Using prescription registries to define continuous drug use:

How to fill gaps between prescriptions

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Abstract

Pharmacoepidemiological studies often use prescription registries to assess patients' drug episodes. The databases usually provide information on the date of the redemption of the prescription as well as the dispensed amount, and this allows us to define episodes of drug use. However, when patients take less medication than prescribed, gaps between prescriptions occur, and most studies handle this issue by allowing for small gaps when defining continuous drug use. This paper argues that it becomes crucial whether gaps are 'filled' by extending each prescription by a fixed amount or whether gaps are filled only if a new prescription gets dispensed within a given time horizon. In the latter case exposure status depends on the patient's future dispensing behaviour and this can lead to severe bias in the findings of the study. In the note, we investigate this potential bias in a study of the risk of acute myocardial infarction for women using hormone therapy, and we show that the second exposure definition introduces an artificially protective effect of hormone therapy.

Key words: Prescription registries, episodes of drug use, gaps in treatment, survival analysis.
1 Introduction

Over the last couple of decades prescription registries have become an important source of information for performing pharmacoepidemiological studies. These registries have been used to study the patterns of drug use in large populations and as indication of drug exposure for studies of the effect of drug treatment (see, eg. [1]).

Since prescription registries only provide us with information about the date of redemption of prescriptions together with some information on the redeemed amount, we need to make assumptions about consumption of dispensed drugs in order to approximate the patients’ actual drug use. This will indeed always be an approximation of the realized treatment course, since we never can be sure if and when the dispensed drugs are obtained.

The discrepancy between the patient's actual drug use and drug use assessed by information on redeemed prescriptions introduces a source of variability which causes bias in estimates from a statistical analysis (see [2]). Several studies have therefore attempted to validate approximations of drug use based on prescriptions by patient interviews (see, [3], [4]) or by survey data (see, [5], [6], [7]). However, survey and interview data cannot serve as a golden standard for drug use, and in most cases we are therefore forced to accept the unknown level of measurement error introduced by lack of information on true drug use.

This note deals with a specific challenge, which rises when approximating episodes of drug use using prescription registries -- the apparent gaps in treatment which are believed to be a consequence of the timing of redemptions and possibly not a result of discontinuation of drug use leading
to wrong assumptions about duration of the drug use. These apparent treatment gaps are often handled by extending the duration of prescriptions, and we argue that a certain class of methods, which is used in the literature, can lead to biased results. To illustrate the points, we investigate this potential bias in a study of the risk of acute myocardial infarction for women using postmenopausal hormone therapy, and we show that this definition of drug use introduces an artificially protective effect of hormone therapy. Finally, we show via simulations how bias can emerge in studies of persistence to treatment.

2 Filling of gaps between prescriptions

In pharmacoepidemiological studies it is often desirable to define episodes of drug use. For example, studies of persistence to treatment concern the duration of drug episodes, and in studies of the effect of drugs we need to assess whether the individual was exposed to the study drug when the event of interest occurred. For this purpose, we can sometimes use the information on the redeemed amount. When this information is not delivered directly as 'days supply' an approximation can be made by making assumptions on the patient's daily consumption and transform the amount of the pills into a duration of therapy. The WHO Collaborating Centre for Drugs Statistics Methodology has developed a guideline (see, www.whocc.no/atcddd/), which occasionally can be used for this purpose -- the Defined Daily Dose (DDD) which equals the assumed average maintenance dose per day for a drug used for its main indication in adults.

A simple way to define episodes of drug use would be to only regard individuals as users from the day of redemption of the study drug until the days supply has elapsed, and only extend the episode
if a new prescription gets redeemed within this period. However, several things can affect the timing of the redemptions, such as deviation from the assumption on the patient's treatment dose, lack of adherence to the treatment and fact that patients might visit the pharmacy before having obtained the last pill from the previous package. Consequently, this simple definition of drug episodes will lead to apparent treatment gaps, which not necessarily coincides with discontinuation of treatment. To counteract this problem, we need to allow for small gaps between expiration of one prescription and a new redemption when defining episodes of drug use.

There are several ways to allow for gaps between prescriptions (i.e. a timegap between the expiration of one prescription and the redemption of a new prescription). One issue is the length of the allowed gap, which can be a fixed number of days or a function of the length of last prescription. The choice of length is an important and challenging task, but we will not discuss it further in this note. Another issue is whether the filling of gaps is done prospectively or retrospectively. In the prospective case an individual is classified as user of the drug at a given point in time if his prescription has not expired or if it expired within \( m \) days (where \( m \) is the allowed gap length). By retrospective filling of gaps, we refer to methods where gaps only get filled if a new redemption occurs within a given time frame. In this case an individual is considered as user if his prescription has not expired or if it expired within \( m \) days and a new redemption occurs within \( m \) days after the last expiration date. Figure 1 gives a graphical illustration of the subtle difference between prospective and retrospective filling of gaps. In the remaining of the note, we will discuss the difference between these two approaches and show that retrospective filling of gaps can lead to biased results.
Episodes of drug use based on prescriptions

![Diagram showing redemptions, redeemed amount, prospective, and retrospective filling of gaps.]

[Figure 1] The figure illustrates the information available from prescription data for one individual. The top line depicts the timing of the redemptions (indicated by ‡). The second line (Redeemed amount) shows the episodes of drug use based solely on the date of redemption and the redeemed amount, the solid line segments indicate current use and the dashed line segments indicate non-use. In the third line (Prospective filling of gaps) each prescription has been extended by a fixed amount, and line four (Retrospective filling of gaps) shows the case where gaps only get filled if a new redemption occurs within a given time frame.

First of all, the retrospective method has the flaw that it allows the exposure variable (user or non-user) at a given point in time to depend on future events, since the $m$ days following an expiration of a prescription will only be classified as part of the treatment period if a new dispensing occurs. This violates the fundamental predictability assumption, which is crucial for applying methods from survival analysis (see, [8]). This means in principle, that all standard methods get unreliable, and
hence cannot be applied. In the following, we give two examples where the usage of standard tech-
niques of survival analysis will create biased results, when using the retrospective method.

One example concerns the investigation of the effect of a drug in cohort studies. In this case, bias
occurs when the event under investigation affects the future dispensing behaviour, since this can
change the exposure status at the time of the event. For the sake of illustration let us consider the
risk of death for individuals on the study drug - this event clearly affects the future dispensing be-
behaviour. In this case an event cannot occur in a filled gap between prescriptions, since if so, a new
prescription could not be redeemed and the individual would have been classified as non-user at the
time of event. Consequently, the allowed gaps between prescriptions become risk-free time which
implies an underestimation of the risk of death for people using the study drug. We will see an ex-
ample of this in Section 3.1. It should be noted that even though the above argument was based on
death by all causes, any event which causes the patient stop redeeming prescription will suffer from
the same phenomenon.

For another example, let us consider cohort studies of persistence to treatment medication, that is,
studies of the time to discontinuation of drug therapy. In this case, the retrospective method will
lead to biased results if the duration of therapy is right censored. To see this, assume that a censor-
ing of an individual occurs in an allowed gap between prescriptions, then the information of a pos-
sible new redemption will not be supplied and the retrospective method will interpret this as a dis-
continuation and not a censoring of the duration of therapy. Treating a censoring as an event will in
general lead to underestimation of the time to event, and hence underestimate the persistence. In
Section 4 we will illustrate this by a simulation study.
3 Hormone Therapy and the risk of Acute Myocardial Infarction

In this section we illustrate the points made in the previous section using data from the Danish Registry of Medicinal Products Statistics. The focus will be on hormone therapy (HT) and the risk of acute myocardial infarction (AMI). The lesson to be learned is that when an event affects the future motivation (or ability) to refill prescriptions, then we will underestimate the effect of current use of HT when using the retrospective filling of gaps technique.

In the analysis, we will distinguish between the occurrence of fatal and nonfatal AMI. We make this discrimination to compare results from an analysis of an endpoint which causes the individual to stop redeeming prescriptions (fatal AMI) with an analysis of an endpoint which does not (nonfatal AMI). This comparison is of interest since the retrospective method then is expected to introduce bias in the analysis of fatal AMI but not in the analysis of nonfatal AMI. Splitting the analysis of AMI into fatal and nonfatal therefore gives us an opportunity to investigate the artificial effect coming from the retrospective filling of gaps technique. The fact that nonfatal AMI events actually do not make the women stop hormone therapy may be verified from the registries as discussed below.

3.1 Data

The Danish Registry of Medicinal Products Statistics includes information about all prescription medicines dispensed from pharmacies in Denmark since January 1, 1995. All prescriptions are registered at an individual level using the civil registration number. As all residents in Denmark are covered by a national health security system and get the cost of drugs partly reimbursed, all phar-
macies are required by law to register all prescriptions dispensed in this nationwide registry. The registry classifies medicines according to the Anatomical Therapeutic Chemical (ATC) system and includes the date of the dispensing as well as the amount, expressed in DDDs. In the study, we included all information on redemptions of either estrogen (ATC code: G03CA03, G03CA04, G03CA53 and G03CA57) or combined estrogen and progestagen (ATC code: G03FA01, G03FA12, G03FB01, G03FB05, G03FB06, G03FB09) in tablets or patches.

Information on events were collected from The National Patient Registry, which keeps records on all patient contact with clinical hospital departments in Denmark since 1977, and The Cause of Death Registry. Furthermore, data on education and place of residence were supplied from Statistics Denmark. Since the aim of the study was to evaluate the effect of hormone therapy in postmenopausal women, the study was restricted to women between 50 and 70 years of age. Finally, the intersection of the different registries resulted in the study period 1995-2001.

In the introduction to this section we postulated that the occurrence of a nonfatal AMI does not make the women stop dispensing prescriptions for HT. To support this statement we identified all nonfatal AMI events which happened when the woman had a valid prescription (ie. in the interval from the dispensing of a HT prescription until the expiration defined by the number of DDDs) and searched the database for a new prescription in the 12 months following the event. According to this, only 10.1 % of the women stopped redeeming prescription after a nonfatal event.

3.2 Definition of exposure
In the analysis we will allow for treatment gaps equal to the length of the last redeemed prescription. For the two different methods this means the following.

Prospective filling of gaps: A woman is considered to be user of HT from the date of dispensing of the prescription until its elapse, defined as the date of dispensing plus \textit{twice} the number DDDs dispensed. Retrospective filling of gaps: A woman is considered to be user of HT from the date of dispensing of the prescription until its elapse, defined as the date of dispensing plus the number DDDs dispensed. If, however, the woman redeems a new prescription within twice the number of DDDs after the last redemption, she is considered to be on continuous use.

For both definitions the remaining DDDs are cancelled if a new prescription is redeemed before the elapse of the present.

As explained earlier, the retrospective method introduces bias when we investigate an event which makes the individual stop dispensing prescriptions, and the bias emerges because the event interrupts the treatment episode. To illustrate this phenomenon will introduce the category 'recent user' which contains the risk time from discontinuation of HT and the following 3 months. Finally, when a woman is neither user nor recent user of HT we will regard her as non-user.

### 3.3 Statistical Analysis

To avoid selection bias due to the fact that women with a history of cardiovascular events may tend to self select into HT, we focus on the risk of the first AMI given no prior cardiovascular events (ie. ischemic heart disease (ICD8: /ICD:), stroke (ICD) or venous thromboembolism (ICD)). That is, we exclude all women who had registered any cardiovascular disease before the beginning of the pre-
scription registry in 1995 and censor the woman after the occurrence of any cardiovascular event when it happened after January 1, 1995.

The statistical analysis was performed using Poisson regression with piecewise constant hazards in the age groups 50-54, 55-59, 60-64 and 65-69. The rate ratios adjusted for age, education and residence can be seen in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>fatal AMI</th>
<th>nonfatal AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current use</td>
<td>0.89 (0.74 ;1.07)</td>
<td>1.18 (1.09 ;1.27)</td>
</tr>
<tr>
<td>recent use</td>
<td>1.40 (0.75 ;2.61)</td>
<td>0.96 (0.68 ;1.35)</td>
</tr>
<tr>
<td>non use</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Retrospective method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current use</td>
<td>0.77 (0.62 ;0.94)</td>
<td>1.17 (1.08 ;1.27)</td>
</tr>
<tr>
<td>recent use</td>
<td>2.28 (1.53 ;3.40)</td>
<td>1.23 (0.96 ;1.57)</td>
</tr>
<tr>
<td>non use</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

[Table 1] Rate ratios adjusted for age, education and residence for the risk of fatal and nonfatal AMI using the two different definitions to assess exposure to HT.

The results for the retrospective method show a significant protective effect of HT on fatal AMI but a significant increased risk for recent use when compared to non-use. These effects dilute when switching to the prospective method, such that they are no longer significant. On the other hand, the results of the analysis of nonfatal AMI almost coincide across methods.
In light of the arguments given in Section 2, we interpret the significantly increased risk of fatal AMI for recent use under the retrospective method as a consequence of the interruption of the treatment period when a fatal event occurs. Along with this, the protective effect of current use follows from the same cause, and hence manifests the bias.

4 Investigation of bias in studies of persistence to treatment

We argued in Section 2 that the retrospective method also leads to bias in studies of persistence to medication. Here we illustrate this issue by an analysis based on simulated data.

[Figure 2] Plot of the Kaplan-Meier curves of the duration of treatment based on the prospective method, the retrospective method and the simulated duration.
We simulate 100,000 individuals with duration of treatment following a gamma distribution with shape parameter equal to 5 and scale parameter equal to 200, that is, with a mean duration of 1,000 days. We then consider the case where all patients dispense a new prescription of length 30 days every 40th day as long as they persist to treatment, and we assume that this is the only information available. This implies gaps between all prescriptions of 10 days. Censoring of information on re- demptions is simulated independently of the duration of treatment using a uniform distribution on the interval (0; 1500). We then applied both the prospective and the retrospective method in order to assess the duration of treatment. Figure 2 now shows the Kaplan-Meier estimator for the two methods together with the true survival curve. The graph clearly supports the statement about the potential bias when using the retrospective technique for cohort studies of the persistence to drug therapy.

5 Discussion

In this note we have discussed two competing techniques used to transform prescription data into episodes of drug use, and argued that one of them - the retrospective filling of gaps – potentially leads to biased results.

Even though the majority of studies based on prescription registries make use of the prospective method several applications of the retrospective method have been published in the pharmacoepi- demiological literature. For example, the paper [9] uses it to study low-ceiling diuretics and the risk of myocardial infarction and stroke, and [10] use it to study medication use and discontinuation after myocardial infarction. In the review paper [11] the retrospective method is even recommended
for estimating medication persistency. The papers [12], [13] and [14] also base their expose definitions on a retrospective logic although they use it in a case-control setting.

Prescription registries offer a large number of possibilities to study the use and effects of drug, and the rapidly growing field of pharmacoepidemiology exploits this potential to manifest its position in medical research. However, prescription data must be handled cautiously to attain meaningful results and to avoid outright false conclusions. In this note we have underlined the importance of this issue when faced with gaps between prescriptions, but in order to fully make use of the large potential offered by prescription registries we need to focus more on methodology and interpretation of information on prescriptions.
References


