Challenges for Improving Medication Adherence

Ross J. Simpson, Jr, MD, PhD

FOR CHRONIC MEDICAL CONDITIONS, SUCH AS HYPERcholesterolemia and hypertension, a wide and persistent separation exists between evidence-based recommendations and the actual care patients receive.[1] Reasons for this gap are not always clear, but some components are obvious, including failing to identify patients in need of treatment, not properly initiating treatment, failing to provide proper drugs at proper doses, and neglecting to involve the patient in the choices inherent in care. Lack of persistence with adherence to prescribed treatments is a critical part of the gap.[2] A sustained high level of adherence identifies a pattern of healthy behaviors[3,4] and allows medications shown to be effective in clinical trials to improve outcomes, but this is difficult to achieve with many chronic conditions. For instance, adherence rates to cholesterol-lowering drugs or antihypertension medications are poor.[5-8]

Despite its importance, adherence to therapy is an individual patient behavior that is difficult to objectively measure, monitor, and improve. Patient characteristics that may lead to poor adherence include advanced age, cognitive impairment, and depression as well as attitudes and beliefs about the importance of the medication, the disease being treated, and the potential for adverse effects. Barriers to target for optimal adherence include adverse effects, polypharmacy, frequent (more than once daily) dosing, and high costs. Health care systems and clinician barriers include insufficient access to physicians, lack of trust between clinician and patient, and in some cases, physicians' negative attitudes and inadequate knowledge about the disease and value of guideline-recommended care.[9,10] Due to this complexity, improving adherence has been difficult to study and adherence rates have been refractory to simple interventions. Successful interventions are often labor intensive and multilayered. They often show limited efficacy[11] and generally target only one disease or risk factor.

Interventions that successfully improve adherence generally involve patient education and structural support such as patient reminders, more frequent clinic visits, or telephone calls from staff or physicians. Attempts are often made to simplify the patient's drug regimen by reducing the number of pills consumed per day and by reducing medication costs.[7-9] Pharmacists are often involved in assessing adherence and offering advice to physicians about simplifying and improving drug regimens.[12-16] Direct counseling of patients by pharmacists may be particularly promising because of pharmacists' specialized training and knowledge of medications and availability to patients.

In this issue of *JAMA*, Lee and colleagues[17] report the results of a pharmacy care program designed to improve medication adherence for patients with multiple chronic medical conditions, including hypertension and elevated cholesterol levels. The study focused on elderly patients who were taking multiple medications and therefore were at risk for poor adherence. They received care at a military hospital and its affiliated retirement home. The study consisted of a sequential observational and a subsequent randomized trial of a comprehensive pharmacy program with educational and structural components. The educational component included intensive and frequent counseling by a pharmacist. The structural component involved packaging of medications in blister packs that contained each patient's daily medications. After a 2-month observation period during which medication adherence was assessed by pill counts, 174 patients were enrolled in the 6-month intervention phase, during which they received pharmacist counseling and were given their medications in individual blister packs. Following this intervention phase, 159 of the patients were randomized by blocks (based on their observed adherence) either to continued use of the blister packs and ongoing counseling or to return to usual care without either continued counseling or availability of the dispensing blister packs.

After 6 months of the intervention, the percentage of patients classified as adherent increased significantly, from 61.2% at baseline to 96.9%, with associated modest reductions in systolic blood pressure and low-density lipoprotein (LDL) cholesterol. Six months after randomization, high adherence persisted (95.5%) in patients assigned to continuing counseling and the blister packs, whereas those in

See also p 2563.

Author Affiliation: Department of Medicine, University of North Carolina at Chapel Hill.
Corresponding Author: Ross J. Simpson, Jr, MD, PhD, Sixth Floor Burnett-Womack, 99 Manning Dr, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 (rsimpson@med.unc.edu).

the usual care group (ie, had the pharmacy care intervention removed) had substantial declines in medication adherence (69.1% at the end of 6 months). There were statistically significant but modest reductions in systolic blood pressure in the pharmacy care group compared with the control group, but no significant differences in LDL cholesterol levels.

This study has several strengths. The intervention was multilayered and included a strong educational component with baseline individual counseling and repeat face-to-face counseling by a pharmacist. The structural component of the intervention was imaginative, using prepackaged medications in daily blister packs. The intervention addressed at least 2 major and undertreated risk factors simultaneously: hypertension and elevated cholesterol levels. The study also adds to current understanding of the reasons for poor rates of medication adherence in older adults. Even in this setting in which medications are free and medical care is accessible and of excellent quality, medication adherence is poor. The study supports the view that a multilayered intervention can improve medication adherence and underscores the value of pharmacists as key providers of patient counseling in correcting poor patient adherence. The interventions also are potentially generalizable. Despite some cost considerations, medication blister packs can be made for individual patients and pharmacists are available, skilled, and interested in providing specific counseling about drugs.

However, the study has several important limitations. A major concern is how well the results might apply to the general population of elderly patients. The study was conducted in a military-affiliated facility, in which medication costs should not have been a barrier to adherence, and involved an apparently homogeneous group of patients. Although detailed information about how the study sample differed from all the eligible patients is not reported, only 8 of 208 eligible patients who were approached for consent refused to participate, suggesting either a remarkably high success rate at recruitment or preselection of potentially eligible patients. Accordingly, the findings may not apply to more representative patient populations, in which cost considerations, cultural issues, and more extensive or more varied disease burden are prevalent.

Despite the observed improvements in adherence, the intervention also has some weaknesses. The intervention does not seem to be guided by a specific behavioral model. In addition, counseling seemed particularly intense and time consuming, and the individual components of the counseling cannot be separated out and their relative value assessed. Likewise, the benefits of the major components of the intervention cannot be disentangled. For instance, it is not clear whether pharmacist involvement, blister packs, or both together were most important.

A more important concern is that the intervention is not simply a combination of pharmacist counseling and blister packs. Because the usual care group was the reference group, the 2 groups in the randomized trial phase of the study had different levels of observation and different frequency of visits to the health facility after randomization, and patients in the usual care group had an intervention that they had been receiving for 6 months removed. This design feature is unusual in comparative clinical trials, in which interventions under study are usually initiated in one group and compared with controls in another group who do not receive the intervention, rather than having the control based on withdrawal of an intervention. Patients in the intervention group were observed more often and with greater intensity than those in the usual care group, thereby introducing a potential observation bias that favored the intervention group, especially because adherence is a behavior and observing a behavior influences the behavior.[18] Controlling for this bias is critical and can be accomplished by masking patients to the intervention or if masking is not feasible, by balancing the measurements and intensity of interaction and observation between the groups being compared. For example, having patients in the usual care group visit the facility and meet with a physical therapist with the same frequency as those in the intervention group had met with the pharmacist might have helped to control for the frequency and intensity of experimental observation.

Despite these concerns, the study by Lee and colleagues[17] adds important information about improving medication adherence in elderly patients and also highlights the challenges inherent in designing and conducting high-quality research in this critically important area. Multifaceted interventions that incorporate structural and counseling components and include appropriately skilled and motivated pharmacists appear useful to promote medication adherence and persistence. Future studies are needed to confirm that interventions incorporating these components will result in increased and sustained patient adherence and, better yet, will improve outcomes.

Published Online: November 13, 2006 (doi:10.1001/jama.296.21.jed60074).
Financial Disclosures: Dr Simpson reports that he has served as a consultant to and receives honoraria from Merck, Schering-Plough, and Pfizer; received research grants from Merck and Schering-Plough; and served as a consultant to GlaxoSmithKline and Immtech.

REFERENCES

1. Pearson T, Kopin L. Bridging the treatment gap: improving compliance with lipid-modifying agents and therapeutic lifestyle changes. *Prev Cardiol*. 2003;6:204-211.
2. O'Connor PJ. Improving medication adherence. *Arch Intern Med*. 2006;166:1802-1804.
3. Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomized, controlled clinical trial. *Lancet*. 2005;366:2005-2011.
4. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*. 2006;333:15. doi:10.1136/bmj.38875.675486.
5. Di Martino M, Degli Esposito L, Ruffo P, et al. Underuse of lipid-lowering drugs and factors associated with poor adherence: a real practice analysis in Italy. *Eur J Clin Pharmacol*. 2005;61:225-230.
6. Foley KA, Denke MA, Kamal-Bahl S, et al. The impact of physician attitudes

and beliefs on treatment decisions in lipid therapy in high risk patients. *Med Care*. 2006;44:421-428.
7. Roumie CL, Elasy TA, Greevy R, et al. Improving blood pressure control through provider education, provider alerts, and patient education. *Ann Intern Med*. 2006; 145:165-175.
8. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment. *JAMA*. 2002;288:2880-2883.
9. Petrilla AA, Benner JS, Battleman DS, Tierce JC, Hazard EH. Evidence-based interventions to improve patient compliance with antihypertensive and lipid-lowering medications. *Int J Clin Pract*. 2005;59:1441-1451.
10. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353: 487-497.
11. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm*. 2003;60:657-665.
12. Ali F, Laurin MY, Lariviere C, Tremblay D, Cloutier D. The effect of pharmacist intervention and patient education on lipid-lowering medication compliance and plasma cholesterol levels. *Can J Clin Pharmacol*. 2003;10:101-106.
13. Tsuyuki RT, Johnson JA, Teo KK, et al. A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). *Arch Intern Med*. 2002;162: 1149-1155.
14. Tsuyuki RT, Olson KL, Dubyk AM, Schindel TJ, Johnson JA. Effect of community pharmacist intervention on cholesterol levels in patients at high risk of cardiovascular risk intervention by pharmacists (SCRIP-plus). *Am J Med*. 2004;116:130-133.
15. Lee SSCL, Cheung PYP, Chow MSSC. Benefits of individualized counseling by the pharmacist on the treatment outcomes of hyperlipidemia in Hong Kong. *J Clin Pharmacol*. 2004;44:632-639.
16. Rehring TF, Stolcpart RS, Sandhoff BG, Merenich JA, Hollis HW Jr. Effect of a clinical pharmacy service on lipid control in patients with peripheral arterial disease. *J Vasc Surg*. 2006;43:1205-1210.
17. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA*. 2006;296:2563-2571.
18. Delgado-Rodriguez M, Llorca J. Bias. *J Epidemiol Community Health*. 2004; 58:635-641.

Postpartum Depression
A Major Public Health Problem

Katherine L. Wisner, MD, MS
Christina Chambers, PhD, MPH
Dorothy K. Y. Sit, MD

POSTPARTUM PSYCHIATRIC DISORDERS, PARTICULARLY depression, have received increasing attention in the United States for several reasons. Postpartum depression is very common. One of 7 new mothers (14.5%) experience depressive episodes that impair maternal role function.[1] The neurobiology of women with postpartum mood instability appears differentially sensitive to the destabilizing effects of hormonal withdrawal at birth.[2] Coupled with entry of the newborn into the family, postpartum depression affects crucial infant and adult developmental processes. The disruption to the early mother-infant relationship contributes to short- and long-term adverse child outcomes.[3] The negative effects of maternal depression on children include an increased risk of impaired mental and motor development, difficult temperament, poor self-regulation, low self-esteem, and behavior problems.[4]

Postpartum psychosis has been associated with tragic outcomes, such as maternal suicide and infanticide.[5] As one example of a policy response to concern about postpartum disorders, legislation that mandates education and screening was enacted recently in New Jersey.[6] The Safe Motherhood Group, which included representatives from multiple agencies within the US Department of Health and Human Services, commissioned an evidence-based evaluation of data about perinatal depression that could be used to inform national policy. In response, the Agency for Healthcare Research and Quality (AHRQ) developed an evidence report.[1]

See also p 2582.

In the AHRQ report,[1] perinatal depression is defined as an episode of major or minor depression that occurs during pregnancy or the first 12 months after birth. The authors noted that the diagnosis and timing of perinatal episodes have not been consistently identified. Two definitional dimensions are relevant: diagnosis and time of onset. The term *with postpartum onset* is used in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.[7] The diagnosis must be either major depression, a mixed or manic episode of bipolar disorder, or brief psychotic disorder. The time criterion is within 4 weeks of birth. The *International Classification of Diseases, 10th Edition*[8] permits classification of mental disorders as associated with the puerperium if they begin within 6 weeks of birth and cannot be classified elsewhere. An international expert panel[9] recommended 3 months as the time frame for defining postpartum onset for a variety of diagnoses, based on the epidemiologic studies of Kendell and colleagues.[10-12] According to the AHRQ report,

> The specifics of the course of a depressive illness with onset during the perinatal period, including the severe physiologic and psychological challenges unique to this period that complicate the identification and management of perinatal depression, seem to suggest that this topic would have a substantial degree of high-quality research. We were surprised by the paucity of such evidence in this area.[1(p90)]

Author Affiliations: Departments of Psychiatry (Drs Wisner and Sit), Obstetrics and Gynecology and Reproductive Sciences (Dr Wisner), Epidemiology (Dr Wisner), and Women's Studies (Dr Wisner), Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pa; and Departments of Pediatrics and Family and Preventive Medicine, University of California, San Diego (Dr Chambers).
Corresponding Author: Katherine L. Wisner, MD, MS, Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, 3811 O'Hara St, Oxford 410, Pittsburgh, PA 15213 (WisnerKL@upmc.edu).