Original Contribution

Duration of Antidepressant Drug Treatment and Its Influence on Risk of Relapse/Recurrence: Immortal and Neglected Time Bias

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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. 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. The Cox proportional hazards model produced a risk ratio of 1.58 (95% confidence interval: 1.02, 2.45) for method 1, suggesting a higher risk of relapse/recurrence for early discontinuers. In method 2, a statistically nonsignificant risk ratio of 0.77 (95% confidence interval: 0.49, 1.21) was produced, indicating no difference in risk of relapse/recurrence. 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.

antidepressant agents; bias (epidemiology); depressive disorder; pharmacoepidemiology; recurrence

Abbreviation: DNSGP-2, Second Dutch National Survey of General Practice.

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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 3 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: 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 Melfi et al.’s. Although there are obvious methodological flaws in the method used to define exposure and measure follow-up, Melfi et al.’s results 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.

MATERIALS AND 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 = 6,891). 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 = 5,253). The study population included only antidepressant drug users who did not use antidepressant drugs during the 6 months prior to the start date (n = 2,070). 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 2 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 4 antidepressant prescriptions were dispensed within the 6 months following the start date. Antidepressant drug users who received at least 4 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 4 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-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, 2 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 drug 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, 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 (standard deviation, 4.7). The mean follow-up time for the study population was 17.7 months (standard deviation, 1.0). All antidepressant drug users were registered in the DNSGP-2 database during the 6-month pretreatment period.

The antidepressant drug users were divided into 255 early discontinuers (35.3%), who received fewer than
4 antidepressant 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 4 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.

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% confidence interval: 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% confidence interval: 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 2 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 2 methods can be explained by 2 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

<table>
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<tr>
<th>Table 1. Characteristics of the Study Population (N = 722) on the Start Date of Antidepressant Drug Treatment, the Second Dutch National Survey of General Practice, The Netherlands, 2001</th>
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<tbody>
<tr>
<td>No.</td>
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<tr>
<td>Female gender</td>
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<tr>
<td>Age, years</td>
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<tr>
<td>Antidepressant drug</td>
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<td>Selective serotonin reuptake inhibitor</td>
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<td>Tricyclic antidepressant</td>
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<tr>
<td>Other</td>
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<tr>
<td>Type of prescriber (start date)</td>
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<tr>
<td>General practitioner</td>
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<tr>
<td>Specialist/other/unknown</td>
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<td>No. of antidepressants dispensed 12 months after the start date</td>
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Abbreviation: SD, standard deviation.

*Includes moclobemide, mianserin, trazodone, mirtazapine, and venlafaxine.
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 2 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 4 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, Melfi et al.’s (2) exposure definition 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 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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