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COMMENTARY

The myths of medication adherence

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1 | INTRODUCTION

Adherence to medication is critical for ensuring the effective, safe, and cost-effective use of therapies to prevent and treat disease. Poor adherence is associated with avoidable emergency room visits, hospitalizations, and higher health care costs.[1-4] Conversely, improvements in adherence are associated with improved health outcomes and even reduced costs.[5-7] In the current era of Accountable Care Organizations (ACOs), shared savings, and value-based payments, promoting medication adherence is essential to achieving population health goals.[8]

Despite the central importance of medication adherence in clinical practice and policy, adherence is difficult to define and measure. This problem stems from an underlying misconception about the nature of adherence—the idea that adherence is a single stable behavior, instead of the reality that adherence encompasses a set of different and dynamic behaviors.[9-12] For example, filling a prescription is a different behavior than ingesting a dose of medication. There are many ways in which patients can be non-adherent: not starting medications that have been prescribed (non-initiation); delaying prescriptions (refill adherence gaps); stopping medications altogether (non-persistence or discontinuation); taking a lower dose than prescribed (eg, pill-splitting); refilling prescriptions more often than required (eg, stockpiling); and improperly administering medications (eg, taking doses at the wrong time). Yet, these behaviors are cumulatively referred to as "medication non-adherence."

This notion of adherence as a set of behaviors is not new, having been described more than a decade ago by researchers including John Urquhart.[11] More recently, Bernard Vrijens and colleagues from Europe developed a taxonomy that classifies adherence along the time continuum, with 3 phases or components: initiation, implementation, and discontinuation.[12] However, most adherence research and policy interventions addressing adherence continue to conflate these components. Moreover, while the new taxonomy is valuable for clarifying phases of adherence with respect to time, it still combines many different specific adherence behaviors within the phases. For example, non-adherence in the implementation phase may involve multiple different non-adherence behaviors; for example not refilling a prescription on time, taking a lower dose than prescribed or in an incorrect fashion, or skipping doses altogether.

Our goal in this paper is to describe 4 myths of adherence measurement, each of which originates from the misconception of adherence as a unidimensional, static construct. These myths remain pervasive in the research literature and in public and political discussions about adherence. We use examples from the published literature to illustrate these points and discuss their implications for research and policy. Each myth and corresponding recommendations for adherence researchers are listed in Table 1.

1.1 | Myth 1: On average, adherence to chronic disease medication is 50%

Most papers that address medication nonadherence begin with a litany of statistics describing the magnitude and importance of the problem. These papers often include the statement that adherence with chronic medications is, on average, 50%. Alternatively, papers may state that only half of patients are adherent to chronic medications.

The origins of these statistics are unclear. Many papers cite a 2003 World Health Organization (WHO) report on adherence, which states that "in developed countries, adherence to long-term therapies in the

TABLE 1 Myths of adherence and corresponding recommendations

Myth	Recommendations
On average, adherence to chronic disease medication is 50%	• when reporting adherence rates, always specify the behavior measured, the component of adherence (initiation, implementation, persistence), the disease, and class of medication • in narrative or quantitative reviews, only pool data that measure the same behavior/denominator (eg, medication filling versus skipping doses).
80% adherence is an appropriate threshold for distinguishing adequate and inadequate adherence	• assess and report relationships between outcomes and varying adherence thresholds • base policies on evidence-based thresholds, rather than arbitrary cutoffs such as 80% of days covered
Adherence is static and can be measured as such	• conduct repeated assessments over time • use all data points in analyses • use advanced statistical modeling techniques instead of summary descriptive statistics to characterize adherence • assess associations between time-dependent measures and outcomes (which are also often time dependent)
Self-reported measures of adherence are less useful than "objective" measures	• specify the behavior being measured • follow best practices for developing and evaluating self-report measures (eg, specify recall period, normalize nonadherence) • only compare self-reported measures to objective measures assessing the same specific adherence behavior

general population is around 50%...".[13] The WHO report, in turn, cites a 1975 study by Sackett and colleagues, who conducted pill counts for 250 male steelworkers in Canada with high blood pressure who were prescribed a thiazide diuretic, alone or in combination with another antihypertensive medication.[14,15] At 6 months, approximately half of the men had "taken" at least 80% of their pills, based on pill counts. As important as this study was in the development of the field—it was one of the first randomized trials of strategies to improve medication taking—its findings are insufficient to establish 50% adherence as the norm across time, medications, disease states, and populations. In fact, in a meta-analysis of over 500 studies reporting adherence to treatment (variably defined), the average rate of adherence from the 328 medication-related studies was 79%.[16]

A related problem with broad statements about average adherence rates is that these rates conflate different adherence behaviors and measures. The denominator used in the calculation of adherence thus differs. Some authors calculate adherence with patients as the denominator (eg, percent of patients who meet a predefined threshold for acceptable adherence), as Sackett did. Other authors use medication as the denominator (eg, average percent of prescribed doses taken) or a measure of time (eg, proportion of days for which medication is available, or timely opening of electronic drug caps). Adherence rates based on different denominators are not directly comparable.

To say that "adherence is 50%" is an oversimplification that, while convenient and motivating, tells us very little about how patients actually take their medications. When comparing studies that report the percent of patients who are adherent, the specific adherence behavior being assessed must be clearly defined and consistently measured; this means not only specifying where in the new taxonomy of adherence the behavior lies,[12] but specifying the actual behavior (eg, ingesting the medication properly, refilling the medication). Statistics can then be pooled across the same behaviors assessed in similar populations, disease states, and medication classes. This practice will provide more accurate and actionable information about average adherence rates in specific populations.

1.2 | Myth 2: 80% adherence is an appropriate threshold for distinguishing adequate and inadequate adherence

In research and quality improvement efforts, adherence is often measured in a binary fashion—adequate versus inadequate adherence. This binary measurement is possible because adherence is viewed as a static, single construct—patients are adherent or they are not. For example, "adequate" adherence is often defined as receiving at least 80% of a given medication over a given (and often highly variable) time period. Like the 50% statistic, this 80% threshold also seems to originate from the Sackett study of steelworkers receiving antihypertensive medications; in that study, the use of the 80% threshold was based on an unspecified "regression analysis which showed that it was only above this level of compliance that diastolic blood-pressure fell systematically."[14,15]

Certainly, many studies demonstrate an association between having sufficient medication for at least 80% of days and improved outcomes, compared with having medication for <80% of days (eg, patients discharged following myocardial infarction).[17,18] However, the 80% threshold is often chosen a priori in these analyses without testing other thresholds or dose-response relationships. Higher and lower thresholds have been identified that best define optimal adherence in some populations, diseases, and medications.[19-23] For example, for antiretroviral medications, adherence thresholds for defining good adherence are often >80%, and there is recognition that different levels of adherence may be required for different medication classes to reach viral suppression (eg, nonnucleoside reverse transcriptase inhibitors compared with protease inhibitors).[24] The optimal threshold for adherence may differ across individuals as well as across medication classes. In an analysis using machine learning in a sample of patients with diabetes, Lo-Ciganic and colleagues demonstrated that the optimal adherence cut-point for identifying hospitalization risk varied based on an individual's health status.[25]

Despite the likelihood that 80% is not a universal cut-point that defines acceptable adherence, this threshold continues to be applied across studies, often with the justification that this is convention. This

cutoff is then used to validate self-report measures, such as by calculating sensitivity and specificity of a self-report measure against 80% of timely opening of electronic drug monitoring caps. The 80% threshold has also been applied in policy, despite the fact that it is arbitrary and, in fact, measures only 1 adherence behavior in the implementation phase. For example, to maximize reimbursement in Medicare Advantage plans, patients must obtain from the pharmacy 80% of the medications prescribed for hypertension, cholesterol, and diabetes over the prior year. In another example, the Core Set of Adult Health Care Quality Measures for Medicaid uses the 80% threshold for defining good adherence to antipsychotics among enrollees with Schizophrenia.[26]

Rather than assuming that 80% is the optimal adherence cut-point across clinical situations, researchers should carefully investigate dose–response relationships to assess whether it is even appropriate to establish a threshold and, if so, examine relationships between varying thresholds and outcomes. With more nuanced information, policies can be revised to encourage patient behaviors that maximize their outcomes and reduce downstream health care costs, rather than relying on arbitrary and non-evidenced-based thresholds.

1.3 | Myth 3: Adherence is static

Clinicians and researchers recognize that adherence changes over time.[27] Yet, this reality is often ignored in studies that measure adherence only once, or over a short interval. Even when measured longitudinally, data are often averaged over time. This practice is also reflected in policy. In the Medicare Advantage STAR ratings, health plans are rated based on the proportion of members who refilled at least 80% of their prescribed medications over the prior year. This obscures the fact that a rate of 80% of pills taken over 1 year can be achieved in many ways, such as taking all pills for 9 months and then stopping for 2 months before taking all pills again the last month, taking 80% of pills each week over the entire duration, or taking 60% of pills 1 week alternating with 100% the following week. Each of these scenarios may have different health consequences and may require different interventions to improve adherence.

To take advantage of repeated measurements, advanced statistical methods can be applied to data obtained with a variety of measurement methods (eg, electronic medication monitoring, refill adherence, self-report). One such method is group-based trajectory models (GBTM).[28-32] Modi and colleagues applied this technique to examine patterns of nonadherence to antiepileptic medications in children, assessed by electronic drug monitoring.[32] The researchers identified 5 different adherence patterns in the first 6 months of therapy, including severe early nonadherence, severe delayed nonadherence, moderate nonadherence, mild nonadherence, and near-perfect adherence. These unique adherence patterns would be masked if one merely calculated the proportion of times that the medication container was opened during the 6-month time period. Franklin and colleagues showed that the underlying dynamics of statin adherence are invisible in cross-sectional measures, and that trajectory models predicted cardiovascular events better than categorical adherence measures in some cases.[28,29] Other statistical approaches have been applied to electronic drug monitoring data with the same goal of identifying distinct trajectories of adherence and evaluating associations between trajectories and outcomes.[33] Such analyses can demonstrate that 2 individuals with the same adherence rate (eg, 50%) have very different patterns of medication-taking, with 1 person alternating taking pills and skipping, and another taking drug holidays in the midst of perfect adherence.[12] Identifying these patterns is important, as each scenario may require a different intervention.

1.4 | Myth 4: Self-reported measures of adherence are less useful than "objective" measures

There is a common misperception that self-reported measures of medication adherence are invalid, due to social desirability and recall biases. Indeed, self-reported adherence rates have been 10% to 20% higher than rates obtained through electronic drug monitoring or refills. Additionally, self-reports have tended to show weaker or less consistent associations with clinical outcomes compared with refill adherence or electronic drug monitoring.[34,35]

Despite these limitations, self-reported adherence measures have many uses in research and practice. Self-report via a clinical interview is the only method that all clinicians have at their fingertips. Furthermore, self-reports can assess reasons for nonadherence as well as the extent of nonadherence, which informs interventions by directly probing specific behaviors (eg, missing doses, taking extra doses, not following instructions regarding food). As such, self-report measures typically assess different behaviors in the adherence cascade than so-called "objective" measures against which they are evaluated, explaining in part the weaker or less consistent relationships of self-reported adherence to other adherence measures. In 1 study of patients with hypertension, while self-report and refill adherence showed poor agreement with one another, they were each independently associated with blood pressure control,[36] suggesting they were measuring different, but similarly important, components of adherence.

Instead of avoiding self-reported measures of adherence, researchers should make efforts to improve them, given their many advantages. The utility of self-report measures could be enhanced by following psychometric principles for scale construction. Voils suggested that the construct should be specified and matched to the appropriate type of latent variable model so that appropriate reliability and validity analyses may be conducted.[37] A panel of experts convened by the National Institutes of Health Adherence Network summarized 10 established measurement recommendations to reduce the influence of social desirability and memory biases, such as specifying the recall period and using an introduction that normalizes nonadherence.[35]

The 2003 WHO report suggested a multi-method approach that combines self-report with another method to achieve a closer approximation to the "true" adherence level. Our position is slightly different. When researchers wish to administer multiple measures to maximize validity, we recommend selecting multiple measures of the same behavior over an identical time frame (eg, a self-report measure that assesses missed doses over the past 7 days, and missed doses over the past 7 days calculated from electronic drug monitoring). When they wish to measure different steps of the adherence "cascade",[10] they can select appropriate measures for each step, recognizing that disagreement between measures may arise from the fact that each measure assesses a different behavior.

2 | IMPLICATIONS/CONCLUSIONS

Each myth about adherence measurement is rooted in the misconception that adherence is a single, static construct, and can be measured as such. To improve the evidence base on medication adherence, researchers should specify where in the time continuum the adherence behavior is occurring, specify which medication-taking behavior they wish to measure, and select corresponding measures—this is true even if each of these behaviors fits within a single component in the new adherence taxonomy. After obtaining repeated measurements, statistical analyses should take advantage of all data points, with the goals of characterizing behavior, whether observationally or in response to a clinical intervention, and identifying clinically relevant thresholds that correspond to clinical outcomes. Findings from comparable studies (assessing the same behaviors in the same populations) can then be pooled in systematic reviews.

In summary, we should stop looking for a gold standard measure of "adherence" because it cannot exist. Clear conceptualization of the adherence domains of interest and the use of interventions and measurement tools that are well-matched to these domains is essential to moving the field forward. Without doing so, we may continue to see marginally effective interventions that have little overall impact on patient health and health care costs.

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DISCLAIMER

The contents represent the views of the authors only and not necessarily those of the Department of Veterans Affairs or the United States Government.

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