as a covariate. We chose to select the dose of the 2nd antidepressant prescription as a covariate to compensate for gradual titration to effective therapeutic dose, as is custom in the beginning of an antidepressant drug treatment. The dose is expressed as amount of defined daily dose (DDD). A 2nd prescription was considered to be a consequent prescription if it was dispensed within 30 days following the theoretical end date (index date plus amount dispensed divided by dose) of the antidepressant drug prescription prescribed on index date. For those antidepressant drug users without a 2nd consequent prescription the dose for the antidepressant prescription on index date was used.

Data analysis

The association between a diagnosis of depression and the potential diagnostic covariates was quantified using univariate logistic regression analysis. The independent contributions of covariates with an univariate association p-value < 0.20 were included in a multivariate logistic model and assessed by forward stepwise multivariate logistic regression analysis. The algorithm resulting from the multivariate logistic regression was reduced by excluding predictors with p-value > 0.10.

The probability of patients having a diagnosis of depression was calculated using the formula $1/(1+e^{-x})$ in which x is the sum of the constant and product terms of the regression coefficients and variables representing different covariates. The logistic regression produced predicted values ranging from 0 to 1, obtained by multiplying the observed values for each independent variable by the coefficients obtained in the regression model. Different possible cut-off probabilities between 0 and 1 were selected to maximize sensitivity and specificity. The amount of patients correctly and incorrectly classified as having a diagnosis of depression for the different cut-off probabilities was determined. Sensitivity (i.e. proportion of people with recorded depression diagnosis correctly classified as such), specificity (i.e. proportion of people without a recorded depression diagnosis correctly classified

as such) and positive predictive value (PPV, i.e. posterior probability of having a recorded depression diagnosis given that patients are classified as such according to the algorithm) were computed.

Validation of the diagnostic algorithm

To validate the algorithm internally we investigated its reliability and discrimination.[29] The reliability (goodness of fit) refers to the correspondence between estimated probability and observed frequencies which was evaluated by using the Hosmer and Lemeshow test.[30] The discrimination, or the ability of our algorithm to separate antidepressant drug users with and without diagnosis of depression, was measured using the area under the receiver operating characteristic (ROC) curve. The area under the ROC curve is the probability that the results are correctly classified, given one antidepressant user with a diagnosis of depression and one without. Area under

Table 1 **Basic demographics of the study population, derivation and validation set**

	Derivation set n=1855 (100%)	Validation set n=3231 (100%)	p-value
Patient characteristics			
female gender	1235 (66.6%)	2112 (65.4%)	0.86
age in years, mean (sd)	50.1 (16.8)	49.1 (16.4)	0.52
Antidepressant (AD) characteristics			
SSRI	1052 (56.7%)	1678 (51.9%)	
TCA	550 (29.6%)	790 (24.5%)	
other [a]	253 (13.6%)	763 (23.6%)	<0.01
Number of AD prescriptions in one year			
only one AD prescription	414 (22.3%)	1067 (33.0%)	
two to four AD prescriptions	490 (26.4%)	1014 (31.4%)	
five or more AD prescriptions	951 (51.3%)	1150 (35.6%)	<0.01
Second AD is different from first AD (switch)	77 (4.2%)	69 (2.1%)	<0.01
Dose			
< 0.5 DDD per day	426 (23.0%)	687 (21.3%)	
0.5–0.99 DDD per day	218 (11.8%)	620 (19.2%)	
≥ 1.0 DDDs per day	1211 (65.3%)	1924 (59.5%)	<0.01
Type of prescriber (index date)			
general practitioner	1555 (83.8%)	3224 (99.8%)	
specialist/other/unknown	300 (16.2%)	7 (0.2%)	<0.01

sd = standard deviation; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; DDD = defined daily dose

a) Other antidepressants: moclobemide, mianserin, trazodone, mirtazapine, venlafaxine.

Table 2 **Antidepressant users (n=1855) from the derivation set divided into those with and without a recorded diagnosis of depression**

	Recorded depression n=961 (100%)	No recorded depression n=894 (100%)	p-value [a]
Patient characteristics			
female gender	638 (66.4%)	597 (66.8)	0.859
age in years, mean (sd)	50.3 (17.0)	49.7 (16.6)	0.519
Antidepressant (AD) characteristics			
SSRI	694 (72.2%)	358 (40.0%)	
TCA	131 (13.6%)	419 (46.9%)	
other [b]	136 (14.2%)	117 (13.1%)	<0.001
Number of AD prescriptions dispensed in one year			
only one AD prescription	131 (13.6%)	283 (31.7%)	
two to four AD prescriptions	249 (25.9%)	241 (26.9%)	
five or more AD prescriptions	581 (60.5%)	370 (41.4%)	<0.001
Second AD is different from first AD (switch)	53 (5.5%)	24 (2.7%)	0.002
Dose			
< 0.5 DDD per day	80 (8.3%)	346 (38.7%)	
0.5–0.99 DDD per day	93 (9.7%)	125 (14.0%)	
≥1.0 DDDs per day	788 (82.0%)	423 (47.3%)	<0.001
Type of prescriber (index date)			
general practitioner	896 (93.2%)	659 (73.7%)	
specialist/other/unknown	65 (6.8%)	235 (26.3%)	<0.001
Medication use 6 months prior to index date (ATC group)			
acid related disorders (A02)	154 (16.0%)	180 (20.1%)	0.021
laxatives (A06)	80 (8.3%)	101 (11.3%)	0.031
diabetic drugs (A10)	45 (4.7%)	56 (6.3%)	0.134
cardiac therapy (C01)	33 (3.4%)	55 (6.2%)	0.006
antiinflammatory & antirheumatic agents (M01)	230 (23.9%)	292 (32.7%)	<0.001
anesthetics (N01)	7 (0.7%)	12 (1.3%)	0.189
analgesics (N02)	168 (17.5%)	213 (23.8%)	0.001
antiepileptics (N03)	20 (2.1%)	33 (3.7%)	0.038
parkinson medicines (N04)	5 (0.5%)	9 (1.0%)	0.226
antipsychotics (N05A)	34 (3.5%)	30 (3.4%)	0.830
anxiolytica (N05B)	296 (30.8%)	246 (27.5%)	0.120
hypnotics/sedatives (N05C)	211 (22.0%)	159 (17.8%)	0.025
other nervous system drugs (N07)	42 (4.4%)	31 (3.5%)	0.318
Medication used 6 months past index date (ATC group)			
acid related disorders (A02)	158 (16.4%)	174 (19.5%)	0.090
laxatives (A06)	95 (9.9%)	110 (12.3%)	0.097
diabetic drugs (A10)	47 (4.9%)	56 (6.3%)	0.197
cardiac therapy (C01)	32 (3.3%)	45 (5.0%)	0.066
antiinflammatory & antirheumatic agents (M01)	199 (20.7%)	258 (28.9%)	<0.001

anesthetics (N01)	10 (1.0%)	13 (1.5%)	0.421
analgesics (N02)	181 (18.8%)	200 (22.4%)	0.060
antiepileptics (N03)	25 (2.6%)	48 (5.4)%	0.002
parkinson medicines (N04)	7 (0.7%)	9 (1.0%)	0.517
antipsychotics (N05A)	49 (5.1%)	44 (4.9%)	0.861
anxiolytica (N05B)	290 (30.2%)	260 (29.1%)	0.606
hypnotics/sedatives (N05C)	207 (21.5%)	162 (18.1%)	0.065
other nervous system drugs (N07)	26 (2.7%)	27 (3.0%)	0.684

sd = standard deviation; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; ATC = Anatomical Therapeutic Chemical

a) Chi Square statistics; the p-values are originated from univariate analysis of each covariate.

b) Other antidepressants: moclobemide, mianserin, trazodone, mirtazapine, venlafaxine.

curve (AUC) ranges from 0.5 (no apparent accuracy) to 1.0 (perfect accuracy). The AUC was calculated through the trapezoidal rule.[31]

For external validation, we assessed the generalizability and applicability of the derived algorithm by applying it to the validation set. The discrimination ability was estimated using ROC curves.

RESULTS

Derivation of the algorithm

The demographic and clinical characteristics of the 1855 antidepressant drug users are presented in Table 1. The derivation set was about 67% female with a mean age (standard deviation; sd) of 50.0 (17.0) years. More than half of the antidepressant drug users received an SSRI and most prescriptions were prescribed by a GP (84%). About 22% received only one antidepressant prescription during the 12 months following index prescription while 51% received five or more prescriptions during this period. With regards to co-medication 29% of the antidepressant drug users received anxiolytics (ATC N05B), 28% anti-inflammatory agents (ATC M01), 20% analgesics (ATC N02) and 20% hypnotics/sedatives (ATC N05C) in the 6 months prior to index date. Of the 1855 antidepressant drug users, 961 (51.8%) patients had a recorded diagnosis of depression in their medical files.

The independent contributions of different covariates with a p-value below 0.20 are presented in Table 2. In Table 2, we also present an overview of use of nervous system drugs (ATC group N) in our derivation set. Although age and gender did not show a p-value below 0.20 they were included in the model. The multiple logistic regression showed that age, SSRIs rather than other antidepressants prescribed on the index date, the dose of the second prescription, GP as prescriber

Table 3 **Variables from multivariate logistic regression of the derivation set that predict a registered depression diagnosis in the antidepressant users medical file**

Variables	β	SE	Exp(β)	95%CI
Patient characteristics				
age	0.014	0.004	1.014	1.007–1.021
Antidepressant (AD) characteristics				
SSRI	0.315	0.145	1.370	1.014–1.852
Number of AD prescriptions dispensed in one year				
only one AD prescription			reference	
two to four AD prescriptions	0.881	0.159	2.412	1.767–3.293
five or more AD prescriptions	1.016	0.143	2.763	2.089–3.655
Second AD is different from first AD (switch)	0.489	0.274	1.631	0.953–2.793
Number of DDDs				
< 0.5 DDD per day			reference	
0.5–0.99 DDD per day	1.214	0.199	3.367	2.279–4.975
≥ 1.0 DDDs per day	1.827	0.192	6.216	4.270–9.048
Type of prescriber (index date)				
general practitioner	1.709	0.163	5.524	4.013–7.605
Medication use 6 months prior to index date				
acid related disorders (A02)	–0.313	0.146	0.731	0.550–0.973
laxatives (A06)	–0.323	0.191	0.724	0.498–1.052
cardiac therapy (C01)	–1.000	0.268	0.386	0.217–0.622
hypnotics & sedatives (N05C)	0.363	0.141	1.438	1.090–1.896
Constant	–4.344	0.303	0.013	

SE = standard error; SSRI = selective serotonin reuptake inhibitor; DDD = defined daily dose

of antidepressants and the number of antidepressant prescriptions dispensed in the 12 months following the index date plus medication dispensed for treating acid related disorders, laxatives, cardiac therapy or hypnotics/sedatives prescribed in the 6 months prior to index date are significant correlates with depression recorded in the GP medical file. In a population of first time antidepressant drug users the probability that an antidepressant drug is prescribed in a patient with recorded depression is therefore $1/(1+e^{-x})$ in which:

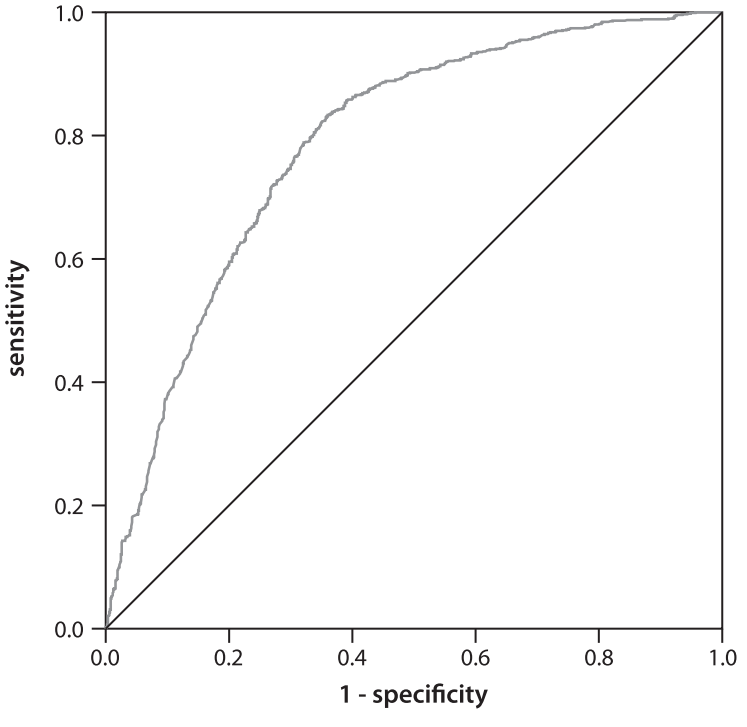
$$x = -4.344 + 0.014 \times \text{age} + 0.315 \times \text{SSRI} + 1.214 \times \text{dose}_{0.5\text{-}0.99\ \text{DDD}} + 1.827 \times \text{dose}_{\geq 1.0\ \text{DDD}} + 0.489 \times \text{switch} + 0.881 \times \text{nr}_{2\text{-}4}\ \text{of Rx's during 12 months} + 1.016 \times \text{nr}_{\geq 5}\ \text{of Rx's during 12 months} + 1.709 \times \text{GP prescriber on index date} - 0.313 \times \text{A02} - 0.323 \times \text{A06} - 1.0 \times \text{C01} + 0.363 \times \text{N05C}$$

The model coefficients are presented in Table 3. The strongest predictors were GP as prescriber on index date (OR 5.5; 95%CI 4.0–7.6), higher doses compared to

lower doses (OR 6.2; 95%CI 4.3–9.0 for 1 or more DDDs versus < 0.5 DDDs) and receiving more than one antidepressant prescription in 12 months following the first prescription (OR 2.8; 95%CI 2.1–3.7 when receiving five or more antidepressant prescriptions).

The Hosmer and Leweshow goodness-of-fit test supported the reliability of the algorithm (p = 0.40). The area under the ROC curve was 0.79 (95% CI 0.77–0.81) and is presented in Figure 1. The probability that the algorithm correctly identifies an antidepressant drug user receiving antidepressant as having a recorded diagnosis of depression was 79%. With a cut-off level of 0.5 for the predicted probability of having a recorded diagnosis of depression when receiving an antidepressant prescription the algorithm had a sensitivity of 79.6% and a specificity of 66.9%. The sensitivity, specificity and positive predictive value for the different cut off values are presented in Table 4.

Figure 1 **Receiver operator characteristic curve (ROC) for the multivariate logistic regression model predicting diagnosis of depression in a population of first time antidepressant users**



The curve shows sensitivity versus 1-specificity based on probabilities computed through multivariable logistic regression. Area under curve = 0.79.

Table 4 Sensitivity, specificity and positive predictive value of the algorithm

Probability	Recorded depression	No recorded depression	Sensitivity (%)	Specificity (%)	PPV (%)
≥ 0.1	949	773	98.7	13.5	55.1
≥ 0.2	930	646	96.8	27.7	59.0
≥ 0.3	885	500	92.1	44.1	63.9
≥ 0.4	832	365	86.6	59.1	69.5
≥ 0.5	765	296	79.6	66.9	72.1
≥ 0.6	671	236	69.8	73.6	74.0
≥ 0.7	531	161	55.2	82.0	76.7
≥ 0.8	137	26	14.3	97.1	84.0

PPV = positive predictive value

External validation of the algorithm

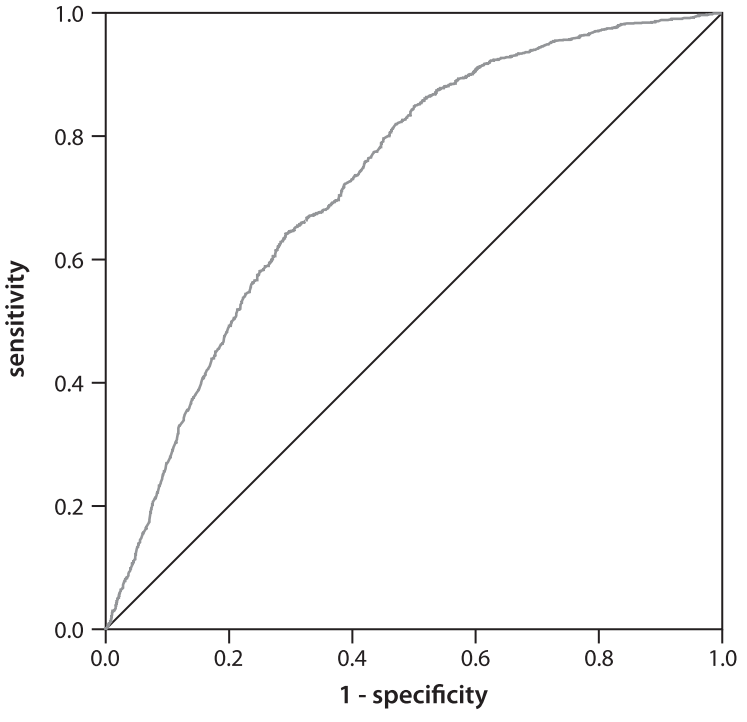
Table 1 shows the demographic and clinical characteristics of the validation study population. There were several differences between the derivation and validation sets. The antidepressant drug users in the validation set were slightly older and almost all received a prescription from a GP (99.8%). A larger proportion of the antidepressant drug users in the validation set received other antidepressants than SSRI or TCA on the index date and more antidepressant drug users receiving only one antidepressant prescription during the 12 months from index date. Switching of antidepressant drug was also less common than in the derivation set. Of 3231 antidepressant drug users, 1494 (46.2%) had a recorded depression diagnosis in their medical files.

When applied to the validation set population, the depression algorithm showed a discrimination property of 73.0% (95% CI 71.3–74.7%). The area under the ROC curve is presented in Figure 2. The sensitivity and specificity, for a cut-off level of 0.5 for the predicted probability, were 81.5% and 53.0%, respectively.

DISCUSSION

We have developed an algorithm that can be used on prescription data to identify patients on antidepressant drug therapy with a diagnosis of depression. To our best knowledge this is the first depression identifying algorithm that uses prescription data only.

Figure 2 **Receiver operator characteristic curve (ROC) for the validation set predicting diagnosis of depression in a population of first time antidepressant users**



The curve shows sensitivity versus 1-specificity based on probabilities computed through multivariable logistic regression. Area under curve = 0.73.

Prescription databases are useful tools to investigate therapeutic treatment and clinical outcomes but often lack information on which diseases or symptoms the drug is being prescribed for. Selecting medicines as a proxy for disease can be problematic as most drugs can be prescribed for more than one illness or symptom. There are differences in the sensitivity of a certain drug for identifying a specific disease. Kolodner et al.[21] showed that using a prescription of antimigraine preparations as a marker for migraine has very low sensitivity of 11.1%, while Shackleton et al.[19] reported that using epilepsy medication polytherapy as a marker for epileptic patients shows high sensitivity (79%). As the antidepressants are being prescribed for various illnesses other than depression, the depression algorithm presented here can serve as a useful tool in observational studies that investigate antidepressant treatment outcomes in depressed patients.

The developed algorithm has been shown to exert a discrimination property of 73% and 79% in two populations. Although there is no measurement reference stating

whether discrimination ability is 'good enough', a rough guide classifies algorithms with a discrimination ability of 70–80% as fair. In addition, the algorithm is easy to use as it includes only basic variables that can be found in most prescription databases. Applying the algorithm would create a more homogenous study cohort from prescription databases when there is need to study patients suffering from depression. It can serve as a tool for researchers that undertake studies in prescription databases that focus on investigating long-term treatment outcomes for depressed patients.

There are some limitations to our algorithm. Firstly, the algorithm is developed in a population of antidepressant drug users and as a result it can not identify patients with a depression diagnosis who are not treated with antidepressants. Secondly, although we did validate our algorithm externally in another population in the Netherlands, it might not be valid for every country. In the Netherlands the GP is a gatekeeper to secondary care. This situation will vary in other countries, where the structure of primary and secondary care differs from that of the Netherlands. Thirdly, the algorithm is developed and validated in data from 2001 and as treatment guidelines and indication scope of antidepressant drug use broadens throughout the years applying it on older data specifically during the years when the SSRIs were newly marketed is not advisable. With regards to newer data, the validity of the algorithm needs to be ascertained. Fourthly, our algorithm identifies patients on antidepressants that have a depression diagnosis recorded in their medical files. This diagnosis is often made by a GP and may not be consistent with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria. In this study, we chose a non-strict definition of depression including both patients with codes for symptoms of depression (P03) and the formal diagnosis (P76). Symptoms of depression are frequently a precursor of a depression diagnosis. Only 17% of the antidepressant drug users had registered symptoms of depression (P03) without a subsequent depression diagnosis. In an earlier study we found that GPs often fail to register the reason for prescribing the antidepressant.[18] We expect a part of these patients to receive a depression diagnosis later on. In addition, the GPs lack of registering the indication for prescribing can lead to a misclassification error that would probably lower the sensitivity of our algorithm. Lastly, the algorithm is based on incident and not on prevalent users, which limits its use in studies of cross sectional design.

Although we believe that the algorithm can be a useful tool to identify patients with a recorded depression diagnosis there are still gaps that need to be filled when studying depression in prescription databases. A marker for depression severity is still missing. In addition, using antidepressants as a proxy to identify depressed

patients leaves out patients suffering from depression that receive other kind of treatment such as psychotherapy.

In conclusion, we have managed to develop and validate an algorithm that can be used to identify depressed patients on antidepressant therapy. The algorithm is a useful tool that can be used to compose cohorts of patients treated for depression from prescription databases.

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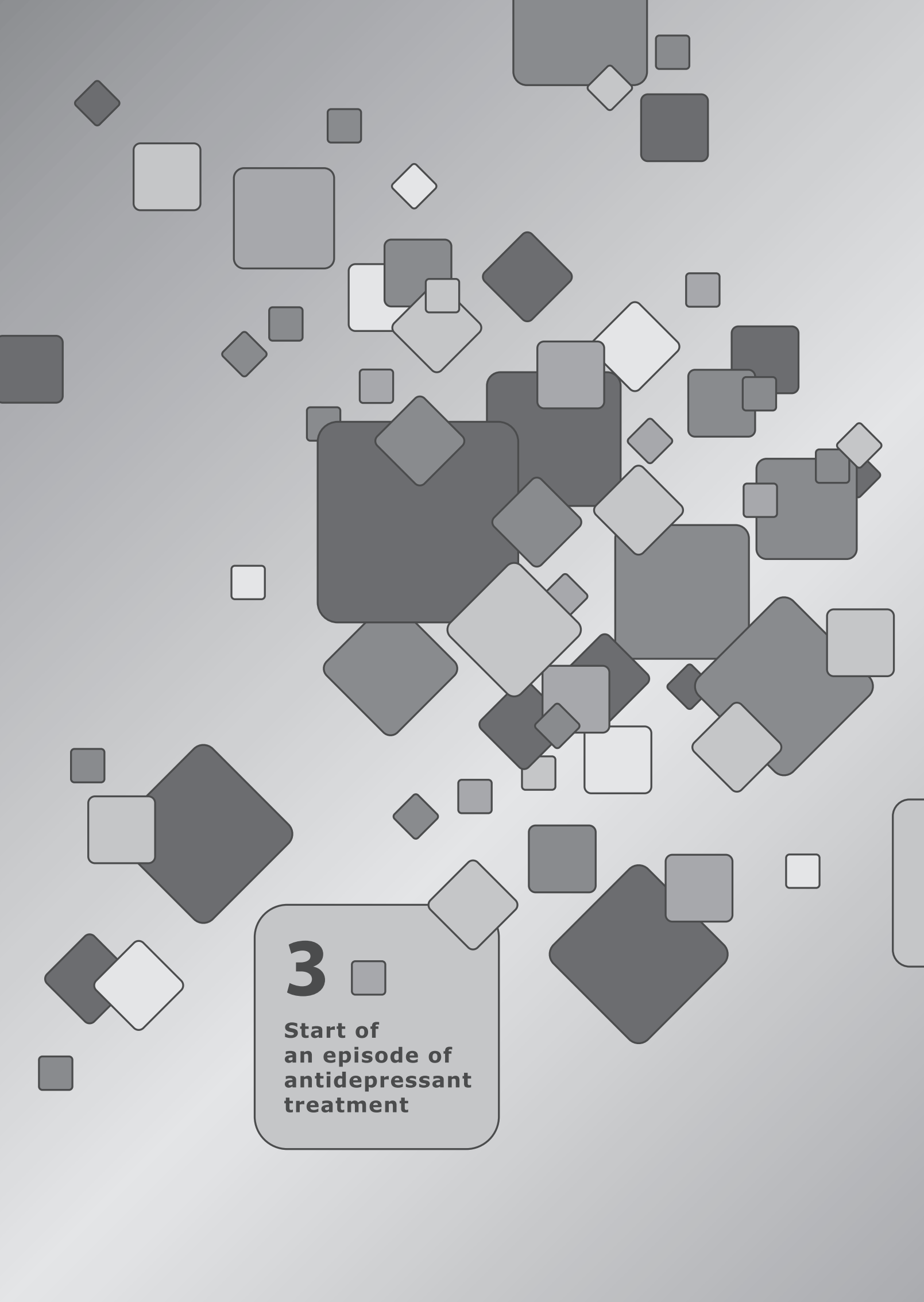

3

Start of an episode of antidepressant treatment

3.1

Initiation of antidepressant therapy: do patients follow the GP's prescription?

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ABSTRACT

Objective

The question whether patients actually start drug taking after having received a first antidepressant prescription is often overlooked. The aim of this study was to determine the incidence of patients who do not fill or fill only a single antidepressant prescription at the pharmacy, and to identify associated patient characteristics.

Methods

This was a retrospective study, linking a general practice to a pharmacy dispensing database. The study population included patients who received a first-time antidepressant prescription from a general practitioner in the Netherlands. Three patient groups were identified: (1) patients who did not fill the prescription (nonfillers); (2) patients who filled only a single prescription (single Rx-fillers); and (3) patients who filled at least two consecutive prescriptions. Nonfillers and single Rx-fillers were combined into a group of decliners.

Results

Of all 965 patients, 41 (4.2%) did not fill the prescription, and 229 (23.7%) filled only a single prescription. Patients who consulted their general practitioner for a non-specific indication, rather than for depression, anxiety, panic or obsessive-compulsive disorder, were almost three times more likely (odds ratio [OR] 2.7; 95% confidence interval [95%CI] 1.8–3.9) to decline treatment. Further, the risk of declining was almost fivefold higher (OR 4.8; 95%CI 2.1–11.3) in non-Western immigrants, and almost two times higher (OR 1.8; 95%CI 1.2–2.8) in patients > 60 years of age.

Conclusion

Over one in four patients who receive a first-time antidepressant prescription decline treatment; they either do not initiate drug taking or do not persist antidepressant use for longer than two weeks.

INTRODUCTION

Initiation of drug taking is a complicated process, as it involves patients and physicians making consecutive decisions. When faced with a health concern, the patient needs to recognise it as a problem and to decide whether to consult a physician. Thereupon, the physician must be able to recognise and diagnose the patient's health problem and may propose treatment, including drug treatment. If the physician–patient encounter results in a prescription for drug treatment, the patient subsequently has to decide whether to present the prescription at the pharmacy for dispensing. Having filled the prescription, the patient has to initiate treatment by taking the first tablet. And finally, the patient has to decide to persist in drug taking. Although this factual sequence of actions leads to a simple dichotomous decision to initiate or not to initiate drug treatment, it in fact involves a complex cognitive process taking many considerations into account. The decision to initiate drug taking is influenced by the way in which patients evaluate their personal need for medication relative to their concerns about potential negative effects of taking it.[1,2] Patients evaluate whether the physician's advice to start drug taking makes common sense in the light of their own understanding and beliefs about the illness and treatment.

Numerous studies have focused on patients who discontinue antidepressant use before the recommended duration of treatment. Between one-third and one-half of patients stop taking the antidepressant within 3 months, and less than half continue to take their antidepressant medication for a full 6 months.[3-8] Multiple factors have been hypothesised to be predictors of early discontinuation, including sociodemographic-, disease-, and treatment-related factors.[4,8-13] However, initiation of antidepressant drug treatment has hardly been addressed in research. Often overlooked is the question of whether the patient collects the drug at the pharmacy, and whether the patient actually starts drug taking. It has been found that overall (that is, all prescriptions and all therapeutic groups), between 7% and 20% of patients fail to redeem their prescription at the pharmacy.[14-16] These studies, however, do not provide insight into the non-filling of antidepressant prescriptions, and first-time prescriptions in particular. Furthermore, it has been shown that of all patients having an antidepressant dispensed at the pharmacy, up to 38% fill only a single prescription.[6,17-20] Of those filling only a single antidepressant prescription, one-third never initiate drug taking.[3,20]

To date, there have been no studies published that specifically explored the extent and determinants of declining the prescription for a new antidepressant treatment. The aim of this study therefore was to determine the incidence of patients who do not fill the first-time antidepressant prescription or redeem only a single

antidepressant prescription at the pharmacy; and to identify patient characteristics associated therewith.

METHODS

Study setting

Data for this study were obtained by linkage of routine registration data collected in general practice to a pharmacy dispensing registration database. In the Netherlands, every individual is listed in a general practice. General practice data were obtained from the Second Dutch National Survey of General Practice (DNSGP-2), which was carried out in 2001 by the Netherlands Institute for Health Services Research (NIVEL) in cooperation with the National Institute for Public Health and the Environment. The DNSGP-2 has been described in detail elsewhere.[21] In short, 195 general practitioners (GPs) in 104 practices registered details for all physician–patient contacts, including prescriptions and referrals, during 12 months in a standardised way. GPs were trained during an intensive course on coding practices and problems by the LINH (Dutch Information Network GPs). The GPs registered and coded all health problems presented within a consultation according to the International Classification of Primary Care.[22] Furthermore, 76.5% of the total source population responded to a sociodemographic census with questions on health insurance, educational level, employment status, and perceived health. Most census data were collected in 2000. Pharmacy dispensing data were collected by the Foundation for Pharmaceutical Statistics (SFK). Medication histories of Dutch pharmacies are virtually complete because almost all patients fill their prescriptions, from GPs and medical specialists, at a single pharmacy. Data from both sources were linked by researchers from Utrecht University.[23] In total, 110 102 patients from 83 general practices participating in DNSGP-2 were identified in 112 pharmacies that delivered data to SFK. The SFK data include dispensing data for the patients from 1999 to 2003. Linking was based on the patient's sex, year of birth, postal code, and prescription characteristics. Prescription characteristics were used in the linking process because the other three linking keys did not provide unique matches for all patients. Linking GP prescribing and pharmacy dispensing data makes it possible to distinguish between drug prescribing and dispensing, which offers the possibility to assess whether prescriptions from the GP are collected at the pharmacy.

Study population

Subjects for the study were patients aged over 18 years, who received a first-time prescription for a second-generation antidepressant (selective serotonin reuptake

inhibitor [SSRI], venlafaxine, or mirtazapine) from the GP in the year 2001. The date of the first antidepressant prescription that the patient received, as registered by the GP, was defined as the prescription date. First-time use was defined as having no antidepressant prescriptions dispensed, according to pharmacy dispensing data, in the 6 months before the prescription date of the study antidepressant. In the Netherlands, guidelines call for a 14-day supply for new prescriptions, and subsequent prescriptions are usually for a 30-day supply.

Outcomes

Three mutually exclusive outcomes were identified: patients who received an antidepressant prescription from the GP, but did not fill that prescription at the pharmacy (non-fillers); patients who filled only a single antidepressant prescription at the pharmacy (single Rx-fillers); and patients who filled at least two consecutive antidepressant prescriptions (initiators). Patients were defined as non-fillers when the first prescription was not dispensed at the pharmacy within 30 days of the prescription date. Patients were defined as single Rx-fillers when the first prescription was dispensed at the pharmacy, but not followed by a second antidepressant dispensing within 30 days after the theoretical end date of the first prescription. All other patients were defined as initiators. The theoretical end date equals the dispensing date of the prescription plus the theoretical duration of drug use, the latter being calculated by dividing the number of units of dispensed drug by prescribed daily dose.

Determinants

To identify patient characteristics associated with declining the first-time antidepressant prescription, three different types of determinants were explored: sociodemographic, health and morbidity, and medication-related characteristics.

Sociodemographic characteristics

Next to age and sex, social status, ethnicity, and living situation were included as sociodemographic characteristics. As indicators for social status, educational level (none/primary school versus secondary school versus college/university), type of health insurance (public versus private), and employment status (employed or in school versus not employed or in school), were included. Furthermore, first- and second-generation immigrants from non-Western countries were compared to the combined population of Western immigrants and the indigenous Dutch population. Finally, variables for living situation (living alone versus living with partner and/or children) and marital status (unmarried versus married/registered partnership versus divorced versus widowed) were included.

Table 1 Characteristics of patients who receive a first-time antidepressant prescription (Rx) in general practice: non-fillers, single Rx-fillers and initiators

Measures	Decliners[a] n=270 (28.0%)		Initiators[d]	p-value[e]	p-value[e]
	Non-fillers[b] n=41 (4.2%)	Single-Rx fillers[c] n=229 (23.7%)	n=695 (72.0%)	Decliners vs Initiators	Non-fillers vs Single Rx-fillers
Sociodemographic characteristics					
Female gender	35 (85.4%)	151 (65.9%)	471 (67.8%)	0.74	0.01
Age in years					
18-30	3 (7.3%)	34 (14.8%)	93 (13.4%)	0.08	0.33
31-45	11 (26.8%)	71 (31.0%)	254 (36.5%)		
46-60	12 (29.3%)	67 (29.3%)	212 (30.5%)		
> 60	15 (36.6%)	57 (24.9%)	136 (19.6%)		
Educational level[f]					
none/primary school	5 (20.0%)	47 (31.1%)	93 (19.4%)	0.01	0.37
secondary school	15 (60.0%)	86 (57.0%)	294 (61.3%)		
college/university	5 (20.0%)	18 (11.9%)	93 (19.4%)		
Employed or in school[f]	9 (34.6%)	69 (46.6%)	248 (51.3%)	0.14	0.26
Non-western background[f]	2 (7.7%)	18 (11.8%)	13 (2.6%)	<0.001	0.54
Marital status[f]					
unmarried	8 (30.8%)	32 (21.2%)	114 (23.3%)	0.33	0.43
married/registered partnership	16 (61.5%)	90 (59.6%)	312 (63.8%)		
divorced	1 (3.8%)	9 (6.0%)	27 (5.5%)		
widowed	1 (3.8%)	20 (13.2%)	36 (7.4%)		
Living together[f]	21 (80.8%)	114 (75.5%)	398 (81.4%)	0.14	0.56
Public health insurance	30 (73.2%)	181 (79.0%)	525 (75.5%)	0.64	0.53

Health and morbidity-related characteristics					
Specific indication for prescribing antidepressant: depression, anxiety, panic, or obsessive compulsive disorder (OCD)	24 (58.5%)	128 (55.9%)	506 (72.8%)	<0.001	0.75
Self-perceived health [f]					
very poor/poor	0 (0.0%)	20 (13.9%)	30 (6.5%)	0.06	0.02
moderate	13 (52.0%)	41 (28.5%)	140 (30.2%)		
good/excellent	12 (48.0%)	83 (57.6%)	293 (63.3%)		
Psychotherapeutic therapy	6 (14.6%)	27 (11.8%)	79 (11.4%)	0.71	0.61
Other chronic diseases	15 (36.5%)	63 (27.5%)	180 (25.9%)	0.35	0.24
Number of other chronic diseases; mean (sd)	0.5 (0.7)	0.4 (0.8)	0.4 (0.7)	0.21	0.67
Number of contacts with GP in previous 6 months; mean (sd)	5.1 (4.6)	5.1 (5.7)	4.8 (5.2)	0.44	0.99
Contact with GP within 28 days after prescription date	25 (61.0%)	107 (46.7%)	487 (70.1%)	<0.001	0.09
Medication-related characteristics					
Use of paroxetine (vs other antidepressants)	17 (41.5%)	113 (49.3%)	387 (55.7%)	0.04	0.35
Co-medication					
benzodiazepines	14 (34.1%)	89 (38.9%)	279 (40.1%)	0.57	0.57
antipsychotics and lithium	1 (2.4%)	9 (3.9%)	18 (2.6%)	0.36	0.64
Number of co-medicines; mean (sd)	3.2 (2.9)	3.9 (4.1)	3.5 (3.8)	0.35	0.33

sd = standard deviation; GP = general practitioer

Percentages of the different measures are calculated with regard to the corresponding subgroup (i.e. non-fillers, single Rx-fillers, and initiators).

a) Decliners: patients who do not fill or only fill a single prescription at the pharmacy (the combined group of non-fillers and single Rx-fillers).
b) Non-fillers: patients who do not fill their first-time antidepressant prescription at the pharmacy.
c) Single Rx-fillers: patients who only fill a single antidepressant prescription at the pharmacy.
d) Initiators: patients who fill at least 2 consecutive antidepressant prescriptions at the pharmacy.
e) Chi-square test was used to compare categorical measures; independent samples *t*-test was used to compare the continues measures.
f) Variables obtained from the patient census which included questions regarding education, personal situation and self-perceived health. Of all patients included in the study, 671 (69.5%) responded to the census.

Health and morbidity characteristics

The physician–patient contact registration includes information on the health problem for which the patient consulted the GP during the study period in the year 2001. The study assessed whether the patient visited the GP during this period due to specific indications for second-generation antidepressants: anxiety/panic disorder (P74), depression (P76), and obsessive-compulsive disorder (OCD)/phobia (P79). These indications are the officially approved indications for the second-generation antidepressants in the Netherlands. The antidepressant drug users could have more than one indication registered in the contact file. If the patient did not visit the GP for any of the specific indications (P74, P76, or P79), the patient was considered as having a non-specific indication for use, including, among others, feeling anxious (P01), depressive feelings (P03), and sleeping problems (P06). The presence of chronic disease and the total number of other chronic diseases for which the patient contacted the GP during 6 months before the prescription date, were also assessed. Furthermore, the total number of contacts the patient had with the GP during the 6 months prior to prescription date, and whether the patient consulted the GP within 28 days after the prescription date, were investigated. Finally, a first referral to a psychotherapist during the study period, and information on self-perceived health (very poor/poor versus moderate versus good/excellent), were included.

Medication-related characteristics

Included as medication characteristics were type of prescribed antidepressant, any use of psychotropic co-medication (benzodiazepines or antipsychotics), and the number of other co-medications during the 6 months before the prescription date. Co-medication variables were obtained from the pharmacy dispensing registration database.

Data analysis

For the analysis, non-fillers and single Rx-fillers were combined into a group of decliners, that is patients who did not fill the prescription, patients who did fill the prescription but did not start drug taking, and patients who filled the prescription but did not persist with antidepressant use for longer than two weeks. χ^2 test (for the categorical measures) and independent samples *t*-test (for the continuous measures) were used to compare the characteristics between decliners and initiators, and between non-fillers and single Rx-fillers. To control for covariates and identify the risk factors for declining a first-time antidepressant prescription, multivariate logistics regression analysis was performed in the group of patients for which consultation, dispensing, and patient census data were available (n=671). Covariates that were significant in the univariate analysis at a p-value less than 0.1,

including patient sex, were included in the logistic regression model. Data were analysed using SPSS (version 14.0).

RESULTS

Of all 965 patients receiving a first-time prescription for a second-generation antidepressant in general practice, 41 (4.2%) did not fill that prescription at the pharmacy (non-fillers), and 229 (23.7%) filled only a single prescription (single Rx-fillers). The mean age of all patients was 48.5 years (± standard deviation 16.8 years) and 657 (68.1%) were female. Of all patients, 517 (53.6%) were prescribed paroxetine, 98 (10.2%) fluvoxamine, 87 (9.0%) mirtazapine, 86 (8.9%) fluoxetine, 74 (7.7%) citalopram, 74 (7.7%) venlafaxine, and 29 (3.0%) sertraline.

Table 1 shows the sociodemographic, health and morbidity, and medication-related characteristics for the non-fillers, single Rx-fillers, and initiators. Non-fillers and single Rx-fillers were combined into a group of decliners, and compared with the group of initiators. For 671 patients (69.5% of all), census data were available.

The results of the multivariate logistic regression analysis for the association between patient characteristics and declining the prescription are shown in Table 2. Patients

Table 2 **Characteristics associated with declining the GP's prescription: patients who do not fill the first-time antidepressant prescription or fill only a single antidepressant prescription at the pharmacy [a]**

Characteristic	Reference category	Crude OR (95%CI)	Adjusted OR [b] (95%CI)
Non-specific indication for prescribing antidepressant	indication of depression, anxiety, panic or OCD	2.61 (1.80–3.78)	2.67 (1.82–3.91)
Non-western immigrants	western origin	3.67 (1.63–8.25)	4.80 (2.05–11.3)
Age above 60 years	all other ages	1.75 (1.17–2.63)	1.81 (1.18–2.78)
Female	male	0.96 (0.65–1.42)	0.92 (0.61–1.39)
Educational level precollege	college/university	1.53 (0.93–2.52)	1.40 (0.83–2.36)
Self-rated health poor/moderate	good/excellent	1.33 (0.93–1.91)	1.11 (0.76–1.63)
Paroxetine prescribed	other antidepressants	0.72 (0.51–1.03)	0.78 (0.53–1.13)

GP = general practitioner; OR= odds ratio; 95% CI = 95% confidence interval; OCD = obsessive compulsive disorder

a) Multivariate logistics regression analysis was performed in the group of patients for which GP consultation, drug dispensing and patients census data were available (n=671).

b) Odds ratios adjusted for the variables shown in Table 1, that is, the covariates that are significant in the univariate analysis at a p-value less than 0.1, including patient sex.

who consulted their GP for a non-specific indication, rather than for depression, anxiety, panic, or OCD, were almost three times more likely (odds ratio [OR] 2.67; 95% confidence interval [95%CI] 1.82–3.91) to decline the antidepressant prescription. In half of the cases, the decliners were not diagnosed with either depression, anxiety, panic, or OCD; 24.4% consulted the GP for the indications feeling depressed, feeling anxious or sleeping problems, and 19.3% for other non-specific indications, such as fatigue, weight loss and relationship problems. Of all patients diagnosed with the indications feeling depressed, feeling anxious, or sleeping problems, 33.8% declined treatment, and of all patients considered having any other non-specific indications, 46.4% did so. In addition, the risk of declining treatment was almost five times higher (OR 4.80; 95%CI 2.05–11.3) in non-Western immigrants, and almost two times higher (OR 1.81; 95%CI 1.18–2.78) in patients > 60 years of age. Overall, the decliners were less likely to consult the GP within four weeks after the prescription date, compared to the initiators. However, comparing the non-fillers and single Rx-fillers, there was a trend that non-fillers were more likely to consult the GP within four weeks after the prescription date.

DISCUSSION

Summary of main findings

The study findings demonstrate the importance of the initiation phase of antidepressant therapy, which has often been overlooked in previous research. Over one in four patients receiving a first-time antidepressant prescription from their GP decline treatment: 4.2% do not fill the prescription at the pharmacy, and 23.7% fill only a single prescription. Declining the first-time antidepressant prescription is more common in patients who consult their GP for a non-specific indication, such as feeling depressed, sleeping problems, fatigue, or relationship problems, rather than for the specific indications depression, anxiety, panic, or OCD. In addition, non-Western immigrants and patients > 60 years of age were more likely to decline treatment.

Strength and limitations of the study

The strength of this study is the availability of the population-based dataset, which combines GP consultation, drug-dispensing, and patient-census data, thereby providing more patient-specific information. Linking GP-prescribing and pharmacy dispensing data enabled determination of the incidence of patients who do not fill their first-time antidepressant prescription. Studies on drug adherence often measure persistence, defined as the time between the first and last taken dose.

These studies, however, often exclude patients who do not fill or fill only a single prescription. In view of the considerable number of patients concerned, namely over one in four patients receiving a prescription for a new treatment, the findings from previous studies need to be placed in a different perspective.
Furthermore, in contrast to most regular dispensing databases, this study had information on the indications for which the patient consulted the GP, which have been shown to be very relevant.
The main weakness of the study is the lack of insight into the decision-making process in the clinical encounters, and into the patients' decision to decline treatment. The study does not provide information on the reasons for not filling or filling only a single prescription, and on whether decline of treatment was intentional or unintentional. Furthermore, it is not known whether the GP was involved or informed of patients' decision to decline treatment. It is, however, unlikely that patients who do not fill their prescription at the pharmacy or fill only a single prescription discuss their decision to decline the prescription with the GP. Previous studies showed that more than half of the patients discontinuing antidepressant treatment in an early stage do not feel the need to inform their GP of stopping.[7,20,24]

Comparison with existing literature

Patients with non-specific psychological symptoms are more likely to decline the first-time antidepressant prescription. In clinical practice, antidepressants are prescribed for a broad range of indications, including mental and psychological problems other than depression or anxiety.[12,25,26] Antidepressants used for indications other than depression and anxiety have been shown to be correlated with discontinuation of drug taking.[12,26] The present study shows that the indication is an important factor during the initiation phase of treatment as well.
There may be several reasons for patients declining antidepressant drug therapy. First, the patient and GP may not have a shared understanding of the problem and its treatment, so the patient does not have the prescription dispensed. There seems to be a disparity between patients' attitude towards antidepressant treatment and GPs' perceptions of their attitudes.[27,28] GPs generally see the depressive symptoms against a background of the patient's family history, physical illness, life events, and degree of disability.[29,30] They seem to use non-specific clinical cues such as distress and impairment, as well as their knowledge of the patient, in diagnosing the illness.[31] Mild depressive symptoms and psychological emotional problems can be associated with significant functional impairment, which physicians may feel inclined to address.[30] Patients, however, may not all expect to receive a prescription when consulting the physician.[32] Studies have shown that the majority of patients

in general practice prefer treatment approaches for emotional problems that go beyond antidepressant medication.[33-35] Most of them just expect the GP to listen to their problems and hope for an understanding attitude.[36] Second, the patient may agree with the decision to prescribe treatment, but changes his or her mind in the light of further information or conversations with others. These patients may either not dispense the prescription or not initiate antidepressant drug taking. Finally, the patient may start taking antidepressants, but stop them quickly. In a previous study in patients filling only a single prescription of an SSRI, it was shown that fear of side-effects and the actual occurrence of side-effects are the main reasons for not filling a second prescription.[20] Antidepressant side-effects may occur immediately after starting to take the drug, while it usually takes some weeks before patients experience recovery of symptoms.[37] The side-effects from the drug treatment can make people feel worse at first. An aversion towards medicine use, and feeling better in the meantime, were considerable reasons for not taking the medication for longer than two weeks.[20]

This study also showed that non-Western immigrants and patients aged > 60 years were more likely to decline the antidepressant prescription. In both groups, declining the prescription might be attributed to a lack of understanding about the illness and treatment. Non-Western immigrants may have difficulties communicating in Dutch, but cultural factors may also influence patients' attitude towards drug taking.[38] A study in the same Dutch population found non-Western immigrants to be more vulnerable for non-adherence in a later stage of treatment as well.[12] Both the mentioned study and a study by Hansen et al, however, do not observe an influence of age on early discontinuation.[12,18] However, the greater proportion of patients included in these studies used the medication for longer than 14 days, which was the maximum duration of use for the majority of patients in this study. The Dutch study further showed that women were less likely to be early dropouts. The present study found in the same population an effect of patient sex only in the group of non-fillers, that is women were more likely not to fill their prescription at the pharmacy. Finally, in contrast to the results from the Danish study, which reported a higher risk for early discontinuation in patients of low socioeconomic status, the present study did not find a clear effect of sociodemographic characteristics on declining the first-time prescription.

Implications for research and practice

The present findings imply that initiation of antidepressant therapy deserves more attention in research and clinical practice. Over one in four patients who receive a first-time antidepressant prescription decline treatment. More research is needed into the implications of declining antidepressant treatment. In addition, the decision

making process in clinical encounters, especially considering the perspective of the patient, requires attention. In practice, GPs could be more aware of the possibility of patients declining a first-time antidepressant prescription. They need to engage with patients' priorities and concerns, and could ask patients whether they believe an antidepressant would be helpful in treating their symptoms.

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3.2

Potential bias in pharmaco-epidemiological 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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ABSTRACT

Objective

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-month drug free period.

Results

When using a 6-month drug free period the measured incidence was about 32 per 1000 individuals (95% confidence interval [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.

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 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 Pharmaco-Morbidity (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 bupropion 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.

RESULTS

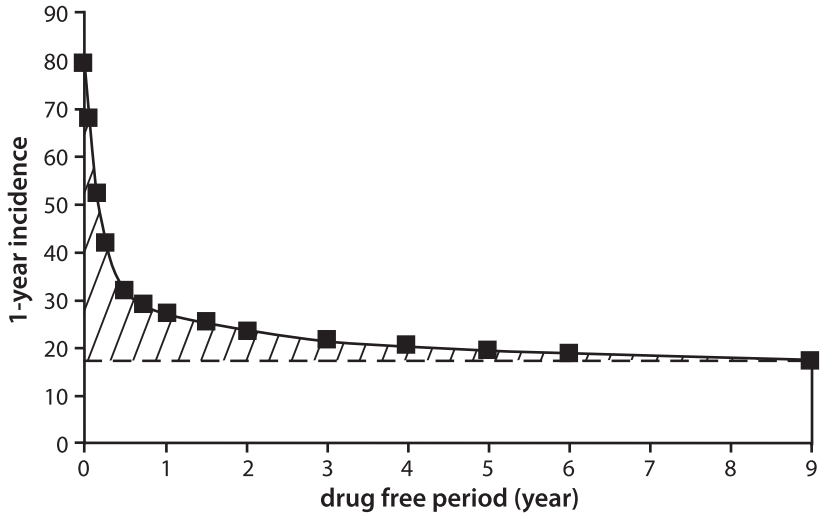
Patient characteristics of the study population are presented in Table 1. The study population was predominantly female (69.2%) with a mean age of 52.6 years. The age distribution within our study population has a slight higher proportion

Table 1 Patient characteristics of the study population

Characteristic	n=21 304 (100%)
Gender	
male	6 564 (30.8%)
female	14 740 (69.2%)
Age (years)	
18-30	1 973 (9.3%)
31-45	5 744 (27.0%)
46-60	7 157 (33.6%)
> 60	6 430 (30.2%)
Prescribed antidepressant	
SSRI	12 515 (58.8%)
TCA	5 797 (27.2%)
other [a]	2 992 (14.0%)
Prescriber	
general practitioner	17 839 (83.7%)
psychiatrist	1 894 (8.9%)
other [b]	1 571 (7.4%)

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant
a) Other antidepressants: moclobemide, mianserin, trazodone, mirtazapine, venlafaxine.
b) Other type of prescriber or information about prescriber not available.

Figure 1 **Overall incidence of antidepressant drug use in the Netherlands, October 2001 to September 2002, per 1000 individuals**



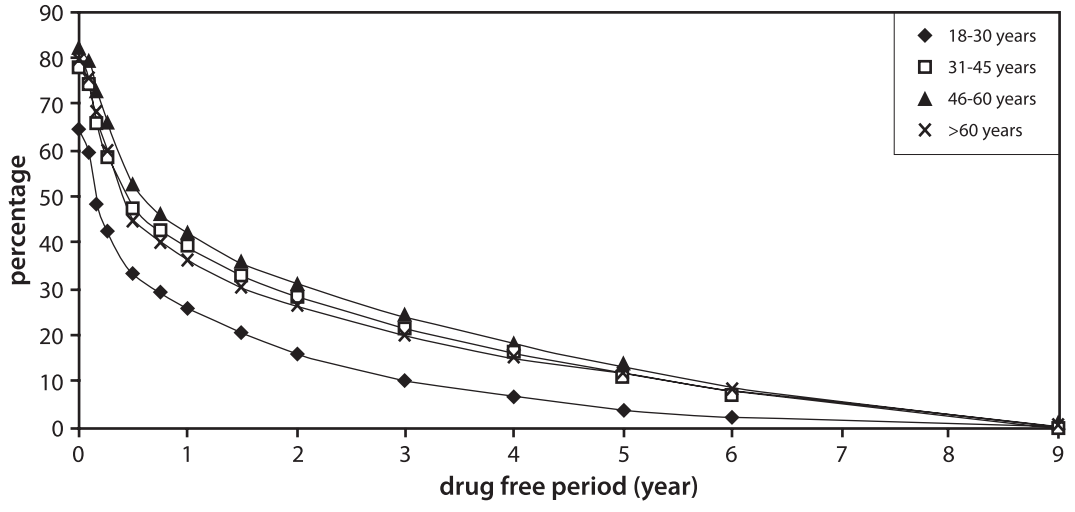
The incidence was measured using drug free periods of different length. The striped area under curve represents misclassified individuals.

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-month drug free period, given that the incident measurements for the 9-year 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 proportion of misclassified individuals are not equally distributed over age. When using a 6-month 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%.

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**



The difference in prevalence of characteristics between the reference incident user cohort (9 years) 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-month 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-month drug free period settings. We did not see any significant difference in the use of SSRIs or TCAs between the cohorts, although the 6 and 12-month 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-year drug free period is substantial.

Table 2 **Odds ratios (ORs) for cohort characteristics, of first time antidepressant drug users, in cohorts using 6, 12, and 24-month drug free periods when compared to a reference cohort**

Characteristic	6 months Misclassified (n=3970)		12 months Misclassified (n=2767)		24 months Misclassified (n=1690)		9 years True (n=4604)
	%	OR (95%CI)	%	OR (95%CI)	%	OR (95%CI)	%
Gender							
male	30.6	1.00 (reference)	29.8	1.00 (reference)	29.1	1.00 (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	1.00 (reference)	8.9	1.00 (reference)	8.2	1.00 (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	1.00 (reference)	27.5	1.00 (reference)	28.4	1.00 (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 [a]	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							
GP	82.6	1.00 (reference)	82.4	1.00 (reference)	83.7	1.00 (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 [b]	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.
SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; GP = general practitioner
a) Other antidepressants; moclobemide, mianserin, trazodone, mirtazapine, venlafaxine.
b) Other type of prescriber or information about prescriber not available.

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 increase 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.

Limitations to our study are that in our measurements, we defined the true first time antidepressants 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 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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3.3

Seasonal patterns of initiating antidepressant therapy in general practice in the Netherlands during 2002-2007

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ABSTRACT

Objective

Studies on seasonality in antidepressant prescribing showed prescribing peaks during autumn and winter. Since then, new antidepressants have become available and indications have broadened, possibly contributing to a change in prescribing practices. This study investigates seasonal patterns of initiating antidepressant use in general practice during 2002-2007 in the Netherlands.

Methods

Data were obtained from the Netherlands Information Network of General Practice. The study population was composed of adult patients initiating antidepressant use from 21 December 2001 to 20 December 2007, with no antidepressant use during at least two years prior to initiation. Seasonal distribution of initiating antidepressant use was investigated for the four seasons. The difference is frequency of initiating use between the seasons, normalized for general practice contacts, was tested using Chi-Square testing.

Results

The majority of the study population (n=16 289) was female (64.0%) with a mean age of 50.5 (standard deviation [sd] 18.0) years. Significant seasonal variation ($p < 0.01$) was found in initiation of antidepressant use, with about 5–35% more patients initiating use during winter than summer. Significant ($p < 0.01$) seasonality of initiating antidepressant use was seen in all patient groups, except within age groups 18–30 years and > 60 years.

Conclusion

The seasonal influence on initiation of antidepressant drug use has not changed with the introduction of the newer antidepressants and is in line with seasonality of depression onset, with most patients initiating use during the winter and fewest during the summer.

INTRODUCTION

Research has shown that human functioning and well being can be influenced by the seasons and seasonality in mood disorders has been studied extensively. Seasonal affective disorder is a well-known and widely described phenomenon.[1-6] It is characterized by recurrent depression during winter and autumn seasons with remission in the spring or summer for at least two successive years.[1,7] Seasonal patterns have also been documented for onset of depressive episodes in both general practice patients and hospitalized patients suffering from unipolar depression, showing a large peak during the winter.[8,9] Other studies have shown seasonal variation in bipolar disorder admissions, with fewer depression admissions during summer time,[10] and shorter duration of hospitalization for depressed female patients during the summer.[11]

In 1981, Williams et al. investigated the cyclic variation in psychotropic drug prescribing.[12] He described a four monthly cycle for antidepressant drug prescribing, with peaks in February, May and October. A few years later, Skegg and colleagues reported that most antidepressant users in the community initiate use during the autumn months and the least during the summer months.[13] Further, Balestrieri and colleagues showed seasonality in the amount of defined daily doses (DDDs) of antidepressants prescribed in general practice.[14] Since then, many new antidepressants have become available and indications for antidepressant drug prescribing have broadened.[15] How these changes in prescribing practices might have influenced the seasonal patterns of prescribing and if seasonality in prescribing complies with seasonality of depression is yet to be investigated.

The aim of this study was to investigate if there is a seasonal pattern of initiating antidepressant drug treatment in general practice during 2002-2007 in the Netherlands.

METHODS

Setting and study population

Data were obtained from the Netherlands Information Network of General Practice (LINH).[16] LINH is a network of 90 general practices with around 350 000 registered patients, which have actively collected health care data for research purposes since 2001. The LINH register information on all health problems presented within a consultation including information on referrals to specialist care and prescribed medicines in a standardized manner. The LINH database includes information on patient gender, date of birth and clinical diagnoses which are coded using the International Classification of Primary Care scheme.[17] Prescriptions prescribed by

the general practitioner are registered in a separate database including information on drug name, date of prescribing and amount prescribed. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[18] Each patient is identified with an anonymous unique patient-identification code. Patients are representative for the Dutch population with respect to age and gender.
For this study, patients 18 years and older who received their first antidepressants at any time from 21 December 2001 until 20 December 2007 were identified from LINH. This specific study period was selected to follow the seasonal division of the year, from winter (21 December 2001 – 20 March 2002) until autumn (21 September – 20 December 2007). All patients had to be registered for at least two years in the LINH prior to receiving their first antidepressant. The date of a first prescribed antidepressant prescription for each patient was set as start date and patients were not allowed to have used any antidepressants during two years prior to start date.

Data analysis

The primary outcome was the seasonal distribution of initiating antidepressant treatment. The distribution of the outcome (patient start date) was investigated for the four seasons (winter: December 21 – March 20, spring: March 21 – June 20, summer: June 21 - September 20, autumn: September 21 – December 20). Each study year was composed of the four seasons and defined as running from 21 December until 20 December. For each year the proportion of patients initiating antidepressant therapy per season was assessed. In case of no seasonality, 25% of patients each year were expected to initiate antidepressant drug use during each season.
General practice contacts might be subject to seasonal variations as during the holiday periods less frequent contacts are to be expected. To account for this variation, the seasonal variance of general practice contacts was assessed. Subsequently, the proportion of patients initiating antidepressant drug use per seasons was normalized for the seasonal variation in general practice contacts. The normalization was performed by investigating the frequency of general practice contacts per season for the study period. General practice contacts were least frequent during the summer, thus summer was denoted with an adjustment factor of 1.0. The other seasons all received an adjustment factor based on how more frequent the contacts were per season when compared to summer, thus if contacts during autumn were 20% higher than during summer, autumn would receive an adjustment factor of 1.20. The adjustment factors were used to normalize the proportion of patients initiating antidepressant drug use.

The significance of seasonal variation in initiating antidepressant drug use, when normalized for seasonal variation in general practice contacts, was tested using the Chi-Square test. Seasonal distribution of initiating antidepressant drug use was investigated for the total study population but also stratified for gender, age group (18–30 years, 31–45 years, 46–60 years and > 60 years) and type of antidepressant treatment therapy. Antidepressant treatment therapy was divided into three groups, namely, tricyclic antidepressants (TCAs; desipramine, imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, dosulepin, maprotiline), selective serotonin reuptake inhibitors (SSRIs; fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram) and other antidepressants (phenelzine, tranylcypromine, moclobemide, mianserin, trazodone, nefazodone, mirtazapine, venlafaxine, duloxetine). Seasonal distribution of initiating antidepressant drug use in patients who received a single antidepressant prescription and those who receive at least two prescriptions during the 12 months from start date was investigated separately. Patients who receive a single antidepressant prescription from the general practitioner often do not initiate therapy or discontinue use within two weeks [19] thus the depressive symptom severity between the two groups might differ. In these two patient groups, the seasonal distribution in initiating antidepressant drug use was investigated from winter 2002 to autumn 2006, as those who initiate use in 2007 could not be followed for 12 months. Data analysis was performed using SPSS for Windows release 14.0 (SPSS Inc. Chicago, IL).

RESULTS

The study population (n=16 289) was predominantly female (64.0%) with a mean age of 50.5 (standard deviation [sd] 18.0) years (Table 1). Roughly half of the antidepressant drug users were prescribed an SSRI on start date (53.4%).

The seasonal variation in initiating antidepressant drug use from winter 2002 to autumn 2007, non-normalized and normalized for seasonal variation in general practice contacts, is displayed in Figure 1. For the non-normalized analysis the peaks in use were mostly seen during the winter or autumn season. When the results were normalized for seasonal variation in general practice contacts most annual new antidepressant drug users initiated use during the winter season. For the normalized analysis, there was a 5 to 35% difference in the amount of antidepressant drug users who initiate antidepressant drug use during summer or winter, apart from in 2002 where proportion of starters initiating use during winter and summer is similar.

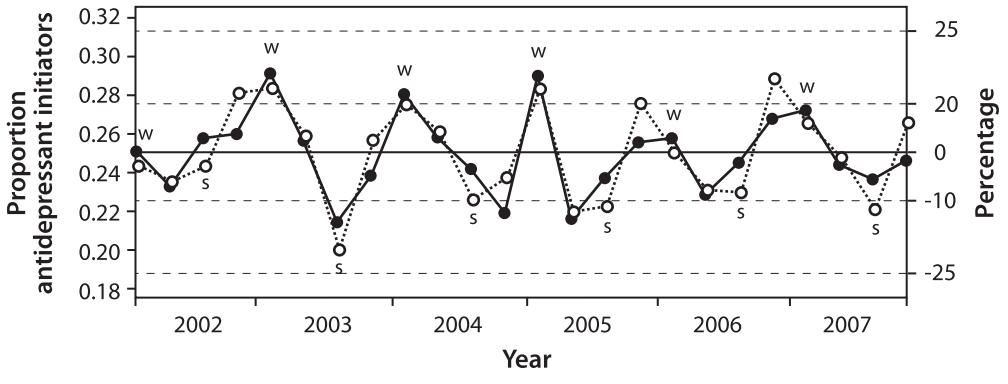
Table 1 **Characteristics of the study population on start date (n=16 289) and proportion of antidepressant drug initiators per season stratified by patient characteristics**

	Total n (%)	Winter	Spring	Summer	Autumn	Chi-Square p-value
All users	16 289 (100%)	0.274	0.241	0.238	0.247	<0.01
Gender						
female	10 426 (64.0%)	0.275	0.245	0.236	0.244	<0.01
male	5 863 (36.0%)	0.271	0.234	0.243	0.252	<0.01
Age in years						
18-30	2 250 (13.8%)	0.266	0.231	0.244	0.259	0.08
31-45	4 881 (30.0%)	0.282	0.233	0.234	0.251	<0.01
45-60	4 586 (28.1%)	0.284	0.247	0.224	0.245	<0.01
> 60	4 572 (28.1%)	0.259	0.249	0.254	0.238	0.23
Type of antidepressant (AD)						
TCA	5 088 (31.2%)	0.271	0.240	0.233	0.256	<0.01
SSRI	8 693 (53.4%)	0.278	0.238	0.243	0.241	<0.01
other [a]	2 508 (15.4%)	0.265	0.254	0.232	0.249	0.11
Number of AD prescriptions						
1 AD prescription [b]	4 307 (31.1%)	0.272	0.242	0.232	0.254	<0.01
> 1 AD prescriptions [b]	9 997 (68.9%)	0.275	0.240	0.242	0.243	<0.01

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor
The proportions are normalized for seasonal variation in general practice contacts.
a) Phenelzine, tranylcypromine, moclobemide, mianserin, trazodone, nefazodone, mirtazapine, venlafaxine, duloxetine.
b) Proportion of patients who initiate use during 2002-2006 (n=14 304), as those who initiate use in 2007 do not all have 12 months of follow up time.

Table 1 additionally presents the total proportion of antidepressant starters who initiate antidepressant drug use during each season, normalized for seasonal variation in general practice contacts. The total proportion that initiates antidepressant drug use per season is presented for the total study population and the different patient characteristics. Statistically significant difference ($p < 0.01$) is seen in initiating antidepressant drug use between the seasons in both men and women, with most initiating use during the winter season. The same was seen in antidepressant initiators in age groups 30–45 and 46–60 years, and those who got a TCA or an SSRI on start date. In both patients who received a single antidepressant prescription and in those who received at least two antidepressant drug prescriptions in 12 months we found statistically significant seasonal differences ($p < 0.01$) in initiating antidepressant drug use, with most patients starting during the winter.

Figure 1 **Proportion of patients who initiate antidepressant drug use per season, during 2002-2007**



w = winter; s = summer
The dotted line (---O---) represents new initiators per season not normalized for variation in general practice contacts, while the solid line (—●—) represents new initiators per season normalized for variation in general practice contacts

DISCUSSION

We found a significant difference in amount of patients who initiate antidepressant drug use between the seasons, with 5–35% more patients initiating antidepressant drug use during the winter when compared to summer. Prior studies report highest use of antidepressants during the autumn or winter months and lowest during the summer months.[12-14] Our finding of the least amount of patients initiating use during the summer months is in accordance with their results. However, for most years we find the largest peaks in use during the winter months and not during autumn as they report. The reason for this might be that in our analysis we normalized for seasonal variation in general practice contacts. In the non-normalized analysis we found peaks of antidepressant initiators during the autumn months. We found that most general practice contacts take place during the autumn. The seasonal variation presented by the non-normalized analysis might therefore include at least two seasonality components. Firstly, the seasonal influence of initiating antidepressant drug use due to seasonal difference in general practice visit frequency and secondly, the seasonal influences of antidepressant drug prescribing. The normalized analysis shows that most antidepressant drug users initiate use during the winter season. This is in line with what Blacker and colleagues have reported for seasonality in depression onset.[9] They interviewed and screened about 2200 consecutive patients in general practice and found the highest incidence of depression during the winter

months. Evidently, the seasonal peaks in initiating antidepressant use apparent from our analysis are strongly related to the more frequent presentation of depressive symptoms during winter.

The stratified analysis showed seasonal differences in initiating antidepressant drug use for almost all characteristics. However, in patients above 60 years no seasonality was found. These findings confirm what has been reported on depressive symptoms in the elderly.[20] The SSRIs are most frequently prescribed for treating depression,[21] and therefore more seasonal variance was expected in this group of patients. In the SSRI group a peak in initiation was seen during the winter season while similar amount of patients initiated use during the spring, summer and autumn seasons. The TCA users, however, represent a more heterogeneous group, i.e. more severely depressed patients where strong seasonality would be expected and patients treated for non-psychiatric indications where seasonal pattern would not be expected. The seasonal pattern of TCA initiators displayed the least amount of patients initiating use during summer with gradual increase and a peak in initiations during the winter. Patients who used other types of antidepressant (not a TCA or an SSRI) did not show significant seasonality in initiating use. The reason might be that although these antidepressants are indicated to treat depression few of them are considered as first choice when treating depression. The introduction of the newer antidepressants has not resulted in differences with regards to seasonality in initiation, as both the old and the new show peaks during the winter season.

The significant difference we found in amount of antidepressant initiators per season is of methodological importance for pharmacoepidemiologic studies. It is likely to be of importance for prevalence and incidence measurements, as well as for patient sampling in some study designs such as cross sectional, case-control and case-crossover studies.

The strength of our study is the large amount of general practice patients investigated and the long follow up time. Our study is bound by the limitation that we only investigated general practice prescriptions. The patients included in our study might undergo treatment by a psychiatrist or have been admitted to closed care facilities where therapy was already started. We, however, think that this only applies to a very small part of the study population as over 80% of patients receive their first antidepressant prescription from a general practitioner.[22] Another limitation is that we did not investigate seasonality in prescribing practices of the general practitioners. If severity of depression could be estimated, i.e. by using a validated depressive symptom rating scale, it would be possible to investigate if reported depressive symptoms of patients who visit the general practitioner during the summer season might be considered more severe than if they would present the same symptoms during the winter season. This would lead to more easily

prescribing of antidepressants during the summer season. On the other hand, the general practitioner might see less reason for treating mild depression symptoms with antidepressants during the summer time than during winter time. In this study we investigated patients who receive at least two antidepressant prescriptions in 12 months and those who receive only a single antidepressant prescription. Although both patient groups showed a significant peak during winter, patients who receive a single antidepressant prescription seem to initiate use during the autumn more frequently than those who receive at least two prescriptions. A study on general practice patients who receive only a single antidepressant prescription showed that around 4% of the patients do not get it dispensed from the pharmacy and of those who initiate use many discontinue within two weeks.[19] Patients who receive at least two antidepressant prescriptions are therefore considered to suffer from more serious symptoms while more uncertainty is of symptom severity in those who only receive a single antidepressant prescription. The difference in seasonal pattern of initiation between the two groups might indicate that there is a seasonal component in antidepressant drug prescribing practices of the general practitioner.

In conclusion, initiation of antidepressant drug use is influenced by seasonality with most patients initiating use during the winter and fewest during the summer. The introduction of the newer antidepressants did not change the seasonal patterns already reported in earlier studies. The winter peaks are in line with what is seen in depression onset in general practice.

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3.4

Does the length of the first antidepressant treatment episode influence risk and time to a second episode?

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ABSTRACT

Objective

Antidepressant treatment in primary care is inconsistent with treatment recommendations, and many patients discontinue treatment within 6 months. How this affects treatment outcomes is unknown. The aim of this study was to assess how length of the first antidepressant episode influences risk and time to a second treatment episode within 5 years time.

Methods

The study population included 9243 adults (67% female, mean age 47.3 years) who initiated selective serotonin reuptake inhibitor use in 1998 or 1999. Based on the length of a first antidepressant treatment episode, patients were divided into early discontinuers (< 6 months), continuing users (6–12 months) and persistent users (> 12 months). The Cox proportional hazards model was used to estimate relative risks (RRs) for the association between length of a first antidepressant treatment episode and time to re-initiating antidepressant treatment.

Results

Time to a second treatment episode did not differ significantly between continuing users and early discontinuers (RR 0.99; 95% confidence interval [95%CI] 0.92–1.07). Persistent users showed a higher risk of experiencing a second treatment episode than early discontinuers (RR 1.23; 95%CI 1.15–1.32).

Conclusions

In conclusion, the risk of experiencing a second antidepressant treatment episode did not differ for those who used antidepressants for 6 to 12 months and those who discontinued early. In general, there is limited information on how length of an antidepressant treatment episode influences the risk of reinitiating treatment of patients in primary care. More research is needed to investigate the effectiveness of antidepressant drug treatment patterns in preventing relapse or recurrence in primary care populations.

INTRODUCTION

Antidepressant drug use has increased substantially in the past decade. Studies show that antidepressants can be effective in dissolving symptoms of depression and in preventing relapse and remission of depressive episodes.[1-6] Currently, it is recommended to continue antidepressant treatment in patients with depression or anxiety for at least 6 months after resolution of symptoms to minimize the risk of relapse and recurrence.[7-9] However, studies on use of antidepressants have shown that in daily clinical practice, more than half of the patients discontinue treatment within 6 months.[10-19]

Early discontinuation is thought to increase the risk of relapse and recurrence. Clinical trial evidence based on this subject is limited, but it has been supported and complemented by the results from observational studies. To our knowledge, three observational studies have been performed which investigated the influence of early discontinuation on the risk of relapse or recurrence in primary care populations.[12,13,20] These studies reported that early discontinuation, that is, patients who received less than 4 antidepressant prescriptions [13,20] or less than 120 prescription days [12] during 6 months, resulted in a higher risk of relapse or recurrence of depression compared to those who continued treatment.

The aim of this study was to contribute further evidence on how the length of the first antidepressant treatment episode influences the risk and time to a second antidepressant treatment episode (if any) during 5 years of follow-up.

METHODS

Setting and study population

Prescription data were collected using the Pharmaco-Morbidity (PHARMO) record linkage system. This database has been described in detail elsewhere.[21] In brief, the PHARMO record linkage system includes pharmacy dispensing records from community pharmacies of approximately 1 million Dutch inhabitants from 1992 onwards. Because virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are near complete about prescription drugs.[22] The computerized drug dispensing histories contain information concerning the patient (anonymous identification, sex and year of birth), dispensed drug, dispensing date, prescriber, amount dispensed, and prescribed medical regimen. The duration of use for each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. The database does not provide information on the indications for use of the medicines.

The source population was composed of antidepressant drug users, 18 years and older, registered in the PHARMO database from 1 January 1996 onwards (n=78 807). The study population included patients from the source population who started using a selective serotonin reuptake inhibitor (SSRI) in the year 1998 or 1999 (n=36 384). The date of the first SSRI prescription, in 1998 or 1999, was defined as start date. Patients who received a prescription for any antidepressant during 2 years before the start date were excluded (n=25 807) leaving only new starters to be included (n=10 577). In addition, patients who received only a single antidepressant prescription throughout the whole study period were excluded (n=1334).

Study design

A follow-up study was performed where the initiation of a second antidepressant treatment episode (if any), within 5 years after having completed a first antidepressant treatment episode, was investigated for antidepressant treatment episodes of different lengths. The first antidepressant treatment episode started with the first antidepressant drug dispensed in 1998 or 1999 (start date) and ended when there was no subsequent antidepressant prescription within 90 days from the theoretical end date of a preceding antidepressant prescription. The theoretical end date equals the dispensing date plus the estimated duration of drug use. To increase the certainty that an antidepressant prescription marked a new treatment episode, and was not a part of the first episode, a gap with a maximum of 90 days was allowed to elapse between prescriptions. Switching to another type of antidepressant was considered as continuation of antidepressant therapy.

The study population (n=9243) was divided into 3 mutually exclusive treatment groups based on the length of their first antidepressant treatment episode. Antidepressant drug users who discontinued treatment within 6 months were defined as 'early discontinuers', patients who received antidepressant therapy for 6–12 months where defined as 'continuing users', and patients who received treatment for more than 12 months were defined as 'persistent users'.

Outcome

The primary outcome measure was the time to initiation of a second treatment episode within 5 years after having completed a first antidepressant treatment episode. When patients did not experience a second antidepressant treatment episode they were followed up from the end of first antidepressant treatment episode for a maximum of 5 years. When antidepressant drug users could not be followed up for 5 years they were followed up until the last registered date in the PHARMO database.

Data analysis

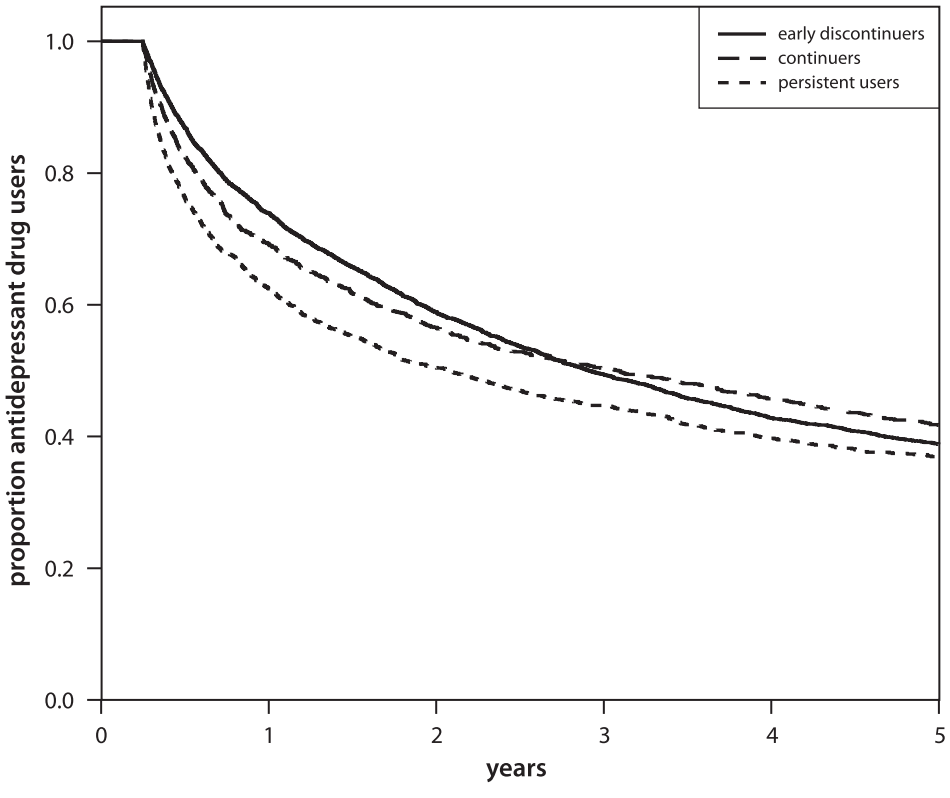
Kaplan-Meier survival curves were constructed to examine the time to initiation of a second treatment episode, using log-rank statistics to evaluate differences between the treatment groups. The Cox proportional hazards model was used to estimate risk ratios (reported as relative risks [RRs]), with 95% confidence interval (95%CI), for the association between antidepressant treatment pattern and initiation of a second antidepressant treatment episode using the early discontinuers as the reference group. Logistic regression was used to test the comparability of characteristics for the 3 treatment groups.

Antidepressants are often prescribed for indications other than depression.[23] Furthermore, antidepressant drug users who suffer from depression may vary in disease severity.[24] Therefore, in addition to the overall analysis, two additional analyses were performed. The first additional analysis was a subgroup analysis performed in patients who use the antidepressant most likely for treating depression. These patients were identified by applying an algorithm that calculates the probability that an antidepressant was prescribed for a patient whose condition was diagnosed with depression.[25] The second additional analysis was performed in a propensity score-matched sample of patients where early discontinuers were 1:1 matched with continuing and persistent users.[26] The propensity score was derived from a logistic regression model with treatment pattern as the dependent variable and age, sex, type of prescriber, psychiatric prescription dispensed in the year before start date, switching antidepressant within first treatment episode, type of antidepressant, chronic disease score,[27] number of comedications received, and use of antipsychotics or benzodiazepines during 6 months before start date as independent variables.

RESULTS

The study population included 9243 patients starting SSRI use with a mean age of 47.3 (standard deviation [sd] 17.2) years of which 67% were women. Most of the SSRI users got their antidepressant prescribed by a general practitioner (83%) and paroxetine was the antidepressant most frequently initially prescribed (68%). The mean number of different comedications dispensed in the 6 months prior to start date was 3.9 (sd 3.4) with half of the patients receiving benzodiazepines. The mean chronic disease score for the study population was 1.5 (sd 2.3). During follow-up time, 48.4% of the study population experienced a second antidepressant treatment episode. The mean follow up time for the study population from the end of first treatment episode until the end of study was 44.0 (sd 23.2) months.

Figure 1 **Kaplan Meier survival curves illustrating the amount of antidepressant drug users experiencing a second treatment episode over time for the different treatment patterns**



Curves for early discontinuers (< 6 months), continuers (6–12 months) and persistent users (> 12 months) are compared.

The mean length of the first treatment episode was 2.5 (sd 1.7) months for early discontinuers, 8.6 (sd 1.7) months for continuing users, and 41.9 (sd 27.3) months for persistent users. A comparison of characteristics for the different treatment pattern groups showed that continuing users were more likely than early discontinuers to receive their first antidepressant prescription from a psychiatrist (odds ratio [OR] 1.31; 95%CI 1.09–1.57) and to belong to the age category 30–45 years (OR 1.20; 95%CI 1.03–1.41). The persistent users were more likely than early discontinuers to be women (OR 1.24; 95%CI 1.12–1.37), to receive their initial antidepressant prescription from a psychiatrist (OR 1.44; 95%CI 1.23–1.67), to use benzodiazepines during the 6 months prior to start date (OR 1.24; 95%CI 1.14–1.36) and to belong to the older age categories.

Figure 1 displays the Kaplan-Meier survival curves for the different treatment patterns, illustrating the time to initiation of a second antidepressant treatment

episode. When continuing users were compared to early discontinuers the Cox proportional hazards model produced a statistically nonsignificant RR of 0.99 (95%CI 0.92–1.07). Persistent users were found to have a 23% higher risk of experiencing a second treatment episode than early discontinuers (RR 1.23; 95%CI 1.15–1.32). The median time to a second treatment episode, for those who experienced a second treatment episode, were 14.1 months for early discontinuers, 9.9 months for continuing users, and 6.4 months for persistent users.
The additional subgroup analysis in antidepressant drug users with a probable depression diagnosis (n=7400) gave similar results as the overall analysis: the RRs of experiencing a second treatment episode were 1.00 (95%CI 0.92–1.10) for continuing users and 1.28 (95%CI 1.18–1.38) for persistent users, with early discontinuers as a reference.

Table 1 **Risk of experiencing a second treatment episode within 5 years for the different treatment patterns presented as RR (95%CI)**

	Unadjusted analysis	Propensity Score Matched	Depression Diagnosis
General			
continuing users	0.99 (0.92–1.07)	0.98 (0.90–1.08)	1.00 (0.92–1.10)
persistent users	1.23 (1.15–1.32)	1.21 (1.12–1.31)	1.28 (1.18–1.38)

Relative risk (RR) for the unadjusted analysis (n= 9243), propensity score-matched analysis (n=3604, n=5898), and for a sample of antidepressant drug users with a registered diagnosis of depression (n=7400).

The additional analysis using propensity score matching in order to create balanced groups in terms of covariates also showed similar results as the overall unbalanced analysis: the RRs of experiencing a second treatment episode for continuing users were 0.98 (95%CI 0.90–1.08) and 1.21 (95%CI 1.12–1.31) for persistent users, when compared with early discontinuers. An overview of the RRs of experiencing a second treatment episode for the different treatment patterns according to the three different analyses is presented in Table 1.

DISCUSSION

The main aim of our study was to investigate how the length of a first antidepressant treatment episode influences the risk of experiencing a second antidepressant treatment episode in primary care in the Netherlands. When antidepressant drug users were followed for 5 years after ending their first treatment episode, we did not

find any difference in time to reinitiation of antidepressant therapy between patients who discontinued antidepressant drug use early and those who continue treatment for 6 to 12 months. However, early discontinuers had a lower risk of experiencing a second antidepressant treatment episode when compared to antidepressant drug users treated for 12 months or longer.

When treating depression, guidelines recommend to continuation of antidepressant drug treatment for 4 to 6 months beyond the time of remission to prevent relapse or recurrence.[7-9] Observational studies have shown that antidepressant use in primary care does not mirror these recommendations, reporting that many antidepressant drug users terminate treatment before 6 months.[10-19] In addition, in our study 45% of the antidepressant drug users were treated for less than 6 months, even after excluding the patients from our study population who only got a single antidepressant prescription dispensed during the study period. The few long-term studies that investigated duration of antidepressant drug use in relation to time to relapse or recurrence have largely been conducted in high risk patients in secondary care settings.[1,5,6] Patients included in such studies are generally more severely depressed and some have experienced multiple prior depressive episodes.[4] It is difficult to extrapolate results from such studies to users of antidepressant drugs in primary care setting. The few studies conducted on antidepressant drug use and initiation of a second antidepressant treatment episode of patients in primary care, as a marker for relapse or recurrence, had short follow-up times, ranging from 6 to 18 months. Three such studies reported that those who continue therapy have a lower risk of relapse or recurrence when compared with those who discontinue early.[12,13,20] This is contrary to what we find in our study. However, the different results might be explained by the different methodology used to estimate the risk of reinitiating antidepressant drug use. The three previously mentioned observational studies all measured the risk of reinitiating antidepressant therapy from the start of the first treatment episode onwards instead of starting follow-up time from the end of the first treatment episode. We showed in a different study that this can lead to immortal and neglected time bias and even lead to reversal of the principal findings.[28] In addition, a recent study by Aikens et al.[29] and van Geffen et al.[24] support our findings. Aikens et al.[29] showed that antidepressant drug users who discontinued treatment early were relatively unlikely to meet depressive disorder criteria at 9 months when compared to those who continued treatment. Van Geffen et al.[24] investigated patients who stopped using antidepressant drugs after having received only one antidepressant prescription dispensed from the pharmacy. They showed that although the adverse effects of the drug were the most frequently reported reason for not continuing antidepressant treatment, a considerable number of patients disagreed with the general practitioner on the depression

diagnosis or were feeling better.[24] This indicates that some of the patients who are prescribed antidepressants might not experience actual or less severe depression, which subsequently would result in a longer time to reinitiation, if there is any reinitiation, of antidepressant drug use in these patients. This phenomenon could partially explain our results, showing that, on the contrary to what is to be expected, those that are treated for longer periods have a higher risk of reinitiation. On the other hand our two additional analyses (one in patients likely to be treated for depression, and one using a propensity score analysis) showed remarkably similar results to the overall unbalanced analysis.

The strength of our study is the large sample of antidepressant drug users included and the long follow-up time. Most of the antidepressant drug users were followed up for 5 years or until they reinitiated antidepressant therapy. The most important limitation, a very common one when using computerized prescription databases, is the lack of information on indication for prescribing. Studies have reported that antidepressants are being prescribed for illnesses and symptoms other than depression. These studies report that tricyclic antidepressants more often used to treat nondepression indications, while the SSRIs are in 54% to 70% of the cases prescribed for treating depression.[17,23,30] In an attempt to minimize the amount of patients using antidepressants due to other symptoms or illnesses than depression, we only included first time users of SSRIs. This, however, does not guarantee that patients, treated for non-depression-related indications are excluded from our study sample. In addition, we performed a sensitivity analysis using a specific algorithm designed to identify antidepressant drug users with a depression diagnosis within our study population. The resulting RRs were very similar to the results for the total study population showing a RR of 1.00 (95%CI 0.92–1.10) for continuing users and 1.28 (95%CI 1.18–1.38) for persistent users, when compared with early discontinuers. The algorithm used to identify the antidepressant drug users with depression was developed in a primary care population. Another limitation is not being able to correct for number of prior episodes of depression and severity of disease. Studies have shown that the number of prior depressive episode is a strong risk factor for recurrence or relapse.[6,31] We chose a 2-year drug-free period, which has been reported to be a reasonable time to exclude those with prior treatment episodes, in an attempt to only capture first time users.[32] Finally, there is always the possibility that some of the antidepressant drug users might have experienced relapse or recurrence but chose nonpharmacological treatments such as psychotherapy. However, we would expect this kind of bias to be nondifferential for the different treatment pattern cohorts.

In conclusion, we found that first time antidepressant drug users who are treated for more than 12 months in primary care show a higher risk of experiencing a second

antidepressant treatment episode within 5 years than those who discontinue early. No statistically significant difference in risk of experiencing a second antidepressant treatment episode within 5 years was seen between those who use antidepressants for 6 to 12 months and those who discontinue early. In general, there is limited information on antidepressant treatment patterns and the risk of recurrence or relapse in primary care patients. This study reports contrasting results to previously published observational studies, in which different methodology is used. More research is needed to investigate the effectiveness of antidepressant drug treatment patterns in preventing relapse or recurrence in primary care populations.

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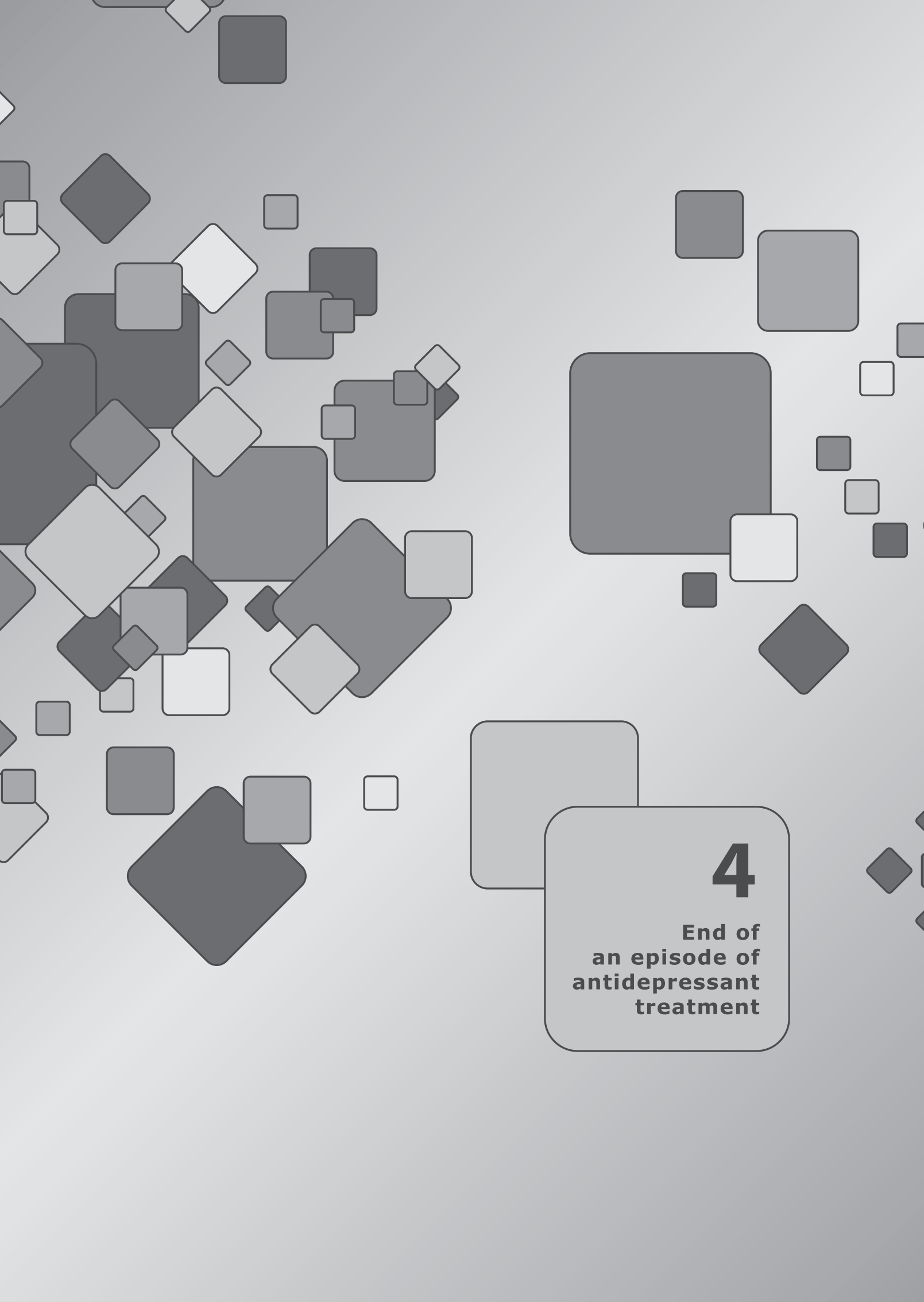

4

End of an episode of antidepressant treatment

4.1

Construction of drug treatment episodes from drug dispensing histories is influenced by the gap-length

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J Clin Epidemiol (in press) 2009

ABSTRACT

Objective

When constructing drug treatment episodes using drug dispensing databases, duration and the number of prescriptions belonging to a single treatment episode need to be defined. We investigated how different methods used to construct antidepressant treatment episodes influence their median estimated length.

Methods

A follow up study among adult antidepressant drug users, identified from the Dutch Pharmaco-Morbidity Record Linkage System, starting selective serotonin reuptake inhibitor (SSRI) use in 2001 was conducted. The influence of varying lengths of the prescription overlap and the gap between prescriptions (number of days or % prescription duration) on the median antidepressant treatment episode length was investigated.

Results

Of the 16 053 SSRI starters, 65.1% were female and mean age was 45.7 years (standard deviation [sd] 17.2). Median antidepressant treatment episode length doubled when the gap-length was expanded from 0 to 10 days. For short gap-lengths the episode interquartile range was 40–200% larger when overlap was accounted for and when % of prescription duration gap-length was used.

Conclusion

Differences in median episode length exist between methods that account for or disregard prescription overlap. These differences are of importance for studies that focus on drug exposure-outcome relationships and could have consequences for epidemiological analysis.

INTRODUCTION

Drug utilization research in pharmacy dispensing databases often requires the construction of drug treatment episodes from a series of drug dispensing records over time for the same patient. Construction of drug treatment episodes is an important part of pharmacoepidemiology as they allow the researcher to investigate drug use in relation to various drug taking related outcomes such as estimation of prevalence/incidence,[1-3] compliance,[4,5] and persistence.[6] The first step in the construction of a drug treatment episode is to estimate the duration of each individual dispensed prescription. As pharmacy dispensing databases vary between countries the data available for this estimation can differ. In the Netherlands, dispensing databases generally include variables such as date of dispensing, type of drug dispensed, amount dispensed and the prescribed dosage regimen, which allows the estimation of the days of use of individual drug dispensings. When information on the dosage regimen is missing, the prescription duration is sometimes based on the amount of defined daily dose or number of pills dispensed.[7,8] The second step is to identify how many consecutively dispensed prescriptions belong to a single drug treatment episode. In daily practice, patients rarely collect a subsequent drug dispensing on exactly the day following the last day of use of the previous dispensing, but earlier (overlap of two dispensed prescriptions) or later (gap between two dispensed prescriptions). To correct for these irregularities in dispensing, researchers usually allow for a certain number of days (gap) to elapse between the dispensed prescriptions. When a prescription is dispensed within the allowed gap, which elapses after the expected end date of a prior prescription, it is considered to belong to the same treatment episode. The gap-lengths used vary and can be defined as a certain number of days, or as a percentage of the estimated duration of a prescription.[1,2,5,9-14] Overlap of two dispensed prescription occurs when a patient collects a subsequent dispensing too early, i.e. before the dispensed quantity from a prior dispensing has finished. In case of overlap where subsequent dispensing is of the same type of drug as the prior dispensing it is possible to add the number of overlapping days to the prescription duration of the second dispensing. Researchers might also disregard the overlap with the reasoning that the gap between dispensing compensates for the overlap. However, this is not always applicable as too short gaps might not always compensate for a large overlap. In case of switching to a different drug overlapping days might be disregarded as it is reasonable to assume that the patient will not continue using the dispensed quantity from the prior dispensing.

In this study, we will use antidepressant drug use as a model for investigating different methods to construct drug treatment episodes. Many illnesses occur or are treated in episodes. An example of such a disease is depression. Definitions for the allowed gap-length between dispensed antidepressant prescriptions vary and in

the literature gap-lengths of 7 days,[15] 15 days,[9,10] 30 days,[1,11-13] 45 days [5] and 90 days [14] have been used. The effect of variation in the length of gaps between antidepressant prescriptions, and if overlap is disregarded or accounted for, on the length of the antidepressant treatment episode has not been investigated.
The aim of this study was to investigate how different methods used to construct an antidepressant treatment episode influence its median estimated length.

METHODS

Setting and study population

Prescription data were collected from the Pharmaco-Morbidity Record Linkage System (PHARMO RLS) , which has been described in detail elsewhere.[16] In brief, the PHARMO RLS includes pharmacy dispensing data for over a million residents in the Netherlands. 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.[17] The PHARMO RLS includes information on gender and year of birth for each patient, in addition to information on patient medication. The database includes information on each 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 system.[18] 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 on the indications for use of the medicines.
The source population comprised patients from the PHARMO RLS database to whom any antidepressant drug was dispensed during 1999 to 2003 (n=220 964). For the study population we selected all patients from the source population who received a selective serotonin reuptake inhibitor (SSRI) (n=149 555) and included only those ≥ 18 years of age who started SSRI therapy in year 2001 (n=56 046). The dispensing date of the first SSRI dispensed in 2001 was defined as start date. To assure that the SSRI received in 2001 marked the beginning of a new antidepressant treatment episode, we excluded (n=35 250) patients with any use of antidepressants during the 24 months prior to start date. In addition, users who only received a single antidepressant prescription during the whole follow up (n=4157) and those who received two antidepressants dispensed on the same date (n=586) were excluded, resulting in a final study population of 16 053 SSRI starters.

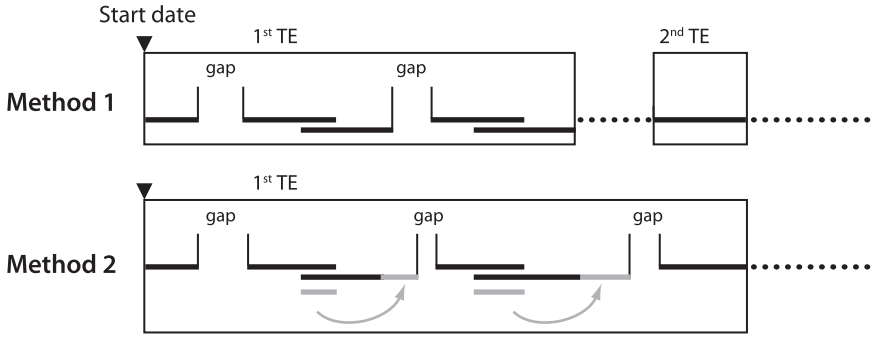
Study design

A follow up study was conducted to compare different methods to construct an antidepressant treatment episode from dispensing histories. An antidepressant treatment episode consists of a sequence of dispensed prescriptions. The methods investigated touch upon two items, i.e. the duration of a dispensed prescription, accounting for or disregarding prescription overlap, and the time (gap) that is allowed to elapse between dispensed prescriptions for these to be considered as belonging to the same treatment episode.

Estimating prescription duration within a treatment episode

Two methods were used to estimate the theoretical duration of use for each dispensed prescription (Figure 1). In Method 1, the duration of a prescription was based on the amount of tablets dispensed and the prescribed dosage regimen. The theoretical end date of each prescription equals the dispensing date plus the estimated duration of drug use. In Method 1, overlapping antidepressant prescriptions days were not accounted for. In Method 2, the duration of a dispensed antidepressant prescription was defined as in Method 1 except that overlap of two subsequent antidepressant prescriptions was taken into account. In case a subsequent antidepressant prescription from the same ATC group was collected prior to the theoretical end date of a previous antidepressant prescription the number of overlapping days was added to the theoretical end date of the subsequent antidepressant prescription. If the subsequent prescription within the same treatment episode included an

Figure 1 **Constructing drug treatment episodes based on estimated duration of a dispensed prescription and gaps of a defined length**



Method 1 does not take an overlap of two subsequent prescriptions into account.
Method 2 takes an overlap of two subsequent prescriptions into account, by adding the number of overlapping days to the expected end date of the overlapping prescription.
TE; drug treatment episode

antidepressant of a different ATC N06A sub-group the patient was considered to have switched therapy and the remaining tablet days from the prior prescription were disregarded. To prevent overestimation in treatment duration for patients treated with two antidepressants simultaneously, all patients that received two antidepressants on the same date were excluded. All antidepressant prescriptions, including non-SSRIs, were included for constructing the antidepressant treatment episodes.

Gap-length between prescriptions within a treatment episode

Antidepressant treatment episodes were constructed for each patient, using the two methods above to define duration of a dispensed prescription. Each antidepressant treatment episode started on start date and ended when there was no subsequent antidepressant prescription dispensed within a defined gap-length from the theoretical end date of a preceding dispensed antidepressant prescription. The gap-length was defined in two ways as 1) an arbitrarily chosen number of days, and 2) a percentage of usage days. For the arbitrary chosen gap-length, lengths of 0, 10, 30, 45, 60, 90, 120, 150 and 180 days were investigated. When this definition is used, the length of the gap does not depend on the number of drug prescribing days i.e. estimated duration of a single prescription. When defining the gap-length based on percentage of usage days per prescription, a percentage of 0%, 10%, 25%, 50%, 100% and 150% of estimated prescription duration were selected. This definition is dependent on the amount of drug prescribing days, e.g. in case of prescription duration of 30 days a 10% allowed gap-length until a subsequent prescription would be translated into three days. In addition, when users receive prescriptions covering different amount of usage days the allowed gaps will vary in length when using percentage of estimated duration.

Data analysis

In our study we investigated how using different methods for defining prescription duration and different gap-lengths between prescriptions influences the median estimated length of an antidepressant treatment episode. The length of an antidepressant treatment episode was measured as days elapsing from the start date until the theoretical end date of a last antidepressant prescription within that treatment episode. The methods, not accounting for and accounting for overlap, were compared. Two definitions of the gap-length were applied, e.g. defined number of days and percentage of usage days.

In addition, the study population was divided into three groups based on antidepressant treatment episode length for each gap-length. The groups investigated were those with an antidepressant treatment episode shorter than 6 months, those

treated for 6–12 months and those treated longer than 12 months. The proportion of patients belonging to each treatment pattern group was measured for each gap-length to investigate eventual changes in the composition of the study population. The results are presented figuratively as box plots. Data analysis was performed using SPSS for Windows release 14.0 (SPSS Inc. Chicago, IL).

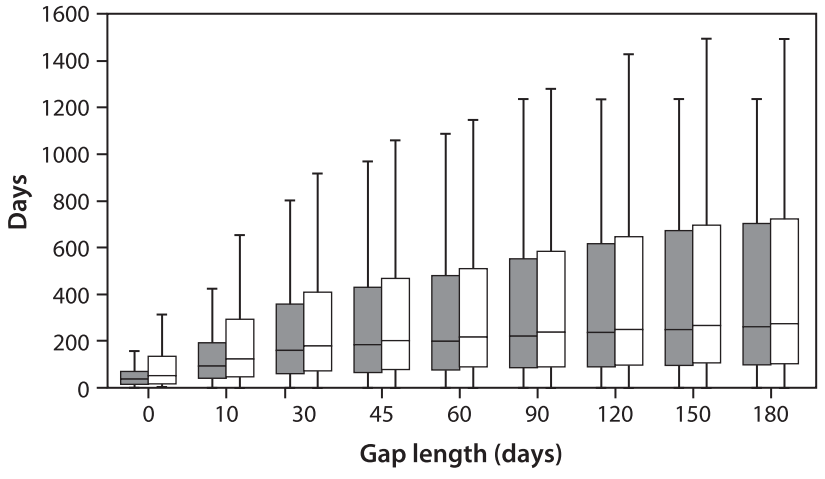
RESULTS

The characteristics of the study population are presented in Table 1. Of the 16 053 antidepressant drug users, 65.1% were female and the mean age for the study population was 45.7 (standard deviation [sd]17.2) years. Most of the antidepressants dispensed on the start date were prescribed by the general practitioner (83.0%) and the most commonly dispensed antidepressant was paroxetine (66.9%). The median duration of the dispensed prescriptions collected by the study population was 30.0 (interquartile range [IQR; the range between the 25th and 75th percentile] 2.0) days.

Table 1 **Baseline characteristics of the study population on start date**

Characteristic	n=16 053 (100%)
Gender	
male	5 597 (34.9%)
female	10 456 (65.1%)
Age in years	
18–30	3 263 (20.3%)
31–45	5 646 (35.2%)
46–60	4 047 (25.2%)
> 60	3 097 (19.3%)
Type of antidepressant	
fluoxetine (N06AB03)	1 642 (10.2%)
citalopram (N06AB04)	2 028 (12.6%)
paroxetine (N06AB05)	10 736 (66.9%)
sertraline (N06AB06)	766 (4.8%)
pluvoxamine (N06AB08)	881 (5.5%)
Prescriber	
general practitioner	13 325 (83.0%)
psychiatrist	1 528 (9.5%)
other	1 200 (7.5%)

Figure 2 **A box plot displaying the median length (days) of an AD treatment episode when gaps of a defined length (days) are used**

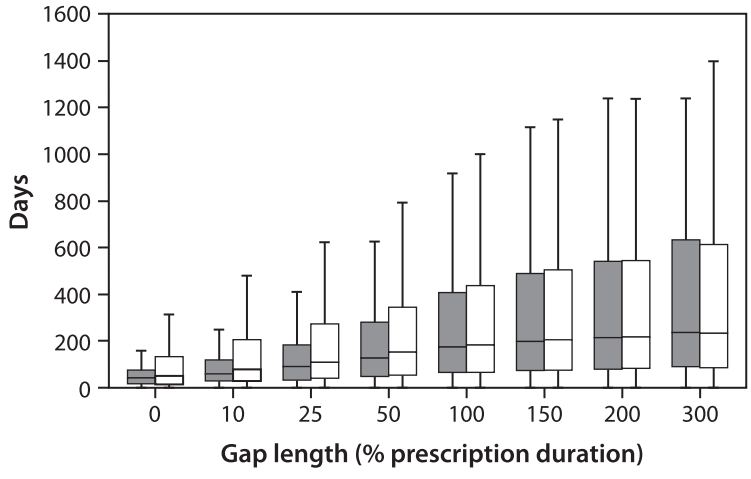


AD = antidepressant
The grey boxes show the median length and the interquartile range (the range between the 25% and the 75% quartile) of an antidepressant treatment episode not accounting for overlap while the white boxes show the median length and the interquartile range of an antidepressant treatment episode when accounting for overlap.

The median length of the antidepressant treatment episode when gaps of different number of days were used is presented as box plots in Figure 2. The two box plots display how the median length changes for the different gap-lengths for both the method where overlapping drug dosing days are disregarded and where overlapping days are accounted for. For both methods the largest changes in the median length are apparent when short gap-lengths are used. The median length more than doubles, when the gap-length is expanded from 0 days to 10 days, showing an increase from 41 days to 98 days for the method not accounting for prescription overlap, and 52 days to 123 days when accounting for overlap. A smaller but still a substantial increase in median length is also seen when changing the gap-length from 10 to 30 days. Only when a gap of 90 days or longer is used the median length ceases to increase substantially. In addition, there is a considerable difference in IQR of the antidepressant treatment episode length when using gaps of 0, 10 or 30 days between the two methods. In Method 2, where overlap is accounted for, larger IQRs are exhibited. When gap-length of 10 days is used the IQR is 154 days when using method not accounting for overlap while the IQR is 245 days when accounting for overlap. When gaps of 45 days or more are used the large difference in IQRs between the two methods disappears.

The median lengths of antidepressant treatment episode when gaps were defined as a percentage of prescription duration are presented as box plots in Figure 3. There

Figure 3 **A box plot displaying the median length (days) of an AD treatment episode when gaps as % of estimated duration for each prescription are used**



AD = antidepressant
The grey boxes show the median length and the interquartile range (the range between the 25% and the 75% quartile) of an antidepressant treatment episode not accounting for overlap while the white boxes show the median length and the interquartile range of an antidepressant treatment episode when accounting for overlap.

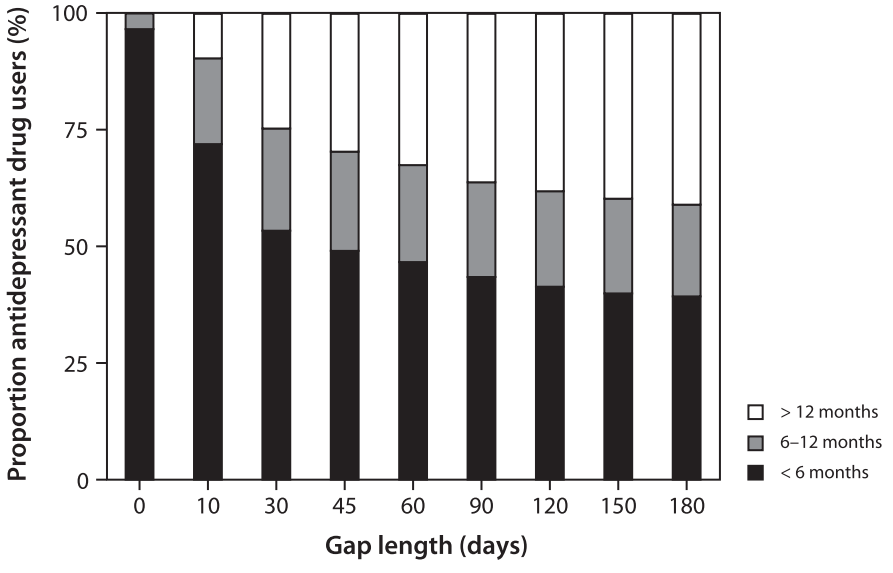
is a continuous increase in median length when using percentages of 0 to 100%. For gaps larger than 150% the median length ceases to increase substantially. The median length when using a gap-length which is 100% the duration of a prescription is similar to when using a gap-length of 30 days for both Methods 1 and 2. However, the IQR is larger when using % of duration as gap-length, indicating more spread in the length of antidepressant treatment episode.

Figure 4 displays how the study population is divided into three different antidepressant treatment groups for the different gap-lengths. The figure shows that short gaps have the largest influence on the antidepressant treatment pattern group including patients that are treated for less than 6 months. Only when a gap-length of 90 days or more is used, the division of the study population into the three antidepressant treatment groups stabilizes.

DISCUSSION

In this study, we investigated how the median length of a constructed antidepressant treatment episode changes when using different methods to estimate prescription duration and when different definitions for gap-lengths are applied. The difference in median length and the IQRs between the two methods is quite large when

Figure 4 **Proportion of antidepressant drug users divided into different antidepressant treatment pattern groups when different gap-lengths are used**



The different antidepressant treatment patterns represent patients where the duration of an antidepressant treatment episode exceeds 12 months, is between 6 and 12 months or shorter than 6 months.

small gaps are used. Only when gap-lengths are set to at least 90 days or 150% of prescription duration do the difference in median length and the IQR for the antidepressant treatment episode between the two methods cease to differ. Using a set number of days, when compared to a percentage of duration, results in similar median lengths of antidepressant treatment episodes. However, the IQRs are larger when using percentage of duration.

In general, our results are of importance for studies that focus on drug exposure-outcome relationships. A larger IQR suggests a larger spread in length of an antidepressant treatment episode in the study sample. This finding has at least three important consequences for epidemiological analysis. Firstly, when the frequency of an outcome during a drug treatment episode (exposed) is investigated, the results would most likely show a higher frequency of the outcome for the exposed when Method 2 is used. In addition, when measuring prevalence of drug use at a specific time point, treatment episode constructed by using Method 2 would lead to a higher prevalence estimate than those constructed according to Method 1. Our results are supported by the findings of Mantel-Teeuwisse and colleagues who measured higher prevalence of drug use when prescription overlap was accounted for.[2] Secondly, due to the difference in median length between the two methods it is

expected that when performing survival analysis, where patients are followed over time, results will also be influence by the method used to construct the treatment episode. As drug treatment episodes are estimated to be longer when using Method 2, time from end of a drug treatment episode until a possible event is expected to be shorter, resulting in a less beneficial survival or hazard rate than if Method 1 would be applied. And lastly, our findings are of importance for composing cohorts based on a specific treatment pattern, such as early discontinuation. Early discontinuation or non-adherence to antidepressant drug use is a current topic which has been extensively investigated using medical or prescription claims databases.[5,9,10,12] Our study shows that the measured proportion of early discontinuers in the study population is highly dependent on the gap-length. The proportion is larger when short gap-lengths are used. The influence of this size variation on the distribution of characteristics, which are often investigated with the purpose of relating them with early discontinuation, is unknown. The Dutch dispensing databases are special due to the availability of information on the prescribed dose regimen. Nevertheless, we find our results also applicable when constructing drug treatment episodes in databases where information on the dosing regimen is missing. The problem of selecting suitable gap-length or adjusting for prescription overlap will always exist, even if the method to estimated prescription duration might differ.

When constructing antidepressant treatment episodes it is important to consider whether a concurrent antidepressant prescription most likely marks a beginning of a new drug treatment episode or if it is a part of a current drug treatment episode. Some symptom free patients who cease antidepressant therapy will later re-initiate antidepressant therapy due to re-emergence of symptoms, i.e. by experiencing a relapse or a recurrence. Using prescription data to identify these two conditions is very difficult, if not impossible. In terms of antidepressant treatment episode construction, the former re-initiation should not be identified as the beginning of a new treatment episode but a part of the current treatment episode. In case of recurrence, re-initiating antidepressant therapy marks the beginning of a new treatment episode. Clinicians suggest that when a patient has been symptom free for at least eight to sixteen weeks (s)he is in recovery.[19,20] For that reason, when short gaps such as 10–30 days are used we would expect the following dispensed prescription to be a part of a current episode. Longer gaps might be more appropriate when the aim is to identify a subsequent individual treatment episode.

Limitation to our study is a common problem when using prescription databases, firstly the lack of information on indication for prescribing. Antidepressants are nowadays prescribed for many symptoms and illnesses other than depression. The antidepressant treatment pattern for those diseases might differ from the one for depression therapy. In our study only SSRI starters are included. It has been shown

that the SSRIs are more frequently prescribed for treating depression than the tricyclic antidepressants (TCAs).[21] In addition, prescription databases only register moments where a prescription is dispensed and collected from the pharmacy. What the patient does with the dispensed medicine is unknown. In case of subsequent dispensations within a treatment episode it is reasonable to assume that the patients are using their medicines. How to measure the duration of the last prescription within a treatment episode is debatable. Possible methods for estimating the last prescription duration would be to include the total prescription duration, to use a life table type of method including half of the total prescription duration or to disregard the last prescription duration. In our study we opted for including the total prescription duration of the last dispensed prescription in a treatment episode. This is based on our belief that the largest part of the patients would finish their therapy.

When constructing drug treatment episodes the nature of the treatment needs to be taken into consideration. The duration of treatment, and number of prescriptions, for different diseases and symptoms varies vastly and can be divided into short time, intermittent, chronic and episodic drug use. Constructing treatment episodes for short time drug use, i.e. treating infection with antibiotics, might only include a single prescription. For intermittent use (use of painkillers as needed), chronic use (hypertension or lipid lowering therapies) and episodic use (treatment of depression or asthma) defining a drug treatment episode can be complex. When constructing treatment episodes for short term medication it is advisable to use strict criteria for the treatment gap e.g. a few days. In case of chronic therapy, the criterion on treatment gap-length is less strict allowing for a longer gap to be used.

In conclusion, it is important how the prescription duration and the allowed gap-length between prescriptions are defined when constructing an antidepressant treatment episode. Large differences exist between methods that account for overlapping tablet days or not. In case of antidepressant treatment episode construction, when investigating re-initiation due to new episode, gaps of 90 days or longer should be used. In general, when deciding on the gap-length the nature of treatment (short, intermittent, chronic or episodic) should be taken into consideration.

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4.2

The association between patient reported drug taking and gaps and overlaps in antidepressant drug dispensing

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(submitted)

ABSTRACT

Objective

Investigation of patient drug use in dispensing databases can show gaps and overlaps in treatment patterns. If the gaps and overlaps are truly associated with non-adherence is not known. The aim of this study is to investigate if patient reported drug taking is associated with length of gaps and overlaps in antidepressant drug dispensing.

Methods

37 Dutch pharmacies sent drug taking questionnaires, including the Medication Adherence Rating Scale, to adult patients who got a second-generation antidepressant dispensed during September-December 2008. Gaps and overlaps between subsequently dispensed prescriptions were investigated. Patients with a gap or an overlap were divided into three subgroups based on the gap/overlap magnitude ($< 5\%$; $\geq 5\%$ and $< 20\%$; $\geq 20\%$). Patient reported drug taking was compared for the three groups and subgroups.

Results

The study population (n=205) was predominantly female (62.9%) with a mean age of 48.0 (standard deviation [sd] 13.6) years. About 71% had a gap, 27% had an overlap and 2% had no gap or overlap between dispensing moments. Patients with a gap $\geq 20\%$ of observed treatment time reported significantly ($p < 0.01$) more often to engage in non-adherent behavior than patients with shorter gaps. In patients with an overlap the differences in patient reporting to be adherent was not statistically significant between the three subgroups.

Conclusion

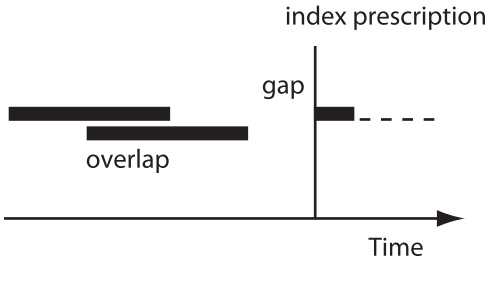
In conclusion, patients with larger gaps in dispensing data report more frequently to engage in non-adherent behavior. These patients more often decide to skip a dose, change their dose or to use less than instructed. Gaps seen in dispensing patterns might not necessarily indicate that the medicine is not used on gap days. Physicians, pharmacists and possibly patients themselves could contribute to improving the registration of actual patient drug taking, which could increase the specificity of definitions aimed at identifying compliant patients.

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants in the Netherlands.[1] It takes two to four weeks for the antidepressants to become effective and guidelines recommend that they should be used for at least six months after symptoms have resolved.[2] However, studies have shown that about 22% of the patients receive only a single antidepressant prescription [3] and up to two thirds discontinue treatment within six months.[4-6] Results from these observational studies indicate that patients use antidepressants differently from what is recommended by clinicians for successful treatment of depression.[7-9]

In daily practice, treatment adherence and persistence have mainly been investigated by using large administrative databases that contain information on prescribing and or dispensing moments.[10-13] Data from such databases can be used to construct drug treatment episodes. A drug treatment episode starts with the first collection of a prescription from a prescriber or a first dispensing in the pharmacy. The duration of an individual prescription is estimated from the amount prescribed or dispensed and the prescribed dosage regimen. Subsequently, the total duration of the treatment episode is estimated by defining how many prescriptions belong to a single treatment episode. However, patients rarely collect a subsequent prescription exactly on the day that the last dose has been consumed from the prior prescription. As a result drug treatment patterns constructed from prescribing or dispensing moments in administrative databases often show an overlap of two prescriptions or a gap between two prescriptions (Figure 1).

Figure 1 **Treatment pattern constructed from dispensing moments, showing gap and/or overlap of subsequently dispensed prescriptions**



Black bars represent the estimated duration of each dispensed prescription.

In real life, we expect patients to continue drug taking without the gaps or overlaps in their drug use and therefore different methods are applied to compensate for

this irregular pick up pattern when treatment episodes are constructed from prescribing or dispensing data.[14] However, we do not know the real reasons for a gap or an overlap in the dispensing pattern, and whether it is truly associated with non-adherence. As an example, overlapping treatment patterns could be observed for patients who make sure to always have enough medicines at home. On the other hand patients who use more than is instructed are likely to show overlaps in their dispensing pattern, while those that use less will show a gap.
The aim of this study is to investigate if patient reported drug taking is associated with gaps and overlaps in antidepressant drug dispensing.

METHODS

Setting

Data were collected with the help of pharmacists belonging to the Utrecht University Pharmacy Practice Research Network (UPPER; http://upper.science.uu.nl). The network includes more than 850 of the total 1900 community pharmacies in the Netherlands. All pharmacies have automated dispensing records, which include information on gender, date of birth and dispensed medicines. Information on dispensed medicines includes dispensing date, type of prescriber, type of medicine, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use is estimated by dividing the number of dispensed units by the prescribed number of units per day. All drugs are coded according to the Anatomical Therapeutical Chemical (ATC) classification index.[15]
Virtually all Dutch inhabitants are registered with a single community pharmacy, independent of prescriber, resulting in a register near complete with regards to dispensed prescription medicines.[16] For this study, 46 pharmacies were approached and asked to participate of which 37 reacted positively. The participating pharmacies were located both in urban and rural areas. The work was reviewed by and conducted in compliance with the requirements of the UPPER institutional review board of the Department of Pharmacoepidemiology and Pharmacotherapy. Patients participating in the study were not required to fill in an informed consent form as the review board did not consider the questionnaires to invade patient integrity.

Study population

The patient selection procedure took place in 37 participating pharmacies from September 2008 to December 2008 (study period). Each pharmacy selected a random sample of 12–15 patients over 18 years of age who collected a prescription

for a SSRI (paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram) or venlafaxine during the study period. The date of the dispensed antidepressant (index prescription) during the study period was defined as the index date. All patients were required to have received at least three antidepressant prescriptions, including the prescription on the index date during 2008. The three prescriptions were required to belong to the same antidepressant treatment episode, e.g., with less than 90 days elapsing between the last dispensed dose of a prescription and a subsequent prescription.[14] Switching to a different antidepressant within a treatment episode was considered continuation of therapy. Patients were not selected if they where treated with two antidepressants simultaneously.

Patients received a questionnaire from the pharmacy, a pre-stamped addressed return envelope and an accompanying letter describing the research and requesting their participation. Questionnaires were labeled with a study ID (identification number) of the patient and did not include any information on the name or address of the patient. Patients received two weeks to complete and return the questionnaire to the pharmacy. Patients who did not returned the questionnaire within two weeks were contacted by the pharmacy by telephone as a reminder. The pharmacies provided anonymous information on patient age, gender and medication use for those patients who participated in the study.

Patient reported drug taking

The questionnaire included questions on medication, disease and sociodemographic characteristics in addition to the 5-item Medication Adherence Rating Scale (MARS). Patients were asked about which type of antidepressant drug they were currently using, if they were still using the antidepressant and for which disease or symptoms they were using the antidepressant. Further, they were asked if they used the antidepressant differently from the instructions on the label and in case they used the antidepressant differently if they reported that to their physician or pharmacist. Patients were also asked if they made sure that they always had sufficient amount of antidepressant drug in house. Patients were asked about employment status, marital/relationship situation, living situation and level of education. Employment status was divided into employed or studying and un-employed including retired patients and patients incapacitated for work. Marital/relationship situation was divided into having a partner or not. Living situation was divided into living with others or living alone. Education was divided into three categories: low (none/primary school), middle (secondary school) and high (college/university).

Self reported adherence was assessed using the 5-item MARS.[17,18] The MARS asks patients to report on how frequently they engage in non-adherent behavior. The five non-adherent behavior questions related to antidepressant drug use were:

"I forget to use it", "I alter the dose", "I stop using it for a while", "I decide to miss out a dose", "I use less than instructed". Each item was rated on a 5-point scale where 5 = "never", 4 = "rarely", 3 = "sometimes", 2 = "often"and 1 = "very often". Scores of the five items are summed and give a total of 5 to 25, where higher scores indicate higher levels of adherence. Patients were considered adherent if they answered all questions with "never" or "rarely".

Gaps and overlaps

Antidepressant drug dispensing moments were investigated for each patient using the information on dispensed prescriptions from the pharmacies. The two latest antidepressant drug dispensing moments prior to index date were selected. Duration of use was estimated for the two dispensed prescriptions based on the amount dispensed and the dosage regimen. For the two dispensed prescriptions, it was investigated if the estimated duration extended past the subsequent dispensing date (overlap) or ended prior to the subsequent dispensing date (gap) (Figure 1). The length of the overlapping period or a gap between the subsequent prescriptions was measured in days. The measured overlaps or gaps for each patient were summed to a single value, where a positive value represented the number of gap days, a negative value represented the number of overlapping days and in case of zero days no overlap or gap was registered. The total time elapsing from the dispensing date of the second antidepressant prescription prior to the index prescription until index date was measured and defined as observed treatment time. For each patient, a gap or an overlap was presented as a percentage of total observed treatment time.

Data analysis

Data from questionnaires was collected and administered manually into a SPSS file. Descriptive statistics were used to describe patient characteristics. The percentage of total overlapping/gap days within an antidepressant treatment episode were investigated in relation to patient reported drug taking. Patients were divided into three groups, those having a gap, those having an overlap and those without a gap or an overlap. Patients with a gap or an overlap were further divided into three subgroups based on the gap/overlap magnitude during the first antidepressant treatment episode. The three subgroups were defined as gap/overlap days < 5.0% of total observed treatment time, gap/overlap days ≥ 5.0% but < 20.0% of total observed treatment time and gap/overlap days ≥ 20.0% of total observed treatment time. Patient reported drug taking was compared for the three subgroups using the Fischer's exact test. Continuous variables were compared using the Mann Whitney test. Cronbach's alpha was estimated to investigate the internal consistency for the

MARS. Data analysis was performed using SPSS for Windows release 14.0 (SPSS Inc, Chicago, IL).

Table 1 **Baseline characteristics of the study population on index date**

Characteristic	n=205 (100%)
Sociodemographic characteristics	
Female gender	129 (62.9%)
Age in years	
18–30	25 (12.2%)
31–45	61 (29.8%)
45–60	87 (42.4%)
> 60	32 (15.6%)
Education [a]	
low	57 (27.8%)
middle	83 (40.5%)
high	60 (29.3%)
Having a partner	118 (57.6%)
Employment or in school	105 (51.2%)
Living with others	141 (68.8%)
Medication and disease characteristics [b]	
Type of antidepressant	
paroxetine	88 (42.9%)
citalopram	48 (23.4%)
fluoxetine	24 (11.7%)
other	45 (22.0%)
Reason for use [c]	
depression	154 (75.1%)
anxiety	100 (48.8%)
Total observed treatment time; mean (sd) days	119.0 (108.5)
Duration of each prescription prior to index date; median (IQR) days	47.5 (60.0)

sd = standard deviation; IQR = interquartile range
a) Missing information for five patients.
b) As reported by the patient.
c) Patients could indicate more than one reason for using the antidepressant.

RESULTS

Of the 530 patients who were asked to participate in the study 245 (46.2%) participated and returned the questionnaire to the pharmacy. Of those who returned the questionnaire 40 were excluded (3 due to insufficient medication data; 7 due to simultaneous use of two antidepressants; 1 patient who received weekly

dosing box which does not give possibility of measuring overlaps or gaps; 13 due to receiving less than three antidepressant prescriptions within an antidepressant treatment episode; and 16 who did not fill in all the MARS items) resulting in 205 patients who were included in the analysis.

The sociodemographic characteristics along with the medication and disease characteristics as reported by the patients are presented in Table 1. The study population was predominantly female (62.9%) and had a mean age of 48.0 (standard deviation [sd] 13.6) years. Most patients were using paroxetine (42.9%) and were treated due to depression (75.1%). The median length of the total observed treatment time was 119.0 (interquartile range [IQR] 108.5) days and the median prescription duration was 47.5 (IQR 60.0) days.

Investigating adherence using the MARS on a continuous scale for the study population resulted in a median of 24.0 (IQR 2.0), which indicates that the patients, in general, considered themselves to be compliant with therapy (Table 2). The Cronbach alpha for MARS was 0.68 indicating a reasonable internal consistence for an attitude questionnaire. When the treatment pattern was investigated for each patient we found that about 71% had a gap, i.e. the estimated duration of the two

Table 2 Patient reported drug taking

Patient group		Adherent (MARS) n (%)	MARS continuous median (IQR)	Stopped using n (%)	Use differently from instructions n (%)
All patients	(n=205)	153 (74.6%)	24.0 (2.0)	6 (2.9%)	38 (18.5%)
Gap days					
any	(n=147)	107 (72.8%)	24.0 (2.0)	5 (3.4%)	31 (21.0%)
< 5% of OTT	(n= 40)	38 (95.0%)[a]	25.0 (1.0)[b]	0 (0.0%)	6 (15.0%)
5% – 19.9% of OTT	(n= 45)	36 (80.0%)[a]	24.0 (2.0)[b]	1 (2.2%)	6 (13.3%)
≥ 20% of OTT	(n= 62)	33 (53.2%)	23.0 (4.0)	4 (6.5%)	19 (30.7%)
Overlapping days					
any	(n= 53)	41 (77.4%)	24.0 (1.5)	1 (1.9%)	7 (13.2%)
< 5% of OTT	(n= 20)	18 (90.0%)	25.0 (1.0)[b]	1 (5.0%)	2 (10.0%)
5% – 19.9% of OTT	(n= 18)	13 (72.2%)	24.0 (2.0)	0 (0.0%)	2 (11.1%)
≥ 20% of OTT	(n= 15)	10 (66.7%)	24.0 (5.0)	0 (0.0%)	3 (20.0%)
No overlap or gap days	(n= 5)	5 (100.0%)	24.0 (1.5)	0 (0.0%)	0 (0.0%)

MARS = Medication Adherence Rating Scale; IQR = interquartile range; OTT = observed treatment time
Including information on the median MARS score, those who stopped using, or used the antidepressant differently from label instruction presented per group (gap, overlap, no gap or overlap). For patients with a gap or an overlap, information is provided per subgroup representing gap or overlap as proportion of OTT.
a) Fischer's exact test, $p < 0.01$; reference group = gap ≥ 20% of OTT
b) Mann Whitney test, $p < 0.05$; reference group = gap/overlap ≥ 20% of OTT

dispensed antidepressant prescription was shorter than the observed treatment time. About 27% had an overlap and 2% had no gap or overlap. For those with a total gap we found that 50% had a gap on both dispensing moments, while 50% had a gap and an overlap, or no gap/overlap and a gap. For most of the patients with a total overlap, the two dispensing moments included a gap and an overlap or no gap/overlap and an overlap (70%). Only 30% had an overlap on both dispensing moments. For all patients with no total gap/overlap the two dispensing moments had a gap and an overlap.

Information on patient reported drug taking within each group is presented in Table 2. Patients with a gap < 5% of observed treatment time or a gap ≥ 5% but < 20% of observed treatment time had higher ($p < 0.05$) MARS scores and reported significantly ($p < 0.01$) more often to be adherent than patients where gap was ≥ 20% of observed treatment time. In patients with an overlap the differences in patient reporting to be adherent was not statistically significant between the three subgroups. In patients with an overlap we only found significant ($p < 0.05$) difference in median MARS scores between patients were overlap was < 5% of observed treatment time and those with an overlap ≥ 20% of observed treatment time. Almost twice as many patients with a gap or an overlap ≥ 20% of observed treatment time when compared with patients where gap or overlap was < 5% or between 5% and 20% reported that they used the antidepressant differently from instructions on the drug label. However, the difference was not statistically significant.

Of all patients who answered questions regarding if they informed the physician or pharmacist when using the antidepressant differently from label instruction, patients with a gap < 5% of observed treatment time reported more frequently ($p < 0.05$) to "always" inform the physician or the pharmacists (65.7% and 40.0%) when compared to patients where gap was ≥ 20% of observed treatment time (39.7% and 19.0%). In patients with an overlap there was no difference in the amount of patients who always informed the physician or pharmacist when the antidepressants were used differently from label instruction between the three groups. About 67.0% of patients with a gap and 70.0% of patients with an overlap reported that they make sure to have sufficient amount of antidepressant drug at home. No significant differences between the three gap/overlap magnitude groups were found with regards to the amount of patients reporting that they make sure to have sufficient amount of antidepressant in house.

DISCUSSION

In this study we found that patients with large gaps in their dispensing histories more often report to engage in non-adherent behavior. They more frequently report to use the antidepressant differently from label instructions, to sometimes skip a dose, change their dose or use less than instructed.

Our findings, however, also showed that not all patients with large gaps in their dispensing histories report to engage in non-adherent behavior. In this study about half of the patients with large gaps report that they are adherent to therapy and 70% said they use the drug according to label instructions.

These discrepancies show that although strict definitions are used to identify compliant patients based on their dispensing histories, there will always be some outliers who do not fit the group.

Others who have investigated self reported adherence in relation to drug exposure estimates have reported a good [19] or bad [20] correlation with drug exposure estimates. Rosa et al. found that high MARS scores were positively correlated with higher lithium plasma levels.[19] However, van den Steeg et al. who estimated the validity of self reported adherence by using medication possession ratio as a reference indicating adherence, concluded that the MARS should not be recommended for measuring adherence.[20] Which drug exposure adherence estimate is used as a golden standard when compared with adherence defined according to the MARS is something that can be debated.

From our study the question arises how well the definitions used to classify patient drug taking in dispensing data actually include adherent patients. Most often when dispensing data is used to study drug taking, it is difficult or costly to contact the patients in question to retrieve extensive information on their drug taking behavior. A possible way to get a more correct picture of patient drug taking would be to improve the registration of prescribing, dispensing or drug use data. Patients with large gaps in their dispensing histories report less frequently to inform the physician or the pharmacist about using the antidepressant differently from label instructions. When patients do not report to the pharmacist or the physician that the antidepressant is used different from label instructions, their observed dispensing pattern continues to show gaps, although they might be using the antidepressant on the observed gap days. In patients who use less than instructed on drug label, the gaps need not represent days of no use but could be due to longer duration of dispensed medicine than what is estimated from label instructions. The resulting treatment patterns, which diverge from the actual patient drug taking, could be adjusted if physicians or pharmacists would engage more in asking the patients about how they use their medicines, or when the patient himself can add this information to his prescription/drug use file of the electronic patient record.

The strength of this study is that it investigates treatment patterns in a dispensing database in relation to how the patients report on drug taking using a validated tool, the MARS. One of the limitations of our study, however, is its small sample size, which could be the cause of our non-significant findings. Another limitation is that only two moments between dispensed antidepressants were investigated. A better estimation of total gaps and overlaps would have been possible if information on all antidepressants dispensed within a treatment episode for each patient was available. The choice to investigate two moments was done so that a single dispensing moment that would show a gap could eventually be compensated if the following dispensing moment would show an overlap.

In conclusion, patients with larger gaps in dispensing data report more frequently to engage in non-adherent behavior. These patients more often decide to skip a dose, change their dose or to use less than instructed. However, some patients with larger gaps in their dispensing histories report to never engage in non-adherent behavior, while patients classified as adherent report otherwise. Gaps seen in dispensing patterns might not necessarily indicate that the medicine is not used on gap days. Physicians, pharmacists and possibly patients themselves could contribute to improving the registration of actual patient drug taking, which could increase the specificity of definitions aimed at identifying compliant patients.

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4.3

Transitions from general practitioner to psychiatrist care (or vice versa) during a first antidepressant treatment episode

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ABSTRACT

Objective

To investigate how frequently patients transit from general practitioner (GP) to psychiatrist care and vice versa during a first antidepressant episode and antidepressant treatment changes associated with transition.

Methods

Antidepressant episodes were constructed for patients (≥ 18 years) initiating selective serotonin reuptake inhibitor (SSRI) use in 2000 (n=10 158). Transition in care within a first treatment episode was investigated. Antidepressant treatment changes were compared for transiting and non-transiting users.

Results

Six percent of patients who initiated use by a GP transited to psychiatrist care, while 39.1% initiating use by a psychiatrist transited to general practice care. Patients transiting from GP to psychiatrist care were more likely to switch between antidepressants (relative risk [RR] 6.16; 95% confidence interval [95%CI] 4.90–7.75) or to undergo dose changes (RR 4.48; 95%CI 3.76–5.34) than non-transiting patients.

Conclusion

About 9% of SSRI initiators transit in care. Transitions from general practice to psychiatrist care lead to antidepressant treatment changes and could possibly serve as a disease severity indicator in observational studies.

INTRODUCTION

In the Netherlands the general practitioner (GP) plays a pivotal role as the gatekeeper in the health care system. Patients with depressive symptoms will first be seen by a GP, who then makes a decision to either diagnose and treat the patient himself, or refer the patient to a specialist, most often a psychiatrist. As a consequence, patients who suffer from mild to moderate depressive symptoms are more likely to be initially treated by a GP, while more severely depressed patients are more likely to be directly referred to a psychiatrist. When it comes to treatment with antidepressants, research has shown that over 80% of antidepressant drug users receive their first antidepressant prescription from a GP.[1] Patients initiating antidepressant use can be solely under the care of a GP or a specialist, during their treatment. A study in general practice patients showed that about 20% of those diagnosed with depression in general practice are referred to specialist care within three months after receiving the diagnosis.[2] Studies that compared patients who are initially treated by GPs with those initially treated by psychiatrists report that those in specialist care are more often younger, male and more educated than those who are treated in general practice.[3,4]

While current studies on antidepressant drug use mainly focus on patients initiating use in general practice or in specialist care, not much is known about the frequency of transition from general practice to specialist care or vice versa after antidepressant treatment initiation. Transitions in care in general, are often associated with changes in medication such as dose changes, switching to a new medication and or adding medication to current therapy.[5-8] Changes specifically in antidepressant drug treatment related to transition in care within a first antidepressant treatment episode have yet to be studied.

The aim of this study was to investigate how frequently patients transit in care, from GPs to psychiatrists and vice versa, during a first antidepressant treatment episode. In addition, changes in antidepressant treatment associated with transition from general practice to psychiatrist care and vice versa will be identified and described.

METHODS

Setting and study population

Prescription data were collected using the Pharmaco-Morbidity Record Linkage System (PHARMO RLS), which has been described in detail elsewhere.[9] In short, the PHARMO RLS includes prescription data of about one million residents in the Netherlands. Virtually all Dutch inhabitants are registered with a single community pharmacy, independent of prescriber, resulting in a register near complete with

regards to dispensed prescription medicines.[10] Each patient is identified with an anonymous unique patient-identification code that allows for observation of patient medicine use in time. The PHARMO RLS includes information on patient gender, date of birth and dispensed medicines. Information about dispensed medicines includes dispensing date, type of prescriber, type of medicine, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use is estimated by dividing the number of dispensed units by the prescribed number of units per day. All drugs are coded according to the Anatomical Therapeutical Chemical (ATC) classification index.[11] The database does not provide information on the indications for use of the medicines.

The source population was composed of adult (≥ 18 years) antidepressant drug users from the PHARMO RLS database who initiated selective serotonin reuptake inhibitor (SSRI) therapy in 2000. The date of first dispensed SSRI for each patient in 2000 was set as start date. The study population was composed of new users from the source populations, which we defined as those who had not received any antidepressant during the two years prior to start date. Studies on antidepressant drug use show that patients who only receive a single antidepressant prescription often do not initiate therapy or discontinue within two weeks.[12] Therefore, patients who received only a single antidepressant prescription during the twelve months following start date were excluded. Finally, only those who got their prescription prescribed by a GP or a psychiatrist on start date were included in the study populations for analysis.

Antidepressant treatment episode

Antidepressant treatment episodes were constructed for each patient. The first treatment episode started on the dispensing date of the first prescription (start date). The theoretical end date of each prescription was defined as the dispensing date plus the duration of drug use. The duration of drug use was based on the amount dispensed and the dosage regimen. When an antidepressant prescription was dispensed within 90 days after the theoretical end date of a prior prescription it was considered to belong to the same treatment episode.[13] If an antidepressant prescription was dispensed on a date later than 90 days, after the theoretical end date of a prior prescription, it was considered to mark the beginning of a new treatment episode. Each treatment episode ended on the theoretical end date of the last prescription within the treatment episode. Switching to a different antidepressant within the treatment episode was considered as continuation of therapy.

Transition from general practice to psychiatrist care or vice versa

The primary outcome in this study was to estimate how frequently antidepressant drug users undergo transition in care from a GP to a psychiatrist (or vice versa) during their first antidepressant treatment episode. In this study, we use the term transition, although we do acknowledge that patient treatment can also be provided by two (or more) different type of prescribers at the same time. In our study transition is defined as filling a prescription for an antidepressant drug after the start date by a type of prescriber different from the type of prescriber on the start date. Patient characteristics were investigated in those who were only treated by a GP or a psychiatrist (no transition) and those who transited from a GP to psychiatrist care or vice versa (transition).

Changes in treatment following transition

A secondary outcome in this study was to describe the possible changes in antidepressant treatment associated with transition in care. This outcome was investigated by conducting two matched cohort studies nested within our cohort of antidepressant users. For the first matched cohort, antidepressant users who experience transition from general practice to psychiatrist care were selected and matched with three randomly selected antidepressant drug users treated by a GP without transition in care during the first treatment episode. The moment of transition was set as index date. The transiting and non-transiting antidepressant users were matched on age (± 5 years), gender and the time elapsed from start of antidepressant treatment episode (start date) to index date. The index date for the non-transiting antidepressant users was defined as start date plus the number of days until transition occurred in the matched transiting antidepressant user, thereby matching index patients and control patients on duration of treatment until index date. In non-transiting antidepressant users the antidepressant prescription that was dispensed closest to the index date (either on or after) was defined as the index prescription. For users who transited in care where the first antidepressant treatment episode was less than a year long, the matching non-transiting users were required to have an antidepressant treatment episode duration expanding at least 45 days past the index date.

For the second follow-up study, antidepressant drug users who experience transition from psychiatrist to general practice care were matched with one randomly selected patient who was only treated by a psychiatrist during the first antidepressant treatment episode. Matching was performed in the same way as for the first follow up study, except with regards to number of non-transiting users matched per transiting user. As fewer patients initiate antidepressant use by the

psychiatrist we were only able to match one non-transiting user to each transiting user.

Antidepressant treatment changes in each user were investigated by comparing the last dispensed antidepressant prior to index prescription to the dispensed antidepressant on index date (index prescription). Changes in antidepressant treatment were defined as switching to a different antidepressant of the same or different type (switch), change to a higher antidepressant dose (higher defined daily doses [DDDs]) or change to a lower antidepressant dose (lower DDDs).

Data analysis

Survival curves were constructed for age and gender subgroups to investigate time to transition within those who did transit and those who did not transit in care. Differences in time to transition were also investigated for antidepressant users with and without a probable depression diagnosis. A previously developed and tested algorithm was used to estimate the predictive probability of having a depression diagnosis. Those with a predictive probability above 0.5 were defined as users with a probable depression diagnosis.[14] The Cox proportional hazards model was used to estimate the relative risk (RR) with 95% confidence intervals (95%CI). In addition to the general analysis, separate analyses were performed for patients where use was initiated by a psychiatrist or by a GP.

Mann Whitney testing was applied to compare median duration of the first antidepressant treatment episode between those who transited and those who did not transit care. In addition, the time to transition for those who underwent transition from GP to psychiatrist and those who undergo transition from a psychiatrist to GP were compared. Changes in antidepressant treatment, such as switching, dose changes (higher DDDs and lower DDDs prescribed) were compared for transiting and non-transiting users using the Cox proportional hazards model. As transition moment and index prescription take place on the same day the time to event for all patients was defined as one day. All analyses were performed using SPSS version 14.0.0 for Windows (SPSS Inc., Chicago, Il).

RESULTS

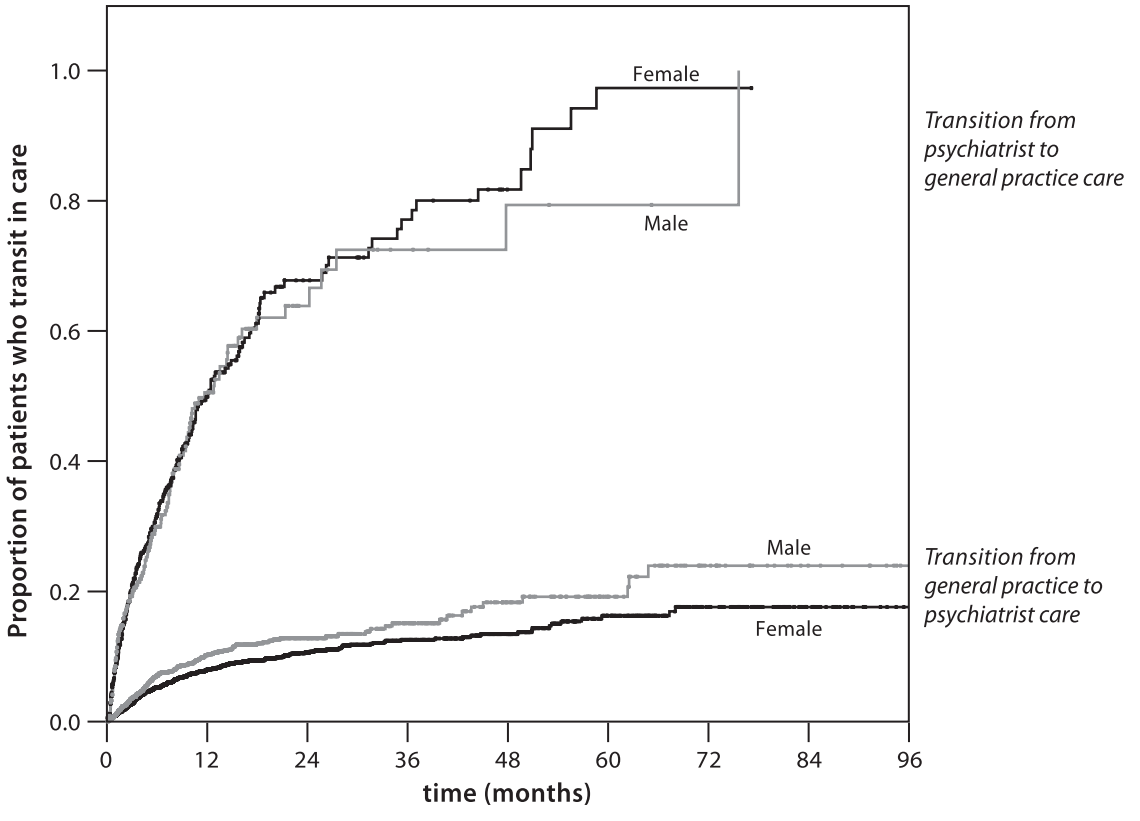
The study population (n=10 158) was predominantly female (68.6%) with a mean age of 49.2 (standard deviation [sd] 14.0) years (Table 1). The majority of patients were prescribed paroxetine on start date (68.3%). The median duration of the first antidepressant treatment episode for the study population was 194.0 (interquartile range [IQR] 402.0) days.

Table 1 **Basic characteristics of the study population (n=10 158) on admission date and transition pattern during the first antidepressant treatment episode**

		General practitioner initiated n=9 284 (100%)	Psychiatrist initiated n=874 (100%)
Patient characteristics			
female gender		6 438 (69.3%)	530 (60.6%)
age in years:	18-30	1 557 (16.8%)	237 (27.1%)
	31-45	3 242 (34.9%)	331 (37.9%)
	46-60	2 653 (28.6%)	203 (23.2%)
	> 60	1 832 (19.7%)	103 (11.8%)
Type of antidepressant			
paroxetine		6 555 (70.6%)	386 (44.2%)
fluoxetine		1 250 (13.5%)	116 (13.3%)
citalopram		429 (4.6%)	231 (26.4%)
fluvoxamine		591 (6.4%)	51 (5.8%)
sertraline		459 (4.9%)	90 (10.3%)
Transition pattern during first episode			
no transition		8 724 (94.0%)	532 (60.9%)
transition		560 (6.0%)	342 (39.1%)

Most patients (85.9%) were treated with antidepressants by a GP only during their first antidepressant treatment episode while about 5.0% were treated with antidepressants by a psychiatrist only. Almost 9.0% of the study population transited in care during their first antidepressant treatment episode. About 6.0% of all patients who initiated use by a GP transited to psychiatrist care, or in total 5.5% of the study population, while 39.1% of all patients who initiated use by a psychiatrist transited from psychiatrist to general practice care, or 3.4% of the study population. For patients where use was initiated by a psychiatrist, we found no significant differences in risk of transiting from psychiatrist to general practice care when stratified by gender or age group. However, in patients in which antidepressant drug use was initiated by a GP we found that males have a 38% higher risk of transiting to psychiatrist care than females (RR 1.38; 95%CI 1.16–1.64) (Figure 1). In addition, patients in the younger age group 18-30 years, 31-40 years and 45-60 years were at a higher risk of transiting to psychiatrist care than patients > 60 years (RR 3.48, 95%CI; 2.51–4.82, RR 2.30; 95%CI 1.69–3.13, RR 1.58; 95%CI 1.14–2.19 respectively) (Figure 2). We found no statistically significant differences in risk of transiting in care between patients with a probable diagnosis of depression and those without a probable diagnosis of depression, both in the

Figure 1 **Time until transition in care for those who transit from general practice to psychiatrist care and those who transit from psychiatrist to general practice care within the first treatment episode for gender**

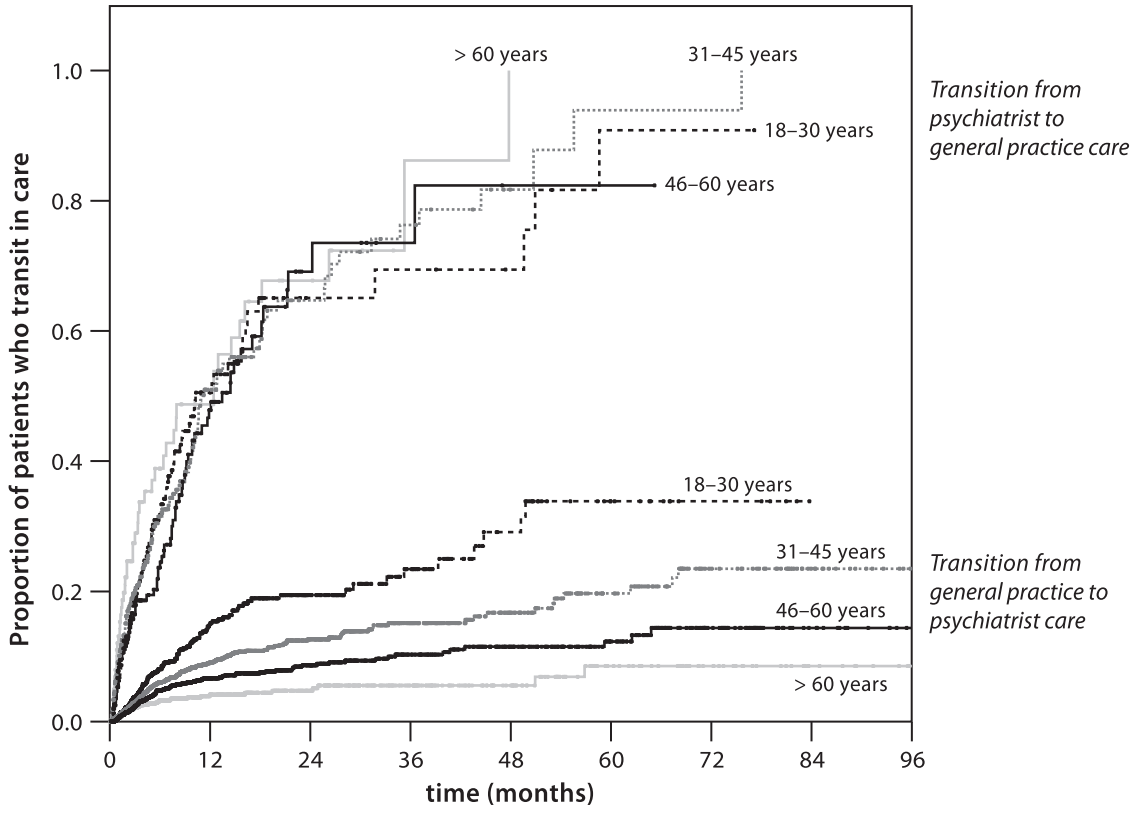


group of patients who initiated use by a GP (RR 1.55; 95%CI 0.77–3.12) and in the group of patients initiating use by a psychiatrist (RR 0.86; 95%CI 0.60–1.23).

Patients who transited from general practice to psychiatrist care (or vice versa) had a significantly longer ($p < 0.01$) median duration of first antidepressant treatment episode than those that did not transit in care (174.0 [IQR 351.0] days compared to 561.5 [IQR 844.0] days). The median time to transition was 128.5 (IQR 211.5) days in those who transited from general practice to psychiatrist care and 118.5 (IQR 241.8) days in those who transited from psychiatric to general practice care. Time to transition differed significantly ($p < 0.01$) between those who transited from general practice to psychiatrist care and those who transited from psychiatric to general practice care.

Five hundred and fifty four users who transited from general practice to psychiatrist care were matched with 1662 users who were only treated by a GP to investigate if changes in antidepressant drug use differed between the two. In general, we

Figure 2 **Time until transition in care for those who transit from general practice to psychiatrist care and those who transit from psychiatrist to general practice care within the first treatment episode for age groups**



found that changes in antidepressant treatment were more common in those who transited from general practice to psychiatrist care (Table 2). Those who transited from general practice to psychiatrist care had a significantly higher risk of switching between antidepressants (RR 6.16; 95%CI 4.90–7.75) or to undergo dose changes (RR 4.48; 95%CI 3.76–5.34) than those who did not transit in care.

To investigate differences in changes in antidepressant drug use in those who are only treated by psychiatrist compared to those who transited from psychiatrist to general practice care during their first treatment episode, 203 users who transited from psychiatrist to general practice care were matched with 203 users who were only treated by a psychiatrist. We found no significant differences in switching or dose changes for antidepressant treatment around index date between those who were treated with antidepressants only by psychiatrists and those who transited from psychiatric to general practice care (Table 2).

Table 2 **Changes in antidepressant treatment (switching, higher DDDs, lower DDDs) on index date (non-transiting patients used as reference)**

	General practice care			Psychiatrist care		
	Transiting	Non-transiting		Transiting	Non-transiting	
	n=554 (100%)	n=1662 (100%)	RR (95%CI)	n=203 (100%)	n=203 (100%)	RR (95%CI)
Patient characteristics						
female gender	356 (64.3%)	1068 (64.3%)	n/a	121 (59.6%)	121 (59.6%)	n/a
age in years (sd)	41.2 (13.9)	40.0 (13.8)	n/a	42.1 (14.8)	40.2 (15.0)	n/a
Median time to index date, days (IQR)	128.0 (205.5)	128.0 (204.0)	n/a	83.0 (194.0)	83.0 (194.0)	n/a
Changes in antidepressant therapy						
switching	224 (40.4%)	109 (6.6%)	6.16 (4.90– 7.75)[a]	10 (4.9%)	7 (3.4%)	0.98 (0.81–1.20)
dose changes	309 (55.8%)	207 (12.5%)	4.48 (3.76– 5.34)[a]	36 (17.7%)	35 (17.2%)	1.02 (0.65–1.64)
higher DDDs	155 (28.0%)	59 (3.5%)	7.88 (5.84–10.64)[a]	15 (7.4%)	25 (12.3%)	0.60 (0.32–1.14)
lower DDDs	154 (27.8%)	148 (8.9%)	3.12 (2.49– 3.91)[a]	21 (10.3%)	10 (4.9%)	2.10 (0.99–4.46)

First follow-up study (General practice) compares those who are treated only by general practitioners (reference) with those who transit from general practice to psychiatrist care. The second follow-up study (Psychiatrist care) compares those who are treated only by a psychiatrist (reference) with those who transit from psychiatrist to general practice care.
DDD = defined daily dose; RR = relative risk; 95%CI = 95% confidence interval; n/a = not applicable; sd = standard deviation; IQR = interquartile range
a) $p < 0.001$

DISCUSSION

This study shows that of all antidepressant drug users about 9.0% transit in care either from general practice to psychiatrist care or vice versa during their first antidepressant treatment episode. In patients where use is initiated by the GP about 6% are referred to psychiatrist care at some point during the first treatment episode and of all patients who start their antidepressant use by a psychiatrist about 34% transit to general practice care.

As others before us, who investigated changes related to transition from general to hospital [6-8] or specialist care,[5] we found that transition in care leads to treatment changes. However, in antidepressant drug users we found the direction of the transition to be of importance. Transition from general practice to psychiatrist care was related to changes in antidepressant use such as switching therapy or dose changes. This indicates that, in these patients, current treatment might not be sufficiently effective to combat symptoms resulting in GP referral to psychiatrist care. That GPs refer these patients to psychiatrist care due to disease severity is further supported by our finding that those who transit to psychiatrist care are 6 times more likely to switch to another antidepressant and 8 times more likely to change to a higher dose of antidepressant than those who continue treatment with the GP. This is in accordance with depression treatment guidelines which recommend dose changes or switching to another antidepressant in case of no response to the original antidepressant.[15] In patients where antidepressant use is initiated by a psychiatrist no significant changes in antidepressant drug use were seen between those who transit and those who are only treated by a psychiatrist during their first antidepressant treatment episode.

Simon et al. investigated patient characteristics in relation to if initial antidepressant was received from general practice or psychiatrist care and found that males and younger patients were more likely to initiate antidepressant use by a psychiatrist.[4] He, however, excluded patients who transited in care from the study. Other studies report significant differences at baseline in antidepressant drug users with males and younger patients being more likely to be treated by a psychiatrist.[2,16] In our study we found that males and younger patients had a significantly higher risk of transiting from general practice to psychiatrist care. Therefore, not only are patients of male gender and younger age more likely to initiate antidepressant drug use in psychiatrist care as previously reported but even when use is initiated by a GP these patients are also more likely to be referred to psychiatrist care.

Conducting observational research on study topics which involve patients treated for depression is often hampered by insufficient information on the severity of symptoms. In antidepressant users, switching or dose changes could be considered as markers of severity. Possibly, in addition to changes in antidepressant treatment,

transition from general practice to psychiatrist care within a treatment episode could be another marker for disease severity.

A limitation to our study is the generalizability of our results. In the Netherlands, the GP serves as the gate keeper to specialist care. In countries with other type of health care system, were patients can self-select if they visit a general practitioner or a psychiatrist with their health complaints, different transition patterns might be expected. Further, we do not have information on patients that might be admitted to in-patient care. However, we would expect patients who are treated with antidepressants initially by a psychiatrist as more likely to be admitted to in-patient care than those initiating treated by a GP.

In conclusion, about 9% of those who initiate SSRI use transit from general practice to psychiatrist care and vice versa. Studies have shown that those who initiate SSRI use in psychiatrist care are more likely to be of male gender and younger age. Our study shows that this also applies to patients who transit from general practice to psychiatrist care. Transition from general practice to psychiatrist care in SSRI users could possibly serve as a severity indicator when performing observational studies on mental health care treatment.

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4.4

Duration of antidepressant drug treatment and its influence on risk of relapse/ recurrence: immortal and neglected time bias

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ABSTRACT

Objective

Several observational studies have found a higher risk of recurrence/relapse of depression for patients who discontinue antidepressant use compared with those who continue. This study demonstrated that measurement of follow-up time can be subject to immortal and neglected time bias.

Methods

Data were obtained from the 2001 Second Dutch National Survey of General Practice. The study population was composed of antidepressant users with a registered depression diagnosis, divided into early discontinuers and continuing users. Two methods were used to measure time to relapse/recurrence. Method 1, used in previously mentioned studies, measured the beginning of follow-up 6 months after starting antidepressant therapy. Method 2 constructed individual treatment episodes for each patient and measured follow-up from actual end-of-treatment episode.

Results

The Cox proportional hazards model produced a risk ratio of 1.58 (95% confidence interval [95%CI] 1.02–2.45) for Method 1, suggesting a higher risk of relapse/recurrence for early discontinuers. In Method 2, a statistically non-significant risk ratio of 0.77 (95%CI 0.49–1.21) was produced, indicating no difference in risk of relapse/recurrence.

Conclusion

The authors found the method used in previous studies subject to bias. Applying a different method, accounting for immortal and neglected time bias, eliminated the protective effects of longer treatments.

INTRODUCTION

Although randomized clinical trials are the best way of investigating the efficacy of drug treatment, they have their disadvantages. The most important limitation is the strict criteria applied to patient inclusion, resulting in a study population not representative of the actual drug-taking population.[1] In addition, follow-up is usually relatively short, while the general-population patient might have to comply with therapy over numerous years. Observational studies performed by using prescription and medical claims databases can provide information on actual use of the medicines in daily practice after they are marketed. These databases often include data spanning many years for larger study populations. Selection of patients in observational studies is less subject to inclusion and exclusion criteria, resulting in increased external validity of such studies. However, the internal validity of observational studies is usually lower than that of clinical trials because observational studies are more prone to bias. While the role of observational studies in estimating effectiveness of therapy is debated, some researchers choose to answer clinical questions by performing observational research. Because numerous limitations need to be taken into account when performing such research, it is very important that proper methodology be used.

In this study, we investigated a potential bias created through different definitions of treatment and follow-up time for patients treated with antidepressants. To our knowledge, only three observational studies have been performed that focus on the influence of duration of antidepressant treatment on time to relapse/recurrence in general practice populations suffering from depression. In 1998, Melfi et al.[2] used Medicaid data to study primary care patients, investigating the effects of adherence to antidepressant treatment guidelines on relapse/recurrence of depression. They concluded that patients who discontinued antidepressant drug treatment early had a higher risk of relapse/recurrence (risk ratio 1.77; 95% confidence interval [95%CI] 1.47–2.14) than those who followed treatment guidelines. In 2000, Claxton et al.[3] and Sood et al.[4] supported these findings with studies both using a design nearly identical to that of Melfi et al. Although there are obvious methodological flaws in the method used to define exposure and measure follow-up, the results of Melfi et al. have been cited numerous times by other researchers,[5-16] and have found their way into treatment guidelines.[17,18]

In the current study, we showed that the approach used by these previously mentioned studies to measure follow-up time is subject to immortal time as well as neglected time bias and can lead to significant distortion of the results. We assessed the impact of these biases using a cohort of primary care antidepressant drug users, diagnosed with depression, in the Netherlands.

METHODS

Setting and study population

Data for this study were obtained from the Second Dutch National Survey of General Practice (DNSGP-2), which was carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001 and has been described in detail elsewhere.[19] In short, 195 general practitioners from 104 practices used a standardized method to register details of all physician-patient contacts during 12 months. The general practitioners registered all health problems presented during a consultation, and diagnoses were coded by using the International Classification of Primary Care.[20] Each patient was identified with an anonymous and unique patient-identification code. The network of SFK (Foundation for Pharmaceutical Statistics) was used to collect drug dispensing data covering the period 1999–2003 for the patients in the DNSGP-2.[21] The linking of pharmacy dispensing data to the prescribing data of the general practitioners has been described elsewhere.[22]

The study population was composed of all patients, aged 18 years or older, whose antidepressant prescription was dispensed by a pharmacy in 2001 (n=6891). The date of the first dispensed antidepressant prescription in 2001 was defined as the start date. In accordance with the study by Melfi et al.[2] each patient was required to be included in the study for at least 18 months: a 6-month pretreatment period prior to the start date and 12 months following the start date (n=5253). The study population included only antidepressant drug users who did not use antidepressant drugs during the 6 months prior to the start date (n=2070). A study of antidepressant drug use in the Netherlands has shown that the antidepressants are indicated for several symptoms and illnesses other than depression.[23] For our study population, we included only those antidepressant drug users for whom it was prescribed for treating depression (n=799). An antidepressant prescription was considered to be prescribed for treating depression when the International Classification of Primary Care codes for depression (P76) and feeling depressed (P03) were identified from the physician-patient contact file within 30 days around the start date. Depressed antidepressant drug users who were also diagnosed with psychosis (P71, P73, P98) or who received antipsychotic drugs were excluded from the study population (n=77). In total, 722 antidepressant users were included in the analysis.

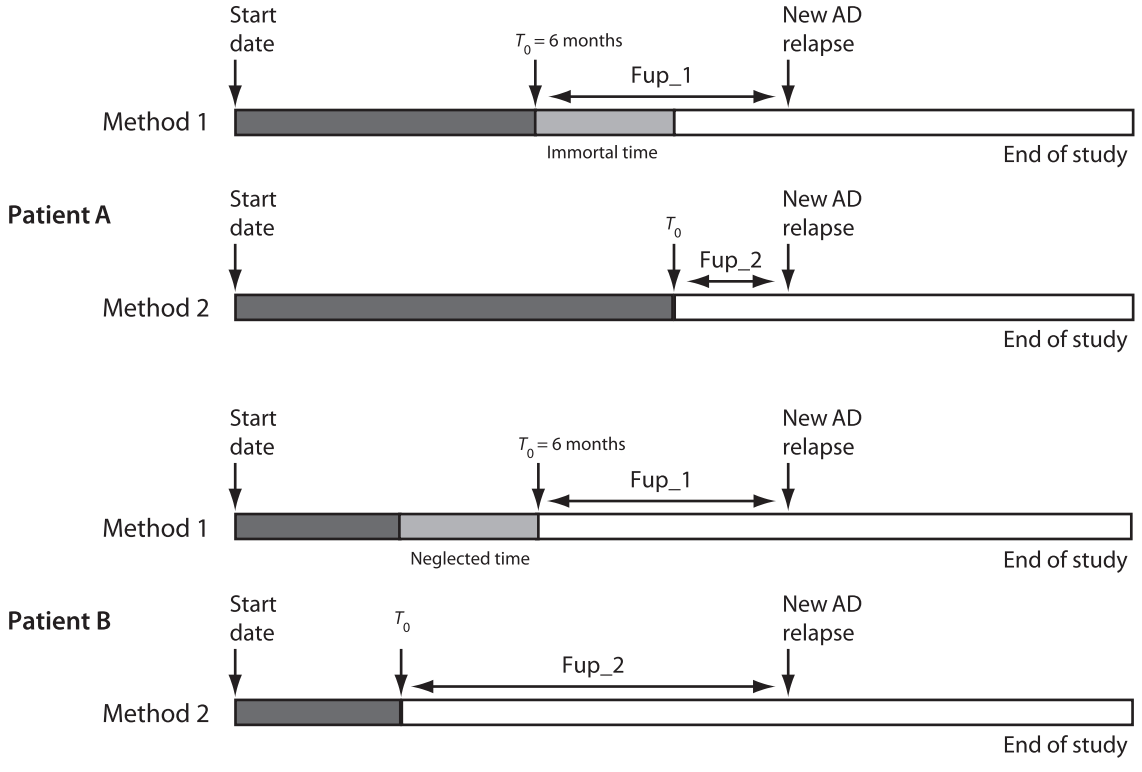
Study design

A cohort study was performed that measured time to relapse/recurrence; subsequently, risk ratios were estimated for continuing users versus early discontinuers. The study population was divided into two treatment groups, early discontinuers and continuing users, in accordance with the study by Melfi et al.[2] The early discontinuer treatment group was composed of antidepressant drug users

for whom fewer than four antidepressant prescriptions were dispensed within the 6 months following the start date. Antidepressant drug users who received at least four antidepressant prescriptions were also defined as early discontinuers if less than 75 days elapsed from the start date until the last antidepressant prescription within the 6 months following the start date. The continuing user treatment group was composed of those for whom four or more antidepressant prescriptions were dispensed within the 6 months following the start date. Next, for each antidepressant drug user, a 30-month episode of depression care was constructed.

Two different methods were used to estimate follow-up time, explained graphically in Figure 1. Method 1, used by Melfi et al.,[2] was replicated by dividing the 30-

Figure 1 **Antidepressant treatment episodes and follow-up time defined for patient A (continuing user) and patient B (early discontinuer)**



Method 1 conforms with Melfi et al.[2], constructing a 6-month antidepressant treatment episode and measuring follow-up time (Fup_1) from time zero (T_0), which is fixed at the end of the 6-month treatment period for each patient.

Method 2 constructs individual antidepressant treatment episodes and measures follow-up (Fup_2) from time zero (T_0), which is set as the expected end date of the last prescription within the antidepressant treatment episode.

■ = antidepressant (AD) treatment episode;

▣ = AD treatment episode with follow-up time wrongly excluded (i.e. neglected time);

□ = AD treatment episode where treatment is wrongly classified as follow-up time (i.e. immortal time).

month episode of depression care into a pretreatment period (6 months prior to the start date), a treatment period (6 months following the start date), and a follow-up period (18 months). Thus, for each patient, follow-up time started at a fixed moment, namely, 6 months (treatment period) after the start date. When Method 1 is used, two problems can be encountered, as displayed in Figure 1. Method 1 does not take into account the possibility that antidepressant drugs can be used for a period of time longer or shorter than the 6-month treatment period. When actual use exceeds the 6-month treatment period, the patient is not at risk of a recurrence during the time from 6 months after the start date up to the end date of the last prescription, that is, immortal time. This time is considered 'immortal' because the patient cannot experience the outcome during this period.[24-26] If an antidepressant is used for a shorter time than the 6-month treatment period, the time during the 6-month treatment period that the patient is not using antidepressants, and is at risk of recurrence, is not taken into account as such, that is, neglected time. The time is considered 'neglected' since this time is discarded from the analysis.

In Method 2, the 30-month episodes of depression care were divided into a pretreatment period (6 months prior to the start date), an individually estimated length-of-treatment episode (*n* months following the start date), and a follow-up period (24 – *n* months). For each antidepressant drug user, a treatment episode was estimated. The treatment episode started with the first dispensed antidepressant drug on the start date. Succeeding prescriptions were considered to be part of the treatment episode as long as fewer than 6 months elapsed between the expected end date of a preceding prescription. The end date of the treatment episode was defined as the expected end date of the last prescription within the treatment episode. The expected end date equals the dispensing date plus the estimated duration of drug use, the latter being calculated by dividing the number of units of dispensed by prescribed daily dose.

Outcome

The outcome measure was time to relapse/recurrence after having completed an antidepressant treatment episode. Relapse/recurrence was defined as reinitiation of antidepressant therapy after at least 6 months had elapsed from the end of the last antidepressant treatment episode. Thus, for Method 1, relapse/recurrence is measured after at least 6 months following a fixed treatment period of 6 months; for Method 2, relapse/recurrence is measured after at least 6 months following the end date of the individual treatment episode. If a patient did not experience a second antidepressant treatment episode, the time from the end of the first antidepressant treatment episode until 18 months was reached, or the last date registered in the DNSGP-2 database, was used (censoring).

Statistical analysis

In accordance with Melfi et al.,[2] Kaplan-Meier survival curves were constructed to examine time to relapse/recurrence for Method 1 and Method 2 using log-rank statistics to evaluate differences between the early discontinuers and continuing users. The Cox proportional hazards model was used to estimate risk ratios with 95% confidence intervals. All analysis were performed with SPSS version 13.0.1 for Windows software (SPSS Inc., Chicago, Illinois).

RESULTS

The demographic and clinical characteristics of the study population are presented in Table 1. The study population included 722 antidepressant drug users; 69.8% were women, and the mean age was 49.7 years (standard deviation [sd] 16.0). About 73% of the antidepressant drug users received a selective serotonin reuptake inhibitor, and almost all had their start-date prescription prescribed by the general practitioner (97.5%). The mean number of antidepressant prescriptions dispensed in the 12 months following the start date was 6.4 (sd 4.7). The mean follow-up time for the study population was 17.7 months (sd 1.0). All antidepressant drug users were registered in the DNSGP-2 database during the 6-month pretreatment period.

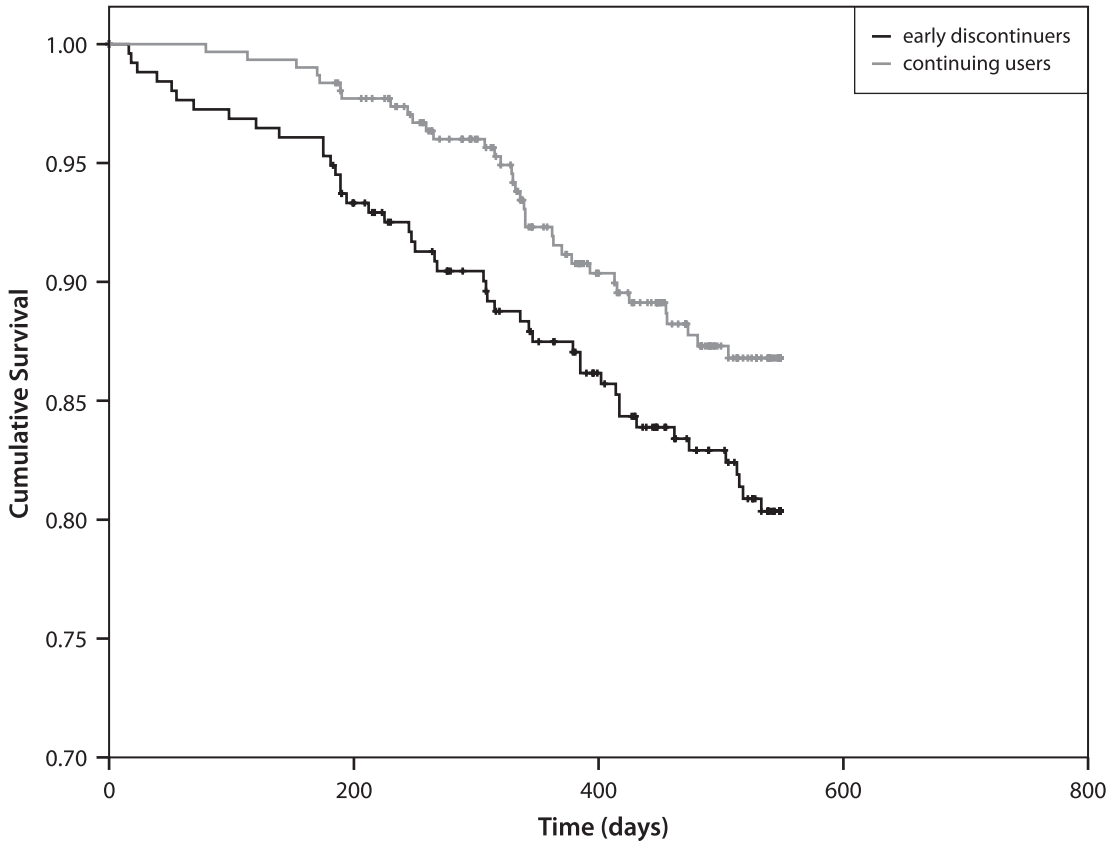
Table 1 **Characteristics of the study population on the start date of antidepressant drug treatment, the second Dutch National Survey of General Practice, the Netherlands, 2001**

	n=722 (100%)	Mean (sd)
Female gender	504 (69.8%)	
Age in years		49.7 (16.0)
Antidepressant drug		
selective serotonin reuptake inhibitor	527 (73.0%)	
tricyclic antidepressant	98 (13.6%)	
other [a]	97 (13.4%)	
Type of prescriber (start date)		
general practitioner	704 (97.5%)	
specialist/other/unknown	18 (2.5%)	
No. of antidepressants dispensed 12 months after the start date		6.4 (4.7)

sd = standard deviation

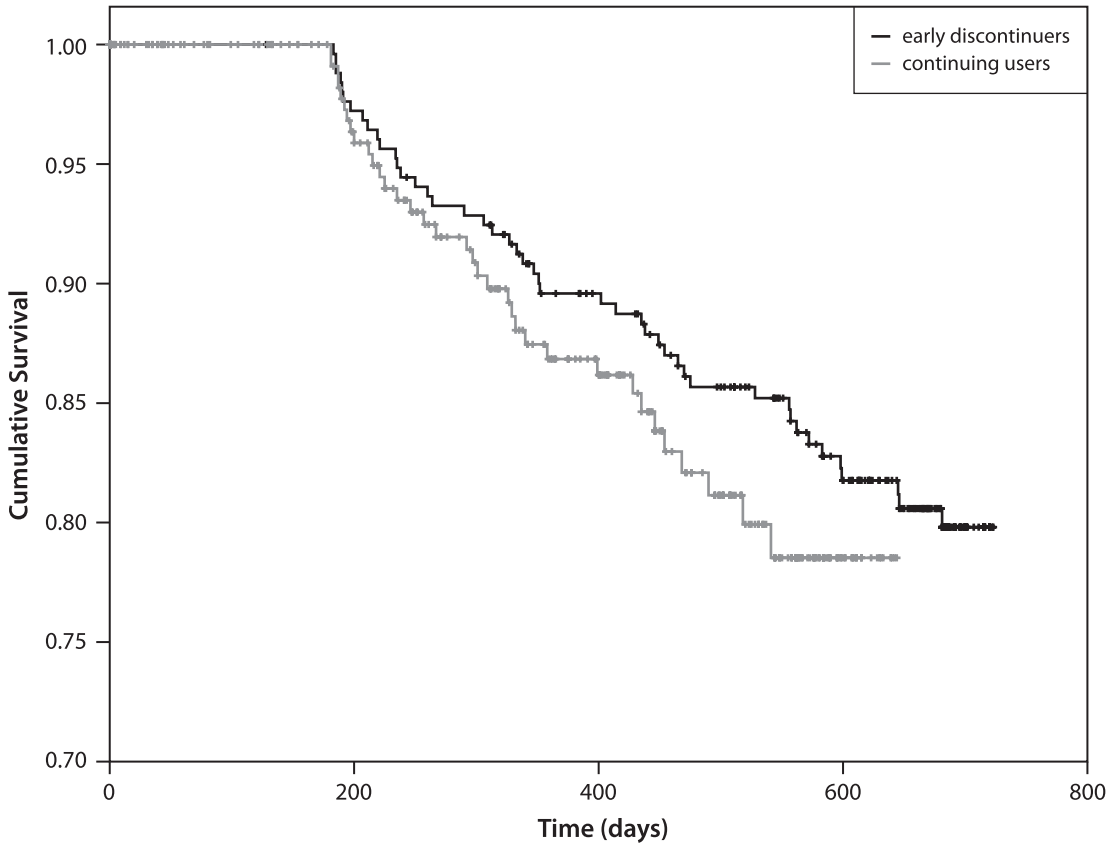
a) Includes moclobemide, mianserin, trazodone, mirtazapine, and venlafaxine.

Figure 2 **Survival curves for Method 1, comparing early discontinuers with continuing users of antidepressants, the Second Dutch National Survey of General Practice, the Netherlands, 2001**



The antidepressant drug users were divided into 255 early discontinuers (35.3%), who received fewer than 4 antidepressant prescription prescriptions or for whom less than 75 days had elapsed from the start date until the last antidepressant prescription, and 467 continuing users (64.7%), who received at least four antidepressant prescriptions within the 6 months following the start date. About 11% of the antidepressant drug users experienced a relapse/recurrence during the follow-up: 18% of the early discontinuers and 7.5% of the continuing users. This large difference between early discontinuers and continuing users suggests that early discontinuers have a higher risk of experiencing relapse/recurrence. However, early discontinuers use antidepressants for shorter periods than continuing users do, allowing more time for follow-up. The actual difference in risk of relapse/recurrence can be estimated only by survival analysis, where time to event is taken into account, and not by comparing proportions.

Figure 3 **Survival curves for Method 2, comparing early discontinuers with continuing users of antidepressants, the Second Dutch National Survey of General Practice, the Netherlands, 2001**



The Kaplan-Meier survival curves for the different treatment patterns, illustrating the time to relapse/recurrence using Method 1, are presented in Figure 2. Cox proportional hazards analysis was used to estimate risk ratios comparing early discontinuers with continuing users. The Cox model produced a statistically significant risk ratio of 1.58 (95%CI 1.02–2.45). When Method 1 was applied, early discontinuers seemed to have a 58% higher risk of relapse/recurrence than those continuing use. The Kaplan-Meier survival curves, when Method 2 was applied, for the different treatment patterns are presented in Figure 3. The Cox proportional hazards model produced a statistically nonsignificant risk ratio of 0.77 (95%CI 0.49–1.21), indicating no difference in risk of relapse/recurrence between the early discontinuers and the continuing users.

DISCUSSION

In this study, we showed that a major bias was present in the observational studies of the beneficial effects of continuing antidepressant drug use to prevent relapse/recurrence. When different definitions were applied to define start of follow-up, we observed two very different results. Method 1, in which the treatment period was set to 6 months for each patient, suggests that continuing users are substantially better protected against relapse/recurrence than early discontinuers are.[2] However, when our method was applied, in which an individual treatment episode was estimated for each patient, the beneficial effect was no longer apparent.

The difference in risk estimates between the two methods can be explained by two types of biases: immortal time bias and neglected time bias. For Method 1, a crucial factor is ignored, namely, the fact that the actual antidepressant treatment episode can be longer or shorter than the time window of 6 months, clearly elaborated in Figure 1. For patient A, the time exceeding the 6-month treatment period, when the patient is still using antidepressants, is wrongly included as event-free follow-up time. Defining this time as event-free follow-up time incorporates so-called immortal time bias into the analysis.[24,25] Patient A cannot experience a relapse/recurrence since relapse/recurrence is defined as reinitiation of antidepressant drug therapy. Because patient A is still undergoing antidepressant therapy during the time exceeding the 6-month treatment period, she or he is not susceptible to the event (i.e. immortal). This type of exposure misclassification has been shown to seriously distort study outcome measures.[25,27]

For patient B, for whom antidepressants are used for a period shorter than 6 months, the unexposed or event-free months are not taken into consideration (i.e. neglected). As a consequence, the amount of event-free follow-up time seems shorter than it actually is. This second type of bias arises from neglected follow-up time and occurs when follow-up time is incorrectly excluded. The risk of neglecting follow-up time can arise when treatment or exposure cohorts, such as early discontinuers and continuing users, are defined within a fixed amount of time, for example, treatment period. Subsequently, follow-up is measured from the end of the fixed treatment period. The time within the treatment period when the patients are not receiving treatment will be incorrectly regarded as treatment time, resulting in a survival/outcome disadvantage for the early discontinuers. The second bias has, to our best knowledge, not been described by name. Thus, we propose the term neglected time bias.

In our study, the two biases arising from Method 1 resulted in more event-free months for continuing users, whereas too few event-free months were measured for the early discontinuers. Although neglected time bias also applies to the continuing users, with at least four prescriptions but a total duration of use of

less than 6 months, the majority of continuing users will gain extra event-free months. As a consequence, the risk estimate will be better for continuing users and worse for early discontinuers, resulting in a large overestimation of the risk ratio toward beneficial effects for the continuing users. We found that the correct way of estimating the risk of relapse/recurrence for the different treatment groups is to construct individual treatment episodes. When individual antidepressant treatment episodes are constructed, each patient has a different follow-up time, resulting in the most accurate estimate of the real risk ratio.

With depression being the fourth leading cause of disease burden in the world,[28] the clinical implications of studies that report on optimizing therapy and improving treatment outcomes are large. Since publication of the study by Melfi et al.[2] on the beneficial effects of continuing antidepressant treatment, their results have been cited numerous times by other researchers [5-16] and in treatment guidelines [17,18] that aim to optimize antidepressant drug treatment outcomes. Given the impact that published data have on decision making by health care providers and policy makers, use of the right methodology is crucial when performing observational studies.

The risk ratios obtained in this study display the possible magnitude of change in risk ratio estimates due to immortal time and neglected time bias and should be interpreted with some caution. Furthermore, the exposure definition of Melfi et al.[2] was used for both methods, that is, for early discontinuers and continuing users defined by number of prescription fills within a 6-month time window. The number of fills does not give sufficient information on duration of use of each prescription. For some users, exposure continues past the set time window, which might influence the risk ratio. A more proper way to estimate the risk ratio would be to divide users into early discontinuers and continuing users based on exposure definitions that consider the actual length of the individual treatment episode, regardless of the number of prescriptions dispensed. In addition, defining relapse/recurrence as reinitiation of antidepressant drug use after 6 months of not using antidepressants will result in a risk ratio equal to 1.0 during these 6 months. Because the 6 months until relapse/recurrence counts for a third of the follow-up time, the estimated magnitude of the bias is most likely underestimated. The risk ratio according to Method 2 shows that there is no difference in risk of relapse/recurrence between those who discontinue use early and those who continue using antidepressants.

An important limitation of our study is the absence of a depression severity measure. In our study population, depression was diagnosed by the general practitioner, including patients 'feeling depressed' who might not have suffered from actual clinical depression. Patients presenting in general practice usually suffer from milder or more moderate depression than patients treated in secondary-care settings. However, our results are in line with a recently published study in which

the effectiveness of selective serotonin reuptake inhibitors in mild to moderately depressed patients was doubted.[29] The authors performed a meta-analysis of data from published and unpublished clinical trials demonstrating that the overall effect of selective serotonin reuptake inhibitors failed to reach criteria for clinical significance, especially for patients suffering from mild or moderate depression.

In conclusion, we found that the method used in the previously mentioned study[2] to estimate antidepressant treatment patterns and risk of relapse/recurrence is biased. When definite treatment periods are used, extra event-free time for patients treated for more than 6 months is wrongly included in the risk analysis. In addition, event-free time for those treated for less than 6 months is wrongly excluded from the risk analysis. The result is a risk ratio more beneficial toward continuing use of antidepressants. Because of the debilitating and chronic nature of depression, observational studies reporting positive outcomes for treating depression can have a large clinical impact. It is therefore of importance that the methodology used for analysis be unbiased.

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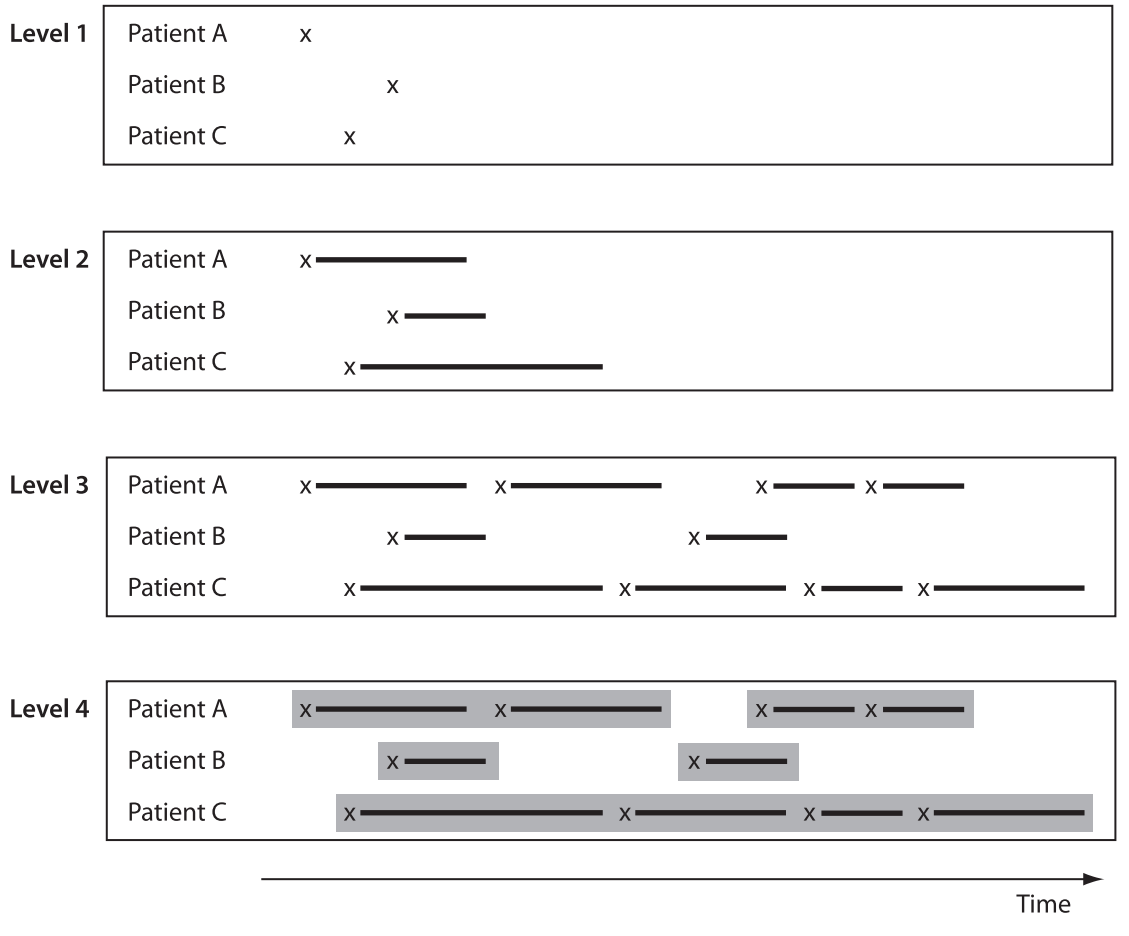
5

General discussion

INTRODUCTION

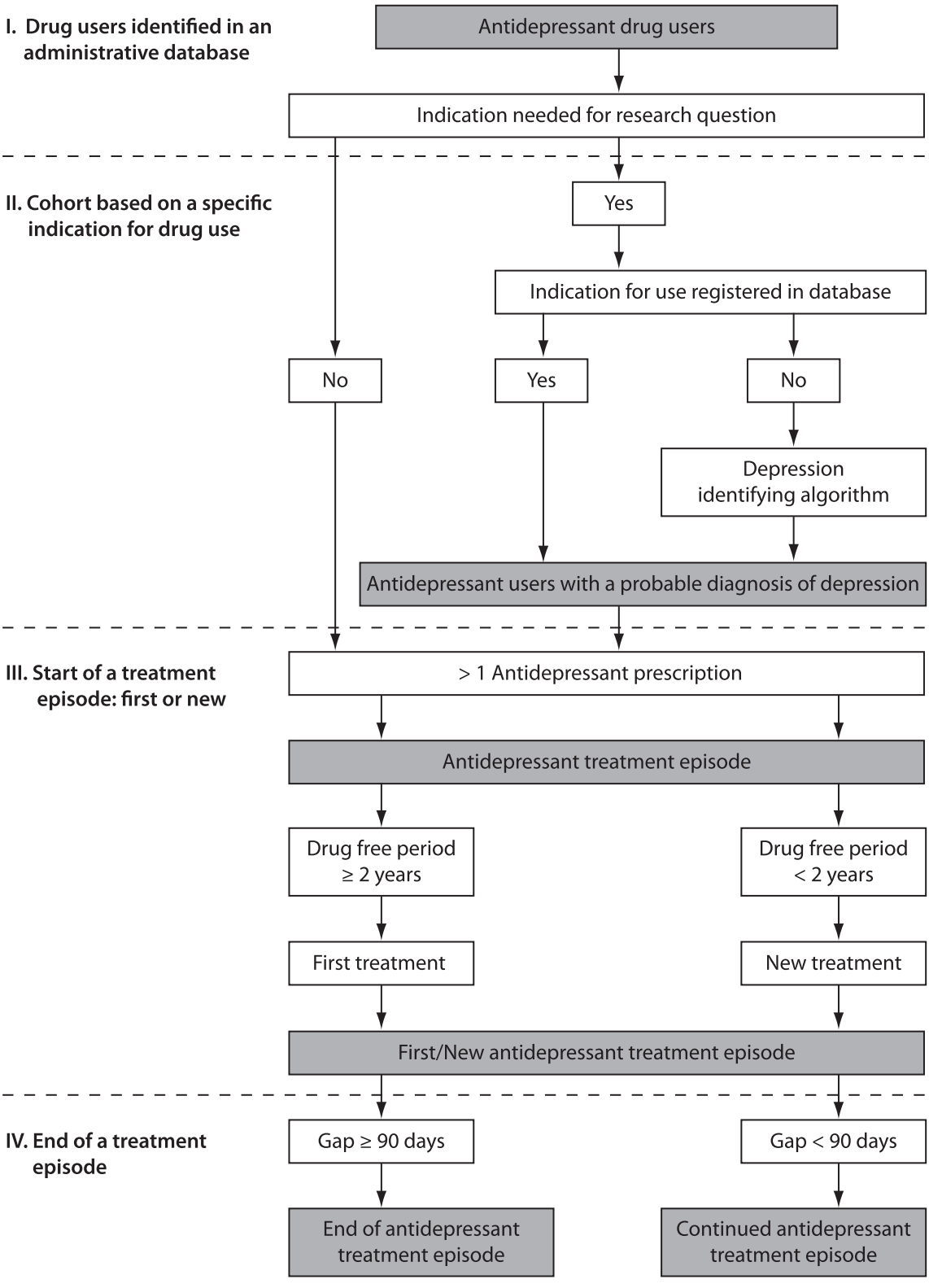
In the introduction of this thesis we describe three levels of drug exposure research according to Leufkens and Urquhart,[1] from a single drug-taking moment to multiple drug-taking moments over a period of time. The studies presented in this thesis expand further on drug exposure research and introduce what could be considered the fourth level (Figure 1), in which drug treatment episodes are constructed on an individual patient level from multiple drug prescribing or dispensing moments.
This general discussion begins by elucidating the different steps of constructing drug treatment episodes using drug exposure data from administrative databases. In each step, from defining the drug exposure cohort to constructing individual drug treatment episodes, we will discuss important definitions and give an example of the methodological aspects that should be taken into consideration when

Figure 1 **The four levels of classifying drug exposure**



x = prescription/dispensing date; black lines = duration of a single prescription; grey boxes = drug treatment episode

Figure 2 **Methodological issues when constructing drug treatment episodes, displaying the different steps involved in the study design when constructing antidepressant treatment episodes**



constructing antidepressant treatment episodes. Next, the generalizability of our findings will be discussed for different study settings and other types of drugs. Finally, we will discuss future perspectives (the fifth level) regarding drug exposure research, aiming to relate patient behavior with drug treatment and taking.

CONSTRUCTING INDIVIDUAL ANTIDEPRESSANT TREATMENT EPISODES

Drug exposure-outcome relationships can be investigated using data from administrative databases. The course of action, with regard to study design, that needs to be undertaken before analyzing drug exposure-outcome relationships spans at least four steps (Figure 2). The first step involves patient selection, where administrative data are used to identify patients (the study population) who have been exposed to an antidepressant drug during a certain time period (study period). Drug exposure data can originate from a prescribing or a dispensing database. These two types of databases include different information (Table 1). Prescribing databases often include patient information collected from a single prescriber, usually the general practitioner, and may include information on indications,

Table 1 **An example of variables available in prescribing and dispensing databases**

	Prescribing databases	Dispensing databases
Patient characteristics		
age and gender	++	++
other (e.g. smoking, body mass index)	+	-
Disease characteristics		
indications for prescribing	+	-
co-morbidities	++	-
Drug characteristics		
type of drug	++	++
amount	++	++
dosage regimen	+	++
(Co)medication information		
main prescriber[a]	++	++
other prescribers	-	++

ATC = Anatomical Therapeutic Chemical
a) From which the prescribing database is originally from.

symptoms, referrals, co-morbidity, and baseline risk factors (weight, smoking, alcohol use, etc). Dutch dispensing databases comprise information on near all medicines dispensed for each patient regardless of the type of prescriber, but often lack information on the reason for drug prescribing and other relevant factors such as lifestyle indicators.[2] Prescribing databases usually include information on medicines prescribed but lack information on which prescriptions are redeemed at the pharmacy. Besides differences in type of information available from a database, the choice of a database will also influence what types of patients will be included. Prescribing databases offer the opportunity to identify patients who use an antidepressant drug due to a specific reason, such as a diagnosis of depression. It is likely that antidepressant users in a general practice database represent type of patients different from those who would be found in a psychiatrist prescribing database, with the latter representing patients that are more severely ill.

The second step involves deciding if the drug exposure itself will be investigated as such or if the drug exposure will be investigated as a marker for patients suffering from a specific health condition. Not all study questions require information on reason for prescribing, such as studies on general adherence to antidepressants, incidence or prevalence measurements or investigation of side-effects related to antidepressant drug taking. However, knowledge on indication for prescribing is essential when investigating efficacy of depression treatment. The antidepressants currently registered in the Netherlands can be divided into tricyclic antidepressants (TCAs; Anatomical Therapeutic Chemical [ATC] Group N06AA: amitriptyline, clomipramine, dosulepin, doxepin, imipramine, maprotiline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs; ATC group N06AB: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and other antidepressants (ATC group N06AF, N06AG, N06AX; bupropion, duloxetine, mianserin, mirtazapine, moclobemide, venlafaxine). Besides being registered for treating depression, antidepressants are also registered for treatment of anxiety disorders, panic disorder, phobias, obsessive-compulsive disorders, eating disorders, enuresis and neuropathic pain.[3] In addition, antidepressants are sometimes used off-label to treat sleeping disorders,[4] headache,[5] and incontinence.[6] We investigated on- and off-label indications for antidepressant treatment in general practice patients (*Chapter 2.1*) and found that only half of the antidepressant users had a code for diagnosis of depression registered in their physician-patient contact file. For about one third of the patients none of the indications we investigated were registered in the physician-patient contact file. When we investigated patients per type of antidepressant we found that only 25% of TCA users had a diagnosis of depression registered, while about 50% did not have any of the investigated on- or off-label indications we investigated registered in their physician-patient contact file. In

patients who used SSRIs or other antidepressants, a diagnosis code for depression was found in the physician-patient contact file in about 54% of the patients. From our results we concluded that when the aim is to investigate depression related outcomes in data where indication for treatment is missing, such as often is the case when dispensing data are used, including all antidepressant users will result in a population with various diagnoses.

When the aim is to investigate depression related outcomes in antidepressant users, a possible option is to include only SSRI users in the study sample, as SSRIs are more frequently prescribed for treating depression than TCAs in a primary care setting (*Chapter 2.1*). We found that about 54–75% of SSRI users are receiving antidepressant treatment due to a diagnosis of depression (*Chapter 2.1*, *Chapter 3.2*), which is in line with results from other studies reporting that 77–82% of SSRI users in primary care are using the antidepressant due to a diagnosis of depression.[7-9] Another option is to use a disease specific algorithm.

For drugs that are indicated to treat more than one condition, disease specific algorithms to identify patients treated for a specific condition have been developed.[10-13] Disease specific algorithms calculate the patient's probability of having a specific condition based on a covariate profile including patient characteristics, prescriber information and drug use. Construction of these disease specific algorithms has some analogy with the use of propensity scores, where observed covariates are used to produce a single measure which summarizes the probability of certain exposure. When information on indication for antidepressant drug prescribing is missing but information on dispensed antidepressants is available, we suggest the use of a specific algorithm that identifies patients with a probable diagnosis of depression. In *Chapter 2.2*, we describe how we developed and validated an algorithm that can be used to identify patients who are likely to have a diagnosis of depression registered in their physician-patient contact file. The algorithm only uses variables that are available in dispensing databases such as age and gender of the antidepressant user, the type of antidepressant prescribed, defined daily dose (DDD) prescribed, type of prescriber, information on antidepressant dispensing during the year from initiating use and co-medication use. The developed algorithm has a discriminatory ability of around 80%, and at a cut-off level of 0.5 for the predicted probability its sensitivity is 80% with a specificity of 67%. By using the algorithm on a population of antidepressant users it can be narrowed from including antidepressant users treated for various indications to a more homogenic sample of users with a probable diagnosis of depression.

When choices have been made with regard to identifying the cohort of antidepressant users with a probable diagnosis of depression, antidepressant treatment episodes of these patients can be defined. Step three involves defining the

start of the treatment episode. When the aim is to investigate outcomes during an antidepressant treatment episode it is important to identify and include those who actually start treatment (inception cohorts). Prior studies show that in general up to 20% of patients fail to redeem a first prescription at the pharmacy.[14,15] Studies on antidepressant drug use have shown that of those who redeem an antidepressant prescription at the pharmacy, 38% only fill a single antidepressant prescription.[7,16] We investigated the incidence of declining antidepressant treatment (SSRI, venlafaxine or mirtazapine) after receiving a first prescription prescribed or dispensed (*Chapter 3.1*) and found that about 4% of the patients did not redeem their antidepressant at the pharmacy while 24% got only a single antidepressant prescription dispensed from the pharmacy. It is reasonable to consider those who do not get a prescription dispensed from the pharmacy as patients who do not start therapy. A study on patients who only received a single antidepressant prescription dispensed from the pharmacy showed that about 30% of the patients reported that they did not start using the antidepressant while the remainder discontinued within two weeks from initiation.[7] When the aim is to investigate outcomes during an antidepressant treatment episode, it would be advisable to only include those who actually engage in therapy by excluding those who receive a single antidepressant prescription.

Next within step three is to decide if the intention is to investigate patients who are recurrent users or those who initiate use for the first time. For some treatment related outcomes or side-effects, it is important to investigate those who are using antidepressants for the first time. Research has shown that patients with prior episodes of depression differ from those who suffer from a first depressive episode with regards to duration of antidepressant treatment,[17] episode severity and time between subsequent episodes,[18] duration of a depressive episode,[19] and risk of recurrence.[20,21] When antidepressant drug users who initiate use for the first time are to be identified, a suitable drug free period needs to be defined. The drug free period represents the time prior to initiation of use in which the antidepressant drug user has not used any antidepressants. Various lengths of drug free periods have been used to construct inception cohorts of antidepressant drug users, ranging from 4 months to 5 years.[22-30] We investigated what effect the length of the drug free period has on the amount of antidepressant drug users correctly identified as first time users (*Chapter 3.2*). In our study, we showed that the length of the drug free period has substantial influence on incidence measurements and when short drug free periods are used, the amount of misclassified first time users is large. We selected a 9-year drug free period as the gold standard and found that when a 2-year drug free period is used the antidepressant user population included 27% misclassified first time users. When drug free periods of one year or six months were selected the amount of misclassified first time users increased to 37% and

46%, respectively. Although data availability is an important limiting factor when defining the drug free period, we recommend that a drug free period of at least two years should be used to minimize misclassification of first time users.

The final step presented in Figure 2 is how to define the end of an antidepressant treatment episode. Usually, when dispensing moments are investigated over time in administrative databases, irregular patterns are seen, including gaps between or overlap of two subsequent prescriptions. To account for these irregular dispensing patterns, researchers allow for a gap of a certain length to elapse between the estimated end date of a prescription and the dispensing date of a subsequent prescription to define which prescriptions belong to the same treatment episode. If a subsequent prescription is dispensed after the defined gap-length, following the estimated end date of a prior prescription, it is not considered a part of the current treatment episode. The subsequent prescription will in that case mark the beginning of a new treatment episode. The gap-lengths used for constructing drug treatment episodes vary and can be defined as a certain number of days, or as a percentage of the estimated prescription duration.[31-38] We investigated the effect of using gaps of different lengths on the estimated length of an antidepressant treatment episode (*Chapter 4.1*) and found that small gaps have large influences on the estimated median length of an antidepressant treatment episode. Only when gaps of at least 90 days were used, the estimated median length ceased to change substantially. When the aim is to identify individual episodes of depression we advise to use at least 90 day gaps to define which antidepressant prescriptions belong to the same antidepressant treatment episode and which mark the beginning of a new one. The reason for selecting a gap of at least 90 days when defining an end of an antidepressant treatment episode is twofold. Firstly, clinicians suggest that when a patient has been symptom free for eight to sixteen weeks (s)he is in recovery.[39,40] In addition, patients sometimes use their medicines differently from label instructions, that is they may skip a dose or decide to use less. The average duration of a dispensed antidepressant prescription in the Netherlands is 30–45 days (*Chapter 4.1, Chapter 4.2*).[41] Patients that use less than advised on label instructions, e.g., patients that want to stop using antidepressants, will show larger gaps than those who are using according to labeled instructions. By selecting a 90 days gap between prescriptions, we allow for the possibility of downward dose titration which would extend the use past the estimated duration of use according to dosing instruction on the drug label. In addition, we allow for extra gap days in accordance with the clinical definition that when a patient has been symptom free for at least eight weeks (s)he can be considered in recovery.

GENERALIZABILITY

All studies presented in this thesis focus on antidepressant drug use in primary care patients in the Netherlands. In this section of the general discussion we will discuss the generalizability of our findings and focus on their applicability when constructing treatment episodes for antidepressant users in secondary care, in international settings and when treatment episodes are constructed for other type of drugs.

Secondary care settings

The studies presented in this thesis are mainly based on data originated from dispensing or general practice databases. As a consequence, our studies focus on antidepressant drug use in primary care patients in the Netherlands. Although the external validity of our findings may be high when applied to Dutch primary care antidepressant users there are limitations when applied to antidepressant users treated in secondary care settings by psychiatrists.

First, we investigated indications for antidepressant drug prescribing in primary care and found that only 50% had a depression coded in their physician-patient contact file (*Chapter 2.1*). We also found that SSRI users more frequently had a psychiatric diagnosis in their physician-patient contact file than TCA users, while TCA users were more likely than SSRI users to use the antidepressant due to non-psychiatric indication. Furthermore, the algorithm (*Chapter 2.2*) we developed for identifying primary care patients with a registered diagnosis of depression in their physician-patient contact file is not applicable to secondary care data. The algorithm is developed and validated in primary care data and includes predicting variables related to antidepressant use in primary care such as SSRI as first dispensed antidepressant and general practitioner (GP) as prescriber of first antidepressant prescription within the treatment episode. In addition, the diagnosis of depression that is identified by the algorithm is based on how the general practitioner identifies and registers depression which may differ from diagnostic procedures of psychiatrists.

In the Netherlands the GP is the gate keeper to secondary care. Patients that are referred to secondary care normally pass through the GP first. The GP can initiate treatment and in case of treatment failure refer the patient to a psychiatrist, or they can refer the patient directly to a psychiatrist. In this thesis we show that transitions from general practice to psychiatrist care are associated with treatment changes in antidepressant drug users (*Chapter 4.3*). In our study those who transit from general practice to psychiatrist care were more likely to switch to a different antidepressant or undergo dose changes. According to treatment guidelines, when treatment is not effective the advice is to change the dosage or switch to a different antidepressant.[42]

Patients admitted to secondary care represent a group more severely ill or more difficult to treat than patients in primary care. However, the definitions used to construct drug treatment episodes for the two patient groups do not differ. When the aim is to measure outcomes during an antidepressant treatment episode our definitions regarding construction of antidepressant treatment episodes for primary care patients are also applicable to secondary care patients. This translates into excluding patients with only a single prescription prescribed or dispensed, a drug free period of at least two years when constructing inception cohorts and the use of at least 90 day gaps between prescriptions to define individual treatment episode. Firstly, antidepressant use in secondary care is most often not intended for short time thus patients treated by psychiatrist are expected to use the antidepressants according to treatment guidelines, i.e. therapy duration exceeding the duration of a single prescription. Secondly, when defining whether the antidepressant treatment episode is a first one our advice of using at least two years drug free period both applies to primary and secondary care settings. This definition is used to investigate prior use, and is not related to type of setting. And finally, using at least 90 day gap-length allows for downwards titration and an amount of time that could constitute the minimum time symptom free to be considered in recovery.

For both settings it should be kept in mind that the validity of our findings may change over calendar time. Prescribing and dispensing patterns observed in administrative databases are strongly dependent on treatment guidelines and the health care re-imbursement system. Substantial changes in either of the two, are likely to change dispensing and prescribing patterns, which would require re-validation of our findings.

International study settings

In the Netherlands the general practitioner is regarded as the gatekeeper to healthcare. Most patients are treated by a single general practitioner and go to a single pharmacy to get their medication dispensed. The Dutch reimbursement system requires that each citizen pay an annual healthcare fee which covers all visits to primary and secondary care physicians and full re-imbursement of most medicines. Although patients are free to get their drugs dispensed at a pharmacy of choice, there are no financial incentives which would stimulate the use of different pharmacies and in general pharmacy shopping behavior is uncommon in the Netherlands.[2]

Drugs are initially prescribed for a maximum duration of 14 days and thereafter for longer periods. Antidepressants are usually prescribed for 30 days at a time and as they are fully reimbursed there are no financial incentives that would stimulate purchase of larger drug packages than 30 days. In other health care systems, such

as in the Nordic countries, only a small number of drugs (such as insulin) are fully reimbursed and most patients are required to pay (a part of) the cost of their medicines.[43-47] There are large similarities between the reimbursement systems in the Nordic countries but they are not completely the same. For illustrative purposes we will only discuss our findings in relation to possible dispensing patterns in Sweden.

The Swedish drug re-imbursement system includes different levels of cost that the patient is required to pay for their drugs. The Swedish patient is required to pay 100% of all drug costs until a total of 900 Swedish krona (SEK; circa 80 Euros) has been paid. After reaching 900 SEK in drug payments the patient is entitled to a discount which increases gradually with the total drug payment costs, paid by the patient. When a maximum of 4300 SEK (circa 400 Euros) has been reached all further drug costs are fully reimbursed. The patient drug cost reimbursement scheme runs for 12 months. After 12 months have elapsed, the patient will again start at 0 SEK in drug payments and start building up costs and getting discounts accordingly. The first prescription usually covers treatment for 30 days but drugs can be prescribed for a maximum of 90 days duration.[28] It is financially beneficial for patients to get the maximum allowed duration, or 90 days, dispensed as larger drug packages are cheaper than smaller ones. In most of our studies on antidepressant dispensing in the Netherlands the average duration of dispensing was 30–45 days. In a Swedish administrative database we would expect this to be 90 days.

The difference in average duration of dispensing is of importance for some of our findings. In the algorithm developed to identify primary care patients with a probable diagnosis of depression, one of the predicting variables is the number of antidepressant prescriptions received in twelve months. In our model, receiving two to four, or five or more prescriptions were predictors for having a registered diagnosis of depression. In the Netherlands receiving two or more antidepressant prescriptions is equal to estimated 45–60 days of antidepressant treatment. In Sweden, two prescriptions of antidepressant drug use are likely to cover at least 120 days and five prescriptions are likely to cover more than a year of use. It is therefore likely that our algorithm would need to be adjusted for these differences in prescription duration and validated in Swedish data.

Further, when treatment episodes are constructed from Dutch data, we advise that gaps of at least 90 days should be used to identify the end of an antidepressant treatment episode. This advice is based on the average duration of an antidepressant prescription and the clinical opinion that when a patient has been symptom free for at least eight weeks (s)he is considered in recovery.[39,40] For Swedish dispensing data the gaps used to indentify the end of a treatment episode should be longer than 90 days. As the average duration of a prescription is 90 days, duration of use exceeding

the 90 days can be expected if patient uses less than indicated on label instructions. It would be wise to use at least gaps of 150 days when the aim is to identify end of an antidepressant treatment episode. Our estimation of at least 150 days includes 90 days which cover for eventual irregular dispensing pattern due to patient using a lower dose than reported on label, and further 60 days which represent the minimum number of symptom free days which are necessary, according to clinical opinion, to consider the patient being in recovery.
In general, when our methodological findings are applied to international settings it is important to consider possible differences in healthcare systems. Regulations may allow for varying duration of drug dispensing, such as longer duration due to financial incentives. In addition, in countries where the GP does not serve as a gatekeeper to secondary care, the composition of patients treated by general practitioner and psychiatrist may differ from what is seen in the Netherlands.

Other drug treatments

In this thesis we constructed antidepressant treatment episodes. Antidepressants are mainly used to treat depression, a disease that comes in episodes thus the treatment patterns are often episodic in nature. The different steps, in which we investigated methodological definitions for constructing antidepressant treatment episodes, can be applied when constructing drug treatment episodes in general regardless of drug type. Although the drug exposure under investigation may not be of episodic nature, the duration of exposure can be defined as an episode of use. For some patients the duration of the treatment episode will be short, such as for antibiotic treatment, while other therapies are intended for chronic use, such as use of antihypertensive or lipid lowering therapy.
Some of the methodological definitions used when constructing drug antidepressant treatment episodes are applicable to construction of drug treatment episodes for long term therapies. Studies have shown that about 11% of patients are prescribed a statin [48] and 18% of patients who get an antihypertensive agent [49] only get a single prescription dispensed. When the aim is to investigate outcomes during a drug treatment episode, for drugs that are intended for use extending the duration of a single prescription, we recommend that patients who only get a single prescription prescribed or dispensed should be excluded from the study cohort. Further, although conditions of high blood pressure or cholesterol levels are generally not episodic the treatment of these conditions may show an episodic pattern. Adherence to therapy and early discontinuation is a problem in antihypertensive and lipid lowering therapy. Studies have shown that 30-40% of all patients using statins discontinue use within a year [50,51] while 50% of patients on antihypertensive drugs discontinue use within a year.[52] Many of these patients are expected to reinitiate therapy. When

a different risk profile can be expected between incident users and those who are restarting therapy, such as in case of antidepressant users, it is of importance to truly capture first time users, and longer drug free periods should be used to ensure the correct identification of a new episode. If, however, no risk differences between new initiators and re-initiators are expected, less stringent criteria for the drug free period can be handled. When defining the end of a treatment episode, thus defining the gap-length, more stringent criteria can be used than for antidepressant drugs. The patient is expected to discontinue antidepressant therapy when the patient has reached recovery. Most patients on antihypertensive and lipid lowering drugs are expected to be treated for the rest of their life.

For all study populations, settings and drug treatment types

One of our methodological studies can be considered to have external validity for all populations, study settings or drug types under investigation. In this thesis we show how wrongly defined drug exposure and follow up time can result in biased results due to two types of bias, immortal time and neglected time bias (*Chapter 4.4*). Immortal time refers to a period of follow-up time in which the outcome cannot occur, due to the exposure definition. The immortal time bias has been widely described and examples have been given of its consequences on estimations when not accounted for.[53-56] The neglected time bias is a term that we suggest should be used for a complementary type of bias that occurs when event free follow-up time is excluded from analysis. To display the consequences of neglected time and immortal time bias two methods to define drug exposure and measure follow up time were compared.

We replicated a study which investigated the relationship between duration of antidepressant treatment and the risk of relapse or recurrence of depression.[57] Two antidepressant drug exposure cohorts, early discontinuers and continuing users, were defined based on the number of prescriptions dispensed within a defined time window of six months. To estimate the risk of relapse or recurrence, which was defined as re-initiation of therapy, time from the end of the defined time window until re-initiation was estimated. The fact that patients could use antidepressants longer or shorter than the defined time window, in which the exposure cohorts were defined, was not taken into account. For patients where drug use exceeded the defined time window, usually the continuing users, the estimated risk of recurrence or relapse resulted in a biased underestimation of the real risk ratio due to immortal time bias. In our example above, the duration of drug exposure that exceeds the length of the defined time window can be considered as immortal, as patients cannot re-initiate antidepressant use while they are still using the antidepressant. In case of patients who were exposed to the antidepressants for a shorter period

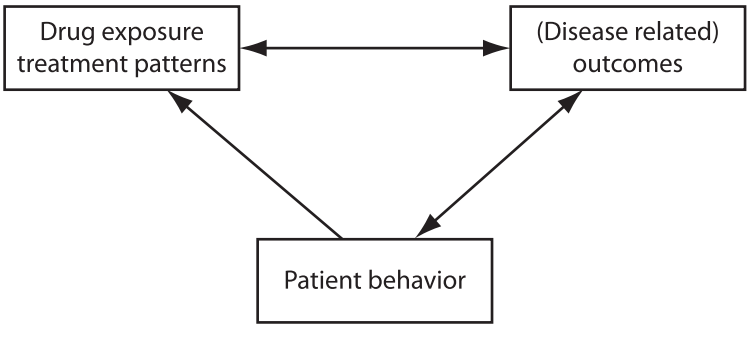
than the defined time window, usually the early discontinuers, the risk of relapse or recurrence was overestimated due to neglected time bias. As the patients were only followed up from the end of the defined time window the outcome free follow-up time from end of use until the end of the defined time window is neglected. For these patients the measured time to re-initiation will seem shorter than it actually is due to the disregarded, or neglected, outcome free follow-up time. When the two exposure cohorts of early discontinuers and continuing users are compared, the early discontinuers with an overestimated risk of the outcome and the continuing users with their underestimated risk of outcome will together give a biased risk ratio towards more beneficial effects in the continuing users.

When time windows of a specific length are used to define drug exposure cohorts and when follow up is estimated from the end of the time window both neglected time and immortal time bias can occur without regard to study population, study setting or type of drug exposure under investigation. A more proper way would be to construct individual drug treatment episodes and define exposure cohorts based on how long the total individual treatment episode is.

FUTURE PERSPECTIVES AND CONCLUSIONS

Nowadays, the majority of pharmacoepidemiologic research uses administrative databases to define drug treatment patterns which are subsequently associated with specific (disease) outcomes (Figure 3). The observed treatment patterns which are used to divide patients into different groups are often based on assumptions on the patient's specific treatment pattern. Future research should investigate patient

Figure 3 **Association between drug exposure treatment patterns, (disease related) outcomes and patient behavior**



behavior in relation to specific treatment patterns seen in administrative databases (the fifth level). Thereby, we would not only describe the treatment patterns and drug taking behavior of the patient but understand why the patient exerts a specific treatment pattern. Many factors can influence patient decision making on whether and how they use their medicines and if they comply with therapy or not. These factors can differ between patients and also within a single patient over the course of time.[58] Understanding what kind of patient behavior results in a specific treatment pattern observed in administrative databases may lead to new definitions when investigating adherence in administrative data.

When designing observational studies and deciding which definitions should be used to compose a study cohort and construct treatment episodes, there are some basic considerations that will influence the choice of definitions. Firstly, does the study question require knowledge on disease status of the patient or only drug use as such? Secondly, does the study aim to investigate patients who receive a prescription, regardless of whether they start therapy or not? Are there possible differences in risk profiles between patients who are experiencing their first treatment episode and those who re-initiate treatment? And finally, is the drug intended for short, episodic or long term use and is it used according to different dosing schemes or as one unit per day dosage regimen?

When the aim is to investigate drug exposure according to the fourth level (Figure 1) in relation to certain outcomes it is important that the drug treatment episodes are well defined. The methodological choices for study definitions depend on the exposure-outcome relationships under investigation. If definitions are not selected properly, it could influence study outcomes and lead to biased estimates.

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6

Summary
Samenvatting
Samantekt

SUMMARY

Drug exposure research can be divided into three levels evolving over time. The first level investigates drug exposure in a dichotomous way (use or no use). The time element is expanded in the second level where duration of use of a single prescription is estimated and further in the third level that focuses on investigating multiple dispensing moments. Currently, pharmacoepidemiological research on drug exposure often classifies drug exposure according to the third level where prescribing and dispensing moments can be used to construct drug treatment episodes. Construction of drug treatment episodes involve many methodological aspects, such as defining the start and the end of a treatment episode, which need to be accounted for.

Antidepressant use has increased dramatically since the introduction of the selective serotonin reuptake inhibitors (SSRI). In the Netherlands, antidepressants are indicated for treating depression, generalized anxiety disorders, obsessive-compulsive disorders, social phobia, panic disorders, eating disorders, neuropathic pain and nocturnal enuresis. In addition, antidepressants are sometimes used for treating off-label indications such as sleeping disorders, urinary incontinence and headache. The diversity in the nature of these conditions is likely to result in a variety of antidepressant treatment patterns. The common use of antidepressants in the general population, in addition to the fact that their treatment pattern does not always represent the traditional episodic nature of depression, makes this particular drug class a suitable model for methodological research on drug exposure.

One of the cornerstones of pharmacoepidemiological research is the study of drug exposure(s) in relation to specific outcome(s). Evidently, the accurate estimation of drug exposure plays a fundamental role. Drug exposure can be studied through the construction of drug treatment episodes. The objective of this thesis is to investigate methodological topics in observational research relevant to the construction of antidepressant treatment episode(s).

This thesis is divided into three topics, the investigation of indications for antidepressant drug prescribing, methodological definitions relevant to defining the start of an antidepressant treatment episode and methodological definitions relevant to defining the end of an antidepressant treatment epiosde. The first topic is covered in **Chapter 2** where patient characteristics of antidepressant users who receive antidepressants indicated to treat depression are investigated in two separate studies. In *Chapter 2.1* the on- and off-label indications for prescribing antidepressants were investigated in patients included in the Second Dutch National Survey of General Practice performed by the Netherlands Institute for Health Services Research (NIVEL) in 2001. General practitioners (GPs) were found to prescribe antidepressants predominantly for treating depression. The frequency of having a registered diagnosis of depression was dependent on the type of antidepressant prescribed. Only 25% of patients who received a tricyclic antidepressant had a diagnosis of depression in their physician-patient contact file while 50% of the SSRI users had a diagnosis of depression registered. About a third of all antidepressant users did not have any of our investigated on- and off-label indications registered in their physician-patient contact file. We concluded that although general practitioners prescribe antidepressants predominantly for treating depression the selection of antidepressant drug use as a proxy for identifying depressed patients in a prescription database should be done with caution and when possible in combination with clinical data.

Two different study populations were used in *Chapter 2.2* to develop and validate an algorithm which can identify antidepressant users from dispensing data with a registered depression diagnosis in their physician-patient contact file. The development of the algorithm was performed in general practice (NIVEL) data which was linked to pharmacy dispensing data, and the validation was performed in data from the Integrated Primary Care Information (IPCI) database. A prediction model was developed by including variables who were significant predictors of having a registered diagnosis of depression into a multivariate logistic regression model. The strongest predictors for having a diagnosis of depression registered in the physician-patient contact file were receiving at least a single defined daily dose of an antidepressant prescribed, if antidepressant use was initiated by the general practitioner and receiving more than a single antidepressant prescription dispensed in a year following initiation. Other predicting factors were age, initiating antidepressant use of SSRI type, switching between antidepressants of different types within the first treatment episode and use of laxatives (ATC group A06), medication for acid related disorders (ATC group A02), cardiac therapy (ATC group C01) or use of hypnotics or sedatives (ATC group N05C) in the six months

prior to initiating antidepressant use. The discriminatory ability of the algorithm was 79%, with a sensitivity of 79.6% and a specificity of 66.9%.

Chapter 3 focuses on methodological definitions related to defining the start of an antidepressant treatment episode. In *Chapter 3.1* initiation of antidepressant drug use after having received a prescription from a GP was investigated using data from NIVEL. In this study we determined the incidence of patients who do not fill or fill only a single antidepressant prescription at the pharmacy (decliners), and identified associated patient characteristics. Of the 965 patients who received their first prescription for a second-generation antidepressant, about 4% did not get it dispensed at the pharmacy. Further, 25% of patients who did fill the antidepressant prescription at the pharmacy only filled a single prescription. Differences were found in characteristics of patients who continued treatment when compared with those who declined treatment. Patients who consulted their GP for a non-specific indication, rather than for depression, anxiety, panic or obsessive-compulsive disorder, were more likely to decline treatment (odds ratio [OR] 2.7; 95% confidence interval [95%CI] 1.8−3.9). In addition, non-Western immigrants (OR 4.80; 95%CI 2.05−11.3) and patients > 60 years (OR 1.81; 95%CI 1.18−2.78) were more likely to decline treatment. We concluded that initiation of antidepressant therapy deserves more attention in research and clinical practice.
Methodological criteria related to defining the start of an antidepressant treatment episode were studied in *Chapter 3.2* where the effect of the length of the drug free period on incidence measurements as well as on cohort characteristics in users of antidepressants was evaluated. For a valid measurement of the incidence of drug exposure, a certain 'drug free' period, that is the time period without use of the drug of interest, needs to be defined. In this study, the one-year incidence of antidepressant drug use was estimated, in data from the Pharmaco-Morbidity (PHARMO) record linking system, using drug free periods varying in length from one month to nine years. We found that altering the drug free period from a short to a longer one resulted in decreased incidence. 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 drug free period can influence the prevalence of cohort characteristics in inception cohorts where first time drug use is an inclusion criterion.
Chapter 3.3 describes a study where the seasonal influence on initiating antidepressant drug use in general practice during 2002−2007 in the Netherlands was investigated using data from the Netherlands Information Network of General

Practice. Significant seasonal variation ($p < 0.01$) was found in initiation of antidepressant use, with about 5−35% more patients initiating use during winter than summer. Significant ($p < 0.01$) seasonality of initiating antidepressant use was seen in all patient groups, except within age groups 18−30 years and > 60 years. We concluded that the seasonal influence on initiation of antidepressant drug use has not changed with the introduction of the newer antidepressants and is in line with seasonality of depression onset, with most patients initiating use during the winter and fewest during the summer. The winter peaks are in line with what is seen in depression onset in general practice.

Antidepressant treatment in primary care is inconsistent with treatment recommendations, and many patients discontinue treatment within six months. How this affects treatment outcomes is largely unknown. In *Chapter 3.4* the PHARMO database was used to assess how length of a first antidepressant episode influences risk and time to a second treatment episode within five years of follow-up. Based on the length of a first antidepressant treatment episode, patients were divided into early discontinuers (< 6 months), continuing users (6–12 months) and persistent users (> 12 months). In addition to the overall analysis, two additional analyses were performed - one in patients who use the antidepressant most likely for treating depression, identified by using the algorithm developed in *Chapter 2.2*, and the other in a propensity score-matched sample where early discontinuers were 1:1 matched with continuing and persistent user. The risk of experiencing a second antidepressant treatment episode did not differ for those who used antidepressants for 6 to 12 months and those who discontinued early (relative risk [RR] 0.99; 95%CI 0.92–1.07). However, persistent users showed a higher risk of experiencing a second treatment episode than early discontinuers (RR 1.23; 95%CI 1.15–1.32). The additional analyses did not change the original risk estimates. This study reported contrasting results to previously published observational studies, but this could be due to use of different methodology when defining drug exposure and measuring follow up (*Chapter 4.4*).

In **Chapter 4** we focus on methodological definitions related to defining the end of an antidepressant treatment episode. When constructing drug treatment episodes using dispensing databases, duration and number of prescriptions belonging to a single treatment episode needs to be defined. As patients rarely collect a subsequent drug dispensing on exactly the day following the last day of use of the previous dispensing, overlaps and gaps in their dispensing patterns are seen. To correct for these irregularities in dispensing, researchers usually allow for a certain number of days (gap) to elapse between the dispensed prescriptions. In *Chapter 4.1* PHARMO data was used to investigate how using different methods to construct

antidepressant treatment episodes influence their median estimated length. Two methods were tested, where overlapping antidepressant prescription days were disregarded or accounted for. For both methods varying gap lengths (number of days or % prescription duration) were used to define prescriptions that belong to the same treatment episode. The difference in median length of an antidepressant treatment episode between the two methods was quite large when small gaps were used, with larger median duration when prescription overlaps were accounted for. Only when gap-lengths were set to at least 90 days or 150% of prescription duration the difference in median length ceased to differ. In general, the median antidepressant treatment episode length doubled when the gap-length was expanded from 0 to 10 days. We concluded that it is important how the prescription duration and the allowed gap-length between prescriptions are defined when constructing an antidepressant treatment episode. Large differences exist between methods that account for overlapping tablet days or not. These differences can be of importance for studies that focus on drug exposure-outcome relationships and could have consequences for epidemiological analysis.

Chapter 4.2 also focuses on gaps and overlaps between dispensed prescriptions by investigating gap and overlap magnitude in relation to patient reported adherence. Questionnaires, including the medication adherence rating scale were sent from 37 Dutch pharmacies to patients who got a second-generation antidepressant prescribed between September and December 2008. Two dispensing moments were used to estimate if patients had a gap, overlap or no gap/overlap in their dispensing pattern. Patients were further divided into subgroups based on gap/overlap magnitude (< 5% observed treatment time, > 5% and < 20% observed treatment time, ≥ 20% observed treatment time). Most patients had a gap (71%) in their dispensing patter. Patients with larger gaps in dispensing data report more frequently to engage in non-adherent behavior. These patients more often decide to skip a dose, change their dose or to use less than instructed. Patients with larger gaps also report that they less frequently inform the physician or pharmacist about changes in drug taking. Gaps seen in dispensing patterns might not necessarily indicate that the medicine is not used on gap days.

In *Chapter 4.3* the frequency of transitions from general practice to psychiatrist care, and vice versa, during a first antidepressant episode were studied in adult SSRI users. In addition, the antidepressant treatment changes associated with transition were investigated. About 9.0% of SSRI initiators transit in care either from general practice to psychiatrist care or vice versa during their first antidepressant treatment episode. In patients where use was initiated by the general practitioner about 6% were referred to psychiatric care during the first treatment episode and of all patients who start their antidepressant use by a psychiatrist about 34% transit to

general practice care. Those who transited from general practice to psychiatrist care had a significantly higher risk of switching between antidepressants (RR 6.16; 95%CI 4.90–7.75) or to undergo dose changes (RR 4.48; 95%CI 3.76–5.34) than those who did not transit in care. No significant differences in switching or dose changes for antidepressant treatment were found between those who transit from psychiatrist to general practice care and those who are only treated by psychiatrists. We concluded that transitions from general practice to psychiatrist care lead to antidepressant treatment changes and could possibly serve as a disease severity indicator in observational studies.

Several observational studies have found a higher risk of recurrence/relapse of depression for patients who discontinue antidepressant use compared with those who continue. In *Chapter 4.4* we used data from NIVEL to demonstrate that measurement of follow-up time can be subject to immortal and neglected time bias which can influence study results. The study population was composed of antidepressant users with a registered diagnosis of depression, divided into early discontinuers and continuing users. Two methods were used to measure time to relapse/recurrence. Method 1, used in previously published studies, measured the beginning of follow-up 6 months after starting antidepressant therapy. Method 2 constructed individual treatment episodes for each patient and measured follow-up from actual end-of-treatment episode. When the two methods were compared, Method 1 resulted in a risk ratio of 1.58 (95%CI 1.02–2.45), suggesting a higher risk of relapse/recurrence for early discontinuers. Method 2, however, produced a statistically non-significant risk ratio of 0.77 (95%CI 0.49–1.21), indicating no difference in risk of relapse/recurrence. We concluded that the method used in previous studies subject to bias. Applying a different method, accounting for immortal and neglected time bias, eliminated the protective effects of longer treatments.

The studies presented in this thesis expand further on drug exposure research and introduce what could be considered the fourth level, in which drug treatment episodes are constructed from multiple drug prescribing or dispensing moments. In **Chapter 5** the findings from studies presented in this thesis are discussed and put in a broader perspective. First, an illustration of the various steps involved when constructing antidepressant treatment episodes using drug exposure data from administrative databases is presented. In each step, from defining the drug exposure cohort to constructing individual drug treatment episodes, important definitions are discussed and examples of the methodological aspects that should be taken into consideration when constructing antidepressant treatment episodes are given.

Next, the generalizability of our findings and their applicability when constructing treatment episodes for antidepressant users in secondary care, in international settings and when treatment episodes are constructed for other type of drug are discussed. Finally, we conclude with future perspectives for research performed in administrative databases.

SAMENVATTING

Onderzoek naar geneesmiddelengebruik kan worden verdeeld in drie niveaus die de afgelopen decennia zijn ontwikkeld. Op het eerste niveau wordt geneesmiddelengebruik onderzocht als een ja/nee vraag: wordt het geneesmiddel wel of niet gebruikt. Op het tweede niveau wordt hier het tijdselement aan toegevoegd, door een schatting te maken van de duur van gebruik van een geneesmiddel. Op het derde niveau wordt het afhalen van meerdere recepten gedurende een tijdsperiode onderzocht. In farmaco-epidemiologisch onderzoek wordt blootstelling aan geneesmiddelen tegenwoordig vaak geclassificeerd op het derde niveau, waarbij episodes van geneesmiddelengebruik worden geconstrueerd aan de hand van voorschrijf- en afhaalmomenten.

Het gebruik van antidepressiva is sterk gestegen sinds de introductie van de selectieve serotonine heropname remmers (SSRIs). In Nederland zijn antidepressiva geregistreerd voor de behandeling van depressieve stoornissen, gegeneraliseerde angststoornis, obsessieve compulsieve stoornis, sociale angststoornis, sociale fobie, paniek stoornis, eetstoornis, neuropathische pijn en nachtelijke incontinentie. Daarnaast worden antidepressiva soms 'off label' voor niet geregistreerde indicaties gebruikt zoals slaapproblemen of hoofdpijn. Deze verschillende indicaties resulteren in een verscheidenheid aan gebruikspatronen van antidepressiva. Het feit dat antidepressiva regelmatig worden gebruikt, terwijl het gebruikspatroon niet altijd de traditionele depressie episode weerspiegelt, maakt antidepressiva bij uitstek interessant voor methodologisch onderzoek naar geneesmiddelengebruik.

Farmaco-epidemiologisch onderzoek houdt zich bezig met de associatie tussen geneesmiddelengebruik en een specifieke uitkomst. Van fundamenteel belang hierbij is een nauwkeurige schatting van de aard en de duur van het geneesmiddelengebruik. De duur van geneesmiddelengebruik kan worden onderzocht door het construeren van episodes van geneesmiddelengebruik. De doelstelling van het onderzoek beschreven in dit proefschrift is om methodologische aspecten van observationeel

onderzoek relevant voor het construeren van episodes van antidepressiva gebruik te bestuderen.

Het proefschrift is verdeeld in drie delen: onderzoek naar de indicatie voor het voorschrijven van antidepressiva, methodologische definities die relevant zijn voor het definiëren van de start van een episode van antidepressiva gebruik en methodologische definities van het eind van een episode van antidepressiva gebruik.
Het eerste deel wordt beschreven in **Hoofdstuk 2**. Hier worden karakteristieken van patiënten die antidepressiva krijgen voorgeschreven voor behandeling van depressie beschreven in twee aparte studies. In *Hoofdstuk 2.1* zijn de on- en off label indicaties onderzocht voor voorschrijven van antidepressiva bij patiënten geïncludeerd in de 'Tweede Nationale Studie naar ziekten en verrichtingen in huisartspraktijk' zoals uitgevoerd door het NIVEL ('Netherlands Institute for Health Services Research') in 2001. Huisartsen schrijven antidepressiva meestal voor ter behandeling van depressie. Het registreren van de indicatie depressie is afhankelijk van het type antidepressivum dat is voorgeschreven. Slechts 25% van de patiënten die een tricyclisch antidepressivum kreeg had een diagnose depressie in het huisartsen bestand geregistreerd, terwijl 50% van de SSRI gebruikers een geregistreerde diagnose van depressie hadden. Ongeveer een derde van alle antidepressiva gebruikers had geen enkele indicatie (on-label danwel off-label) geregistreerd in het huisartsen bestand. Wij concludeerden dat, hoewel huisartsen antidepressiva voornamelijk voorschrijven voor het behandelen van depressie, het gebruiken van antidepressiva als een aanwijzing voor het identificeren van depressieve patiënten in een medicatiebestand gedaan moet worden met terughoudendheid en daar waar mogelijk moet dit gecombineerd worden met klinische data.
In *Hoofdstuk 2.2* zijn twee verschillende studie populaties gebruikt om een algoritme te ontwikkelen en te valideren om antidepressiva gebruikers uit een database te identificeren met een geregistreerde diagnose van depressie. Het ontwikkelen van dit algoritme werd gedaan met behulp van huisartsen data gekoppeld aan aflevergegevens uit de apotheek. De validatie werd gedaan met behulp van de geïntegreerde IPCI ('Integrated Primary Care Information') database. Een voorspellend model is ontwikkeld door het includeren van variabelen die significante voorspellers zijn van het hebben van een geregistreerde diagnose van depressie in een multivariabel regressie model. De sterkste voorspellers voor het hebben van een diagnose van depressie waren een voorgeschrift voor een antidepressivum met een dosering van tenminste één DDD ('defined daily dose'), het starten van het antidepressiva gebruik door de huisarts en het afhalen van meer dan één antidepressiva recept in het jaar nadat het eerste antidepressiva recept was

opgehaald. Andere voorspellende factoren waren leeftijd, het starten van een SSRI antidepressivum, wisselen van antidepressiva binnen de eerste behandelepisode, het gebruik van laxantia ('Anatomical Therapeutic Chemical' [ATC] groep A06), gebruik van medicatie voor dyspepsie (ATC groep A02) gebruik van cardiovasculaire medicatie (ATC groep C01) of gebruik van hypnotica of sedativa (ATC groep N05C) in de zes maanden voorafgaand aan start van antidepressiva gebruik. Het onderscheidend vermogen van het algoritme was 79%, met een gevoeligheid van 80% en specificiteit van 67%.

In **Hoofdstuk 3** worden methodologische definities rondom het starten van een episode van antidepressiva gebruik bestudeerd. In *Hoofdstuk 3.1* wordt de start van antidepressiva gebruik na het ontvangen van een recept van de huisarts onderzocht met behulp van data van het NIVEL. In deze studie is de incidentie bepaald van patiënten die geen of slechts een enkel recept voor een antidepressivum afhaalden bij de apotheek. Van de 965 patiënten die een eerste recept voor een tweede generatie antidepressivum ontvingen, werd ongeveer door 4% dit recept niet afgehaald bij de apotheek. Daarnaast haalde 25% van deze groep slechts éénmaal een recept af bij de apotheek. Er werden verschillen gevonden tussen de patiënten die hun behandeling continueerden en patiënten die hun behandeling stopten. Patiënten die geen specifieke diagnose zoals depressie, angst stoornis, paniek stoornis of obsessieve compulsieve stoornis, hadden gekregen van hun huisarts, wezen vaker de behandeling met antidepressiva af (odds ratio [OR] 2.7; 95% betrouwbaarheidsinterval 1.8–3.9). Daarnaast wezen niet westerse immigranten (OR 4.80; 95% betrouwbaarheidsinterval 2.05–11.3) en patiënten ouder dan 60 jaar (OR 1.81; 95% betrouwbaarheidsinterval 1.18–2.78) de behandeling met antidepressiva vaker af. We concludeerden dat het starten van antidepressiva meer aandacht nodig heeft, zowel binnen het onderzoek als binnen de klinische praktijk.
Methodologische criteria die gerelateerd zijn aan het starten van een episode van antidepressiva gebruik werden onderzocht in *Hoofdstuk 3.2*. Het effect van de lengte van een geneesmiddelvrije periode op zowel incidentie metingen als karakteristieken van antidepressiva gebruikers werd hier geëvalueerd. Voor een goede meting van de incidentie van geneesmiddel gebruik, moet een bepaalde geneesmiddelvrije periode, de periode waar het geneesmiddel in kwestie niet word gebruikt, worden gedefinieerd. In deze studie is een schatting gemaakt van de incidentie van antidepressivagebruik met behulp van data uit het PHARMO RLS ('Pharmaco-Morbidity Record Linkage System'), waarbij geneesmiddelvrije periodes werden gebruikt van 1 maand tot 9 jaar. Hieruit komt naar voren dat de berekende incidentie daalt bij een langere geneesmiddelvrije periode. Als

een geneesmiddelvrije periode van 6 maanden wordt gebruikt was de indicentie 32 per 1000 persoonsjaren (95% betrouwbaarheidsinterval 31.3–32.6) terwijl de incidentie 27.5 (95% betrouwbaarheidsinterval 26.9–28.1), 23.5 (95% betrouwbaarheidsinterval 22.9–24.0) en 17.2 (95% betrouwbaarheidsinterval 16.7–17.7) was per 1000 persoonsjaren als een geneesmiddelvrije periode van respectievelijk 12, 24 maand of 9 jaar werd gebruikt. Daarnaast kan de lengte van de geneesmiddelvrije periode de karakteristieken van inceptie cohorten waarin eerste keer van geneesmiddel gebruik een inclusie criterium is, beïnvloeden.

Hoofdstuk 3.3 beschrijft een studie waar de invloed van de seizoenen op het starten van het gebruik van antidepressiva in de huisartsenpraktijk gedurende 2002-2007 is onderzocht met behulp van data van het Landelijk Informatie Netwerk Huisartsenzorg (LINH). Significante verschillen tussen de seizoenen ($p < 0,01$) werden gevonden bij het starten van gebruik van antidepressiva, waarbij ongeveer 5-35% meer patiënten starten in de winter dan in de zomer. Significante seizoensverschillen ($p < 0,01$) werden gevonden in alle patiëntgroepen, behalve de groep van gebruikers van 18-30 en > 60 jaar. We concludeerden dat seizoensvariaties bij het starten van gebruik van antidepressiva niet zijn veranderd na de introductie van de nieuwere antidepressiva. De variatie in starten van antidepressivumgebruik komt overeen met de seizoensvariaties in het krijgen van depressie, waarbij ook de piek in de winter ligt.

In de dagelijkse praktijk komt het gebruik van antidepressiva niet overeen met de richtlijnen voor behandeling in de eerste lijn: veel patiënten stoppen hun therapie binnen zes maanden. In hoeverre dit gevolgen heeft voor het slagen van de behandeling is onbekend. In *Hoofdstuk 3.4* wordt de PHARMO database gebruikt om te onderzoeken hoe de duur van een eerste episode van antidepressiva gebruik het risico op en de tijd tot het krijgen van een tweede episode beïnvloedt binnen een periode van 5 jaar. Gebaseerd op de duur van een eerste episode van antidepressiva gebruik werden patiënten verdeeld in 'vroege stoppers' (< 6 maanden), continue gebruikers (6–12 maanden) en persistente gebruikers (> 12 maanden). De analyses werden ook apart uitgevoerd in patiënten die antidepressiva waarschijnlijk gebruikten voor de behandeling van depressie. Deze patiënten waren geïdentificeerd met behulp van het algoritme ontwikkeld in Hoofdstuk 2.2. Het risico van het krijgen van een tweede antidepressieve periode was niet verschillend voor degenen die 6–12 maanden gebruikten en voor de vroege stoppers (relatieve risico [RR] 0.99; 95% betrouwbaarheidsinterval 0.92–1.07). Echter persistente gebruikers hadden een hoger risico op het krijgen van een tweede antidepressieve episode (RR 1.23; 95% betrouwbaarheidsinterval 1.15–1.32). Door vroegtijdige stoppers met behulp van propensity scores te matchen met continue en persistente gebruikers is gecorrigeerd voor mogelijke confounders, dit veranderde de risicoschattingen

niet. Ook in de patiënten met een waarschijnlijke diagnose van depressie werd geen ander risico gevonden. Deze studie gaf tegenstrijdige resultaten met de tot op heden gepubliceerde studies, maar dit kan komen door het gebruik van een andere methode bij het definiëren van geneesmiddelgebruik en het meten van de follow up tijd (Hoofdstuk 4.4).

In **Hoofdstuk 4** gaan we in op methodologische definities gerelateerd aan het einde van een episode van antidepressiva gebruik. Wanneer episodes van geneesmiddelengebruik op basis van gegevens uit afleverdatabases worden samengesteld, moet de duur van het recept en het aantal recepten dat tot een enkele behandelperiode behoort, worden gedefinieerd. Omdat patiënten zelden een vervolgrecept exact ophalen op de dag dat het oude recept zou zijn, worden patronen gezien met daarin overlap en gaten. Om voor deze afwijkingen te corrigeren, hanteren onderzoekers meestal een aantal bufferdagen die tussen twee opeenvolgende recepten mogen liggen. In *Hoofdstuk 4.1* worden PHARMO data gebruikt om te onderzoeken hoe verschillende periodes van antidepressiva gebruik de geschatte mediaan lengte van deze episodes beïnvloeden. Twee methoden zijn getest: een methode waarbij geen rekening werd gehouden met overlappende antidepressiva recepten en een methode waarbij wel rekening werd gehouden met overlappende antidepressiva recepten. Voor beide methoden werden verschillende hiaten (uitgedrukt in aantal dagen of in percentage van de duur van het recept) gebruikt om recepten te definiëren die tot dezelfde behandel episode behoren. Het verschil in duur van de gemiddelde behandelepisode met antidepressiva tussen de twee methoden was vrij groot als kleine hiaten werden gebruikt, een langere gemiddelde duur van antidepressiva gebruik werd gevonden als grotere hiaten werden gebruikt. Alleen wanneer de hiaten minimaal 90 dagen of 150% van de duur van het recept waren, werd geen verschil meer gevonden in de duur van de mediaan lengte van de episode van antidepressiva gebruik. De gemiddelde duur van een antidepressiva behandelepisode verdubbelde wanneer de duur van de hiaten werd verhoogd van 0 naar 10 dagen. Hieruit concludeerden we dat het belangrijk is hoe de duur van een recept en de duur van de hiaten tussen recepten wordt gedefinieerd als een behandelepisode wordt samengesteld. Er bestaan grote verschillen tussen methoden die wel of niet voor overlappende dagen corrigeren. Deze verschillen kunnen van belang zijn voor studies die gericht zijn op de relatie tussen geneesmiddel gebruik en uitkomsten en kunnen invloed hebben op epidemiologische analyses.
Hoofdstuk 4.2 richt zich op hiaten en overlap tussen verschillende afgehaalde recepten door te onderzoeken hoe de gaten en overlap zich verhouden tot door patiënten gerapporteerde therapietrouw. Dit is gemeten met behulp van een

gevalideerde vragenlijst, de Medication Adherence Rating Scale (MARS), die vanuit 37 Nederlandse apotheken is verstuurd naar patiënten die een tweede generatie antidepressivum afhaalden tussen September en December 2008. Twee afhaalmomenten werden gebruikt om te schatten of patiënten een hiaat, overlap of geen hiaat/overlap hadden in hun recept afhaalpatroon. Patiënten werden verdeeld in subcategorieën, gebaseerd op de grootte van hiaat/overlap (< 5% geobserveerde behandelingstijd, > 5% en < 20% geobserveerde behandelingstijd, ≥ 20% geobserveerde behandelingstijd). De meeste patiënten hadden een hiaat (71%) in het recept afhaal patroon. Patiënten met grotere hiaten tussen het afhalen van recepten gaven vaker aan therapie ontrouw te zijn. Deze patiënten sloegen vaker een dosis over, veranderden hun dosis of gebruikten minder dan aangegeven op het recept. Patiënten met grotere gaten in het afhaal patroon gaven aan minder vaak de huisarts of apotheker te informeren over veranderingen bij het geneesmiddel gebruik. Hiaten in de recept afhaalhistorie hoeven niet noodzakelijkerwijs te betekenen dat het geneesmiddel niet wordt gebruikt op de dagen van het hiaat.

In *Hoofdstuk 4.3* werd de frequentie van verwijzingen van de huisarts naar de psychiater en vice versa onderzocht bij SSRI gebruikers binnen hun eerste episode van antidepressiva behandeling. Ook werd onderzocht hoe SSRI gebruik veranderd, als gevolg van aan een verwijzing. Ongeveer 9% van de SSRI gebruikers wordt verwezen van de huisarts naar de psychiater of vice versa gedurende de eerste antidepressieve episode. Bij patiënten waar het eerste gebruik van SSRI's werd gestart door de huisarts werd ongeveer 6% verwezen naar de psychiater gedurende de eerste episode van antidepressiva gebruik. Van alle patiënten waar het SSRI gebruik werd gestart door de psychiater werd 34% verwezen naar de huisarts. Degenen die werden verwezen van de huisarts naar de psychiater hadden vergeleken met degenen die niet werden verwezen een significant verhoogd risico op het wisselen van SSRI (RR 6.2; 95% betrouwbaarheidsinterval 4.9–7.8) of het aanpassen van de dosis van het SSRI (RR 4.5; 95% betrouwbaarheidsinterval 3.8–5.3). Geen significante verschillen in het wisselen of het aanpassen van de dosis van de SSRI werden gevonden bij het verwijzen van de psychiater naar de huisarts. Hieruit concludeerden we dat verwijzingen van de huisarts naar de psychiater vaker resulteerden in wisselingen van de behandeling, dit kan mogelijk worden gebruikt als een indicator voor de ernst van de ziekte in observationele studies.

Diverse observationele studies hebben een hoger risico op terugkeer van depressie aangetoond bij patiënten die stoppen met antidepressiva vergeleken met patiënten die antidepressiva gebruik continueren. In *Hoofdstuk 4.4* hebben we data van het NIVEL gebruikt om aan te tonen dat de methode van bepalen van de follow-up tijd oorzaak kan zijn van 'immortal time bias' en 'neglected time bias' waardoor onderzoeksresultaten worden beïnvloed. De studie populatie was samengesteld uit

antidepressiva gebruikers met een geregistreerde indicatie depressie, verdeeld in vroege stoppers en continue gebruikers. Twee methoden werden gebruikt om de tijd tot terugkeer van antidepressiva gebruik te meten. In Methode 1, gelijk aan de methode van reeds gepubliceerde studies, werd het begin van de follow-up gemeten 6 maanden na het starten van antidepressiva. In Methode 2 werden voor elke patiënt individuele antidepressiva behandel episodes geconstrueerd en werd de follow-up time gemeten vanaf de exacte eind datum van een behandel episode. Toen we de twee methoden vergeleken bleek dat methode 1 resulteerde in een risico ratio van 1.58 (95% betrouwbaarheidsinterval 1.02–2.45), dit suggereert een hoger risico op terugkeer van een antidepressiva behandel episode in de 'vroege stoppers' groep. Methode 2, echter, resulteerde in een statistisch niet significant risico ratio van 0.77 (95% betrouwbaarheidsinterval 0.49–1,21), dit suggereert geen verschil in risico op terugkeer van een antidepressiva behandel episode tussen de twee groepen. Op basis hiervan concludeerden we dat methode 1 gevoelig is voor bias. Het gebruik van de door ons gesuggereerde methode, waarbij rekening wordt gehouden met immortal en neglected time bias, sluit deze bias uit.

De studies uit dit proefschrift gaan dieper in op blootstelling aan geneesmiddelen en introduceren wat gezien kan worden als een vierde niveau van onderzoek naar geneesmiddelengebruik. In het vierde niveau worden episodes van geneesmiddelengebruik samengesteld vanuit meerdere geneesmiddel voorschrijf- en aflevermomenten. In **Hoofdstuk 5** worden de resultaten van de gepresenteerde studies in een breder perspectief geplaatst. Allereerst wordt illustratief weergegeven hoe de verschillende stappen bij het construeren van antidepressiva gebruiksepisodes met behulp van administratieve database worden doorlopen. Bij elke stap, van het definiëren van gebruik van een geneesmiddel tot het construeren van individuele episodes van geneesmiddelengebruik, worden belangrijke definities besproken en volgen voorbeelden van methodologische aspecten die van belang zijn bij het construeren van episodes van antidepressiva gebruik. Vervolgens wordt beschreven in hoeverre de gevonden resultaten in het algemeen toepasbaar zijn bij het construeren van episode van antidepressiva gebruik in de tweede lijn, in internationale perspectief en wanneer behandel episodes voor andere type geneesmiddelen worden geconstrueerd. Als laatste bespreken we toekomstige perspectieven voor onderzoek dat wordt gedaan met behulp van administratieve databases.

SAMANTEKT

Rannsóknum á lyfjanotkun sjúklinga, þar sem upplýsingar um lyfjaáreiti (drug exposure) eru fengnar úr gagnagrunnum, er hægt að skipta í þrjú stig. Fyrsta stig felur í sér rannsókn á lyfjaáreiti þar sem spurningunni "notar sjúklingur lyf X" er svarað á einfaldan hátt með já eða nei. Á öðru stigi er tímaþátturinn víkkaður þar sem tímalengd notkunar á stakri lyfjaávísun er áætluð. Á þriðja stigi er tímaþátturinn víkkaður enn frekar með því að taka tillit til margra lyfjaávísanna/afgreiðslna eins sjúklings yfir lengra tímabil. Í dag er lyfjaáreiti í lyfjafaraldsfræðirannsóknum oftast flokkuð samkvæmt þriðja stigi, þar sem fleiri lyfjaávísanir/afgreiðslur eru settar saman í lyfjameðferðarþætti (treatment episode). Notkun upplýsinga um lyfjaávísanir/afgreiðslur til að skilgreina lyfjameðferðarþætti felur í sér marga aðferðarfræðilega þætti sem þarf að taka tillit til, eins og til að mynda hvernig upphaf og lok lyfjameðferðarþáttar eru skilgreind.

Þunglyndislyfjanotkun hefur aukist gífurlega frá markaðssetningu sérhæfðra serotónín endurupptöku hemlanna (SSRI). Í Hollandi eru þunglyndi, kvíði, ofsakvíði, áráttu-þráhyggjuröskun, félagsfælni, átröskun, útlægir taugaverkir og næturvæta hjá börnum skráðar ábendingar fyrir notkun þunglyndislyfja. Þar að auki eru þunglyndislyfin stundum notuð fyrir óskráðar ávísanir (off-label) eins og við meðhöndlun á svefntruflunum, lausheldni þvags og höfuðverk.

Vegna margbreytileika þessara sjúkdóma og einkenna er líklegt að mynstur þunglyndislyfjanotkunar séu margvísleg. Hin algenga notkun þunglyndislyfja í samfélaginu og sú staðreynd að meðferðarmynstur þeirra fylgir ekki ávallt hinu hefðbundna tímabundna eðli þunglyndis, gera þennan lyfjaflokk sérlega hentugan fyrir aðferðafræðilegar rannsóknir á lyfjaáreiti.

Einn af hornsteinum lyfjafaraldsfræðirannsókna er athugun á sambandi milli lyfjaáreitis og ákveðinnar útkomu. Með það í huga þá er það ljóst að nákvæmt mat á lyfjaáreiti gegnir lykilhlutverki. Lyfjaáreiti er hægt að rannsaka með því að skilgreina lyfjameðferðarþætti. Markmið þessa doktorsverkefnis er að rannsaka

aðferðarfræðilegar skilgreiningar fyrir áhorfsrannsóknir (observational research) sem hafa að gera með þunglyndislyfjameðferðarþætti (antidepressant treatment episodes).

Þessi ritgerð skiptist í þrjú efni, þ.e. rannsókn á ábendingum þunglyndislyfjameðferðar, aðferðarfræðilegar skilgreiningar tengdar því að skilgreina upphaf þunglyndislyfjameðferðarþáttar og aðferðarfræðilegar skilgreiningar tengdar því að skilgreina lok þunglyndislyfjameðferðarþáttar. Farið er ítarlega í fyrsta efnið í **Kafla 2** þar sem tvær rannsóknir eru kynntar sem lýsa þunglyndislyfjanotendum og ábendingum sem skráðar eru í sjúkraskrár þunglyndislyfjanotenda. ***Kafli 2.1*** fjallar um rannsókn þar sem ávísanir þunglyndislyfja fyrir skráðum og óskráðum ábendingum voru athugaðar í sjúklingum frá Second Dutch National Survey of General Practice sem var framkvæmd af The Netherlands Institute for Health Services Research (NIVEL) árið 2001. Rannsóknin sýndi að heimilislæknar í Hollandi ávísa þunglyndislyfjum í flestum tilvikum til meðhöndlunar á þunglyndi. Algengi þunglyndisábendingar í þunglyndislyfjanotendum var háð tegund þunglyndislyfs. Aðeins 25% af notendum þríhringlaga þunglyndislyfja var með ábendinguna þunglyndi skráða sem ástæðu fyrir notkun á meðan að rúmlega 50% af sjúklingum sem notuðu SSRI voru með þunglyndi sem skráða ábendingu fyrir notkun. Hjá um þriðjungi þunglyndislyfjanotenda var ekki hægt að finna ástæðu fyrir ávísun þar sem engin af ofannefndum skráðu og óskráðu ábendingum fundust í sjúkraskrá þunglyndislyfjanotenda. Sú ályktun var dregin af rannsókninni að þrátt fyrir að þunglyndislyf séu aðallega ávísuð til meðhöndlunar á þunglyndi sé varhugavert að nota þunglyndislyfjanotkun í lyfjagagnagrunnum sem staðgengil (proxy) við val á sjúklingum með þunglyndi í lyfjagagnagrunnum. Við val á sjúklingum sem eru meðhöndlaðir vegna þunglyndis skal samhliða þunglyndislyfjanokun ávallt styðjast við klínísk gögn þegar notast er við lyfjagagnagrunna við val á sjúklingum meðhöndluðum við þunglyndi í þýði.
Í ***Kafla 2.2*** voru tvö mismunandi þýði notuð til að hanna og réttmæta algóriþma sem hægt er að nota í lyfjagagnagrunnum til að velja þunglyndislyfjanotendur sem nota þunglyndislyfið vegna meðhöndlunar við þunglyndi. Hönnun algóriþmans var framkvæmd í heimilislæknagagnagrunni (NIVEL) sem var tengdur við lyfjagagnagrunnsgögn, og réttmæting hans fór fram í þýði úr Integrated Primary Care Information (IPCI) gagnagrunninum. Spálíkan var hannað með því að taka tillit til þátta sem tölfræðilega marktækt gátu sagt fyrir um hvort þunglyndislyfjanotandi var með þunglyndi sem skráða ábendingu á lyfseðli. Allir tölfræðilega marktækir þættir voru settir saman í spálíkan með margar breytistærðir. Þættir sem sterkast gátu sagt fyrir um hvort þunglyndislyfjanotandi væri með ábendinguna þunglyndi voru ef að ávísað var að minnsta kosti einum skilgreindum dagsskammti (DDD)

af þunglyndislyfi, ef heimilislæknir hóf þunglyndislyfjameðferðina í stað geðlæknis og ef sjúklingur fékk afgreidda fleiri en einn þunglyndislyfjalyfseðil á þeim tólf mánuðum sem liðu frá því að þunglyndislyfjameðferð hófst. Aðrir þættir sem sögðu fyrir um hvort þunglyndislyfjanotendur voru með ábendinguna þunglyndi í heimilislæknagagnagrunninum voru aldur, notkun SSRI lyfja, ef víxlað var á milli þunglyndislyfja í fyrstu þunglyndislyfjameðferðarþættinum og notkun hægðalyfja (ATC flokkur A06), notkun lyfja gegn sýrutengdum sjúkdómum (ATC flokkur A02), notkun hjartasjúkdómalyfja (ATC flokkur C01) eða notkun svefnlyfja eða róandi lyfja (ATC flokkur N05C) á sex mánaða tímabili áður en þunglyndislyfjanotkun hófst. Áreiðanleiki algóriþmans við að greina á milli þunglyndislyfjanotenda með ábendinguna þunglyndi skráða í heimilislæknagagnagrunn á réttan hátt mældist 79% og mældist hann með 79.6% næmi (sensitivity) og 66.9% sértæki (specificity).

Kafli 3 tók fyrir aðferðarfræðilegar skilgreiningar tengdar því þegar upphaf þunglyndislyfjameðferðarþáttar er skilgreint. Í ***Kafla 3.1*** var upphaf þunglyndislyfjameðferðar rannsakað í sjúklingum sem fengu þunglyndislyfjalyfseðil frá heimilislækni. Nýgengi sjúklinga sem fengu lyfseðilinn ekki leystan út í apóteki og þeirra sem fengu aðeins einn lyfseðil útleystan í apóteki var ákvörðuð (skilgreint sem höfnun meðferðar), og eiginleikar þessara sjúklinga voru skilgreindir. Af 965 sjúklingum sem fengu ávísað lyfseðli af SSRI gerð, fengu um 4% lyfseðilinn ekki leystan úr apótekinu. Af þeim sem að fengu lyfseðil leystan úr apótekinu leystu um 25% sjúklinganna aðeins einn lyfseðil úr apótekinu. Munur fannst á sjúklinga sem höfnuðu meðferð og þeirra sem hófu meðferð (leystu út fleiri en einn lyfseðil). Sjúklingar sem lýstu ónákvæmum einkennum hjá heimilislækninum voru líklegri (áhættuhlutfall [OR] 2.7; 95% öryggisbil [95%CI] 1.8−3.9) til að hafna meðferð miðað við þá sem tilkynntu einkenni þunglyndis, kvíða, ofsakvíða eða áráttu-þráhyggjuröskun. Einnig voru sjúklingar sem ekki voru af vestrænu bergi brotnir (OR 4.80; 95%CI 2.05−11.3) og sjúklingar yfir sextíu ára (OR 1.81; 95%CI 1.18−2.78) líklegri til að hafna þunglyndislyfjameðferð. Þær ályktanir voru dregnar af niðurstöðum þessarar rannsóknar að ástæða sé til að auka athygli á upphafi þunglyndislyfjameðferðar í klínískum rannsóknum.

Aðferðarfræðilegur mælikvarði til að skilgreina upphaf þunglyndislyfjameðferðar-þáttar eru rannsakaðar frekar í ***Kafla 3.2*** þar sem áhrif af lengd "lyfjalausa tímabilsins" (drug free period) á nýgengismælingar sem og á eiginleika sjúklingaþýðis voru metin. Til að meta nýgengi lyfjaáreitis þarf að skilgreina hið svokallaða 'lyfjalausa tímabil´. Í þessari rannsókn var eins árs nýgengi þunglyndislyfjanotkunar mælt í PHARMO lyfjagagnagrunninum, með því að nota "lyfjalaus tímabil" frá 1 mánuði upp í 9 ár að lengd. Niðurstöður sýndu að eftir því sem lyfjalausa tímabilið lengist þá lækkar nýgengi þunglyndislyfjanotkunar. Nýgengi þunglyndislyfjanotkunar

mældist 32.0 (95%CI 31.3−32.6) á 1000 einstaklinga þegar lyfjalausa tímabilið var skilgreint sem 6 mánuðir á meðan að nýgengið var 27.5 (95%CI 26.9−28.1), 23.5 (95%CI 22.9− 24.0) og 17.2 (95%CI 16.7−17.7) þegar lyfjalausa tímabilið var skilgreint sem 12 mánuðir, 24 mánuðir eða 9 ár. Einnig kom í ljós að lyfjalausa tímabilið getur haft áhrif á algengi sjúklingahópseiginleika þýðis þegar að aðeins nýir notendur eru valdir í þýði.

Kafli 3.3 lýsir því hvernig árstíðir hafa áhrif á hvenær þunglyndislyfjanotkun hefst á árunum 2002 til 2007 í Hollandi. Tölfræðilega marktæk árstíðarbundin áhrif ($p < 0.01$) fundust þar sem 5−35% fleiri sjúklingar hefja þunglyndislyfjameðferð um vetur miðað við sumar. Þessi árstíðarbundu áhrif fundust í öllum hópum þunglyndislyfjanotenda, nema í aldurshópunum 18−30 ára og yfir 60 ára. Sú ályktun var dregin að árstíðarbundin áhrif á að hefja þunglyndislyfjameðferð hefur ekki breyst með tilkomu nýju þunglyndislyfjanna og fylgir árstíðarbundnum sveiflum í nýgengi þunglyndis, þar sem flestir sjúklingar greinast á veturna og fæstir á sumrin.

Þunglyndislyfjameðferð veitt af heimilislæknum hefur verið á skjön við það sem meðferðarviðmiðunarreglur segja til um og margir sjúklingar hætta þunglyndislyfjameðferð innan sex mánuða. Áhrifin af því að hætta þunglyndislyfjameðferð of snemma eru að vissu leyti ókunn. Í **Kafla 3.4** var PHARMO lyfjagagnagrunnurinn notaður til að meta hvernig lengd á fyrsta þunglyndislyfjameðferðarþætti hefur áhrif á áhættu og tíma fram að næsta þunglyndislyfjameðferðarþætti. Þunglyndislyfjanotendum var skipt í þrjá hópa eftir lengd fyrsta þunglyndislyfjameðferðarþáttar, þ.e. þá sem hætta of snemma (< 6 mánuði), notendur sem fylgja meðferðarviðmiðunarreglum (6−12 mánuðir) og langtíma notendur (> 12 mánuðir). Auk heildargreiningarinnar voru tvær auka greiningar framkvæmdar, ein í notendum sem nota þunglyndislyf vegna þunglyndisábendingar samkvæmt algóriþma úr ***Kafla 2.2*** og ein í 1:1 hneigingarskorssamanstefndu (propensity score matched) úrtaki þar sem sjúklingar sem hætta meðferð of snemma voru stefndir saman við þá sem fylgdu meðferðarviðmiðunarreglum og langtíma notendur. Enginn munur var á áhættunni að hefja aftur þunglyndislyfjanotkun á milli sjúklinga sem hættu notkun of snemma og þeirra sem voru meðhöndlaðir samkvæmt meðferðarviðmiðunarreglum (hlutfallsleg áhætta [RR] 0.99; 95%CI 0.92−1.07). Aftur á móti voru langtíma notendur í aukinni áhættu á að hefja þunglyndislyfjameðferð á ný miðað við þá sem hættu notkun of snemma (RR 1.23; 95%CI 1.15−1.32). Auka greiningarnar leiddu til sömu niðurstöðu og aðalgreiningin. Niðurstöðurnar úr þessari rannsókn eru þvert á það sem áður hefur verið birt en líklega má þar um kenna mismunandi aðferðarfræði sem er notuð við skilgreiningu á lyfjaáreiti og eftirfylgni (***Kafli 4.4***).

Í **Kafla 4** er áhersla lögð á aðferðafræðilegar skilgreiningar sem notast er við þegar lok á þunglyndislyfjameðferðarþættir eru skilgreind. Þegar þunglyndislyfjameðferðarþættir eru skilgreindir út frá lyfjagagnagrunnum þarf að skilgreina tímalengd lyfseðils og áætla fjölda lyfseðla sem tilheyra einum lyfjameðferðarþætti. Þar sem sjúklingar sækja sjaldan lyfseðla í apótekin á nákvæmlega þeim degi þegar síðasti skammtur síðasta lyfseðils er tekinn inn má oft sjá bil og skörun í lyfjaafgreiðslumynstri í lyfjagagnagrunnum. Til að leiðrétta þessi bil og skaranir í afgreiðslumynstrinu er yfirleitt leyft að ákveðinn dagafjöldi (leiðréttingarbil) megi líða á milli lyfseðla. Í ***Kafla 4.1*** var PHARMO lyfjagagnagrunnurinn notaður til að rannsaka hvernig mismunandi aðferðir við að búa til þunglyndislyfjanotkunarþætti hafa áhrif á miðgildislengd þeirra. Tvær aðferðir voru rannsakaðar þar sem leiðrétt var fyrir skörun í annarri en ekki í hinni aðferðinni. Hjá báðum aðferðum var notast við mismunandi löng leiðréttingarbil til að skilgreina þær lyfjaafgreiðslur sem tilheyra einum og sama þunglyndislyfjameðferðarþættinum. Munur á miðgildislengd þunglyndislyfjameðferðarþáttar var mikill þegar smá leiðréttingarbil voru notuð og var miðgildislengd þunglyndislyfjameðferðarþáttar meiri ef leiðrétt var fyrir skörun. Breytingar á miðgildislengd þunglyndislyfjameðferðarþáttar hættu ekki fyrr en leiðréttingarbil voru skilgreind sem að minnsta kosti 90 dagar eða 150% af tímalengd einnar lyfjaávísunar. Ályktanir úr þessari rannsókn voru að skilgreining tímalengdar einnar lyfjaávísunar og lengd leiðréttingarbils eru mikilvægar þegar þunglyndislyfjameðferðarþættir eru skilgreindir út frá gögnum úr lyfjagagnagrunnum. Mikill munur er á aðferð þar sem leiðrétt er fyrir skörun og þar sem ekki er leiðrétt fyrir skörun. Þessi munur er mikilvægur og getur leitt til mismunandi niðurstaðna í rannóknum sem einbeita sér að lyfjaáreiti-útkomu samböndum og geta haft afleiðingar fyrir faraldsfræðilegar greiningar. ***Kafli 4.2*** tók einnig fyrir efnið bil og skörun á milli lyfjaafgreiðsla með því að rannsaka bil og skörun í sambandi við hvernig sjúklingar greina frá eigin meðferðarfylgni. Spurningalistar sem innihéldu m.a. Medication Adherence Rating Scale (MARS) voru sendir frá 37 hollenskum apótekum til sjúklinga sem sóttu lyfseðil af nýrri gerð þunglyndislyfja á tímabilinu september til desember 2008. Tvær afgreiðslur voru notaðar til að meta heildarbil eða skörun í þunglyndislyfjaafgreiðslum sjúklinganna. Sjúklingarnir voru einnig flokkaðir í hópa eftir stærð bils eða skörunar ($< 5\%$ meðferðartíma, $\leq 5\%$ og $< 20\%$ meðferðartíma, $\geq 20\%$ meðferðartíma). Flestir sjúklingar voru með bil (71%) í lyfjaafgreiðslumynstri sínu. Sjúklingar með stór bil skýrðu oftar frá því að þeir sýndu ekki góða meðferðarfylgnishegðun. Þessir sjúklingar skýrðu einnig oftar frá því að þeir ákveddu sjálfir af og til að sleppa úr lyfjaskammti, að breyta ávísaðri skömmtun eða að þeir notuðu minna magn en var ávísað. Sjúklingar með stærri bil sögðu einnig oftar að þeir tilkynntu ekki þessar breytingar á lyfjanotkun til heimilislæknis eða lyfjafræðings.

Í ***Kafla 4.3*** var rannsökuð tíðni á flutningi frá heimilislækni til geðlæknis (og öfugt) innan fyrsta þunglyndislyfjameðferðarþáttar hjá sjúklingum sem nota SSRI lyf. Að auki voru rannsakaðar breytingar á þunglyndislyfjameðferð í kringum þennan flutning. Um 9% af SSRI notendunum skipta frá heimilislækni yfir í geðlækni (eða öfugt) innan fyrsta þunglyndislyfjameðferðarþáttar. Af öllum sjúklingum sem hófu meðferð hjá heimilislæknum, skiptu um 6% yfir í meðferð hjá geðlæknum, en um 34% af sjúklingum sem hófu meðferð hjá geðlæknum skiptu yfir í meðferð hjá heimilislækni. Þeir sem skiptu frá heimilislæknismeðferð yfir í geðlæknismeðferð innan fyrsta þunglyndislyfjameðhöndlunarþáttar voru líklegri til þess að þunglyndislyfjameðferð þeirra væri breytt með því að skipta um gerð þunglyndislyfs (RR 6.16; 95%CI 4.90−7.75) eða að þunglyndislyfjaskammti væri breytt (RR 4.48; 95%CI 3.76−5.34) miðað við þá sem fengu eingöngu meðferð hjá heimilislæknum. Enginn tölfræðilega marktækur munur fannst á breytingum á þunglyndislyfjameðferð þeirra sem skiptu úr meðferð hjá geðlæknum yfir í meðferð hjá heimilislæknum og þeirra sem fengu einungis meðferð hjá geðlæknum. Niðurstöður úr þessarri rannsókn gefa til kynna að það að flytja meðferð sína frá heimilislækni til geðlæknis innan sama þunglyndislyfjanmeðferðarþáttar hefur í för með sér breytingar á þunglyndislyfjameðferð. Mögulegt er að líta á þennan flutning sem vísi fyrir alvarlegri þunglyndiseinkenni sjúklinga í áhorfsrannsóknum.

Nokkrar áhorfsrannsóknir fundu aukna áhættu á endurkomu þunglyndis í sjúklingum sem hættu þunglyndislyfjameðferð of snemma miðað við þá sem fylgdu meðferðarviðmiðunarreglum. Í ***Kafla 4.4*** var NIVEL gagnagrunnurinn notaður til að sýna fram á að mæling á eftirfylgni getur orðið fyrir áhrifum ódauðlegs tímaskakka (immortal time bias) og vanrækslu tímaskakka (neglected time bias) sem geta haft áhrif á rannsóknarniðurstöður. Þýðið í þessarri rannsókn samanstóð af þunglyndislyfjanotendum með skráða þunglyndisábendingu sem var skipt í sjúklinga sem hættu meðferð of snemma og sjúklinga sem fylgdu meðferðarviðmiðunarreglum. Tvær aðferðir til að mæla tíma fram að endurkomu þunglyndis voru bornar saman. Fyrsta aðferðin, sem notast hefur verið við í áður birtum rannsóknum, mældi upphaf á eftirfylgni sex mánuðum eftir að þunglyndislyfjameðferð var hafin. Seinni aðferðin skilgreindi þunglyndislyfjameðferðarþætti fyrir hvern sjúkling og mældi eftirfylgni frá þeim tíma þegar þunglyndislyfjameðferðarþætti lauk. Þegar aðferðirnar voru bornar saman kom í ljós að samkvæmt aðferð 1 mældist aukin áhætta á endurkomu þunglyndis í sjúklingum sem hættu meðferð of snemma (RR 1.58; 95% CI 1.02−2.45) á meðan að aðferð 2 sýndi engan mun á áhættu milli hópanna (RR 0.77; 95%CI 0.49−1.21). Sú ályktun var dregin að aðferðin sem notast var við í áður birtum greinum sé undirorpinn skakka. Þegar annari aðferð var beitt, þar sem tekið

var tillit til ódauðlegs tímaskakka og vanrækslu tímaskakka, hurfu verndandi áhrif langtíma þunglyndislyfjameðferðar á endurkomu þunglyndis.

Niðurstöður þessarar doktorsritgerðar útvíkka hugtakið lyfjaáreiti og innleiða það sem hægt er að skilgreina sem fjórða stig rannsókna á lyfjanotkun með hjálp lyfjagagnagrunna þar sem lyfjameðferðarþættir eru skilgreindir út frá mörgum lyfjaávísunum/afgreiðslum. **Kafli 5** inniheldur almenna umræðu um niðurstöður ritgerðarinnar. Fyrst er útskýrt flæðirit sem sýnir hin ýmsu stig tengd því þegar þunglyndislyfjameðferðarþættir eru skilgreindir í lyfjagagnagrunnum. Í hverju stigi, frá skilgreiningu á lyfjanotkunarþýðinu fram að skilgreiningu á þunglyndislyfjameðferðarþættinum, eru kynntar mikilvægar skilgreingar og dæmi tekin um aðferðafræðilega þætti sem þarf að taka tillit til. Þá er alhæfni niðurstöðvanna rædd og nothæfni þeirra þegar þunglyndislyfjameðferðarþættir eru skilgreindir fyrir sjúklinga sem eru meðhöndlaðir af geðlæknum, fyrir þunglyndislyfjanotendur í öðrum heilbrigðiskerfum en því hollenska og þegar lyfjameðferðarþættir eru skilgreindir fyrir aðra lyfjaflokka. Að lokum er framtíðaryfirsýn gagnagrunnsrannsókna rædd.

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About the author

DANKWOORD

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During and directly after her studies she volunteered for the International Pharmaceutical Students Federation (IPSF) working at their headquarters in the Hague, The Netherlands. She also served on the ISPF board, two years as a treasurer and one year as the vice-president of the organisation. From 2002 until the beginning of 2004 she worked for the International Pharmaceutical Federation (FIP). In 2004, she finished the last phase of her Pharmacy Practice internship and received her PharmD. In June 2004 she started her PhD research at the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences at the University of Utrecht. During this period she obtained a Master of Science degree in Epidemiology from the University of Utrecht.

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