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TECHNICAL
REPORT

A Review of Barriers to Medication Adherence: A Framework for Driving Policy Options

Walid F. Gellad, Jerry Grenard, Elizabeth A. McGlynn

Sponsored by Mehlman Vogel Castagnetti

RAND HEALTH

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1200 South Hayes Street, Arlington, VA 22202-5050
4570 Fifth Avenue, Suite 600, Pittsburgh, PA 15213-2665
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Preface

This work was sponsored by Mehlman Vogel Castagnetti and was requested as background for a conference focusing on policy options to improve medication adherence. RAND was asked to discuss the prevalence and importance of medication adherence and to review the barriers to medication adherence in order to set a framework for the policy discussion. To do this, RAND performed a systematic review of the literature on non–cost-related barriers to medication adherence; these findings were supplemented with results from prior systematic reviews of cost-related barriers and prior systematic reviews of adherence interventions to give a broad overview of this important problem. From the RAND systematic review and from the prior reviews, this report identifies barriers to medication adherence with a strong evidence base—which were the focus of this study—and discusses key lessons from the literature that are relevant for the policy discussion. RAND Health is a division of the RAND Corporation. A profile of RAND Health, abstracts of its publications, and ordering information can be found at www.rand.org/health.

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Executive Summary

What can be done about a problem that has been studied in thousands of articles and yet barely improved in decades? Failure to adhere to recommended medication regimens is a real problem that has negative consequences for patients, providers, health plans, employers, industry, and society. The national dialogue on health reform that is currently under way includes a discussion of ways to improve care for persons with chronic disease and to improve the value and efficiency of health care. Strategies to improve adherence to medication therapy fall squarely in these discussions, since nonadherence affects the ability to effectively manage and control chronic diseases and contributes to the costs society incurs.

To provide an evidence base and framework for the development of policy options to improve adherence, we review here the literature on barriers to medication adherence. We conducted a systematic literature review of the nonfinancial barriers to medication adherence, and, to complement this systematic review, we summarized prior reviews on adherence, including those dealing with financial barriers. The literature on barriers to medication adherence is heterogeneous and of variable quality, which detracts from our ability to form policy recommendations rooted in the literature. The literature we reviewed uses different measures of adherence, some of which are validated and some that are not, and measures adherence with different instruments and over different periods of time for different diseases with small samples.

Despite these limitations, we identified, through our systematic review and prior reviews, four key potentially modifiable barriers that are conceptually sound and evidence-based:

- cost-sharing
- regimen complexity
- medication beliefs
- depression (in patients with diabetes).

Evidence is clear that higher copayments contribute to lower adherence to medication. Cost-sharing could thus be reduced as a barrier when the appropriate use of a particular medication has health or financial benefits, such as avoiding future complications, functional decline, or more-expensive future treatments. Regimen complexity is another barrier to medication adherence that has clear evidence in the literature, and prior systematic reviews of interventions to improve adherence have identified decreasing regimen complexity as a successful intervention. A variety of other nonfinancial factors are likely to affect adherence, and the literature we reviewed points to beliefs about medications generally and depression (most consistently in patients with diabetes) as important barriers. For these barriers, policy options will have to

be flexible, rather than global, since one-size-fits-all programs are unlikely to work. Additional prevalent barriers included lack of knowledge about illness and treatment, side effects, and provider factors, including patient-provider trust and patient satisfaction.

We additionally identified several key points gleaned while performing this literature review that are relevant to the discussion on policy solutions:

- A research agenda that addresses the shortcomings in the current literature would be helpful to guide the policy agenda.
- Potential policy solutions that address one barrier must not worsen another—for example, programs that lessen regimen complexity should not also increase cost-sharing.
- Researchers and policymakers must be clear about the type of adherence they are addressing, since adherence is a multistep process, from being prescribed the correct medication, to filling the prescription, to continuing to take the medication, to taking the medication as directed.
- Programs for improving adherence must find a balance between "customized" interventions to address individual barriers and effective programs that work for large groups or classes of patients.

The literature does not identify how barriers interact and cannot identify any one individual patient's barriers; thus, programs or screening tools that can identify nonadherent individuals and successfully address their individual barriers should be supported. Health information technology and comparative-effectiveness research, two major components of health reform, have the potential to play important roles in promoting adherence to medications and better research on adherence interventions.

Abbreviations

CI	confidence interval
CMG	cumulative medication gap
HAART	highly active antiretroviral therapy
HIT	health information technology
HIV	human immunodeficiency virus
IOM	Institute of Medicine
JAMA	*Journal of the American Medical Association*
LDL	low-density lipoprotein
MCBS	Medicare Current Beneficiary Survey
MEMS	Medication Event Monitoring System
MeSH	Medical Subject Headings
MPR	medication possession ratio
NCPA	National Community Pharmacists Association
NCPIE	National Council on Patient Information and Education
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PDC	proportion of days covered
VA	U.S. Department of Veterans Affairs
VBID	value-based insurance design
WHO	World Health Organization

SECTION ONE

Introduction

Failure to adhere to recommended medication regimens is a serious problem that has negative consequences for patients, providers, health plans, employers, industry, and society.

We have written this review in order to provide an evidence base and framework for the development of policy options to improve adherence. We begin by reviewing what is known about the importance of adherence and the consequences of nonadherence. We also provide a more-nuanced classification of problems with adherence that recognizes that adherence requires execution of a sequence of steps. We then provide a framework within which to consider the factors that contribute to adherence. We describe the methods used to identify and select articles for the systematic review of nonfinancial barriers to adherence. Our results are presented highlighting the most-common and -consistent findings from prior studies. We then summarize previous reviews of the literature, including those dealing with financial barriers, to provide a more-comprehensive context for policymakers. Finally, we offer some initial thoughts about the priorities for developing policy options that address the key barriers to medication adherence.

Importance of Adherence

Health-reform discussions in the United States often emphasize the poor return on investment realized on the billions of dollars spent on health care. The United States spends orders of magnitude more money on health than any other country but fares worse on many measures of quality.[1] The United States, other developed nations, and many developing nations, however, fare equally poorly on one particular and important aspect of health care: adherence to medical regimens. A 2003 World Health Organization (WHO) report on the prevalence, causes, and potential solutions to nonadherence to therapies in chronic diseases frames adherence as a worldwide problem, with significant impact on health and productivity.[2]

In the United States, published reviews of adherence estimate that 20 percent to 80 percent of patients do not adhere to medical therapies, including medication regimens.[2–4] The range in estimates reflects the inconsistency in the definitions, methods, and aspects of adherence studied. The range for medication-related studies may be narrower and is suggestive of a significant problem. In a comprehensive meta-analysis of 569 studies reporting adherence to medical treatment, the average rate of adherence from the 328 studies related to medications was 79.4 percent.[3] In the overall sample, mean adherence rates across the studies ranged from 67.5 percent for patients with diabetes to 88.3 percent for patients with human immunodeficiency virus (HIV) disease. A survey commissioned by the National Community Pharma-

cists Association (NCPA) and summarized in the 2007 National Council on Patient Information and Education (NCPIE) report indicates that nearly 75 percent of American consumers say that they do not always take their prescription medicine as directed.[4] Even in published studies in the United States using nationally representative data, the prevalence of nonadherence varies. In a 2006 survey of seniors who were taking medication, 20 percent reported not filling or delaying filling a prescription because of cost;[5] in the 2006 Medicare Current Beneficiary Survey (MCBS), 11.5 percent of seniors reported cost-related nonadherence.[6] How adherence is defined, assessed, and measured, and in what populations it is measured, all affect reported adherence rates. These reporting issues, and other nuances of the literature, are discussed in Section Three and Appendix A.

Consequences of Nonadherence

In 2006, 187.5 million people purchased one or more prescription drugs in the United States, representing 63 percent of the country's civilian noninstitutionalized population.[7] What effect does nonadherence have on health? A detailed review of the relationship between medication nonadherence and health outcomes is beyond the scope of this report, but an often-referenced review by Osterberg and Blaschke concludes that nonadherence accounts for "substantial worsening of disease, death, and increased health care costs."[8] Many studies report the adverse outcomes that are associated with nonadherence;[9–14] for example, Osterberg reports on studies that find that 33 to 69 percent of medication-related hospital admissions in the United States are due to poor medication adherence, with a cost of around $100 billion per year.[8] Better adherence to medications has even been associated in large cohort studies with decreased mortality among patients after heart attack and among patients with diabetes.[10,15]

Adherence Defined

A significant challenge in summarizing the literature on nonadherence is the lack of consensus on a definition of *adherence* or on ways to measure adherence. In the WHO report on adherence to long-term therapies, adherence to medications is just one aspect of overall adherence, which is defined as "the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider."[2] Several of the meta-analyses examining the relationship between adherence and outcomes also include other behaviors in their definition of *adherence*, including following dietary recommendations and making appointments.[3, 16–18] While all of these behaviors involve provider recommendations and patient decisions, the issues surrounding medication use are often very different from those involving dietary adherence, adherence to follow-up appointments, or adherence to diagnostic testing recommendations.[19] In this report, we focus exclusively on medication adherence.

Within the area of medication adherence, there are several types of nonadherence. The first is what is commonly called *nonfulfillment*, in which providers write prescriptions but the medication is never filled (also known as *primary nonadherence*). In this case, providers have made recommendations about a course of therapy that the patient ultimately does not initiate. This first type of nonadherence includes patients who fill the first prescription for a

new medication but never take it. A second type of nonadherence is called *nonpersistence*, in which patients decide to stop taking a medication after starting it, without being advised by a health professional to do so. Most patients who stop their medication will do so within the first six months of starting.[20] Nonpersistence can happen, though, at any point in time and is only rarely unintentional (e.g., when patients and providers miscommunicate about therapeutic plans). A third type of nonadherence we call *nonconforming*, which encompasses a variety of ways in which medications are not taken as prescribed; this behavior can range from skipping doses, to taking medications at incorrect times or at incorrect doses, to even taking more than prescribed. The types of nonadherence underscore the challenges in achieving full adherence: A medication must be appropriately prescribed, filled, initiated, continued, and taken as intended. Failure at one or more of these junctures will have consequences for patients' health. Additionally, what constitutes nonadherence for one medication may be clinically insignificant for another medication; for example, skipping one dose of an HIV medication is not recommended and can lead to development of viral resistance, and stopping an antibiotic dose can similarly be a problem. Skipping one dose of thyroid hormone or cholesterol medication will have little clinical significance, although these skipping behaviors are rarely isolated, and, thus, the cumulative effect of this kind of nonadherence can be very serious.

The heterogeneity in how adherence is assessed, measured, and defined is a major limitation to the data on barriers to adherence. We discuss some of the specific methodological issues about the measurement of adherence in Appendix A.

SECTION TWO

Conceptual Framework

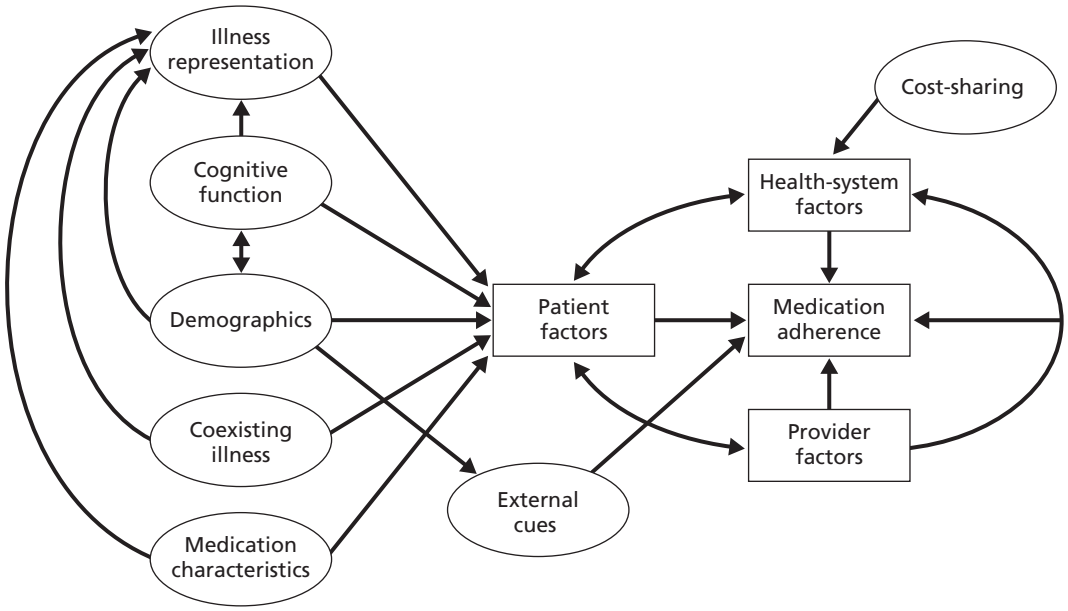
Many conceptual models have been used to help understand the barriers to medication adherence, including the transtheoretical model of change, the theory of reasoned action, locus of control, the health belief model, social learning theory, and theory of self-regulation.[2, 21] None of these models dominates the other or fully explains the barriers to medication adherence. McHorney used the proximal-distal continuum model in developing a three-item adherence predictor, in which patients' beliefs, skills, and experiences that are "most proximal" to a decision about taking a medication are the most important (identified by McHorney as perceived needs, perceived concerns, and perceived affordability of medication).[19] The WHO report on adherence and a recent review of adherence in hypertension by Cooper summarize factors that affect adherence in five dimensions: social and economic factors, condition- and therapy-related factors, health-system and clinician factors, patient factors, and patient-provider relationship factors.[2, 22] Osterberg, in his review of medication adherence, also summarizes barriers to adherence as patient, provider, and health-system factors, with interactions among them all.[8] There are thus many ways to organize the study of barriers to medication adherence.

For this review, we adapted a conceptual framework published by Park and Jones in explaining adherence among the elderly.[23] Our model (Figure 2.1) combines the provider- and health system–related factors described in the studies noted, with Park's framework describing patient-related factors, and serves as a guide for both our literature review and the policy discussion.

Patient Factors

Patients are influenced by each of the domains in ovals in Figure 2.1. *Illness representation* includes important elements of health beliefs, including beliefs about medications (both positive and negative) and knowledge about illness. *Cognitive function* includes comprehension and memory, as well as presence of dementia and is particularly important in the elderly. *Demographics* includes age, gender, and ethnicity, as well as health literacy, physical limitations (eyesight, difficulty swallowing), and unstable living situations. *Coexisting illness* includes medical and psychiatric conditions, as well as alcohol use and smoking. Finally, *medication characteristics* includes regimen complexity, number of prescriptions, and side-effect profiles. Each of these patient-related factors affects the other, such that the complexity of a medication regimen and the presence of coexisting depression, for example, will certainly affect the patient's perceived need for medication and perceived risk of side effect, in addition to affecting medication adherence in other ways.

Figure 2.1
Conceptual Framework Guiding Evidence Review



Health-System Factors

In addition to cost (specifically, the effect of cost-sharing and out-of-pocket costs on patient adherence), health-system factors include formularies, prior-authorization requirements and benefit caps, fragmentation of care, and access to care. Each of these factors affects the ease with which patients are able to access their medication and discuss medication-related issues with their providers.

Provider Factors

These include patient-provider trust and satisfaction, time spent discussing medications, and other communication issues. Providers in these cases include not only physicians but also pharmacists, nurse practitioners, and physician assistants, who play important roles in the medication use process. The model graphically represents the fact that patient, health-system, and provider factors interact to produce observed adherence. For example, patients and providers, by definition, exist within a health-care system; any impact of patient illness representation on adherence is necessarily affected by how patients and providers interact, which is affected by the time and reimbursement that are available for office or pharmacy visits in the current system. This interaction also explains the challenge in isolating a single factor that represents a critical barrier to adherence, as well as the difficulty in understanding why particular interventions did or did not improve adherence.

SECTION THREE

Systematic Review of Non–Cost-Related Barriers to Medication Adherence

We used the prior literature and the conceptual framework to create a list of barriers to medication use to inform our search strategy. We begin by explaining in detail the methods we used to conduct our systematic review of the non–cost-related barriers to medication adherence. We then present results of the review. In Section Four, we summarize the barriers that others have identified in previously published reviews specific to medication use, including financial barriers, along with a discussion of some of the limitations of those reviews.

Methods

Inclusion and Exclusion Criteria

We included only U.S.-based studies of adults, since the adherence issues in other countries are less relevant to the U.S. policy debate for which this report provides a framework. We limited our analysis to studies of adults over age 18, since adherence barriers for children may be very different from those for the majority of adults with chronic disease. We excluded any studies focused specifically on people who were homeless or substance abusers, or patients with schizophrenia or other psychotic disorders, tuberculosis, or HIV, because of the unique circumstances that surround medication adherence for each of these populations. We began by searching the literature for systematic reviews of adherence to medical therapy (whether medication or other therapies) to identify topics recently reviewed, and found a large body of literature on the relationship between dose complexity and medication adherence.[24–27] Therefore, we exclude individual studies in our current review that exclusively address this relationship between adherence and dose complexity, and use prior reviews in our summary of key barriers in Section Four. Similarly, we excluded individual studies of cost-sharing as a barrier to nonadherence, since this important area has been recently reviewed and will be discussed in more detail below.[28, 29]

Databases and Search Terms

A literature search was done on the PubMed and PsycINFO® databases, covering the time period from January 1998 to April 2009, limiting to English-language publications and omitting the publication types of "letters," "editorials," and "comments." The search strategy utilized both Medical Subject Headings (MeSH®) and non-MESH terms and resulted in 3,908 citations. We also conducted forward and related searches on relevant articles, which added 752 articles, for a total citations reviewed of 4,660. Our search strategy is outlined in detail in the text box and in Figure 3.1.

Search Terms

noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher*

AND

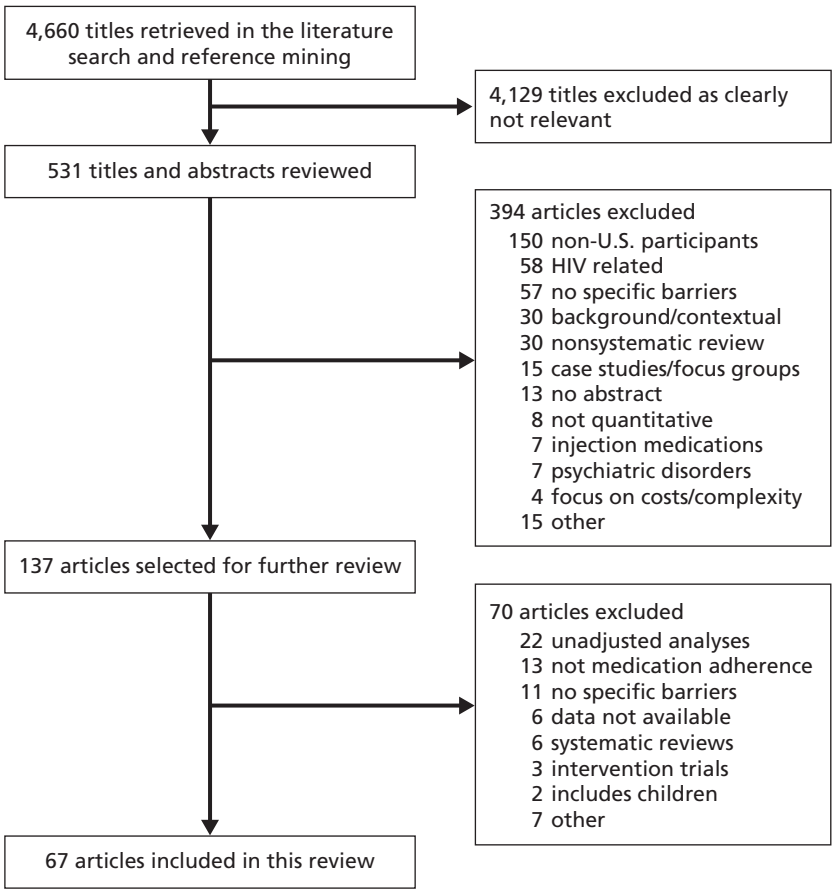
drug therapy OR pharmaceutical preparations OR medication* OR prescription* OR medicine OR pharmaceutical* OR drug OR drugs

AND

predict*[ti] OR barrier*[ti] OR challeng*[ti] OR factor[ti] OR factors[ti] OR determin*[ti] OR relationship*[ti]

NOT animals, NOT letter[pt] OR editorial[pt] OR comment[pt]

Figure 3.1
Flow-Chart Summary of Literature Search



RAND *TR765-3.1*

We searched for articles that examined barriers to medication adherence among U.S. adults, including articles that described "predictors," "facilitators," or "determinants" of medication adherence and those articles that examined the "relationship" between a specific barrier and adherence. The articles must have been published in a peer-reviewed, English-language journal (thus excluding conference proceedings, dissertations, and book chapters). We included articles that (1) reviewed specific modifiable barriers to medication adherence and did not

solely describe nonmodifiable predictors of adherence (e.g., demographics, marital status); (2) were not interventions designed to address adherence (as DiMatteo has done[18]); (3) must have defined adherence or compliance and specified its method of measurement; (4) involved U.S. participants only.

Each of the citations was reviewed independently and in parallel by two of the authors of this report. Of the 4,660 titles reviewed, 531 were deemed relevant to the analysis, and abstracts were pulled for review. The reviewers then screened each of the abstracts for inclusion based on the criteria listed, and 137 met the criteria. These articles were retrieved in full. The reviewers then independently coded each article on the following dimensions: (1) study design; (2) participant characteristics; (3) recruitment method; (4) sample size; (5) disease studied; (6) type of nonadherence (i.e., nonfulfillment, nonpersistence, nonconforming [labeled *nonadherence* in evidence table], overadherence); (7) how adherence was assessed and measured (i.e., self-reported, pharmacy claims, electronic monitoring, pill count, and exact scale or method used); (8) the length of time over which adherence was measured, if specified; (9) specific barriers and predictors of adherence discussed, along with an indicator if standard validated assessment of the barriers were included (e.g., Beck Depression Inventory®). The individual barriers were assessed in each article using a standardized collection form that was created based on the conceptual framework. Disagreements on articles to be included and on coding were resolved by consensus between the two reviewers.

Among the 137 articles reviewed in full, 22 contained only unadjusted analyses without controlling for standard demographic factors and thus were excluded. In total, 67 articles met final inclusion criteria and are the basis of this review. These observational studies varied in their methods of analysis, study population, and identification of exposure (barriers) and outcome variables (adherence). The result is tremendous heterogeneity in these studies, so no attempt was made to combine these results into a meta-analysis, and our results are thus qualitative.

Results

Overview

Details from the 67 studies in this review,[30–99] including study sample, disease, method of assessing adherence, barriers discussed, and key findings, are summarized in Appendix B. A majority of the articles (47 articles) focused on three diseases: hypertension, diabetes, and hyperlipidemia, which are asymptomatic, chronic conditions for which long-term medical therapy is often necessary. Very few articles assessed nonfulfillment (three articles) or nonpersistence in the first six months (six articles). Most studies evaluated adherence in general for those patients who were chronically on medications. In seven cases, it was unclear from the study what type of adherence was being measured. Articles rarely included more than one type of adherence. Self-reported measures of adherence were by far the most common way in which adherence was assessed, with 19 articles using questionnaires, 19 using in-person interviews, and four using telephone interviews. Of those articles using self-reported measures of adherence, only 18 used a validated scale, with the rest using either modified scales or one-, two-, or three-item questions that were developed solely for the purpose of the study. Only two studies had nationally representative samples—one used the National Health and Nutrition Examination Survey (NHANES),[38] and the other used a large national survey known as the Healthstyles survey.[90] In each of these surveys, however, the measure of adherence was limited. In

the NHANES survey, patients were asked whether they were prescribed high–blood-pressure medicine, and then study staff examined the medications brought to the physical exam to see whether antihypertensives were included; if they were not, the respondent was defined as nonadherent. In the Healthstyles survey, patients responded to several questions about what made it difficult for them to take their medication. Some of the measures specified actual nonadherence ("I don't always remember"), but some did not ("Other reasons"), and the final multivariate analysis is performed combining all these measures.

Most of the barriers addressed in the articles fit into the categories created in the conceptual model. The potential barriers most often studied in the reviewed papers are listed in Table 3.1.

Additional prevalent barriers included lack of knowledge about illness and treatment, side effects, and other provider factors, including patient-provider trust, patient satisfaction, and other communication issues. Barriers like health literacy, forgetfulness, transportation, access to care, and cognitive function and memory were rarely assessed in these studies. Regimen complexity and costs were evaluated in several articles but not included in this review to prevent duplication with recently published systematic reviews. Four of the five potential barriers most commonly studied in the articles reviewed (depression, beliefs about medications, number of prescriptions, and social support) are described in more detail next. Perceived health status had no relationship to medication adherence in the articles studied.

Depression

We found 33 articles published between 1998 and 2009 that either assess the relationship between depression and nonadherence or include depression as a predictor of nonadherence; most of these articles were published within the past few years. Only seven of these articles use

Table 3.1
Five Most Commonly Studied Potential Barriers in Reviewed Articles of Medication Adherence

		How Adherence Is Assessed (no. of studies with each method; some articles may use more than one method)				
Barrier	No. of Articles	Questionnaire	Interview	Pharmacy Records	Electronic Monitor	References
Depression	33	8	10	10	7	30, 33, 35, 36, 40, 43–45, 47, 49, 52–57, 59–61, 63, 64, 68, 70, 73, 78, 81–83, 85, 90, 92, 93, 96
Beliefs about medication	24	7	11	3	4	34, 35, 37, 38, 44, 50, 52, 56, 57, 66, 68–71, 73–76, 81, 88, 94, 96–98
No. of prescriptions	20	5	6	12	1	43, 45, 48, 49, 58–60, 67, 75, 79–81, 83, 84, 87, 90–92, 94, 98
Social support	17	5	6	4	3	32, 33, 48, 49, 54, 55, 61, 64, 66, 67, 73, 78, 88, 91–93, 96
Perceived health status	17	6	6	4	2	34, 42, 45, 46, 52, 56, 58, 64–66, 75, 82, 83, 91, 95, 98, 99

electronic monitoring, and 18 use either in-person interviews or questionnaires. Twenty-eight of the articles measured adherence for patients with hypertension, diabetes, hyperlipidemia, or asthma. Of the 33 articles dealing with depression as a barrier, one article had an unclear association between depression and nonadherence, and, of the other 32, half demonstrated a significant relationship between depression and nonadherence and half did not. In one analysis of adherence to antidepressants in depression, depression severity was not associated with adherence in final analysis that controlled for beliefs about medications.[30] In three of the papers, depression was associated with worsened adherence in univariate analysis, but the relationship did not persist after adjustment.[52, 53, 70] One additional important pattern was that the effect of depression on adherence varied across disease states; however, in studies of patients with diabetes, depression emerged as a consistent independent predictor of medication nonadherence.

These results differ from a prior meta-analysis published in 2000 that found that patients with depression had a significantly higher likelihood of noncompliance with all medical treatments, including diet, exercise, and medications (overall odds ratio [OR] of 3.03 [95-percent confidence interval (CI) 1.96–4.89]). This analysis included only five articles that dealt with medications, involving a total of 284 patients, with each of them published prior to 1992, except one from 1998.[18] Note that, in most cases in our review, depression was not a primary predictor of interest but was used as a covariate in the final models. In only four studies was the relationship between depression and adherence the primary inquiry of the study—each of these studies used a validated scale to measure symptoms, and each found a significant relationship between depression and worsened adherence.[55–57, 68] Thus, we conclude that, while depression is potentially an important barrier to adherence, the evidence is mixed, and the relationship may differ based on disease state. In diabetes, there was a clear association between depression and medication nonadherence.

Beliefs About Medication

Patients' beliefs about medications are key barriers to and facilitators of medication adherence. Perceived risks of having a side effect and perceived impact and need for the medication were common themes throughout the literature, with 24 articles in our review covering one of these topics. In the 21 articles in which the relationship between beliefs about medications and adherence was clearly identified, 16 of those relationships were strongly positive in adjusted analysis. Only four articles used electronic monitoring to measure adherence; the majority used self-report. The specific beliefs discussed in each article are variable, and, in some articles, certain beliefs might be strongly associated with adherence, and others not. For example, Aikens and Piette interviewed 806 patients with diabetes and hypertension in several clinics in Flint, Michigan, using the well-validated Beliefs About Medication questionnaire.[31] Concerns about the long-term effects of medication use were negatively associated with adherence to medication after controlling for costs and demographics, whereas beliefs about the necessity of the medication to maintain health were not associated with adherence. Beliefs about medications are complex but vital to understand in shaping interventions and policy solutions.

Number of Prescriptions

In 20 of the papers reviewed, the number of prescriptions each subject was taking was included in the analysis and discussed. The total burden of medication a person is using is separate from the complexity of a particular regimen (e.g., taking once per day versus three times per day). The effects of the number of medications on adherence are also quite varied. Of the 20 articles

that included the number of prescriptions, 14 showed a significant association between number of prescriptions and adherence. However, half of those showed that patients taking more medications had better adherence. For example, Pedan, Varasteh, and Schneeweiss studied 6,436 patients who initiated statin therapy using pharmacy claims records.[76] They found that adherence to statin medications decreased with rising cost-sharing but increased as the number of medications patients were prescribed for other conditions increased ($p < 0.01$). Similarly, Ren et al., in a cross-sectional study of veterans, found that a larger number of medications was associated with better medication adherence ($\beta = 0.41$, $p < 0.01$).[79] The relationship between number of prescriptions and medication adherence may be an artifact of scientific method, as patients who are more likely to be adherent are thus more likely to be on other medications. Nonetheless, the results are in conflict with clear research that shows that higher dosing demands and regimen complexity are associated with poorer adherence.

Social Support

How social support affects medication adherence is complex, stemming in part from the different ways in which support is measured. In only four of the 17 reviewed articles that include an assessment of the relationship between social support and adherence do the studies use a well-validated instrument to measure social support (e.g., Perceived Social Support Scale [see Wu, 2008], Duke Social Support Index [see Voils, 2005]). In other cases, support is measured through various questions that assess either how a patient's family understands his or her illness or how comfortable a patient seems to discuss his or her illness with family or friends, or even family size as a surrogate for support. In six of the 17 studies,[49, 55, 61, 73, 91, 96] social support was positively associated with improved adherence, but, in the remaining, there was no significant association between support and adherence. Even in the six studies with a positive relationship, there are nuances that deserve mention. Dew et al. studied 304 heart- and lung-transplant patients from one transplant center and measured nonadherence as self-reporting missing immunosuppressants at least once per month.[49] Social support from a family caregiver was associated with better medication adherence (OR 2.6), whereas social support from friends was not significantly associated with adherence. Similarly, Gehi at al. studied almost 1,000 U.S. Department of Veterans Affairs (VA) patients with heart disease, measuring social support as having contact with someone to whom the patient feels close;[55] poor social support, in this case, was associated with higher odds of forgetting to take medication but was not associated with intentionally deciding to not take medication as prescribed or to skip medication. The results of this review suggest that interventions that address social support alone may not be the most-efficient means of improving adherence because most of the studies did not show an association between social support and adherence, and those that did have a number of caveats. Like any conclusion based on this review, the statement about social support does not mean that social support cannot work to improve adherence—it only means that, on average, based on the literature, it does not appear to have a consistent strong, independent effect on adherence. In no cases, however, did social support worsen adherence.

Limitations of the Review

Two reviewers abstracted these articles independently and in parallel, which is designed to reduce reviewer bias. This was the case for title, abstract, and full-article reviews. We did not

include dissertations, conference abstracts, or other "gray literature"; thus, publication bias (the potential for only positive studies to be included) is possible. We also did not include qualitative studies in our analysis, but we acknowledge that they likely provide valuable information about barriers in selected populations. Our search strategy, as outlined in the beginning of this section, focused on barriers, predictors, challenges, factors, determinants of adherence and included "relationship" to find articles that assessed a relationship between adherence and some other factor. We also included forward searches and related searches on relevant articles. As such, our search is comprehensive, although it is possible that there are studies that describe noncost barriers to medication adherence that do not fall under those search terms. Additionally, our search necessarily focuses on specific barriers and cannot assess the evidence for how these barriers interact with each other to affect adherence; it should be understood, however, as represented in the conceptual framework, that each of these barriers can affect and interact with the others, creating a complex environment in which to study adherence. Finally, although our search strategy did not exclude health-system or provider factors, most of the articles identified from our search related to patient barriers to medication adherence.

SECTION FOUR

Previous Reviews of Medication Adherence

Here we discuss barriers to medication adherence identified from previous reviews, and we discuss the financial barriers to adherence, which have recently been reviewed in detail. These previous reviews must play a role in complementing our own systematic review of the nonfinancial barriers to adherence in order to set the framework for a discussion of policy options to improve adherence.

Regimen Complexity and Cost-Related Nonadherence

There are two specific barriers to adherence that we elected not to include in our systematic review, because they have recently been reviewed in detail by others: regimen complexity and cost-sharing. Most recently, Saini and colleagues conducted a systematic review of four databases for articles published between 1986 and August 2007 studying the effect of daily medication dosing frequency on adherence, as measured by Medication Event Monitoring System (MEMS) only.[27] Twenty studies were included in the review, and the reviewers found that each of the studies reported higher adherence in patients using medications dosed less frequently. In those studies comparing once-daily to twice-daily dosing, patients with once-daily dosing had 2 percent to 44 percent more adherent days. In another recent systematic review of "regimen factors" on medication adherence, Ingersoll and Cohen studied 61 articles found from 1998 to 2007 in three databases and again concluded for all diseases studied that dosing frequency and regimen complexity (defined by those authors as multiple medications, multiple doses, and specific time requirements) are related to poorer adherence.[25] Two older systematic reviews, one published in 2001 and another in 2002, both conclude that daily dosing regimens are associated with higher rates of adherence than twice-daily or multiple-daily dosing.[24, 26]

Cost-related nonadherence is another well-studied area in the peer-reviewed literature that our review of nonfinancial barriers did not address. Goldman, Joyce, and Zheng published a comprehensive systematic review of 132 articles examining an association between pharmacy utilization and prescription copayments, formulary tiers, coinsurance, pharmacy benefit caps or monthly prescription limits, formulary restrictions, and reference pricing.[29] They found that increased cost-sharing for medications is associated with lower rates of initiation of prescriptions, poorer adherence among users, and more-frequent discontinuation of medication. They estimate that, for each 10-percent increase in cost-sharing for medications, drug spending decreased by 2 to 6 percent and that, in some cases, higher cost-sharing was associated with worse outcomes. In a slightly older systematic review of 30 articles by Gibson, Ozminkowski, and Goetzel, the authors found similar results.[28]

General Reviews

There have been few prior general reviews on the barriers to medication adherence. In one of the most highly cited peer-reviewed pieces, Osterberg and Blaschke review the general topic of adherence to medication, including a summary of methods to measure adherence, predictors and barriers to adherence, interventions, and a specific discussion of adherence in HIV, hypertension, and psychiatric illness.[8] The review is limited, however, because it is not systematic. For example, the description of patient-related barriers to adherence comes from one reference to a textbook from 1991, and the major list of predictors of poor adherence come from small studies of specific populations, including Japanese community-dwelling elderly, HIV-infected children, and patients with schizophrenia and inflammatory bowel disease. Krueger and colleagues published a large and comprehensive review of medication adherence and persistence in 2005, covering papers and dissertations from 1994 through 2004.[21] The article includes both barriers to adherence and interventions and lists every factor that is described in the articles and whether each factor increases or decreases adherence. The review identified a supporting and trusting relationship between patient and provider as one of the most important health care–system factors affecting adherence, with an increase in adherence in ten of the 12 articles studying this factor. Depression, cognitive function, limited English proficiency, inability to pay, and fear of side effects were other identified barriers.

Adherence in Older Adults

Two past specific systematic reviews examined predictors of medication adherence in the elderly (65 or older), who have high rates of chronic disease, comorbidity, and polypharmacy. Balkrishnan published a review of articles indexed in Medline® from 1962 to 1997 that included 14 studies and reported clear associations between medication adherence and dosage forms, number of medications, cost, insurance, and physician-patient communication.[97] Other findings were inconsistent, including the effect of beliefs about health and adherence. Vik, Maxwell, and Hogan published a similar review of studies assessing medication adherence in older adults, searching several databases for papers published between 1966 and 2002 and characterizing barriers and predictors and whether they were associated with increased or decreased adherence or no effect.[98] Those authors report much inconsistency across studies and conclude that polypharmacy and poor patient-provider relationships are major determinants of nonadherence among older persons, although it is worth noting that many studies included in their review also showed no effect of polypharmacy on adherence.

Adherence in HIV

Several recent systematic reviews have been published examining the factors associated with adherence to highly active antiretroviral therapy (HAART) in patients with HIV disease. In a review of articles from several databases (through June 2005) as well as conference abstracts, Mills et al. describe 84 studies on HIV adherence.[99] Reported important barriers include stigma associated with HIV disclosure, substance abuse, regimen complexity, number of prescriptions, and beliefs about medications, including anticipated side effects and effectiveness of HAART.

In another recent piece from 2008, Malta et al. perform a systematic review of 41 studies discussing HAART adherence among drug users;[100] substance abuse was strongly associated with poor adherence, with patients in structured settings, such as directly observed therapy, having better adherence. In an earlier review of studies published prior to 1999, Fogarty et al. studied 18 articles and 57 abstracts and also concluded that complex regimens were associated with decreased adherence and that positive attitudes toward disease and treatment, provider support, and regimen aids (pill boxes) were associated with improved adherence.[101] Patients with HIV disease have unique barriers to maintaining adherence to their medications, in addition to the barriers faced by those with more-common chronic diseases, such as hypertension, diabetes, and high cholesterol. For our systematic review, we excluded papers exclusively studying patients with HIV disease, although we include the important results, noted here, in our overall discussion.

Reviews of Intervention Studies

The purpose of our systematic review and the discussion about prior reviews of adherence barriers form the basis for our policy discussions. However, understanding how the health-care system has already attempted to address nonadherence is vital in planning how to move forward. There are several recently published systematic reviews of randomized trial interventions to improve adherence that are worth noting. Most notably, from the 2007 Cochrane review of interventions for enhancing medication adherence by Haynes et al., are two key sentences in the discussion:

> With the astonishing advances in medical therapeutics during the past two decades, one would think that studies of the nature of non-adherence and the effectiveness of strategies to help patients overcome it would flourish. On the contrary, the literature concerning interventions to improve adherence with medications remains surprisingly weak.[102]

In their updated review, Haynes et al. focus on unconfounded randomized clinical trials of interventions to improve adherence with medication in articles that measure both medication adherence and treatment outcome and have at least six months follow-up for studies with positive initial findings. Because of the heterogeneity of results, those authors conducted only qualitative analysis. The interventions reviewed were often complex and multifaceted, making it difficult to isolate what exactly was successful about each intervention; these interventions included combinations of more-convenient care, information and reminder systems, and some form of supportive care. Only 36 of 83 interventions reported in 70 randomized trials were associated with significant improvements in adherence, and only 25 of those led to improvement in a treatment outcome. Haynes et al. also note that, since only published studies were considered in the review, publication bias suggests the presence of many more ineffective interventions.

Nonetheless, there are examples of interventions that worked. For example, Lee et al., in 2006, published the results in the *Journal of the American Medical Association* (JAMA) of a pharmacy care program of 200 patients over the age of 65 with high blood pressure and cholesterol at Walter Reed Army Medical Center.[103] Patients were given an intensive, pharmacy-based intervention that included education, blister packs, and regular, every-other-month meetings

with pharmacists. Adherence improved substantially after six months, but the group that was subsequently randomized to usual care lost most of its benefit at 12 months. The intervention group, however, had significantly improved adherence at 12 months, which was associated with improved systolic blood pressure (but not low-density lipoprotein [LDL] level or diastolic blood pressure). It is not at all clear what part of this intervention worked (blister pack, education, frequent follow-up), and it is also not at all clear whether this intervention might work in a setting in which financial barriers are a problem. The fact that six months of intervention produced little effect at 12 months in the usual-care arm means that an intensive, yearlong program with resource-intensive blister packs would be needed, and the cost-effectiveness of such an intervention is unknown. Note that the Lee trial had only 200 patients in one setting, and the largest trial reported in the Cochrane review had only 1,113 patients. This study is just one of many included in the Cochrane review.

In a related publication, Kripalani, Yao, and Haynes report on a systematic review of 37 randomized trials that aim to improve medication adherence in chronic medical conditions.[104] Twenty of the 37 trials reported significant improvement in adherence, and Kripalani, Yao, and Haynes report that adherence improved most consistently with behavioral interventions that reduced dosing demands and those involving monitoring and feedback. In a review of reviews on medication adherence, van Dulmen et al. summarize 38 systematic reviews published between 1990 and 2005.[105] Those authors show that what they identify as "technical solutions," such as simplifying a medication regimen, were often found to be effective interventions to improve adherence; the difficulty in using this review, however, is that its contents include reviews that summarize non–medication-related adherence in addition to medication adherence. It is also important to note that the authors found only two of 38 reviews that limited their analysis to interventions with six months of follow-up or more, which was a criterion in the Cochrane review.

SECTION FIVE

Summary

We reviewed the literature on barriers to adherence in order to provide an evidence base for consideration of policy options to address this important problem. Prior reviews have established that more-complex regimens with more-frequent doses and higher cost-sharing are associated with worsened medication adherence. These two barriers, regimen complexity and cost-sharing, have an evidence base and are important potential targets for policy solutions. Building on the existing evidence base, our systematic review of the non–cost-related barriers suggests that beliefs about medications and depression are two potentially important barriers—beliefs about medications more generally and depression likely as it relates to patients with diabetes. In addition to being supported by the current literature review, beliefs about medications and depression are supported by prior evidence as important factors in medication adherence. Each of these four barriers fits squarely into the conceptual framework described in this report, thus lending support for their importance as being conceptually sound in addition to prominent in the literature. In an effort to focus the policy discussion around a set of clear barriers with evidence behind them, we discuss these four barriers in more detail in Section Six. Patient-provider communication, trust, knowledge about illness and treatment, and side effects were also identified in the literature, although were less prominent.

Our systematic review identified few provider-related factors and health-system factors other than cost-sharing and could not identify how the factors interact; nonetheless, we believe that providers of all types and the health-care system in general have important roles to play in addressing the patient barriers, which we also discuss in more detail in Section Six.

These conclusions come with a critically important caveat, however, which prior reviews have also emphasized: The literature on barriers to medication adherence is heterogeneous and of relatively poor quality, which detracts from our ability to form policy recommendations rooted in the literature. The literature we reviewed uses different measures of adherence, some of which are validated and some that are not, and measures adherence with different instruments and over different periods of time for different diseases with small samples. While medication adherence is a complex behavior in which one universal form of measurement will likely not suffice, more-standardized assessment of adherence and the type of nonadherence would be helpful in pushing the literature forward and guiding the policy agenda.

SECTION SIX

Framework for Discussing Policy Options

We begin the discussion of policy options by outlining four key general points about barriers to adherence and potential solutions for overcoming them, gleaned from performing the systematic review. Perhaps most important is the finding that the literature is weak when it comes to identifying barriers to adherence. As mentioned in the NCPIE report,[4] more-robust funding and organization of research in medication adherence is needed to counter the limitations that are constantly cited in the literature, including small sample sizes, nonstandardized adherence measurement, and heterogeneous patient populations. A research agenda that addresses these shortcomings is necessary, and, as mentioned in Section Five, would be helpful to guide the policy agenda.

A second key point is that potential policy solutions that address one barrier must not worsen another. For example, the likelihood of a significant improvement in adherence with a policy that simplifies a regimen will be reduced if it comes at the expense of higher cost-sharing. Potential reforms must send signals that are consistent. The literature does not deal at all with this balancing act or with quantifying the level of importance of one barrier over another. The literature also does not do an adequate job of studying how these various barriers interact.

The third key point is that each patient, in reality, has his or her own unique barriers, which can vary by disease and by medication. Programs for improving adherence must find a balance between "customized" interventions and effective programs that work for large groups or classes of patients. This is not to say that society needs thousands of different programs for each barrier, but it needs programs that can identify these barriers and take the diversity of individuals and barriers into account.

The final key point relates to the different types of nonadherence. Adherence is, after all, a multistep process: The patient must first obtain the right prescription from the provider, then fill that prescription (nonfulfillment), then continue with the medication through the first six months, when the risk of stopping is highest (nonpersistence), and then, once on the medication chronically, he or she must take it as intended (nonconforming). "Adherence" is the result of getting through these four steps successfully, and a single policy option is not going to address each of these challenges to adherence. It is incumbent on policymakers, as they incorporate adherence programs into policies aimed at improving health-care quality and outcomes, to be clear about what kind of adherence they are addressing. The same holds true for the literature, which, at times, does not and focuses disproportionately on the last step, where patients do not take the medication as intended.

Barriers and Stages of Adherence

How, then, do the four identified barriers to adherence discussed in this report (cost-sharing, regimen complexity, beliefs about medications, and depression) fit into these four steps of adherence? Table 6.1 presents our conceptualization of these relationships, based on the literature. Whether patients are prescribed the correct prescription is a function of provider and system factors that are not necessarily addressed in the reviewed literature (the first column). These factors, however, are essential for ensuring that the medication being prescribed is necessary and the best choice for the patient. Programs to improve adherence must recognize that adherence is valuable only if the medication is helpful to the patient.

The subsequent three steps can each be affected by cost-sharing. Evidence is clear from prior reviews that higher copayments contribute to lower adherence to medication (including nonfulfillment, nonpersistence, and nonconformance). Cost-sharing could thus be reduced as a barrier when the appropriate use of a particular medication has health or financial benefits, such as avoiding future complications, functional decline, or more-expensive future treatments. The scientific evidence is not yet definitive, however, that lowering copayments actually increases adherence, as would be expected from the literature. There are several ongoing controlled clinical trials using value-based insurance design (VBID) that are measuring the effect on adherence of lowering copayments for those drugs that are beneficial to patients; the results of these studies should be watched closely.

Regimen complexity is another barrier to medication adherence that has clear evidence in the literature, and systematic reviews of interventions to improve adherence have identified decreasing regimen complexity as a successful intervention.[104, 105] The impact of regimen complexity is really a characteristic of the available treatment choices—if more- and less-complex therapies are therapeutically equivalent and available, incentives could be provided to encourage use of less-complex alternatives. Likewise, if a complex therapy is the only alternative, incentives to provide additional support for adherence could be made available (i.e., reimbursable). It is not clear from the evidence that regimen complexity would affect whether patients fill their prescription (hence the blank in this cell in Table 6.1), but there is evidence that it affects their persistence with the medication and long-term adherence.

A variety of other factors are likely to affect adherence, and the literature points to beliefs about medications generally and depression in some patients as important barriers. For these barriers, policy options will have to be flexible, rather than global, since one-size-fits-all programs are unlikely to work. Identifying and solving specific barriers for each patient will likely

Table 6.1
Stages of Adherence and Adherence Barriers

Prescribe the Right Prescription	Fill the Prescription	Stay on the Prescription	Take the Prescription as Intended
Provider and system factors	Cost-sharing	Cost-sharing	Cost-sharing
		Complexity	Complexity
	?	?	Depression (diabetes)
	?	?	Beliefs

NOTE: Each cell represents what the literature indicates about the role of the four barriers on the steps of adherence.

be necessary and will involve education and communication and patient engagement; it is an open question as to what types of providers can serve this role, whether the prescriber in the clinic or the pharmacist filling the prescription, nurse case managers, or other professionals. All providers would nonetheless benefit from better tools and flexibility in payment policies to use those tools. The literature we reviewed on depression and beliefs about medication focused almost exclusively on nonconforming nonadherence, and we believe that it is still an open question in the literature whether these same barriers have similar effects on nonfulfillment and nonpersistence. The significance of the relationship between nonadherence and depression in those patients with diabetes should be further explored and addressed.

Adherence in the Context of Health Reform

To conclude our discussion of the concepts that should frame policy options to improve adherence, and to serve as a springboard for discussion, we consider how medication adherence fits into two of the major tools being discussed in the context of health reform: health information technology (HIT) and comparative-effectiveness research. One of the promising applications of HIT is the ability to continuously measure adherence using routinely collected measures. While claims-based measures of nonadherence are limited, they are predictive of adverse outcomes. The specific application of HIT to identifying those at risk for all forms of nonadherence (including nonfullfillment) based on pharmacy fill records, or health-plan or Medicare claims data, means that this information can be reported back to patients and providers. Advancements in functionality could lead to the information being available in real time, rather than lagged three to six months, as is currently the case. This also allows for standardized assessments of adherence. HIT could also help providers identify patients with depression or use tools to communicate more effectively with patients about their beliefs about medications. Specific interventions using HIT for these purposes are in line with the government's goal of using HIT to improve value and quality.

Better and more-comprehensive research on adherence interventions should complement more-rigorous research on adherence barriers. The Haynes Cochrane review on adherence interventions states that "*high priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions*."[102] As the government promotes research on comparative effectiveness, medication-adherence research can factor prominently. In fact, the Institute of Medicine (IOM) recently released its top 100 priorities for comparative-effectiveness research, and comparing the effectiveness of strategies for improving medication adherence was identified as a second-quartile (high) research priority.[106] Studies of how one therapy works better than another are not useful in settings in which patients do not use either or do not use either correctly. Research on adherence interventions should clearly identify the barriers they are addressing. Research should also identify what kind of adherence is being measured, and more research on nonfulfillment and nonpersistence should be encouraged.

The national dialogue on health reform that is currently under way includes discussions of ways to improve care for persons with chronic disease and to improve the value and efficiency of health care. Strategies to improve adherence to medication therapy should fall squarely in the middle of these discussions, since nonadherence affects the ability to effectively manage and control chronic diseases and contributes to the costs society incurs. While the scientific

literature on adherence barriers is far from definitive, it does offer some important clues to the directions policy can take to solve this important problem.

APPENDIX A

Measurement of Medication Adherence

Further complicating the definition of *medication adherence* is that the actual study of adherence is extremely difficult. First and foremost, as Park and Jones explain in a review of medication adherence and aging, medication-taking is a "private behavior" and is not easily measurable.[23] Second, as Park and Jones also describe, the study of medication adherence is subject to the Hawthorne effect, in which subjects change their behavior because they know they are being studied.[23] To fully understand how patients take their medications, they cannot know they are being studied, which is rarely the case. Finally, the methods of actual measurement of adherence—e.g., self-report, pharmacy claims, electronic monitoring—have strengths and weaknesses and are used in different ways in different studies. There is an extensive literature comparing different methods for measuring adherence, and our aim in this appendix is to summarize the major measurement methods and not to fully explore all of the literature comparing and validating these methods.[14]

How to Measure Adherence

Several methods of measuring adherence are used in the medical literature and deserve mention.[108] Self-reported adherence is commonly used, either through self-administered questionnaires or in face-to-face or telephone interviews. One of the most commonly used measures is the Morisky scale, originally developed as a four-item scale more than 20 years ago to predict adherence to blood-pressure medications among outpatients and subsequently adapted into an eight-item scale. Two other scales are the 14-item Hill-Bone Compliance Scale, also developed for hypertension medications, and the 32-item Medication Adherence Scale developed in congestive heart failure.[109] Aside from these validated scales, many studies use one-, two-, or three-item questions to assess medication adherence, such as reporting whether patients ever forget to take their medicines or whether patients took less than the prescribed amount of their medication in the past month. All self-report measures suffer from recall bias and may overestimate adherence.[108] Electronic devices to monitor medication adherence consist of MEMS and similar devices that are used with eye droppers in glaucoma or inhalers in asthma, which electronically record the date and time when patients open a pill bottle or use an inhaler. These devices are quite accurate but are expensive and measure only what they are intended to measure (meaning patients can open the device but may not necessarily consume the medication). Pill counts are another method of objectively measuring the amount of medication taken. Patients bring in their pill bottles, and study staff will count pills that are remaining; this method is limited again in that the use of pills is assumed if not counted in the bottle, and the

method can overestimate adherence and cannot give any information about timing or pattern of doses taken.[2]

Another commonly used method to measure adherence uses administrative databases from pharmacies or health plans to capture the amount of medication obtained by patients. These methods have the advantage of being objective and providing information over a large time span, but they are limited in that they include only what is in the database: If patients fill their prescriptions by mail, or at another pharmacy, or another health plan, or receive samples, these fills will not be captured. There are several different ways to measure adherence from these databases.[110] Commonly used is the medication possession ratio (MPR), which is a ratio of the days of medication supplied divided by the days between the first fill and the last fill of the medication. Also measured are the proportion of days covered (PDC), for which pharmacy fills are used to determine what proportion of all days within a specified time period a patient had enough medication, and the percentage of doses taken as prescribed, which is, as expected, the percentage of prescribed doses taken as directed by the patient during a specified time. Finally, the cumulative medication gap (CMG) sums up the number of days in which a medication was not available divided by the time between the first and last fills. This measure of gaps in medication rather than total availability is viewed by some as an improved measure over MPR or PDC, since it does not allow a gap in medication in one time period to be erased by later stockpiling.[21, 22]

APPENDIX B

Evidence Table for Systematic Review of Non–Cost-Related Barriers to Medication Adherence

This appendix contains the evidence table for our systematic review of non–cost-related barriers to medication adherence.

Table B.1
Evidence Table for Systematic Review of Non–Cost-Related Barriers to Medication Adherence

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Aikens et al. 2005 (30)	Invited: 171 Responding at BL: 81	1	Multiple clinic: Mich.	1	Depression	1	Questionnaire	Validated scale: Morisky, PDC	Perceived health status Beliefs about meds* Depression* Side effects Social desirability Duration of illness	Adherence to med was higher when med beliefs about the necessity for antidepressant med were stronger than the concerns about the harms of med use (necessity minus concerns composite score, F(1,72)=11.23, $p = 0.001$) after adjusting for demographics, depression severity, and duration of illness. Depression severity not associated with adherence in final analysis.
Aikens et al. 2009 (31)	Responding at BL: 806	1	Multiple clinic: Mich.	2	Diabetes Hypertension	1	In-person interview	Less than prescribed due to cost and less due to reason other than cost	Perceived risk of side effects Perceived necessity Health literacy* Time spent discussing meds Costs, insurance	Concerns about the long-term effects of med use (reverse coded) were negatively associated with adherence to antihyperglycemic ($\beta = 1.7$, $p < 0.005$) and to antihypertensive ($\beta = 1.9$, $p < 0.005$) meds after controlling for demographics, costs, and disease characteristics, whereas beliefs about the necessity of the meds to maintain health were not associated with adherence.
Albright et al. 2001 (32)	Responding at BL: 397	1	Multiple clinic: Tex.	2	Diabetes	1	Questionnaire	I forget to take my medicines	Patient satisfaction* Social support at home Personal stress	Patient satisfaction with diabetes care ($F = 5.790$, $p = 0.003$) was positively associated with adherence, but personal stress level was not. Social support was significantly associated with better adherence in a bivariate model but not in a multivariate model that controlled for demographics and other barriers to adherence.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Apter et al. 2003 (33)	Invited: 109 Enrolled: 88 Responding at FU: 85	2	Multiple clinic: Univ. of Pa.	2	Asthma	1	Electronic monitoring	Prescribed doses taken within specified period	Perceived impact of med Perceived risk of side effects Beliefs about meds Knowledge about illness and treatment Self-efficacy* No. of children Depression* Smoker Other communication issues Social support at home* Past adherence	Knowledge, communication, social support, and depression were not associated with adherence. Belief about meds was positively associated with adherence (β = 1.21, 95% CI: 1.07–1.37, p = 0.002).
Apter et al. 1998 (34)	Enrolled: 54 Responding at BL: 54 Responding at FU: 50	2	Multiple clinic: Conn.	2	Asthma	1	Electronic monitoring	Prescribed doses taken within specified period, cutoff: 0.70	Perceived impact of med Knowledge about illness and treatment Locus of control* Patient satisfaction Language	Poor patient-clinician communication (OR = 6.72, 95% CI: 1.10–41.0) was associated with poor adherence after adjusting for demographics, asthma severity, and health beliefs. In bivariate analysis, health loci-of-control factors (internal, powerful people, physician, and chance) were not associated with adherence.
Balkrishnan et al. 2006 (35)	Enrolled: 275	2	Health plan: southeast U.S.	1	Overactive bladder	1	Pharmacy records/ claims data	MPR	Perceived quality of life* Physical activity Depression* Smoker Substance abuse	Adherence was positively associated with perceived health status (p = 0.05) and negatively associated with number of prescribed meds (p = 0.001). Depression, alcohol consumption, smoking, and physical activity were not significantly associated with adherence.
Balkrishnan et al. 2003 (36)	Enrolled: 775 Responding at BL: 775 Responding at FU: 667	2	Health plan: N.C.	1	Diabetes	1	Pharmacy records/ claims data	MPR	Perceived quality of life* Physical activity Depression* Smoker Use of injectables	Adherence was not significantly associated with depression severity, smoking, alcohol consumption, physical activity, hospitalization, or perceived health status.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Batal et al. 2007 (37)	Enrolled: 3,386	2	Single clinic/ hospital/pharmacy: Denver, Colo.	1	Hyperlipidemia	5	Pharmacy records/ claims data	MPR, cutoff: 0.80	Costs/insurance Days supply of med	Receiving 60-day versus 30-day supply of statin med (OR = 1.40, 95% CI: 1.27–1.55) was associated with better med adherence after adjusting for demographics, comorbidities, and copayment costs.
Bautista 2008 (38)	Enrolled: 6,733 Responding at BL: 6,100	1	National: NHANES	3	Hypertension	5	In-person interview	Review of med bottles by interviewer	Perceived health status BMI Smoker Alcohol intake Language No. of clinic visits	In bivariate analysis, more alcoholic drinks per day ($p = 0.007$), being a current smoker ($p < 0.001$), and having no medical visits in the past year ($p < 0.001$) were associated with nonpersistence to antihypertensive therapy. In a multivariate analysis, having no medical visits in the past year (OR = 10.36, 95% CI: 6.95–16.29) was associated with nonpersistence after adjusting for demographic and insurance-related factors.
Billups et al. 2000 (39)	Enrolled: 1,054 Responding at BL: 1,054	2	Multiple sites: VA	4	Other—not specified	1	Pharmacy records/ claims data	PDC, cutoff 80%	Perceived quality of life* No. of prescriptions No. of drug changes	General health-related quality-of-life measures (general health perception, physical functioning index, and mental-health index) were not associated with med adherence. In bivariate analyses, the number of chronic conditions ($p < 0.001$) and the number of concurrent prescriptions ($p = 0.001$) were positively associated with adherence.
Brown et al. 2005 (40)	Invited: 456 Enrolled: 192 Responding at BL: 192	2	Multiple clinic: Pa.	2	Depression	1	In-person interview	Validated scale: Morisky-4	Beliefs about meds* Depression* No. of clinic visits	Adherence was negatively associated with depression symptom severity ($\beta = -0.02$, $p = 0.003$) and perceived risk of meds ($\beta = -0.25$, $p = 0.025$).

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Burge et al. 2005 (41)	Enrolled: 150 Responding at BL: 150	1	Multiple clinic: Tex.	2	Diabetes Hyperlipidemia Hypertension	1	Questionnaire	Validated scale: Morisky-4	Perceived health status Knowledge about illness and treatment Physical limitations (eyesight, dysphagia) Side effects Regimen complexity Patient satisfaction Language No. of clinic visits Costs/insurance Motivation to adhere No. of prescriptions	More confidence to take meds as prescribed ($\beta = 0.340$, $p < 0.001$) and a larger number of prescription medicines ($\beta = 0.320$, $p < 0.001$) were associated with higher med adherence after adjusting for demographics, health status, and side effects. Factors in the multivariate model showing no association with adherence included med knowledge and patient satisfaction with medical care.
Chambers et al. 1999 (42)	Invited: 694 Enrolled: 435 Responding at BL: 394	1	Multiple sites: tristate area (Pa., Del., N.J.)	1	Asthma	1	Questionnaire	Frequency of inhaler use	Perceived health status Hospitalization Health beliefs* Living condition	Health beliefs including being more active in making decisions with a physician (OR = 4.6, 95% CI: 2.8–7.5) and taking asthma more seriously (OR = 2.3, 95% CI: 1.4–3.7) were associated with better med adherence after adjusting for demographic, severity of asthma, and health status. Other health beliefs not associated with adherence included motivation to maintain health, frustration with adhering to therapy, understanding the benefits of adhering to asthma therapy, and perceived uncontrollable barriers to adhering.
Chao et al. 2007 (43)	Invited: 1,700 Responding at BL: 445	1	Health plan: Mich.	3	Diabetes	1	Questionnaire	Modified Horne scale	Depression* Side effects Duration of illness	Depression ($\beta = 0.13$, $p < 0.0001$) and the perception of having a side effect from taking diabetes med ($\beta = -0.15$, $p < 0.01$) were associated with lower med adherence after adjusting for demographic and illness variables.
Chapman et al. 2005 (44)	Enrolled: 8,406	2	Health plan	1	Hyperlipidemia Hypertension	2, 3, 1	Pharmacy records/ claims data	PDC	Depression No. of prescriptions No. of clinic visits	Adherence rate was positively associated with therapies initiated closer together in time ($p < 0.001$) and fewer meds ($p < 0.001$). The relationship between depression and adherence was not significant ($p = 0.51$).

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Chapman et al. 2008 (45)	Enrolled: 4,052	2	Health plan	1	Hyperlipidemia Hypertension	3, 1	Pharmacy records/ claims data	MPR, cutoff: 80.00	Memory and comprehension Depression Dementia No. of prescriptions No. of visits	Adherence rate was positively associated with therapies initiated closer together in time (OR = 1.13, 95% CI: 1.00–1.29, $p = 0.06$) and fewer meds (OR = 0.43, 95% CI: 0.36–0.50, $p < 0.0001$). The relationship between depression and adherence was not significant (OR = 0.78, 95% CI: 0.60–1.03, $p = 0.08$).
Clark et al. 1999 (46)	Enrolled: 570 Responding at BL: 570 Responding at FU: 485	2	Multiple clinic: Mich.	2	Coronary heart disease	1	Questionnaire	How closely following doctor's instructions	Perceived impact of med Self-efficacy Reminder system	Self-efficacy or confidence in the ability to follow a specific drug therapy was significantly associated with better medicine use at 4 and 12 months after controlling for demographic and outcome expectancy variables.
Cukor et al. 2009 (47)	Enrolled: 159 Responding at BL: 159	1	Single clinic/ hospital/pharmacy: N.Y.	2	Kidney transplant Hemodialysis	1	Questionnaire	Validated scale: med therapy adherence scale	Locus of control Depression*	Depression ($\beta = -0.287$, $t = -2.97$, $p < 0.01$) was negatively associated with adherence after adjusting for demographic and treatment factors, but measures of loci of control (internal, powerful others, and chance) were not related to adherence.
De Smet et al. 2006 (48)	Invited: 1,270 Enrolled: 573	1	Health plan: Mich.	1	Asthma	1	Questionnaire	4-item scale	Perceived health status Perceived quality of life Perceived severity of illness Perceived impact of med* Self-assessed inhaler technique No. of inhaler instructions Social support at home Access to care Duration of illness Barrier scale	Predisposing factors, including avoidance of asthma triggers ($\beta = 0.298$, $p < 0.001$), perceived benefits of asthma med ($\beta = 0.222$, $p < 0.001$), and years since diagnosis ($\beta = 0.109$, $p = 0.006$), were associated with higher med adherence after adjusting for demographics, illness characteristics, mental-health status, and quality of life. In addition to the predisposing factors, more persons providing instructions for the metered-dose inhaler ($\beta = 0.087$, $p = 0.03$) and a higher perceived severity of asthma ($\beta = 0.150$, $p < 0.001$) were associated with better adherence.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Dew et al. 2008 (49)	Enrolled: 304 Responding at BL: 304 Responding at FU: 239	2	Single clinic/ hospital/phar-macy: Pa.	1	Heart trans-plant Lung transplant	1	In-person in-terview	Validated scale: health-habit survey	Cognitive function Locus of control Depression Other affective dis-order Side effects Social support at home Hospitalization Distance to clinic	Social support from a family caregiver (OR = 2.59, 95% CI: 1.20–2.58) was as-sociated with better med adherence, whereas social support from friends was not significant after controlling demographic variables, side effects, and type of transplant (lung or heart). Other variables that were not associ-ated with adherence in the multivariate model included depressive symptoms, anxiety symptoms, internal locus of control, and care-provider locus of control.
Fincke et al. 1998 (50)	Invited: 1,648 Responding at BL: 1,256	1	Unclear	8	Other—not specified	1	Questionnaire	No. of missed doses last week	Perceived overmed	Those who perceived that they took too much med were more likely than those who perceived that they took the right amount to forget to take med ($p < 0.05$) and miss one or more doses per week ($p < 0.05$).
Friedman et al. 2008 (51)	Responding at BL: 300 Responding at FU: 297	2	Unclear	9	Glaucoma	1	Pharmacy re-cords/ claims data	MPR	Knowledge about ill-ness and treatment Side effects Receipt of samples Time spent discuss-ing meds Visit reminders Costs/insurance Duration of illness Travel away from home	Modifiable barriers associated in a multivariate model with lower med adherence included (a) learning all of what you know about glaucoma from your physician compared to learning some/none ($\beta = 0.16$, $p = 0.002$), (b) not believing that reduced vision may be caused by nonadherence ($\beta = 0.17$, $p = 0.005$), (c) having high difficulty taking meds away from home compared to low difficulty ($\beta = -0.14$, $p = 0.01$), (d) receiving free samples on a regular basis compared to receiving none ($\beta = -0.14$, $p = 0.03$), and (e) receiving a phone-call reminder for an office visit compared to no reminder ($\beta = 0.18$, $p = 0.01$).

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Friedman et al. 2009 (52)	Enrolled: 282 Responding at FU: 196	2	Multiple sites	1	Glaucoma	1	Electronic monitoring	Prescribed doses taken within specified period, cutoff: 75.00	Perceived health status* Perceived impact of med Perceived risk of side effects Beliefs about meds Knowledge about illness and treatment Forgetfulness Depression* Side effects	Self-reported health status and perceived health outcome were positively associated with med adherence ($p < 0.05$) after mean adherence rate is controlled as a continuous variable. When adherence rate was dichotomized, self-reported health status and perceived health outcome were no longer significant. Depression was significantly associated with adherence in univariate analysis.
Gatti et al. 2009 (53)	Invited: 459 Enrolled: 301 Responding at BL: 281 Responding at FU: 275	1	Multiple clinic: Atlanta, Ga.	2	Other—not specified	5	In-person interview	Validated scale: Morisky-8	Beliefs about meds* Health literacy* Self-efficacy* Depression*	Low adherence rate was positively associated with negative beliefs about meds (OR = 2.12, 95% CI: 1.3–3.7, $p = 0.006$) and low self-efficacy (OR = 4.34, 95% CI: 2.5–7.5, $p < 0.001$) after controlling for a range of demographic variables. Health literacy was not significantly associated with med adherence. Depression was associated with low adherence in univariate, not multivariate, analysis.
Gazmararian et al. 2006 (54)	Enrolled: 3,260 Responding at BL: 1,540	2	Health plan	1	Coronary heart disease Diabetes Hyperlipidemia Hypertension	1	Pharmacy records/ claims data	CMG less than 20%	Perceived health status Cognitive function Health literacy* Depression Smoker Substance abuse No. of prescriptions Social support at home Exercise	Regimen complexity was negatively associated with med adherence (OR = 0.77, 95% CI: 0.73–0.95) after controlling for health literacy, age, race, sex, and education. Neither depression nor social support was associated with adherence.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Gehi et al. 2005 (55)	Enrolled: 940 Responding at BL: 940	1	Multiple clinic: VA Calif.	1	Coronary heart disease	1	In-person interview	3 questions	Depression* Smoker Substance abuse No. of meds Social support at home BMI Exercise capacity Type of med	Depression was positively associated with two self-reported measures of nonadherence—not taking med as prescribed (OR = 2.2, 95% CI: 1.2–3.9) and deciding to skip meds (OR = 2.1, 95% CI: 1.1–4.0) after adjusting for demographics, medical history, med use, and cardiac function. Other psychosocial and behavioral factors that were not associated with adherence in the multivariate model included living alone, current smoking, regular alcohol use, and BMI.
Gonzalez et al. 2007 (56)	Invited: 1,648 Enrolled: 953 Responding at BL: 909	1	Multiple clinic: Mass.	2	Diabetes	1	Questionnaire	No. of missed doses, not validated one question	BMI Depression* No. of prescriptions Duration of illness	Depression-symptom severity was negatively associated with adherence to general diet ($\beta = -0.15$, $p < 0.001$), specific recommendations of diet ($\beta = -0.21$, $p < 0.001$), exercise ($\beta = -0.17$, $p < 0.001$), and glucose monitoring ($\beta = -0.07$, $p = 0.044$).
Gonzalez et al. 2008 (57)	Enrolled: 1,317 Responding at BL: 909 Responding at FU: 208	2	Multiple clinic: Mass.	9	Diabetes	1	In-person interview	Prescribed doses taken within specified period, cutoff: 100.00	Depression* Other med characteristics Duration of illness	HANDS scores (depression-symptom severity) were associated with lower adherence to general diet recommendations ($\beta = -0.27$, $p < 0.001$), lower adherence to specific recommendations for diet ($\beta = -0.26$, $p < 0.001$), less exercise ($\beta = -0.20$, $p = 0.004$), and poorer foot care ($\beta = -0.17$, $p = 0.015$). Nonadherence to prescribed med was positively associated with HANDS scores (OR = 1.08, 95% CI: 1.00–1.16, $p = 0.047$).
Hyre et al. 2007 (58)	Invited: 1,017 Responding at BL: 295	1	Multiple clinic: La.	1	Hypertension	1	Telephone interview	Validated scale: Morisky-8	Knowledge about illness and treatment Smoker Time spent discussing meds Other communication issues Ease of seeing doctor Access to care Duration of illness	Adherence was positively associated with being comfortable asking doctor questions ($p = 0.03$) and negatively related to wanting to spend more time with the doctor ($p = 0.04$). Smoking and knowledge of disease were not significantly associated with adherence.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Insel et al. 2006 (59)	Enrolled: 100 Responding at BL: 100 Responding at FU: 95	2	Other: Community sample	2	Hyperlipidemia Hypertension Arthritis	1	Electronic monitoring	PDC	Cognitive function* Memory and comprehension* Executive function* Depression*	A composite score for executive working memory ($\beta = 0.44$, $t = 3.05$, $p \leq 0.05$) was associated with better med adherence after adjusting for demographic characteristics, illness severity, mental-health status, and financial status, whereas a memory composite score and depression were not associated with adherence.
Janson et al. 2008 (60)	Responding at FU: 113	1	Multiple clinic: Northern Calif.	2	Asthma	1	In-person interview	Prescribed doses taken within specified period, cutoff: 50.00	Perceived health status* Perceived quality of life* Perceived severity of illness* Perceived asthma control* Depression*	Adherence to ICS was not significantly associated with depression, perceived disease severity, or perceived health status. Nonadherence to IBA was positively associated with perceived disease severity (OR = 4.46, 95% CI: 1.56–12.89, $p = 0.006$).
Kaplan et al. 2004 (61)	Invited: 657 Enrolled: 578 Responding at BL: 510	1	Multiple clinic: Bronx, N.Y.	2	Hyperlipidemia	1	In-person interview	Taking med as prescribed	Perceived health status Depression Smoker Substance abuse Side effects Language Social support at home Costs/insurance Children in home	Noncompliance was positively associated with perceived risk of side effects (OR = 3.9, $p < 0.01$) and depression (OR = 1.9, $p = 0.05$) after adjusting for demographic factors and health-insurance status.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Khanderia et al. 2008 (62)	Invited: 387 Enrolled: 132 Responding at BL: 132	1	Single clinic/ hospital/pharmacy	1	Coronary heart disease Post-CABG	5	Questionnaire	Validated scale: med-adherence scale, self-report persistence	Perceived health status Beliefs about meds* Living status Access to med	Beliefs about meds that were associated with lower med adherence in bivariate analysis included general concerns about physician overuse of meds ($p = 0.01$) and concerns about long-term harm from med use ($p = 0.04$). Only general concerns about overuse (OR = 0.83, 95% CI: 0.72–0.95) remained significant in a multivariate model controlling for demographic variables. Two other med beliefs (concerns about a specific med and belief in the necessity of a specific med) were not significant.
Kilbourne et al. 2005 (63)	Invited: 287 Enrolled: 203 Responding at FU: 196	2	Single clinic/ hospital/pharmacy: VA	1	Diabetes	1	Questionnaire, electronic monitoring, pharmacy records/ claims data	Prescribed doses taken within specified period, PDC and one item	Depression* Substance abuse No. of prescriptions Regular pill-box use	Depression was associated with lower oral hypoglycemic med adherence based on self-report (OR = 0.2, 95% CI: 0.1–0.7) and pharmacy records ($\beta = -20$, $p < 0.04$) in separate models adjusted for demographics, no. of meds, binge alcohol drinking, and cognitive impairment. No. of meds was not a significant predictor of adherence.
Kim et al. 2007 (64)	Enrolled: 243 Responding at BL: 208	1	Other: Baltimore-Washington area	5	Hypertension	1	In-person interview	Modified Hill-Bone compliance scale	Beliefs about meds Knowledge about illness and treatment* Self-efficacy* Depression* Side effects Patient satisfaction Social support at home Duration of illness	Intentional nonadherence, but not unintentional adherence, was associated with lower knowledge about high blood pressure (OR = 0.888, 95% CI: 0.794–0.994) after adjusting for demographic variables. Neither intentional nor unintentional nonadherence was associated with depression, self-efficacy in controlling blood pressure, beliefs about blood pressure, social support, or satisfaction with care.
Le et al. 2008 (65)	Enrolled: 86 Responding at FU: 86	2	Single clinic/ hospital/pharmacy: Johns Hopkins	6	Asthma	1	Electronic monitoring	Prescribed doses taken within specified period	Perceived impact of med Perceived risk of side effects Beliefs about meds Perceived need	Adherence was negatively associated with negative med beliefs ($\beta = -0.046$, $p = 0.002$).

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Li et al. 2007 (66)	Invited: 249 Enrolled: 200 Responding at BL: 200	1	Single clinic/ hospital/ pharmacy: San Francisco, Calif.	2	Hypertension	1	Questionnaire	Modified Morisky	Perceived outcome* Perceived impact of med Beliefs about meds* Belief in Chinese herbs Social support at home Length of time in U.S. Perceived susceptibility	Perceived severity of disease, perceived outcome, and social support were not significantly associated with adherence.
Li et al. 2006 (67)	Invited: 249 Enrolled: 200 Responding at BL: 200	1	Single clinic/ hospital/ pharmacy: San Francisco, Calif.	2	Hypertension	1	In-person interview	Modified Morisky	Perceived outcome* Beliefs about meds Social support at home* Health-related social support Length of time in U.S. Beliefs about susceptibility	Med nonadherence was associated with lower perceived severity of illness (OR = 3.77, 95% CI: 1.19–12.01), higher perceived impact of Chinese herbs (OR = 2.21, 95% CI: 1.02–4.81), and lower perceived impact of Western meds (OR = 2.78, 95% CI: 1.13–6.84). Social support was not significantly associated with adherence.
Lin et al. 2004 (68)	Invited: 9,063 Enrolled: 4,839 Responding at BL: 4,463 Responding at FU: 2,655	2	Health plan: Wash.	1	Diabetes	1	Pharmacy records/ claims data	PDC	Depression* Treatment intensity	Nonadherence to meds (oral hypoglycemic, lipid lowering, ACE inhibitors) was positively associated with major depression ($p < 0.05$) after adjusting for demographic and treatment factors.
Mann et al. 2007 (69)	Invited: 82 Enrolled: 71 Responding at FU: 64	2	Single clinic/ hospital/ pharmacy: VA medical center	1	Hyperlipidemia	3	In-person interview	Validated scale: Morisky, cutoff less than 11	Perceived outcome Perceived impact of med Perceived risk of side effects Beliefs about meds Knowledge about illness and treatment Perceived need	Nonadherence was positively associated with low perceived risk of side effects (OR = 2.5, 95% CI: 1.0–6.3) and high perceived severity of illness (OR = 3.1, 95% CI: 1.1–8.7) and negatively associated with expected treatment duration (OR = 3.6, 95% CI: 1.4–9.4).

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Mann et al. 2009 (70)	Enrolled: 151 Responding at FU: 151	1	Single clinic/ hospital/pharmacy: New York, N.Y.	2	Diabetes	1	In-person interview	Validated scale: Morisky	Illness representation* Perceived impact of med* Perceived risk of side effects* Beliefs about meds* Knowledge about illness and treatment* Depression*	Poor med adherence was positively associated with negative knowledge about diabetes (believing you have diabetes only when your sugar is high, OR = 7.4, 95% CI: 2–27.2; saying there was no need to take medicine when the glucose was normal, OR = 3.5; 95% CI: 0.9–13.7), perceived side effects (OR = 3.3; 95% CI: 1.3–8.7), perceived negative outcome (OR = 2.8, 95% CI: 1.1–7.1), and med characteristics (feeling that medicines are hard to take, OR = 14.0, 95% CI: 4.4–44.6).
McHorney et al. 2007 (71)	Invited: 3,274 Enrolled: 1,092 Responding at BL: 1,015	1	Other: Pharmacy chains	1	Osteoporosis	3	Telephone interview, pharmacy records/ claims data	MPR, 210 days in reporting period, are you taking medicine?	Perceived health status Perceived impact of med Perceived risk of side effects Forgetfulness Side effects Regimen complexity No. of prescriptions Costs/insurance Risk of disease	Nonadherence to meds was associated with lower beliefs in drug effectiveness (OR = 5.70, 95% CI: 3.65–8.92) and lower drug-safety beliefs (OR = 2.26, 95% CI: 1.49–3.42) after adjusting for demographic, illness, and med characteristics.
Mochari et al. 2007 (72)	Responding at BL: 214	1	Single clinic/ hospital/pharmacy: N.Y.	2	Hyperlipidemia Hypertension	5	In-person interview	Taking meds less than 80% time	Knowledge about illness and treatment Perceived need Side effects	Nonadherence was significantly associated with beliefs about meds ($p = 0.004$) after controlling for age, sex, race/ethnicity, education, and insurance status.
Nau et al. 2007 (73)	Invited: 1,700 Enrolled: 694 Responding at BL: 391	1	Health plan: Mich.	3	Diabetes	1	Questionnaire	Modified Horne scale	Self-efficacy Depression* Regimen complexity Social support at home Duration of illness	Depression ($F = 4.82$, $p = 0.03$) had a negative main effect on adherence, and, although there was no main effect of gender on adherence, there was a significant interaction between depression and gender ($F = 5.93$, $p = 0.01$). Adherence among women was unaffected by level of depression, whereas men with depression were less adherent than men without depression. Social support at home and regimen complexity were both predictors.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Nguyen et al. 2009 (74)	Responding at FU: 235	1	Single clinic/ hospital/ pharmacy: Baltimore, Md.	7	Inflammatory bowel disease	5	Telephone interview	Modified Hill-Bone Compliance Scale	Perceived quality of life* Patient-provider trust*	Patient-physician trust was positively associated with med adherence (OR = 1.41, 95% CI: 1.14–1.75) and overall adherence (OR = 1.36, 95% CI: 1.09–1.69).
Patel et al. 2002 (75)	Responding at BL: 240	1	Single clinic/ hospital/pharmacy	1	Hypertension	1	Telephone interview	Validated scale: Morisky	No. of prescriptions Duration of illness Illness attributions Other perceived control Not specified	Perceived control over hypertension was negatively associated with med adherence (r = –0.31, $p < 0.01$). No significant relationship was found between adherence and no. of meds.
Pedan et al. 2007 (76)	Enrolled: 6,436	2	Other: Pharmacy chains	1	Hyperlipidemia	2, 3, 1	Pharmacy records/ claims data	No. of 30-day refills	Region residence No. of prescriptions Formularies No. of refills prescribed Med dose	Adherence was negatively associated with higher dose ($p < 0.001$), higher volume of patients per physician ($p < 0.001$), and higher copayments ($p < 0.001$). Adherence was positively associated with the no. of prescribed refills ($p < 0.001$).
Phatak et al. 2006 (77)	Invited: 316 Enrolled: 252 Responding at BL: 250	1	Single clinic/ hospital/pharmacy: Ind.	2	Other—not specified	1	Questionnaire	Validated scale: Morisky	Perceived risk of side effects* Beliefs about meds* Perceived need* No. of prescriptions Beliefs about overprescribing*	Med nonadherence was positively associated with number of meds ($\beta = 0.22$, $p = 0.047$), specific concerns about meds ($\beta = 0.11$, $p = 0.01$), and negatively associated with beliefs about meds ($\beta = -0.12$, $p = 0.021$).
Platt et al. 2008 (78)	Invited: 259 Enrolled: 136 Responding at BL: 111 Responding at FU: 111	2	Multiple clinic: Univ. of Pa.	2	Anticoagulation therapy	3	Electronic monitoring	PDC	Perceived health status Perceived quality of life* Cognitive function* Memory and comprehension Depression* Smoker Social support at home No. of other doctors visited	Nonadherence was positively associated with lower cognitive function (OR = 2.9, 95% CI: 1.7–4.8) and lower mental function (OR = 1.4, 95% CI=1.1–1.6). Adherence was not significantly associated with smoking, perceived health status, or depression.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Ren et al. 2002 (79)	Invited: 4,137 Enrolled: 2,425 Responding at BL: 2,425	1	Multiple clinic: VA	2	Hypertension	1	Pharmacy records/ claims data	MPR	Perceived health status Forgetfulness No. of prescriptions Provider factors Patient satisfaction Propensity to participate in treatment decisions Perceived amount of med	A larger number of meds ($\beta = 0.41$, $p < 0.01$) and more involvement by the patient in treatment decisions ($\beta = 0.60$, $p < 0.05$) were associated with better med adherence after adjusting for patient and physician characteristics. Perceived quality of care entered in the multivariate model was not associated with adherence.
Schectman et al. 2002 (80)	Enrolled: 1,984	2	Single clinic/ hospital/pharmacy: Va.	1	Diabetes Hyperlipidemia Hypertension	1	Pharmacy records/ claims data	MPR, cutoff: 0.80	Regimen complexity No. of prescriptions Costs/insurance Distance from pharmacy No. of clinic visits Length of drug supply	The no. of days supplied per prescription ($\beta = 0.19$, $p < 0.0001$) and the no. of prescriptions ($\beta = 0.76$, $p = 0.0001$) were both associated with better med adherence, whereas the number of primary-care visits, once-daily dosing, and travel distance to a pharmacy were not significant.
Schoenthaler, Chaplin, et al. 2009 (81)	Invited: 1,101 Enrolled: 526 Responding at BL: 439	1	Multiple clinic: N.Y.	5	Hypertension	1	Questionnaire	Validated scale: Morisky	Health literacy* Depression* Other communication issues* Provider degree No. of years provider in practice	Provider communication rated as more collaborative (reverse scored) was significantly associated with better med adherence in both bivariate ($r = -0.15$, $p = 0.003$) and multivariate ($\beta = -0.11$, SE = 0.007, $p = 0.03$) analysis controlling for demographic and disease characteristics. Depressive symptoms were negatively associated with adherence ($\beta = -0.18$, SE = 0.11, $p = 0.001$).
Schoenthaler, Ogedegbe, et al. 2009 (82)	Invited: 330 Enrolled: 190 Responding at BL: 190 Responding at FU: 167	2	Multiple clinic: New York, N.Y.	1	Hypertension	1	In-person interview	Validated scale: Morisky	Self-efficacy* Depression*	Depression-symptom severity was positively associated with poor med adherence ($\beta = 0.013$, $p = 0.036$). Self-efficacy was negatively associated with med adherence ($\beta = -0.612$, $p < 0.001$). After controlling for self-efficacy, depressive symptoms were no longer significantly associated with med adherence ($\beta = 0.010$, $p = 0.087$).

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Siegel et al. 2007 (83)	Enrolled: 40,492	2	Regional: VA VISN 21	1	Hypertension	1	Pharmacy records/ claims data	MPR, med gap ratio	Depression Regimen complexity No. of prescriptions Dementia	The no. of hypertensive meds (OR = 1.158, $p < 0.001$) and the no. of all meds (OR = 1.012, $p < 0.001$) were both associated with better adherence to antihypertensive meds. Depression (OR = 0.861, $p < 0.001$) was negatively associated with adherence.
Sirey et al. 2001 (84)	Enrolled: 247 Responding at FU: 134	2	Multiple clinic: N.Y.	7	Depression	1	In-person interview	Interviewer assessment	Perceived severity of illness* Perceived outcome* Perceived need* Unstable living condition Presence of interpersonal problems Side effects No. of clinic visits Perceived stigma*	Higher perceived stigma (OR = 0.93, 95% CI: 0.87–0.99) and higher self-rated severity of illness (OR = 0.93, 95% CI: 0.87–0.99) were associated with lower med adherence after adjusting for a range of demographic, clinical, and personality factors. Otherwise, perceived need for med was not associated.
Smith et al. 2006 (85)	Invited: 111 Enrolled: 82 Responding at BL: 82 Responding at FU: 59	2	Single clinic/ hospital/pharmacy: Johns Hopkins	7	Asthma	5	Electronic monitoring	Prescribed doses taken within specified period	Depression*	The presence of more depressive symptoms ($\beta = -0.016$, SE = 0.007, $p = 0.028$) after discharge from the hospital was associated with lower adherence to asthma therapy (inhaled or oral corticosteroid use) after adjusting for demographic variables.
Stoehr et al. 2008 (86)	Enrolled: 343 Responding at FU: 337	1	Multiple clinic: Southwestern Pa.	2	Other—not specified	1	In-person interview, pill count (by someone other than patient)	Nurse overall assessment	Cognitive function* Memory and comprehension* Regimen complexity No. of prescriptions	Adherence was negatively associated with no. of prescription meds (OR = 0.45, 95% CI: 0.21–0.95, $p = 0.04$). The relationship between adherence and dosing frequency was not significant.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Sung et al. 1998 (87)	Responding at BL: 772	2	Health plan	5	Hyperlipidemia	1	Pharmacy records/ claims data	MPR, cutoff: 0.90	Perceived health status* Previous adherence Use of alcohol Regimen complexity No. of prescriptions Patient satisfaction Pharmacist satisfaction	Patient satisfaction with provider and pharmacy interactions were not associated with meds compliance, although less perceived bodily pain (OR = 1.023, 95% CI: 1.002–1.045) and higher perceived vitality (OR = 0.97, 95% CI: 0.945–0.993) were associated with small but negative effects on adherence after adjusting for demographic and disease-related variables.
Thorpe et al. 2009 (88)	Invited: 816 Enrolled: 588 Responding at BL: 562	2	Single clinic/ hospital/ pharmacy: VA N.C.	5	Hypertension	1, 4	In-person interview, pharmacy records/ claims data	Validated scale: Morisky, PDC	Knowledge about illness and treatment Health literacy* Smoker Substance abuse Side effects Duration on med Social support at home* No. of prescriptions Perceived mental health Perceived control over disease Perceived barriers to med use Perceived stress	A composite score for perceived barriers to meds (OR = 1.74, 95% CI: 1.09–2.77), was significantly associated lower med adherence based on pharmacy records, whereas other variables in the Health Decision Model, such as knowledge about hypertension, perceived control, health literacy, perceived stress, mental-health status, and social support, were not associated with adherence. None of these variables was associated with an oversupply of med.
Trivedi et al. 2008 (89)	Invited: 1,325 Enrolled: 636 Responding at BL: 636	1	Multiple clinic: N.C.	5	Hypertension	1	Questionnaire	Validated scale: Morisky	Smoker Side effects Emotional well-being*	Emotional well-being (OR = 1.01, 95% CI: 1.00–1.03) had a small but significant association with better adherence to med after adjusting for demographics and med side effects. Current smoking status ($r = -0.09$, $p < 0.05$) was associated with lower adherence in bivariate analysis but not in the multivariate model.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Vawter et al. 2008 (90)	Invited: 6,168 Enrolled: 4,819 Responding at BL: 1,432	1	National	3	Hypertension	1	Questionnaire	Difficulty taking medicine	Perceived need Forgetfulness Depression Other affective disorder Side effects No. of prescriptions No. of clinic visits Costs/insurance No regular provider	Difficulty in taking antihypertensive med was positively associated with lower mental function (depression/anxiety/migraines) (OR = 1.6, 95% CI: 1.1–2.2, $p = 0.0005$), after controlling for a range of demographic variables. Increased no. of clinic visits and decreased no. of meds were associated with better adherence.
Voils et al. 2005 (91)	Enrolled: 85 Responding at BL: 85	1	Single clinic/hospital/pharmacy: Duke	1	Depression	1	Questionnaire	Validated scale: Morisky-4	Perceived health status Health locus of control* Physical limitations (eyesight, dysphagia) Social support at home* Instrumental social support* Social-network size* Other social-network size* Nonfamily interaction*	Med adherence was positively associated with social support ($\beta = 0.30$, $p < 0.01$) using the Duke social-support scale and negatively associated with internal locus of control ($\beta = -0.22$, $p < 0.05$).
Wang et al. 2002 (92)	Invited: 993 Enrolled: 496 Responding at BL: 496	1	Multiple clinic: Boston, Mass.	3	Hypertension	1	Pharmacy records/claims data	PDC	Beliefs about meds* Knowledge about illness and treatment Locus of control Depression* Smoker Substance abuse Patient satisfaction Social support at home*	Depression-symptom severity (OR = 0.93, 95% CI: 0.87–0.99) was associated with lower antihypertensive-med adherence after controlling for a range of demographic variables. Two psychosocial factors (external locus of control and social support), two patient factors (knowledge of hypertension and belief in the importance of hypertension med), and a provider factor (patient satisfaction with medical care) were not associated with adherence.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Wells et al. 2008 (93)	Invited: 1,833 Responding at BL: 1,006	2	Health plan	5	Asthma	1	Pharmacy records/ claims data	MPR, 180 days in reporting period	Beliefs about meds* Knowledge about illness and treatment* Perceived need of med Self-efficacy Readiness to change* Depression Patient-provider trust Other communication issues Wait to get appointment Social support at home Costs/insurance Access to care Transportation Duration of illness Past med experience Perceived discrimination Exposure to crime Locus of control	Adherence was positively associated with med beliefs ($p = 0.001$) and knowledge about med ($p = 0.001$), and negatively associated with difficulty in affording med ($p = 0.024$) and inability to get an appointment ($p = 0.037$). Social support at home had no relationship to adherence.
Williams et al. 1998 (94)	Enrolled: 126	3	Single clinic/ hospital/pharmacy: N.C.	2	Other—not specified	5	In-person interview, pill count (by someone other than patient)	Composite pill count, self-report	Perceived health status Beliefs about meds Locus of control Regimen complexity No. of prescriptions Other communication issues Duration of illness Motivation for taking med	In bivariate analysis, more perceived physician support for the patient's wishes ($r = 0.19$, $p < 0.05$), more patient autonomy for improving health ($r = 0.58$, $p < 0.0005$), & fewer perceived barriers ($r = -0.19$, $p < 0.05$) were associated with better med adherence; locus of control (internal, powerful others, & chance) & no. of meds were not associated with adherence. In a structural equation model, autonomous motivation to improve health was a predictor of better med adherence & mediated the relationship between perceived support from the physician for patient having autonomous control of health & med adherence.

Table B.1—Continued

Citation	Sample Size	Study Design[a]	Recruitment Site	Sample Description[b]	Disease Studied	Type of Adherence[c]	How Adherence Is Assessed	Measure of Adherence	Barriers Addressed	Key Findings
Wroth et al. 2006 (95)	Invited: 4,879 Enrolled: 3,926 Responding at BL: 3,926	1	Regional: Southeast	3	Other—not specified	2	Telephone interview	Did you delay filling prescription or not get at all?	Perceived health status Patient-provider trust Patient satisfaction Access to care Transportation Satisfaction with concern shown Satisfaction with questions answered Satisfaction with quality of care Satisfaction with office staff	Nonadherence was positively associated with lower perceived health status (OR = 1.69, 95% CI: 1.35–2.12), transportation problems (OR = 1.78, 95% CI: 1.35–2.38), and lower patient-provider trust (OR = 1.37, 95% CI: 1.04–1.79).
Wu et al. 2008 (96)	Enrolled: 134	2	Multiple clinic: Ky.	2	Heart failure	5	Electronic monitoring	Prescribed doses taken within specified period, cutoff: continuous, PDC	Knowledge about illness and treatment* Attitude toward med* Depression* Regimen complexity Patient-provider trust* Social support at home* Pill box Barriers to use*	Adherence was not significantly associated with depression, no. of prescribed meds, med frequency, or patient-provider relationship. Social support at home measured with the social-support scale was associated with adherence using dose count and dose days but not dose timing.

[a] 1 = cross-sectional. 2 = observational cohort. 3 = unclear.

[b] 1 = all patients with disease from study site. 2 = convenience sample. 3 = random sample. 4 = at risk for nonadherence. 5 = participants in clinical trial. 6 = volunteers, response to ads. 7 = consecutive patients. 8 = longitudinal cohort. 9 = unclear

[c] 1 = nonadherence. 2 = nonfulfillment. 3 = nonpersistence. 4 = overadherence. 5 = other-unclear.

NOTE: Numbers in parentheses in the "Citation" column refer to the numbered references in the report. med = medication. * = validated assessment. BL = baseline. PDC = proportion of days covered. FU = follow-up. OR = odds ratio. CI = confidence interval. MPR = med possession ratio. NHANES = National Health and Nutrition Examination Survey. BMI = body mass index. VA = U.S. Department of Veterans Affairs. CMG = cumulative med gap. HANDS = Harvard Department of Psychiatry/National Depression Screening Day Scale. ICS = inhaled corticosteroid. IBA = inhaled beta-agonist. CABG = coronary-artery bypass graft. ACE = angiotensin-converting enzyme. SE = standard error. VISN = Veterans Integrated Service Network.

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