



Review Article

Improving the assessment of medication adherence: Challenges and considerations with a focus on low-resource settings

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ABSTRACT

Improving patient survival and quality of life in chronic diseases requires prolonged and often lifelong medication intake. Less than half of patients with chronic diseases globally are adherent to their prescribed medications which preclude the full benefit of treatment, worsens therapeutic outcomes, accelerates disease progression, and causes enormous economic losses. The accurate assessment of medication adherence is pivotal for both researchers and clinicians. Medication adherence can be assessed through both direct and indirect measures. Indirect measures include both subjective (self-report measures such as questionnaire and interview) and objective (pill count and secondary database analysis) measures and constitute the mainstay of assessing medication adherence. However, the lack of an inexpensive, ubiquitous, universal gold standard for assessment of medication adherence emphasizes the need to utilize a combination of measures to differentiate adherent and nonadherent patients. The global heterogeneity in health systems precludes the development of a universal guideline for evaluating medication adherence. Methods based on the secondary database analysis are mostly ineffectual in low-resource settings lacking electronic pharmacy and insurance databases and allowing refills without updated, valid prescriptions from private pharmacies. This significantly restricts the choices for assessing adherence until digitization of medical data takes root in much of the developing world. Nevertheless, there is ample scope for improving self-report measures of adherence. Effective interview techniques, especially accounting for suboptimal patient health literacy, validation of adherence questionnaires, and avoiding conceptual fallacies in reporting adherence can improve the assessment of medication adherence and promote understanding of its causal factors.

KEYWORDS: *Assessment, Diabetes, Hypertension, Low-resource settings, Medication adherence*

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INTRODUCTION

Improving patient survival and quality of life in chronic diseases such as diabetes, cardiovascular disease, hypertension, cancer, chronic obstructive pulmonary disease (COPD), and HIV-AIDS requires prolonged and often lifelong medication intake which is regular, uninterrupted, timely, and with no or minimum of missed doses. Chronic disease burden from noncommunicable diseases (NCDs) and HIV-AIDS is among the highest in low- and middle-income countries [1-6]. However, less than half of these patients are adherent to their medications [7]. Although a global challenge, nonadherence to medications is estimated to be a much bigger problem in the developing world [7].

Medication nonadherence or nonadherence to medications signifies the patient drug-taking behavior does not correspond to

that recommended by the physician. This precludes the patients from achieving the complete benefit of the prescribed treatment, worsens therapeutic outcomes, aggravates disease with early onset of complications, and increases the frequency of hospital admissions [7-9]. Avoiding medication nonadherence can save billions in avoidable direct health-care costs apart from the indirect losses due to lowered economic productivity [9-11].

The accurate assessment of medication adherence is pivotal for both researchers and clinicians [12]. The interpretation of clinical trials can be invalidated due to misclassification of the

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adherent and nonadherent cases [12,13]. A spuriously low estimation of nonadherence to experimental drug treatment can underestimate the incidence of side effects and overestimate the optimum dosage necessary for attainment of therapeutic efficacy [13]. In clinic settings, the inability to correctly identify medication nonadherence can promote unwarranted intensification of therapy which increases health costs, the risks of adverse effects, and may lower adherence due to the higher pill burden and increased regimen complexity [12-15].

It is well-established that primary care physicians enable patients in their self-care practices [16]. Patient-provider concordance at the primary care level by ensuring patient continuity of care for chronic NCDs can improve their medication adherence and achieve optimal health outcomes while also reducing the need for specialist referral [17]. The regular and correct evaluation of medication adherence represents a critical function of primary care.

Despite the decades of research on medication adherence, no gold standard exists for assessment of medication adherence [13-15,18]. Furthermore, most medication adherence measures have been previously validated in developed world clinic settings that differ considerably in terms of resource availability. However, it is well recognized that translating research evidence into practice in developing countries is often ineffectual due to failure to assess and bridge the resource gaps [19]. The generation of research evidence on medication adherence represents one such domain where the challenge of estimating patient medication adherence is compounded in low-resource settings that are frequently characterized by poor record keeping, high-patient load with poor doctor-patient ratio, and suboptimal patient health literacy [7]. Moreover, there exists a high burden of unintentional adherence due to lack of universal health coverage, especially among the socio-economically disadvantaged populations.

In this narrative review, we assess the appropriateness and feasibility of the well-established methods for estimating medication adherence in low-resource outpatient settings and explore approaches for enhancing the identification of medication nonadherence in these settings. We conducted literature searches on MEDLINE (accessed by PubMed) and SCOPUS using the search terms: “Medication Adherence” (MeSH and entry terms), “Assessment” (MeSH and entry terms), and “Evaluation” (MeSH and entry terms) used individually or in combination until July 2018. The reference list of the selected articles was also screened to find other relevant articles.

MEDICATION ADHERENCE: DEFINITION AND CONCEPTS

Medical adherence has been defined as, “the extent to which a person’s behavior – taking medication, following a diet, and executing lifestyle changes, corresponds with agreed recommendations from a health-care provider” [7]. The concept of adherence involves an autonomous “active, voluntary and collaborative engagement of the patient” involving “a range of medical behaviors to produce a desired therapeutic result” [20]. Adherence thus differs from “noncompliance” which implies a

passive conforming of the patient to the medical judgment of the prescriber.

Medication adherence is the “extent to which a patient acts by the prescribed interval and dose of a prescribed regimen” [21]. Achieving medication adherence in a patient involves at least three steps of acceptance, persistence, and execution of a treatment regimen. Acceptance of the medication regimen prescribed to the patient refers to the adoption and initiation of a prescribed medication regimen by the patient. Persistence estimates the length of time from initiation to the discontinuation of therapy during which the patient continues treatment [22]. Nonpersistence indicates that the patient decided to stop taking medication after starting it, without being advised by a physician to do so. Noninitiation of the treatment also indicates a mode of nonpersistence [23]. Execution represents the extent to which the patient conforms to the medication use recommendations specified by the prescriber (e.g., frequency/interval of administration, the strength of dosage)” [24]. Undermedication or infrequent medication is a more likely phenomenon compared to overmedication. However, overmedication can be of significant concern with drugs which have high toxicity and potential for adverse effects or in the drugs and disease conditions where there exists the risk of drug overuse resulting in addiction and abuse.

Nonacceptance, nonpersistence, or improper execution of a prescribed medication regimen indicates the presence of medication nonadherence. Medication nonadherence can be further classified into the following types: (1) primary nonadherence: due to failure to initiate medications which have been prescribed to them; (2) Secondary nonadherence: medications are acquired through refill but are not taken as prescribed [12,18]; (3) Unintentional nonadherence: refers to nonadherence when a patient is unable to procure refills due to lack of financial resources or lacking the capacity to collect refill for instance from a hospital pharmacy; and (4) Intentional (volitional) nonadherence: medication nonadherence despite the availability of drug stocks due to patient-related factors [25] such as forgetfulness, carelessness, lack of belief in the usefulness of medication, or fear of side effects whether real or perceived.

MEASURING ADHERENCE: METHODS, APPLICABILITY, AND CHALLENGES IN LOW-RESOURCE SETTINGS

The correct assessment of medication adherence is universally recognized as a medical challenge. The practical methods for estimating medication adherence (direct and indirect methods) along with the lacunae in their application in low-resource settings are described below [12,18].

Direct (objective) measures

These measures can be used to validate subjective measures and provide the most accurate estimate of medication adherence. However, they are not feasible for a large population, nonclinic and community settings and also require substantially more resources compared to indirect methods.

Direct observation of therapy

The patient act of consuming the recommended medication is observed by an external observer like a family member or a trained provider. It can be considered as the closest to the gold standard for assessing medication adherence. Direct observation of patient adherence by attendants or family members can be used to corroborate patient testimony or when the patient is incapable of reporting adherence like in children or dementia patients. When a family member is specifically involved in supporting patient adherence like through reminders for medication intake or application of an injectable drug, direct observation becomes a particularly useful measure for assessing medication adherence.

Drug assays and biomarkers

These methods are limited by the need for obtaining patient blood and urine samples, differing rates of drug metabolism which renders it difficult for quantification of drug concentration of very fast-metabolizing and very slow-metabolizing drugs which remain in the blood in small concentration even after drug cessation. There is also a tendency for patients to improve their adherence just before physician appointments (white coat adherence) while remaining nonadherent in the intervening periods [9].

Indirect measures

These methods imply that the medication intake has been initiated and is being used by the patient. They can be both subjective and objective measures. Most indirect measures rely on calculating an average percentage of medication consumed or refilled over time. However, treatment outcomes are also related to treatment execution factors such as timing of drug intake and correctness of drug dosage, especially for nonpill regimens which remain unassessed with these standard measures for assessing medication adherence.

Indirect subjective measures

These can be applied in patient care or community settings as they facilitate rapid patient self-reported assessments of medication adherence.

- i. Patient interviews: It is used to calculate a numerical proportional value between 0 and 100 which is known as the drug adherence rates (DAR). It is calculated as the proportion of prescribed medication pills taken by the patient over a specified time interval. However, the results are subject to recall bias, particularly when the specified duration for the recall is long. The cutoff value for patient adherence is based on the expected DAR required to induce treatment outcomes. The DAR should be $\geq 95\%$ or preferably 100% for antiretroviral therapy in HIV-AIDS [26], $\geq 90\%$ in tuberculosis, and $\geq 80\%$ for most of the other chronic diseases [7].

When querying patients regarding their medication use, an important validated question is “have you missed any pills in the past week?” The question has high specificity but low sensitivity due to the patient tendency to please the physician by denying any missed doses [27,28]. Prefixing the question with an empathetic statement like “patients often have difficulties in remembering to take all their medications” can help

reassure patients and make them more amenable to telling the truth [13]. When quantifying the extent of medication nonadherence, a similar question can be used, “how often you forget taking your medications” or “how often you miss taking your medications in the previous (time interval).”

Illiterate or low educational status patients often show poor health literacy or the inability to understand necessary health information required for making appropriate health decisions [29]. Assessment of medication adherence in these patients should ascertain their ability to identify the drugs for their disease condition correctly, the correct frequency of administration and adherence to the prescribed dosage.

- ii. Questionnaires for assessment of adherence for various disease conditions are summarized in Table 1. Medication Adherence Questionnaires (MAQs) or scales with good psychometric properties and high predictive validity are recommended for assessment of adherence. Items in these questionnaire scales assess different aspects of patient behavior relating to medication nonadherence such as carelessness, forgetfulness, the frequency of missed doses, difficulty in adherence due to work, travel or when engaged in occupational activities, perceived side effects, self-modification of medication frequency or dosage, and adherence during weekends or extended holidays. Assessment by questionnaire unlike other methods apart from identification of nonadherence can also recognize behavioral causes of patient nonadherence which may be modifiable through suitable behavior change interventions.

The MAQs are particularly useful for assessing medication adherence in community settings through surveys, particularly in areas where continuity of care and conscientious medical record keeping is lacking that precludes assessment through most other methods.

Overestimation of adherence due to the self-desirability bias of the patients to avoid criticism and gain approval of their treating physician is a major drawback of indirect subjective measures [40,41]. Some patients perceive reporting of nonadherence as stigmatizing since it reflects being nonchalant of their welfare and insubordination of their physician's instructions. However, it has also been argued that medication intake represents a pivotal health behavior which the patient should be able to self-report correctly [42]. The interval period for which adherence should be estimated through self-report can vary from a period of 1 week to several months. Shorter periods may lack validity and association with a clinical response, while extended periods are biased by patient recall.

In the low-resource settings of the developing world, the existing MAQs need to be cautiously applied for the following reasons: First, most of these questionnaire scales which were originally validated in the Western world should be assessed for cross-cultural equivalence. Second, questionnaires with more items take proportionally more time to fill which in overcrowded clinic settings is a drawback. Third, most adherence questionnaires should preferably be self-administered, but in patients with low-literacy, they need to be verbally administered by an assessor that can influence their reliability and validity while introducing the risk of bias. Similarly,

Table 1: Summary of important self-report measures for assessing medication adherence

Name of the scale	Type of scale	Number of items	Parameter of assessment	Validation
Morisky, Green, and Levine Scale [30]	Generic	4	Medication adherence	Hypertension
MMAS-8 [31,32]	Generic	8	Barriers to adherence	Hypertension
			Medication adherence	
Brief medication questionnaire [33]	Generic	9	Medication adherence	Diabetes
			Barriers to adherence	Depression
Medication subscale of the SDSCA [34,35]	Specific	2	Medication adherence	Diabetes mellitus
ARMS-D [35]	Specific	11	Medication adherence	Diabetes mellitus
Hill bone compliance [36]	Specific	14/9	Barriers to adherence	Hypertension
			Medication adherence	
			Restriction of sodium	
MARS [37]	Specific	10	Medication adherence	Chronic mental illness
			Attitude toward adherence	
			Attitude toward illness	
Aids Clinical Trial Group [38]	Specific	5	Medication adherence	HIV-AIDS
Tuberculosis Medication Adherence Scale [39]	Specific	12	Medication adherence	Tuberculosis
			Barriers to adherence	

MMAS: Morisky Medication Adherence Scale-8, SDSCA: Summary of diabetes self-care activity, ARMS-D: Adherence to Refills and Medication Scales for diabetes, MARS: Medication Adherence Rating Scale

in comorbid patients on multiple drug regimens showing poor health literacy, ascertaining the adherence for the individual drugs can be challenging and time-consuming.

iii. Medication diaries: Patients or participants of a trial keep a record of the date and time of consumption of each dose of medication and whether it was consumed with or without food. This permits the investigator to assess and track patient execution of adherence. Like self-report measures, medication diaries are susceptible to overreporting due to the self-desirability bias of the patient. Underreporting may also occur if the patient out of carelessness omits to record some of the medication doses taken into the diary. In patients who are functioning illiterate, the method is not feasible unless assisted by a literate caregiver or family member.

Indirect objective measures

These can be applied in research and administrative settings.

Electronic medication packaging devices

Electronic medication packaging devices provide real-time monitoring and feedback on adherence performance. The most commonly used instrument is the Medication Event Monitoring System which is a medication bottle cap with a microprocessor that records the occurrence and time of each bottle opening. However, despite their high accuracy, the high cost of such devices renders them unsuitable for large sample size studies [43].

Pill counts

Pill counts are calculated by counting the number of dosage units consumed by the patient between two scheduled appointments or clinic visits. The medication bottle or strips dispensed during the previous visit are brought by the patient. The number of pills taken by the patient is then calculated by

subtracting the count of the number of pills remaining from the total number of pills dispensed which is divided by the product of prescribed doses and the number of days between those two visits to obtain the proportion of days covered (PDC). However, the pill count method cannot ascertain if the patient actually consumed the medication and if was taken as per prescribed dose and frequency [44]. Pill count measures are cumbersome for both the patient and the assessor and can be time-consuming. The presence of surplus medication with the patient is also not accounted for in this method. Pill counts are also not feasible in circumstances when patients do not usually preserve their empty medication vials and strips. However, pill count measures have been successfully applied in public health facilities in the developing world when estimating adherence in HIV and TB patients, diseases which are associated with considerable stigma and discrimination. This suggests that patients are likely to adhere to pill count requirements when it is mandated to do so. Pill count methods can evaluate medication adherence in community settings also.

Prescription or pharmacy records (secondary database analysis)

These methods are used for assessment of refill adherence, in which prescription refilling behavior of the patient is considered to correspond with medication intake behavior. The pharmacy supply adherence measures are classified as based on the medication supply (possession with the patient) and supply not made (treatment gap). Two of the most common measures based on the medication possession are as follows: (a) Medication Possession Ratio: it is calculated as the number of days for which medication was supplied divided by the number of days during the period from index fill to the last scheduled refill [44] and (b) the PDC: it is calculated as the number of days in which a medication was available with the

patient divided by the total number of days in the data analysis period [18].

Secondary database analysis has several advantages compared to self-report methods: secondary data, when extracted from electronic records, is less prone to error and takes less time for analysis and can be done retrospectively at any specific period, ethical issues are minimal, and patient-related biases are absent.

A major drawback of secondary database analysis methods is their assumption that medication possession with patients corresponds with their medication intake. Furthermore, in low-resource settings, their application is hindered due to the following reasons: First, the validity of secondary data analysis for assessing medication adherence is fundamentally dependent on the data quality. Electronic health records are needed for analysis of large retrospective databases which may be missing in these settings. Second, the utilization of pharmacy and insurance records is unsuited to environments where a significant proportion of patients lack health insurance and are not assigned designated physicians and health facilities for their treatment purposes. Third, if the patient has access to private pharmacies and other health-care facilities where medicine can be dispensed on an outdated prescription or even without it, the prescription filling data is rendered ineffective for evaluation of patient adherence [45]. In these circumstances, the prescription or pharmacy record has to be supplemented with patient self-report for the duration of missing refills which undermines to a large extent the objectivity and validity of the original measure. For instance, a patient who misses his clinic appointment can self-report medication purchases from out of pocket. The accuracy of such statements is difficult to verify in health systems where the fulfillment of medication refills on old prescription is not uncommon.

Avoiding simple errors and fallacies in the assessment of medication adherence

Errors in research methodology can generate adherence rates which may be of doubtful or reduced validity and preclude comparison with adherence estimates from other studies. Some of the key steps for preventing avoidable errors in the estimation of medication adherence are discussed below:

- a. Report the method used for assessment of medication adherence: Failure to report the method used for estimation of medication adherence reduces the validity of the study and precludes comparison with other studies [46]. The researcher should also state the recall period over which adherence was estimated
- b. Report medication adherence through self-report methods for both continuous and categorical outcomes: Medication adherence outcomes evaluated from self-report measures which were originally continuous can be categorized or recoded into two (or more) categories such as adherent/nonadherent or good/medium/poor adherence. There have been instances when researchers only report the categorical outcomes for the single item summary of diabetes self-care activities measure (SDSCA) although it is the mean of the continuous outcome which explains the population medication adherence level [47,48]

- c. Reporting of adherence in comorbid patients: Since comorbid patients are taking medications for multiple disease conditions, a combined assessment of medication adherence precludes the identification of the specific disease conditions for which nonadherence is present. Medicine pills for two different diseases prescribed to be taken at the same time are expected to correlate, but such assumptions can be misleading since the patient's perceived susceptibility to the disease and perceived barriers such as side effects may differ significantly between drugs for two different disease conditions. For instance, a research study found the rate of antidiabetes and antihypertension medication adherence to vary significantly in the comorbid patients [49]. Similarly, tuberculosis and HIV medication adherence rates can be dissimilar in the comorbid patients [50].

Moreover, generic MAQ scales need to be validated for the specific disease conditions due to which a scale validated for medication adherence assessment in hypertension may not be accurate in identifying nonadherence in diabetes patients.

IMPROVING THE ASSESSMENT OF MEDICATION ADHERENCE: APPROACHES AND CONSIDERATIONS PARTICULARLY IN LOW-RESOURCE SETTINGS

Multimeasure approaches

Using more than one measure of medication adherence is recommended since a single measure cannot encompass all aspects and steps of medication adherence behavior [12,18]. The validity of the patient adherence status interpreted from the data collected increases on selecting two (or more) medication adherence measures. A study by Nelson *et al.* assessed diabetes medication adherence with two validated self-report measures, namely, the Adherence to Refills and Medications Scale for diabetes and the SDSCA medication subscale [51]. Furthermore, combining a questionnaire scale with a pharmacy record method is particularly useful since it assesses both medication possession and the patient's medication intake behavior. This is since the validated MAQs often identify behaviors predicting nonadherence but do not determine medication possession with the patient. A study by Nundy *et al.* reported diabetes medication adherence using both a self-report measure and the PDC method [52].

Even when a secondary database or pharmacy record-based analysis is not feasible, questionnaire scales should be supplemented with patient interviews which record the presence of unintentional nonadherence by assessing the duration for which the patient did not possess his medication. Although these methods are subjective, prone to recall bias, and inferior to objective methods based on secondary database analysis, they can still provide useful information in estimating the reality of patient adherence status. For instance, in a study by Basu *et al.*, among Type 2 diabetes patients in a tertiary care hospital in Delhi, the rate of medication nonadherence assessed by the Morisky Medication Adherence Scale-8 item and self-reported lack of medication possession during the previous 3 months differed significantly at 25.5% and 41%, respectively [45].

Enable disease-specific approaches and considerations

Medication adherence in chronic diseases is particularly challenging since adherence is a dynamic process which varies with time. Medication adherence may be higher during the first few months from initiation of treatment or when symptomatic of the disease compared to later months if the patient becomes asymptomatic. Some other issues specific to certain chronic conditions are also discussed below.

Diabetes

Estimating medication adherence in diabetes patients is particularly challenging since the primary therapeutic outcome which is glycemic status does not necessarily correlate with medication adherence levels. This is because elements of treatment adherence in diabetes include lifestyle factors such as diet and exercise which are less likely to be adhered to compared to medication [17,45,53]. Moreover, therapeutic inertia due to the failure to initiate insulin in poorly controlled diabetes patients shows a high prevalence in low-resource settings [54]. Thus, a poorly controlled diabetes patient otherwise adherent to his or her prescribed oral hypoglycemic agents (OHA), but needing treatment with insulin will continue to show poor glycemic control. Patient adherence should preferably be triangulated with prescription adherence of the treating physician toward evidence-based intensification of antidiabetic therapy.

Studies in low-resource settings also show a higher prevalence of suboptimal glycemic control in patients on insulin compared to those on OHA despite similar or higher levels of self-reported adherence [55-57]. Such findings can arise from overreporting of insulin adherence by patients, inability of patients to procure their prescribed insulin medication (low refill adherence), or the presence of inadequate self-efficacy and minimum health literacy necessary for making correct dose adjustments. This also suggests that refill adherence alone is an inappropriate measure for assessment of insulin adherence.

A comprehensive evaluation of insulin adherence in diabetes patients, especially in those suspected of unintentional adherence should, therefore, include: (i) assessment of medication persistence (i.e., continuity of insulin therapy without discontinuation), (ii) medication possession (access to insulin through refill adherence), and (iii) medication adherence (frequency of missed doses and frequency of taking less than prescribed doses of insulin).

Chronic obstructive pulmonary disease

Medication nonadherence in COPD patients can be from underuse, overuse, or improper use. Overuse of rescue medications by patients during exacerbations is characteristic of COPD [58]. Errors in inhalation techniques reflect nonadherence resulting from improper usage. The assessment of medication nonadherence in COPD patients should explore all these three domains.

HIV-AIDS

The rate of ART adherence which is adequate for viral suppression can range from $\geq 95\%$ to also 100% [26,59]. Studies estimating ART adherence when dichotomizing people living with HIV-AIDS (PLHIV) into adherent and nonadherent categories should use both the acceptable cutoffs ($\geq 95\%$ –100%) to enable comparison with previous studies which may have used

only a single cutoff [60]. The challenge of selecting a suitable adherence interval is also particularly relevant in PLHIV due to the very high rate of adherence and persistence of treatment required to maintain a satisfactory virological response [26].

Use of information–communication–technology-based methods

Remote communication technology can be applied for monitoring adherence through patient self-report through text messages, web-enabled mobile phone applications, and interactive voice response systems. Although the efficacy of information–communication–technology (ICT)-based systems in monitoring and enhancing adherence has been reported in studies predominantly concentrated in the developed world, the rapid expansion of ICT services in the developing world considerably expands the potential for their application [61,62].

CONCLUSION

The prevention of poor medication adherence in patients with chronic diseases is essential for maximizing public health outcomes globally. The vast disparities in public health spending drive a dual burden of unintentional and intentional nonadherence in low- and middle-income countries. The WHO, therefore, considers “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments” [1]. Adherence represents a dynamic behavior whose level can be influenced by both patient and health system-related factors. The accurate identification of medication nonadherence and its determinants can thereby promote the development of effective interventions for reducing nonadherence and maintaining patient adherence to therapy.

The absence of an easily accessible, universal gold standard for assessment of medication adherence emphasizes the need to utilize a combination of measures to differentiate adherent and nonadherent patients. Furthermore, the global heterogeneity in health systems precludes the development of a universal guideline for evaluating medication adherence. Methods based on secondary database analysis are mostly ineffectual in low-resource settings lacking electronic pharmacy and insurance databases and allowing refills without updated, valid prescriptions from private pharmacies. This significantly restricts the choices for assessing adherence until digitization of medical data takes root in much of the developing world. Nevertheless, there is ample scope for improving self-reported measures of adherence. The use of effective communication regarding adherence, especially in patients with suboptimal health literacy, the use of validated medication adherence assessment tools and avoiding conceptual errors can improve the assessment of medication adherence and promote understanding of its causal factors.

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Conflicts of interest

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