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Studies of Medication Adherence

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In this chapter, we will describe the importance of adherence in pharmacoepidemiologic research, the methods for measuring adherence, methodologic issues that arise once adherence has been measured, and future directions. While we use many different drug–disease examples, we focus on examples from HIV and cardiovascular diseases because these areas have been major focuses of adherence research.

The underuse of essential medications imposes significant clinical and financial burdens on healthcare systems. Data show that as many as half of patients do not take their medications as prescribed, resulting in more than $100 billion in excess annual spending in the US [1]. Nonadherence is also thought to contribute to 11% of US hospitalizations each year [1]. Without accurate measurements of adherence incorporated into research and practice, the problem will remain underappreciated and poorly addressed.

Despite its importance, medication adherence is difficult to define. Earlier research has used the term *compliance*, or "the extent to which the patient's dosing history conforms to the prescribed regimen," to describe this behavior [2]. However, this term implies that patients passively "conform" to the prescriber's directions; therefore, the term *adherence* is now strongly preferred [3]. *Adherence* better conveys the idea of a patient–provider relationship where the patient implements the provider's recommendations.

Another reason why adherence has been difficult to define is that it is not a single static behavior but instead encompasses a set of behaviors over time. One common taxonomy developed by a scientific consensus group classifies adherence along three phases: (1) initiation, (2) implementation, and (3) persistence (Figure 38.1) [4]. *Initiation* describes initial engagement with the prescribed medication. Research suggests that as many as 30% of newly prescribed therapies are never actually filled by patients [5], which is often referred to as primary nonadherence. *Implementation* represents how well the patient follows the prescribed regimen while s/he is engaged with treatment. While varying greatly across diseases, approximately 50% of patients are thought to not correctly follow prescribed regimens. *Persistence* refers to how long the patient continues to follow the regimen [6].

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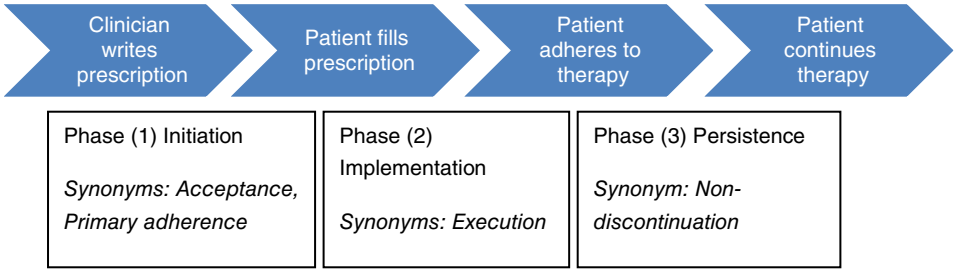

Figure 38.1 Phases and taxonomy of adherence.

Poor treatment adherence can occur along any of these phases.

The actual behaviors involved in taking a prescribed medication as directed become more complicated when considering each adherence phase. This taxonomy helps distinguish patients who never initially fill a prescription from patients who occasionally forget to take doses as well as patients who take a medication regularly at first but then later discontinue. Classifying all three types of patients simply as "nonadherent" ignores the fact that each of these patients may differ with respect to treatment outcomes and likely have different adherence barriers requiring different interventions [3]. This taxonomy also highlights the multifactorial behaviors required for sustained medication adherence and why measuring it, identifying the barriers, and then improving adherence has been difficult. Regardless, practical approaches to measuring and analyzing adherence have been successfully developed, and we will discuss the challenges and utility of various approaches to measuring adherence throughout the chapter.

Clinical Problems Addressed by Pharmacoepidemiologic Research

Adherence research confronts the truism attributed to former US Surgeon General C. Everett Coop, MD that "drugs don't work in patients who don't take them" [7]. Measuring adherence is essential in order to address several issues in the interpretation of studies of beneficial and adverse effects of medications. In randomized trials, treatment adherence can be an important factor that affects the estimates of efficacy and safety of the tested medications (see Chapter 32). Poor adherence to the drug being tested can lead to underestimates of drug efficacy [8]. Further, information about adherence allows for a more accurate assessment of drug safety because those who do not take the drug cannot experience its toxicity. Because perfect adherence is not attainable, even in clinical trials, measurements of adherence can elucidate whether a drug fails to exert an effect because it did not work or because it was not taken properly. Poor adherence may itself also be a marker of toxicity or adverse events.

Once a medication is marketed, information from clinical trials gives only a limited view of how drugs are used by patients. Patients who volunteer for clinical trials are thought to be more motivated than those in usual care [8,9]. Therefore, measuring adherence in observational studies of drug effectiveness and safety may be even more important than in clinical trials. Furthermore, assessing adherence in observational studies provides a more "real-world" estimate of adherence in clinical populations. Finally, because adherence itself is a major determinant of treatment outcomes, it can also be the specific focus of pharmacoepidemiologic research.

Nonadherence can be intentional or unintentional. Studies have identified many potential barriers to adherence, broadly categorized as patient-, system-, and medication-specific factors. Common patient barriers consist of forgetting to take the medication, lack of knowledge or health literacy, and psychosocial factors such as depression and lack of social support [10–12]. System barriers include logistical difficulty in obtaining the medication and, in some settings, sporadic drug unavailability ("stock outs") [13,14]. Key medication-specific factors include regimen complexity and adverse effects [15,16]. Further, patients may decide on a dose-by-dose basis whether to take medicine as prescribed, perhaps to avoid side effects at inconvenient times (like avoiding increased urination at night). Finally, postmarketing studies have observed "pill fatigue" (in that adherence can decrease over time from being emotionally overwhelmed by taking medication), particularly when patients are followed for longer than typically done in trials [17,18]. It is a well-known phenomenon that the optimal adherence seen early in therapy often decreases over time [19]. Thus, observational adherence studies provide unique data not available from trials.

While missed doses are a more common adherence problem, taking extra doses can also be a problem. For example, extra doses of drugs with a narrow therapeutic window, such as warfarin for anticoagulation, may result in toxicity [20]. Patients may also take extra doses of narcotics prescribed for the treatment of pain because of inadequate pain relief or for potential abuse (see Chapter 28).

Measuring adherence can also be useful for determining the threshold of how much medication must be taken to obtain desired clinical outcomes; these dosing thresholds likely differ by drug and disease. In hypertension, taking at least 80% of prescribed medication has been an acceptable standard for blood pressure control [21]. However, in HIV, 80% adherence is often insufficient. For example, in a study of patients starting protease inhibitors for HIV, those who took 80–95% of doses were more likely than those with lower adherence to achieve complete suppression of viral replication [22]. Unfortunately, such detailed information is not available for most drugs and diseases. Despite the likelihood that 80% of doses taken is not the optimal universal cut-point for acceptable adherence, this threshold persists across research and quality measures [23]. Therefore, the default adherence goal should be to encourage the patient to take as many prescribed doses as possible, and future research is focusing on identifying more empiric and robust dose–response thresholds for various diseases.

Finally, adherence can also impact public health, especially in infectious diseases. For example, in tuberculosis and HIV, nonadherence can actually lead to resistance to medications. Because these resistant diseases are transmissible [24], the measurement of nonadherence and adherence interventions takes on greater public health importance.

Methodologic Problems to be Solved by Pharmacoepidemiologic Research

Challenges in the Measurement of Adherence

The gold standard for measuring adherence to treatments is directly observed therapy [14]. However, this approach is only practical in limited settings, such as the administration of a novel agent in a controlled environment. While many approaches exist, as will be discussed later, whatever the approach, the discovery of nonadherence in clinical settings can be embarrassing for patients, because it can imply lack of respect for the provider's advice or for one's welfare. Thus, knowledge that one's adherence is being monitored risks influencing the behavior it is

measuring (i.e., a Hawthorne effect). Moreover, tracking a daily activity can be burdensome regardless of whether individuals are aware of their own nonadherence. Therefore, measuring adherence requires creative approaches to accurately capture a daily activity performed at different times per day for different individuals.

Challenges in the Analysis of Adherence Data

Once adherence is measured, there are various approaches to analyzing the data depending on the data sources used. In clinical trials, adjusting results for adherence is complicated by the fact that being adherent itself is associated with better outcomes (i.e., placebo effect). For example, in a randomized double-blind placebo-controlled trial of propranolol after myocardial infarction, poor adherers had a 2.8 higher odds of mortality compared with good adherers in the same active arm, after adjustment. However, the adjusted odds ratio of mortality in those with poor adherence to placebo was, similarly, 2.7 [25]. Presumably, adherence to either agent, whether propranolol or placebo, was strongly associated with other unmeasurable lifestyle factors associated with mortality. How to control for this healthy adherer effect is an important analytic consideration.

Other analytic challenges include the duration and timing of adherence measurements. Because adherence behaviors vary over time, individuals may have substantial changes across the observational period. For example, individuals are prescribed lifelong regimens for many chronic diseases. When initiating treatment, adherence over the first 12 weeks may not be the same as adherence over the final 12 weeks. Simply summing adherence over an entire 52-week interval will provide an average of adherence, but short periods of nonadherence can substantially impact clinical outcomes [26]. Therefore, when conducting adherence analyses, researchers need to carefully consider the appropriateness of the adherence "interval(s)". Many adherence studies of chronic medications choose intervals that are at least 180 or 365 days long to capture enough variation in use; however, this choice must be balanced with the length of follow-up available on patients to ensure external generalizability [27].

Whatever the interval, the summation of adherence data can also be accomplished in different ways. The simplest is the percent of doses taken, but this may not be the most clinically relevant metric. Depending on drug pharmacokinetics and pharmacodynamics, gaps and variability in adherence may be more important than the proportion of prescribed doses taken. However, a composite measure of percentage of doses taken over an entire time period is often still used as the sole adherence measurement in research publications and measures of healthcare quality. There have been recent advancements in measuring adherence, which are discussed later in this chapter.

Additionally, many diseases are treated with combination therapy (either multiple medications in the same formulation or multiple separate formulations). When drugs are studied in combination to determine their effect (e.g., antihypertensive or antituberculous therapies), it is challenging to determine how to weight differential adherence or switching among the drugs [27]. Many of these issues can be addressed with currently available solutions, although methodologic challenges remain to be solved.

Currently Available Solutions

There are many different methods for measuring medication adherence, and each method has strengths and weaknesses. Which method is most appropriate depends upon the situation in which it will be used and how precise the measurement needs to be. Some measurements require more intensive patient-level contact than others, and some provide more granular

data with respect to timing of dose taking. For example, in prospective clinical trials, because of the direct patient contact, many of these techniques can be used. In other settings like retrospective studies using databases, options are more limited. Therefore, the use of multiple measures or sources of data may be helpful to confirm findings. For all approaches, the interpretation of adherence findings may also change depending on whether incident users or prevalent users of medication are examined, as adherence tends to be higher among prevalent users, in part because discontinuation is highest in the first few months after initiation. Therefore, many studies focus on incident users, but there are situations in which studying prevalent users may be more relevant, especially because new initiators are only a small proportion of all patients using a therapy at a given time [28–30].

We will describe each of the strategies, their strengths and weaknesses, and discuss considerations for the timing of assessing adherence.

Specific Techniques for Measuring Adherence

Self-reports

Among many approaches to assessing adherence, patient self-reported measures asking respondents about their adherence behaviors have been the most common method. They are simple, relatively inexpensive, quick and feasible, and can be obtained over the telephone, in person, or with paper or electronic surveys. Self-reported measures vary greatly in the phrasing of their questions, recall periods, and response items. Several different validated methods for assessing self-reported adherence are described here.

Self-reported adherence measures range from one-item questions inquiring about the frequency of missed doses to longer multi-item assessments evaluating beliefs associated with adherence and identifying barriers to adherence [31]. Most self-reported measures involve count or estimation-based recall focused on the implementation phase, in which respondents report the number of doses missed or taken within an interval or to estimate their overall execution of adherence. Some scales use a recommended adherence cutpoint while other scales identify a continuous measure of the degree of adherence.

In a systematic review, Nguyen *et al*. identified 43 validated self-reported adherence scales in the English language [32]. Perhaps the most common self-reported adherence tool historically used is the eight-item Morisky Medication Adherence Questionnaire (MMAS-8) [33,34]. However, the use of this scale requires licensing fees. The adult AIDS Clinical Trials Group (ACTG) adherence questionnaire [12] and Brief Medication Questionnaire [35] are other examples of common, publicly available tools that explore both behaviors and barriers to adherence. A recent three-item tool by Wilson *et al*. queries patients about how many days they missed medications over the last 30 days [36]. Other studies have used a single measure such as a visual analog scale, which asks participants to mark a point on a line from 0% to 100% to indicate the amount of medication taken over a specified recent time period [37]. Overall, the choice of measure may depend on the context of its use (e.g., clinical use or research), the burden to patients, and the disease states in which it has been validated. In addition, self-report may be the easiest method for clinicians to administer and more easily used to isolate the reasons for poor adherence for targeting interventions.

Self-reported adherence measures are moderately correlated with methods using electronic drug monitoring (EDM) or pharmacy dispensing data (described later in the chapter), though concordance can vary depending on the patient's level of adherence or the measurement window [31,38–40]. For example, in a study comparing three-day, seven-day, and one-month self-reports, the one-month window best approximated adherence obtained using EDM [41,42]. On the other hand, because of potential

overreporting, self-reported measures are thought to have high specificity and low sensitivity (i.e., self-reported nonadherence is generally accurate, while high self-reported adherence may not be accurate) [31]. Either way, self-reported measures have shown weaker associations with clinical outcomes than EDM or dispensing data [31,42].

There are some additional limitations to self-reported adherence measurements. Though they can be self-administered in high-literate patients or conducted by an interviewer, they are all limited by a patient's ability to recall missed doses and may be subject to social desirability bias (i.e., overreporting adherence to please providers or researchers). Social desirability can be mitigated by acknowledging the difficulty of always taking all medications. Interviews are also potentially limited by language barriers, poor literacy, time burden, and difficulty with medication names. Using computer-assisted self-administered interview can reduce these barriers by reading instructions and questions aloud and including high-resolution photographs of the medicines. These questions can be administered at a kiosk or computer in a waiting room. Empirical data suggest that computer-aided self-reports are less likely to overestimate adherence [43]. However, poor patient recall is still a problem, and self-reported measures are also limited by their ability to precisely describe the timing or patterns of dose taking.

Pharmacy Dispensing Data

Pharmacy dispening measurement was pioneered in the late 1980s and has been widely used in various chronic diseases [44]. These measures typically derive from secondary data from health insurers and are some of the most common ways of measuring adherence in pharmacoepidemiology.

Pharmacy dispensing data are generally considered to be accurate because the dispenser (e.g., a pharmacy) would not get reimbursed by insurance if the medication fills are not recorded. Compared with self-reported data, pharmacy dispensing data are not biased by poor recall, can be obtained from computerized records, and can be assessed retrospectively [38]. Another advantage is that the data can be easily processed by software and are available on large numbers of patients (often millions in the same database). However, the data quality may be less assured in settings where such tracking is less crucial for reimbursement or if prescriptions are obtained outside insurance plans [45]. Some approaches use data from pharmacies directly to capture all medications dispensed to patients and not just those paid by insurers. Also, in the US, these pharmacy dispensing data are generally only accurate for medications dispensed in the outpatient setting, because medications are not specifically paid for separately during hospitalization [46]. For questions related to adherence to one-time prescriptions (e.g., short courses of antibiotics), these data may not be useful beyond studying primary nonadherence because repeat dispensings are required to calculate an amount of medication consumed.

There are several different methods for measuring adherence using pharmacy dispensing data. In all approaches, adherence is measured indirectly based on patterns of medication dispensings (using the dispensing date and days supplied) by generating a "drug supply diary" that strings together consecutive medication dispensings based on the dates on which medications are dispensed to the patient at the pharmacy and the duration of the supply dispensed [19,47]. This supply diary can adjust for overlapping fills (e.g., truncating the days supplied for medications which are refilled before the medication supply from the prior dispensing would have been exhausted) and any known interruptions that may have occurred (e.g., by hospitalization). When generating the supply diary, researchers generally consider medications that are chemically related and not intended for use in combination to be interchangeable (e.g., two beta-blockers). For example, patients may

initiate one beta-blocker and later switch to a different beta-blocker. In this case, beta-blocker adherence is often measured continuously, rather than separately measuring adherence to each medication, to generate one continuous exposure episode. Sometimes, medications within the same disease state but chemically different (e.g., beta-blockers and calcium channel blockers) could be considered interchangeable.

Several types of adherence metrics can be calculated using these data, such as a continuous variable for adherence assessed from the first to last prescription record, a dichotomous variable in which patients are classified as adherent or nonadherent based on a threshold, or examining the time between dispensings. In the most common approach, the proportion of days that patients had an available supply of medication, or the proportion of days covered (PDC), is calculated. The PDC is calculated by dividing the number of days with an available supply of medication by the number of days in the interval being evaluated (an interval-based measure) [48]. Other approaches include calculating the medication possession ratio (MPR). MPR is calculated as the quotient of (1) the total number of days supplied of all dispensings in a given analysis interval for the medication under investigation, and (2) the total number of days in the analysis interval. The primary difference between the PDC and MPR adherence metrics is how overlapping days supplied of the same medication are handled. MPR assesses the total daily medication supply from all dispensings in a given analysis interval whereas PDC assesses the total days where a medication supply "covered" each day in a given analysis interval. The specific approach is typically determined by researcher preference, although may depend to some degree on the structure of the database or the pharmacodynamics of the drug/disease in question. Regardless, the results of the different approaches are typically very similar [23].

In addition, these data can be used to measure persistence (e.g., the time until medication discontinuation) by evaluating whether clinically meaningful treatment gaps or discontinuations are observed in the dispensing data [49]. Potential approaches include evaluating whether a dispensation overlaps with the end of a follow-up period (i.e., 365 days after initiation) or measuring the availability of drug supply at a fixed time after the last medication dispensing (e.g., whether patients have a gap of at least 30, 45, or 60 days with no medication after the supply is presumed to be exhausted). Whichever method is chosen, investigators should conduct sensitivity analyses of the "gap rule" to determine the robustness of the findings.

These adherence measures are limited in additional ways. The vast majority of dispensings for chronic medications in the US are for supplies of 30 days, and increasingly 90 days [47,50]. Measuring adherence in intervals shorter than 180 days can then make it difficult to observe variation in adherence since by definition, the first 30 or 90 days are always considered as full adherence (100%), regardless of actual patient behavior [51]. This problem becomes less pronounced with longer measurement intervals. However, shorter intervals may be more clinically desirable since they might allow nonadherence to be detected and acted upon sooner [52].

Although adherence metrics, using pharmacy dispensing data, often estimate the supply of medication during a given time period, they do not measure or monitor actual pill-taking behavior, either on average or day to day. Consequently, they cannot be used when the timing of missed doses is pivotal. However, the estimation of adherence with pharmacy dispensing data has been shown to be valid for chronic medications where measuring overall exposure between refills is clinically relevant [38]. Pharmacy dispensing measures of adherence have also been shown to be strongly associated with clinical outcomes [53,54]. For example, a time-to-dispensing measure of adherence has been associated with changes in HIV viral load [55]

and changes in blood pressure [44]. Furthermore, the measure has been shown to provide additional information beyond self-reports. In a study of antiretroviral therapy, individuals who self-reported 100% adherence actually varied in their treatment response based on adherence metrics from pharmacy dispensing data. As expected, those with higher adherence, as defined using pharmacy dispensing data, had higher rates of treatment response, despite claims of perfect self-reported adherence in both groups [56].

A limitation of adherence measures derived from pharmacy dispensing data is the estimate of the maximum potential adherence, since these metrics assume all medication supplied has been consumed between dispensations. It is also difficult to disentangle clinically directed medication discontinuation wherein persistence is no longer the behavior being studied, from patient-directed discontinuation against provider recommendation, which is defined as nonpersistence. Furthermore, pharmacy dispensing data may also overestimate adherence measures when dispensing programs automatically dispense a new supply on a prespecified schedule, irrespective of patient request for resupply [57].

A final consideration is how to accurately measure adherence to multiple medications for the same condition (e.g., antihypertensives). One common approach is to measure adherence at the therapeutic class level and "average" adherence across the entire chronic condition for patients exposed to any medication for that condition [27].

Pill Counts

While less commonly used, adherence can also be measured indirectly by pill counts. Pill counts are similar to pharmacy dispensing data in that percent adherence is calculated by dividing the days supply consumed by the number of days observed. Data collected include the dispensing date, quantity dispensed, number of pills per dose, and number of pills left in the bottle, adjusted for doses taken that day and any additional pills left over from the last count.

Like adherence measures estimated using the medication dispensing date and days supplied (e.g., MPR and PDC), adherence measures using pill count data also cannot determine if the medication was actually consumed or the patterns of consumption. However, they do provide direct evidence that the medication was not taken when pills are left over. Pill counts are susceptible to deception since "dumping" pills on the way to the pill count visit is simple and can be done impulsively before a visit. Unannounced pill counts, in person or by telephone, are valid alternatives to mitigate this type of misclassification [55]. During calls, subjects review the contents of each of their pill bottles. Of course, this approach is also susceptible to intentional deception; however, the estimated adherence from pill bottle review was shown to be associated with treatment response [58]. The time for both staff and participants is a potential disadvantage of pill counting and an additional source of error. In addition, missing data can result when patients do not bring in their pill bottles or have them available during telephone calls. Reinforcing the importance of accuracy with staff is vital to ensure validity of this measure.

Medication Diaries

Although the adherence measures described above summarize how much medication was taken over a specified time period, they provide no detail on the timing of missed doses. Depending on drug pharmacokinetics and pharmacodynamics, missing doses may have different consequences depending on whether the doses were missed consecutively or at separate times that are evenly spaced. These data may in fact be vital to classifying adherence, and medication diaries can provide a solution. In this method, participants keep a record of the date and time of each dose of medication and often whether or not it was taken with or without food. These data can be collected either

electronically or handwritten; with newer technologies like smartphones, data collection could be even easier [59]. Diaries may be particularly useful for medications like insulin or inhalers that are difficult to track using other methods [60]. For example, medication diaries are regularly used in pediatric patients [61].

However, medication diaries are susceptible to both overreporting and underreporting of adherence. Social desirability results in patients listing doses even though they were not taken, but the potential is lessened somewhat by the burden of creating a detailed falsified record. In fact, the risk of underreporting may be greater because of the burden of tracking each dose. It is also not easy to employ this method at scale for larger studies. Newer approaches are exploring the use of apps on enabled smartphones to track these more nuanced medication-taking patterns.

Electronic Drug Monitoring Technology

Electronic drug monitors (EDMs) feature the same advantages as medication diaries, but are less susceptible to deception, forgetting, or ignoring the need to write down the dose data. In contrast to the prior approaches, EDMs provide time-stamped data for adherence behaviors to enhance precision of adherence measures. While there are several different hardware options, electronic drug monitors employ electronic date/time stamp technology that is triggered by opening a container (i.e., pill bottle), puncturing a blister pack to obtain a dose, or ingesting a dose. The data are downloaded to a computer or smartphone via hardwired or wireless linkage.

Electronic drug monitor data have been shown to have some correlation with other measures, including pharmacy dispensing and self-report, though EDM measures are more sensitive (i.e., they are more likely to identify poor adherence) than self-reported measures [31,62]. While EDMs are less susceptible to deception than self-report, they could theoretically could be more susceptible than pharmacy dispensing data [63]. However, it is highly unlikely that subjects will open and close the monitor to record doses over long periods of time without actually taking the medication, though this does occasionally happen accidentally [63,64]. EDMs are also less susceptible to underreporting than diaries because they often do not require the subject to do anything other than take the prescribed medication.

Though EDM technology is advancing rapidly, the packaging and cost of EDMs can still be burdensome and difficult to scale [64]. For example, EDMs have been found to be particularly hard for patients with psychiatric conditions to use [64–66]. In addition, they often preclude the use of pillboxes by generally requiring that the medication remain in the package until taken. Consequently, they are susceptible to underestimating adherence (e.g., a one-week supply taken from the container at one time will appear as one dose taken). However, EDMs could be used even when the medication is not kept in the container. In a warfarin study, individuals using pillboxes were given an EDM in an empty pill container and asked to open the empty bottle whenever they took warfarin from the pillbox. The association between adherence and outcome was nearly as strong as those who kept the warfarin in the monitored bottle [20].

Newer approaches are being developed, such as integrating EDM technology with text messaging that reminds patients when they miss doses. In 2015, the US Food and Drug Administration approved the first ingestible sensor technology that measures actual intake time through ingestion of a medication that communicates with an adhesive patch. The device sends a signal to the doctor or research team monitoring adherence [67]. Other research is exploring the utility and accuracy of adherence measures in which patients take date- and time-stamped photographs of themselves or their pills each time they take a dose.

Drug Concentrations

Identification of the presence of a drug in plasma or other tissues provides direct evidence of drug ingestion. However, the use of drug concentrations to measure adherence is limited by variability across patients (i.e., absorption, distribution, metabolism, and clearance – see Chapter 2). The more frequently concentrations are measured, the fuller the picture of adherence behavior that can be obtained but the cost and patient inconvenience may be a limitation. Measurement of drug concentrations in hair using liquid chromatography and confirmed by mass spectrometry can be a useful indicator of long-term medication exposure. For example, antiretroviral drug levels in hair give an average of the exposure to drug over the past weeks to months and predict HIV viral response better than serum drug levels [68].

Unfortunately, many assays are unavailable commercially. Furthermore, the serum drug level is not the relevant measure for many drugs when the site of action is elsewhere (e.g., intracellularly rather than in serum or in hair) [69]. Finally, unless these assays are done quickly, they are not useful clinically.

Another approach to assessing drug concentrations is to use a marker drug that is easily added to a formulation and can be measured more easily than the actual drug of interest. The primary example here is the incorporation of riboflavin into active drugs as a urine metabolite drug marker to assess adherence to medication in clinical trials [70]. Of course, this strategy is only relevant in settings where researchers have control over the formulation and direct access to the patient (e.g., clinical trials).

Measuring Primary Adherence

Each of the approaches described above has focused on later adherence phases (e.g., implementation and persistence). Measuring medication initiation (i.e., primary adherence) has been difficult using some of these methods, particularly because secondary data require a medication to be dispensed for adherence behaviors to be monitored. Some techniques, for example self-report, may allow for easier study of primary adherence. Without linkage to other types of data (e.g., electronic health records that include provider medication orders), it can be difficult to evaluate initiation without knowledge of what was prescribed [5]. Newer approaches are beginning to link these data sources to allow better assessment of the full cascade. On their own, electronic health record data limited to physician orders are not useful at evaluating patient adherence because they do not provide information about medication consumption.

Measuring Adherence to Nonpill Formulations

Measuring adherence to nonpill formulations can be difficult for several reasons, largely because these medications are generally administered with a variable dosing schedule. Injectable medications like insulin may be administered based on a sliding scale, with doses adjusted as needed, so measuring adherence using indirect dispensing data may be imprecise. Recently, other insulin persistence-based measures have been developed to overcome some of these limitations [60,71]. Inhaled medications are also difficult to measure; for those with specific schedules (e.g., tiotropium), dispensing data could be used [72]. Medication diaries and self-report could also theoretically be used but are subject to the same biases as pill formulations. EDMs have been used for metered dose inhalers [73] and ophthalmologic solutions [74]. The monitors increase the size of packaging, but the inhalers and solutions cannot be taken out of the package, unlike pill formulations. Measuring adherence will continue to be a challenge for newer nonpill formulations, including biologics, and in disease states in which both oral and injectable formulations are used interchangeably (e.g., osteoporosis or venous thromboembolism).

Topical treatments pose a particular challenge. For transdermal formulations in patches

(e.g., nicotine, testosterone), adherence based on dispensation data is a viable option because the supply is typically fixed. However, for creams and ointments, because the amount used at each application varies by the size of the lesion being treated or the size of the individual, self-reports and medication diaries may be the only currently viable options [75]. Adherence to intravaginal gels could be monitored by counting the number of empty tubes and used applicators returned at each visit, but this measure is subject to self-report errors due to intentional falsification or mixture of used and unused applicators in the same bag.

Analysis Issues in Adherence

Using Adherence Data in Clinical Trials and Comparative Effectiveness Studies

While clinical trial participants may be more motivated to adhere to treatments than those in clinical practice, nonadherence occurs for all types of self-administered therapies. Missed doses will typically make the active drug less effective and diminish observed differences compared to placebo in intention-to-treat analyses. In order to compensate for this effect, Phase III trials may inflate sample sizes to account for this variability in drug exposure [8]. Clinical trials may also incorporate run-in periods to try to minimize poor adherence (see Chapter 32).

In analyzing trials, the standard approach remains intention to treat. This approach limits the introduction of bias and makes the results more generalizable [76]. However, secondary analyses can be performed on subgroups of adherent patients, but these patients may differ for reasons that may not be easily measurable (i.e., more willing to take therapy, a type of healthy adherer bias) [77,78]. The benefits of randomization would therefore be negated. Moreover, when lifestyle changes are co-interventions along with medication in a trial, the results of secondary analyses will not be true measures of drug efficacy. Of course, medication adherence itself can also be a primary or secondary outcome in randomized trials, particularly for studies of interventions [79–83].

The inclusion of adherence data in analyses of trials is particularly important when a treatment fails. Reasons for failure might include lack of biological effect or lack of adherence. Unless adherence is measured and identified as the cause of failure, the results of the trial will be only partly useful. While regulators will only approve a drug for the studied indication if it is shown to result in improved outcomes, it is important for the drug developer to know if the efficacy of the drug was potentially limited by poor adherence. For example, in one trial, rates of coronary heart disease events were compared in patients randomized to receive either cholestyramine or a placebo [84]. Adherence in the cholestyramine group (defined as taking at least five out of six prescribed packets of cholestyramine per day) was only 50.8% compared to 67.3% adherence in the placebo group due to side effects. Because of the poor adherence, treatment response in the cholestyramine group was attenuated. Thus, because adherence was measured, it was possible to determine that the high rate of intolerable side effects resulted in lower adherence and thus, perhaps, lower treatment effectiveness.

Similarly, observational cohort studies of comparative effectiveness and safety of medications often benefit from measuring and evaluating the relationship between medication adherence and treatment response. First, "as-treated" analyses of safety evaluations often censor follow-up in patients who discontinue therapies for reasons other than toxicity to decrease bias toward the null. Second, marginal structural modeling approaches often include medication adherence as a time-varying exposure. Exploring the relationship between adherence observed between comparators may enrich the conclusions derived from these studies.

Selecting Adherence Intervals

For all adherence measures, a prespecified window for assessing and evaluating adherence must be chosen. The selection of the duration of an adherence interval depends on two important factors: the pharmacokinetics/pharmacodynamics and the granularity of the adherence measurement. For drugs with short half-lives and short onset of action, short intervals are likely to be more clinically relevant than when the drugs have long half-lives and longer onsets of action. For adherence measures that can accurately assess adherence over short periods of time, such as electronic data monitors, shorter intervals can be calculated. By contrast, when measures derived from pharmacy dispensing data are used, adherence analysis intervals must be longer because adherence is based on evaluating patterns between medication dispensing dates in conjunction with the days supplied per dispensing (e.g., 30 days).

The relationship between adherence and outcomes has been well described in antiretroviral therapy and oral contraceptives. Using pharmacy dispensing data, intervals of adherence as long as one year [56] and as short as 30 days [85] have been associated with viral load outcomes with antiretroviral therapy; however, a 90-day measure was found to be more strongly associated with viral load than a 30-day measure. For oral contraceptives, two consecutive days of nonadherence resulted in an unacceptably high rate of treatment failure (i.e., pregnancy) [86].

Unfortunately, for many medications, the most clinically relevant adherence interval may be unknown, and more research is needed to optimize the assessment of adherence. While the choice of interval length depends on the research goals, in general, monitoring adherence over shorter intervals would be desirable, because interventions can be more rapidly implemented. However, shorter intervals are subject to decreased accuracy regarding true adherence behavior. In general, without direct guidance, choices for an adherence interval should be made based on pharmacokinetic and pharmacodynamic data (see Chapter 2).

Statistical Analysis

The simplest approach to summarizing adherence across different methods is the percentage of doses taken (or missed). For electronic monitors, because the timing of each dose is available, percentage of doses taken "on time," standard deviation of time between doses, duration of maximum time gap between doses, and many others can be calculated [4]. For adherence metrics derived from pharmacy dispensing data, the analysis focuses on either the percentage of available medication or the duration of gaps between dispensings [44]. Self-reports focus on the proportion of doses the patients have taken or the time since the last dose was missed [31].

Whichever metric is used, one must choose whether to include adherence as a continuous or dichotomous variable. As previously described, dichotomous thresholds must consider both the likelihood of failure and clinical consequences of treatment failure. Few thresholds have been established based on evidence, yet in research and quality improvement efforts, to dichotomize these adherence variables, patients are often defined as fully adherent if they take at least 80% of prescribed doses. Certainly, many studies in cardiovascular diseases have demonstrated this association; however, there is recognition that different levels of adherence may be required for viral suppression in HIV. In treatment settings with a linear relation between amount of drug taken and therapeutic response, evaluating differences in adherence on a continuous scale would be clinically more meaningful than binary measures. Alternatively, when neither dichotomous nor continuous measures capture the clinically relevant dose–response relationship, assigning ordinal adherence categories (e.g., <70%, 70– < 80%, 80– < 90%, etc.) may be preferable [87].

In addition, evaluating regimens with multiple medications poses analysis challenges [88]. Many classify adherence based on optimal adherence to at least one medication for that disease state (e.g., hypertension) to be fully adherent, although this misclassifies individuals who are nonadherent to some but not all components of the regimen. Fortunately, there is some evidence to suggest that for medications taken simultaneously, adherence to one is highly collinear with adherence to the other [89]. However, differential nonadherence has been documented [90].

Finally, it is difficult to determine whether an individual is poorly adherent or whether the medication is no longer being prescribed when access to medical records is unavailable. This phenomenon poses the greatest challenge for adherence measures derived from pharmacy dispensing data. Further, even when medical records are available and the provider documents the recommendation to discontinue, the exact date of patient medication discontinuation can be difficult to determine.

Time-Varying Nature of Adherence and Trajectory Modeling

Adherence is a nonstatic behavior, and methods are needed to capture changes in adherence over time. This phenomenon has historically been ignored in studies that measure adherence only once or over short intervals. Even when measured longitudinally, adherence data are often averaged. For example, quality measures in the US are based on the proportion of patients with ≥80% adherence (e.g., MPR or PDC) of their prescribed medications over the prior year. However, patients may experience substantial increases and decreases in adherence that are not fully captured by these composite measures.

Consider, for example, one patient who takes a medication perfectly for the first six months but then discontinues for a six-month gap compared with another patient who alternates taking medications perfectly every other week interspersed with week-long gaps over a year. Both patients would have the same calculated adherence (50%) but very different medication use patterns. Composite, cross-sectional measures obfuscate the potential for each patient to experience different health outcomes and require different adherence interventions.

Advanced statistical methods are beginning to take advantage of repeated measurements in adherence data, particularly in dispensing data, to enhance analysis beyond composite measures. One such method applied is group-based trajectory modeling which estimates changes in an outcome that is measured repeatedly over time and identifies individuals with similar longitudinal patterns [91]. In brief, this approach fits a semiparametric (discrete) mixture model and assigns groupings in longitudinal data (e.g., monthly PDC) based on probability distributions for a prespecified number of groups [92]. The probability of belonging to each potential group is modeled as a multinomial logistic regression, and within each group, adherence is modeled as a smooth function of time using up to a fourth order polynomial. The statistical output includes each individual's estimated probabilities of group membership and estimated trajectory curve of adherence over time for each group. For example, a study by Franklin *et al.* of statin initiators identified six distinct patterns of adherence over 15 months, including patients who had (1) near-perfect adherence, (2) poor adherence initially and then improvement, (3) slowly declining adherence, (4) rapid declines in adherence, (5) occasional use, and (6) immediate discontinuation [92].

Researchers ultimately select the best trajectory models based on fit criteria, having sufficient members in each trajectory group (i.e., at least 5% of the overall cohort in each group), narrow confidence intervals and posterior probabilities of membership ≥0.7 (in which each member assigned to that group has at least a 0.7 probability of being in that group) [91].

Trajectory modeling can be accomplished using statistical software with continuous, binary, and count data.

Overall, group-based trajectory models have been shown to summarize adherence patterns better than composite approaches and are strongly associated with clinical outcomes [93]. However, trajectories provide general patterns for adherence behaviors; that is, no one individual follows the exact pattern described by the trajectory of the group to which they are assigned. For example, although a rapid declining trajectory group might be depicted as having adherence decrease starting at month 4, any one individual assigned to that group might begin to be nonadherent at month 3 or month 5. Also, the number of distinct adherence trajectory groups, while guided by the fit criteria above, can also be subjectively based on researchers' interpretations and differ by disease state. Additionally, describing the individual patterns in words can be challenging; labels such as "mid-year discontinuation" and "early nonadherence followed by later return to partial adherence" can be cumbersome. More research is needed to optimize the approach, explore applicability in other adherence data sources, and facilitate communication of findings.

Prediction of Adherence for Interventions

Unfortunately, low rates of adherence have persisted despite extensive efforts to identify and predict patients at risk of poor adherence with the goal of developing interventions to improve adherence. Despite the expansion of databases with rich patient data, prediction of future adherence remains poor. Traditional approaches have focused on clinical and demographic factors at the time of medication initiation, with discriminative ability that is modest at best even with dozens of predictor variables (e.g., c-statistics ranging between 0.6 and 0.7) [52]. Even machine learning, with the capability of measuring complex interactions among predictor variables, has not led to drastically improved prediction, likely because the true factors associated with poor adherence are usually not observable in databases.

One of the more successful approaches has been evaluating patterns of medication filling shortly after initiation. For example, in pharmacy dispensing data, researchers have found that failing to refill in the second and third months after initiation is highly predictive of poor adherence over the following year (i.e., past adherence predicts future adherence) [51]. Predictions of adherence by providers have also been shown to be no better than chance [94], so they should not be used routinely in adherence studies or in practice.

Future Directions

As outlined throughout this chapter, though many methods have been developed to evaluate adherence, many challenges remain. Better methods for detecting and addressing poor adherence as well as the reasons for poor adherence will be welcome developments. Objective measurement of adherence to nonpill formulations in particular is difficult, especially for injectable, liquid, and topical treatments. The optimal adherence metric for most drug–disease dyads remains unknown. This is further complicated by the enormous number of possible combinations of regimens.

Adherence studies are likely to advance in several ways. First, because optimal adherence thresholds may differ across individuals and diseases, researchers are beginning to explore personalized adherence targets. For example, in a machine-learning analysis among patients with diabetes, Lo-Ciganic *et al*. observed that optimal adherence thresholds for an individual's hospitalization risk varied greatly based on their underlying health status [95,96]. Novel approaches using other types of data are likely to emerge as well, including the use of more advanced microelectronic technology, often

linked with communication systems that both identify and report nonadherence, or the enhancement of mobile and smartphone technology for tracking and intervening on adherence. Refinements to currently available electronic monitors will also likely include more convenient packaging that can both help with adherence (e.g., a reminder or organizer system) and provide two-way personalized communication with patients.

Hopefully, with greater recognition of the importance of nonadherence, more research will be conducted over the next several decades to solve some of these problems as well as develop better approaches to improving adherence so that evidence-based medications can be optimally used.

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