

Understanding Medication Adherence

Implications for dual-antiplatelet therapy.

BY MARIE T. BROWN, MD, FACP, AND TED E. FELDMAN, MD, FESC, FACC, FSCAI

Since the start of our careers as clinicians, we have all recognized medication adherence as an important problem. In the past, the term “noncompliance” was commonly used. Medication adherence suggests a more complex story of individual medication-taking behavior.

The era of drug-eluting stents (DES) and the critical need for dual-antiplatelet therapy (DAPT) for prevention of stent thrombosis has brought this problem into greater prominence in the coronary interventional arena. We often instruct our patients about the importance of DAPT compliance in dramatic terms, to emphasize the real risks of stent thrombosis and the importance of medication adherence.

Almost 75% of patients do not follow doctors’ orders for prescription medications, resulting in 125,000 deaths annually.¹ Also, approximately 25% of new prescriptions are never filled, as demonstrated in a 2011 analysis of more than 280,000 patients and 3,634 prescribers.² Other patients fail to pick up their medicines from a pharmacy, skip doses, take their pills off schedule, or take either too much or too little. Among those who adhere at the start, some eventually stop taking their medication altogether.

Several common cardiovascular problems highlight both the complexity of medication-taking behavior and the impact of medication adherence on clinical outcomes.

Inadequate anticoagulation for atrial fibrillation is well recognized. In a large Canadian registry, only 10% of patients with acute stroke with known atrial fibrillation were therapeutically anticoagulated upon admission. In stroke patients with atrial fibrillation and a previous transient ischemic attack or ischemic stroke, only 18% had a

therapeutic international normalized ratio on admission for stroke. A subtherapeutic international normalized ratio was found in 39%, and remarkably, 15% were on no anti-thrombotic therapy at all.³

Risk factors for stent thrombosis are well described, but the magnitude of risk is greater after DES implantation for ST-segment elevation myocardial infarction. The potential for lethal effects from failure to take DAPT after stenting for acute myocardial infarction (MI) was first brought to light in the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) study. Among 500 DES-treated MI patients discharged on DAPT, 13.6% stopped therapy within 30 days. Surprisingly, those who stopped were more likely to have preexisting cardiovascular disease. They were also less likely to have received discharge instructions about their medications or a cardiac rehabilitation referral. Patients who stopped DAPT by 30 days were nine times more likely to die during the next year (7.5% vs 0.7%) and almost twice as likely to be rehospitalized (23% vs 14%).⁴ In the HORIZONS-AMI trial (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), when mandated, protocol-defined instructions kept patients on DAPT for at least a year, patients had significantly improved DAPT adherence.⁵

Understanding the many reasons patients have for medication nonadherence is crucial for solving the problem.

IDENTIFYING NONADHERENCE

Measuring medication adherence before a preventable catastrophic event occurs is the first and most important step in addressing the problem; unfortunately, it is not always assessed.

TABLE 1. THE MORISKY 4-ITEM SELF-REPORT MEASURE OF MEDICATION-TAKING BEHAVIOR (MMAS-4)⁶

1. Do you ever forget to take your (name of health condition) medicine?
2. Do you ever have problems remembering to take your (name of health condition) medication?
3. When you feel better, do you sometimes stop taking your (name of health condition) medicine?
4. Sometimes if you feel worse when you take your (name of health condition) medicine, do you stop taking it?

Reprinted from the *Journal of Clinical Epidemiology*, Volume 64, Issue 3, Morisky M, DiMatteo R, Improving the measurement of self-reported medication nonadherence: response to authors, 255-257, 2011, with permission from Elsevier.

What's Missing in the Following Scenario?

A patient is treated with percutaneous coronary intervention and placed on DAPT; he is seen in follow-up within the month. The receptionist asks him to list his medications; the nurse reviews the list and reconciles it with the discharge medication list. The nurse then reviews the timing of the medicine, the side effects, stresses the importance of taking the medicine in a timely fashion, and answers any questions the patient has about the medicine using the “teach back method.” The medication list is entered into the electronic health record, and the medication reconciliation box is checked off. The physician completes the examination, and a return visit is scheduled.

One week later, the ER calls and tells you the patient is being admitted with ST elevation, chest pain, and probable stent thrombosis. What was missing during the visit with the patient last week? The patient was never asked if he was actually taking the medicine prescribed!

We Didn't Ask, and They Didn't Tell

Because more than 50% of patients do not take medicine as prescribed, early identification of the nonadherent

patient is critical. Asking about an individual's medication-taking behavior in a blame-free environment is of paramount importance. If patients feel comfortable and assured they will not be reprimanded harshly or treated differently, they will more likely share their actual medication use. The Morisky 4-Item Self-Report Measure of Medication-taking Behavior (MMAS-4) is a useful series of questions to evaluate medication use (Table 1).⁶

After patients share their medication-taking behavior, two-way conversations addressing their rationale can begin—a necessity prior to any intervention aimed at changing their behavior. Only after medication nonadherence is identified can a new differential diagnosis be queried. A differential diagnosis of nonadherence includes numerous causes of medication nonadherence and goes far beyond many of our stereotypical notions of noncompliance. Interviews with real patients that illustrate these issues can be seen at www.drmariebrown.com.

CAUSES OF NONADHERENCE

Medication-taking behavior is extremely complex. Drawing a distinction between unintentional (forgetting to take medicine) and intentional (missing doses purposefully) nonadherence is helpful.⁷ Although many physicians assume the main obstacles are unintentional, in fact, only 30% of nonadherence is due to forgetfulness (Table 2).⁸

Unintentional causes of nonadherence are more closely associated with socioeconomic issues and demographics, low health literacy, lack of understanding of the regimen, mental health issues, access/cost, forgetfulness, and complicated multidrug regimens.

Intentional nonadherence is influenced by the balance of patients' reasons for and against taking medication, and include only those values that patients consider relevant to them personally. Patients weigh the pros and cons of taking medications based on their personal beliefs and the information at their disposal. Deciding to miss doses may appear irrational to their physicians because of the personal opinions on which the decision

is based.⁷ Causes of intentional nonadherence include mistrust of the pharmaceutical industry, mistrust of the health care system, misunderstanding of the disease process, fear of side effects, lack of belief in benefit, fear of dependency, and lack of belief in a quality future life.⁹

SOLUTIONS

In a recent large database review of more than 70 randomized trials, no one simple intervention was found to be effective at improving long-term medication adher-

TABLE 2. NONADHERENCE: DIFFERENTIAL DIAGNOSIS⁸

Unintentional	Intentional
Forgetting	Fear of side effects
Shift work	Mistrust
Cost	Mental illness
Low health literacy	Lack of belief in benefit
Work restrictions	Fear of dependency
Mental Illness	Fear medication is dangerous
	Lack of desire
	No apparent benefit

TABLE 3. THE IMPATIENT PATIENT¹¹

1. Doctors are future-oriented, whereas patients may not consider themselves as having a future to look forward to.
2. Many patients have an innate tendency to prefer smaller/sooner rather than larger/later rewards.
3. The nonadherent patient may prefer immediate rewards to efforts linked to long-term therapy and be less capable of giving priority to their future.
4. The reward of adherence in the management of chronic disease is "to avoid complications." Paradoxically, this type of reward is never "received."

ence and health outcomes, highlighting the difficulty of improving medication adherence.¹⁰

Multifactorial interventions targeting three specific factors (patient, physician, health care system) were shown to improve adherence and outcomes and provide a framework to address this important problem.

Patient Factors: The Impatient Patient

In chronic diseases, the adherent patient strives to achieve a long-term goal of preserving health; the impatient, nonadherent patient achieves only immediate rewards each day—not having to make time to purchase the medicine, avoiding side effects, and not needing to remember to take the medicine (Table 3).¹¹ The impatient patient chooses a smaller reward perhaps because he gives less priority to his future.¹¹

"The choice between adherence and nonadherence can indeed be seen as a choice that the patient will have to make, day after day, between a larger delayed reward for adherence (prevention of complications) and a smaller but more immediate reward for non-adherence (eg, an extra portion of cake, the forbidden cigarette, avoiding the boring task of looking for the tablets, avoiding the side effects of the medication)," Gerard Reach, MD, described in his article on nonadherence. "There is therefore a paradox of nonadherence to long-term therapies, in that nonadherent individuals prefer a reward that is more immediate but smaller."¹¹

Dr. Reach suggests that understanding how our patients view their future and then tailoring treatment and conversation to their viewpoint would be more effective than the one-size-fits-all approach currently in use. Mutually identifying an immediate advantage of being adherent to the impatient patient, such as avoiding lost income from being away from work or undergoing additional costly hospitalizations, may be more effective than stressing avoidance of a potential medical complication years in the future. As summarized by Dr. Reach, "Since it may be difficult, or impossible, or even unethical, to want to change peoples' characters, the art of medicine may consist in

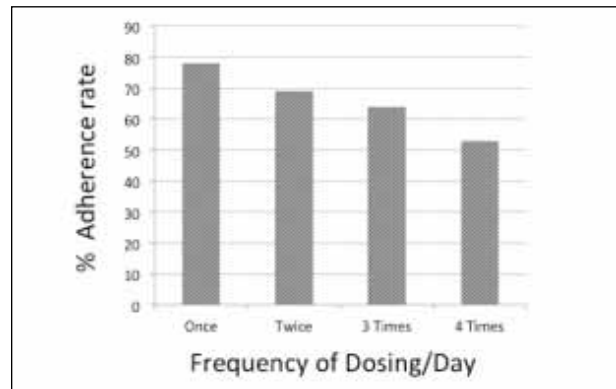


Figure 1. Medication adherence is inversely related to the frequency of dosing and the number of medications. Adapted from Osterberg L, Blaschke T. *N Engl J Med.* 2005;353:487–497.⁸

offering advice that is not only objectively sound but is also adapted to the patient's own priorities, understanding of the situation, and character."¹¹

Physician Factors

Medication adherence is inversely related to the frequency of dosing and the number of medications

(Figure 1).^{8,12} The average adult patient fills 12 prescriptions each year, may see seven different physicians annually, and has multiple comorbidities. The need for physicians to coordinate care, minimize total medication burden, strive for once-daily dosing, and address medication interactions is the responsibility of each treating physician. However, less than 34% of discharge summaries are available at first visits after discharge.¹³

In a study of physician prescribing behavior, 19% of cardiologists, 40% of internists, and 33% of family practitioners informed the patient of the duration of therapy.¹⁴ In an era of electronic prescribing, with common default messages such as “take one pill every day for 90 days,” it is not surprising that thoughtful patients would stop the medicine after 90 days when the vast majority of the time, no physician informed them of the duration of the medication. The protracted and often lifelong nature of therapy for chronic diseases such as coronary artery disease and hypercholesterolemia are implicit to physicians but not clear to many patients.

Physician Solutions

Simplifying the regimen by decreasing the number of doses (ideally to once daily), using long-acting preparations, or prescribing more forgiving drugs (such as those with fewer adverse effects if a dose is missed) are successful strategies. Many patients ask about taking statins in the morning so that they can take all of their once-daily medications at the same time. For example, while there is a good pharmacokinetic rationale to recommend nighttime dosing, there is little evidence that it makes any meaningful clinical difference.^{15,16} Every increase in dosing decreases adherence. If the patient is unable to remember the additional nighttime dose, it is more beneficial to take a statin daily during the day rather than not at all. Clearly state the duration of therapy for a medication, whether it be 12 months or lifelong.

Systems-Related Factors

Health systems and the team-based approach facilitate the identification of nonadherence. Encouraging patients to bring in all of their medications at each visit for review by the health care team will help assess adherence and facilitate education and medication reconciliation, decreasing adverse side effects and preventing errors. Pharmacists are an important source of additional oversight and can provide alerts when medications have not been refilled appropriately—allowing the team to be proactive and improve adherence prior to an adverse event.

In a study of more than 19,000 patients by Yu, et al,¹⁷ dispensation delay (the gap between the most recent physician or hospital visit and the fill date of a statin) predicted future nonadherence. Identifying patients

early (even before medications are or are not taken) who are at greater risk for nonadherence may be possible. Allocating limited resources to intervene in these high-risk patients may prevent avoidable adverse events.

CONCLUSIONS

The health care and monetary costs of nonadherence are staggering. Patients with chronic conditions are non-compliant approximately half the time. Each year, 125,000 people die due to medication noncompliance, and \$290 billion is spent annually on care needed because of medication noncompliance.¹ The World Health Organization has stated, “increasing the effectiveness of adherence interventions may have a far greater impact on health than any improvement in specific medical treatments.”¹⁸ The multifactorial nature of medication-taking behavior must be recognized and addressed by multipronged interventions in a coordinated and consistent manner. ■

Marie T. Brown, MD, FACP, is an Assistant Professor of Medicine, Rush University Medical Center in Chicago, Illinois, and Governor, American College of Physicians, Illinois Northern Chapter. She has disclosed that she has no financial interests related to this article. Dr. Brown and Dr. Feldman may both be reached at (708) 524-2121; mbrown@mbrownmd.net.

Ted E. Feldman, MD, FESC, FACC, FSCAI, is with the NorthShore University HealthSystem in Evanston, Illinois. He has disclosed that he has no financial interests related to this article.

1. O'Reilly KB. Tactics to improve drug compliance. Posted Oct 3, 2011. Available at: <http://www.ama-assn.org/amednews/2011/10/03/pisa1003.htm>. Accessed on August 26, 2012.
2. Fischer MA, Choudhry NK, Brill G, et al. Trouble getting started: predictors of primary medication nonadherence. *Am J Med.* 2011;124:1081.e9-22.
3. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke.* 2009;40:235-240.
4. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation.* 2006;113:2803-2809.
5. Suh JW, Mehran R, Claessen BE, et al. Impact of in-hospital major bleeding on late clinical outcomes after primary percutaneous coronary intervention in acute myocardial infarction interventional cardiology: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *J Am Coll Cardiol.* 2011;58:1750-1756.
6. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: final response. *J Clin Epidemiol.* 2011;64:262-263.
7. Wroe AL. Intentional and unintentional nonadherence: a study of decision making. *J Behav Med.* 2002;25:355-372.
8. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353:487-497.
9. Brown MT, Russell JK. Medication adherence: who cares? *Mayo Clin Proc.* 2011;86:304-314.
10. Haynes RB, Ackloo E, Sahota N, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2008;2:CD000011.
11. Reach G. Is there an impatience genotype leading to non-adherence to long-term therapies? *Diabetologia.* 2010;53:1562-1567.
12. Benner JS, Chapman RH, Pettrilli AA, et al. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. *Am J Health Syst Pharm.* 2009;66:1471-1477.
13. Kripalani S, Lefevre F, Phillips CO, et al. Deficits in communication and information transfer between hospital based and primary care physicians: implications for patient safety and continuity of care. *JAMA.* 2007;297:831-841.
14. Tarn D. Physician communication when prescribing new medications. *Arch Intern Med.* 2006;166:1855-1862.
15. Ozaydin M, Dede O, Dogan A, et al. Effects of morning versus evening intake of atorvastatin on major cardiac event and restenosis rates in patients undergoing first elective percutaneous coronary intervention. *Am J Cardiol.* 2006;97:44-47.
16. Lund TM, Torsvik H, Falch D, et al. Effect of morning versus evening intake of simvastatin on the serum cholesterol level in patients with coronary artery disease. *Am J Cardiol.* 2002;90:784-786.
17. Yu AP, Yu YF, Nichol MB, Gwady-Sridhar F. Delay in filling the initial prescription for a statin: a potential early indicator of medication nonpersistence. *Clin Ther.* 2008;30:761-774.
18. Report WHO (January 2003). Adherence to long-term therapies, evidence for action. World Health Organization Publications, Geneva. Available at: www.who.int/chp/knowledge/publications/adherence_introduction.pdf. Accessed on August 28, 2012.