A Multistate Model and an Algorithm for Measuring Long-Term Adherence to Medication: A Case of Diabetes Mellitus Type 2

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Abstract

Objectives: To develop a multistate model and an algorithm for calculating long-term adherence to medication among patients with a chronic disease. Methods: We propose definitions of the different states of waiting, persistence, with sufficient supply to implement the prescribed dosing regimen, gaps, nonpersistence, and nonacceptance and an algorithm for transitions between states to describe long-term adherence to medication treatment. The model and algorithm are operationalized for use in a case with a retrospective cohort of patients with type 2 diabetes mellitus, with access to records of prescribed drugs from a Danish diabetes research hospital and records of filled prescriptions at Danish pharmacies from the Danish Health and Medicines Authority. Results: Calculations of long-term adherence to medication are shown for patients with type 2 diabetes mellitus on metformin and/or simvastatin. The study shows how

Introduction

Adherence to medication defined as “the extent to which a person’s behavior with regard to taking medication corresponds with agreed recommendations from a health care provider” [1] has been explored extensively for more than four decades [2,3]. Adherence to long-term therapy for chronic illnesses in developed countries is estimated to average 50% by the World Health Organization (WHO) [4]. Studies have shown that poor adherence is associated with worsening of the patients’ clinical status/health [5,6], higher risk of hospitalization [7], risk of preventable drug-related hospital admissions [8], and higher mortality risk [9]. Losing adherence has been shown to be associated with higher outcome of hospitalizations and emergency department visits [10].

It has been argued, however, that “The term ‘adherence rate’, as used by the WHO, is ill considered and meaningless” [11] because it cannot distinguish whether poor adherence stems from poor acceptance, poor execution, or early discontinuation of treatment. The need for methods and models on how to improve the consistency and quality of measures of adherence to medication has been addressed [3,12,13] with efforts to meet these needs [14,15], but there is still no uniformity in the terminology used to describe how patients deviate from prescribed medication therapy [16]. It can be argued that poor adherence among some patients probably is a relapsing condition over time similar to relapses in attempting smoke cessation among smokers and relapses in retaining weight loss among overweight persons. Whether intentionally or unintentionally [17] on the part of the patient, a mismatch between the health care professionals’ assumptions about the drug intake based on the electronic medical records of prescribed medication and what in reality has been collected and ingested by the patient signifies a problem in the pharmacotherapeutic chain. Extended pharmacoepidemiological research to devise methods to identify therapeutic lapses and to estimate the extent and magnitude of discrepancies between written prescriptions issued by the physician and prescriptions filled by the patient has been called for [11].

Long-term adherence to medication should comprise measures of initiation, acceptance, implementation of dosing regimen, and persistence [11,16,18], which entails that more than one type
of event is of interest: when the patient is prescribed with the drugs for the first time, when he or she initiates treatment, when he or she runs out of supply, or when he or she or the prescribing doctor discontinues the treatment. We set up a multistate model to describe the events of interest allowing the same type of event to occur more than once [19].

Along with development of the multistate model, rules for an algorithm describing how and when a patient moves between the different states must be defined.

Type 2 diabetes mellitus (T2DM) has been chosen as the case of a chronic illness because it is the main focus of the research team, and we have access to extensive data. T2DM is a complex metabolic disorder and prevalent in both industrialized and developing countries [20]. Guidelines [21] for the treatment of T2DM recommend long-term multifactorial medication therapy for hyperglycemia, hypertension, hypercholesterolemia, and anticoagulation to prevent/postpone diabetes complications.

Metformin (ATC code: A10BA02, recommended as first-choice blood glucose–lowering medication in T2DM [21]) and simvastatin (ATC code: C10AA01, recommended as first choice for dyslipidemia in T2DM in Denmark [22]) were chosen as case drugs. ATC codes refer to WHO’s Anatomical Therapeutic Chemical classification system codes [23]. The multistate model and the corresponding estimation algorithm can be used for any type of long-term medication used by patients with a chronic disease, for example, human immunodeficiency virus-positive patients, cancer patients, or organ transplanted patients.

Thus, the aim of the current study was to develop a multistate model to be used as a tool to describe and measure long-term adherence to treatment for patients with a chronic disease on lifelong medication. The model can cover either one drug at the time (as in this study) or a group of drugs.

Case Material

Study Population

A cohort of patients with T2DM from the Danish diabetes research hospital Steno Diabetes Center (Steno), a specialized diabetes tertiary referral hospital for patients with both type 1 diabetes mellitus and T2DM, was used. A total of 4322 patients with T2DM with at least one written prescription of either metformin or simvastatin and enrolment at Steno during the period 1998 to 2009 were included.

Daily Doses Prescribed by the Physician

Since 1998, the physicians at Steno have made electronic registrations of their recommendations of medication to the patients. The recommendations are recorded for each drug identified by the ATC code with a starting date and a daily dose. Cessation of a recommendation is recorded with an ending date. These recommendations are the basis for the actual (electronic) written prescription of the drugs issued by the physician, which enables the patients to pick up the drugs at any Danish pharmacy of their choice.

Prescriptions Filled by the Patient

Every filled prescription (Rx) is registered with information about the date of purchase, purchased amount of the drug in defined daily doses (DDDs) [24], ATC code, and the patient’s identity number. Since 1995 this information is stored in the Register of Medicinal Product Statistics (RMPS) owned by the Danish Health and Medicines Authority and was made available to us via Statistics Denmark.

Every person in Denmark is identified by a unique identity number (the Danish Civil Registration number), which is used for linkage of registers in this analysis.

Methods

Patients enter the study on the day of the first written prescription at Steno after January 1, 1998, for the drugs in question. End of follow-up per patient per type of drug is the earliest of date of death, the last date of referral of the patient from Steno to a physician or another specialist unit before December 31, 2009, or December 31, 2009.

The drugs are classified according to WHO’s ATC codes at level 5 as of January 1, 2010. Amounts of prescribed and purchased drugs are transformed into units of DDD by using WHO’s DDD values as of January 1, 2010.

For the definition of this multistate model and algorithm, adherence to medication is restricted to prescriptions of drugs in which the prescribed daily dose is known as well as the amount of the drug being filled. Drugs prescribed to be used “as needed” (e.g., insulin) and over-the-counter drugs can therefore not be covered by this model and algorithm.

For each type of drug for each patient, records with prescribed daily dose including starting and ending dates are extracted from Steno’s Electronic Medical Record (EMR). All records on Rx from the RMPS are sorted by patient, by type of medicine, and by day of purchase in ascending order and handled one by one consecutively.

Duration of the first Rx starts on the day of purchase and lasts until the amount has been spent according to the daily prescribed dose. The daily prescribed dose can in theory vary every day. This information is used to compute the duration of a given Rx. If subsequent prescriptions are filled within the previous Rx’s duration time, the duration of these will be pasted to the end of the previous Rx. Adjustment for waste of the drug is not included. Any oversupply is capped only at the very end of the follow-up period.

The medication process, shown graphically in Figure 1 and concepts detailed in Figure 2, starts with the first written prescription of a daily dose of a given drug to the patient by the physician. The patient can adhere to the timing and dosage of taking the drug only if he or she initiates treatment by filling the prescription and hereafter refills the prescription with a frequency that allows for a sufficient supply of the drug. If the patient runs out of supply before refilling the next prescription, we say that a gap occurs. In the absence of a Medication Event Monitoring System in register-based studies, we are forced to assume that medication corresponding to the prescribed daily dose is taken every day until the available supply has been used. A scenario in which a patient from time to time skips days to extend supply—perhaps to save money—will postpone the day for when the next refill is needed. But a date for when the next refill is needed cannot be modeled or estimated without unreasonable extra assumptions. Instead, such scenarios will present themselves as one period with sufficient supply followed by a gap. A patient is defined as persistent when he or she has a sufficient supply to implement the prescribed dosing regimen with gaps between refills that are smaller than a predefined number of days (here 180 days). If the patient has been without supply for more than the predefined number of days, then we assume that treatment has been discontinued by the patient and he or she is no longer persistent. This is shown with the red dotted line in Figure 1. Discontinuation may be followed by a later resumption of treatment, starting the process over again. Treatment can also be discontinued by the physician, and then in
some cases resumed with a new written prescription at a later point.

With the above definitions, the medication process can be transformed into a multistate model as described in Figure 2. The figure explains the events leading to a change of state and how cutoff values in an algorithm determine when a gap turns into discontinuation of treatment and termination of persistence. A patient’s acceptance of treatment is defined as having filled at least two prescriptions, the first fill of a prescription within 360 days after the physician prescribed the medication and the second fill within 360 days after fill of the first. If not, the patient is regarded as not accepting treatment (sometimes denoted as early non-persistence [25]).

As shown in Figure 3, during time at Steno, a patient, on any given day for a particular medicine, will be in one of the following six states: 1) waiting to initiate treatment; in treatment and persistent; either 2) with a sufficient supply to implement the dosing regimen; or 3) in a gap without supply of medication; 4) nonpersistent, because treatment has been discontinued; 5) non-accepting, because treatment has not been accepted with at least two Rxs within the allowed span of time; or 6) without a prescription for the drug, either because the physician has not prescribed it or because the physician has discontinued the prescription for the drug.

All the arrows in Figure 3 show the possible transitions between states. With the described data, incidence rates can be calculated for each transition, and is a way of describing the variability in the refill behavior.

Calculations and analyses were performed by using SAS, version 9.2 (SAS Institute, Inc., Cary, NC). Graphs were done in R, version 2.15.2 (http://www.R-project.org/).

**Results from the Case**

The prevalence of the five different states while prescribed with metformin and simvastatin, respectively, during up to 5 years of follow-up, is shown in Figure 4. The date of entry (index date) per patient per ATC code is the date of the first written prescription in EMR after January 1, 1998, and time since this date is used as our primary time scale. The graphs show that the proportion of patients with sufficient supply to implement the prescribed dosing regimen reaches a relatively stable level within the first 3 months. Some 10% of metformin patients fail to fill the first prescription within 360 days and are categorized as nonaccepting. Some of these patients gradually over time initiate treatment shown by the decrease in the nonaccepting proportion of patients.

The degree of persistence during the first year and the fifth year among the patients prescribed with simvastatin is 77.0% (95% confidence interval [CI] 72.7–81.3%) and 84.4% (95% CI 80.2–88.2%), respectively. The difference in the degree of implementation during the first year and the fifth year among patients persistent to simvastatin is less pronounced with 85.1% (95% CI 81.5–88.8%) and 88.3% (95% CI 85.0–91.6%), respectively.

If the definition of a gap is changed from 180 days to 100 days or 50 days, the prevalence for gaps and nonpersistence changes substantially as is shown in the center and right panels in Figure 4. Decreasing the cutoff value shifts person-time from the gap state to the nonpersistent state, and vice versa when the cutoff value is increased.

The median waiting time to fill a prescription for the first time among those who filled were as follows: for metformin, 7 days (interquartile range 1–28 days); for simvastatin, 9 days (interquartile range 1–49 days).
Where the prevalence describes the adherence pattern for the entire population, the incidence rates explain the volatility of the patients’ transitions between states. Empirical incidence rates for selected transitions (indicated with $\alpha$, $\beta$, $\gamma$, and $\mu$ in Fig. 3) are shown in Table 1.

Time to first gap and time to first discontinuation after the date of initiation is shown in Figure 5. On comparing metformin with simvastatin, we found that more patients on metformin commence earlier on a gap than do patients on simvastatin. More patients on simvastatin discontinue treatment earlier than do patients on metformin, regardless of the choice of the cutoff value (50, 100, or 180 days).

**Discussion**

**Principal Findings**

We developed a multistate model by defining the possible states of a patient, and when transitions between states occur. The model provides a tool to use prescription data to estimate transition rates between states over time. Thus, changes in transition rates and prevalence over time can be estimated on several time scales (calendar time, age of the patients, and time since indication for medication).

Adherence to medication has often been reported as a binary outcome (poor adherence $<80\%$ or good adherence $\geq 80\%$) [26,27]. It is hard to believe that a dichotomization of long-term patient behavior related to adherence to medication (poor or good) provides much useful information. The model we have proposed overcomes the limitations that analyses based on summary statistics face because it uses the time points for transitions between states and differentiates between several types of poor adherence: patients who do not accept treatment initially; patients who discontinue early; or patients with a low degree of implementation, which indicate many or long gaps. This is more useful when identifying which patients or drugs to target for counseling or other types of intervention to improve adherence.

The multistate model also has the potential for looking into health outcomes (e.g., long-term diabetes complications) related to specific patterns of adherence to medication and to analyze determinants of changes in transition rates and prevalence of the different states over time (socioeconomic factors, medication complexity, comorbidity, etc.).

If treatment of the chronic disease under study is characterized either by (frequent) switches between drugs or by add-ons of more drugs from the same therapeutic class, which is common in T2DM, it would make sense to model the entire group of drugs. This can be done by transforming prescribed doses into DDD units and adding up to a total for the group of drugs. A similar procedure must be used for the filled amounts and then the model must be applied as shown. Analyses of patients’ health outcomes related to their pattern of adherence to medication would benefit from

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**Fig. 2 – Definitions of states and events related to adherence to medication.**

<table>
<thead>
<tr>
<th>States</th>
<th>Description of state</th>
<th>Content of algorithm</th>
<th>Events leading to a move INTO the state</th>
<th>Events leading to a move AWAY from the state</th>
<th>Dates and Measures of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not prescribed with medication</td>
<td>Days when the physician has not prescribed the medication to the patient.</td>
<td>The physician discontinues prescription of the medication.</td>
<td>The patient discontinues prescription of the medication.</td>
<td>Waiting time to initiation: Time (in days) from date of first written prescription to date of first filled prescription (Rx).</td>
<td></td>
</tr>
<tr>
<td>Waiting</td>
<td>Days until the patient fills a prescription for the first time after having been prescribed with the medication.</td>
<td>The physician starts prescribing the medication.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With supply of medication to implement the dosing regimen</td>
<td>Days where the patient is with efficacious supply of medication to be able to implement the dosing regimen according to the prescribed daily dose.</td>
<td>The patient fills a prescription at the pharmacy after having been without supply.</td>
<td>The patient runs out of supply. OR the physician discontinues prescription of the medication. OR the second of the two 56-day limits in the algorithm is exceeded.</td>
<td>Degree of implementation: Proportion of days covered with sufficient supply of medication during the time, when the patient is persistent. Degree of persistence: Proportion of days being persistent during the time, when the patient is prescribed with medication.</td>
<td></td>
</tr>
<tr>
<td>Non-Persistent</td>
<td>Days after the patient has discontinued treatment and until treatment is restarted or until treatment is discontinued by physician.</td>
<td>The patient runs out of supply.</td>
<td></td>
<td>Date of discontinuation: The day on which a prescription for the medication is filled for the first time after the medication has been prescribed, which makes it possible for the patient to receive treatment.</td>
<td></td>
</tr>
<tr>
<td>Gap</td>
<td>Days when the patient is without supply of medication to be able to implement the dosing regimen according to the prescribed daily dose.</td>
<td>The number of consecutive days without supply of medication exceeds the maximum acceptable length of a gap.</td>
<td></td>
<td>Date of acceptance: The day on which a prescription for the medication is filled for the second time after the medication has been prescribed.</td>
<td></td>
</tr>
<tr>
<td>Non-Accepting</td>
<td>Days after the patient has failed to fill the first prescription within 365 days after having been prescribed with the medication, or after the patient has failed to fill the second prescription within 365 days after having filled the first prescription and until treatment is restarted or until treatment is discontinued by the physician.</td>
<td>Minimum acceptable length of time between first written prescription and first filled prescription (Rx) is set to 560 days. Minimum acceptable length of time between first and second filled prescription (Rx) is set to 560 days.</td>
<td>The patient runs out of supply. OR the physician discontinues prescription of the medication. OR the second of the two 56-day limits in the algorithm is exceeded.</td>
<td>Date of non-acceptance: The first day on which the one of the two 560-day limits in the algorithm is exceeded. Days to acceptance: Time (in days) from date of first written prescription to second filled prescription. Valid range: $\geq 56$ days based on the algorithm.</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 3 – Multistate model and moves between states. The five colored boxes inside the dotted lines represent the five different states during time of follow-up for adherence to medication. Follow-up for adherence to medication is irrelevant for the brown box to the left where the medication is not prescribed. The patient is regarded as persistent when he or she has a sufficient supply to implement the dosing regimen or experience gaps without supply between refills that are smaller than 180 days each. The arrows, regardless of color, show all the possible moves between states. Between some of the states, the patient can move both ways (a bidirectional multistate model). Some of the moves (arrows) have been highlighted with a color for further comments. α next to the orange arrow is the incidence rate for patients moving from being with sufficient supply to implement the dosing regimen to a gap without supply. γ next to the red arrow is the incidence rate for patients discontinuing treatment by moving from a gap to being nonpersistent. The βs next to the green arrows are the incidence rates for changing status into being with sufficient supply to implementing the dosing regimen again. The μs next to the purple arrows are the incidence rates for changing status to not having accepted treatment. Incidence rates for the colored moves (arrows) are shown in Table 1. GP, general practitioner.

applying the model to a group of drugs. If focus is differences in adherence between two drugs, the model must be applied on each drug and then compared, as shown with metformin and simvastatin.

Strengths and Limitations

In contrast to most studies using registers with reimbursement claims, Danish data offer a link between data on prescribed medication and data on (re)filled medication. In the Danish universal tax-funded nationwide health care system [28], patients must pick up prescription drugs at a Danish pharmacy, where all purchases are captured by the RMPS. Reimbursements are subtracted at payment of the drug at delivery, and so it is considered very unlikely that patients get hold of their prescription drugs from sources other than the Danish pharmacies.

This is a study based on electronic registers, and thus does not depend on patients’ self-reported adherence to medication. We argue that it must be difficult to remember something you previously have forgotten, why self-reported adherence to medication presumably can be heavily biased. Significant differences between self-reported adherence and adherence measured by Medication Event Monitoring Systems have been reported [29]. Our study does not include data from a Medication Event Monitoring System as is often seen in clinical trials [30].

Our data record to which extent the drugs are available to the patient, but not the extent to which the drugs are actually ingested. Drugs wasted, lost, or shared with other users contribute to the difference between drugs available and drugs ingested and we have no data on this.

Underestimating adherence using this methodology can be triggered in three instances: 1) if the prescription of the drug has been discontinued by a physician without a registration in the EMR. This may also happen if physicians outside Steno intervene. The RMPS captures transactions of all Rx’s that have been prescribed by physicians at outpatient clinics at other Danish hospitals, but information on the prescribed doses from these doctors outside Steno is not available in our data. In case of overlapping prescriptions from medical doctors outside Steno, which can occur, a discontinuation from another doctor without Steno’s knowledge will erroneously induce poor adherence or nonpersistence in this analysis; 2) if the true prescribed dose is smaller than the actual registered dose in EMR; 3) if the patient is supplied with drugs from a hospital during hospitalization because the RMPS does not capture information on drugs administered to patients from the hospitals’ stocks during hospitalization at an individual level.

False-positive adherence using this methodology may be triggered if the true prescribed dose is larger than the actual registered dose in the EMR.

Strengths and Weaknesses in Relation to Other Studies

By using these Danish data, it is possible to investigate long-term adherence to medication among patients for up to 11 years. Investigation of adherence to medication from initiation of therapy to up to typically 3 years after has often been seen in other studies [2,31–36].

Use of patients’ self-reporting of adherence to medication is avoided in this study. Self-reported adherence to medication may overestimate adherence to medication because a disproportionate number of healthy users may sign up to the study [37,38], because of recall and reporting bias [39], or because the attention from the clinical trial staff may produce an improvement in human behavior among the participants (the "Hawthorne" effect) [40].

Studies using reimbursement claims data may underestimate the adherence to medication for some of the individuals in the population under investigation, if not all dispensed medication has been reimbursed [40] or if the health care system does not offer universal coverage [13,41]. These types of biases are absent when using the Danish data.

This model captures all patients prescribed with the medication in question, including the patients who never fill a prescription or fill only once, which is not always the case in studies using reimbursement claims data, which may overestimate the proportion of adherent individuals among the
population under investigation, because the person-years in the waiting state are not recorded [25,42].

Studies investigating persistence/possession measures do not necessarily take the actual prescribed doses into account, but assume that every Rx lasts a fixed number of days or do require only a minimum number of refills during a prespecified period of time. That may over- or underestimate adherence to medication [32,42,43].
Generalizability

The algorithm requires definition of cutoff values for acceptance and gaps. It is outside the scope of this article to discuss the “correct” choice of the maximum acceptable length of a gap before a patient is considered to have discontinued treatment and has become nonpersistent. Even rather long gaps may not be a problem in cases of drugs with a long half-life or forgiveness, or in cases in which the outcomes of the medication are linked to long-term medication effects [43]. It is known that the carry-over effect of a drug in many cases lags well behind changes in the drug concentration in plasma [11]. For other types of medication, it will only make sense to operate with a very short maximum acceptable length of a gap before a patient must be considered as nonpersistent. The choice of cutoff values must always depend on the drugs under study and hence is a clinical decision.

The multistate methodology, detailed here, is applicable in cases in which detailed information on prescribed and filled medication is available at an individual level. Thus, in Scandinavian countries, Scotland, and Healthcare Management

<table>
<thead>
<tr>
<th>Table 1 – Incidence rates for metformin and simvastatin.</th>
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<tbody>
<tr>
<td><strong>Incidence rate (95% CI)</strong> transitions/person-year</td>
</tr>
<tr>
<td><strong>To state</strong></td>
</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>Commencing a gap α</td>
</tr>
<tr>
<td>Discontinuation to nonpersistent γ</td>
</tr>
<tr>
<td>Refilling of medication after a gap β1</td>
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<tr>
<td>Refilling of medication after being nonpersistent β2</td>
</tr>
<tr>
<td>Not accepting treatment μ</td>
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<tr>
<td>Simvastatin</td>
</tr>
<tr>
<td>Commencing a gap α</td>
</tr>
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<td>Refilling of medication after being nonpersistent β2</td>
</tr>
<tr>
<td>Not accepting treatment μ</td>
</tr>
</tbody>
</table>

Note. Incidence rates for number of transitions per person-year from one state to another. Based on a maximum acceptable length of 180 d for a gap.

* The four states are 1) with supply to implement dosing regimen, 2) a gap, 3) nonpersistent, and 4) waiting.

Fig. 5 – Time to first gap and first discontinuation after date of initiation. Time to discontinuation is shown in three different versions using a maximum acceptable length of a gap of 50, 100, and 180 days, respectively.
Future Research

This study and WHO’s estimates of a low degree of adherence to long-term therapies in general indicate a large potential for improved health and quality of life among patients with poor adherence to medication, if identified and helped to improvement of adherence. We will pursue to develop a tool for the identification of patients with different types of poor adherence to medication. Associations between measures of adherence to medication based on this model and health outcomes are also to be investigated.

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