Helping Patients Follow Prescribed Treatment
Clinical Applications

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Low adherence to prescribed medical regimens is a ubiquitous problem. Typical adherence rates are about 50% for medications and are much lower for lifestyle prescriptions and other more behaviorally demanding regimens. In addition, many patients with medical problems do not seek care or drop out of care prematurely. Although accurate measures of low adherence are lacking for many regimens, simple measures, such as directly asking patients and watching for appointment nonattendance and treatment nonresponse, will detect most problems. For short-term regimens (≤2 weeks), adherence to medications is readily achieved by giving clear instructions. On the other hand, improving adherence to long-term regimens requires combinations of information about the regimen, counseling about the importance of adherence and how to organize medication taking, reminders about appointments and adherence, rewards and recognition for the patient's efforts to follow the regimen, and enlisting social support from family and friends. Successful interventions for long-term regimens are all labor-intensive but ultimately can be cost-effective.

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MEDICAL RESEARCH DURing the past few decades has produced efficacious treatments for many health care disorders and, increasingly, these treatments can be self-administered. Unfortunately, low adherence can undermine the effectiveness of care at many steps in the process.[1] For example, 49% of patients who demonstrated elevated blood pressure on community screening failed to follow through with a referral for follow-up assessment. Of those who enter the medical care system, more than a third may drop out, especially during the first few months. While in care, the average consumption of medication has been found to be about 50%, with a very wide range from none to substantially more than 100%. Compliance with instructions to lose weight or stop smoking is substantially lower, with long-term success rates less than 10%.[2]

One of the important difficulties in managing low adherence is lack of accurate and affordable measures. Clinicians must frequently rely on their own judgment but unfortunately demonstrate no better than chance accuracy in predicting the adherence of their patients,[3] even among patients for whom they feel confident about their predictions.[4] A pragmatic approach to measuring adherence is presented in BOX 1. Based on a systematic review of studies adherence measures,[3] asking nonresponders about their adherence will detect more than 50% of those with low adherence, with a specificity of 87%. Even when patients indicate that they have not taken all their medications as prescribed, their estimates usually substantially overestimate their actual adherence. Thus, the key validated question is "Have you missed any pills in the past week?" and any indication of having missed 1 or more pills signals a problem with low adherence. Overestimation of adherence by patients is difficult to study and is presently poorly documented. Reasons for overestimation could include difficulty recalling the details of medication taking, attempting to please practitioners or to avoid confrontation, or a combination of these factors. Other practical measures to assess adherence include watching for those who do not respond to increments in treatment intensity and patients who fail to attend appointments.

More objective measures of compliance can also be of use when available. For example, drug levels in body fluids (blood, saliva, urine) can help in assessing patient compliance (eg, serum digoxin levels and levels of anti-

See also p 2868.

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epilepsy medications), but these measurements are affected by dose and timing and can be misleading if the patient takes the dose only just before clinic visits. Furthermore, drug levels are often not routinely available for most medications. Pharmacy records can also be helpful in a health care system that includes integrated pharmacy services, provided that patients use only the pharmacy where monitoring occurs and do not stockpile drugs or give them to others. Finally, medication monitors can provide both frequency and patterns of use but to date have been too expensive and cumbersome for routine practice.

Several ethical issues must be addressed when considering and attempting to improve patient adherence.[5,6] First, before adherence becomes a legitimate concern, the clinical diagnosis must be correctly established. Second, the treatment being prescribed must be of known efficacy for this diagnosis and appropriate for the patient's circumstances. Third, methods for helping the patient to follow the treatment must be of established effectiveness (or otherwise will be a waste of resources, at best). Fourth, the patient's right to refuse treatment must be respected at all times. Attempts to coerce the patient to adhere by, for example, threatening dire outcomes from poor control of the disorder, are doubly unethical because negative reinforcement has not been shown to work any better than positive reinforcement and because some patients with high anxiety levels simply withdraw from care when threatened.[7]

Our recommendations for assisting patients to follow prescribed medical regimens are based on the best evidence available from randomized controlled trials of adherence interventions.[8] In the Scientific Review,[8] so few studies of short courses of treatment reported on clinical outcomes that randomized trials were added in which only adherence was measured.[9-11] Interventions are summarized in BOX 2 and BOX 3 and we discuss their applications in the context of questions that commonly arise in practice about adherence.

Is This Patient Following the Treatment as Prescribed? If Not, What Can I Do About It?

A 57-year-old obese, white, male smoker with type 2 diabetes and mild proteinuria, dyslipidemia, hypertension, and ischemic heart disease (prior myocardial infarction) attends a routine follow-up. He complains of some urinary frequency, including nocturia 2 to 3 times a night, but otherwise feels well. He provides a record of 11 self-assessed blood glucose readings in the past month, with a range of 90 to 216 mg/dL (5-12 mmol/L).

His current regimen consists of a calorie-fat-salt reduced diet, regular exercise, self-monitoring of blood glucose and blood pressure, 50 mg of atenolol twice daily, 25 mg of hydrochlorothiazide daily, 20 mg of simvastatin at night, 10 mg of glyburide twice daily, and a request that he stop smoking. He has not been able to lose weight despite attempting to follow a calorie-restricted diet and walking about half a mile once or twice a week. When asked whether he had missed taking any of his medications during the past week, he indicated that he "might have missed 1 or 2 on Saturday night when he was out at a movie."

On examination, he weighs 109 kg, has a blood pressure of 172/98 mm Hg, scattered dot hemorrhages on funduscopy, and decreased sensation in his feet on monofilament testing. Incidental inquiry during the examination revealed that he had started drinking cranberry juice, 2 to 3 L per day, after seeing an infomercial claiming that it is a vascular cleanser with antioxidants that can prevent heart disease. The patient's blood glucose meter is checked at the visit and found to be giving falsely low readings. Recent tests include hemoglobin A_{1c} of 12.3%, total cholesterol of 264 mg/dL (6.84 mmol/L) and triglycerides of 486 mg/dL (5.5 mmol/L), serum creatinine of 1.4 mg/dL (124 µmol/L), and a urinary microal-

Box 1. Measures of Adherence*

Practical methods (apply to all patients)
- Asking the patient
- Treatment response
- Attendance at appointments

If applicable
- Drug levels
- Pharmacy refills
- Medication event monitors

*Based on Stephenson et al.[3]

Box 2. Increasing Adherence With Short-term Treatments*

- Counseling about the importance of adherence
- Written instructions about taking medicines
- Reminder packaging (eg, calendar packs, dosettes)

*Based on references 8-11.

Box 3. Increasing Adherence With Long-term Treatments*

Combinations of
- Instruction and instructional materials
- Simplifying the regimen (eg, less frequent dosing, controlled release dosage forms)
- Counseling about the regimen
- Support group sessions
- Reminders (manual and computer) for medications and appointments
- Cuing medications to daily events
- Reinforcement and rewards (eg, explicitly acknowledging the patient's efforts to adhere)
- Self-monitoring with regular physician review and reinforcement
- Involving family members and significant others

*Based on McDonald et al.[8]

bumin/creatinine ratio of 61.9 mg/g (7 mg/mmol) (normal <26.8 mg/g [<3 mg/mmol]).

This patient's difficulties include low adherence to his prescribed diet, exercise regimen, antismoking advice, and medications. Furthermore, he will need additional treatments for the problems detected on examination, namely retinopathy and nephropathy, thereby, adding to his adherence burden. Indications of his low adherence include his persistently high weight, self-report of little regular exercise, admission of missing pills, a discrepancy between his self-reported blood glucose and the hemoglobin A_{1c}, as well as infrequent self-reported glucose monitoring. It is essential to recognize that a self-report indicating missing any medications is consistent with a medication adherence rate of less than 60%.[3]

It is important to recognize that he has been prescribed a very complicated regimen of diet, exercise, smoking cessation, and medications, including 8 pills per day. Although this type of regimen is both consistent with practice guidelines and commonplace to prescribe, few are able to follow such a regimen closely for any length of time. The patient has also been treating himself with cranberry juice, which has a substantial glucose content that he indicates he was not aware of (despite having been given dietary advice about checking the nature and calorie content of all foods ingested).

The first step is to eliminate the factors that are aggravating his diabetes. The cranberry juice should be stopped if he will agree and the glyburide, which is associated with weight gain, should be switched to metformin, which is not.[12] Ramipril, an angiotensin-converting enzyme inhibitor that reduces cardiovascular risk and incipient nephropathy, and also lowers blood pressure and blood glucose,[13] should be substituted for the thiazide diuretic, which can increase insulin resistance. As a matter of priority, diet, exercise, and smoking cessation can be deferred until the blood glucose is brought under control. Managing the dyslipidemia may also be deferred for now; the lipids may come under control as the blood glucose improves. Finally, the patient's blood glucose meter should be replaced. Because so many changes are being made to the patient's regimen, written instructions of what to start and what to stop should be provided. The patient should be requested to take all medications as prescribed, to the best of his ability, during the next 2 weeks, and a follow-up visit should be scheduled at that time for a review and reassessment.

This approach is insufficient compared with the guideline of making diet and exercise the foundation for diabetes control.[14,15] Rather, it follows the evidence from observational studies of nonadherence that show that the complexity and behavioral demand of the regimen are strong determinants of low adherence[2] and that simplification of the regimen is often needed to achieve adequate adherence. Furthermore, it follows the evidence for improving adherence both for short periods (Box 2),[8-11] namely giving clear instructions about regimens, and for longer periods (Box 3),[8] namely reinforcing the importance of high adherence, negotiating priorities with the patient, and providing an opportunity for follow-up reinforcement sooner rather than later. Once the medication regimen is addressed, fine-tuning can begin on the other aspects of the regimen. If necessary, follow-up can be shared with nurses, specialists, pharmacists, or even family members, if the patient and his significant others are willing. As a matter of urgency, an eye examination by an ophthalmologist should also be arranged.

This patient's case also illustrates 2 problems that are not due to low adherence with prescribed treatments but that can still adversely affect management. First, the patient has taken on a nonprescribed alternative treatment, copious amounts of cranberry juice, in the unfounded belief that this will reduce his cardiovascular risk. In fact, the sugar in the cranberry juice will materially affect his blood glucose and weight control. Second, home monitoring (of blood pressure and blood glucose in this case) can be a useful part of an effective adherence intervention but also can be inaccurate and misleading through faulty equipment, faulty technique, and falsified reports.

Has This Patient Dropped Out of Care?

A 47-year-old woman with hypertension misses her scheduled appointment without canceling it. Previously, she has shown regular attendance but has complained from time to time about adverse effects from her medication.

In the midst of a busy clinic, this event can easily go unnoticed or may even be seen as transient relief from the demands of the day. If noticed, one can speculate that the patient forgot the appointment, had other commitments, does not feel that a follow-up is needed at this time, has decided to discontinue care, or is pursuing a competitor's practice. Missing appointments is correlated with lower adherence rates to prescribed regimens[16,17] and is the first signal of dropping out of care entirely, the most severe form of nonadherence, and thus should be followed up by the clinic if ongoing care is clinically indicated.

A systematic review[18] indicates that this problem is relatively easily overcome by appointment reminders by letter or telephone, by contracting with patients to keep appointments, and by contacting patients immediately if appointments are missed. Calling patients who miss appointments is logically the most important method of helping patients adhere to prescribed regimens, because reminding or recalling patients is effective and relatively inexpensive[13] and dropping out of care results in zero adherence to prescribed medications. However, the effect on medication adherence of keeping patients from dropping out of care has not been isolated from other interventions in a controlled trial.

Conclusions

To reap the benefits of modern medical therapies, better, more effective, and

more efficient interventions for helping people to follow regimens are needed. For long-term self-administered medications, the methods of helping patients adhere to regimens that have been tested and found successful to date typically have been complex and labor-intensive, and have modest effects at best on adherence and inconsistent effects on clinical outcomes. Perhaps researchers and manufacturers should rethink the current methods of product development that typically result in pills that must be taken several times per day for as long as the medical condition persists.

Nevertheless, a combination of keeping the regimen as simple as possible, negotiating priorities with the patient, providing clear instructions, reminding patients about appointments, monitoring adherence with treatments and appointments, calling patients who have missed appointments for needed follow-up care, and reinforcing the importance of high adherence at each visit will provide practical and effective help for many patients to follow their regimens. If resources permit, one can add counseling and continuing support from other health care professionals. If needed, and with the patient's permission, the help of family members and significant others can be sought. In our view, success in reaching treatment goals, rather than the extent to which the regimen matches recommended care guidelines, should be the arbiter of whether the approach is helping the individual patient.

Of importance, detriment also can arise from interventions that enhance adherence. First, the regimen can be oversimplified. For example, Girvin et al[19] compared 20 mg of enalapril once daily with 10 mg of enalapril twice daily for high blood pressure and found that overall medication adherence was improved, but blood pressure was slightly better controlled on the twice daily group, presumably because the percentage of days when no doses were taken was also significantly higher in the once daily regimen. Second, patient instruction does not have a lasting effect on long-term adherence[8] and can have adverse effects especially if it emphasizes the adverse consequences on disease outcomes of failing to adhere.[7] Finally, attempting to enhance adherence can be expensive, especially in personnel costs. Fortunately, at least 1 trial[20] has shown that adherence intervention was cost-effective.

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