REVIEW ARTICLE

DRUG THERAPY

Adherence to Medication

Lars Osterberg, M.D., and Terrence Blaschke, M.D.

Drugs don't work in patients who don't take them.

— C. Everett Koop, M.D.

From the General Medicine Division, Veterans Affairs Palo Alto Health Care System, Palo Alto (L.O.); and the Division of Clinical Pharmacology, Stanford University Medical Center, Stanford (T.B.) — both in California. Address reprint requests to Dr. Osterberg at the VA Palo Alto Health Care System, 3801 Miranda Ave., Palo Alto, CA 94304, or at larso@stanford.edu.

N Engl J Med 2005;353:487-97.

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. The word "adherence" is preferred by many health care providers, because "compliance" suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician. Both terms are imperfect and uninformative descriptions of medication-taking behavior. Unfortunately, applying these terms to patients who do not consume every pill at the desired time can stigmatize these patients in their future relationships with health care providers. The language used to describe how patients take their medications needs to be reassessed, but these terms are still commonly used.[1] Regardless of which word is preferred, it is clear that the full benefit of the many effective medications that are available will be achieved only if patients follow prescribed treatment regimens reasonably closely.

Rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period. Some investigators have further refined the definition of adherence to include data on dose taking (taking the prescribed number of pills each day) and the timing of doses (taking pills within a prescribed period). Adherence rates are typically higher among patients with acute conditions, as compared with those with chronic conditions; persistence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy.[2-4] For example, approximately half of patients receiving hydroxymethylglutaryl–coenzyme A reductase inhibitor therapy will discontinue their medication within six months of starting the therapy.[5]

The average rates of adherence in clinical trials can be remarkably high, owing to the attention study patients receive and to selection of the patients, yet even clinical trials report average adherence rates of only 43 to 78 percent among patients receiving treatment for chronic conditions.[3,6,7] There is no consensual standard for what constitutes adequate adherence. Some trials consider rates of greater than 80 percent to be acceptable, whereas others consider rates of greater than 95 percent to be mandatory for adequate adherence, particularly among patients with serious conditions such as infection with the human immunodeficiency virus (HIV). Although data on adherence are often reported as dichotomous variables (adherence vs. nonadherence), adherence can vary along a continuum from 0 to more than 100 percent, since patients sometimes take more than the prescribed amount of medication.[8-10]

The ability of physicians to recognize nonadherence is poor, and interventions to improve adherence have had mixed results. Furthermore, successful interventions gener-

ally are substantially complex and costly.[11-14] Poor adherence to medication regimens accounts for substantial worsening of disease, death, and increased health care costs in the United States.[15-19] Of all medication-related hospital admissions in the United States, 33 to 69 percent are due to poor medication adherence, with a resultant cost of approximately $100 billion a year.[15,17,20,21] Participants in clinical trials who do not follow medication regimens or placebo regimens have a poorer prognosis than subjects in the respective groups who do.[22-24] Adherence to medication and placebo regimens, therefore, both predict better outcomes, and collecting adherence data from subjects is now considered an essential part of clinical trials.[25,26] Given the magnitude and importance of poor adherence to medication regimens, the World Health Organization has published an evidence-based guide for clinicians, health care managers, and policymakers to improve strategies of medication adherence.[27]

MEASURES OF ADHERENCE

Adherence to medication regimens has been monitored since the time of Hippocrates, when the effects of various potions were recorded with notations of whether the patient had taken them or not. Even today, patients' self-reports can simply and effectively measure adherence.[28,29] The methods available for measuring adherence can be broken down into direct and indirect methods of measurement (Table 1). Each method has advantages and disadvantages, and no method is considered the gold standard.[30,31]

Directly observed therapy, measurement of concentrations of a drug or its metabolite in blood or urine, and detection or measurement in blood of a biologic marker added to the drug formulation are examples of direct methods of measures of adherence. Direct approaches are expensive, burdensome to the health care provider, and susceptible to distortion by the patient. However, for some drugs, measuring these levels is a good and commonly used means of assessing adherence. For instance, the serum concentration of antiepileptic drugs such as phenytoin or valproic acid will probably reflect adherence to regimens with these medications, and subtherapeutic levels will probably reflect poor adherence or suboptimal dose strengths.

Indirect methods of measurement of adherence include asking the patient about how easy it is for him or her to take prescribed medication, assessing clinical response, performing pill counts, ascertaining rates of refilling prescriptions, collecting patient questionnaires, using electronic medication monitors, measuring physiologic markers, asking the patient to keep a medication diary, and assessing children's adherence by asking the help of a caregiver, school nurse, or teacher. Questioning the patient (or using a questionnaire), patient diaries, and assessment of clinical response are all methods that are relatively easy to use, but questioning the patient can be susceptible to misrepresentation and tends to result in the health care provider's overestimating the patient's adherence.

The use of a patient's clinical response as a measure is confounded by many factors other than adherence to a medication regimen that can account for clinical outcome. The most common method used to measure adherence, other than patient questioning, has been pill counts (i.e., counting the number of pills that remain in the patient's medication bottles or vials). Although the simplicity and empiric nature of this method are attractive to many investigators, the method is subject to many problems, because patients can switch medicines between bottles and may discard pills before visits in order to appear to be following the regimen. For these reasons, pill counts should not be assumed to be a good measure of adherence.[8,9,32] In addition, this method provides no information on other aspects of taking medications, such as dose timing and drug holidays (i.e., omission of medication on three or more sequential days), both of which may be important in determining clinical outcomes.

Rates of refilling prescriptions are an accurate measure of overall adherence in a closed pharmacy system (e.g., health maintenance organizations, the Department of Veterans Affairs Health Care System, or countries with universal drug coverage), provided that the refills are measured at several points in time.[33-35] A medical system that uses electronic medical records and a closed pharmacy can provide the clinician or research scientist with readily available objective information on rates of refilling prescriptions that can be used to assess whether a patient is adhering to the regimen and to corroborate the patient's responses to direct questions or on questionnaires.

Electronic monitors capable of recording and stamping the time of opening bottles, dispensing drops (as in the case of glaucoma), or activating a

Table 1. Methods of Measuring Adherence.

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

canister (as in the case of asthma) on multiple occasions have been used for approximately 30 years.[32,36-38] Rather than providing weekly or monthly averages, these devices provide precise and detailed insights into patients' behavior in taking medication, but they are still indirect methods of measuring adherence; they do not document whether the patient actually ingested the correct drug or correct dose. Patients may open a container and not take the medication, take the wrong amount of medication, or invalidate the data by placing the medication into another container or taking multiple doses out of the container at the same time. The cost of electronic monitoring is not covered by insurance, and thus these devices are not in routine use. However, this approach provides the most accurate and valuable data on adherence in difficult clinical situations and in the setting of clinical trials and adherence research[10,39] and has advanced our knowledge of medication-taking behavior.[40] Although certain methods of measuring adherence may be preferred in specific clinical or research settings, a combination of measures maximizes accuracy.[10,41,42]

EPIDEMIOLOGY OF MEDICATION-TAKING BEHAVIOR

Electronic medication-monitoring devices have provided very detailed information about the patterns of medication-taking behavior. Most deviations in medication taking occur as omissions of doses (rather than additions) or delays in the timing of doses.[11,43] Patients commonly improve their medication-taking behavior in the 5 days before and after an appointment with the health care provider, as compared with 30 days after, in a phenomenon known as "white-coat adherence."[44,45] Stud-

ies using these monitors have shown six general patterns of taking medication among patients treated for chronic illnesses who continue to take their medications. Approximately one sixth come close to perfect adherence to a regimen; one sixth take nearly all doses, but with some timing irregularity; one sixth miss an occasional single day's dose and have some timing inconsistency; one sixth take drug holidays three to four times a year, with occasional omissions of doses; one sixth have a drug holiday monthly or more often, with frequent omissions of doses; and one sixth take few or no doses while giving the impression of good adherence.[40,46]

Simple dosing (one pill, once daily) helps to maximize adherence, particularly when combined with frequent reinforcing visits, despite the fact that 10 to 40 percent of patients taking these simple regimens continue to have imperfect dosing.[47,48] In a large systematic review of 76 trials in which electronic monitors were used, Claxton and colleagues[7] found that adherence was inversely proportional to frequency of dose (Fig. 1), and patients taking medication on a schedule of four times daily achieved average adherence rates of about 50 percent (range, 31 to 71 percent).

IDENTIFYING POOR ADHERENCE

Indicators of poor adherence to a medication regimen are a useful resource for physicians to help identify patients who are most in need of interventions to improve adherence.[5,49,50] Table 2 lists major predictors associated with poor adherence. Race, sex, and socioeconomic status have not been consistently associated with levels of adherence.[59,61] When these predictors, listed in Table 2, are present, physicians should have a heightened awareness of the possibility of poor adherence, but even patients in whom these indicators are absent miss taking medications as prescribed. Thus, poor adherence should always be considered when a patient's condition is not responding to therapy.

The simplest and most practical suggestion for physicians is to ask patients nonjudgmentally how often they miss doses. Patients generally want to please their physicians and will often say what they think their doctor wants to hear. It can be reassuring to the patient when the physician tells them, "I know it must be difficult to take all your medications regularly. How often do you miss taking them?" This approach makes most patients feel comfortable in telling the truth and facilitates the identification of poor adherence. A patient who admits to poor adherence is generally being candid.[29,62] Patients should also be asked whether they are having any side effects of their medications, whether they know why they are taking their medications, and what the benefits of taking them are, since these questions can often expose poor adherence to a regimen.[63]

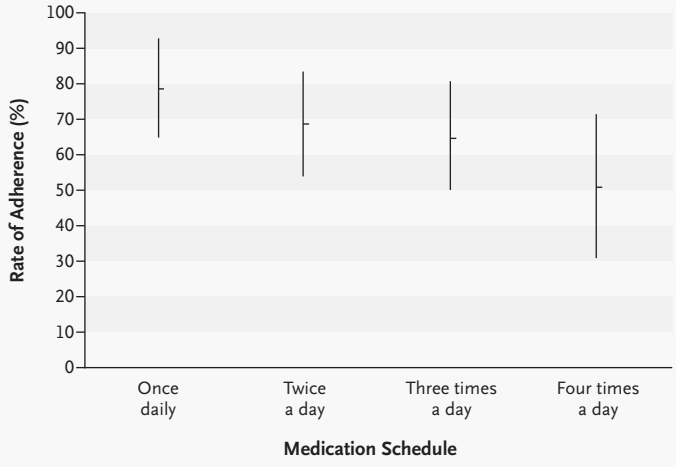

Figure 1. Adherence to Medication According to Frequency of Doses.
Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars). Data are from Claxton et al.[7]

BARRIERS TO ADHERENCE

Research on adherence has typically focused on the barriers patients face in taking their medications. Common barriers to adherence are under the patient's control, so that attention to them is a necessary and important step in improving adherence. In responses to a questionnaire, typical reasons cited by patients for not taking their medications included forgetfulness (30 percent), other priorities (16 percent), decision to omit doses (11 percent), lack of information (9 percent), and emotional factors (7 percent); 27 percent of the respondents did not provide a reason for poor adherence to a regimen.[64] Physicians contribute to patients' poor adherence by prescribing complex regimens, failing to explain the benefits and side effects of a medication adequately, not giving consideration to the patient's lifestyle or the cost of the medications, and having poor therapeutic relationships with their patients.[49,65-67]

More broadly, health care systems create barriers to adherence by limiting access to health care, using a restricted formulary, switching to a different formulary, and having prohibitively high costs for drugs, copayments, or both.[60,68,69] To improve the patient's ability to follow a medication regimen, all potential barriers to adherence need to be considered. An expanded view that takes into account factors under the patient's control as well as interactions between the patient and the health care provider and between the patient and the health care system will have the greatest effect on improving medication adherence (Fig. 2).[70,71]

INTERVENTIONS

Methods that can be used to improve adherence can be grouped into four general categories: patient education; improved dosing schedules; increased hours when the clinic is open (including evening hours), and therefore shorter wait times; and improved communication between physicians and patients. Educational interventions involving patients, their family members, or both can be effective in improving adherence.[72,73] Strategies to improve dosing schedules include the use of pillboxes to organize daily doses, simplifying the regimen to daily dosing, and cues to remind patients to take medications. Patients who miss appointments are often those who need the most help to improve their ability to adhere to a medication regimen; such patients will often benefit from assistance in clinic scheduling and what is called "cue-dose training" to optimize their adherence. Clinic-scheduling strategies to improve adherence include making follow-up visits convenient and efficient for the patient. Delays in seeing patients and problems with transportation and parking can undermine a patient's willingness to comply with a medication regimen and to keep follow-up appointments. Interventions that enlist ancillary health care providers such as pharmacists, behavioral specialists, and nursing staff can improve adherence.[12,74,75] Finally, enhancing communication between the physician and the patient is a key and effective strategy in boosting the patient's ability to follow a medication regimen.[11,18,76,77]

Most methods of improving adherence have involved combinations of behavioral interventions and reinforcements in addition to increasing the convenience of care, providing educational information about the patient's condition and the treatment, and other forms of supervision or attention.[12,78-80] Successful methods are complex and labor intensive, and innovative strategies will need to be developed that are practical for routine clinical use.[12] Given the many factors contributing to poor adherence to medication, a multifactorial approach is required, since a single approach will not be effective for all patients.[81,82] Table 3 lists some simple strategies for optimizing a patient's ability to follow a medication regimen.

Table 2. Major Predictors of Poor Adherence to Medication, According to Studies of Predictors.

Predictor	Study
Presence of psychological problems, particularly depression	van Servellen et al.,[51] Ammassari et al.,[52] Stilley et al.[53]
Presence of cognitive impairment	Stilley et al.,[53] Okuno et al.[54]
Treatment of asymptomatic disease	Sewitch et al.,[55]
Inadequate follow-up or discharge planning	Sewitch et al.,[55] Lacro et al.[56]
Side effects of medication	van Servellen et al.[51]
Patient's lack of belief in benefit of treatment	Okuno et al.,[54] Lacro et al.[56]
Patient's lack of insight into the illness	Lacro et al.,[56] Perkins[57]
Poor provider–patient relationship	Okuno et al.,[54] Lacro et al.[56]
Presence of barriers to care or medications	van Servellen et al.,[51] Perkins[57]
Missed appointments	van Servellen et al.,[51] Farley et al.[58]
Complexity of treatment	Ammassari et al.[52]
Cost of medication, copayment, or both	Balkrishnan,[59] Ellis et al.[60]

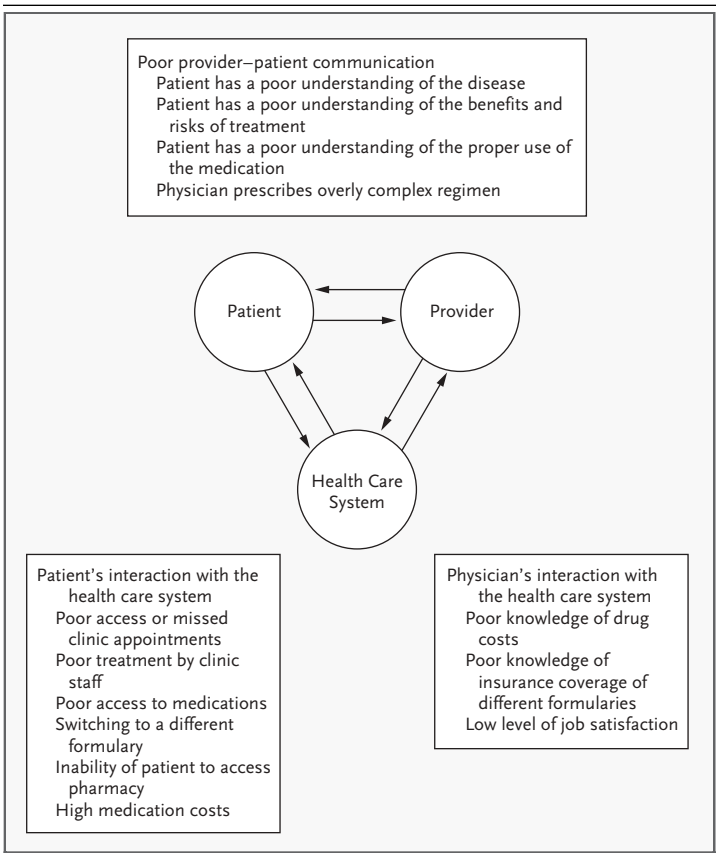

Figure 2. Barriers to Adherence.

The interactions among the patient, health care provider, and health care system depicted are those that can have a negative effect on the patient's ability to follow a medication regimen.

EXAMPLES OF CHALLENGES TO ADHERENCE

HIV INFECTION

In the treatment of patients with HIV infection or the acquired immunodeficiency syndrome, it is essential to achieve more than 95 percent adherence to highly active antiretroviral therapy (HAART) in order to suppress viral replication and avoid the emergence of resistance.[84,85] Achieving such high rates of adherence is very challenging to such patients, because their regimens include multiple, often expensive medications that have complex dosing schedules and may cause food interactions and side effects that result in poor tolerability. In addition, lifestyle factors and issues in the patient–provider relationship may make adherence difficult.[85]

Promising strategies for improving adherence to HAART that have been studied in randomized clinical trials include pharmacist-led individualized interventions, cognitive–behavioral educational interventions based on self-efficacy theory, and cue-dose training in combination with monetary reinforcement.[75,79] Cognitive–behavioral approaches have resulted in more than 90 percent of patients achieving 95 percent adherence, but these approaches require considerable resources, and adherence is typically not sustained after the intervention is withdrawn.[86,87] Federally funded trials of strategies to improve patients' ability to follow treatment regimens are ongoing, including the use of handheld devices, two-way pagers, medication vials equipped with alarms, and the enhancement of social and emotional support.[75]

HYPERTENSION

Consistent control of blood pressure requires that patients with hypertension follow medication and dietary regimens. However, antihypertensive therapy may have untoward side effects and result in little symptomatic relief, since hypertension often causes no symptoms. No matter how effectively the clinician communicates the benefits of antihypertensive therapy, patients are still ultimately responsible for taking their medications. Since adherence is enhanced when patients are involved in medical decisions about their care and in monitoring their care, the traditional model of the authoritarian provider should be replaced by the more useful dynamic of shared decision making by the health care provider and the patient.[78,88,89] The patient must actively participate in the selection and adjustment of drug treatment and in changes in lifestyle in order to maximize the usefulness of the therapeutic regimen. When feasible, self-monitoring of blood pressure can also enhance adherence.[78,90] Simplifying instructions to the patient and medication schedules is essential, and minimizing the total number of daily doses has been found to be more important in promoting adherence than minimizing the total number of medications.[48,91]

When inadequate adherence to medication has been identified and the available strategies for improving adherence have not achieved the target level of blood pressure, selecting "more forgiving" antihypertensive agents that either do not depend on half-life or have a longer half-life — drugs whose efficacy will not be affected by delayed or missed doses — will probably help to maintain a more stable blood pressure, despite imperfect adher-

Table 3. Strategies for Improving Adherence to a Medication Regimen.*

Identify poor adherence
Look for markers of nonadherence: missed appointments ("no-shows"), lack of response to medication, missed refills
Ask about barriers to adherence without being confrontational
Emphasize the value of the regimen and the effect of adherence
Elicit patient's feelings about his or her ability to follow the regimen, and if necessary, design supports to promote adherence
Provide simple, clear instructions and simplify the regimen as much as possible
Encourage the use of a medication-taking system
Listen to the patient, and customize the regimen in accordance with the patient's wishes
Obtain the help from family members, friends, and community services when needed
Reinforce desirable behavior and results when appropriate
Consider more "forgiving" medications when adherence appears unlikely†
Medications with long half-lives
Depot (extended-release) medications
Transdermal medications

* Information in this table was adapted from Osterberg and Rudd.[83]

† Forgiving medications are drugs whose efficacy will not be affected by delayed or missed doses.

ence.[40,46] When choosing among the major classes of antihypertensive agents — calcium-channel blockers, angiotensin-converting–enzyme inhibitors, angiotensin II type 1–receptor antagonists, alpha blockers, and direct vasodilators — the practitioner should consider selecting the agent with the longest half-life in each class. The antihypertensive effect of some drugs, such as the thiazide diuretics, is not related to plasma concentrations or drug half-life, and for these drugs, timing doses and short lapses in adherence are probably clinically unimportant. The most forgiving medications, such as the thiazides or modified formulations such as the transdermal clonidine patch, are more likely than less forgiving drugs to achieve an acceptable therapeutic outcome if they are otherwise tolerated.

Another strategy used by Burnier and colleagues[92] in a study of a highly selected group of patients with refractory hypertension was to monitor adherence objectively with the use of microelectronic monitors. In more than 30 percent of patients initially identified as having refractory hypertension, blood pressure became controlled merely as a result of monitoring, and an additional 20 percent of patients were identified as having lapsed adherence. Further control of blood pressure was achieved in a subgroup of subjects with poor adherence who agreed to continued monitoring and adjustment of their medications.[92]

PSYCHIATRIC ILLNESS

Patients with psychiatric illness typically have great difficulty following a medication regimen, but they also have the greatest potential for benefiting from adherence.[80,93] Half of patients with major depression for whom antidepressants are prescribed will not be taking the drugs three months after the initiation of therapy.[94] Rates of adherence among patients with schizophrenia are between 50 and 60 percent, and among those with bipolar affective disorder the rates are as low as 35 percent.[56,57,95] In a systematic review by Cramer and Rosenheck, among patients with physical disorders, the mean rate of medication adherence was 76 percent (range, 40 to 90 percent), whereas among those with psychoses the mean rate was 58 percent (range, 24 to 90 percent) and among those with depression the mean rate was 65 percent (range, 58 to 90 percent).[96]

A number of interventions to improve adherence to medication regimens among patients with psychiatric illnesses have been tried. Successful approaches include a combination of educational interventions (involving both patient and family), cognitive–supportive interventions, and the periodic use of reinforcement techniques.[73,89,97,98] Educational approaches appear to be most effective when they are combined with behavioral techniques and supportive services.[80] Reinforcements include a wide variety of techniques, such as monetary rewards or vouchers, frequent contact with the patient, and other types of personalized reminders.[79,99-101] Unfortunately, these interventions require trained personnel and repeated sessions if increased adherence is to be maintained; without these resources, adherence falls with time.

New antidepressant drugs and antipsychotic agents generally have fewer side effects than do older medications, and, consequently, their use results in reduced rates of discontinuation.[57,102-105] New agents may be preferred to older agents for a variety of reasons, but factors such as cost and effi-

cacy may be more important for some patients in achieving optimal adherence. Depot neuroleptic agents are often the treatment of choice for patients with schizophrenia who are not adhering to a regimen of oral agents.[106,107] The recent development of atypical depot neuroleptic drugs has the potential to improve adherence, since these agents combine the better efficacy and tolerability of the atypical agents with the reliability of the depot formulation.[106,108]

ILLNESS IN PEDIATRIC PATIENTS

Anyone who has seen a child with clenched teeth and a caregiver struggling desperately to administer the next dose of a medication understands the challenge of adherence to a medication regimen in the treatment of children. Achieving full adherence in pediatric patients requires not only the child's cooperation but also a devoted, persistent, and adherent parent or caregiver. Adolescent patients create even more challenges, given the unique developmental, psychosocial, and lifestyle issues implicit in adolescence.[109-112] Although the factors that contribute to poor adherence in children and adolescents are similar to those affecting adults, an added dimension of the situation is the involvement of patients' families.[113-115] Rates of adherence to medication regimens among children with chronic diseases are similar to those among adults with chronic diseases, averaging about 50 percent, with decrements in adherence occurring with time.[116-118]

Many interventions to improve adherence have been tried in pediatric patients but have had limited success. Most of the successful interventions in patients with chronic childhood illnesses have used behavioral interventions or a combination of behavioral and other interventions. The most common intervention is the token reinforcement system,[119-122] which involves motivating adherence by providing tokens or other rewards for taking medications successfully. The tokens can be used to obtain privileges, access to certain activities, or other rewards. Behavioral strategies often require resources and trained staff, yet simple reinforcement systems are practical for use by parents or other caregivers. The use of a more palatable medication than was initially prescribed has met with some success in improving adherence,[123,124] and the involvement of family members, schools, and other social supports are valuable strategies for maximizing children's ability to adhere to medication regimens.[113,115]

CONCLUSIONS

Poor adherence to medication regimens is common, contributing to substantial worsening of disease, death, and increased health care costs. Practitioners should always look for poor adherence and can enhance adherence by emphasizing the value of a patient's regimen, making the regimen simple, and customizing the regimen to the patient's lifestyle. Asking patients nonjudgmentally about medication-taking behavior is a practical strategy for identifying poor adherence. A collaborative approach to care augments adherence. Patients who have difficulty maintaining adequate adherence need more intensive strategies than do patients who have less difficulty with adherence, a more forgiving medication regimen, or both. Innovative methods of managing chronic diseases have had some success in improving adherence when a regimen has been difficult to follow.[99,125-127] New technologies such as reminders through cell phones and personal digital assistants and pillboxes with paging systems may be needed to help patients who have the most difficulty meeting the goals of a regimen.

Dr. Blaschke reports having received consulting fees from Jazz Pharmaceuticals, Portola Pharmaceuticals, Gilead Sciences, Aerogen, Depomed, Kai Pharmaceuticals, and Pharsight, and reports having shares in Johnson & Johnson and Procter & Gamble.

REFERENCES

1. Steiner JF, Earnest MA. The language of medication-taking. Ann Intern Med 2000;132:926-30.
2. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462-7.
3. Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. Value Health 2003;6:566-73.
4. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA 2002;288:2880-3.
5. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002;288:455-61.
6. Waeber B, Leonetti G, Kolloch R, McInnes GT. Compliance with aspirin or placebo in the Hypertension Optimal Treatment (HOT) study. J Hypertens 1999;17:1041-5.
7. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296-310.
8. Rudd P, Byyny RL, Zachary V, et al. Pill

count measures of compliance in a drug trial: variability and suitability. Am J Hypertens 1988;1:309-12.
9. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? Clin Pharmacol Ther 1989;46:163-8.
10. Spilker B. Methods of assessing and improving compliance in clinical trials. In: Cramer JA, Spilker B, eds. Patient compliance in medical practice and clinical trials. New York: Raven Press, 1991:37-56.
11. Burnier M. Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. Blood Press Monit 2000;5:Suppl 1:S31-S34.
12. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev 2002;2: CD000011.
13. Miller LG, Liu H, Hays RD, et al. How well do clinicians estimate patients' adherence to combination antiretroviral therapy? J Gen Intern Med 2002;17:1-11.
14. Murri R, Ammassari A, Trotta MP, et al. Patient-reported and physician-estimated adherence to HAART: social and clinic center-related factors are associated with discordance. J Gen Intern Med 2004;19:1104-10.
15. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36:1331-6.
16. Schiff GD, Fung S, Speroff T, McNutt RA. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. Am J Med 2003;114:625-30.
17. Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm 2001; 58:1126-32.
18. Misdrahi D, Llorca PM, Lancon C, Bayle FJ. Compliance in schizophrenia: predictive factors, therapeutical considerations and research implications. Encephale 2002;28: 266-72. (In French.)
19. Rodgers PT, Ruffin DM. Medication nonadherence: Part II — a pilot study in patients with congestive heart failure. Manag Care Interface 1998;11(9):67-9, 75.
20. Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. Clin Pharmacol Ther 2000;68:586-91.
21. Berg JS, Dischler J, Wagner DJ, Raia JJ, Palmer-Shevlin N. Medication compliance: a healthcare problem. Ann Pharmacother 1993;27:Suppl 9:S1-S24.
22. The Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. N Engl J Med 1980;303:1038-41.
23. LaRosa JC. Poor compliance: the hidden risk factor. Curr Atheroscler Rep 2000;2: 1-4.
24. Horwitz RI, Horwitz SM. Adherence to treatment and health outcomes. Arch Intern Med 1993;153:1863-8.
25. Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: a framework for clinical research and clinical care. J Clin Epidemiol 1997;50:385-91.
26. Kastrissios H, Suarez JR, Hammer S, Katzenstein D, Blaschke TF. The extent of non-adherence in a large AIDS clinical trial using plasma dideoxynucleoside concentrations as a marker. AIDS 1998;12:2305-11.
27. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization, 2003. (Accessed July 11, 2005, at http://www.who.int/chronic_conditions/en/adherence_report.pdf.)
28. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. AIDS 2002;16:269-77.
29. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? Hypertension 1980;2:757-64.
30. Wagner JH, Justice AC, Chesney M, Sinclair G, Weissman S, Rodriguez-Barradas M. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. J Clin Epidemiol 2001;54:Suppl 1:S91-S98.
31. Alcoba M, Cuevas MJ, Perez-Simon MR, et al. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. J Acquir Immune Defic Syndr 2003; 33:253-8.
32. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA 1989;261:3273-7. [Erratum, JAMA 1989;262:1472.]
33. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 1997;50:105-16.
34. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997; 50:619-25.
35. Christensen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, LoGerfo JP. Assessing compliance to antihypertensive medications using computer-based pharmacy records. Med Care 1997;35:1164-70.
36. Spector SL, Kinsman R, Mawhinney H, et al. Compliance of patients with asthma with an experimental aerosolized medication: implications for controlled clinical trials. J Allergy Clin Immunol 1986;77:65-70.
37. Norell SE. Monitoring compliance with pilocarpine therapy. Am J Ophthalmol 1981; 92:727-31.
38. Kass MA, Meltzer DW, Gordon M. A miniature compliance monitor for eyedrop medication. Arch Ophthalmol 1984; 102:1550-4.
39. Paterson DL, Potoski B, Capitano B. Measurement of adherence to antiretroviral medications. J Acquir Immune Defic Syndr 2002;31:Suppl 3:S103-S106.
40. Urquhart J. The electronic medication event monitor: lessons for pharmacotherapy. Clin Pharmacokinet 1997;32:345-56.
41. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001;134:968-77. [Erratum, Ann Intern Med 2002;136:175.]
42. Turner BJ, Hecht FM. Improving on a coin toss to predict patient adherence to medications. Ann Intern Med 2001;134: 1004-6.
43. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. Diabetes Care 1997;20:1512-7.
44. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Arch Intern Med 1990;150:1377-8.
45. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990;150:1509-10.
46. Urquhart J. The odds of the three nons when an aptly prescribed medicine isn't working: non-compliance, non-absorption, non-response. Br J Clin Pharmacol 2002;54: 212-20.
47. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592-9.
48. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150:1881-4.
49. Golin CE, Liu H, Hays RD, et al. A prospective study of predictors of adherence to combination antiretroviral medication. J Gen Intern Med 2002;17:756-65.
50. DiMatteo MR, Sherbourne CD, Hays RD, et al. Physicians' characteristics influence patients' adherence to medical treatment: results from the Medical Outcomes Study. Health Psychol 1993;12:93-102.
51. van Servellen G, Chang B, Garcia L, Lombardi E. Individual and system level factors associated with treatment nonadherence in human immunodeficiency virus-infected men and women. AIDS Patient Care STDS 2002;16:269-81.
52. Ammassari A, Trotta MP, Murri R, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. J Acquir Immune Defic Syndr 2002;31:Suppl 3:S123-S127.
53. Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. Ann Behav Med 2004;27:117-24.
54. Okuno J, Yanagi H, Tomura S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community? Eur J Clin Pharmacol 2001;57: 589-94.
55. Sewitch MJ, Abrahamowicz M, Barkun A, et al. Patient nonadherence to medication

in inflammatory bowel disease. Am J Gastroenterol 2003;98:1535-44.
56. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002;63:892-909.
57. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63:1121-8.
58. Farley J, Hines S, Musk A, Ferrus S, Tepper V. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr 2003;33:211-8.
59. Balkrishnan R. Predictors of medication adherence in the elderly. Clin Ther 1998;20:764-71.
60. Ellis JJ, Erickson SR, Stevenson JG. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. J Gen Intern Med 2004;19:638-45.
61. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HER Study. J Acquir Immune Defic Syndr 2001;28:124-31.
62. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination: is this patient taking the treatment as prescribed? JAMA 1993;269:2779-81.
63. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67-74.
64. Cramer J. Identifying and improving compliance patterns. In: Cramer JA, Spilker B, eds. Patient compliance in medical practice and clinical trials. New York: Raven Press, 1991:387-92.
65. Elliott WJ, Maddy R, Toto R, Bakris G. Hypertension in patients with diabetes: overcoming barriers to effective control. Postgrad Med 2000;107:29-32, 35-6, 38.
66. Black HR. Will better-tolerated antihypertensive agents improve blood pressure control? JNC VI revisited. Am J Hypertens 1999;12:225S-230S.
67. Ickovics JR, Meade CS. Adherence to HAART among patients with HIV: breakthroughs and barriers. AIDS Care 2002;14:309-18.
68. Murphy DA, Sarr M, Durako SJ, Moscicki AB, Wilson CM, Muenz LR. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. Arch Pediatr Adolesc Med 2003;157:249-55.
69. Stuart B, Zacker C. Who bears the burden of Medicaid drug copayment policies? Health Aff (Millwood) 1999;18(2):201-12.
70. Wilson J, Axelsen K, Tang S. Medicaid prescription drug access restrictions: exploring the effect on patient persistence with hypertension medications. Am J Manag Care 2005;11(Special Issue):SP27-SP34.
71. Zyczynski TM, Coyne KS. Hypertension and current issues in compliance and patient outcomes. Curr Hypertens Rep 2000;2:510-4.
72. Patton K, Meyers J, Lewis BE. Enhancement of compliance among patients with hypertension. Am J Manag Care 1997;3:1693-8.
73. Ran MS, Xiang MZ, Chan CL, et al. Effectiveness of psychoeducational intervention for rural Chinese families experiencing schizophrenia — a randomised controlled trial. Soc Psychiatry Psychiatr Epidemiol 2003;38:69-75.
74. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoes AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. J Card Fail 2003;9:404-11.
75. Simoni JM, Frick PA, Pantalone DW, Turner BJ. Antiretroviral adherence interventions: a review of current literature and ongoing studies. Top HIV Med 2003;11:185-98.
76. Maro EE, Lwakatare J. Medication compliance among Tanzanian hypertensives. East Afr Med J 1997;74:539-42.
77. Ross FM. Patient compliance — whose responsibility? Soc Sci Med 1991;32:89-94.
78. Feldman R, Bacher M, Campbell N, Drover A, Chockalingam A. Adherence to pharmacologic management of hypertension. Can J Public Health 1998;89:I16-I18.
79. Rigsby MO, Rosen MI, Beauvais JE, et al. Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. J Gen Intern Med 2000;15:841-7.
80. Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002;159:1653-64.
81. Cramer JA. Optimizing long-term patient compliance. Neurology 1995;45:Suppl 1:S25-S28.
82. Crespo-Fierro M. Compliance/adherence and care management in HIV disease. J Assoc Nurses AIDS Care 1997;8(4):43-54.
83. Osterberg LG, Rudd P. Medication adherence for antihypertensive therapy. In: Oparil S, Weber MA, eds. Hypertension: a companion to Brenner and Rector's The Kidney. 2nd ed. Philadelphia: Elsevier Mosby, 2005:848.
84. Ickovics JR, Cameron A, Zackin R, et al. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. Antivir Ther 2002;7:185-93.
85. Chesney M. Adherence to HAART regimens. AIDS Patient Care STDS 2003;17:169-77.
86. Tuldra A, Fumaz CR, Ferrer MJ, et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2000;25:221-8.
87. Safren SA, Otto MW, Worth JL, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther 2001;39:1151-62.
88. Golin CE, DiMatteo MR, Gelberg L. The role of patient participation in the doctor visit: implications for adherence to diabetes care. Diabetes Care 1996;19:1153-64.
89. Shon KH, Park SS. Medication and symptom management education program for the rehabilitation of psychiatric patients in Korea: the effects of promoting schedule on self-efficacy theory. Yonsei Med J 2002;43:579-89.
90. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. Control Clin Trials 1997;18:187-203.
91. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch Intern Med 2004;164:722-32.
92. Burnier M, Schneider MP, Chiolero A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens 2001;19:335-41.
93. Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment nonadherence in psychosis: meta-analysis. Br J Psychiatry 2003;183:197-206.
94. Vergouwen AC, van Hout HP, Bakker A. Methods to improve patient compliance in the use of antidepressants. Ned Tijdschr Geneeskd 2002;146:204-7. (In Dutch.)
95. Colom F, Vieta E, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. J Clin Psychiatry 2000;61:549-55.
96. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv 1998;49:196-201.
97. Mundt JC, Clarke GN, Burroughs D, Brenneman DO, Griest JH. Effectiveness of antidepressant pharmacotherapy: the impact of medication compliance and patient education. Depress Anxiety 2001;13:1-10.
98. Pekkala E, Merinder L. Psychoeducation for schizophrenia. Cochrane Database Syst Rev 2002;2:CD002831.
99. Molassiotis A, Lopez-Nahas V, Chung WY, Lam SW. A pilot study of the effects of a behavioural intervention on treatment adherence in HIV-infected patients. AIDS Care 2003;15:125-35.
100. Fulmer TT, Feldman PH, Kim TS, et al. An intervention study to enhance medication compliance in community-dwelling el-

derly individuals. J Gerontol Nurs 1999;25:6-14.
101. Dunbar PJ, Madigan D, Grohskopf LA, et al. A two-way messaging system to enhance antiretroviral adherence. J Am Med Inform Assoc 2003;10:11-5.
102. Mitchell PB, Mitchell MS. The management of depression. Part 2: the place of the new antidepressants. Aust Fam Physician 1994;23:1771-3, 1776-81.
103. Nemeroff CB. Improving antidepressant adherence. J Clin Psychiatry 2003;64:Suppl 18:25-30.
104. Rosenheck R, Chang S, Choe Y, et al. Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. J Clin Psychiatry 2000;61:382-6.
105. Hoffman L, Enders J, Luo J, Segal R, Pippins J, Kimberlin C. Impact of an antidepressant management program on medication adherence. Am J Manag Care 2003;9:70-80.
106. Love RC. Strategies for increasing treatment compliance: the role of long-acting antipsychotics. Am J Health Syst Pharm 2002;59:Suppl 8:S10-S15.
107. Gillis LS, Trollip D, Jakoet A, Holden T. Non-compliance with psychotropic medication. S Afr Med J 1987;72:602-6.
108. Bhanji NH, Chouinard G, Margolese HC. A review of compliance, depot intramuscular antipsychotics and the new long-acting injectable atypical antipsychotic risperidone in schizophrenia. Eur Neuropsychopharmacol 2004;14:87-92.
109. Tebbi CK, Cummings KM, Zevon MA, Smith L, Richards M, Mallon J. Compliance of pediatric and adolescent cancer patients. Cancer 1986;58:1179-84.
110. Friedman IM, Litt IF. Adolescents' compliance with therapeutic regimens: psychological and social aspects and intervention. J Adolesc Health Care 1987;8:52-67.
111. Friedman IM, Litt IF, King DR, et al. Compliance with anticonvulsant therapy by epileptic youth: relationships to psychosocial aspects of adolescent development. J Adolesc Health Care 1986;7:12-7.
112. Michaud PA, Suris JC, Viner R. The adolescent with a chronic condition. Part II: healthcare provision. Arch Dis Child 2004;89:943-9.
113. Tebbi CK. Treatment compliance in childhood and adolescence. Cancer 1993;71:Suppl 10:3441-9.
114. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. Am J Manag Care 2003;9:155-71.
115. Brackis-Cott E, Mellins CA, Abrams E, Reval T, Dolezal C. Pediatric HIV medication adherence: the views of medical providers from two primary care programs. J Pediatr Health Care 2003;17:252-60.
116. Jay S, Litt IF, Durant RH. Compliance with therapeutic regimens. J Adolesc Health Care 1984;5:124-36.
117. Rapoff MA. Compliance with treatment regimens for pediatric rheumatic diseases. Arthritis Care Res 1989;2:S40-S47.
118. Festa RS, Tamaroff MH, Chasalow F, Lanzkowsky P. Therapeutic adherence to oral medication regimens by adolescents with cancer. I. Laboratory assessment. J Pediatr 1992;120:807-11.
119. Rapoff MA, Lindsley CB, Christophersen ER. Improving compliance with medical regimens: case study with juvenile rheumatoid arthritis. Arch Phys Med Rehabil 1984;65:267-9.
120. Greenan-Fowler E, Powell C, Varni JW. Behavioral treatment of adherence to therapeutic exercise by children with hemophilia. Arch Phys Med Rehabil 1987;68:846-9.
121. Epstein LH, Beck S, Figueroa J, et al. The effects of targeting improvements in urine glucose on metabolic control in children with insulin dependent diabetes. J Appl Behav Anal 1981;14:365-75.
122. Magrab PR, Papadopoulou ZL. The effect of a token economy on dietary compliance for children on hemodialysis. J Appl Behav Anal 1977;10:573-8.
123. Tucker CM, Fennell RS, Pedersen T, Higley BP, Wallack CE, Peterson S. Associations with medication adherence among ethnically different pediatric patients with renal transplants. Pediatr Nephrol 2002;17:251-6.
124. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. Clin Ther 2004;26:1876-89.
125. Weingarten SR, Henning JM, Badamgarav E, et al. Interventions used in disease management programmes for patients with chronic illness — which ones work? Meta-analysis of published reports. BMJ 2002;325:925-8.
126. Ofman JJ, Badamgarav E, Henning JM, et al. Does disease management improve clinical and economic outcomes in patients with chronic diseases? A systematic review. Am J Med 2004;117:182-92.
127. Farris KB, Cote I, Feeny D, et al. Enhancing primary care for complex patients: demonstration project using multidisciplinary teams. Can Fam Physician 2004;50:998-1003.