Medication Adherence—Landscape, Strategies, and Evaluation Methods

Washington Marriott at Metro Center
775 12th St NW, Washington, DC 20005
December 10, 2019

Discussion Guide

Introduction

Medication adherence—the extent to which patients take medications as prescribed in agreement with their health care provider—is essential for ensuring the safe and effective use of therapies to prevent and treat disease. Optimal medication adherence may not only improve health outcomes for individual patients, but also improve population level health (e.g., reduced overall health care utilization, prevention of infectious disease transmission, and reduced drug resistance). Medication adherence is a function of complex and dynamic behaviors influenced by an array of factors related to patient, provider, and health care systems. Such factors include, but are not limited to, treatment regimen complexity and cost, health literacy, and extent and effectiveness of communication between patients and health care providers.¹

Non-adherence can occur at several points along a continuum of medication taking behaviors. For example, patients may choose not to fill a medication prescription, not to refill it on time, or not to take the medication as prescribed with respect to interval and/or dosage. In one classification scheme, medication adherence was described in terms of initiation (i.e., starting a recommended medication), implementation (i.e., executing the prescribed dosage scheduled), and discontinuation (i.e., stopping a recommended medication); the term persistence denoted the length of time between initiation and discontinuation of medication.²

Focused efforts to improve medication adherence can improve health and reduce economic burden due to health conditions. Medication non-adherence varies by disease and condition; for example, non-adherence is generally more prevalent among patients with chronic conditions.³⁴ Various strategies and interventions have been proposed to improve medication adherence. Such approaches include patient education, simplifying medication regimens, clinical pharmacist consultations, cognitive behavioral therapy, and medication reminders (e.g., phone calls or text messages).⁵ A confluence of scientific and technological advances is also spurring digital technology innovations—examples include drug-device combination products with built-in electronic modules and ingested medication sensors to provide an electronic record of when a drug was administered, and mobile applications that provide tailored feedback regarding medication utilization.*

* The U.S. Food and Drug Administration has not approved any drug-device combination that has demonstrated improved medication adherence.
Although these innovative tools and technologies hold promise, measuring the impact of interventions on adherence and clinical outcomes remains a challenge. Various metrics are available to quantify medication adherence, and each measurement has unique advantages and disadvantages. As an overview, direct measures of adherence include observing patients taking a medication, measuring levels of medication and metabolites in the blood, and measuring biologic markers in the blood (based on a known correlation between dosage and biomarker levels). These measures tend to be accurate, but can be difficult to employ in clinical settings, especially over long periods of time.

Indirect measures of medication adherence include patient self-report, pill counts, and monitoring with electronic devices. In addition, pharmacy claims data can be used to calculate medication possession ratio (MPR) and prescription days covered (PDC). These indirect measures may be easier to use in large studies and clinical settings, but they make assumptions about medication-taking behavior and can overestimate adherence. For example, if a patient fills or refills their prescription, standard MPR and PDC measurements presume that patients have taken the medication as prescribed with respect to timing, dosing, and frequency. In addition, various claims databases often used to calculate MPR and PDC may not provide complete or up-to-date information. Examples of categories of medication adherence metrics are available in the published literature, including descriptions of corresponding advantages and disadvantages.

In many situations, the extent and presumed impact of adherence are assessed using thresholds. Achieving 80% adherence is often considered clinically acceptable and a standard threshold, yet little empirical evidence supports this specific level. Discrete thresholds for levels of adherence—and corresponding impacts on clinical outcomes—likely depend on the patient population, condition, and medication being studied. In this context, a specific aspect of assessing adherence is its association with clinical outcomes. For example, a study of the levels of adherence needed to prevent all-cause hospitalizations found variability across conditions, with adherence of 80% for certain conditions (e.g., schizophrenia), but higher for other conditions (e.g., diabetes). In addition, and as an example of thresholds changing over time, adherence of 95% or greater was cited as optimizing virologic and clinical outcomes for treatment of human immunodeficiency virus (HIV) approximately 20 years ago, but advances in therapeutic regimens have shown that lesser levels of adherence have still achieved disease control.

In addition to the difficulties in defining metrics to evaluate adherence, challenges also exist in the design of research studies to rigorously evaluate improvements in adherence, with or without consideration of innovative tools and technologies. Additional difficulties arise in establishing a direct link between adherence and clinical outcomes. These challenges include, but are not limited to, selection of a suitable patient population, assessment of adherence in the control (comparator) arm, “blinding” of the intervention (as appropriate), identifying an
appropriate study duration, and acquiring data on medication adherence across acute and chronic conditions.

Although randomized controlled trials (RCTs) are considered the optimal study design to study the effects of interventions in health care, unique challenges exist when studying medication adherence. Specifically, results can be misrepresented by the Hawthorne effect, wherein trial participants may be more adherent when they know they are being monitored.\textsuperscript{15,16} Conversely, poor adherence in a RCT can lead to underestimation of efficacy or side effects, as well as overestimation of proposed dosing. Non-randomized study designs are available but would need to account for the various factors that can influence medication adherence and controlling for such factors in observational analyses is challenging. Additionally, there are considerations around the quality and relevance of real-world data especially when indirectly measuring adherence.\textsuperscript{17} Reviewing prior and ongoing studies of medication adherence can highlight lessons learned regarding approaches to promote internal validity and enhance generalizability.

To explore the state of the science of clinical research evaluating medication adherence involving FDA-regulated products, the Duke-Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), will convene a public meeting on December 10, 2019. Specific areas of discussion will include: (a) the current landscape of interventions intended to track (monitor) medication adherence, improve medication adherence, and improve clinical outcome(s) secondary to increased medication adherence; (b) metrics of (i.e., methods of measuring) medication adherence; and (c) study designs to evaluate interventions that improve adherence, with or without an impact on relevant clinical outcomes.

**Summary of Sessions**

**Overview of Medication Adherence**

This session will feature a presentation that introduces the concept of medication adherence and characterizes the impact of non-adherence on patient outcomes and the health care system. The overview is intended to provide a foundation for the subsequent discussions.

**Session I: Key Barriers to Effective Medication Adherence**

This session, building on the overview presentation, will consider key barriers to effective medication adherence. Such barriers can arise at the level of patients, health care providers, and health care systems, and may include complex treatment regimens, comorbid conditions (e.g., depression), ineffective communication between clinicians and patients, costs of medications, and limited health literacy. Panelists will discuss the range of barriers to effective medication adherence across and within therapeutic areas, and emerging trends of key drivers contributing to non-adherence.
Discussion Questions:

- What are major contributors to non-adherence of FDA-regulated products (e.g., complex treatment regimens, communication barriers, lack of health information technology, cost, limited health literacy)? What factors can be modified to address these barriers?
- Do different barriers to non-adherence impact certain therapeutic areas disproportionately?
- What roles can patients, health care providers, caretakers, and other stakeholders play in promoting medication adherence? What are the key limitations or gaps in how these stakeholders implement or coordinate medication adherence interventions?

Session II: Interventions to Track and/or Improve Medication Adherence

Many approaches have been employed to improve adherence of FDA-regulated products, including patient education, reminders, simplifying medication regimens (e.g., switching to single pill combination therapies), and cognitive behavioral therapy. Recent technological advances have opened the door for more sophisticated approaches, including sensors that detect pill ingestion or administration of medication and mobile applications that provide reminders and tailored feedback about medication use. This session will delve into the current landscape of existing interventions and explore emerging developments to track and improve medication adherence.

Discussion Questions:

- How do interventions attempt to overcome barriers to medication adherence, and how have interventions for medication adherence evolved over time?
- What tools and technologies are currently in use, or are in development, that are intended to track and/or improve medication adherence? What are the corresponding lessons learned?
- What emerging opportunities and potential best practices exist to track and/or improve medication adherence?

Session III: Measuring and Evaluating Medication Adherence

Methods for measuring medication adherence can vary in their accuracy and the ease with which they can be assessed. Direct measures of adherence, such as observing patients ingesting medication, may be more accurate, but may not be feasible for use in studies with large populations. Indirect measures of adherence, such as patient self-reporting, can overestimate levels of adherence. This session will explore measurements of medication adherence, including commonly-used measures of medication adherence and potential best practices across different conditions. Panelists will also consider how these methods are being used to assess the impact of adherence improvements on clinical outcomes.
Discussion Questions:

- How well do various data sources enable the calculation of medication adherence?
- What measurements have been and are being used to assess medication adherence to single and multiple therapies? Overall, is there a preferred approach to measure medication adherence, either in general or in specific therapeutic areas?
- In the context of medication adherence, how is the impact of improved adherence, with or without an association with clinical outcomes, typically quantified?
- What approaches are used to determine whether an improvement in medication adherence is clinically meaningful?
- What evidence is available to support the extrapolation of results from adherence studies from one medication to others with the same indication or same drug class?

Session IV: Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

Randomized, controlled trials may not capture representative patterns of non-adherence that occur in the real-world, due to more homogenous study populations and enhanced monitoring that can lead to “white coat adherence.” Pragmatic clinical trials or observational studies provide additional methodological approaches to generate real-world evidence on adherence, but such designs are not without challenges. This session will discuss details of study designs that are used (or proposed) to evaluate tools and technologies intended to track or improve medication adherence or improve clinical outcomes secondary to increased adherence.

Discussion Questions:

- What study designs could be used to document tracking of medication adherence, improvement in medication adherence, and improvement in clinical outcomes secondary to increased adherence? What are the strengths and limitations of such study designs?
- How can relevant methodological issues be identified and addressed, including: (a) assessing the impact of study participation itself on adherence, (b) measuring adherence in control (comparison) arms, (c) specifying a study duration to establish durability, and (d) evaluating applicability across acute versus chronic conditions?
- What specific challenges exist when examining the relationship between effective tracking of medication adherence and improvements in adherence?
- What specific challenges exist when examining the relationship between medication adherence and clinical outcomes?

References


*Funding for this meeting was made possible in part by a grant from the U.S. Food and Drug Administration. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the U.S. Food and Drug Administration nor does mention of trade names, commercial practices, or organizations imply endorsements.*