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ORIGINAL REPORT

Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method

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ABSTRACT

Purpose Accurate measurement of drug adherence is essential for valid risk-benefit assessments of pharmacologic interventions. To date, measures of drug adherence have almost exclusively been applied for a fixed-time interval and without considering changes over time. However, patients with irregular dosing behaviour commonly have a different prognosis than patients with stable dosing behaviour.
Methods We propose a method, based on the proportion of days covered (PDC) method, to measure time-varying drug adherence and drug dosage using electronic records. We compare a time-fixed PDC method with the time-varying PDC method through detailed examples and through summary statistics of 100 randomly selected patients on statin therapy.
Results We demonstrate that time-varying PDC method better distinguishes an irregularly dosing patient from a stably dosing patient and demonstrate how the time-fixed method can result in a biassed estimate of drug adherence. Furthermore, the time-varying PDC method may be better used to reduce certain types of confounding and misclassification of exposure.
Conclusions The time-varying PDC method may improve longitudinal and time-to-event studies that associate adherence with a clinical outcome or (intervention) studies that seek to describe changes in adherence over time. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—adherence; methods; longitudinal; time dependence; pharmacoepidemiology

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INTRODUCTION

Accurate measurement of drug adherence is essential for valid risk-benefit assessments of pharmacologic interventions.[1–3] Patient adherence has a direct influence on whether the patient receives the prescribed drug dose or whether underdosing or overdosing of prescribed medication occurs. In clinical trials, because of strict protocols, higher levels of adherence are achieved than in observational study designs, which may potentially lead to differences in drug efficacy or safety estimates between these designs.[4–7] Hence, accurate drug adherence measurements are a prerequisite for bridging the gap between biological efficacy estimates from experimental trials on the one hand and clinical effectiveness estimates from observational studies on the other hand.

To date, measures of drug adherence such as the proportion of days covered (PDC) method have almost exclusively been applied for a fixed-time interval and without considering changes over time. Such an application ignores the fact that adherence within patients may vary over time.[8] In a fixed-time interval, a patient that receives the drug irregularly may have the same adherence estimate as a patient that steadily receives the drug in the same time interval, yet the real differences in dosing behaviour may result in a totally different patient prognosis. In other words, using time-constant measures of drug adherence in a fixed-time interval will bias the association between a clinical outcome and drug use. In all, time-constant drug adherence measures are disadvantageous both in studies assessing cumulative incidence ratios and incidence rate ratios.

There is a wide variety of methods to estimate adherence, each with their specific advantages and

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disadvantages.[6,9–13] Methods that use electronic records (e.g. pharmacy records), rather than patient reports or direct observation, have as their advantage that they are noninvasive and can often be used for large numbers of patients over a long time span. Given the fact that in Western countries, chronic diseases are becoming more prevalent, and both preventive and therapeutic drugs are used over a longer period of time and recorded in Big Data health care registries (e.g. [14,15]); methods that use electronic records are indispensable. Of the methods designed for this purpose, the PDC method is most commonly applied (e.g. [16]).

This paper describes an extension of the time-fixed PDC method that enables the estimation of time-varying drug adherence using pharmacy prescription or dispensing records; it illustrates the method and discusses its strengths and limitations. In the Supporting Information, we provide an annotated syntax for the statistical programming language 'R', and we provide a detailed example of the calculation of time-varying dosage.[17]

METHODS

Drug prescription or dispensing records

The extended PDC method is intended to be applied to the data from drug prescription or dispensing records. Initially, data should be ordered such that each row represents a single drug prescription (or dispensed prescription). The information needed to apply the method is represented by variables (columns) in the dataset including a patient identification number (ID), date of dispensing, number of pills dispensed and number of pills per day. Once prescriptions are chronologically ordered, a variable 'prescription number' can be added, which is given value k for the k'th prescription (Figure 1).

Estimating time-varying drug adherence

First, we calculated the length of time in days for each interval ('Interval length' in Figure 1). To stabilize the adherence estimate, an interval is not the length in time between one prescription (k) and the next ($k+1$) but between each prescription k and the date of the second prescription afterwards ($k+2$). Secondly, we calculated the expected number of days covered ('Total days' in Figure 1) by dividing the number of pills dispensed by the pills per day for each row and summing these numbers for rows k and $k+1$. Then, 'adherence' as a proportion (Figure 1) in each row was calculated by dividing the expected number of days covered by the length of time in the interval ('Total days'/'Interval length' in the figure). The adherence value may exceed 1 if the length of the interval is shorter than the expected number of days covered. This may occur if the patient is stockpiling the drugs (e.g. to go on holiday). In the case of stockpiling, we carried over the pills that are in excess of the expected number of days covered to the next interval until no interval has an 'adherence' estimate above 1 (Figure 2). If stockpiling is not possible for the drug in question, for example, if the drug is not chemically stable for a long time, this estimation step

	ID	*Prescription number*	Date (dd-mm-yy)	Pills dispensed	Pills per day	*Interval length*	*Total days*	*Adherence*
1	003011	1	13-01-02	30	1	72	60	0.83
2	003011	2	17-02-02	30	1	73	60	0.82
3	003011	3	26-03-02	30	1	131	60	0.46
4	003011	4	01-05-02	60	2	132	60	0.45
5	003011	5	04-08-02	60	2	56	60	1.07?
6	003011	6	10-09-02	60	2	117	67.5	0.58
7	003011	7	29-09-02	75	2	129	67.5	0.52
8	003011	8	05-01-03	60	2	66	60	0.91
9	003011	9	05-02-03	60	2	?	60	?
10	003011	10	12-03-03	60	2	?	?	?
11	088610	1	27-01-94	30	1			

Figure 1. Electronic records of a patient with irregular dosing behaviour. Rows of pharmacy dispensing records showing patient ID, date of dispensing, number of pills dispensed and pills per day. Interval length, total days and adherence are added later; they are intentionally left blank for the 11th row because that row belongs to a new patient

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	Interval length	Total days	Adherence
4	132	60	0.45
5	56	60 - 4 = 56	1.00
6	117	67.5 + 4 = 71.5	0.61
7	129	67.5	0.52

Figure 2. Incorporating drug stockpiling

should be skipped, and intervals with adherence values above 1 should be set to 1.

When estimating 'adherence' using intervals based on the length of time between prescriptions k and $k+2$, this leaves part of the information of the last two prescriptions unused because the length of time of the interval cannot be established; that is, prescription $k+2$ does not exist when k is the last or next to last prescription. This is not problematic if the final prescriptions take place outside the study period. In other cases, an end point of utilization of the drug can be established by assuming that the last observed adherence value will be continued in the final interval. The length of the last interval will then be the sum of the expected number of days covered by the last and second to last prescription and divided by the last observed adherence value. This represents the length of time that a patient would be able to continue to use the drug if the last observed adherence is continued into the final interval.

Because intervals for adherence calculation are constructed between prescriptions k and $k+2$, two intervals will overlap at most time points. To any time point with such overlapping intervals, we assigned the adherence value from the first of these two intervals.

To calculate adherence over a longer time period (e.g. over 30-day periods), an average adherence over the desired time period can be computed after execution of the previous step.

Finally, patients may switch between drugs over time; if this is not detected, it will lead to erroneous estimates of drug adherence. A patient can be considered to have switched a drug if he or she receives a prescription for one drug, then later in time receives a prescription for a different drug in the same class as the first prescription and does not refill the old prescription.[16] Before calculating drug adherence, switchers should first be identified, and rows of both the old and the new drug can be ordered chronologically as in Figure 1. The calculation of time-varying drug adherence can then proceed as described in this paper.

Comparison between time-constant and time-varying proportion of days covered

In order to empirically test the differences between the time-constant and time-varying PDC measures, we randomly sampled 100 patients which started on statin therapy (anatomical-therapeutic-chemical code C10AA) and whom received dispensings for longer than 1 year from the IADB.nl database. The IADB is a pharmacy dispensing database and is considered representative for the Netherlands.[18] For each patient, we calculated the time-constant PDC measure by dividing the number of days covered in 1 year by 365. The number of days covered in the first year of follow-up was calculated taking into account drug stockpiling and excluding excess pills from prescriptions that carry on into the next person–year of follow-up. The time-varying PDC measure was also calculated over 1 year using the method as described in the previous paragraphs. For each patient, we then compared the time-constant and time-varying PDC measures by subtracting the time-constant PDC value from the time-varying PDC values and removing the sign (i.e. taking the absolute value). Because each patient has multiple time-varying measurements, we then calculated the average absolute difference over the entire year of follow-up.

EXAMPLE APPLICATIONS

Example 1: patient with irregular dosing behaviour

The information in the first five columns of Figure 1 comes from a patient with patient number 003011. This patient had irregular dosing behaviour: in the first 3.5 months, the patient visits the pharmacy about every 30 days to pick up enough pills for a month, then there is a gap in visits of about 3 months, then a short period with more frequent visits, and then once again a three month gap, and finally another set of frequent visits. For this individual, the length of the first interval was 72 days, starting on the 13th of January 2002 (date of first prescription) and ending on 26th of March 2002 (date of third prescription), thereby covering prescription numbers 1 and 2. Both of these prescriptions were dispensings of 30 pills of which 1 should be taken per day. Using the pills dispensed and the pills per day, we calculated the theoretical days covered by the drug in each interval. For the first interval, this was $30/1 + 30/1 = 60$ days. To illustrate how this changes when the number of pills changes, in the sixth interval, this was $60/2 + 75/2 = 67.5$ days. Finally, adherence was calculated by dividing the theoretical days covered by the length of the interval. For the first interval,

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this was 60/72 = 0.83 (rounded down). Stockpiling can be witnessed in the fifth interval; here, the adherence value would exceed one (60/56 = 1.07). Therefore, the four excess days are carried forward to the sixth interval, which, as a consequence, receives the adherence value of (67.5 + 4)/117 = 0.61, representing drug stockpiling (Figure 2). The last adherence value that can be calculated using this algorithm is the one corresponding to the third to last row. Using this adherence value (0.91) and placing it in the second to last row, we can calculate the length of the last interval, which is 60/0.91 = 66 days. The total length in days that we follow this patient is the difference between the first date (13th of January 2002) and the date of the start of the last interval (5th of February 2003), plus 66 days (length of last interval). This is 389 + 66 = 455 days. We then assigned adherence values to each individual day by using the adherence from the interval that ends earliest after that day; therefore, all days from 13th of January 2002 to 26th of March 2002 were assigned an adherence of 0.83 (adherence of the first interval); the days from 27th of March 2002 to 1st of May were assigned an adherence of 0.82 (adherence of the second interval), etc.

Plotting these adherence measures in a graph shows that the method adequately captures the irregular dosing behaviour of the patient; the estimates of adherence fluctuate strongly over the time period (Figure 3). If we had instead made a time-constant PDC estimate of drug adherence over a 1-year time period, we would have counted the total days covered in the first year, noting that from the last dispensing in the first person–year, only eight pills can still be used in this year, we get (30/1*3 + 60/2*3 + 75/2 + 8)/365 = 0.62 (Figure 3). Compared with the information generated by the time-varying adherence method, this number provides very little information about the actual adherence behaviour. Furthermore, the interval stops after 1 year, while the patient continues to receive the drug for about three additional months. Finally, because we also had information on other variables that were measured every 30 days for each patient, we chose to aggregate the adherence measurements to 30-day periods. The first two 30-day periods are in the period 13th of January 2002 to the 13th of March 2002. Because the first interval does not end until the 25th of March 2002, we can simply assign the adherence of the first interval (0.83) to the first two 30-day periods. The third 30-day period goes from the 14th of March to the 12th of April. We, therefore, calculated adherence in this 30-day period as (12*0.83 + 18*0.82)/30 = 0.824. In the fourth period, it became (18*0.82 + 12*0.46)/30 = 0.676, etc. Using 30-day periods has a smoothing effect on the dynamic adherence measurements, but these still provide more detailed information than a time-constant measurement (Figure 3).

Example 2: patient with low intensity dosing behaviour and with regular visits

Contrasting irregular dosing behaviour, consider a patient that is not fully adherent but with a stable regularity of pharmacy visits (Figure 4). The patient started with a lower dose (prescribed one pill per day) for the first 30 days, and afterwards received a dose that should have lasted for 60 days each time, but the patient instead visited approximately every 90 days.

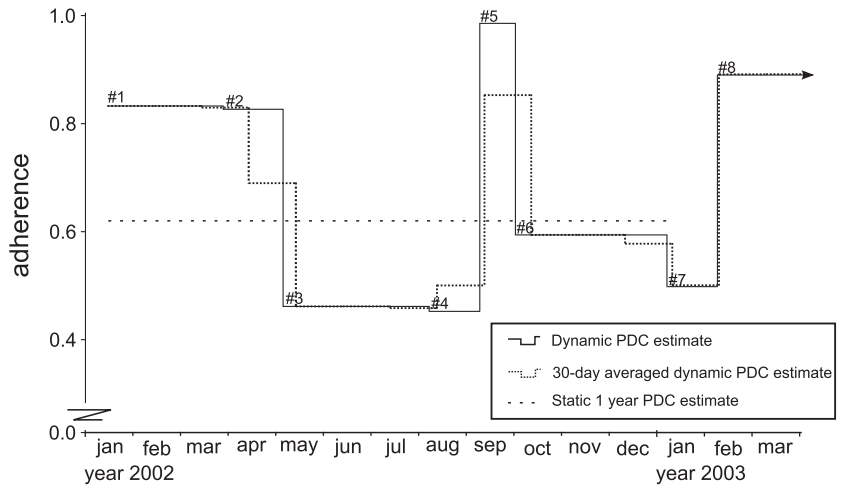

Figure 3. Comparisons of time-varying versus time-constant PDC estimates of drug adherence from a patient with irregular dosing behaviour. Each interval is represented by a horizontal line and labelled by # and its number. Interval #8 continues beyond the displayed range

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	ID	*Prescription number*	Date (dd-mm-yy)	Pills dispensed	Pills per day	*Interval length*	*Total days*	*Adherence*
225	004312	1	07-05-06	30	1	141	90	0.64
226	004312	2	16-06-06	60	1	179	120	0.67
227	004312	3	25-09-06	120	2	183	120	0.66
228	004312	4	12-12-06	120	2	185	120	0.65
229	004312	5	02-03-07	120	2	185	120	0.65
230	004312	6	14-06-07	120	2			

Figure 4. Electronic records of a patient with low adherence and a stable visit pattern

Therefore, approximately (60/90) = 0.66 adherent would be a correct estimate. For this patient, the estimates using the time-varying method are all close together and around 0.66 adherent, correctly showing a stable adherence over time. However, in this example, a time-constant adherence estimate over the 365-day period (1 year) would be biassed upwards. The patient would be calculated as being covered for (30/1 + 60/1 + 3*120/2) = 270 days. Because 270/365 = 0.74, the patient was estimated to be more adherent than in the time-varying estimation. The reason for this is that the final interval that falls within the 365-day range (drugs dispensed in row 5, Figure 4) occurred on the 2nd of March 2007, and pills to last for (120/2) = 60 days were dispensed on that date. Therefore, these pills could be said to have lasted until the 1st of May 2007, while the 365-day period ends on the 7th of May 2007. Therefore, using the logic of time-constant PDC adherence calculation, all of these pills from the last dispensing could be used in this year. The problem with this is that the time-constant method does not take into account the timing between intervals; after the batch picked up on the 2nd of March, the next batch was picked up on the 14th of June; more than 1 month after the 365 time-fixed period ended. In other words, the time-constant method here assumes that the patient was highly adherent between the 2nd of March, and the 7th of May, but looking at the timing between intervals shows that this was unlikely to be true. This second example shows the usefulness of the time-varying method in calculating adherence in dynamically generated intervals.

Time-constant and time-varying proportion of days covered in one hundred statin users

Figure 5 shows the average absolute differences between the time-constant and time-varying estimates for 1 year of follow-up for 100 patients on statin therapy. Out of the 100 patients, 55 had an average difference between 0 and 0.05, 20 had an average difference between 0.05 and 0.15 and 25 had a difference larger than 0.15. In the Supporting Information, we show the adherence trajectories of three exemplary patients, which had a large average difference.

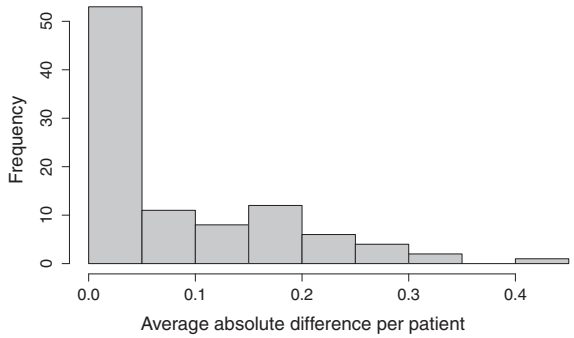

Figure 5. Histogram of average absolute differences between time-constant and time-varying adherence estimates per patient in the first year of follow-up in a sample of 100 patients on statin therapy

DISCUSSION

In this paper, we extended the existing PDC method by allowing it to estimate time-varying adherence. Compared with the time-constant PDC method, we demonstrated that time-varying adherence measures may lead to less-biassed estimates of adherence using two example patients and showed that differences between time-constant and time-varying estimates can differ strongly using data from 100 patients on statin therapy.

Limitations of the time-varying proportion of days covered method

Like any method that uses electronic records, observation of drug utilization by the PDC method is indirect; therefore, its most important limitation is that it is unknown if patients actually take the drugs that are prescribed or dispensed. Nevertheless, these methods are considered a good alternative when direct observation

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of patient adherence is not feasible (e.g. when large sample sizes are desired).[19] Note that the method can also be seen as a direct method of obtaining rather than taking the drug, which has also been shown to predict health outcomes. Furthermore, the method cannot determine adherence when less than three dispensings (or prescriptions) have been recorded, and therefore is not applicable to determine the effect of primary or early nonadherence on an outcome. We have here chosen to make intervals for adherence calculation on the basis of the timing of three dispensings: this choice is a bias variance tradeoff; intervals based on more dispensings will vary less, but as interval size increases, the measure will become more time-constant, and thereby be subjected more to the biases that we have shown to be present in such a measure. The main limitation of the time-varying PDC method is likely the difficulty in estimating adherence for the final interval. We have suggested to continue with the previously observed adherence value, so that the length of the final interval can be determined. However, this assumption may not be realistic, depending on the setting. For example, the assumption is likely valid for patients with stable adherence behaviour, such as the patient from example 2, but may be less correct for patients with erratic adherence behaviour, such as the patient from example 1. Furthermore, for some drugs, a tapering-off period may be indicated by guidelines. In that instance, the period as indicated by the guideline could be substituted, granted that this does not directly interfere with the research objective. A more data-driven alternative would be to model the adherence trajectory based on some number of final observations for each individual patient and to extrapolate that pattern to estimate adherence in the final interval. A similar assumption is in place at the start of the interval but is less apparent because we choose the date of dispensing as the start-date of being covered by the drug, while the true start date is unobserved.

Empirical comparisons

In our analysis of 100 patients on statin therapy, the absolute difference between the time-constant and time-varying estimates could differ strongly. Even seemingly small differences in adherence such as 0.05 may be clinically relevant, and estimates larger than that were observed for nearly half of these patients. We used patients on statin therapy as an example because the drug should be used chronically and has side effects that can result in lower adherence.[20] The differences between estimates from time-constant and time-varying methods may vary per drug and clinical setting. We did not compare our method with a clinical outcome, but other studies have found that time-varying adherence is more strongly associated with clinical outcomes than time-fixed adherence; this was found for adherence to metformin on a glycated haemoglobin (HbA1c), adherence to simvastatin on LDL cholesterol, adherence to antihypertensives on blood pressure and adherence to beta-blockers on heart rate.[21,22]

Medication possession ratio

The (time-constant) PDC method is similar to the medication possession ratio (MPR).[23] The PDC method results in estimates between 0 and 1, while the MPR can exceed 1. It should be possible to extend the MPR into a time-varying method, using a technique similar to the one presented in this paper. We have here chosen to extend the PDC method because this method was evaluated more positively.[16]

Drug switching

We proposed a way to include drug switching by calculating adherence values of the old and new drug together, ordered chronologically. While this is technically feasible, this choice depends also on clinical sensibility; the new drug likely has other properties than the old and may consequently have other effects on the outcome. In such a case, if those other properties are relevant to the study at hand, it may be better to stop the adherence calculation for the old drug, with the day of switching as the stop date, and possibly calculate adherence for the new drug, starting from the moment of switching (if both drugs are included in a single analysis, e.g. identified through an indicator variable).

Misclassification of exposure

By using a time-varying adherence measure, the effect of interactions between drugs being used at the same time may be more realistically investigated than with a time-constant adherence measure. For example, using a time-constant measure during some fixed-time interval, a patient may be 50% adherent to drug A and 40% adherent to drug B. Both drugs could have been used at low intensity throughout the whole time period, in which case they may have interacted. However, it is also possible that drug A was used intensively in the first half of the interval and drug B intensively during the second half of the interval; this means they would not have been used in the same time, and therefore would not have interacted. If our time-varying method is applied to drug A and B separately,

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and adherence values then put on the same time axis, these two scenarios can be better distinguished from each other.

Longitudinal modelling

The time-varying PDC method is primarily intended for use in longitudinal analysis. In longitudinal analysis, time-varying adherence and dosage can be used either as outcomes or as explanatory variables. A major strength of following adherence within patients over time is that, depending on the study design, patients can act as their own control; the effect of changing adherence on some outcome can be measured within a patient. This design automatically controls for between-patient confounding factors. In a design where each patient has only one adherence value, the effect of adherence can only be assessed by doing a between-patient comparison, for example, comparing the outcomes of low-adhering patients with those of high-adhering patients. However, when using time-varying covariates, the possibility of time-varying confounding may arise and should therefore be considered.[24] Time-varying confounding can be guarded against by considering a causal diagram of the study and dealt with by using methods such as inverse probability weighting or the G-formula.[25,26]

When using time-varying covariates in general, including time-varying adherence, it may be wise to introduce time lag between the values of the covariate and the outcome. That is, the outcome at any point in time can be related to the adherence value that was observed a few days, weeks or even months earlier. Without time lag, the causal relations between variables may be reversed; for example, in a study of the effect of adherence on disease onset, we would expect the adherence value to affect disease onset and not vice versa. However, patients with a worsening health condition may also become less adherent; thus, the causal relations can become reversed. Implementing a time lag can prevent this from occurring. The exact size of the time lag is dependent on the study objective and drug in question; a time lag can be large if the drug is believed to have long-term effects but must be short if the drug primarily has short term effects.

For some drugs, it may be assumed that a patient's larger adherence history also plays a role. This could be represented by a variable that, at any time, contains the sum, mean or some other mathematical transformation of observed adherence values of previous time points, depending on what is clinically sensible.

In longitudinal analysis, it is commonly a requirement that the timescale of the exposure (e.g. adherence) corresponds the timescale of the outcome. In our method, we have demonstrated how to calculate adherence in 30-day intervals, which is the shortest supply period for many chronic medications, and have noted that it can easily be changed to longer time periods. This makes the method especially suitable for measuring the associations between adherence and chronic conditions; the aspects of which would also change in the scale of weeks or months. Other methods, for example those designed to use data from electronic monitoring of medication taking, should be employed for studying the associations with outcomes that vary on a daily or hourly basis.

Especially when building predictive models, using information from future observations should be limited, so as not to artificially increase the predictive power of a model. For this reason, when multiple intervals overlap, the adherence value that we assign to patients at any time point comes from the estimated adherence of the interval that will end most soon after that point. Finally, when the adherence variable is used as an outcome instead of as an explanatory variable, it should be noted that adherence observations within a patient that are close to each other in time are likely correlated. This should be taken into account by modelling some covariance structure for the data, such as an autoregressive covariance structure.

Adherence is often measured as a continuous variable, but then it is dichotomized.[27] For example, patients that are below 0.8 adherent may be categorized as non-adherent, whereas patients with 0.8 adherent or more are considered adherent. The time-varying adherence measure described in this paper may be similarly dichotomized, though we suggest that this is not needed; firstly, it is often unclear what the choice of the cut-off value should be based on, and secondly, by keeping adherence as a continuous variable and using squared terms or splines (e.g.[28–30]), the response curve between adherence and some outcome may be described in greater detail. Knowing the response curve in detail can be useful because a desired outcome may already be achieved at lower levels of adherence. In such a situation, resources that would otherwise have been spent to achieve higher adherence levels in patients can be saved.[3]

CONCLUSION

Accurate measurements of adherence are essential for the assessment of pharmacologic interventions. We have demonstrated that the extended proportion of days covered method better accounts for changes over time in drug utilization behaviour, such as being better

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able to discern erratic dosing from continuous low-intensity dosing behaviour. This may improve longitudinal or time-to-event studies that associate adherence with another outcome or (intervention) studies that seek to describe changes in adherence over time.

CONFLICT OF INTEREST

All authors report no conflict of interests.

KEY POINTS

- To date, measures of drug adherence have almost exclusively been applied for a fixed time interval, and without considering changes over time. Yet time varying differences in drug adherence may have real effects on patient prognosis.
- We demonstrate a method to measure time varying drug adherence, which better distinguishes an irregularly dosing patient from a stably dosing patient, and which is less likely to produce biassed estimates.
- The time varying PDC method may improve longitudinal and time-to-event studies that associate adherence with a clinical outcome, or (intervention) studies that seek to describe changes in adherence over time.

ETHICAL STATEMENT

Ethical approval was not required to perform this study.

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