Understanding and Overcoming Barriers to Medication Adherence: A Review of Research Priorities

Seth A. Seabury, PhD; Charu N. Gupta, MSc; Tomas J. Philipson, PhD; Laura E. Henkhaus, BSc; and the PhRMA Medication Adherence Advisory Council

SUMMARY

Improving medication adherence has been identified as a crucial step towards improving health outcomes for patients with chronic disease and has provided the motivation for many changes in our health care system. Despite the volume of research done on this topic, however, we still lack important basic information about how to improve adherence in a cost-effective way. There is a need for a better understanding of what areas of research are most likely to produce advances that can be used by policymakers, providers, payers, or other stakeholders to generate real improvements in medication adherence. To address this, we developed a set of research priorities designed to improve understanding about whom to target for adherence interventions and which particular interventions to employ for specific subpopulations.

To produce this research agenda, we synthesized information from the existing literature with a series of stakeholder interviews and expert panel meetings. We identified 6 key areas for research: (1) predicting nonadherence, (2) behavioral factors affecting nonadherence, (3) measuring the impact of nonadherence on health and cost outcomes, (4) effectiveness of existing interventions, (5) misaligned incentives between payers and providers, and (6) provider training and coordination of care. We provide detailed descriptions and example topics within each area.

As the health care system continues to embrace reforms designed to improve the value of care, more and better information is needed to guide efforts designed to improve medication adherence. Addressing the topic areas identified here will be an important step towards accomplishing this goal.

J Manag Care Pharm. 2014;20(8):775-83

Copyright © 2014, Academy of Managed Care Pharmacy. All rights reserved.

Improving medication adherence has been identified as a crucial step toward improving health outcomes.1-7 While the burden of chronic disease continues to rise,8-10 people prescribed self-administered medications typically take less than one-half of prescribed doses.11 To this end, the Patient-Centered Outcomes Research Institute, the Agency for Healthcare Research and Quality, and the National Institutes of Health, among other bodies, have dedicated funds to support research on medication adherence.12 Moreover, since 1996, nearly 60,000 peer-reviewed articles have been published on patient adherence or compliance, and thousands of new studies begin each year.13 Despite this volume of work, gaps persist in our knowledge about how to improve adherence and target interventions to specific patients.

Among the numerous changes facing our health care system are requirements and incentives directed toward providers and both public and private payers to improve patient health outcomes, including medication adherence.14 For example, the Centers for Medicare & Medicaid Services (CMS) require all Part D sponsors to develop medication therapy management programs to reduce risk of adverse events, ensure appropriate medication use, and otherwise improve adherence by facilitating patient-prescriber engagement.15 While Part D plan designs are supposed to reflect efforts to improve adherence, actual success in doing so influences the volume of funds transferred from CMS to health plans. The CMS Five-Star Quality Rating System for Medicare Advantage plans includes adherence metrics, thereby providing direct financial incentives to improve adherence for targeted conditions.16,17 Similarly, enrollment restrictions are relaxed for stand-alone Part D prescription drug plans with high ratings, while consistently poor performing plans are penalized.16

In this changing health care landscape, improving patient adherence will have important implications for new payment models, care coordination, and overall health care costs. However, despite the volume of research on the topic, the literature is inconclusive on what influences patient adherence, how adherence relates to patient outcomes and health care costs, which interventions are most effective at improving adherence, and how all of these factors vary at the individual level. There is a need for a better understanding of what research areas are most likely to produce advances that could be used by policymakers, providers, payers, or other stakeholders to improve medication adherence. To facilitate this goal, we combined reviews of the extant literature with expert opinion to identify knowledge gaps and to develop a framework to guide future adherence research. We identified several areas for research to improve our understanding about how to identify patients at greatest risk of nonadherence and target them with personalized, effective interventions.

Research Priorities for Medication Adherence

To develop a research agenda for medication adherence, we synthesized information from 3 sources. First, we reviewed the extant literature to identify key knowledge gaps. Second, we interviewed physicians, pharmacists, academics, adherence researchers, health care executives, and payers to identify areas where additional research might have the greatest impact. Third, we convened 2 expert meetings with the Pharmaceutical Research and Manufacturers of America (PhRMA) Medication Adherence Advisory Council to seek advice, review the literature and interview findings, and identify an agenda for future research. The Adherence Advisory Council includes academics...
and other researchers, in addition to representatives from the pharmaceutical industry, pharmacy management, and insurance companies. The authors did not solicit patient perspectives on nonadherence; however, the review of the known literature included studies containing patient surveys.

From these 3 sources, 6 key topic areas for research were identified: (1) measuring adherence and nonadherence, (2) identifying factors that drive nonadherence, (3) evaluating the impact of nonadherence on health outcomes and costs, (4) remediating problems with existing evidence on the effectiveness of interventions, (5) improving adherence through care coordination, and (6) understanding provider and payer behavior. Figure 1 depicts the relationship among these topic areas. The first 2 topics focus on understanding patient heterogeneity—that is, identifying which patients are nonadherent and why. The third topic identifies the consequences of nonadherence. However, simply knowing which patients are nonadherent and the consequences of nonadherence identifies the problem but does not identify how actually to improve adherence. Therefore, topic 4 aims to improve the understanding of the effects of different interventions on distinct subpopulations. In topics 5 and 6, barriers to implementing any optimally targeted interventions are considered. This includes structural barriers such as fragmented care or poor coordination among multiple caregivers, as well as barriers arising from misaligned incentives for payers and providers. Within each topic area, several priorities for future research were identified. Each topic is described in detail below.

### Measuring Adherence and Nonadherence

Interviewed health care providers expressed difficulty connecting what happens within their offices to patients’ actions outside of the office. While electronic prescription systems can inform providers that a prescription has been filled, whether patients actually comply with their treatment regimen is unknown.\(^{18}\) Consequently, an important priority is to improve measurement of whether and when patients consume their medications. For instance, while special pill containers exist with electronic monitoring units to record the date and time a dose was removed, these cannot indicate whether the patient actually consumed the dose.\(^{18}\) Other data sources used in adherence research may not represent accurately what a doctor prescribed. For example, a physician may recommend that a patient discontinue treatment after an adverse event, but the reason for discontinuation is not readily apparent to researchers observing claims data; as a result, this may be categorized as a nonadherence episode.

Incomplete data on medication use is 1 reason no standard metric exists for adherence.\(^{11,19,20}\) The lack of a standard measure along with researcher use of measurements of varying quality render it difficult to compare results across studies and to identify differences due to patient, medication, or disease characteristics. This makes it difficult for stakeholders to interpret results from adherence research and apply this information. Given inaccurate and incomplete data on adherence measurement as well as a lack of standard metrics, stakeholders expressed a lack of confidence in adherence measures. Thus, there is a need to improve confidence in adherence measurement, ideally through the application of rigorous scientific methods that lead to improved metrics or demonstrate how these metrics relate to improved outcomes (see Table 1).

### Identifying Factors that Drive Nonadherence

#### Identifying Those at Risk of Nonadherence

There is considerable heterogeneity in patient risk of nonadherence, and this heterogeneity is not well understood. Patients vary in disease status and severity, comorbidities, and demographics, all of which have been associated with nonadherence; however, patients also differ in less discernible traits, such as their beliefs about therapy effectiveness, preferences for

---

**Figure 1** Overview of the Research Agenda

<table>
<thead>
<tr>
<th>Tackling the Problem</th>
<th>Identifying Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOPIC 1</strong> Measuring adherence and nonadherence</td>
<td><strong>TOPIC 4</strong> Remediying problems with existing evidence on the effectiveness of interventions</td>
</tr>
<tr>
<td><strong>TOPIC 2</strong> Identifying factors that drive nonadherence</td>
<td><strong>TOPIC 5</strong> Improving adherence through care coordination</td>
</tr>
<tr>
<td><strong>TOPIC 3</strong> Evaluating the impact of nonadherence on health outcomes and costs</td>
<td><strong>TOPIC 6</strong> Understanding provider and payer behavior</td>
</tr>
</tbody>
</table>
suggesting that simplified regimens may lead to better adherence between medication regimen complexity and adherence, tantamount to evaluate how other factors influence patient behavior. For instance, Chernew et al. (2007, 2008, and nonadherence risk. Cost is a well-established barrier to proper medication consumption, and while addressing financial barriers is necessary for improving adherence, it may not be sufficient. It is important to evaluate how other factors influence patient behavior. For instance, several studies have examined the relationship between medication regimen complexity and adherence, suggesting that simplified regimens may lead to better adherence.

Another research priority is to study the effectiveness of different approaches to modify patient behavior in a way that results in improved adherence. For instance, the literature demonstrates that providing patients with educational information about therapy benefits and side effects along with instructions for self-administration is associated with improved adherence. This suggests that health literacy is an important behavioral component to adherence likelihood, but more research is needed to determine how best to intervene to improve patient understanding.

Even when patients recognize the value of their medications, some still have difficulty adhering to treatment regimens. Research has demonstrated that technologies reminding patients to take their medications, such as smartphone applications, effectively can improve adherence. Yet, a survey of patients who discontinued medications for chronic disease indicated forgetfulness as less of a barrier than cost, side effects, other medication concerns, and a belief that therapy was unnecessary. This highlights the importance of identifying which patients, such as those more prone to forgetfulness, are most likely to respond to particular interventions so that resources can be appropriately allocated.

**TABLE 1**

**Research Priorities: Measuring Adherence and Nonadherence**

<table>
<thead>
<tr>
<th>Improve measurement of whether and when patients consume their medications.</th>
</tr>
</thead>
<tbody>
<tr>
<td>How well do various data sources (i.e., pharmacy-dispensing records, payer claims, electronic medical records, electronic-monitoring devices) characterize actual medication use?</td>
</tr>
<tr>
<td>What are the primary sources of error in these measurement approaches, and how can they be reduced?</td>
</tr>
<tr>
<td>How can stakeholder confidence in adherence measures be improved?</td>
</tr>
<tr>
<td>What data sources and measurement methods are most strongly associated with health and economic outcomes?</td>
</tr>
<tr>
<td>How does the association between various adherence measurement approaches and outcomes vary by condition and patient population?</td>
</tr>
</tbody>
</table>


data sources and measurement methods are most strongly associated with health and economic outcomes.24-26 In a survey of Medicare beneficiaries, over half of patients describe cost as a barrier to making drug administration and pick-up more convenient for patients on multiple medications via polypills or medication synchronization—the coordination of refill dates across a patient’s medications—are examples of adherence interventions meriting further study.

It is also important to note that properly identifying non-adherence risk may involve more than looking individually at any given characteristic that influences adherence. Often, the interaction of different factors is important in understanding and influencing patient behavior. For example, a complex treatment regimen combined with the presence of comorbid depression may raise patient nonadherence risk beyond the effect of either factor in isolation.11

**Modifying Patient Behavior**

Another research priority is to study the effectiveness of different approaches to modify patient behavior in a way that results in improved adherence. For instance, the literature demonstrates that providing patients with educational information about therapy benefits and side effects along with instructions for self-administration is associated with improved adherence. This suggests that health literacy is an important behavioral component to adherence likelihood, but more research is needed to determine how best to intervene to improve patient understanding.

Even when patients recognize the value of their medications, some still have difficulty adhering to treatment regimens. Research has demonstrated that technologies reminding patients to take their medications, such as special pill bottles or smartphone applications, effectively can improve adherence. Yet, a survey of patients who discontinued medications for chronic disease indicated forgetfulness as less of a barrier than cost, side effects, other medication concerns, and a belief that therapy was unnecessary. This highlights the importance of identifying which patients, such as those more prone to forgetfulness, are most likely to respond to particular interventions so that resources can be appropriately allocated.

**Evaluating the Impact of Nonadherence on Health Outcomes and Costs**

**Relationship Between Adherence and Health Outcomes**

While numerous studies have documented patient adherence across diseases and patient populations,11,34-36 less attention has been paid to the consequences of nonadherence or the effects of improving adherence on patient outcomes. Among studies demonstrating a link between adherence and outcomes, Choudhry et al. (2013) found, in heart attack patients, only those attaining proportion of days covered (PDC) greater than 80% were less likely to experience a vascular event compared with controls. While partially adherent patients
There remains much opportunity for research on the impact of adherence improvement on health outcomes to supplement and confirm knowledge in this area. In particular, studies should examine how the relationship between adherence and outcomes changes across different adherence levels for various therapeutic classes and disease states. This may identify where resources are best spent and at what adherence levels efforts to raise adherence are less likely to result in improved patient outcomes. Also, the impact of improved adherence on patient outcomes may vary by patient characteristics beyond baseline adherence level. Thus, an important research priority is to understand the implications of patient heterogeneity on the relationship between adherence and outcomes. In particular, this would help identify patients for whom adherence is particularly important and for whom intervention is most likely to be beneficial, particularly under cost constraints.

### Impact of Improving Adherence on Costs

There is a growing literature that demonstrates the impact of improved adherence, not only on health outcomes but also on costs. In reviewing this literature, the Congressional Budget Office estimated in 2011 that a 1% increase in prescriptions filled by Medicare beneficiaries would lead to an average 0.2% reduction in Medicare expenditures on medical services due to, for instance, reduced hospitalizations. However, more work in this area is needed as gaps in our knowledge about the relationship between adherence and outcomes persist, particularly outside the Medicare population (see Table 3).

### Remediing Problems with Existing Evidence on the Effectiveness of Interventions

#### Methodological Limitations in Adherence Research

While hundreds of studies have evaluated interventions to improve adherence, many suffer from potentially important limitations, including small sample sizes and inconsistent approaches to adherence measurement, study design, intervention execution, and reporting. For example, a meta-analysis of trials testing the effectiveness of adherence interventions found that many studies did not report the study subjects’ baseline characteristics. Research has noted that socioeconomic factors such as race, age, gender, education, and income level influence adherence in particular patient samples and settings, although these relationships do not persist across all patient groups and therapy classes. To improve understanding of which patients benefit most from particular interventions, future studies should make efforts to characterize study populations and conduct subgroup analyses.

Given the limitations of existing literature, a natural research priority is to improve future program evaluations. This could involve determining standard criteria necessary to improve the study quality, such as the use of randomized controlled trials (RCTs) with clearly defined treatment and control groups. However, conducting RCTs within the context of real-world quality improvement can be challenging. Thus, developing standard methods for observational studies may be even more important. Improving intervention quality may also involve evaluating the reproducibility of existing studies across different disease states and payer systems. For example, while adherence has been more heavily studied for indications such as diabetes, hypertension, and human immunodeficiency virus, it may very well be that effective interventions among diabetes patients are not as effective for patients with arthritis.

### Applicability and Impact of Existing Interventions in Increasing Adherence

As noted, research across multiple therapeutic areas have demonstrated adherence benefits with no accompanying improvements in patient health outcomes, and this is due in many cases to small sample sizes; however, it may also be the case that patients were not followed long enough to detect differ-
 TABLE 3  Research Priorities: Evaluating the Impact of Nonadherence on Health Outcomes and Costs

1. Evaluate the relationship between adherence measures and clinical and economic outcomes.
   - How does improving adherence impact health outcomes and costs?
   - What are the consequences of nonadherence on health outcomes and costs?
   - What is the impact of nonadherence on patients’ work and productivity?
   - How do these effects differ across therapies and different patient sub-populations?

2. Examine how the relationship between adherence and outcomes changes across different levels of adherence for various therapeutic classes and disease states.
   - At higher adherence levels, do improvements in adherence provide the same benefit in health outcomes as do equal improvements in adherence at lower baseline adherence?
   - Do the effects of improved adherence differ across diseases or treatment options?
   - Which drug classes or therapeutic areas have existing evidence on how adherence is related to patient outcomes?

3. Understand the implications of patient heterogeneity for the relationship between adherence and outcomes.
   - For whom is adherence particularly important to maintain or achieve improved health states?
   - For which patient groups would spending on adherence interventions yield the most benefit in terms of averted future medical costs?

 TABLE 4  Research Priorities: Remedying Problems with Existing Evidence on the Effectiveness of Interventions

1. Improve methodology of program evaluations.
   - What standard criteria are necessary to improve the quality of research studies?
   - Can existing studies be replicated across different disease states and payer systems?

2. Determine whether and how promising interventions to improve adherence can be adapted for broader populations.
   - What is the practicality and effectiveness of implementing potentially promising interventions in large patient populations?
   - How can promising interventions be altered to benefit the broader patient population within resource constraints?
   - Can interventions identified as effective in improving adherence for particular indications be effective for other indications as well?
   - What have been the impacts of lesser-known interventions applied in nonpublicized settings or published outside the peer-reviewed literature?
   - How does combining multiple strategies modify the effects of interventions?
   - What time periods of evaluation are appropriate for different therapeutic areas and for different therapies?

Improving Adherence Through Care Coordination

The Fragmented Health System

Patient care is often fragmented between a number of providers, including primary care physicians (PCPs), specialists, hospitals, emergency departments, urgent care centers, diagnostic centers, nursing homes, and pharmacies. In fact, 1 study found that patients with chronic conditions may visit up to 16 different physicians annually.31 Multiple stakeholders commented that a fragmented health care system can contribute to poorer quality of overall care and patient nonadherence. Consider a patient prescribed medication from his or her PCP but later admitted to the hospital for a cardiovascular event. The treating physician at the hospital may have no knowledge of the patient’s current medications and thus prescribe a new set. After discharge, the patient has 2 sets of prescriptions and instructions from different doctors and may be uncertain about which medications to take. Many studies have documented similar failures in the coordination of patient care.32-34

Improving Collection and Communication of Patient Data

In a fragmented health system, it is important to understand how institutional barriers may render providers ill-equipped to monitor medication history and adherence. For example, there is little information about the tools providers have or believe they need to have to improve adherence. Electronic medical records (EMR) may facilitate an immediate transfer of patient information between providers, payers, and pharmacies, but as of 2012, only 40% of U.S. PCPs and 44% of U.S. hospitals had at least basic electronic health systems.35,36 While EMR can be useful, a cluster-randomized trial demonstrated that sharing adherence data from pharmacy fills with physicians did not improve adherence or that the causal effect was masked due to confounding. The protective effects of medications against disease progression realize gains over different time horizons. To improve evidence on intervention effectiveness, research designs should consider what time periods would allow meaningful study of patient outcomes, considering the particular disease of interest.

Another issue to consider is how promising interventions can be appropriately scaled to larger or more general patient populations. For instance, interventions that involve health professionals sitting down with individual patients to review their entire medication regimen and providing regular personal follow-up may be extremely effective in raising adherence but too resource intensive to be applied to large patient populations or in real-life clinical interactions.

Lastly, existing studies often combine several strategies to improve adherence, making important the detailed description of intervention components. A review of RCTs of adherence interventions found almost all effective interventions for long-term care were complex, involving combinations of more convenient care, reminders, reinforcement, and psychological and family therapy, among other components.37 An interviewed health plan executive contrasted the large gamut of tested approaches with what is often only little published detail on the interventions. The interviewee stressed the need for studies to describe interventions thoroughly so that evaluations can be replicated or the interventions put into practice (see Table 4).
adherence across all patients but only for those patients whose doctors actually evaluated the data. Along with EMR, there may be other tools providers could use in efforts to improve patient adherence, including interactive voice recognition and automated personalized calls. However, research has not yet demonstrated the relative effectiveness or cost-effectiveness of individualized, technology-based interventions compared with increased patient-provider communication.

Communication with Caregivers

It is important to recognize that coordination of care is not strictly a problem among treating physicians. Caregiver involvement and health literacy are crucial issues for children, the elderly, and others who may require additional support. One interviewed researcher identified caregivers as the most important but least studied subpopulation in the adherence arena. In most patient cases involving a caregiver, the prescribing physician delivers medication instructions to the caregiver, who then administers medication to the patient. Without a thorough understanding of the prescribed therapy’s importance for patient health and how patient outcomes may differ with the dosage administered, caregivers may stray from treatment protocol. For instance, parents who know their children dislike certain medication tastes may let them take partial, perhaps ineffective, doses. Winnick et al. (2005) elaborate on how adherence can be improved in the pediatric population, noting that the caregiving environment can substantially impact adherence, especially when patients are taken to a health provider by someone other than the primary caregiver, when a patient has multiple caregivers who must coordinate among themselves, or when family communication is poor. Research opportunities include exploration of the most efficient and effective communication design between health care professionals and patients via their caregivers to address beliefs about medication efficacy and safety before treatment plans commence (see Table 5).

Understanding Provider and Payer Behavior

Misaligned Incentives

The misalignment of provider and payer incentives with the goal of improving adherence could have important outcomes for patients. Such misalignment can occur when, for example, reimbursements are tied to the quantity of services provided but not to patient outcomes, leading to potentially inefficient patterns of care. New payment reforms are being implemented with the aim of better aligning incentives, for instance, by providing performance bonuses to health care providers for meeting certain quality measures, including adherence-based metrics. An important area for research will be to develop and publish evidence that informs and guides these efforts, including evidence connecting adherence to the broader set of clinical and economic quality measures for which providers and payers are held accountable and the specific interventions that may be best at improving adherence in a cost-effective manner.

Evolving Payment Systems

Changing payment schemes could have significant impact on provider incentives and provider behavior—and may affect efforts to improve adherence. For instance, shared savings programs, in which payers share with providers the savings incurred when total health care spending for their patients falls below a pre-established threshold, are being tested by multiple insurers and in Medicare demonstration programs as a potential means to improve provider incentives; however, there is not yet substantial evidence about the results of these efforts. A Cochrane Collaboration review of the impact of varied financial incentives for PCPs on quality of care concluded there is insufficient evidence to support the use of payment systems as a tool to improve patient outcomes. Rather, the literature on incentive design currently is based more heavily on theory. Empirical work to assess the impact of emerging payment schemes and other policy development on adherence is needed. In particular, more work is needed to understand both what behavior on the part of payers and providers could actually influence medication adherence and how willing they would be to engage in this behavior (see Table 6).

Discussion and Conclusions

Medication nonadherence is costly to the health care system and to society, with estimates of the costs of nonadherence ranging from $100 billion to $300 billion per year. Improving adherence has the potential to generate cost savings while improving patient outcomes. In fact, many changes planned for our health care system are directed toward giving providers and payers the incentives to improve adherence. Innovators have designed numerous technologies that remind patients to take their
2. Evaluate impact of ongoing payment reforms on adherence.

- How do changing payment systems impact adherence?
- How would proposed payment schemes affect patient health and total costs?

medications, deliver educational messages to those identified as nonadherent, and help providers collect and share patient information so that those at greater risk of nonadherence can be identified more easily. However, the effectiveness and cost-effectiveness of many of these system changes and new technologies have yet to be established. Given the potential savings from reduced nonadherence, the health consequences of nonadherence, and the evolving landscape for health care delivery and reimbursement, improving our understanding of adherence merits further exploration. Addressing the topic areas identified here will be an important step towards accomplishing this goal.

TABLE 6
Research Priorities: Understanding Provider and Payer Behavior

1. Understand and align provider and payer incentives with the goals of improving adherence and overall health.
   - How do incentive and reimbursement issues impact medication adherence?
   - How are payer organizations currently addressing nonadherence?
   - What implications would performance-based bonuses to improve provider financial incentives have on adherence?
   - How would implementation of adherence-related quality measures impact provider incentives and patient outcomes?

2. Evaluate impact of ongoing payment reforms on adherence.
   - How do changing payment systems impact adherence?
   - How would proposed payment schemes affect patient health and total costs?


