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Standardizing Terminology and Definitions of Medication Adherence and Persistence in Research employing Electronic Databases

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Abstract

Objective—To propose a unifying set of definitions for prescription adherence research utilizing electronic health record prescribing databases, prescription dispensing databases, and pharmacy claims databases and to provide a conceptual framework to operationalize these definitions consistently across studies.

Methods—We reviewed recent literature to identify definitions in electronic database studies of prescription-filling patterns for chronic oral medications. We then develop a conceptual model and propose standardized terminology and definitions to describe prescription-filling behavior from electronic databases.

Results—The conceptual model we propose defines two separate constructs: medication adherence and persistence. We define primary and secondary adherence as distinct sub-types of adherence. Metrics for estimating secondary adherence are discussed and critiqued, including a newer metric (New Prescription Medication Gap measure) that enables estimation of both primary and secondary adherence.

Discussion—Terminology currently used in prescription adherence research employing electronic databases lacks consistency. We propose a clear, consistent, broadly applicable conceptual model and terminology for such studies. The model and definitions facilitate research utilizing electronic medication prescribing, dispensing, and/or claims databases and encompasses the entire continuum of prescription-filling behavior.

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Conclusion—Employing conceptually clear and consistent terminology to define medication adherence and persistence will facilitate future comparative effectiveness research and meta-analytic studies that utilize electronic prescription and dispensing records.

Keywords

medication adherence; medication persistence; medication discontinuation; refill compliance; refill persistence; administrative; database; electronic health record; computerized medical record systems

BACKGROUND

The construct of medication adherence comprises a set of inter-related health behaviors.[1] One of these behaviors, the act of filling a medication prescription, can be estimated objectively using electronic databases such as electronic insurance claims or pharmacy dispensing databases. Numerous studies have assessed patterns of prescription refills among individuals who obtain at least one fill of a medication. [2-11] Over the last several years, advances in electronic prescribing and medication order entry within the electronic health record (EHR) have expanded our ability to assess whether or not patients obtain their initial prescriptions, another of the health behaviors within the adherence cluster.[12-17] Although EHR prescribing databases vary in whether or not they contain information on dispensed prescriptions, their use can enhance widely available pharmacy dispensing and pharmacy insurance claims database to better describe the sequence of behaviors that are necessary to achieve desirable treatment outcomes.

The addition of this new source of information about prescription-filling emphasizes the long-recognized lack of uniform terminology and precise definitions to describe prescription-filling behavior.[18,19] Organizations such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the World Health Organization (WHO) have put forward definitions of adherence and persistence; however these definitions did not encompass the entire range of data sources for adherence. Further, existing definitions do not define terms consistently, do not address the issues of medications that are prescribed but not dispensed, and do not address behaviors such as medication discontinuation.[20,21] Finally, adherence-related publications sometimes neither define their terms carefully nor explain their choice of metrics, leaving readers to make assumptions about why metrics were chosen and how they were calculated.

Applying a uniform conceptual framework to electronic database studies of medication adherence and employing standardized terminology and definitions within that framework will enhance both rigor and generalizability of medication adherence research, as well as the ability of researchers to formally compare the findings of studies in systematic reviews. In this paper we propose a unifying set of definitions for use when studying prescription-filling for chronic oral medications in EHR, in pharmacy insurance claims databases, and in pharmacy dispensing databases and provide a framework to operationalize these definitions consistently across studies.

METHODS

Literature Review of Chronic Oral Medication Adherence Definitions in Electronic Database Studies

The purpose of this literature review was to inform development of the conceptual model by identifying definitions and metrics for terms such as medication adherence, persistence, and discontinuation used in published studies based on electronic databases, and the rationale

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provided by the authors of these studies for selecting definitions and measurement tools. To accomplish this, two authors of the current paper (JLK and MAR) searched published literature to identify EHR, pharmacy dispensing, and pharmacy insurance claims-based studies where medication adherence, persistence, and/or discontinuation was stated as a primary outcome. Although the purpose of this review was narrowly focused and a comprehensive literature review was neither intended nor undertaken, the authors utilized search techniques from the literature on systematic reviews. Retrospective observational studies, randomized controlled trials, and non-randomized comparative studies were included. The National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases was employed. The search was limited to studies published in English from January 1, 2000 through December 15, 2011, and to articles indexed in PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL®), Google Scholar, or the Web of Science. MeSH terms applied during the preliminary search were revised and refined based on expert input from a medical librarian and review of the MeSH terms identified from relevant publication titles retrieved in the preliminary search.

In the medical literature, the word *adherence* is applied to a broader variety of behaviors and regulatory topics than the focus of this work. Thus, studies that focused on adherence to or compliance with lifestyle, guidelines, exercise, diet, preventative screenings or follow-up, dental screenings/procedures, radiation/imaging, hospitalization/surgery, quality of care recommendations, medication reconciliation, drug administration/efficacy/adverse effects, device use, medical visits recommendations, isolation or hand washing precautions, cognitive/behavioral therapies, vaccination/immunization, and Health Insurance Portability and Accountability Act (HIPAA) regulations were excluded. Moreover, we excluded studies that used the degree of risk factor control as the indicator of adherence, rather than directly measuring medication use or non-use.

The title of each citation retrieved was reviewed and the abstract retrieved if the title indicated adherence or persistence to, or discontinuation of, chronic oral medications was the focus. Abstracts of articles dealing with validation of adherence measures used in electronic database studies were also included. Potentially relevant citations were imported into an electronic database. Abstracts of these citations were reviewed and the full texts of relevant articles were retrieved and read by the two individuals that conducted the literature search (MAR and JLK). As articles were read, the definitions and terminology used for adherence, persistence, and/or discontinuation in the articles were extracted and cataloged.

This literature scan retrieved 2484 articles, 315 (13%) of which utilized electronic data sources that included as the primary outcome chronic oral medication adherence or that evaluated adherence metrics. Studying the definitions and terminology we extracted from these publications confirmed our subjective impression of variation, inconsistency, and confusion in the terminology used. It also demonstrated that terms were used imprecisely and interchangeably to refer to different constructs in different papers. This background work reinforced the fact that a conceptual model of and uniform definitions for the adherence continuum were lacking. It also informed the standardized terminology and definitions we developed (Tables 1 and 2).

Developing the Conceptual Model of Standardized Terminology and Definitions of Medication Adherence for Electronic Database Methods

The overall intent of developing a conceptual model was to set out a series of general definitions that could be broadly applied across the fields of electronic data methods and medical informatics and that were applicable to estimating adherence to oral medications for chronic diseases. These definitions were intended to encompass the many opportunities for

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patients to accept or decline medication within the prescribing and dispensing components of the adherence, persistence, and discontinuation continuum of behaviors. In developing the conceptual model, we applied the following principles: 1) Develop a clear, concise, and broadly applicable model that described a sequence of discrete behaviors over time, 2) Articulate key constructs and sub-constructs of the continuum, 3) Express and organize categories in a logical and systematic manner, 4) Provide sufficient detail to clarify the approach and enable its use, and 5) Avoid restricting appropriate study-specific decisions (e.g., observation windows).

Adherence and persistence definitions require study-specific decisions to yield operational definitions of, for example, the period of observation ("observation window"), the patient sample under study, and the period over which the prescription must be filled after the initial order is written. The duration of the observation window is often conditional on the context, type of medication or disease state, unique details (e.g., usual days' supply of drug dispensed) and selection criteria (e.g., patients with at least two dispensings). Other study-specific decisions often include specifying an observation timeframe after the medication was dispensed as well as measurement metrics and tools such as formulas to calculate medication possession or gaps in medication availability. The definitions outlined here are focused on the structure of the definitions rather than on the specifics of the operational definitions. However, some operational definitions are provided to remind researchers that these decisions must also be clearly documented. Although the primary focus of developing this conceptual model was to provide broadly applicable definitions, we also identify and classify existing metrics that enable use of these definitions. The Kaiser Permanente Colorado Institutional Review Board (IRB) determined that the activities involved in writing this paper met the federal and institutional criteria for exemption from IRB review.

RESULTS

Our proposed conceptual model, terminology and definitions of medication adherence for electronic-data-based methods (Figure 1 and Table 1) is predicated on two key constructs: medication adherence and medication persistence. Adherence connotes the degree or extent to which the patient conforms to the medication use recommendations specified by the prescriber (e.g., frequency/interval of administration, time of day ingested, strength of dosage).[20] In contrast, persistence encompasses the time over which a patient continues treatment or continues to re/fill the prescription, from starting to stopping therapy.[20,22]

In this conceptual model (Figure 1), adherence is subdivided into two main categories: Primary adherence and secondary adherence. Primary adherence is a discrete event that assesses whether or not the patient received the first prescription. In contrast, secondary adherence is an ongoing process that measures whether or not the patient received dispensings or refills as prescribed during a defined observation period. Only after these adherence sub-constructs have been acknowledged and assessed can the next level of secondary adherence—whether it is adequate or inadequate—be assessed. In these proposed definitions, the converse of each adherence term is simply "non" as in "primary non-adherence" and "secondary non-adherence."

Medication persistence implies that the patient must have exhibited at least primary adherence because persistence over time cannot be measured unless the patient has received at least the first dispensing (Figure 2). We propose that early-stage persistence be defined to include individuals with at least two dispensings and later-stage persistence as including individuals with three or more dispensings of the medication and with evidence of medication availability. For consistent terminology, we propose the converse of each

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persistence category to also be “non” as in “early-stage non-persistence” and “later-stage non-persistence.”

Medication discontinuation implies that a patient has terminated therapy as evidenced by not refilling a prescription, but no subjective inference regarding appropriateness is made, since discontinuation may be initiated either by the clinician or the patient. Further, in claims database studies, it is usually not possible to determine whether discontinuation was prescriber-initiated or patient-initiated. Medication discontinuation in electronic database studies can only be assessed within the context of a pre-specified operational definition for the required number of days without medication available. Thus, very low measured levels of adherence (MPR or PDC < 40%; CMG or NPMG > 60%) can in some circumstances represent, or be confused with, discontinuation.

Metrics that have been used to calculate medication adherence and/or persistence using electronic databases are summarized in Table 2. In general, these metrics enable calculation of either medication possession (i.e., possession measures) or gaps in medications availability (i.e., gap measures)[18,23-25] and most estimate adherence only among individuals with secondary adherence. Most metrics are continuous measures, but they are often categorized (e.g., low or inadequate versus moderate versus high or adequate adherence). These measures require data including the date of medication dispensing, days’ supply dispensed with each dispensing, and previous (stockpiled) medications (or an indication that it will be set to zero) to estimate medication availability and consumption, usually estimated between the first and terminal dispensings within an observation window. A minority of metrics estimate availability within a single dispensing interval (e.g., the Continuous, Single interval measure of medication Acquisition, CSA). The metrics also vary in whether or not the days’ supply dispensed with the terminal dispensing is included in the calculation. The time between any one dispensing and the subsequent dispensing is known as the refill interval. Person-time is censored at the last dispensing date, at the time of exhaustion of the last days’ supply, or at a fixed number of days after exhaustion of the last days’ supply. Most gap measures of secondary adherence censor after the last dispensing once stockpiled medications have been exhausted.

The two most commonly used secondary adherence medication possession measures are the Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC),[18,22,23,26-28] Both report medication availability by estimating the proportion of prescribed days’ supply obtained during a specified observation period over refill intervals and both are becoming widely applied in health care settings[29] in large part because they are easily calculated (a SAS macro has been written for MPR and PDC). For example, as operationalized by the Pharmacy Quality Alliance,[29] the PDC has been endorsed by the National Quality Forum as a tool to measure health care quality.[30] The main difference between the PDC and the MPR is that with the PDC any oversupply is truncated, whereas adherence values of greater than 100 percent are allowed with the MPR. There is controversy about whether “over adherence,” often considered as MPR between 100 and 120 percent, has clinical meaning.[26] A shortcoming of these (and other) secondary adherence measures is that, when integrating across several observation periods of multiple refills each, delayed dispensing(s) in one observation period can be numerically counterbalanced by early dispensing in a later observation period, thus potentially under-ascertaining adherence in one observation period and overestimating it in another. The converse can also occur. This drawback is of particular importance in longitudinal assessments where changes in adherence behavior are assessed across multiple observation periods by calculating the adherence metric separately within each period. Other strengths and weaknesses of the medication possession and gap measures are summarized in Table 2.

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Because most measures of adherence require at least two dispensings, the least adherent patients (primary non-adherent) are excluded. Within the last few years measures have been developed that include patients with either primary or secondary (non-)adherence.[6] One such metric, the New Prescription Medication Gap (NPMG) measure, is defined as the proportion of days within an interval bounded by the prescriber's initial EHR prescription medication order date and the end of the observation period (or end of follow-up if censored or the therapy is switched or discontinued).[6] As with older gap measures, NPMG is a continuous measure, ranging from one hundred percent for patients who obtain no medication to zero percent for those who consistently refill their medication in a timely fashion. Unlike secondary adherence measures, NPMG was designed to evaluate medication supply starting at prescribing and ending at a fixed censoring point, thus comprehensively capturing (non)-adherence for those who never start the prescribed medication or who discontinue it early as well as for those who have at least two dispensings. An additional strength of NPMG is that because it enables evaluation from the point of prescribing in the EHR, person-time can be censored if the prescriber switches or discontinues therapy and documents those orders in the EHR.

DISCUSSION

In this paper we offer a standardized set of definitions and terminology for assessing medication adherence and persistence in electronic database studies, whether the databases employed are medications ordered within an EHR, medications dispensed and documented in a pharmacy database, or pharmacy claims processed through an insurance database. These conceptual models and terminology are more comprehensive than current, commonly used definitions. The models we propose include clear and systematic definitions of adherence and persistence developed to facilitate EHR-based research, are specific to *medication* adherence, and extend to adherence and persistence subcategories and medication discontinuation. We also point out the importance and utility of developing precise operational definitions for adherence research as these definitions enhance the precision of ascertaining whether a patient was likely exposed to a specific medication on a particular date for a specific research purpose (e.g., on the date of some clinical measure, event, or outcome).

Research focusing on adherence is voluminous. As obtaining the initial prescription medication and taking the medication are prerequisite health behaviors for medication effectiveness, these are key explanatory variables when observed effectiveness is lower than the efficacy demonstrated in controlled trials. As a consequence, comparative effectiveness studies may be designed to evaluate the effectiveness of various interventions to improve these adherence behaviors in their own right. Meta-analytic studies are also useful in assessing adherence as an outcome, and the level of adherence necessary to achieve treatment goals. To facilitate these types of studies, it is critical that the adherence measure be accurately estimated and consistent across studies.

There are limitations to this work. Our conceptual model is specific to prescription-filling and has not been compared with frameworks for other prescription behaviors such as medication-taking.[20,31] Definitions are only part of the decision-making process in adherence research. Many important methodological considerations that should be addressed were beyond the scope of this paper such as identifying clinically meaningful categorizations for adherence (e.g., < 20% CMG; >= 80% MPR) based on observed relationships between adherence and clinical outcomes for specific disease states, the role of informative censoring (e.g., medication stop orders and switches), comprehensive assessment of discrete events (e.g., appropriate time frames to consider for medication discontinuation), and bias associated with assuming dispensing data are complete (e.g.,

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prescriptions transferred outside an integrated healthcare system, paying cash for prescriptions resulting in no prescription insurance claims being filed).

CONCLUSION

We offer a set of standardized medication adherence terminology and definitions for use with electronic database research. The medication adherence and persistence conceptual models and definitions we present will enable future meta-analytic and comparative effectiveness research, as standardized terminology facilitates rigorous comparisons. As such, this paper is foundational for adherence methods.

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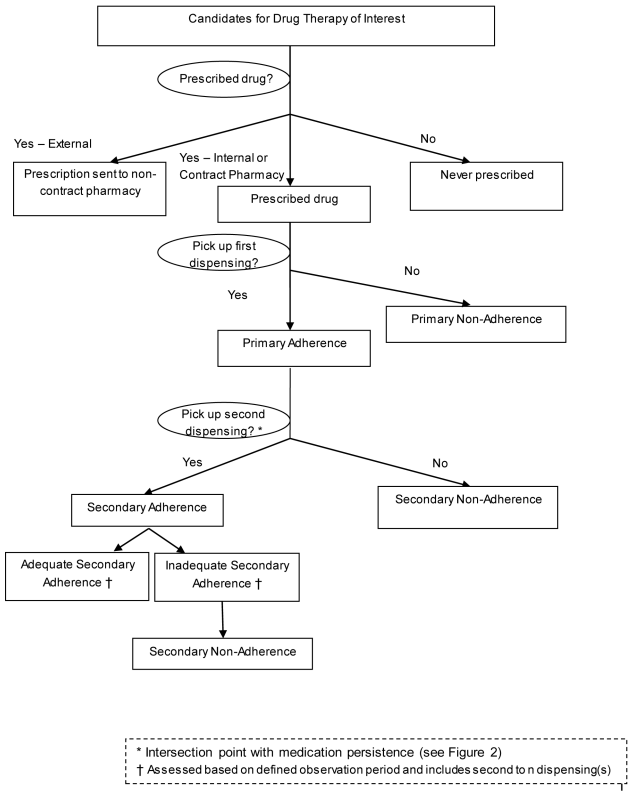

Figure 1.
Medication Adherence Conceptual Model and Terminology for Electronic Data Methods

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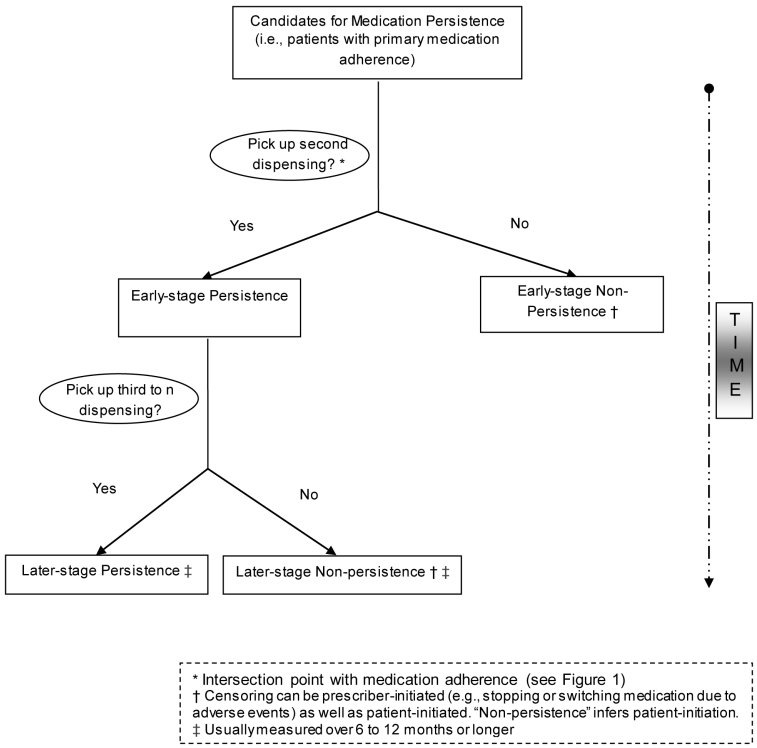

Figure 2.
Medication Persistence Conceptual Model and Terminology for Electronic Data Methods

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TABLE 1

Recommendations for Standardized Terminology and Definitions of Medication Adherence and Persistence for Electronic Data

Terminology for Medication Adherence or Persistence Construct	Recommended Foundational Definition	Components of Definition Requiring Study-Specific Decisions to Operationalize	Examples of Other Terms Previously Applied to the Same Construct *
Adherence			
Primary Adherence[6,15]	A new prescription was dispensed ("filled" or sold) within a defined number of days after the medication was ordered	Definition of "new prescription:" How far to look back to determine if the medication has been previously dispensed; 12 or 24 months commonly used Definition of "defined number of days:" The prescription must be dispensed within "x" days after the order was written, with "x" commonly60 or 30 days [6,13,17]	First-fill adherence[13] Adoption[32] Initiation[33]
Primary Non-adherence[15-17]	Failure to have a new prescription dispensed (did not pick up the first prescription) within a defined number of days after the medication was ordered	Definition of new prescription(see Primary Adherence) Definition of "defined number of days:" The prescription must *not* be dispensed within "x" days after order was written, with "x" commonly 60 or 30 days[6,13,17]	Dispensation delay[34]
Secondary Adherence[6]	Adherence measured among patients with Primary Adherence) and who have the prescription refilled within a defined number of days following the end of the days' supply of the first dispensing. Secondary adherence is usually measured over 6 or 12 months or longer [†]	Definition of "prescription refill…defined number of days:" The prescription must be refilled within "x" days after exhaustion of the days' supply of the first dispensing. Sometimes referred to as the grace period	Ongoing dispensing/use[17] Implementation[31]
Adequate Secondary Adherence	Secondary adherence with either an overall a) gap in days of medication possession not exceeding 20% of the days between the date of initial dispensing and the date of the end of the measurement period (gap measures) or b) number of days of medication possession of no less than 80%of the days between the date of initial dispensing and date of the end of the measurement period (possession measures)	By convention – only rarely with supporting evidence – the following cut-points have commonly been used: Gap: CMG < 20% NPMG < 20% Possession: MPR >= 80% PDC >= 80%	Adequate adherence[35] Adherence[33] Ongoing adherence[6] Compliance
Inadequate Secondary Adherence	Secondary adherence with either an overall a) gap in days of medication possession exceeding 20% of the days between the date of initial dispensing and the date of the end of the measurement period or b) number of days of medication possession of less than 80% of the days between the date of initial dispensing and the date of the end of the measurement period	By convention – only rarely with supporting evidence – the following cut-points have been used: CMG > 20% to < 60% or upper cut-point can be as high as 100% NPMG > 20% to < 60% or upper cut-point can be as high as < 100% MPR > 40% to < 80% or lower cut-point can be as low as 0%) PDC > 40% to < 80% or lower cut-point can be as low as 0%) Sometimes further subcategorized into MPR or PDC ≥ 60 – 80%, ≥ 40 – 60%, and < 40%	Partial adherence Poor adherence[36] Inadequate adherence Non-compliance

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Terminology for Medication Adherence or Persistence Construct	Recommended Foundational Definition	Components of Definition Requiring Study-Specific Decisions to Operationalize	Examples of Other Terms Previously Applied to the Same Construct *
Persistence			
Early-stage Persistence[6]	A new prescription was dispensed (Primary Adherence) and at least one refill of that prescription was dispensed over a time period consistent with (implying) current use of the drug	Definition of time period allowed or considered between the new prescription dispensing and the one refill.	Point-of-Time Persistence Early Persistence Persistence[37]
Early-stage Non-persistence[10,38]	Failure to have the new prescription refilled over a time period consistent with current use of the drug	Definition of time period allowed or considered between the new prescription dispensing and the one refill.	Early Non-persistence
Later-stage Persistence	Two or more refills (i.e., the new prescription was dispensed and at least 2 refills of that prescription were dispensed) over a time period consistent with current use of the drug. The time period can span several refills that occur over 6 months, 12 months, or longer	Definition of time periods allowed or considered between refills; can include definition of time period allowed after last refill in the measurement period	Second stage persistence[6] Refill compliance Persistent/Persistence[31,38-43]
Later-stage Non-persistence	Failure to have two or more refills over a time period consistent with current use of the drug. Can imply either that the patient has discontinued the medication or that usage is inconsistent over time	Definition of time periods allowed or considered between refills; can include definition of time period allowed after last refill in the measurement period	Second stage non-persistence Suboptimal persistence Not persistent Non-persistence[34,44]
Discontinuation			
Discontinuation[32,45-48]	Failure to have a medication dispensing within a defined number of days after exhaustion of the days' supply of the previous dispensing (often includes exhaustion of any stockpiled medication accumulated from previous dispensings)	Definition of "defined number of days after exhaustion of the days' supply of the previous dispensing;" 180 days often used	Termination[40] End of therapy

* The terms listed in this column are provided as examples of terminology used in the published literature. The terms and their use within the cited publication(s) can be quite different from the Recommended Foundational Definition presented here. In some cases these example terms can have been used imprecisely or were incorrectly applied in the cited publication(s).

† Secondary adherence can only be measured among patients who have at least early-stage persistence.

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TABLE 2

Metrics for Evaluating Medication Adherence and Persistence using Electronic Health Data

Type and Name of Measure	Description and Calculation	Strengths	Weaknesses
Based on Medication Possession *			
Medication Possession Ratio (MPR) and Medication Possession Ratio Modified (MPRm)[18,23,26,28]	Estimate of proportion (or percentage) of days' supply obtained during a specified time period or over a period of refill intervals. Ratio of total days' supply to number of days in observation period Variations: 1) Most common: Days' supply of medication dispensed during a specified observation period (e.g., 1 year), divided by number of days in observation period from first dispensing to end of observation period; multiplied by 100 to obtain percent 2) Also known as MPR modified (MPRm): Days' supply of medication dispensed during specified observation period excluding last refill, divided by number of days between first and last dispensing; multiplied by 100 to obtain percent 3) Less common: Days' supply of medication dispensed during specified observation period from first to last dispensing, divided by number of days between first and last dispensing PLUS days' supply dispensed with last dispensing; multiplied by 100 to obtain percent (This has also been referred to as MPRm) 4) Uncommon: Days' supply dispensed during observation period; divided by number of days until next dispensing Mathematically similar to MRA and CMA	• Categorical or continuous • Ease of calculation • SAS macro available • Can be averaged across study patients to determine overall study adherence value • Calculation variations that define the interval from the first dispensing until the end of a measurement period do account for a patient's discontinuation of medication (example: variation #1) • Provides nearly identical results to PDC when examining adherence to a single drug	• Confusion in literature due to multiple calculation methods • Cannot be calculated for patients with primary non-adherence (i.e., those with no first dispensing do not appear in claims databases); systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise (requires a complete, bounded dispensing interval and the initial days' supply to calculate) • Improved precision when calculated over at least 3 dispensings • If number of days of observation period differ across patients, ratios cannot be combined (must be divided and averaged to provide overall study adherence value) • Calculation variations that define the interval as the time between the first dispensing and the last dispensing do not account for medication discontinuation (example: variation #2) • Likely to overestimate true rate of adherence when a patient receives early refills which may result in an "extra fill" during a measurement interval. If ratio is not capped at 1.0, then reports on average MPR will be skewed upwards • When calculated for a medication class, a

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Type and Name of Measure	Description and Calculation	Strengths	Weaknesses
			switch between medications in the same class during the interval, with an overlap of the new drug with the prior drug, will inflate the MPR. A similar situation occurs when a patient takes more than one medication concurrently from within the same class
Medication Refill Adherence (MRA)[23,28]	Total days' supply divided by number of days in observation period and multiplied by 100 to obtain percent Mathematically similar formulas include MPR and CMA	Categorical or continuous Ease of calculation Mean of each patient's MRA value provides an overall study adherence value	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise • Improved precision when calculated over at least 3 dispensings
MEDSUM[49]	Number of daily doses dispensed in a period divided by number of days in period; if applied continuously, measures continuous med acquisition.	• Categorical or continuous • Ease of calculation • Accounts for oversupply	• Does not accurately reflect n of days a patient may be without meds (unless modified) • Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise
Proportion of Days Covered (PDC)[18,23,26-28]	Total number of days' supply dispensed during specified observation period divided by number of days in patient's observation period (i.e., this denominator is number of days between first dispensing during observation period and end of the observation period) multiplied by 100 to obtain percent; capped at 1 Rather than summing days' supply across multiple drugs, should create time arrays to reflect dates encompassed by each dispensing of each drug within the patient's observation period	• Categorical or continuous • Mean of each patient's PDC provides an overall study adherence value • Ease of calculation • SAS macro available • SAS code available for calculating time arrays[50] • Provides similar results to MPR when examining single drug adherence • Provides a more conservative estimate	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise • Improved precision when calculated over at least 3 dispensings • Ignores non-adherent time after the last refill • Underestimates non-possession within

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Type and Name of Measure	Description and Calculation	Strengths	Weaknesses
		of adherence when examining adherence to drugs with frequent switches and concomitant therapy with multiple drugs within a class • Adjustment for inpatient hospital stays does not significantly alter population adherence estimate	refill intervals if followed by subsequent early dispensings
Continuous multiple-refill-interval measure of Medication Availability OR Continuous measure of Medication Acquisition (CMA)[23,28]	Total days' supply of medication obtained throughout study period divided by number of days from first dispensing until study completion date (number of days in observation period); mean of each patient's CMA value provides overall study adherence value Mathematically similar formulas include MRA and MPR	• Categorical or continuous • Ease of calculation • Can be averaged across study patients to determine overall study adherence value	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise • Improved precision when calculated over at least 3 dispensings • Ignores non-adherent time after last refill
Continuous, Single interval measure of medication Acquisition (CSA)[28]	Single-interval measure of medication availability; provides an adherence value for each patient between dispensings (not overall study period); mean of all dispensing adherence values provides overall study adherence value Number of days' supply dispensed divided by number of days in interval from dispensing date up to (not including) next dispensing date	• Categorical or continuous • Ease of calculation	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise
Compliance Rate or Compliance Ratio (CR)[23]	Sum of days' supplies for each patient, minus days' supply obtained at last dispensing divided by number of days from first up to (not including) last dispensing date Denominator can also be listed as: "last claim date minus index date"	• Provides an overall adherence rate based on day of last refill • Does not require study completion date	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise
Based on Medication Gaps *			
New Prescription Medication Gap (NPMG)[6]	Time between date provider first prescribes medication until first of the following: end of follow-up, censoring due to patient being switched to alternate therapy or medication discontinued by prescriber; total days without sufficient supply summing across	• Can assess primary (non) adherence and patients with only one dispensing • Evaluates medication supply starting at prescribing (rather	• Primarily useful for assessing adherence to newly-prescribed medication rather than adherence of existing medication use

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Type and Name of Measure	Description and Calculation	Strengths	Weaknesses
	each refill interval within follow-up period, divided by total number of days from point of a new electronic prescription to end of follow-up	than dispensing) and ending at a fixed point. More comprehensively captures non-adherence than other measures • Quantifies non-adherent time after discontinuation or after exhaustion of stockpiled medication • Categorical or continuous	
Continuous measure of Medication Gaps (CMG)[28,51]	Subtract total days' supply obtained throughout study period from total number of days of observation period (gives number of days of treatment gaps); total days of treatment gaps is then divided by number of days of observation period The mean of each patient's CMG value provides an overall study non-adherence value based on lack of available medication; 0% reflects complete adherence and 100% reflects complete non-adherence	• Sums proportion of days without medication across all refill intervals starting with first dispensing and ending with last dispensing, providing a cumulative assessment of gaps in supply	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise • Improved precision when calculated over at least 3 dispensings • Provides negative values where patient obtained days' supply exceeds days of study participation • Assumes discontinuation after last dispensing once stockpiled medications exhausted (Note: a modified CMG has been developed that accounts for stockpiling)[48] • Person-time censored at last fill date
Continuous Multiple interval measure of OverSupply (CMOS)[23,28]	Total number of days' supply (if gap) or surplus divided by days in observation period or total days to next fill Mean of each patient's CMOS value provides an overall study non-adherence value	• Ease of calculation	• Cannot be calculated for patients with primary non-adherence; systematically excludes the most non-adherent patients • Calculation for those with only one dispensing is imprecise • Can provide negative values • Ignores non-adherent time after last refill • Underestimates gaps within refill intervals

Type and Name of Measure	Description and Calculation	Strengths	Weaknesses
			if they are followed by subsequent early dispensing dates

* Other less commonly used medication possession measures include: Adherence Ratio, Refill Adherence, Adherence Index, Compliance Ratio, Compliance Index, Refill Compliance Rate (RCR), Refill compliance (ReComp), Medication-Total (MED_TOT), and Medication Interval (MED_INT). Other less commonly used gap measures include: Cumulative Gap Ratio, Medication Out (MED_OUT or MEDOUT), and Days Between fill adherence Rate (DBR)

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