Specialty Healthcare Benefits Council
Defining Specialty Health

Does Taking Prescription Medication as Prescribed Make a Difference?

William N. Kelly, PharmD, FISPE; and James Jorgenson, MS, RPH, FASHP

Former US Surgeon General C. Everett Koop is often credited with stating that "Drugs don't work in patients who don't take them." The unfortunate truth is that people often do not have their prescriptions filled, or do not pick up their medication at the pharmacy. The further reality is that nearly half of those who do pick up their prescriptions do not take their medication as prescribed. When asked, patients offer various reasons for not following through properly with their prescriptions. These behaviors should make us pause and consider the burden that we must share to cover the cost and human suffering that can result through unnecessary morbidity and mortality.

The rates of and reasons for medication-taking (or -avoidance) behavior have been studied extensively. The term *adherence* is used to describe the extent to which a person's behavior (by taking medication, following diets, or performing lifestyle changes) coincides with medical or health advice. This can be contrasted with *compliance*, which means a passive acceptance of a patient's physician's orders regardless of the patient's involvement in that process. Another term, *persistence*, refers to the act of continuing treatment for the prescribed duration. Rarely used in the literature, persistence often appears in pharmaceutical industry statistics when measuring prescription refill rates.

Measuring Adherence

The question of how to measure adherence properly has challenged researchers for some time. The complexity of this issue prevents the developing of a "gold" standard. There are direct methods to verify proper ingestion of medications, such as: observing therapy participation, measuring the medicine or metabolite in the blood, or measuring a biological marker in the blood. Indirect methods are less specific and rely on patients completing self-reports, questionnaires, or patient diaries. Other indirect measurements use pill counts, prescription refills, electronic medication monitors, and assessment of the patient's clinical response by measuring physiological markers (eg, heart rate in patients taking beta-blockers).

How Good Is Medication Adherence?

No matter how it is measured and quantified, medication adherence, irrespective of disease, prognosis, or setting, is expected in only 50% to 70% of all patients.[1] For example, despite strong evidence proving the benefits of statin therapy for lowering lipid levels in the primary and secondary prevention of acute coronary events, most patients do not adhere to these medication regimens. In a recent study, only half of all patients continued to take statins prescribed for them after 6 months, and only 30% to 40% continue to take them at the end of the first year.[2]

In the **Table**, medication adherence rates for the first year of therapeutic intervention are reported for several common chronic diseases in the United States.

Types of Nonadherence

Reasons cited for nonadherence can be thought of as qualitative or quantitative in nature. In the United States, patients not filling their prescription happens 30.5% of the time for paper, phone, or fax prescriptions, and 23.5% for e-prescriptions.[1] Even when prescriptions make it to the pharmacy, 3.7% of traditional prescriptions, and 5.3% of e-prescriptions, are not picked up by the patient.[1] These are quantitative results of nonadherence. A qualitative distinction would be whether the nonadherence was intended or unintended. Examples of unintentional nonadherence include forgetting to take the medication or misunderstanding how to carry out a specific regimen. Not filling a prescription because the cost is considered prohibitive is intentional nonadherence.

Table. **Medication Adherence Rates for Some Diseases in the First Year of Therapy**[2]

Disease	Adherence Rate
Gout	36.8%
Hypertension	72.3%
Hypercholesterolemia	54.6%
Hyperthyroidism	68.4%
Osteoporosis	51.2%
Seizure disorders	60.8%
Type 2 diabetes mellitus	65.4%

No matter the reason, there is consensus that nonadherence is higher with regimens for chronic versus acute diseases. Rapoff found that "Global estimates are that about one-third of patients fail to finish a course of medications for acute illnesses, while adherence averages between 50% and 55% for chronic disease regimens."[3]

Consequences and Costs of Nonadherence

Potentially serious health outcomes can result from nonadherence to prescribed medications, such as therapeutic failure, unnecessary hospitalization, and even death. This is borne out in the findings from many studies:

- Chaudry and McDermott determined that poor adherence to immunosuppressive drugs can be linked to heart, kidney, and liver transplant failures.[4]
- A meta-analysis of 21 studies sought to discover the relationship between nonadherence and mortality.[5] The definitions for good and poor adherence were used from each individual study. When compared with poor adherence, good adherence was associated with lower mortality. The authors concluded that "good adherence to drug therapy is associated with positive health outcomes."
- The National Consumers League estimates there are 125,000 deaths per year from medication noncompliance.[6]
- The relationship of treatment adherence to mortality after myocardial infarction was investigated in 2175 patients.[7] Those who did not adhere well (took ≤75% of prescribed medication) were 2.6 times more likely than good adherers to die within a year of follow-up.
- In a recent population-based study, the importance of being on the correct medication after myocardial infarction was shown.[8] Among statin users, the risk of mortality was greatest for low adherers and was intermediary for intermediate adherers compared with the high-adherence members of the study.

The cost of medication nonadherence for all patients (adult and pediatric) in the United States is estimated to be $100 billion every year.[9] The National Consumers League states that the resulting cost for avoidable healthcare due to medication noncompliance is $290 billion each year.[6] Also, the cost to the consumer of medication was found to be inversely related to adherence.[10,11] In one study, it was discovered that patients whose average monthly statin prescription copayment equaled or exceeded $20 were more than 4 times as likely to stop statin therapy as those patients who paid less than $10.[11] A study to evaluate the relationship between medication adherence, hospitalization risk, and healthcare cost revealed that for diabetes and hypercholesterolemia a high medication adherence was associated with lower disease-related medical costs.[12]

A significant part of the cost of nonadherence is from hospitalization and readmission rates. Hospital admission rates for patients with diabetes, hypertension, hypercholesterolemia, and congestive heart failure and having high medication adherence were significantly lower than for patients with these diseases who had low medication adherence. For heart failure patients, nonadherence to a medical regimen is a worrisome consequence, since the 1-year mortality in the Medicare population approaches 40%.[13] It is also the most common readmission diagnosis in the Medicare population.

For those suffering from mental health diagnoses, nonadherence to prescribed therapeutic regimens also results in higher rates of hospitalization. In a study of patients with schizophrenia, irregular users of their medication had significantly higher rates of hospitalization (42% vs 20%), more hospital days (16 days vs 4 days), and higher hospital costs ($3992 vs $1048).[14] In another study of patients who were previously hospitalized for treatment of bipolar disorder, those who were adherent to their antipsychotic medication at least 75% of the time had a lower risk of all-cause rehospitalization and mental health–related rehospitalization.[15]

What Can We Do to Improve Medication Adherence?

To improve adherence to prescribed regimens, one must understand the reasons for nonadherence. The explanations people give for not following through with their prescribed regimens vary widely. For some it is a matter of forgetting to take medications or not knowing exactly when or how they are to be taken. Some medications make swallowing pills difficult. Side effects

that come with many medications can make people feel worse, wondering if they need to take them. Sadly, there are growing segments of the population that do not fill their prescriptions because of the cost. Some will try to make prescriptions last twice as long by cutting the pills in half.

Methods to improve adherence fall into 4 general categories: patient education, behavioral interventions, improved dosing and dosing schedules, and improved communication between prescribers and patients.

1. ***Patient Education:*** These interventions include oral education (by physicians, nurses, or pharmacists), audiovisual education, written education, telephone education, mailed education, and e-mailed education.

2. ***Behavior Interventions:*** These include skill building by healthcare professionals, providing rewards, pill counting, calendars, pill boxes, mail reminders, telephone reminders, and e-mail reminders.

A *meta-analysis* of trials of interventions to improve medication adherence reviewed 61 studies.[16] Each intervention was counted as a separate study resulting in 95 cohorts totaling 9604 subjects receiving an intervention, and 9318 subjects who served as controls. Behavioral interventions accounted for 41 cohorts, educational interventions for 22 cohorts, and combined interventions for 32 cohorts. Overall, adherence for all interventions increased adherence from 4% to 11%. The effect sizes for the interventions were: education 0.11, behavior 0.07, and combined 0.08. When stratifying the combined intervention group by behavior intervention, mail reminders had the largest impact. Thus, interventions targeting behavior changes or using a combination of methods was determined to work best.

3. ***Improved Dosing and Dosing Schedule Interventions:*** These include dosing changes, reducing medication burden, dosage schedule changes, and packaging changes.

Once-daily dosing: Greater dosing frequency and regimen complexity are associated with poorer adherence.[17] Once-daily dosing was studied among a group of patients taking antiretroviral therapy.[18] The participants on once-daily regimens were half as likely to miss a dose during the 4 days before being interviewed about adherence.

Fixed-dose combinations: The Medication Regimen Complexity Index (MRCI) is used to track regimen attributes. Making simple dosing and dosing schedules and reducing medication burden improves adherence. There are more advantages to using fixed-dose combinations of antihypertensives (one being, they improve adherence) than disadvantages.[19] Using fixed-dose combinations of any antihypertensive agent has been shown to produce significantly higher adherence than using individual agents.[20] However, these fixed combinations cannot be used for titration.

Reminder packaging: A Cochrane review sought to discover if reminder packaging improved adherence to self-administered long-term medications.[21] Data from 6 intervention groups in 4 clinical trials were analyzed. The use of reminder packaging resulted in patients showing a significant decrease in diastolic blood pressure and glycated hemoglobin levels, but had no effect on systolic blood pressure in the same group.

4. ***Improved Provider/Patient Communication Interventions:*** Several physician behavioral factors have been identified with the problem of medication adherence: prescribing complex regimens, communication barriers, not taking the time to explain why the medication is needed and the importance of taking it, and ineffective communication of information about adverse effects. Inadequate communications between physicians, hospitalists, primary care physicians, and consultants also contribute to medication errors and potentially avoidable hospital readmissions. It has been found that on hospital discharge direct communication between hospitalists and primary care physicians occurred in less than 20% of hospitalizations, and discharge summaries were available at less than 34% of first post-discharge physician office visits.[22]

A study sought to determine whether pharmacists giving advice to patients upon starting a new medicine for a chronic condition would improve adherence.[23] It was found that nonadherence was lower in the intervention group compared with the control group (9% vs 16%). In a follow-up study of this patient population, it was discovered that the number of patients reporting medication problems was significantly lower in the intervention group compared with the control group, and that the intervention group was less costly (£187.7 vs £282.8, or US$294.69 vs US$444.00).[24]

The Impact of Improved Adherence

Sokol and colleagues evaluated the impact of medication adherence on healthcare utilization and cost for 4 chronic conditions that are major drivers of drug spending. In this study they examined the records of 132,277 patients younger than 65 years with a diagnosis of diabetes, hypertension, hypercholesterolemia, or congestive heart failure.[25] For diabetes and hypercholesterolemia, a high level of medication adherence was associated with lower disease-related medical costs. For all 4 conditions, patients who maintained 80% to 100% medication adherence were significantly less likely to be hospitalized compared with patients with lower levels of adherence. For diabetes, hypertension, and hypercholesterolemia, high levels of adherence with condition-specific drugs were associated with lower medical costs across all of the patients' treated conditions. For all 4 conditions, all-cause hospitalization rates were lowest for patients who had the highest medication adherence.

Summary

The rate of nonadherence to taking medications as prescribed is estimated to be 30% to 50% in the United States. Poor medication adherence is correlated with poorer patient outcomes and 125,000 deaths yearly. Nonadherence is responsible for more than one-third of medication-related hospitalizations that add as much as $290 billion to the cost of healthcare each year. Despite these numbers, interventions to improve adherence have had only modest success.

Research evidence shows that interventions targeting behavior changes or using a combination of methods work best. Single interventions that have shown some success include those that reduce the number of daily doses of medications, use motivational strategies, package medications into special containers (eg, pill boxes, blister packs), provide more convenient care, educate patients, or involve monitoring and feedback. As the US healthcare system attempts to move from a volume-based curve to one that is value-based with the emphasis on improved quality and reduced cost, medication adherence presents an opportunity to address both elements. It also presents a significant opportunity for pharmacists as the "medication therapy experts" on the healthcare team to take a leading role in improving medication adherence.

Acknowledgment

The generous assistance of Lisa McBain, MPS, senior director, operations, and senior consultant with Visante, in editing this manuscript is acknowledged.

Author Affliations: William N. Kelly is vice-president for scientific affairs, Visante, Inc. James Jorgenson is chief pharmacy officer and vice president of Indiana University Health.

Funding Source: None reported.

Author Disclosures: The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Address correspondence to: William N. Kelly, PharmD, FISPE, 2147 Warwick Dr, Oldmar, FL 34677. E-mail: wnkellyu@earthlink.net.

REFERENCES

1. Surescripts. E-prescribing shown to improve outcomes and save healthcare system billions of dollars. February 1, 2012. http://www.surescripts.com/news-and-events/press-releases/2012/february/212_eprescribing.aspx?fullscreen=true&background=off&mode=print. Accessed February 7, 2012.
2. Briesacher BA. Comparison of drug adherence rates among patients with different medical conditions. *J Pharmacotherapy.* 2008;28(4):437-443.
3. Rapoff MA. Definitions of adherence, types of adherence problems, and adherence rates. In: *Adherence to Pediatric Medical Requirements.* Springer Science+Business Media, LLC; 2010.
4. Chaudry HJ, McDermott B. Recognizing and improving patient nonadherence to statin therapy. *Curr Atheroscler Rep.* 2008;10(1):19-24.
5. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality [published online ahead of print June 21, 2006]. *BMJ Online.* doi:10.1136/bmj.38875.675486.55.
6. Maher I. Doctor's orders optional, for many. *St. Petersburg Times.* Health and Science section, page 10A. November 24, 2011.
7. Horwitz RI, Viscoli CM, Berkman L, et al. Treatment adherence and risk of death after a myocardial infarction. *Lancet.* 1990;336(8714):542-545.
8. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA.* 2012;297(2):177-186.
9. Rapoff MA. Adherence to pediatric medical regimens. In: *Issues in Clinical Child Psychology.* Springer Science+Business Media, LLC; 2010.
10. Balkrishnan R. Predictors of medication adherence in the elderly. *Clin Ther.* 1998;20(4):764-771.
11. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *J Gen Intern Med.* 2004;19(6):638-645.
12. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical Care.* 2005;43(6):521-530.
13. Hauptman PJ. Medication adherence in heart failure. *Heart Fail Rev.* 2008;13(1):99-106.
14. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatric Services.* 2001;52(6):805-811.
15. Hassan M, Lage MJ. Risk of rehospitalization among bipolar disorder patients who are nonadherent to antipsychotic therapy after hospital discharge. *Am J Health-Syst Pharm.* 2009;66(4):358-365.
16. Peterson A, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health-Syst Pharm.* 2003;60(7):657-665.
17. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence in chronic treatment: a review of the literature. *J Behav Med.* 2008;31(3):213-224.
18. Raboud J, Walmsley S, Copper C, et al. Once daily dosing improves adherence to antiretroviral therapy. *AIDS Behav.* 2011;15(7):1397-1409.
19. Boswoth HB. Medication adherence. In: *Improving Patient Treatment Adherence.* Springer Science+Business Media; 2010.
20. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of anthihypertensive agents. *Hypertension.* 2010;55(2):399-407.
21. Mahtani KR, Heneghan CJ, Glasziou PP, et al. Reminder packaging for improving adherence to self-administered long-term medications. *The Cochrane Collaboration.* John Wiley & Sons; 2011.
22. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc.* 2011;86(4):304-314.
23. Clifford S, Barber N, Elliott R, Hartley E, Horne R. Patient-centered advice is effective in improving adherence to medicines. *Pharm World Sci.* 2006;28(3):165-170.
24. Elliott RA, Barber N, Clifford S, Horne R, Hartley E. The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medications. *Pharm World Sci.* 2008;30(1):17-23.
25. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical Care.* 2005;43(6):521-530. ajpb