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ORIGINAL REPORT

Assigning exposure duration to single prescriptions by use of the waiting time distribution†

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ABSTRACT

Purpose The purpose of this study is to develop and present a method to calculate which exposure duration should be assigned to single prescriptions for use in databases where information on expected duration is not recorded.

Methods We propose a method, based on the waiting time distribution (WTD), which estimates how frequently prevalent users redeem new prescriptions. However, we added two steps to the WTD-approach. First, we excluded incident users, representing noise in the analysis. Second, we calculated the cumulative percentage of users that had presented themselves after a given number of days. Using a cutoff value of 80%, we thus calculated the number of days for the majority of prevalent users to present themselves, that is, the exposure duration that should be assigned to the single prescription. The primary strength of the method is that it can be applied in a standardized fashion and that it does not require information on dosage instructions. The primary weakness of the method is that it is only usable on drugs with predominantly chronic use patterns. The method was tested using four model drugs: bendroflumethiazide, warfarin, levothyroxine, and non-steroidal anti-inflammatory drugs (NSAIDs).

Results We found exposure period estimates of 92, 86, 69, and 210 days for bendroflumethiazide, levothyroxine, warfarin, and NSAIDs prescriptions, respectively. NSAIDs were found not to comply with the requirements of the method. The calculated number of exposed days was only slightly influenced by the assumptions of the method.

Conclusions The method provides a useful approach to generate automated estimates of exposure duration that should be assigned to each prescription. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—pharmacoepidemiology; methods; registries; drug prescriptions; drug utilization

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INTRODUCTION

Constructing treatment episodes from individual users' prescription data is one of the key elements in almost any pharmacoepidemiological endeavor, for example, analyzing persistence,[1] incidence,[2] compliance,[3] drug survival,[4] or when assigning exposure in studies of drug effects. One of the core problems is that nearly all drugs in common use can be taken either indefinitely or episodically by the individual patient. The resulting treatment episodes may depend critically on which prescription are deemed as belonging to the same episode.[1] The usual approach is to assign a period of exposure to each prescription and then decide which prescriptions belong to the same episode.[5] However, information on prescribed dosage or refill instructions is often not recorded in the drug registries used, for example, as seen in the Nordic drug registries.[6] A direct assessment of the duration of each prescription is therefore not possible, and assumptions need to be made. This usually implies taking account of the dispensed amount and the assumed dosage (often unknown) and then assigning a grace period to each prescription, depending on assumptions about, for example, non-compliance, stockpiling, or changes in dosage. This can, depending on the clinical context, become very complicated, and if the clinical assumptions, for example, regarding daily dose, are incorrect, it might affect the validity of the study.

We here present a simple method to assign treatment episodes to prescription data, based on the waiting-time distribution.[7,8] It does not require assumptions about the used dosages and may be applicable to a variety of drugs with different utilization pattern.

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†The data used for the article has not been used previously for any other kind of presentation and no related articles have been submitted to either Pharmacoepidemiology and Drug Safety or other journals.

METHODS

Setting

We used data from Odense PharmacoEpidemiological Database (OPED).[9] In brief, OPED is a research prescription database with full coverage of all redeemed and reimbursed prescriptions in the Region of Southern Denmark (1.2 million inhabitants). Drugs that are not qualified for re-imbursement (a.o., oral contraceptives, hypnotics, sedatives, dieting products, certain antibiotics, and drugs obtained over-the-counter) are not recorded. Among the data included are unique identifiers of the patient, the pharmacy and the prescriber, a full account of the dispensed product and the date of dispensing. The indication, dosage, and refill instruction are not recorded. The product is among other things described in terms of the defined daily dose and the hierarchical anatomical-therapeutic-chemical (ATC) code developed by the WHO for drug utilization studies.[10] OPED also contains a demographic module with information on residency, migration, births, and deaths.

To illustrate the proposed method, we extracted all prescriptions redeemed between 1 January 2007 and 31 December 2010 for the following drugs: bendroflumethiazid (ATC C03AA01), warfarin (B01AA03), non-steroidal anti-inflammatory drugs (NSAIDs; M01A excluding M01AX) and levothyroxine (H03AA01). In Denmark, no upper limit exists for the amount of drug that can be prescribed per prescription.

Waiting time distribution

The waiting time distribution (WTD) was first proposed in 1997 by Hallas *et al*.[7] It essentially asks the question of when users of a particular drug will first appear inside a time window, when all information outside the time window is disregarded. In brief, the method is used as follows: for a given drug and a given time window, for example, a calendar year, the first prescription redeemed within this time window is identified for each user of the particular drug. Users are then grouped according to which part of the time window they first appeared in, for example, using monthly or weekly intervals. Figure 1A shows a stylistic example of a WTD for bendroflumethiazide. Here, we have highlighted the two principal components of the WTD: The white area represents persons who were users at the beginning of the time window, whereas the shaded area represents new, incident users. From the first half of Figure 1A, we see that most prevalent users present themselves within the first 4 months of the time window. As there are very few chronic users who will redeem prescriptions with larger intervals than 4 months, nearly all prevalent users will be captured within this interval. From the last half of Figure 1A, we see that there is a steady influx of incident users of approximately 100 users/month.

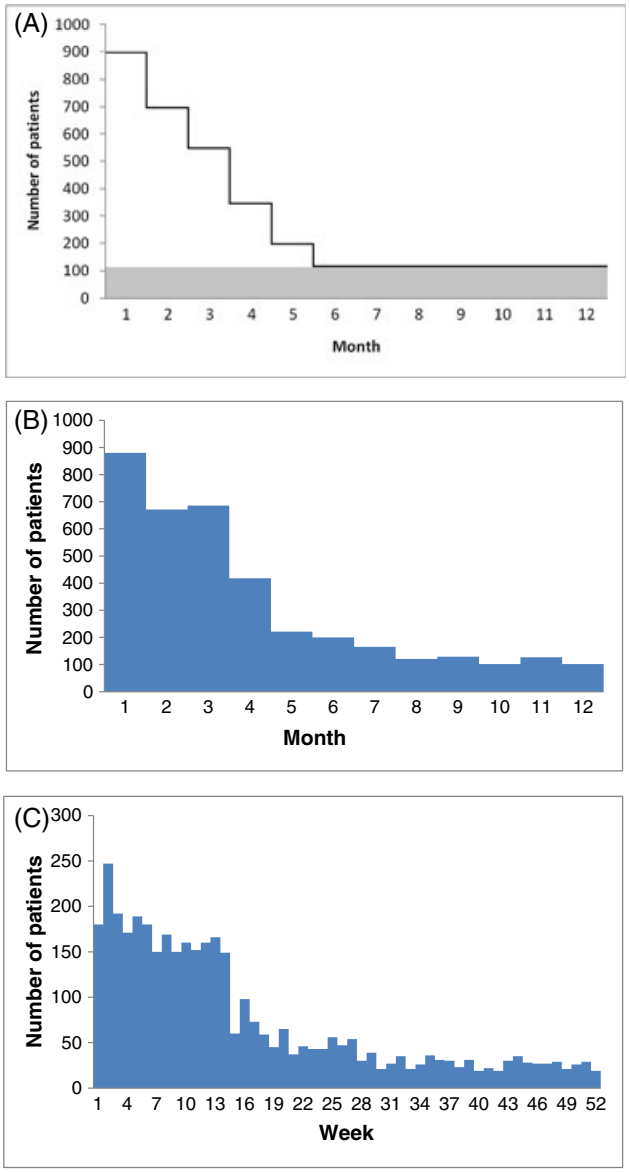

Figure 1. Three waiting time distributions (WTDs) for bendroflumethiazide (ATC, C03AA01) and the time window 2009. (A) A stylistic representation showing the two theoretical principal components of the WTD. The gray area represents incident users, the white area represents users who were prevalent at the beginning of the time window. (B) The actual WTD created from Odense PharmacoEpidemiological Database (OPED), using monthly intervals. (C) The actual WTD created from OPED, using weekly intervals

Application of the WTD

The WTD allows assessment of utilization parameters as point prevalence, incidence rate, relapse rate,

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prescription renewal rate and seasonality.[7,8,11] These parameters will not be further discussed in this paper. However, as explained earlier, the WTD estimates the "amount of time one has to wait for drug users to appear." In other words, we can estimate how frequently prevalent users redeem new prescriptions, expressed as a maximum length of the interval between prescriptions. For databases that do not contain information allowing a direct assessment of the expected duration for the single prescription, this feature can be used to produce an overall estimate of duration per prescription.

In the example given in Figure 1B, showing an interval of four months, we conclude that most prevalent users of bendroflumethiazide will redeem their next prescription within 4 months of a given prescription. In effect, we have thereby estimated the duration that we should assign to the single prescription: 4 months. Using weekly intervals (Figure 1C), we get a more accurate estimate of 14 weeks.

This useful feature of the WTD has been used in several analyses, for example, assigning exposure duration to prescriptions for vitamin K antagonists.[12] Each prescription is assigned an exposure period derived from the WTD. If the next prescription occurs within this exposure period, treatment is assumed to be continuous. If it occurs later, it is assumed that treatment has been paused. As the duration is estimated as a maximum interval between prescriptions, no allowance for overlap should be made and no added grace period is necessary. Furthermore, when assigning the same exposure period to single prescriptions and the last prescription in a treatment episode, we avoid the introduction of bias, as exposure classification is not dependent on future events.[13]

However, using the WTD to calculate exposure periods has two obvious disadvantages. First, the method has an inherent inaccuracy introduced by the manual evaluation of the WTD. In the example given in Figure 1C, this weakness is evident, as one could argue that the exposure period should be set to more than 14 weeks. Second, when using the WTD to assign exposure periods, the incident users, depicted as the shaded area in Figure 1A, represent noise in the analysis, containing no actual information. In fact, when looking at drugs with increasing or decreasing treatment incidences, thereby producing a skewed contribution from incident users, the inclusion of incident users introduces error in the estimation of treatment durations.[7]

Assigning exposure

In the following, we present a method to calculate which exposure periods to assign single prescriptions. The method is based on the aforementioned principle behind the WTD but is free from the two weaknesses explained earlier.

For a given drug, we use 2 years of data. We then create a WTD using the latter year as the time window, classifying users by when they first present themselves during this year. However, contrary to the classical WTD, we do so using daily intervals, and more importantly, we only include users in this WTD if they have redeemed one or more prescriptions for the given drug within the year prior to our time window, that is, the first year of our data. As we hereby disregard incident users, we remove the noise introduced by incident users in the original WTD. In Figure 2A, we show a WTD created using this principle, however grouping by week for simplicity. This graph corresponds to Figure 1C, however excluding the incident users. Using Figure 2A to assign an exposure period, we confirm our estimate of 14 weeks.

We then add another step, to produce a standardized estimation of the duration that should be assigned to each prescription. Using the WTD (Figure 2A), we count the total number of unique users included in our WTD and subsequently calculate the cumulative percentage of users that has presented themselves within a given number of days. This produces a "cumulative WTD graph" fixed into 0% at day 0 and 100% at day 365. Figure 2B shows such a cumulative WTD graph, using the same data as in Figure 2A. The exposure period assigned to the single prescription is read directly from this graph as the number of days (x-value) corresponding to a cumulative percentage (y-value) of 80%, that is, the number of days required for 80% of prevalent users to present themselves. In Figure 2B, this corresponds to an exposure period of 92 days. This value is used as a fixed value for assigning exposure windows to bendroflumethiazide prescriptions.

Testing the method

To test the applicability of the method, we chose four drugs with different utilization patterns: bendroflumethiazide (ATC, C03AA01), levothyroxine (H03AA01), warfarin (B01AA03), and NSAIDs (M01A excluding M01AX). Levothyroxine is almost exclusively used for chronic treatment. Bendroflumethiazide is also mostly used for chronic conditions, but the average duration of treatment is somewhat shorter than for levothyroxine. Warfarin treatment is known to be either chronic or episodic. Last, the NSAIDs are known to have a predominantly sporadic use pattern.

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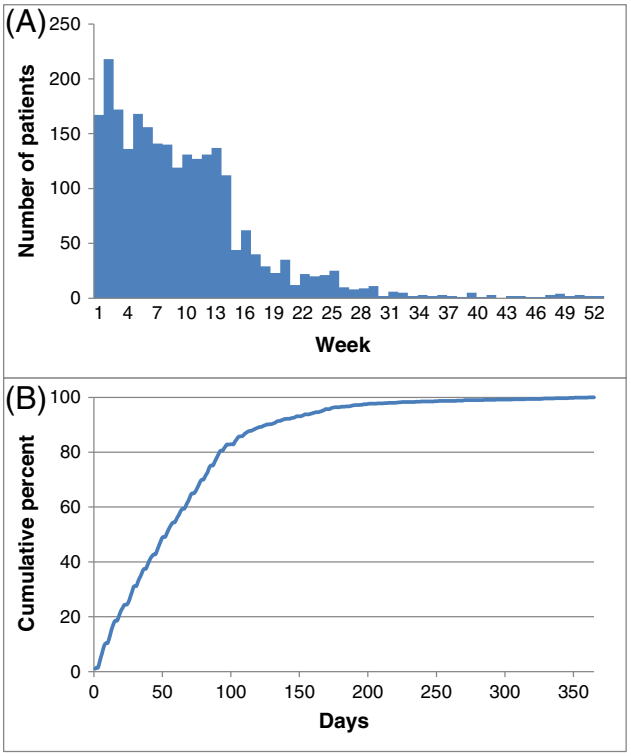

Figure 2. Graphical examples of the alternative use of the waiting time distributions (WTDs). Data represents bendroflumethiazide (ATC, C03AA01) and the time window 2009, however also using data from 2008. (A) WTD for 2009, using weekly intervals. However, users are only included if they had redeemed one or more prescriptions for bendroflumethiazide during 2008. This figure corresponds to Figure 1C excluding incident users. (B) Cumulative percentage of prevalent users (≥1 prescription in 2008) who by a given number of days into the time window of 2009 have presented themselves for the first time

For these four drugs, we attempted to estimate the exposure period that should be assigned to the single prescription, using the method described earlier. We used 2009 as the time window (and 2008 as the run-in year) and a cutoff of the cumulative percentage of users of 80%. To evaluate the sensitivity of the estimates towards choices of cutoff value for cumulative capture of users, we also used other cutoff values ranging from 70% to 90%. For each drug and cutoff value, we further calculated the total number of treatment episodes and total number of treated days in our data material (2007 to 2010). This was carried out by adding the estimated exposure period to each prescription and then, for each subject, creating treatment episodes from overlapping prescriptions, that is, periods with assumed continuous drug treatment.

To test whether we could exclude sporadic users we performed a sensitivity analysis varying the requirement of one prescription during the run-in year to two and three prescriptions respectively.

Ethics

Approval from an Ethics Committee was not required.

RESULTS

We obtained a total of 2 453 785 prescriptions for the four model drugs issued to a total of 470 661 different persons. The number of prescriptions within our primary time window of 2009 was 112 864 for levothyroxine, 12 110 for bendroflumethiazide, 82 164 for warfarin, and 400 709 for NSAIDs.

Using the method explained earlier, with a cutoff of a cumulative percentage of 80%, we calculated exposure period estimates of 92, 86, 69, and 210 days for bendroflumethiazide, levothyroxine, warfarin, and NSAIDs, respectively (Table 1). While the number of unique treatment episodes was found to be highly dependent on the cutoff value used, the exposure period estimate varied somewhat less and the total number of treated days was found to be quite stable across different cutoff values (Table 1).

Requiring two or three prescriptions during the run-in year had no significant impact on the exposure period estimate (data not shown).

DISCUSSION

We have presented a simple method to estimate the exposure duration that should be assigned to the individual prescription, based on the WTD.

The primary strength of the method is that it is easy to apply and that it can be applied in a standardized fashion. Furthermore, the method does not require information on dosage or refill instructions. Lastly, the data-driven approach secures an estimate that is valid within the cohort of subjects under study. These latter two strengths distinguish the method from algorithms based on assumptions about dosages, for example, that the patient should take one defined daily dose,[10] which easily leads to erroneous estimates if these assumptions are wrong.

The weaknesses of the method are that it does not take into account characteristics within the individual subjects (e.g., patterns of use) or the amount of drug that is dispensed with each prescription. Here, one can use the initial segment of the cumulative WTD for guidance: If this is linear, it suggests that assigning a uniform exposure period to prescriptions is appropriate. Furthermore, the method is only applicable to drugs that have a predominantly chronic use pattern. Drugs used on a short-term basis would have a WTD dominated by recurring users, thereby causing the

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Table 1. Estimated exposure duration for prescriptions for bendroflumethiazide, levothyroxine, warfarin, and NSAIDs, using cutoff values ranging from 70% to 90%, including the derived values for the total number of treatment episodes and the number of days considered to be exposed in the complete material (2007–2010). Index values were calculated relative to the estimate produced using an 80% cutoff value. Exposure duration was estimated using prescriptions obtained within 2009

Drug	Cutoff (%)	Estimated exposure duration for one prescription (days)	Index (exposure duration)	Number of episodes	Index (number of episodes)	Number of days	Index (number of days)
Warfarin	70	54	78	181 758	143	14 757 976	88
	72.5	56	81	169 509	134	15 093 755	90
	75	61	88	152 525	120	15 843 766	94
	77.5	63	91	143 796	113	16 120 568	96
	80	**69**	**100**	**126 797**	**100**	**16 863 993**	**100**
	82.5	74	107	112 489	89	17 396 282	103
	85	81	117	97 984	77	18 041 354	107
	87.5	88	128	84 303	67	18 583 123	110
	90	96	139	72 845	58	19 098 262	113
Bendroflumethiazide	70	81	88	28 300	113	2 822 599	91
	72.5	83	90	27 885	112	2 877 983	93
	75	86	93	26 989	108	2 958 869	95
	77.5	90	98	25 936	104	3 062 740	98
	80	**92**	**100**	**25 019**	**100**	**3 112 621**	**100**
	82.5	97	105	22 840	91	3 229 631	104
	85	105	114	17 187	69	3 382 425	109
	87.5	113	123	14 313	57	3 499 579	112
	90	126	137	12 087	48	3 651 947	117
Levothyroxine	70	70	81	224 380	122	21 826 241	88
	72.5	74	86	214 583	117	22 636 852	91
	75	77	90	206 451	112	23 219 292	94
	77.5	82	95	195 639	106	24 135 136	97
	80	**86**	**100**	**184 102**	**100**	**24 821 778**	**100**
	82.5	90	105	174 599	95	25 465 318	103
	85	95	110	158 817	86	26 201 755	106
	87.5	104	121	116 534	63	27 269 706	110
	90	113	131	88 646	48	27 997 572	113
NSAIDs	70	158	75	693 023	109	148 305 938	84
	72.5	168	80	679 604	107	154 094 524	87
	75	180	86	666 089	105	160 821 950	91
	77.5	193	92	652 137	103	167 858 807	95
	80	**210**	**100**	**635 380**	**100**	**176 690 483**	**100**
	82.5	228	109	620 498	98	185 623 446	105
	85	243	116	609 010	96	192 772 131	109
	87.5	259	123	597 756	94	200 118 980	113
	90	278	132	586 225	92	208 502 046	118

cumulative WTD to be flat. For this reason, the estimate based on the 80% limit should be less than 180 days. When looking at the four drugs, we thus confirm that the method is not applicable to NSAIDs, as this drug is known to have a use pattern dominated by recurrent use and as the estimated treatment duration exceeds 180 days.

To secure the best exposure-duration estimate, the method should be applied within the subjects under study in the cohort or case–control study where the estimate is to be used. For example, in a study of the weak opioid tramadol as a cause of over-anticoagulation among patients treated with vitamin K antagonists,[12] it would be wrong to use the entire population's tramadol prescriptions to produce an estimate of the exposure period, as this estimate could be influenced by, for example, younger subjects using tramadol for minor injuries. Instead, the tramadol users included in the estimate of the exposure period might be restricted to the age and gender distribution of the subjects under study, or the estimate should be calculated directly within this cohort. This could, for added precision, be taken even further, and different estimates could be calculated within different subgroups in the study, such as within strata of age or sex.

As seen from Table 1, the different cutoff values have limited influence on the total number of exposed days in our data material. Even extreme cutoff values for cumulative WTD such as 70% or 90% changed the exposure index by as little as 9–17%. The stability of the exposure index around the cutoff value of 80% along with the break on the curves in Figure 3 seen

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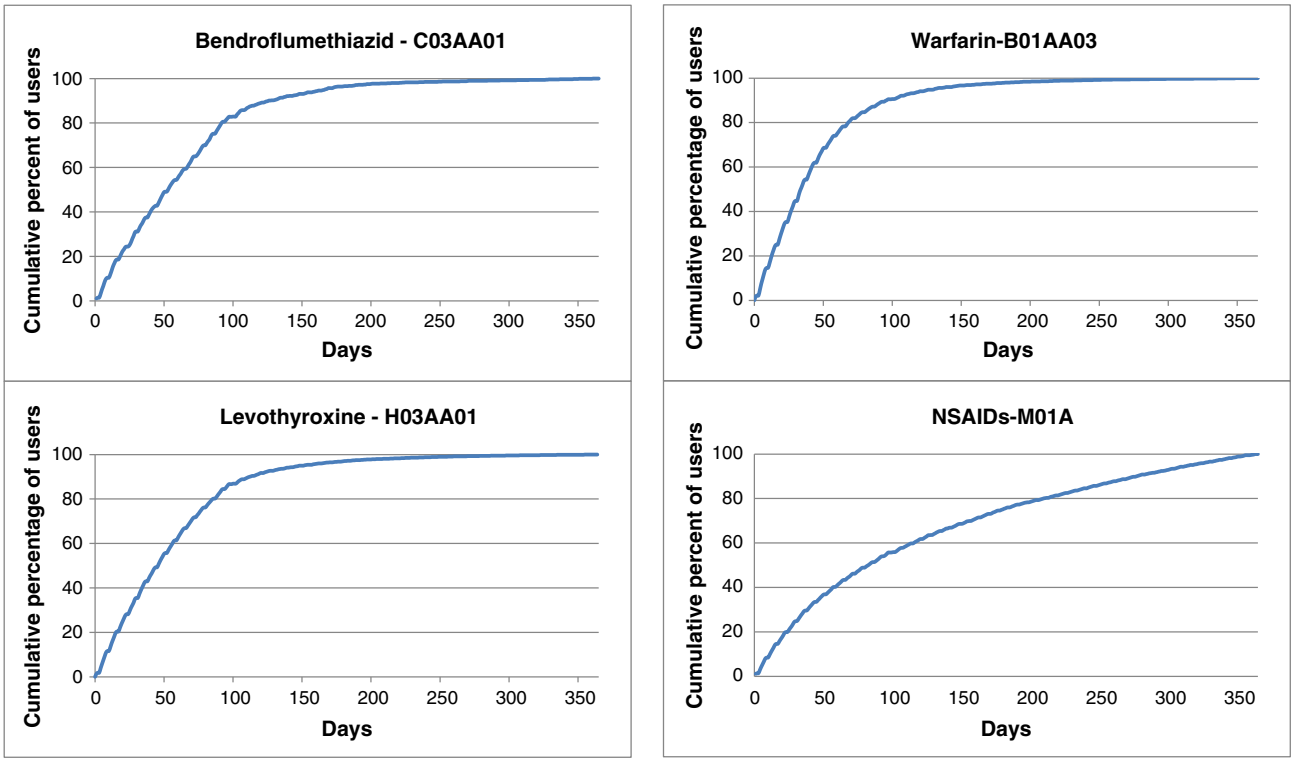

Figure 3. Cumulative percentage of prevalent users (≥1 prescription in 2008) who by a given number of days into the time window of 2009 have presented themselves for the first time, for the four model drugs. The cutoff of a cumulative percentage of 80% was 92, 86, 69, and 210 days for bendroflumethiazide, levothyroxine, warfarin, and NSAIDs, respectively

around 80% is the main reason for choosing this cutoff value, although other cutoff values can also meaningfully be used. Changes in the estimated duration of the single prescription mostly influence the amount of overlap between prescriptions, which is disregarded when constructing treatment episodes. On the other hand, the number of treatment episodes (corresponding to the number of treatment "breaks") is highly dependent on the cutoff value. This demonstrates that the calculated estimates are not usable for drug-survival analysis and underlines the need for adding a sufficient grace period to each prescription in such studies.[1,4]

Although the method was conceptualized as a means to calculate cumulative duration of exposure, the method can also be used to asses if a subject is exposed at any given day, by deciding whether the index date falls within the exposure period of the last prescription. The robustness of this approach can be visualized from Table 1, as the stable index for the number of days not only represents the total number of exposed days but also the likelihood that a given day among users of the drug is considered exposed. Thus, the WTD approach would be useful for situations where the relevant exposure is either current use (e.g., in a study on antithrombotics and bleeding) or cumulative exposure time (e.g., in a study of the link between chronic warfarin use and cancer risk). Cautious interpretation is advised when looking at exposure windows that are likely to influence drug use, such as the first trimester of a pregnancy, where the woman is likely to abruptly cease treatment. In these cases, individualized exposure algorithms should be developed.

In conclusion, we suggest that this method be used to calculate automated estimates of exposure duration that should be assigned to each prescription when estimating cumulative exposure duration in pharmacoepidemiological research.

CONFLICT OF INTEREST

Jesper Hallas has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, Nycomed, Astellas, and Alkabello with grants paid to the institution where he was employed. He has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers and from Nycomed, Astellas, Pfizer, Novartis, Astra Zeneca, Menarini, Leo Pharmaceuticals, and Ferring. Anton Pottegård declares that he has no conflicts of interest.

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KEY POINTS

- We propose a simple method to calculate the exposure duration that should be assigned to single prescriptions.
- The method was tested and found to be only slightly affected by choices in the assumptions.
- The method is easy to apply and does not require information on dosage instructions.
- The method is only usable for drugs with a predominantly chronic use pattern.

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