Estimating Medication Persistency Using Administrative Claims Data

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Objectives: To review the definitions and methods for measuring medication persistency, and to propose a uniform definition of and calculation for persistency using pharmacy claims data.

Study Design: Literature review.

Methods: A MEDLINE search (1966 to present) was performed to identify articles detailing a definition or method of persistency measurement based on automated pharmacy data. Articles were screened for relevance by title and abstract. References from identified articles were used to expand the search results.

Results: The concept behind medication persistency measurement is to capture the amount of time that an individual remains on chronic drug therapy. The methods to calculate medication persistency can be classified into 1 of 3 categories: (1) Persistency as a function of the medication possession ratio; (2) persistency as a function of medication availability at a fixed point in time; and (3) persistency as a function of the gaps between refills.

Conclusions: The common goal of all persistency measures should be to reflect the continuity of medication usage and to capture the timeliness and the frequency of refilling. The measurement of persistency as a function of the gaps between refills provides the best assessment of refill compliance across a variety of medication and disease states and lends itself to the well-established measurements of survival analysis.

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Pharmaceuticals have become the primary treatment modality for a variety of acute and chronic medical conditions. Unfortunately, the mere receipt of a prescription does not guarantee better health. A medication's success in producing beneficial effects depends on a patient's compliance with a therapeutic regimen. Failure to take medication appropriately or for the prescribed length of time could lead to detrimental health outcomes and increased healthcare expenditures.[1]

Enhancing patient medication compliance has assumed a prominent role in initiatives directed at improving the quality of medical care. Improving compliance first requires the development of accurate and easily interpretable measures of medication adherence. Traditionally, medication adherence has been based on patient self-report, clinician perception, pill counts, pharmacologic tracers, or electronic measurement devices. More recently, pharmacy claims data have become a common tool in the assessment of medication compliance. These large population databases afford access to a vast amount of information regarding medication dosing and refilling patterns. Still, the challenge remains to convert these large quantities of claims data into intuitive and meaningful surrogate measures of medication compliance.

Sclar and colleagues provided the first uniform methodology for estimating medication compliance from pharmacy claims data, with the introduction of the medication possession ratio (MPR).[2,3] Their work has led to the widespread adoption of the MPR as a measurement of drug adherence.[4-15] The MPR is often defined as the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill. This calculation usually results in a ratio less than 1.0 if there are lapses in prescription refilling. Early refilling would lead to an MPR of more than 1.0; the MPR in such a case is often truncated at the maximum value of 1.0, indicating the potential for perfect compliance.

Although the MPR provides insight into the availability of medication, it does not provide information on the timeliness and consistency of refilling. Consider a patient who refills medication every other month during a 1-year period. Compare this individual with someone who refills during the first month, followed by a 6-month gap, and then continuous refilling until the end of the year. Both patients have an identical MPR. But, during the course of the entire year, the first patient is more consistent and timelier with refilling behavior. The MPR fails to capture this particular dimension of patient medication adherence.

Persistency with medication refilling is calculated to fill this void in the estimation of medication compli-

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ance. Unfortunately, unlike the MPR, the literature lacks a consistent definition of persistency and a uniform method of calculation. Our objective was to review the various definitions and methods for measuring medication-refill persistency and to propose a uniform definition and calculation for persistency using pharmacy claims data.

METHODS

Literature Search

An Ovid MEDLINE search (1966 to present) was performed using the key word *persistency* (346 citations). A search was also conducted cross-linking the key word *persistence* (27 792 citations) with the key words *patient compliance* (27 046 citations), *prescriptions, drug* (12 603 citations), and *drug utilization* (9934 citations). These key words are terms with predefined subject headings in MEDLINE that were searched according to key word. All articles were screened for relevance by title and abstract. In addition, references from identified articles were used to expand the search results. Inclusion criteria were that an article had to specifically detail a definition or method of persistency measurement based on automated pharmacy data. Although studies measuring medication discontinuation may have used similar methodologies, these analyses were not within the scope of this review.

Persistency Definitions

The measurement of medication persistency attempts to capture the amount of time that an individual remains on chronic drug therapy.[16-20] This dimension of medication compliance introduces an element of chronology that is absent from a simple MPR measure.[17] Under this framework, patients are classified as either persistent or nonpersistent with medication therapy for some duration of time. Individuals who are persistent with therapy are continuous with their medication-taking behavior during a certain period. Persistent individuals refill their medications frequently and regularly. In contrast, nonpersistent individuals either have sporadic refilling practices or have discontinued refilling their medications completely.[19,21]

Although the literature often blurs the distinction between nonpersistency and discontinuation, the 2 concepts are not necessarily equivalent. An individual who is nonpersistent with medication therapy may have a momentary, significant lapse in treatment, but may still resume medication at some point in the future.[22,23] In contrast, medication discontinuation implies a complete cessation of drug therapy with no future resumption of treatment.[22] Medication discontinuation is difficult to determine with absolute certainty because of the long time horizon involved. As a result, a gap in treatment observed during a shorter, more definite period is often used as an indicator of medication discontinuation. Although many analyses equate the presence of these gaps to discontinuation, individuals with such gaps may represent a degree of noncompliance and may still resume their treatment in the near future.[22,23] These individuals may be appropriately classified as nonpersistent but not necessarily discontinued.

RESULTS

Persistency Measurements

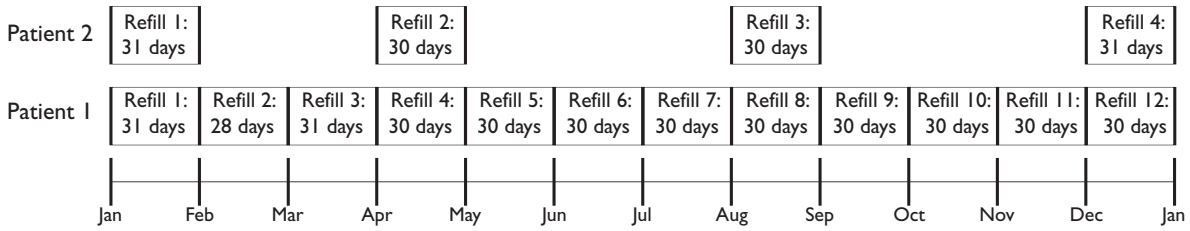
In our review of medication compliance studies measuring refilling persistency, we identified 3 methods to calculate persistency with medication. Persistency may be calculated as a function of the MPR, as a function of medication availability at a fixed point in time, or as a function of the gaps between refills.

Persistency as a Function of the Medication Possession Ratio. Persistency may be defined as an MPR (or similarly calculated ratio, including proportion of days covered) greater than or equal to a predetermined threshold, such as 80%.[18,24-29] The MPR is a continuous variable assessing medication availability over multiple refill intervals. The selection of an absolute cut-off for medication persistency yields a dichotomous persistency measure for each individual: persistent or nonpersistent.

Several studies have used the concepts of MPR calculation and persistency interchangeably, without the use of a threshold MPR value to imply persistency.[30-34] However, an important distinction is that the calculation of the MPR by itself does not convey information on the timeliness of refilling or persistency. However, if a certain minimum MPR classifies a patient as persistent, then this measure can convey information on the duration of therapy and the consistency of refilling. An MPR of 80% is a reasonable threshold for persistence because it suggests very few days without drug on hand and, consequently, fairly continuous medication usage. An alternate MPR threshold for persistency could be selected given an appropriate clinical or pharmacologic rationale.

The calculation of persistency as a function of the MPR is limited because of its reliance of a uniform follow-up period for all individuals. For instance, individuals with a 3-month follow-up period have fewer days of observation and fewer opportunities for noncompliance than individuals with a follow-up period of 12 months. A uniform follow-up period is required to prevent indi-

Figure 1. Limitations of Persistency as a Function of a Medication Possession at a Fixed Point in Time



This methodology classifies a patient as persistent if he or she possesses medication at a fixed time in the observation period, in this case 12 months. Because patient 1 and patient 2 both have a refill at 12 months, they are both classified as persistent for 1 year. The more consistent refilling of patient 1 is not factored into the measurement.

viduals with shorter follow-up times from biasing the MPR upward.[35] As a result, individuals with less claims data due to plan ineligibility or insurer switching must be excluded from analysis.

Persistency as a Function of Medication Possession at a Fixed Point in Time. This methodology measures the patient's possession of medication on a fixed date after the initial prescription. If patients possess medication on that specific date, then they are classified as persistent from the initial prescription until that date, for that entire length of time.[36-45] Medication possession may be defined as either available medication on hand or the presence of a medication refill. For example, a patient is classified as persistent at 1 year if, at 12 months, he or she has a single day's supply of medication or a refill available. Similarly, the presence of a refill within a predefined number of days of a specific date or at any point in a given month would also classify a patient as persistent at that point in time.[37,42-45]

This persistency measure classifies individuals as persistent or nonpersistent by measuring medication possession at a single refill interval. The timing and gaps between other refills is not a consideration. This failure to account for the possibility of large gaps between refills yields a persistency measurement insensitive to discrete changes in refill behavior.

For example, **Figure 1** compares a patient who refills a prescription monthly during a 12-month period with an individual who refills only 4 times during the same period. Both individuals possess medication at 12 months and both individuals are classified as persistent at 1 year. Intuitively, however, the first patient is more consistent with therapy throughout the year.

This example illustrates a limitation associated with this method of persistency measurement. This persistency measure will accurately reflect the timeliness of medication refilling only if the gaps between refills are known to be small and insignificant.

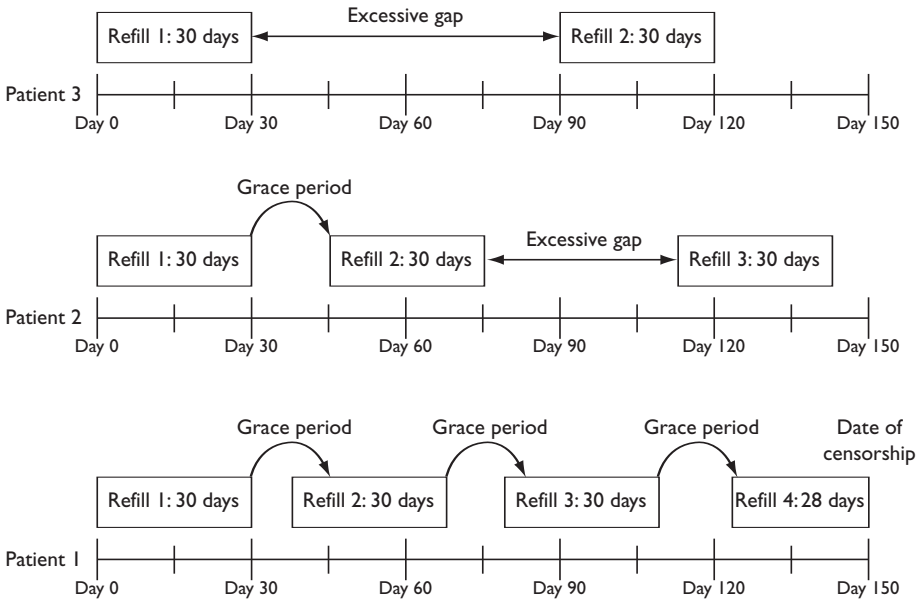
Persistency as a Function of the Gaps Between Refills. The most widely used method for measuring medication persistency relies on quantifying the gaps between prescription refills (**Figure 2**).[23,46-65] Each individual has a certain grace period to obtain an additional refill. This grace period commences at the end of the supply of the previous prescription and is equal to one-half the days' supply of 1 prescription (in this case one-half of 30 days, or 15 days). If the patient refills the prescription by the end of the grace period, he or she is classified as persistent. However, if a patient's refill gap exceeds the predetermined grace period, that patient is considered nonpersistent at that point in time.

This persistency measure is a continuous variable assessing the gaps over multiple refill intervals. Unfortunately, the literature lacks a uniform definition for the appropriate length of this permissible gap. The permissible gap can be a fixed length of time that does not depend on the days' supply of the previous refill. This permissible gap has a reported range between 15 and 120 days after the previous refill.[48,51,52,54-59,61,64] Alternatively, the permissible gap may depend on the length of the days' supply of the previous prescription. A range from one-half to 3 times the days' supply of the preceding prescription has been used as the length of the permissible gap.[47,49,50,53,60] In several analyses of ophthalmologic medications, the allowable grace period factored in the number of bottles dispensed and a knowledge of historical refilling patterns.[23,62,63,65]

This method of persistency measurement shares an intuitive relationship with the calculation of the MPR. If the days' supply of a prescription refill is fixed, then the MPR can be made mathematically equivalent to persistency as measured by the gaps between refills. If we consider refills of 30-day supplies of medications and a permissible gap of 15 days, on average this measure is equivalent to an MPR of 66% (30/[30 + 15]). Similarly, if we assume refills of 30-day supplies of medication, then an MPR of 80% corresponds to a grace period of about 7 days between refills (30/[30 + 7]).

But compared to the MPR measure, the measurement of persistency as a function of the gaps between

Figure 2. Persistency as a Function of the Gaps Between Refills



Each patient has a grace period to obtain a refill of medication. In this case, the grace period or allowable gap is defined as one-half the previous days' supply (15 days). The grace period begins on the last day of supply of the previous refill. Patient 1 always refills within the allowable gap and is considered persistent until the end of the observation period (150 days). The timing of the third refill of patient 2 exceeds the allowable gap. Patient 2 is considered persistent until the last day of supply of the second refill (75 days). Patient 3 does not refill in a timely manner and is considered persistent only until the last day of supply of the first refill (30 days).

refills inadvertently may not consider all the refilling behavior across the observation period. Once an individual is classified as nonpersistent, refilling behavior is no longer considered in an analysis. For instance, consider an individual who misses the permissible gap by only 1 day early in the observation period, but has near continuous refilling after the classification of nonpersistence. This individual will be classified as nonpersistent early on and the remaining refilling behavior will not be considered.

However, persistency measurement as a function of the gaps between refills possesses a unique advantage over other measures because this method readily lends itself to survival analysis.[23,46,48,49,51,52,54,57-63,65] Survival analysis is used to describe data defined from some origin in time until the occurrence of a specific event. With regard to medication compliance, the origin in time is the start of an observation period and the specific event is the first occurrence of a gap that exceeds the allowable grace period. Individuals who are persistent until the end of the observation period are right-censored because the event of interest, an inappropriately long gap, has not been observed.

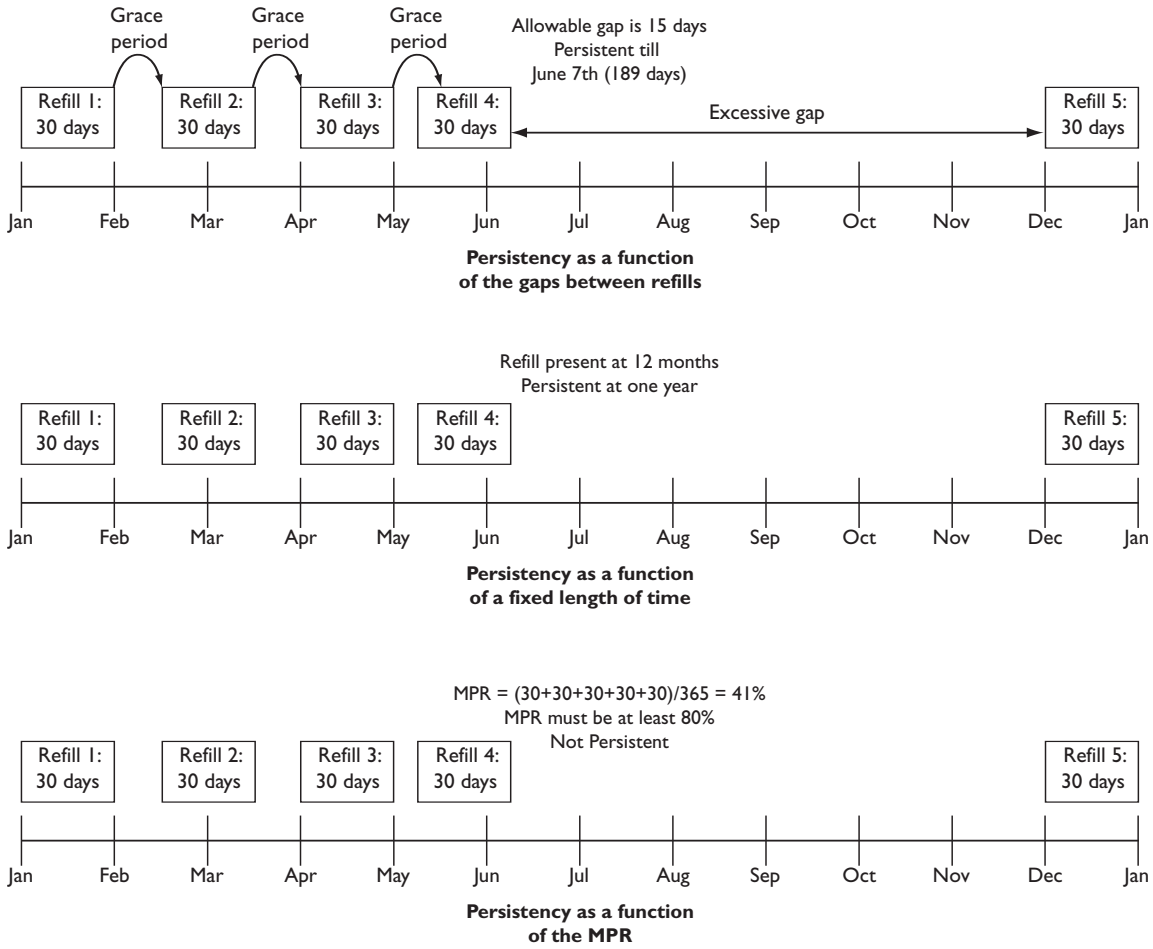
This interpretation of refilling behavior permits the construction of a survival function and facilitates a graphical representation of medication persistency. Using Kaplan-Meier estimates, the distribution of survival times can be computed to describe the persistency of a patient population. The survival function can also incorporate and control for demographic and clinical variables that affect persistency, thus permitting a meaningful comparison of the correlates of compliance among different populations. Changing the allowable grace period for an additional refill also has a direct impact on the survival curves and patient persistency. Lengthening the grace period provides a less stringent requirement for refilling and typically increases the number of individuals persistent with therapy.

Comparison of Persistency Measures

Each of the discussed measures has several limitations in common. Medication refill patterns do not necessarily reflect the intent or directions of the prescribing physician. Gaps in therapy may appropriately result as a consequence of clinical considerations such as abnormal laboratory results, medication titration, adverse drug interactions, or medication side effects. In addition, the assumption is that a new refill of a prescription implies complete ingestion of the previous refill. However, the possibility exists that an individual may be providing medication to others, dumping medication prior to the refilling, or stockpiling medication for future usage. Despite all of these clinical and usage possibilities, for chronic-use medications, administrative data are good sources for estimating medication compliance and persistency and identifying patients at risk for therapeutic failure.

Each method of persistency measurement may yield different results for an individual. **Figure 3** illustrates the application of each methodology to the refilling pattern of a hypothetical patient. If an MPR of 80% is used as a criterion for persistency, then this individual is classified as nonpersistent for the entire observation

Figure 3. Comparison of Different Persistency Methodologies



MPR indicates medication possession ratio.

period. When persistency is determined by the presence of medication possession at 12 months, then the patient is considered persistent for 1 year. However, if the persistency measure is based on a refill gap greater than one-half of the days of the previous prescription's supply, then the patient is persistent up to 189 days of the 12-month period.

Although analyses use these measures to report persistency, each method of persistency measurement may be actually measuring different phenomena. A useful method to elicit these distinctions involves the use of the Steiner typology for refill compliance measurement.[9] According to Steiner, refill compliance measurements can be assessed according to 3 characteristics: (1) the distribution of the compliance variable as either continuous or dichotomous; (2) the evaluation of either single or multiple refill intervals; and (3) the measurement of either medication availability or medication gaps (**Table 1**).[9]

The measurement of persistency as a function of the MPR classifies individuals as persistent or nonpersistent by evaluating multiple refill intervals. The selection of an appropriate MPR cut-off directly affects this measure's accuracy of providing information on the continuity of medication usage. In addition, all individuals must have a uniform follow-up period to prevent biases in calculating the MPR.[35]

The measurement of persistency as a function of medication possession at a fixed point in time is also a dichotomous variable. Individuals are classified as persistent or nonpersistent based on medication on hand or the presence of a refill at a fixed time interval. This method accurately measures persistency if the refill gaps are small and infrequent.

Table 1. Comparison of Persistency Measures According to the Steiner Typology[9]

Persistency Measure	Distribution of Compliance Variable	Number of Refill Intervals Evaluated	Measurement of Medication Availability or Gaps
Persistency as a function of the MPR	Dichotomous	Multiple	Availability
Persistency as a function of medication possession at a fixed point in time	Dichotomous	Single	Availability
Persistency as a function of the gaps between refills	Continuous	Multiple	Gaps

MPR indicates medication possession ratio.

The measurement of persistency as a function of refill gaps distinguishes itself by assessing refill gaps over multiple intervals. The length of the follow-up period across a cohort of individuals may vary. This measure also can be applied to a population without knowing the size of their refill gaps in advance. However, a disadvantage of the measurement of persistency as a function of refill gaps is that consistent refilling behavior that occurs after the designation of nonpersistency is not considered in the analysis.

Further analyses are needed to determine which persistency measurement possesses superior external validation to costs or clinical outcomes. However, the measurement of persistency as a function of the gaps between refills has been utilized most frequently in the literature. The determination of survival times provides additional information for individuals with an intermediate MPR. The underlying medication compliance of the population also does not restrict the implementation or the interpretation of this measure. Measuring the gaps between refills captures the duration of therapy and the consistency attributes of persistency and also informs us of the moment when medication refilling becomes irregular. The determination of the specific time when a patient becomes nonpersistent also allows the application of the well-developed techniques of survival analysis.

Implementation of a Persistency Measurement

Which Measure to Use to Assess Compliance? Persistency measurement is only 1 component of the process of describing an individual's medication-taking behavior. The use of this measure does not preclude the use of other measures (including the MPR) that describe different aspects of medication compliance. Painting the most accurate picture of an individual's medication compliance may require multiple different measures and techniques.

As noted, the measurement of persistency as a function of the gaps between refills is used in most persistency studies. However, this approach does not negate the value of other methods of persistency measurement. Competing methodologies may require less sophisticated statistical training and may be easier to implement. Other methodologies may be used as long as the results generated are interpreted in light of their discussed limitations.

All 3 techniques of persistency measurement have similar data requirements for implementation. But the use of survival analysis in the measurement of persistency as a function of the gaps between refills may pose some additional hurdles. Organizations without the technical or personnel resources can still perform these analyses with add-on packages for common spreadsheet software and software downloaded from the Internet. The remainder of this section discusses specific aspects associated with the implementation of a persistency measure as a function of the gaps between refills.

Medication Compliance Analysis Using Persistency Measure as a Function of the Gaps Between Refills. The first steps in a medication compliance analysis are identification of the population and medication of interest and the selection of an analytic start date. Persistency measurement can be applied to a population of new medication users, current users, or a combination of both. A persistency analysis also typically considers the compliance of 1 medication or medication class at a time. If new medication users are being studied, then the analytic start date should be the first identified prescription. If the persistency analysis involves current users, then the start time of the analytic period can be either a fixed date or the date of the first refill identified after a fixed date.

Once the population of interest and the analytic start date have been chosen, the next most important issue to be determined is the selection of the length of the permissible gap between refills. The length of the grace period between refills can reflect issues related to medication half-life, clinical efficacy, dosage titration, or source of refilling. Often, a grace period may be selected that is a function of the number of days in the previous prescription's supply. For instance, a retail claim

Table 2. Calculation of Survival Data From Administrative Claims for a Patient New to Medical Therapy

Claim No.	Retail or Mail Order	Start Date of Claim	Days' Supply	Date of Last Day of Supply	Length of Grace Period	Last Date to Obtain Refill	Next Date of Refill	Persistent With Therapy
1	Retail	02/05/01	30	03/6/01	15	03/21/01	03/10/01	Yes
2	Retail	03/10/01	30	04/08/01	15	04/20/01	04/01/01	Yes
3	Mail order	04/01/01	90	07/06/01	30	08/05/01	08/01/01	Yes
4	Mail order	08/01/01	90	10/29/01	30	11/28/01	12/1/01	No
5	Mail order	12/1/01	90	2/28/02	30	—	—	—

Survival time = 177 days (02/05/01 through 10/29/01).

with a supply of 30 days or less will be assigned a grace period of one-half the number of days in the previous prescription's supply. This strategy may be problematic with mail-order prescriptions, which typically involve a 90-day drug supply. An allowable gap of one-half the previous days' supply for mail-order claims may be too generous, often resulting in a 45-day period for an additional refill. A stricter but somewhat arbitrary grace period for refilling of mail-order claims may be 30 days.

Typically, once an individual exceeds the permissible gap, his or her refilling behavior after the classification of nonpersistency is not considered in an analysis. This limitation may be partially corrected by either a sensitivity analysis or a secondary analysis of the refilling behavior of nonpersistent individuals. In a sensitivity analysis, the length of the permissible gap can be varied in small increments. If a small change in the permissible gap results in a large change in the length of time an individual is persistent, this result would indicate an individual who has fairly continuous refilling after the initial nonpersistent event. In addition, a secondary analysis could be performed of individuals who are initially classified as nonpersistent. The refilling behavior of this cohort could be studied separately to determine the true extent of poor or intermittent compliance after the initial nonpersistent event.

Table 2 illustrates the calculation of persistency from the claims of an individual new to medical therapy. The administrative data for each claim consist of a start date and the number of days' supply of medication. This information is used to determine the start and the end dates of each medication claim and to evaluate the gap between the end of the previous supply and the beginning of the subsequent claim. If a patient refills early, prior to the end date of the previous claim (as in claim number 3), the end date for the current refill is extended to account for the overlapping days of medication. The evaluation continues through subsequent claims within the observation period until the occurrence of the first prolonged gap exceeding a predetermined threshold value. In this particular analysis, the grace period was 15 days after a refill with 30 days' supply and 30 days after a refill with 90 days' supply. The survival time for an individual is then calculated by taking the difference in days from the start date of the first claim to the end date of the last claim preceding the prolonged gap.

This process is repeated on all patients. Patients who do not have a prolonged gap during the observation period and who remain on treatment beyond the observation period contribute information only until the last day of the observation period. These individuals are right-censored because their exact survival time becomes incomplete during the follow-up, or right side, of the observation period. Using Kaplan-Meier estimates, the distribution of survival times can be computed to describe the persistency of a patient population. Plotting the survival function along a time scale creates a survival curve depicting the proportion of patients persistent at any given point in time.

The information from a survival analysis can be used to assess the effect of an intervention aimed at improving medication persistency. Clinical and demographic factors between the control and intervention groups can be controlled in the construction of the survival function. An intervention to improve medication persistency would be expected to result in a larger proportion of individuals categorized as persistent at the end of the observation period, compared with the control group. Also, the percentage of people clas-

sified as persistent would be greater in the intervention group at any given point in time.

CONCLUSIONS

Compared with other techniques for measuring patient medication compliance, the use of administrative claims databases is relatively new. Within this domain, the MPR has become an easily applied and validated tool for measuring refill compliance. However, the MPR does not provide information on the continuity of medication usage. The measurement of medication persistency is an attempt to remedy this limitation. A persistency measurement should capture information regarding the duration of consistent and timely medication-taking behavior. An intuitive starting point is to measure the gaps between medication refills. Establishing a threshold for failure to refill in a timely fashion allows us to draw upon the techniques of survival analysis to measure persistency.

The combination of an MPR and a persistency metric could provide timely information on the dynamics of patients' medication compliance. This strategy could permit targeted interventions for individuals and populations at risk for medication noncompliance. The creation of survival curves could also be used to assess the effect of an intervention on medication compliance. As pharmacy claims data assume a more prominent role in assessing the quality of care, the techniques of persistency measurement will require additional validation as a means of measuring the continuity of medication refilling behavior.

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