

SPECIAL SUPPLEMENT TO

M A N A G E D

Care

Compliance and Persistence With Medication Therapy

HIGHLIGHTS

- A Retrospective Study of Persistence With Single-Pill Combination Therapy vs. Concurrent Two-Pill Therapy in Patients With Hypertension

- Medication Noncompliance: What Is the Problem?

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INTRODUCTION

BY LAWRENCE BLONDE, M.D.

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Removing Polytherapy As a Barrier to Adherence

Patients' failure to adhere to medication regimens is a major problem. The factors that beget nonadherence are complex and interwoven. Patients' ability to understand their treatment routines or the reasons for them, side effects, financial barriers, simple forgetfulness — or any combination of these and myriad other determinants — can influence adherence to therapy and, ultimately, the potential for positive outcomes.

One such factor is the complexity of a patient's treatment regimen. With every additional medication a patient must take — each with its own dosing instructions — the potential for error becomes greater. There is, as yet, relatively little information about patients who must take more than one medication, relative to those who are on monotherapy, for a specific illness. However, it seems intuitive that a medication that combines two or more components of a treatment regimen in a single pill — as has been available in the hypertension market and was recently introduced in the diabetes market — would have the potential to improve adherence to therapy.

In this special supplement to MANAGED CARE, poor persistence (in this case, failure to renew a prescription within three times the number of days supplied by the prescription) is documented for patients with hypertension who were prescribed a concurrent two-pill therapy of lisinopril and a diuretic, and also for those prescribed a concurrent two-pill regimen of enalapril maleate and a diuretic. However, when patients were prescribed respective single-pill therapies that combined these agents, persistence improved significantly. While the author appropriately identified some limitations of the study, he concluded that simplifying treatment for these patients enhanced their adherence to therapy — and thus their prospects for positive outcomes.

Nonadherence with medication therapy substantially impairs treatment results. To the extent that physicians, pharmacists, managed care organizations, and pharmaceutical manufacturers can recognize and remove barriers to treatment — and thus encourage better adherence to therapy — the health care delivery system can better fulfill its mission, and patients are likely to benefit from improved medical outcomes.

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**A Retrospective Study of Persistence
With Single-Pill Combination Therapy
Vs. Concurrent Two-Pill Therapy
In Patients With Hypertension 2**

Christopher M. Dezii, R.N., M.B.A.

**Medication Noncompliance:
What Is the Problem? 7**

Christopher M. Dezii, R.N., M.B.A.

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A Retrospective Study of Persistence With Single-Pill Combination Therapy Vs. Concurrent Two-Pill Therapy In Patients With Hypertension

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Abstract

Context. Patients with hypertension often fail to control their blood pressure because they do not comply with pharmacologic therapy. It was hypothesized that a greater percentage of patients receiving a single pill combining an ACE inhibitor and a diuretic would persist with therapy than patients receiving both drugs as separate pills.

Methods. Prescription data were obtained from a large commercial pharmacy benefit manager (PBM). The records of presumably newly diagnosed hypertensive patients for whom lisinopril combined with hydrochlorothiazide in a single pill (lisinopril/HCTZ) was prescribed ($n = 1,644$) were compared with those of patients for whom lisinopril and a diuretic were prescribed concurrently ($n = 624$). Likewise, the records of patients for whom enalapril maleate combined with hydrochlorothiazide in a single pill (enalapril/HCTZ) was prescribed ($n = 969$) were compared with those of patients for whom enalapril maleate and a diuretic were prescribed concurrently ($n = 705$). Patients were regarded as persisting if they renewed their prescription within three times the number of days supplied by the previous prescription. Patients were followed for one year from the date of the initial prescription.

Results. At 12 months, the percentages of patients persisting with lisinopril/HCTZ (68.7 percent) and enalapril/HCTZ (70.0 percent) therapy were 18.8 percent and 21.7 percent greater, respectively, than the percentages of patients persisting with lisinopril plus concurrent diuretic therapy (57.8 percent) or enalapril maleate plus concurrent diuretic therapy (57.5 percent). Statistical significance ($p < 0.05$) was demonstrated at 6 and 12 months for both comparisons.

Conclusion. The simplification of a drug regimen by using combination therapy in a single pill for hypertension resulted in significant increases in persistence with prescribed therapy.

Manag Care (Suppl). Sept 2000;9(9):S2–S6.

Introduction

The objective of this study was to use pharmacy benefit data to retrospectively evaluate persistence with antihypertensive therapy consisting of combination therapy in a single pill vs. two-pill combinations.

In the United States, only about 25 percent of the 50 million people with high blood pressure have their hypertension controlled to $< 140/90$ mm Hg. For most patients, behavior modification — weight loss, increased physical activity, smoking cessation — fails to produce lasting results. Pharmaceutical therapy therefore becomes mandatory, yet it too is difficult to maintain. Many patients with hypertension are asymptomatic and otherwise healthy. They find it difficult to understand why they need to take an antihypertensive agent every day when they generally feel fine. Moreover, monotherapy fails to control blood pressure in about 50 percent of patients, including most high-risk patients, thus requiring that a combination of drugs be used. One advantage of combination therapy is that low doses of two antihypertensive agents tend to be more effective and better tolerated than higher doses of either drug alone, as has been shown with combination therapy using low-dose felodipine and enalapril (Morgan 1992).

Although more effective than monotherapy, combination therapy increases the complexity of the dos-

ing regimen if multiple pills are required, and the increased complexity may diminish patients' compliance with therapy. The use of antihypertensive combination therapy in a single pill, therefore, holds a certain obvious appeal, even if its use diminishes the physician's ability to carefully titrate the dosages of the components. The combination of ACE inhibitors and diuretics has been found to be especially effective and well tolerated, achieving appropriate blood pressure control in about 80 percent of patients (Skolnick 2000). In the present study, we compare the persistence rates with two ACE inhibitors prescribed concurrently with diuretics versus two products combining an ACE inhibitor and a diuretic in a single pill.

Methods

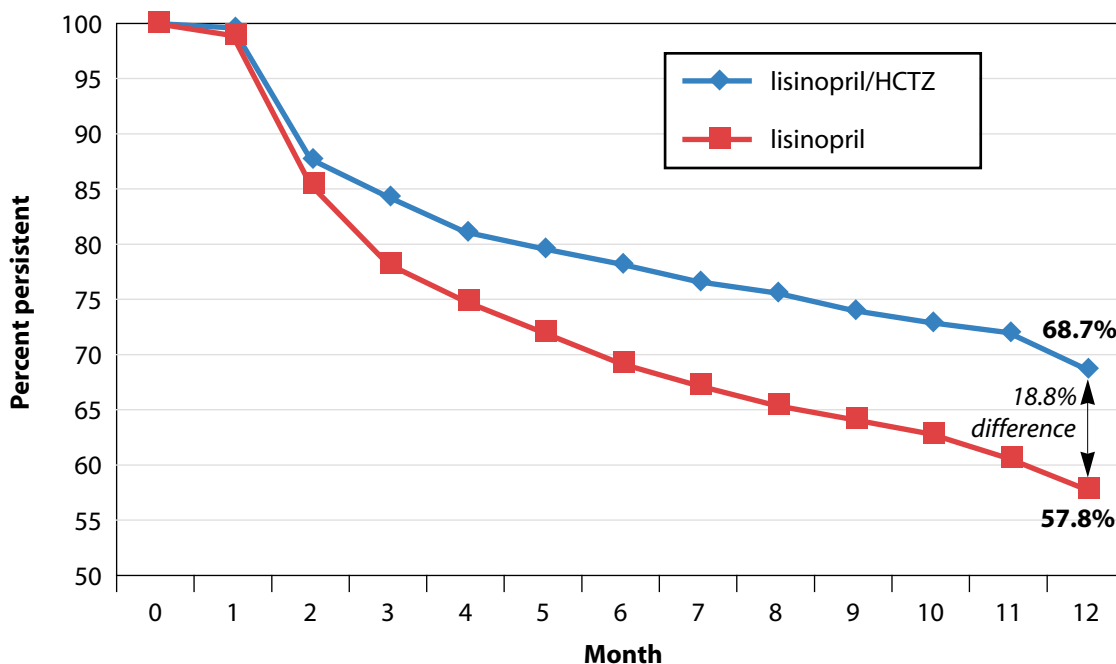
Retrospective data were obtained from the database of a national commercial PBM with 4.8 million members for patients who received certain antihypertensive agents between the second quarter of 1995 through the fourth quarter of 1999. An attempt to restrict the analysis to patients new to therapy was made by identifying specific agents (e.g., lisinopril, enalapril/HCTZ) in their PBM records and then looking back-

ward into the pharmacy records for six months; if no antihypertensive agents were found, the patients were presumed to be new to therapy.

The index date was the date on which a patient's first antihypertensive prescription was filled. Patients were followed for one year post-index. Continuous eligibility was established through the presence of any kind of claim beyond the one-year horizon. We compared data for patients who filled an initial prescription for the ACE inhibitor lisinopril combined in a single pill with the diuretic hydrochlorothiazide (n = 1,644) to data for patients who filled initial prescriptions for lisinopril and concurrent therapy with a diuretic (n = 624). We also compared data for patients who filled an initial prescription for the ACE inhibitor enalapril maleate combined in a single pill with hydrochlorothiazide (n = 969) to data for patients who filled initial prescriptions for two-pill therapy with enalapril maleate and a diuretic (n = 705).

Patients were identified as not persistent with therapy if they failed to renew a prescription within three times the number of days supplied by each prescription. That is, a patient who filled a 30-day prescription would be allowed 90 days (3 x 30) to refill the prescrip-

FIGURE 1 Persistence curves for lisinopril and lisinopril/HCTZ



(lisinopril/HCTZ n = 1644, lisinopril n = 624)

*Statistical significance (p<0.05) demonstrated at months 6 and 12 for both comparisons.

tion before being classified as not persistent with therapy. Failure to refill prescriptions did not have to be in consecutive months; patients were identified as not persistent if any three scheduled refills were not obtained. Mail order prescriptions were excluded.

Results

In both comparisons (lisinopril/HCTZ versus lisinopril plus a diuretic, and enalapril/HCTZ versus enalapril maleate plus a diuretic), a greater percentage of patients receiving oral combination therapy in a single pill were deemed to have persisted with therapy after 12 months, in comparison to patients who received the ACE inhibitor and a diuretic as separate pills.

Figure 1 (Page 3) shows the persistence curves for patients for whom concurrent two-pill therapy with lisinopril and a diuretic or the single-pill lisinopril/HCTZ was prescribed. At 12 months, 18.8 percent more patients remained on the single-pill combination therapy lisinopril/HCTZ than on concurrent therapy with lisinopril and a diuretic. Specifically, 68.7 percent of the lisinopril/HCTZ patients persisted with therapy, versus 57.8 percent of the patients receiving concurrent therapy.

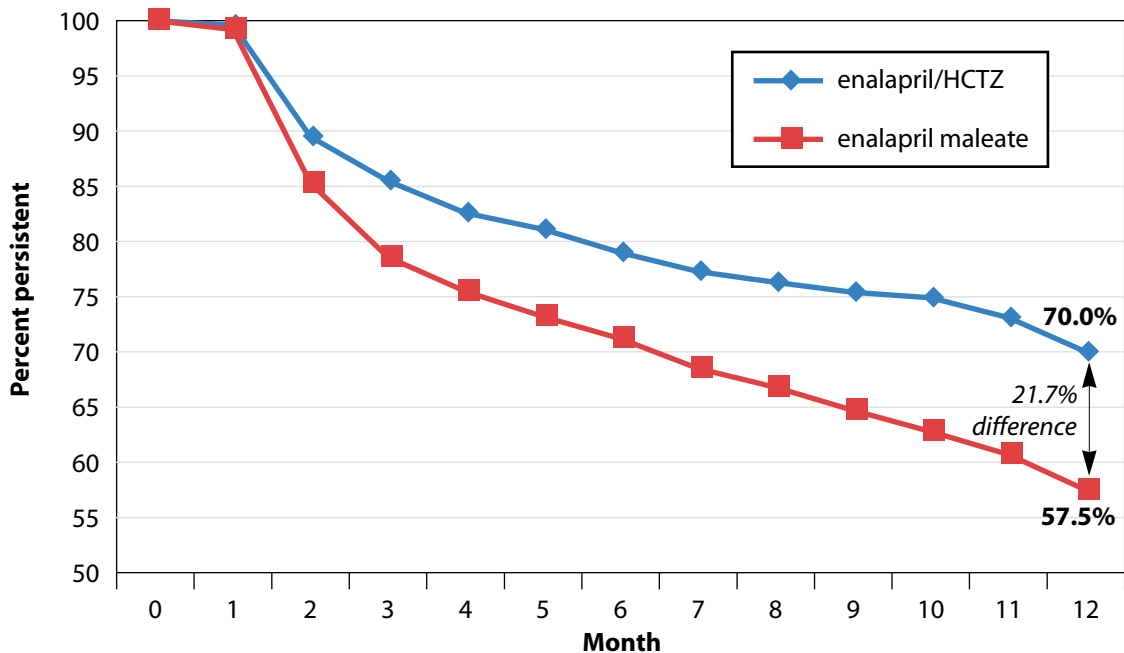
Figure 2 shows the persistence curves for patients for whom concurrent two-pill therapy with enalapril maleate and a diuretic or the single-pill combination therapy enalapril/HCTZ was prescribed. At 12 months, 21.7 percent more patients remained on the single-pill combination therapy with enalapril/HCTZ than on concurrent therapy with enalapril maleate and a diuretic. Specifically, 70.0 percent of the enalapril/HCTZ patients persisted with therapy, versus 57.5 percent of the patients receiving concurrent therapy.

Discussion

Comparing Figure 1 and Figure 2, the persistence curves for the single-pill combination medications are virtually identical, as are the curves for the concurrent therapies. In both figures, the greatest drop-off occurs during the second month of therapy, during which time the decline in persistence with combination therapy is similar to the decline in persistence with concurrent therapy. Thereafter, the curves gradually diverge until, at 12 months, persistence with the two single-pill combination products is about 20 percent greater than persistence with concurrent therapy.

In another study of patients who discontinued anti-

FIGURE 2 Persistence curves for enalapril maleate and enalapril/HCTZ



(enalapril/HCTZ n = 969, enalapril maleate n = 705)

*Statistical significance ($p < 0.05$) demonstrated at months 6 and 12 for both comparisons.

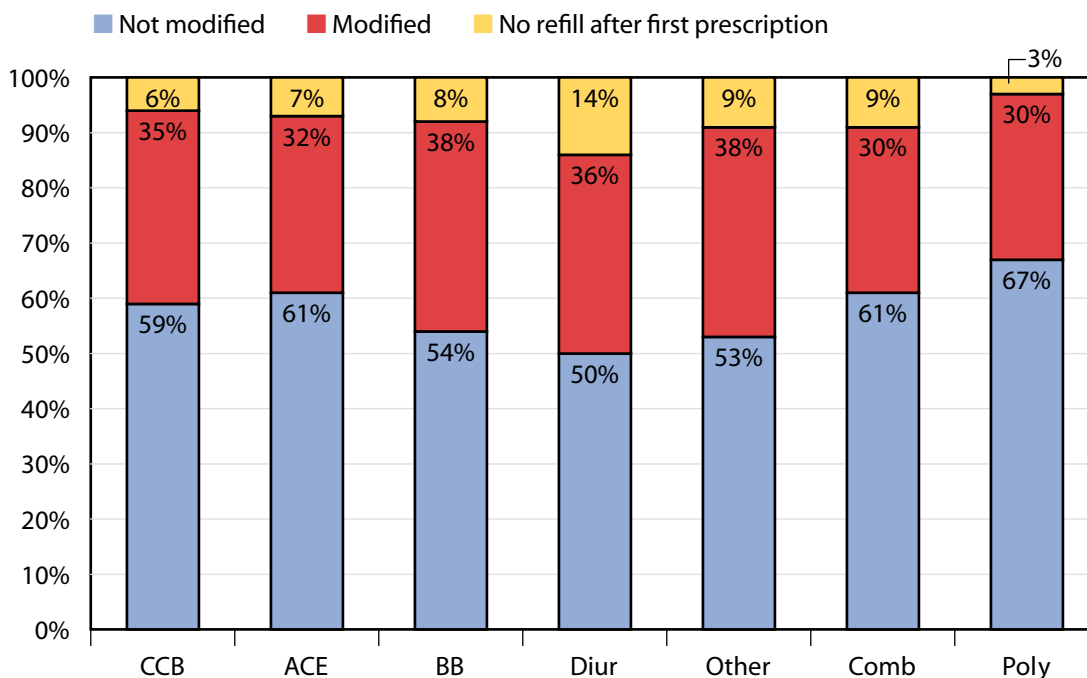
hypertensive therapy within one year (and who did not switch to a different therapy), the median time to discontinuation was about three months, regardless of the class or agent (Benson 2000). A Canadian study found that barriers to persistence occur in the early stages of therapy (Caro 1999a). Among 27,364 patients newly diagnosed with hypertension, 78 percent were persistent with therapy at the end of one year, compared with 97 percent of the 52,227 patients with established hypertension. After 4.5 years, persistence with therapy among patients with established hypertension was 82 percent, but persistence among newly diagnosed patients was only 46 percent.

It is possible that the simplified dosing regimen afforded by combination therapy would help at least some newly diagnosed patients to persist with their antihypertensive therapy long enough for it to be of some benefit, which requires years of treatment, not mere months.

Limitations. Our study did not take therapeutic switches into consideration. That is, patients who modified their therapy by switching to another ACE

inhibitor or, more likely, a drug from another class of antihypertensive would not have been captured by our analysis. Even though such patients might have remained persistent with antihypertensive therapy in general, they would have been classified as failing to persist with the therapies that were examined in our study. However, we previously studied the rate at which patients modified their initial antihypertensive therapy, either by switching to a different therapy or by adding another drug from a different class. Figure 3 depicts rates of such modifications over the course of 12 months of follow-up. Among the patients who began with combination therapy (n = 1,426) or polytherapy (n = 2,510), 30 percent in each group modified their therapy. More than 95 percent of these modifications involved the addition of a new drug rather than a switch. This supports the likelihood that modification patterns were similar in our study, and that little switching occurred. It should be noted that because these data date back to 1995, angiotensin II receptor blockers (ARBs) may be underrepresented when compared to current prescribing patterns.

FIGURE 3 Modification rates by class



Abbreviations: CCB = calcium channel blocker (n = 3,223), ACE = ACE inhibitor (n = 3,106), BB = beta blocker (n = 1,336), Diur = diuretic (n = 1,169), Comb = combination therapy (two agents given as one pill; n = 1,426), Poly = polytherapy (two agents given as two pills; n = 2,510). Other (n) = 627.

SOURCE FOR ALL FIGURES: PROTOCARE SCIENCES, HERNDON, VA.

Another limitation of our study is that it is restricted to PBM data that are not linked to medical records and clinical measures. Presumably some patients were prescribed lisinopril or enalapril maleate because of heart failure or acute myocardial infarction instead of hypertension, although many of these patients would be expected also to be hypertensive. For patients with hypertension, persistence with therapy is not an end in itself. The immediate goal of therapy is to reduce blood pressure, toward the ultimate goal of reducing the risk of morbidity and mortality. The next steps would be to demonstrate that improved persistence as a result of single-pill combination therapy, as opposed to concurrent therapy, leads to reductions in blood pressure and, of course, improved clinical outcomes, given that lowered blood pressure is not an end in itself, either.

In a review of interventions to improve patients' compliance, Haynes and colleagues found that with antihypertensive therapy, single daily dosage was among the interventions that improved compliance — but even the most effective interventions did not result in substantial improvements in compliance (Haynes 1996). The Canadian Coalition for Blood Pressure Prevention and Control nevertheless recommends once-daily dosage and simplified treatment regimens as one of four means to improve compliance. This recommendation clearly implies increased use of single-pill combination products as initial therapy.

Meanwhile, in the United States, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends monotherapy with a diuretic or beta blocker as initial pharmaceutical treatment for uncomplicated hypertension — after lifestyle modification has failed to reach goal — on the grounds that randomized controlled trials have shown improved outcomes (reduced mortality and morbidity) with these agents. Given the low percentage of patients with high blood pressure whose hypertension is controlled despite the presence of many effective agents, and given that failure to control hypertension often stems from patients' failure to persist with therapy, it may be time to rethink our approach toward the treatment of hypertension in the United States.

Persistence with antihypertensive therapy has been shown to vary according to the choice of initial agent (Caro 1997, Caro 1999b). Providing patients with a positive experience — rapid effectiveness and minimal

adverse effects — with their initial therapy may serve to improve long-term compliance. Combination therapy employing a single pill — particularly if one of the components is a diuretic — would seem to be a step in that direction. Our study does not establish the superiority of single-pill combinations of ACE inhibitors and hydrochlorothiazide over other possible combinations of antihypertensive agents, but it does show that a greater percentage of patients for whom lisinopril/HCTZ or enalapril/HCTZ are prescribed persist with therapy in comparison with patients for whom the components of those drugs are prescribed as concurrent medications.

Conclusion. The simplification of a drug regimen by using single-pill combination therapy for hypertension results in significant increases in persistence with prescribed therapy.

References

- Benson S, Vance-Bryan K, Raddatz J. Time to patient discontinuation of antihypertensive drugs in different classes. *Am J Health-Syst Pharm.* 2000;57:51–54.
- Caro JJ. Stepped care for hypertension: are the assumptions valid? *J Hypertens (Suppl).* 1997;15:S35–S9.
- Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *CMAJ.* 1999a;160:31–37.
- Caro JJ, Speckman JL. Existing treatment strategies: does noncompliance make a difference? *J Hypertens (Suppl).* 1998;16: S31–S4.
- Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ.* 1999b; 160: 41–46.
- Cramer JA. Consequences of intermittent treatment for hypertension: the case for medication compliance and persistence. *Am J Manag Care.* 1998;4:1563–1568.
- Epstein M, Bakris G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med.* 1996;156:1969–1978.
- Flack JM, Bledsoe K. Combination antihypertensive drug therapy: a therapeutic option long overdue. *Am Fam Physician.* 2000; 61:2974,2977.
- Freis ED. Improving treatment effectiveness in hypertension. *Arch Intern Med.* 1999;159:2517–2521.
- Haynes RB, McKibbin KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet.* 1996;248:383–386.
- Messerli FH, Michalewicz L. Fixed drug combinations in the treatment of hypertension: how to identify the optimal dose. *J Hypertens (Suppl).* 1998;16:S81–S84.
- Myers MG. Compliance in hypertension: why don't patients take their pills? *CMAJ.* 1999;160:64–65.
- Protocare Sciences, Herndon, Va. Unpublished data.
- Skolnik NS, Beck JD, Clark M. Combination antihypertensive drugs: recommendations for use. *Am Fam Physician.* 2000; 61:3049–3056.
- Weir MR. When antihypertensive monotherapy fails: fixed-dose combination therapy. *South Med J.* 2000;93:548–556.

Medication Noncompliance: What Is the Problem?

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The continuum of outpatient medical care usually begins with a decision by a patient (or the patient's guardian) to seek medical advice, and it ends with an outcome — positive or negative — that follows in part from the patient's compliance or lack of compliance with the professional advice rendered, often in the form of a prescription. If the patient takes the medication as prescribed, the success of the therapy can be evaluated and altered as necessary. In the best case, the patient agrees with the physician's decision (and also has been a full partner in the decision-making process), takes the medication as instructed, and enjoys the benefits of therapy that were envisioned when the prescription was written. In the worst case, the patient grudgingly accepts the physician's prescription — and either does not fill it or does not take it as directed.

A patient's compliance with therapy sometimes is framed in terms of an authoritarian relationship between the physician and the patient, in which the patient is expected to obey the orders received from the physician. Some observers of the patient-physician relationship object to the words *comply* and *compliance*, contending that they reinforce an essentially unhealthy — and subservient — relationship. These critics prefer the words *adhere* and *adherence*, which they perceive as bearing fewer negative connotations. Although *adhere* and *adherence* have begun to appear more often in the published literature, many writers use them as synonyms for *comply* and *compliance* without making any distinction regarding which words, if any, reinforce this presumed authoritarian relationship. In this article, *compliance* and *adherence* are used synonymously.

In addition, these two terms are intended to describe people who take improper doses of a medication and/or who skip doses on occasion — or who do not take a prescribed medication at all — as opposed

to patients who accidentally or willfully take medications other than those that are prescribed for them.

Consequences of noncompliance

The consequences of noncompliance are far-reaching, both from an economic standpoint and in terms of morbidity and mortality. Failure to take medications correctly has been estimated to cost the U.S. economy \$100 billion per year. Of this, \$30 billion is in direct medical costs — \$25 billion due to hospital admissions, \$5 billion because of unnecessary nursing home placement — while lower productivity and premature death add \$70 billion to the tab (Shorter 1993).

Increased morbidity and mortality are likely negative outcomes among patients who fail to comply with therapy that is medically sound. Whether such outcomes develop over the long term or the short term depends on the disease or condition in question. A patient who fails to comply with therapy for hypertension or osteoporosis may not experience a negative outcome for years or even decades, but a patient who ceases to adhere to treatment for psychosis or diabetes may suffer the negative consequences in a matter of days.

In some cases, a patient's noncompliance increases the risk of morbidity and mortality, among others. Patients' failure to comply with their antibiotic regimens is a reason for the emergence of treatment-resistant strains of microbes. In one survey, 26 percent of adults randomly selected on a city street admitted to having saved antibiotics from a prescription that had not been completed (that is, patients had been noncompliant with the original prescription), and half of them said they would take or had taken the leftover drugs to treat a self-diagnosed illness (Ceaser 2000). Some respondents said they even would share their leftover antibiotics with other people, thus compounding the problem of antibiotic resistance.

Needless changes in therapy can result when a patient is deemed unresponsive to a drug when, in fact, the drug would have produced the desired effects had it been taken as instructed. Even when drugs are taken faithfully as instructed, they sometimes fail to produce the desired outcome. In the case of hypertension, about 30 percent of patients fail to reach their blood pressure goals despite therapy. However, genuine treatment-resistant hypertension¹ occurs in <10 percent of patients with essential hypertension (Oparil 1998). Noncompliance may be responsible for as many as half of antihypertensive drug “failures” (Stephenson 1999). It is important, in theory, for the physician to be able to distinguish a drug failure due to nonadherence from another that is due to true treatment resistance, but this is difficult to accomplish in practice. Being eager to please their physicians, patients may say what they think doctors want to hear — first claiming that they understand their dosing instructions when, in fact, they are confused, and later overreporting good compliance and underreporting poor compliance (Gottlieb 2000).

It would stand to reason that the highest rates of compliance with drug therapy would be found among health care professionals, who presumably are highly educated and highly motivated, and who understand and endorse the reasons for complying with therapy. Corda and colleagues recently found, through a self-administered survey, that the compliance rates among 301 physicians and nurses were 77 percent for short-term medications and 84 percent for long-term medications (Corda 2000). Thus, without specific interventions, real-world compliance rates among members of the general public (as opposed to the artificially high rates achieved in most clinical trials) should be expected to be, at their very best, in the vicinity of 80 percent.

Real-world compliance rates tend to average between 50 and 60 percent (Figure 1), but they can be much lower. In a recent Scottish study of 2,920 patients receiving oral hypoglycemic drugs for type 2 diabetes, 31 percent of patients receiving a sulfonylurea and 34 percent of patients receiving metformin adhered to therapy over the course of 12 months, and compliance among patients receiving sulfonylurea

¹ Hypertension that remains uncontrolled despite an optimal two-drug regimen that has been in place for at least one month since the last change in drug or dosage.

and metformin in combination was only 13 percent (Morris 2000).

Reasons for noncompliance

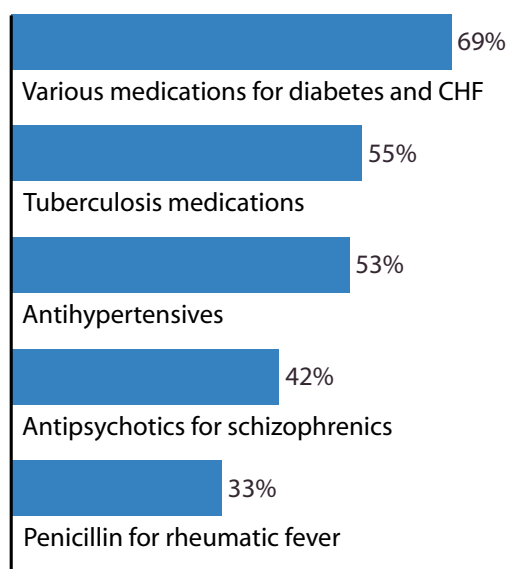
The reasons for noncompliance are varied and complicated. Noncompliance is not necessarily a willful decision to be disobedient or contrary. The patient’s personality, culture, values, mental capacity, understanding of the disease, and social support system; the physician’s compassion (or lack thereof) and skills (or lack thereof) as a communicator and educator; the characteristics of the therapy and the therapeutic regimen; and financial considerations are among the many interwoven factors that influence adherence to therapy.

The patient encounter. Barriers to adherence may be set in place during the patient’s initial visit with the physician. Some patients who believe they were made to wait too long to be seen or who think they were not treated with sufficient compassion retaliate through noncompliance (Gottlieb 2000). More often, they leave the physician’s office without a complete understanding of the rationale for therapy or the therapeutic regimen. In a study of members of a California managed care plan who failed to pick up one or more prescriptions at pharmacies after having them filled, one of the most common reasons cited for abandoning the prescription was because the physician was difficult to understand and patients had no recall of the prescription (Lash 1995).

Adverse effects. After the prescription has been filled, adverse effects are a common reason for noncompliance. For example, weight gain is a common adverse effect associated with atypical antipsychotics, and impotence and dizziness are associated with some antihypertensive drugs. If unwanted weight gain leads a patient with schizophrenia to stop taking a medication, recurrence of psychotic episodes is likely. Likewise, if impotence — or the fear of it — causes a patient to cease taking an antihypertensive, the patient’s long-term risk of cardiovascular disease increases.

Adverse effects also can arise if a patient fails to take a drug as instructed. For example, the osteoporosis drug alendronate must be taken the first thing in the morning with water only, and the patient must remain in an upright position and refrain from eating for at least half an hour. Failure to comply with these instructions can lead to esophageal irritation and even eso-

FIGURE 1 Medication compliance rates for selected illnesses



SOURCE: NATIONAL COUNCIL ON PATIENT INFORMATION AND EDUCATION

phageal erosion. Moreover, because of the drug's low bioavailability, taking the drug with food or any beverage except water eliminates its therapeutic value.

Drug-drug and drug-food interactions also can result in adverse effects that lead to noncompliance. Polypharmacy increases the risk of drug interactions.

Complicated regimen. A complicated dosing regimen hampers compliance, especially if multiple dosing of multiple drugs is involved. The simpler the regimen, the greater the degree of compliance. The administration of a drug also may require the patient to master a certain technique. For example, patients with asthma need to learn the proper inhalation technique if an inhaled corticosteroid (ICS) has been prescribed as a long-term control medication. If a patient is switched from one ICS to another, a new inhalation technique may have to be learned because the delivery devices are different. Moreover, patients' inhalation techniques tend to deteriorate over time, leading to inadvertent noncompliance through inadequate dosing.

Complicated instructions can impede compliance, too, as with the previous example of alendronate. Although each element of these dosing instructions is simple in itself, in totality these elements may present a set of obstacles that patients may be unwilling to

overcome. Waiting for 30 minutes before eating or drinking anything but water may seem unreasonably long for a patient who awakens with hunger pangs, and a patient who feels the need to recline may do so before 30 minutes has passed. Further, with some drugs, patients who forget or otherwise skip a dose are instructed to take their next dose as soon as possible without regard to time of day or meals, but the same advice does not apply to alendronate. If a dose is missed, the next dose should be taken upon arising the next day, but a patient easily could confuse the instructions for alendronate with those for, say, an antihypertensive.

Patients' beliefs. Patients' beliefs about the seriousness or nature of their illness often affect their willingness to adhere to therapy. If taking a medication is viewed by the patient as admitting that, "Yes, I have a serious illness," failure to comply with therapy may be a means by which the patient denies having the illness. Patients also may believe that they have no need to take a medication if they are free of symptoms. Such an

attitude is bound to thwart therapy directed toward preventing the long-term deleterious effects of hypertension, hypercholesterolemia, and osteoporosis, for example. If a drug to treat an asymptomatic condition proves to be inconvenient or associated with adverse effects, a patient well may decide to forgo further treatment until the patient believes it is necessary.

Other diseases wax and wane in their symptoms, which, too, can cause patients either to conclude that they are "better," or to forget to take their medications entirely when symptom relief occurs. A patient may erroneously conclude that the lifting of the black cloud of depression means that the prescribed antidepressant no longer is necessary. An asthma patient who finds it easier to breathe may decide to set aside the long-term control medication and rely only on the quick-relief medication.

Some drugs, including antidepressants and long-term asthma control medications, may be slow to produce effects that can be noticed by the patient. If the patient believes that the slowness of action means the drug isn't working, the patient may become noncompliant.

Some illnesses carry a social stigma. The mere display of an inhaler by an asthmatic child may mark the

child as a target for schoolyard bullies — and lead the child to conclude that the inhaler is better left at home.

Physicians' beliefs. Many physicians feel they have little control over patient compliance. Further, physicians as a whole may have little interest in or knowledge of techniques that can improve medication compliance, given that medical training still tends to be oriented toward diagnosis and treatment of acute illness and not toward health maintenance or management of chronic conditions. In the latter situation, positive outcomes often require routine monitoring of compliance with a medication regimen.

Depression. Depression has been identified as a substantial and significant risk factor for non-compliance (DiMatteo 2000). Further research is needed to determine whether depression is a cause or an effect of noncompliance, or whether some third variable causes concomitant depression and non-compliance. Nevertheless, depressed patients are three times as likely as nondepressed patients to be non-compliant with therapy, be it drug therapy or behavior modification. DiMatteo and colleagues speculate that because depression is accompanied by a degree of hopelessness, depressed patients may lack the positive attitude regarding the benefits and efficacy of treatment that is necessary for adherence. Depressed patients also may have withdrawn from the social support systems that encourage adherence, and they may lack the cognitive functioning to follow through with therapeutic recommendations.

Cognitive disorders. As the U.S. population ages, the prevalence of Alzheimer's disease and related disorders is increasing. Patients with Alzheimer's disease experience the same common chronic diseases as other patients in their cohort, but their ability to take drugs to treat their hypertension, diabetes, or osteoporosis may be compromised by their diminished mental capacity. Even patients without cognitive impairment have difficulty adhering to therapy as the number of drugs increases. As Alzheimer's disease and similar disorders progress, it becomes increasingly difficult for a patient with dementia to remember what pills to take, and when, and it also becomes more difficult for the patient to report adverse effects (Brauner 2000). These circumstances also can add considerable stress to the patient's caregiver.

Financial barriers. The health care system may impose hurdles that impede compliance. For patients

covered by managed care, high copayments for drugs in the upper tier of a formulary may dissuade some patients from filling or refilling a prescription. Similarly, financial considerations can influence the choices made by members whose pharmacy benefit is exhausted before the benefit period expires; one study of Medicare HMO members in Arizona found that 16 percent stop taking medications when their prescription benefit runs out, then resume taking them when a new benefit year begins (Cox 1999). Further, many patients in indemnity plans or who are enrolled in Medicare lack drug coverage of any kind, and patients in the Medicaid population may face restrictions on the number of prescriptions they may receive, which could force them to drop one drug in favor of another.

However, in a study of parents who failed to fill prescriptions for their children following a visit to an emergency department, financial constraints were found to be minimal. Rather, noncompliance seemed to stem from a breakdown in communication between the physician and the child's caregiver (Matsui 2000). Likewise, in a Canadian study of patients newly diagnosed with hypertension, the lowest levels of persistence with therapy were associated with the less-expensive drugs (diuretics), while the highest levels of persistence were associated with the more-expensive drugs (calcium channel blockers and ACE inhibitors) (Caro 1999). The investigators speculated that the different persistence rates instead were due to class-related side effects.

Strategies to enhance compliance

Improving patients' adherence to therapy begins with the recognition by physicians of the necessity for patients to be participants in the management of their disease or condition (Funnell 2000). Patients need to understand the nature of their illness, the options for treating it, and their responsibility in its management, particularly the fact that most of the day-to-day decisions are theirs, not the physician's. If the physician and the patient work together toward a mutual goal, compliance with therapy is likely to be enhanced.

Patient involvement. One tactic for involving patients in management of their illness is drawing up a written treatment plan — especially if the therapy is complex, such as with diabetes or asthma. Such a plan lays out the steps for routine care, and also makes it clear when urgent or emergency medical care is nec-

essary. The plan is important for helping patients with asthma to adhere to long-term control therapy instead of relying on quick-relief medications (Mellins 2000). “Contracts” that are treated as quasi-legal documents also are recommended (Gottlieb 2000). Additionally, involving the patient’s whole family may create the social support system needed to improve compliance with therapy.

Simplified therapy. In the previously mentioned Scottish study of patients taking oral hypoglycemic drugs for type 2 diabetes, once-daily dosing or fewer total tablets, or both, were associated with improved adherence. Each increase in the frequency of the daily dose was associated with a 22-percent decrease in adherence (Morris 2000). Combination therapy, in which two active products are combined in a single pill, is one means of simplifying therapy for patients with hypertension or type 2 diabetes. Products that provide once-daily dosing also may increase compliance.

Routine compliance and pill checks. As the number of prescription and nonprescription drugs taken by a patient increases, so does the likelihood of non-compliance, along with the risk of adverse effects due to drug-drug or drug-food interactions. For these reasons, physicians should ask patients about compliance at every visit to determine whether and which barriers to appropriate medication use may exist. Further, physicians may want to consider conducting periodic checks of a patient’s prescription and nonprescription drugs. The time spent examining the bottles and asking the patient about the use (or lack of use) of each product may increase adherence to therapy now — and save time, money, and angst or agony later.

Telephone reminders. Similarly, a telephone call from a health care professional can boost compliance by serving as a reminder of the need to take the medication and by giving the patient an opportunity to discuss any problems that may be interfering with therapy. Interestingly, in a study of patients with major depression, regular calls from nurses over the course of 16 weeks resulted in improved outcomes, in comparison with patients who received usual care (no calls) — but the better outcomes did not stem from improved medication adherence, as the investigators had hypothesized (Hunkler 2000). The investigators speculated that some unknown psychosocial mechanism was involved.

Selecting drugs to minimize adverse effects. If adverse effects (or the fear of adverse effects) threatens to impede compliance, the physician should not hesitate switching to another therapeutic option. Indeed, the likelihood of adverse effects and the resulting non-compliance may suggest that selection of the initial drug be made with the intention of minimizing adverse effects and thereby enhancing compliance.

Using managed care databases to the patient’s advantage. Managed care organizations share a responsibility for assuring medication compliance among their members, thereby improving outcomes. For example, pharmacy benefit manager data can be used to help determine when medications for chronic problems are not being refilled. Programs then can be developed to educate those members about the importance of medication compliance, and physicians and pharmacists can be encouraged to personalize this message *vis a vis* a patient’s specific treatment regimen. Development of computerized systems that allow cross-departmental sharing of clinical patient information can facilitate such efforts.

Conclusion

A prudent working assumption on the part of the prescribing physician should be that many patients, perhaps even a majority of patients, will fail to adhere to therapy. Noncompliance arises not necessarily from self-destructive or spiteful tendencies (although it *could*), but from a variety of factors — some of which may be beyond the patient’s ken. Suspicion of non-compliance therefore need not cast aspersions upon the patient’s motives or intelligence, but rather acknowledges the fact that people forget, people become confused, and people can be distracted. About 20 percent of health care professionals fail to adhere to therapy themselves. Acknowledging the likelihood of non-compliance is the first step toward addressing the problem. Empowering the patient and the patient’s family to be active participants in the management of the patient’s disease is the second step toward improved compliance and the ultimate goal of improved clinical outcomes and quality of life.

References

- Avorn J, Solomon DH. Cultural and economic factors that (mis-)shape antibiotic use: the nonpharmacologic basis of therapeutics. *Ann Intern Med.* 2000;133:128–135.
- Balas EA, Weingarten S, Garb CT, et al. Improving preventive care by prompting physicians. *Arch Intern Med.* 2000;160:301–308.

- Bedell SE, Jabbour S, Goldberg R, et al. Discrepancies in the use of medications. Their extent and predictors in an outpatient practice. *Arch Intern Med.* 2000;160:2129–2134.
- Brauner DJ, Muir JC, Sachs GA. Treating nondementia illnesses in patients with dementia. *JAMA.* 2000;283:3230–3235.
- Caro JJ, Speckman JL. Existing treatment strategies: does non-compliance make a difference? *J Hypertens* (Suppl 7). 1998; 16:S31–S34.
- Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ.* 1999;160:41–46.
- Ceaser S, Wurtz R. “Leftover” antibiotics in the medicine cabinet. *Ann Intern Med.* 2000;133:74.
- Chaufan C. Patient compliance: in search of the real question in diabetes care. *Am Fam Physician.* 2000;61:644,647.
- Corda RS, Burke HB, Horowitz HW. Adherence to prescription medications among medical professionals. *South Med J.* 2000;93:585–589.
- Cox ER, Coons SJ. Pharmaceuticals and Medicare managed care: pharmacoeconomic considerations. *Clin Ther.* 1998 Nov-Dec;20(6):1238–1240.
- Cushman WC, Reda DJ, Perry HM, et al. Regional and racial differences in response to antihypertensive medication use in a randomized controlled trial of men with hypertension in the United States. *Arch Intern Med.* 2000;160:825–831.
- Dalzell MD. Pharmacy copayments: a double-edged sword. *Manag Care.* 1999 Aug;8(8):26–31.
- DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160:2101–2107.
- Funnell MM. Helping patients take charge of their chronic illnesses. *Fam Pract Manag.* 2000;7:47–51.
- Gottlieb H. Medication nonadherence: finding solutions to a costly medical problem. *Drug Benefit Trends.* 2000;12:57–62.
- Hunkler EM, Meresman JF, Hargraves WA, et al. Efficacy of nurse telehealthcare and peer support in augmenting treatment of depression in primary care. *Arch Fam Med.* 2000;9:700–708.
- Jacobson TA, Schein JR, Williamson A, Ballantyne CM. Maximizing the cost-effectiveness of lipid-lowering therapy. *Arch Intern Med.* 1998;158:1977–1989.
- Katon W. Improvement of outcomes in chronic illness. *Arch Fam Med.* 2000;9:709–710.
- Lash S, Harding H. “Abandoned prescriptions”: a quantitative assessment of their cause. *J Managed Care Pharm.* 1995;1:193–199.
- Matsui D, Joubert GI, Dykxhoorn S, Rieder MJ. Compliance with prescription filling in the pediatric emergency department. *Arch Pediatr Adolesc Med.* 2000;154:195–198.
- Mellins RB, Evans D, Clark N, Zimmerman B, Wiesemann S. Developing and communicating a long-term treatment plan for asthma. *Am Fam Physician.* 2000;61:2419–2428,2433–2434.
- Melfi CA, Chawla AJ, Croghan TW, et al. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Intern Med.* 1998;158:1128–1132.
- Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. *Circulation.* 1997;95:1085–1090.
- Morris AD, Brennan GM, Macdonald TM, Donnan PT. Population-based adherence to prescribed medication in type 2 diabetes: a cause for concern. *Diabetes.* 2000;49(S1):abstract 307. Available at «<http://www.diabetes.org/am2000/abstractsearch>». Accessed Aug. 8, 2000.
- Oparil S, Calhoun DA. Managing the patient with hard-to-control hypertension. *Am Fam Physician.* 1998 Mar 1;57(5):1007–1014, 1019–1020.
- Shorter H. Noncompliance with medications: an economic tragedy with important implications for health care reform. Task Force for Compliance Report 1993.
- Stephenson J. Noncompliance may cause half of antihypertensive drug “failures.” *JAMA.* 1999;282:313–314.
- Ziegelstein RC, Fauerback JA, Stevens SS, et al. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med.* 2000;160:1818–1823.