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Medication Adherence: Hope for Improvement?

In this issue of *Mayo Clinic Proceedings*, 2 important articles underscore the magnitude of the problem of medication nonadherence, one in the context of cardiovascular disease[1] and one more generally,[2] but also offer suggestions for improvement. The original research article by Dunlay et al[1] investigated the proportion of patients prescribed drugs for heart failure who did not adhere to the medication regimen and the factors underlying their poor adherence. Brown and Bussel[2] performed a systematic review of the literature to examine the origins of, and solutions to, poor medication adherence and explored the efforts of organizations such as the World Health Organization to address existing deficiencies. Beyond the clinical implications described in these articles, The New England Healthcare Institute has recently suggested that the economic consequences of medication nonadherence across all categories of care account for $290 billion of annual health care expenditures in the United States.[3] Given this problem's clinical and economic consequences, we must make progress sooner rather than later. Why have we not moved faster on medication adherence, which has been acknowledged as a problem in the literature for more than 3 decades? Can new techniques bring change faster? Can all stakeholders align around this issue and close these gaps in patient care?

Where Adherence Works

Incredibly high medication adherence, even for cardiovascular therapy, is achieved in the ecosystem where researchers evaluate experimental premarketed drugs, also known as *efficacy evaluation* settings. For example, the landmark 4S clinical trial of the lipid-lowering drug simvastatin prospectively studied 4444 patients newly starting this investigational drug vs placebo and followed up patients for an average of 5.4 years for major cardiovascular events and mortality. Astonishingly, 90% of patients were still receiving active therapy at the close of the trial.[4] Contrast those statistics to patients taking simvastatin in the post–product launch "real-world" community environment, in which nearly 50% of patients initiating lipid-lowering therapy had discontinued their medication completely at the end of just the first year of therapy.[1]

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Clearly, we are not experiencing remotely similar drug adherence in trial and "real world" settings, and therefore we cannot expect the same benefits to the general population as seen in the trial settings.

The Table illustrates some of the key differences between the ecosystem of *efficacy* and the real world experience of *effectiveness*. An important goal of our health care system and of all stakeholders must be to move the effectiveness paradigm closer to what is achievable in efficacy settings. From the Table, it appears that more intense and explicit patient education, incentives for health care professionals and patients, intensive and systematic medication monitoring, inclusion of monitoring by allied health care professionals, and the use of new technologies separate these environments and provide some additional means for improvement beyond the ideas suggested by Brown and Bussell.[2]

The Wired World of Medications: An Upside Opportunity

The only aspect of our health care system that is 100% wired on a national basis and interactive in a real-time environment is our outpatient system of pharmacy. Stimulated by the Omnibus Reconciliation Act (OBRA) of 1990,[5] which tied Medicaid pharmacy reimbursement to mandatory real-time drug-drug interaction evaluation, all US pharmacies (>60,000) became electronically wired and currently use the exact same data definitions and coding nomenclature to both send and receive interactive messages. For insured Americans, a prescription filled in Hawaii one day and another prescription filled in Minnesota the next day are electronically reconciled and systematically evaluated for drug-drug interactions, copays, and a variety of issues on-

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TABLE. **Characteristics of Medication Care in Efficacy vs Effectiveness Settings**

Characteristic	Efficacy	Effectiveness
Patients	Tight inclusion/exclusion criteria Few comorbid conditions	Broad patient populations Average number of comorbid conditions
Physicians	Academicians, opinion leaders	Community-based physicians
Incentives	Clinicians pay for recruitment and trial management Patients receive free care	Usual reimbursement per visit Copays, coinsurance
Protocol of care	Frequent, systematic visits with tight follow-up	Infrequent visits with limited systematic follow-up
Monitoring	Pill counts, outbound calls	Refill reminders from pharmacies
Technology	Electronic capture of self-reported diary entries with interactive outbound calls	Web-based tools
Information	Informed consent Explicit and extensive education regarding the risks and benefits of therapies	No informed consent Limited patient education
Care team beyond the physician	Routine study monitors and study nurses monitoring for confusion about the drug, adherence issues, and adverse effects	Pharmacists observing refill frequency

line and in real-time. Pharmacists regularly receive real-time messages on their computer screens and can discuss with patients or their clinicians the issue that is flagged, depending on its nature and level of importance, before even dispensing the second drug. In recent years, pharmacies have been using this same system increasingly to flag patients who are late to refill their prescriptions and then communicating with them or their health care professionals to ensure that any barriers to adherence are promptly identified and addressed.

The Medicare Improvements for Patients and Provider Act of 2008 was an important milestone legislation that initially provided financial incentives from Medicare Part B funds to physicians (2% of additional revenue from their annual Part B billing) to use electronic prescribing devices (for >80% of patients) in a real-time environment.[6] Like the OBRA legislation for pharmacies, this act will move us toward a national "wired" system of electronic prescribing, but this time the electronic and interactive data will be in physicians' hands. In the future, systematic online searches of patient databases, cross-linked to our already wired pharmacies, will likely allow physicians to receive a daily listing of their patients who have not refilled their medications. Clinicians or their office staff may then contact patients electronically or via telephone, which could help improve their medication adherence. Even while in the examining room, clinicians could use electronic methods to learn of actual refill behavior by their patients, a teachable moment for consultation. This type of scaleable solution is deeply warranted not only for eliminating errors due to misunderstanding handwritten prescriptions but also for alerting clinicians to adherence issues related to long-term drug therapy.

New Opportunities for Improving Adherence

A key finding in the article by Dunlay et al[1] was that economic concerns may prevent consistent medication adherence among patients with chronic heart failure. As noted in this study of patients treated in Rochester, MN, many more nonadherent patients report economic concerns as a key reason for skipping doses or stopping drugs altogether, whereas fewer adherent patients report having this issue. As substantially more small-molecule drugs lose patent protection and become generic, and as biosimilar drugs enter the marketplace in the next few years, medication choices that do not carry steep copays should become even more commonly prescribed, and thus the economic barriers could become less prominent. Additionally, value-based benefit designs are being developed and implemented by various payers (eg, employers and health insurance companies) to see whether dropping copays for drugs used to treat selected important chronic conditions may improve adherence and, if so, among whom.

The emerging science of pharmacogenomics offers another possibility to improve medication adherence as well as dosing itself. The recently completed Medco–Mayo Clinic study of warfarin pharmacogenomics showed that physicians changed dosing on the basis of test results, reducing subsequent hospitalizations.[7] Arming consumers with their genetic information may also provide a unique way to change behavior. As Anita Cosgrove, Director of Strategic Alliances at 23andme (Mountain View, CA), a firm specializing in providing access to genetic information, has suggested, "knowing your molecular identity is irresistible" (personal oral communication, February 14, 2011). Many studies are under way to determine whether patients would adhere to a prescribed therapy longer and more consistently if they knew they were at high risk of a disease or knew that a particular therapy had been shown to really work for them *on the basis of their specific genetics*. We are currently testing this hypothesis by providing free *KIF6* genetic tests to patients in whom statin therapy has been initiated. Recent reanalyses of 4 major cardiovascular trials suggest that the greatest benefit from statin therapy is among the 60% of

people who carry a particular genetic variant of this gene.[8-10] For example, in the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22) trial, carriers of this variant who were receiving treatment experienced more than a 40% decrease in coronary events compared with a nonsignificant 6% decrease among treated noncarriers.[8] Our ongoing study will compare statin adherence in those who learn about their carrier status vs those who do not.[11]

New sensor technologies offer additional amazing possibilities to improve patient adherence. One technology involves embedding a natural substance in pills that triggers an electric charge within the patient, which is then transmitted via the computer cloud to a cell phone that indicates exactly when a particular medication is swallowed (or not). This opens the way to engage patients, clinicians, and other caregivers in real-time medication monitoring. Early indications from pharmaceutical company–sponsored research suggest this may become a powerful new platform. Other technologies are focusing on timed alarms set inside the lids of medication bottles or even cell phone applications to remind patients when their drug is to be taken.

Health care systems would be wise to consider pay-for-performance techniques to provide an incentive to all stakeholders to work harder to track and improve adherence for important chronic clinical conditions. Certainly, changes to Medicare Part D (envisioned in the recently passed Patient Protection and Affordable Care Act of 2010) that reduce and close the coverage gap for Medicare beneficiaries (the so-called doughnut hole) are an obvious and warranted attempt by the government to remove that adherence barrier. Some disease-management programs already reward members with lowered insurance premiums if they control their risk factors, so it would seem reasonable to expect that similar incentives will be provided for patients who adhere to particular medications above a certain threshold.

Given that pharmaceutical companies have mastered adherence in the experimental setting, it is not surprising that they have recently stepped up efforts to support patients through various programs, such as the activation of hotlines to bolster adherence after a product launch. Additionally, new drugs are coming to the market with unique formulations that allow less frequent and/or verifiable dosing (eg, once-yearly injections) and thus will presumably foster improved adherence. This sort of administration can ensure the product is consumed or absorbed, and a tickler system can remind patients of the timing of their next administration. Other new methods include implantable drug-release devices with prolonged dosing intervals (eg, the implantable birth control products that are currently marketed) and skin patches that slowly release drugs (eg, to treat Alzheimer disease) and provide visible proof that the drug is being taken. Nanotechnology, which allows the delivery of injectable drugs in nonpainful ways (eg, through microneedles or even nanoneedle skin patches), is also a part of this equation.

The consequences of medication nonadherence are readily apparent. When possible, it is in the best interests of all stakeholders to close these gaps in health management and help patients better achieve the benefits of prescribed therapies. Advances on the technological and policy fronts as well as lessons learned from the efficacy environment can help improve the effectiveness of daily health care delivery to large, diverse populations of patients. Bringing about this needed change will require participation by all stakeholders, whether they are patients, clinicians, pharmaceutical companies, policy makers, health plan managers, pharmacy benefit managers, or payers. The challenge on a national level is to harness the best science and to finance and implement a systematic way to educate patients, monitor adherence and intervene when necessary, and measure improvement over time. The confluence of evolving health care policy, payer interest, electronic prescribing by clinicians, consumer empowerment, pharmaceutical company innovation, and systems integration offers hope that we will finally begin to make a dent in the problem of medication adherence in the coming years.

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1. Dunlay SM, Eveleth JM, Shah ND, McNallan SM, Roger VL. Medication adherence among community-dwelling patients with heart failure. *Mayo Clin Proc.* 2011;86(4):273-281.

2. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc*. 2011;86(4):304-314.

3. Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease. New England Healthcare Institute Web site. http://www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease. Accessed February 28, 2011.

4. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.

5. Omnibus Budget Reconciliation Act. Public Law No. 101-508, 104 Stat 1388 enacted 5 November 1990.

6. Electronic prescribing (eRx) incentive program. Centers for Medicare & Medicaid Services (CMS) Web site. https://www.cms.gov/ERXIncentive/. Accessed February 28, 2011.

7. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness Study). *J Am Coll Cardiol*. 2010;55(25):2804-2812.

8. Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. *J Am Coll Cardiol*. 2008;51:449-455.

9. Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary heart disease in 2 prospective trials: the CARE and WOSCOPS trials. *J Am Coll Cardiol*. 2008;51:435-443.

10. Iakoubova OA, Robertson M, Tong CH, et al. KIF6 Trp719Arg polymorphism and effect of statin therapy in elderly patients: results from the PROSPER study. *Eur J Cardiovasc Prev Rehabil*. 2010;17(4):455-461.

11. Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS). Clinical Trials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT01068834?term=akrobats&rank=1. Accessed February 28, 2011.