

Estimating medication stopping fraction and real-time prevalence of drug use in pharmaco-epidemiologic databases. An application of the reverse waiting time distribution

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ABSTRACT

Purpose To introduce the reverse waiting time distribution (WTD) and show how it can be used to estimate stopping fractions and real-time prevalence of treatment in pharmacoepidemiological studies.

Methods The reverse WTD is the distribution of time from the last dispensed prescription of each patient within a time window to the end of it. It is a mirrored version of the ordinary WTD, which considers the first dispensed prescription of patients within a time window. Based on renewal process theory, the reverse WTD can be analyzed as an ordinary WTD with maximum likelihood estimation. Based on Danish prescription data for NSAIDs, warfarin, bendroflumethiazide and levothyroxine in the years 2013 and 2014, we compared estimates from the reverse WTD to those of the ordinary WTD regarding prevalence, stopping fractions and the 80th percentiles of the inter-arrival distributions.

Results The fraction of all users in 2013 stopping treatment varied from 73.1% (NSAID) to 9.3% (levothyroxine). Comparing prevalence estimates of the reverse WTD at the end of 2013 with those of the ordinary WTD at the start of 2014, relative differences did not exceed 4.8%. For the estimated 80th percentiles of the inter-arrival distribution, differences did not exceed 3.3%.

Conclusions The reverse WTD allows estimation of the aggregated fraction of users stopping treatment and prevalence, especially when the WTD reliably separates current users from users who have stopped treatment. It may replace ad-hoc decision rules for automated implementations, and it yields estimates of real-time prevalence. Copyright © 2017 John Wiley & Sons, Ltd.

KEY WORDS—treatment stopping; prevalence; waiting time distribution; maximum likelihood; parametric modeling; pharmacoepidemiology

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INTRODUCTION

The ordinary waiting time distribution (WTD) arises as the distribution of patients' first redemption of a prescription within a time window after an index date, e.g., it addresses a question like "For all persons who redeemed a prescription in 2015, when did they do so for the first time in 2015?". As described by Hallas *et al.* in 1997, the distribution consists of two components corresponding to users prevalent at the index date and incident users, respectively.¹ The prevalent component is a decreasing distribution located at the beginning of the time window, which reflects that prevalent users will renew their prescription

within a rather short period after the index date. By contrast, incident users will tend to have their first prescription redemption occurring uniformly within the time window, the incident component. Based on the difference in shape, the WTD allows estimation of the incidence rate and the prevalence at the index date without having to use a run-in period or define a decision rule for prescription durations.^{1,2} In fact, we recently showed how the parametric WTD can estimate percentiles of the inter-arrival distribution, which allows automated and valid definitions of prescription durations based solely on the timing of prescriptions.³ This is useful in settings where durations of prescriptions are not recorded or are known to be unreliable.

Although useful, the ordinary (forward) WTD approach requires substantial follow-up after the index date to allow reliable separation of the two components of the distribution, i.e., the declining forward recurrence density (FRD) of users prevalent at the index date and

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the constant density of incident users.² As a consequence, the method cannot be used to study prevalence in real time, as one has to wait for a completed time window, typically one year, before prevalence can be estimated. In addition, the method only provides estimates of the incidence rate and prevalence, but not the stopping rate. When interpreting changes over time in prevalence, it is crucial to have estimates on patients initiating treatment as well as patients stopping treatment to reveal the dynamics underlying the changes in prevalence.^{4,5}

In this paper, we suggest to use the reverse WTD to overcome both shortcomings of the ordinary WTD. The reverse WTD is defined by mirroring in time the definition of the ordinary WTD. In other words, instead of considering time until first prescription redemption within a time window, we consider time from the patient's last prescription redemption within a time window to the end of the time window, the reverse waiting times (Figure 1).

According to renewal process theory, the reverse waiting times for users prevalent at the end of the time window will follow a so-called backward recurrence distribution (BRD), which is mathematically identical to the forward recurrence distribution (FRD) governing the waiting times of the same prevalent users to their next prescription in the subsequent time interval. As it is the FRD, which is modeled as the prevalent component in the ordinary WTD, the ordinary and reverse WTD will be similar with regard to the prevalent component. Further, if we assume constant stopping rates, the incidence component of the ordinary WTD will be mimicked in the reverse

WTD by a stopping component. This represents waiting times for patients not prevalent at the end of the time interval, because they have stopped treatment after their last prescription in the interval. As such, if we assume the incidence and stopping rate to be constant, the reverse WTD will have the same shape, albeit mirrored, as the ordinary WTD. It follows directly that the reverse WTD can therefore be estimated using the same statistical model and estimation procedure as the ordinary WTD.

In this paper, we introduce the reverse WTD and show how it may be used to estimate stopping fractions of medication use and prevalence at the end of a time window. We first provide basic formulas based on renewal process theory from which we demonstrate how maximum likelihood estimates for the reverse WTD can be obtained similarly to the ordinary WTD. Further, we consider what parameters can be estimated both by the reverse and the ordinary WTD, because this allows evaluation of the reverse WTD by comparison of its estimates to the corresponding estimates obtained from the ordinary WTD. We also describe how prevalence at the end of a year can be estimated by the prevalence at the end of the previous year plus the difference in incidence and stopping during the year—this offers a further evaluation of the consistency of the two types of WTDs. All analyses are based on Danish data for the four drugs NSAIDs, warfarin, bendroflumethiazide and levothyroxine, respectively, which have been chosen to represent distinctly different usage patterns.

METHODS

In pharmacoepidemiologic databases, we for each patient record a sequence of prescription redemptions over time. For a single patient, we can label the time of redemptions as occurring at T_1, T_2, \dots . Further, we can consider the distance in time between subsequent redemptions and label these by $D_i = T_{i+1} - T_i$, i.e., the time from prescription redemption i to the next, $(i+1)$. If we assume that the distributions of the inter-arrival times, D_i , are independent of each other and that they follow the continuous distribution F , then the redemption times T_1, T_2, \dots form a renewal process. Associated with the distribution F is the density function f , which in this context is known as the inter-arrival density, and the mean, M , which is the average time from one prescription redemption to the next. Let us next assume that the first prescription redemption of the patient occurred at a random point in time before t_0 . The time from the last redemption, T_i ,

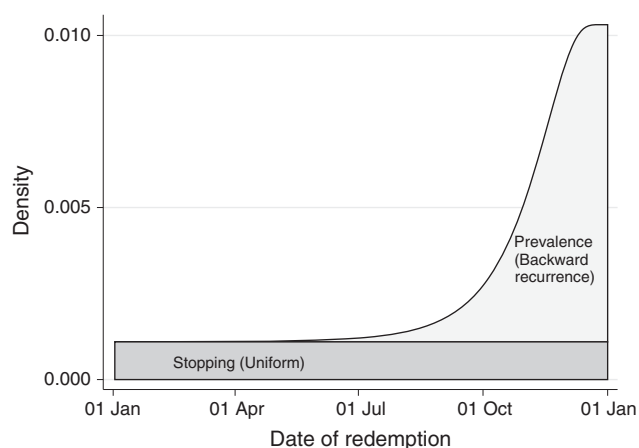


Figure 1. Theoretical reverse waiting time distribution over a 1-year interval—the density of last prescription redemptions for each patient over the year. The constant level at the left tail corresponds to patients stopping treatment, whereas the component rising up on the right corresponds to prevalent patients that remain in treatment at the end of the year

occurring before the interception point t_0 , until t_0 is then a so-called backward recurrence time, formally defined as $R = t_0 - \max(T_i | T_i < t_0)$. The distribution of R is characterized by the following density function

$$g(r) = \frac{1 - F(r)}{M}$$

The shape of this backward recurrence density (BRD) is a consequence of length biased sampling (i.e., that longer intervals between redemptions have a proportionately higher probability of being sampled), and that the interception point will be uniformly distributed on the intercepted interval. The density g is mathematically identical with the density for the corresponding forward recurrence times, $Y = \min(T_i | T_i > t_0) - t_0$, whenever the T_i s form a renewal process.

When we observe all last redemptions of individual patients within the time window (t_{-1}, t_0) , the distances from their last redemptions to t_0 , the reverse waiting times, will for users prevalent at t_0 follow the BRD. By contrast, for users stopping treatment after their last redemption in the interval, the reverse waiting times will follow a uniform distribution on (t_{-1}, t_0) if we assume the population size and the stopping rate to be constant during the observation window. If we let η denote the proportion of prevalent users at t_0 among all with a redemption in (t_{-1}, t_0) , then $1 - \eta$ will be the proportion of users who have stopped treatment after their last redemption in the time window and before t_0 . Based on this, we can write the likelihood contribution for a single observed reverse waiting time r as

$$L(r; \eta, \theta) = \eta \cdot g(r; \theta) + \frac{1 - \eta}{\delta}$$

where η is the fraction of prevalent users among the observed users in the observation window; δ is the width of the observation window, $t_0 - t_{-1}$; and $g(r; \theta)$ is the BRD for prevalent users, which depends on parameters θ . This is identical to the previous formulation for the ordinary WTD, except that the uniform part now corresponds to stopping, and not incidence.³ Note that as η is the fraction of prevalent users, $(1 - \eta)$ is the fraction of users stopping treatment. The two components of the likelihood can be estimated provided that the time window is sufficiently long to ensure that the BRD is essentially zero for $r \geq \delta$.²

Also, in line with our previous paper, we consider two parametric distributions for the BRD, Log-Normal and Weibull, which are parameterized as follows³:

(1) Log-Normal BRD:

$$g(r) = \frac{1}{M} \Phi\left(\frac{\log r - \mu}{\sigma}\right)$$

where Φ is the cumulative standard normal distribution function and M is the inter-arrival mean given by

$$M = \exp\left(\mu + \frac{\sigma^2}{2}\right)$$

(2) Weibull BRD:

$$g(r) = \frac{1}{M} \exp(-(\beta \cdot r)^\alpha)$$

where M is the corresponding inter-arrival mean given by

$$M = \frac{1}{\beta} \Gamma\left(1 + \frac{1}{\alpha}\right)$$

and where Γ is the Gamma function defined by $\Gamma(s) = \int_0^\infty x^{s-1} e^{-x} dx$.

To improve convergence and stability of the maximum likelihood estimation procedure, we log-transformed the parameters σ , α and β , as they are required to be larger than zero by definition, and we logit-transformed η as it is a probability. This is similar to a previous implementation of estimation for the parametric WTD.²

Note that above we have defined r such that it is positive, because this makes the likelihood contributions have the same form as the ordinary WTD. When plotting the reverse WTD, it is however more intuitive to plot it with $-r$ as the time scale, because this will have the same direction as the ordinary calendar time.

Application

We analyze the same four model drugs as Pottegård and Hallas (2013) and Støvring *et al.* (2016): NSAIDs, warfarin, bendroflumethiazide and levothyroxine.^{3,6} Data were obtained for the Region of Southern Denmark (1.2 million inhabitants) where prescription redemptions are captured in Odense PharmacoEpidemiological Database (OPED).⁷ For each of the drugs, we analyze two samples corresponding to the calendar years 2013 and 2014. The indication and dosage instruction are not recorded in OPED, and thus it is not observed when patients actually stop treatment. This is even more so, because

in Denmark, no formal upper limit exists for the amount of a drug which can be prescribed in a single prescription.

In our applications of the reverse WTD, our primary aim was to evaluate it against the ordinary WTD. First, we considered the two adjacent calendar years, 2013 and 2014, where we applied the reverse WTD to time from last prescription redemptions observed in 2013 to the end of that year, and the ordinary WTD to time from start of the year 2014 to first prescription redemptions observed in that year. In theory, both WTDs should then estimate the same prevalence on the night between 31 December 2013 and 1 January 2014. Further, the estimated BRD and FRD for each of the two calendar years should coincide (be mirrored), if the intercepted process of prevalent patients' redemptions can be considered a stable renewal process at the index time t_0 . Specifically, this would imply that estimated percentiles of the inter-arrival density should be the same, and we therefore estimated the 80th percentile of the inter-arrival density based on both the BRD and the FRD.

In a second evaluation approach, we analyzed data from the year 2014, both with the ordinary WTD and the reverse WTD. The change in prevalence from the end of year 2013 (estimated above) to the end of 2014 should theoretically correspond to the difference between the absolute number of incident users in 2014, as estimated by the ordinary WTD, and the number of users stopping treatment in 2014, as estimated by the reverse WTD. To examine this, we estimated the number of prevalent users at the end of 2014 as the number of prevalent users at the end of the previous year plus the number of incident users during the year minus the number of users stopping treatment during the year. This estimate was then compared with the estimate of prevalent users at the end of 2014 obtained from application of the reverse WTD to data from 2014.

When comparing estimates (number of prevalent users, percentiles of the inter-arrival density) from the ordinary WTD and the reverse WTD, we reported the relative difference in percent with respect to the average of the two estimates.

From diagnostic plots, we concluded that the Log-Normal distribution provided a better fit to the data than the Weibull BRD, although differences were generally small (see Figures A1–A4 in the Appendix). We therefore only report estimates for the Log-Normal distribution, but estimates based on the Weibull distribution are presented in the Appendix. All four medications exhibited a nearly constant stopping rate

in the empirical WTD and the source population for OPED had virtually identical size in 2013 and 2014 with an increase of 0.36% from 1 January 2013 to 1 January 2015.

All statistical analyses were conducted in Stata 14.1.⁸ A dedicated software package (`wtdttt`) implementing the method is provided at the IDEAS repository (<http://ideas.repec.org>) and may be installed in Stata using a search for the package name, i.e., `-search wtdttt, all-`.

RESULTS

When we used the reverse WTD to estimate stopping fractions during 2013, we found large variations in the fraction of users stopping treatment, with a stopping fraction of 9.3% for levothyroxine and 73.1% for NSAIDs (Table 1). The absolute number of prevalent users at the end of 2013 estimated by the reverse WTD and at the start of 2014 estimated with the ordinary WTD were very similar (Table 1). For warfarin and levothyroxine, the relative difference did not exceed 1.5%, whereas for NSAIDs and bendroflumethiazide, it was slightly higher at 1.6% and 4.8%, respectively. Using the Weibull distribution, relative differences were consistently larger, although not exceeding 10% in any of the examples. (Appendix, Table A1).

When estimating the 80th percentile of the inter-arrival distribution, relative differences between estimates of the ordinary and the reverse WTD were slightly smaller than for prevalence as they ranged from -2.9% (warfarin) to 5.2% (bendroflumethiazide) (Table 1), and again with smaller differences for the Log-Normal model than for the Weibull model (cf. Table A1).

We saw no systematic direction in differences of prevalence and percentile estimates between the reverse and the ordinary WTD.

The estimated cumulative distributions of the BRD and the FRD were very similar for all four drugs—see Figure 2 for a comparison of the two for warfarin.

The proportion of patients who were prevalent at the end of 2013 relative to the total number of patients with a prescription in 2013 differed substantially between drugs. For NSAIDs, only 28.3% of patients were prevalent at the end of 2013 meaning that 71.7% of all who redeemed at least one NSAID prescription in 2013 stopped their treatment before the end of the year. At the other extreme, more than 90% of all users of levothyroxine during 2013 were prevalent users at the end of the year.

Table 1. Analyses of prescription redemptions in years 2013 and 2014 using a Log-Normal recurrence distribution for the reverse and ordinary WTD, respectively. η is the estimated proportion of prevalent users among all users in the respective year. The number of prevalent users is found as the product $n \cdot \eta$. The 80th percentile is the estimated duration of a prescription in days. Relative differences are found as the difference in estimates from 2013 and 2014 divided by the 2013 estimate. Data from OPED, Southern Denmark

Drug	2013 reverse WTD				2014 ordinary WTD				Relative difference (%)	
	n	η (95%CI)	# of prevalent users ($n \cdot \eta$)	80th percentile (95%CI) (days)	n	η (95%CI)	# of prevalent users ($n \cdot \eta$)	80th percentile (95%CI) (days)	# of prevalent users	80th percentile
NSAID	164 559	0.269 (0.264; 0.274)	44 241	120.5 (118.1; 122.8)	174 692	0.254 (0.249; 0.259)	44 381	124.1 (121.3; 126.9)	0.32	3.01
Warfarin	21 675	0.792 (0.783; 0.802)	17 175	91.6 (90.0; 93.1)	21 696	0.797 (0.788; 0.807)	17 301	91.4 (89.7; 93.0)	0.73	-0.21
Bendroflumethiazide	64 668	0.698 (0.690; 0.706)	45 157	125.3 (123.8; 126.8)	60 770	0.791 (0.784; 0.799)	48 090	131.3 (129.9; 132.7)	6.50	4.80
Levothyroxine	28 883	0.907 (0.907; 0.921)	26 406	115.2 (113.8; 116.6)	29 901	0.871 (0.864; 0.878)	26 046	112.4 (111.0; 113.8)	-1.36	-2.45

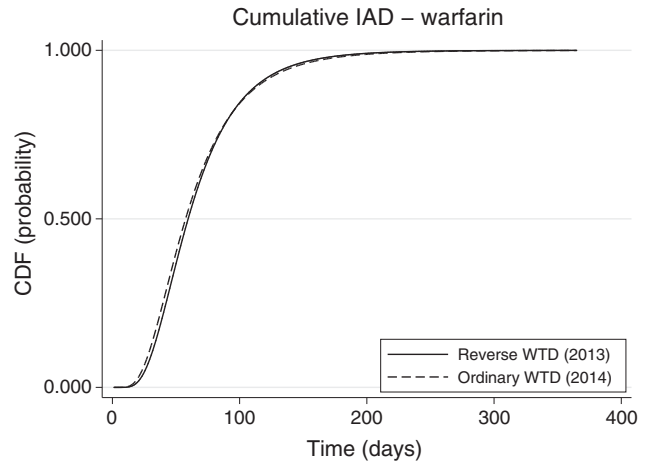


Figure 2. Estimated cumulative distribution function of the inter-arrival times for prescription redemptions of warfarin based on the reverse WTD (data from 2013—full line) or the ordinary WTD (data from 2014—dashed line). The two WTDs were fitted using a Log-Normal backward or forward recurrence distribution, respectively. Data from OPED, Southern Denmark

In the analysis where we used both the ordinary WTD and the reverse WTD on data for 2014, we found that the estimated difference in number of patients starting and stopping treatment fitted well with the estimated difference in the number of prevalent patients at the end of 2013 and 2014 (Table 2). The relative differences between the predicted prevalence at the end of 2014 (prevalence at the end of 2013 plus the difference between incidence and stopping during 2014) and the estimated prevalence at the end of 2014 based on the reverse WTD were in the range -6.3% (bendroflumethiazide) to 1.4% (levothyroxine) (Table 2).

DISCUSSION

As expected from renewal process theory, the reverse WTD gave estimates very similar to those obtained from the ordinary WTD, when applied to adjacent years sharing the same index date. Specifically, when analyzing data from 2013 with the reverse WTD and data from 2014 with the ordinary WTD, the two procedures yielded prevalence estimates, which were almost identical for the four drugs studied (NSAIDs, warfarin, bendroflumethiazide and levothyroxine). Also, with respect to the estimated 80th percentile of the inter-arrival distribution, we found almost identical results. Because the reverse WTD could be used to estimate the number of patients stopping treatment,

Table 2. Ordinary and reverse WTD analyses with a Log-Normal recurrence distribution of prescriptions in 2014 with data from OPEd, Southern Denmark. The comparison targets the difference in estimated prevalence at the end of the year (ultimo) based on the reverse WTD and the corresponding predicted prevalence based on prevalence at the end of the previous year, 2013, plus the difference between incidence and stopping during 2014

Drug	Ordinary WTD				Reverse WTD				Comparison			
	Estimated # of prevalent users—ultimo 2013	n	η	Estimated # of incident users $n \cdot (1 - \eta)$	Estimated # of prevalent users—ultimo 2014 $(n \cdot \eta)$	n	η	Estimated # of stopped users $n \cdot (1 - \eta)$	Increment (inc—stop) *	Increment (prevalence ultimo 2014—ultimo 2013)	Predicted prevalence—ultimo 2014 ***	Relative difference (%)—prevalence ultimo 2014 ***
NSAID	44 241	174 692	0.254	130 311	47 816	174 692	0.273	126 876	3435	3575	47 676	-0.30
Warfarin	17 175	21 696	0.797	4394	17 429	21 696	0.803	4267	128	254	17 303	-0.72
Bendroflume-thiazide	45 157	60 770	0.791	12 680	44 904	60 770	0.739	15 866	-3186	-253	41 971	-6.31
Levothyroxine	26 406	29 901	0.871	3855	27 392	29 901	0.916	2509	1347	987	27 752	1.35

*Difference in estimated number of incident patients minus estimated number of patients stopping treatment during 2014.

**Prevalence ultimo 2013 plus the increment (difference in incidence and stopping) during 2014.

***Computed as the difference in predicted and estimated prevalence ultimo 2014 divided by the estimated prevalence ultimo 2014.

we could estimate end-of-year prevalence from prevalence at the end of the previous year plus the difference between incidence and stopping during the year. Again, we found good overall agreement with the end-of-year prevalence estimate obtained from the reverse WTD. We therefore consider the reverse WTD to provide valid estimates in accordance with the underlying theory based on renewal processes.

We are not aware of other validated methods for estimating prevalence at the end of a time window. For analyzing stopping of treatment, other studies have relied on defined durations of prescriptions although no consensus exist on how best to do so, and with results found to be sensitive to the defined duration.⁹⁻¹¹

A primary justification for considering the reverse WTD is that its' estimates complement those from the ordinary WTD. First, the reverse WTD provides an estimate of the proportion of patients stopping treatment during the study period. When combined with estimates of prevalence and incidence based on the ordinary WTD, this allows a more detailed examination of the driving forces underlying changes in prevalence. Specifically, questions such as "Does prevalence rise primarily because incidence increases or because stopping decreases?" can be answered with the ordinary and reverse WTD. Second, the reverse WTD allows estimation of prevalence in real time. At any given point in time right up until now, the prevalence can be estimated, provided data have been collected in the past for a sufficient length of time such as one year, say. This is in contrast to the ordinary WTD, which requires follow-up after the time point at which prevalence is estimated. In settings where real-time drug surveillance is desired, this is of key interest. The real-time estimated prevalence could therefore be a useful addition to the armament of methods used for drug surveillance.¹²

As the underlying statistical model for the reverse WTD mimics that of the ordinary WTD, although with stopping substituted for incidence and with reversal of the time scale, the main limitations are the same. The time window in which data are accrued for the reverse WTD should have a sufficient length to allow reliable separation of the prevalent and the stopping sub-distributions. Because the estimation method is based on parametric maximum likelihood, the model is sensitive to misspecification. We have however previously shown that with moderate misspecification, estimates are largely unbiased, and more severe misspecification can be detected with

the use of diagnostic plots.^{2,3} This finding is supported by the fact that estimates based on either Log-Normal or Weibull distributions were very similar. Of special interest is whether the assumption of a constant stopping rate is reasonable, and this should in any application be examined using diagnostic plots. In our applications, prevalence estimates of the reverse and ordinary WTD were in agreement for the NSAIDs, although they are used sporadically by a substantial fraction of patients. We are not aware of alternative methods, which have consistently estimated prevalence of a drug with substantial sporadic use without making strong assumptions a priori regarding prescription durations.

While the reverse WTD provides an aggregate estimate of the proportion of patients stopping treatment, it is important to note that it does not provide any insight into reasons for patients stopping treatment. Some patients may die or emigrate, others may not need their medication due to improved health, others again may explicitly or implicitly decide to become non-adherent, while yet others again may switch to another medication type, which will not be captured when studying a single drug. The stopping fraction estimated by the reverse WTD will therefore be the combined measure of all these. Several studies have examined treatment discontinuation and its reasons based on defined durations of individual prescriptions, see for example the illustrative papers by Gichangi *et al.* (2006) and Gardarsdottir *et al.* (2010).^{11,13} The reverse WTD can, as the ordinary WTD, be used to estimate percentiles of the inter-arrival density, which may be used to define treatment gaps. Incorporating reasons for stopping treatment into the reverse WTD could be a future research topic, perhaps with explicit modeling of migration and mortality along the lines used for modeling censoring with the ordinary WTD.²

In conclusion, we suggest that the parametric reverse WTD may be used to estimate stopping fractions of prescription drugs and real-time prevalence, and that this can be used in an automated monitoring of drug use patterns and in pharmacoepidemiological research. Future studies should consider how to incorporate information on migration and mortality to allow decomposition of stopping fractions into its underlying causes.

SPONSORS

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Many pharmacoepidemiological databases do not record information on prescription duration
- Reversing the waiting time distribution (WTD) to consider the last dispensed prescription of each patient before an index time point allows estimation of medication stopping fractions and real-time prevalence
- The parametric reverse WTD allows estimation of interarrival density percentiles as does the ordinary parametric WTD. Estimates of the two methods are virtually identical
- The reverse WTD does not require information on redemptions in a subsequent period and may be automated
- Estimates can be found in Stata using the publicly available `-wtdttt-` package

ETHICS STATEMENT

Approval from an Ethics Committee was not required, according to Danish law.¹⁴

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