

REVIEW

Medication Adherence and Persistence as the Cornerstone of Effective Antihypertensive Therapy

Michel Burnier

Achieving optimal outcomes in the treatment of hypertension—a prevalent and largely asymptomatic disease—necessitates that patients take their medications not only properly (medication adherence) but also continue to do so throughout long-term treatment (persistence). However, poor medication-taking behavior is a major problem among patients with hypertension, and has been identified as one of the main causes of failure to achieve adequate control of blood pressure (BP). In turn, patients with hypertension who have uncontrolled BP as a result of their poor medication-taking behavior remain at risk for serious morbidity and mortality (eg, stroke, myocardial infarction, and kidney failure), thereby accounting for a significant cost burden through avoidable hospital admissions, premature deaths, work absenteeism, and reduced productivity. Improving medication-taking behavior during antihypertensive therapy therefore represents an important

potential source of health and economic improvement. Whereas many factors may contribute to poor medication-taking behavior, the complexity of dosage regimens and the side effect profiles of drugs probably have the greatest therapy-related influence. Central to any strategy aimed at improving outcomes for patients with hypertension, therefore, are efficacious antihypertensive agents that facilitate good medication-taking behavior through simplified dosing and placebo-like tolerability, along with the development of programs to detect poor medication adherence and to support long-term medication persistence in daily practice. *Am J Hypertens* 2006;19:1190–1196 © 2006 American Journal of Hypertension, Ltd.

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The optimal prevention and treatment of ill health requires efficacious and well tolerated medications. However, such benefits cannot be realized if patients take their medication incorrectly or not at all, either intentionally or unintentionally. The problem of poor medication-taking behavior is apparent for symptomatic conditions such as asthma or epilepsy, in which patients are generally aware that the consequences of not closely following their drug regimens or withdrawing from treatment altogether could result in serious adverse outcomes or even death.¹ However, this problem is particularly relevant for the treatment of chronic asymptomatic diseases such as hypertension, in which no immediate physical symptoms resulting from missing doses, on either an occasional or permanent basis, are apparent. In the longer term, however, the inadequate control of elevated blood pressure (BP) that culminates from poor medication-taking behavior during antihypertensive therapy means that patients remain at significant risk for costly micro- and

macrovascular complications (eg, stroke, myocardial infarction, and kidney disease) that can result in premature mortality. In view of the growing prevalence of hypertension in the United States and other industrialized nations, and increasing awareness of the need for effective BP control,^{2,3} medication-taking behavior is becoming an increasingly important aspect of hypertension management. The aim of this review, therefore, is to discuss the issue of medication-taking behavior, including terms and definitions, the scope of the problem, reasons for and consequences of the problem, as well as methods to improve medication adherence and persistence in the growing population of patients with hypertension.

Terminology and Measurement of Medication-Taking Behavior

Medication-taking behavior encompasses both medication adherence and persistence, terms for which distinct defi-

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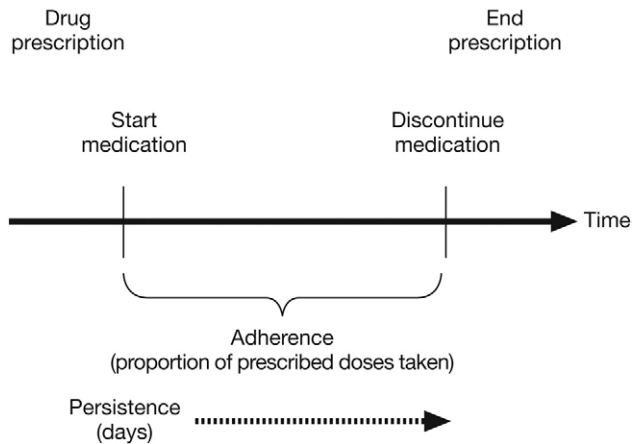


FIG. 1. Aspects of medication-taking behavior.

nitions have been developed. “Medication adherence” can be defined as the extent to which a patient’s behavior, with respect to taking medication, corresponds with agreed recommendations from a healthcare provider.¹ “Medication persistence” represents the accumulation of time from initiation to discontinuation of therapy (Fig. 1). The term “concordance” has been suggested as a broader term beyond adherence, encompassing shared goals in which patients’ medication-taking behavior matches healthcare recommendations.^{4,5} Persistence is measured in terms of time, whereas medication adherence is reported in terms of the percentage of prescribed doses taken per defined period of time. An important point to consider is that medication adherence is a dynamic parameter that is not stable over time. This is eloquently demonstrated by partial adherence, for example, in patients with highly variable medication adherence whose medication-taking behavior often improves around the time of a scheduled clinic visit but declines thereafter.⁶ Recognition of the dynamic nature of medication adherence is therefore important when considering ways in which poor medication-taking behavior could be improved.

Various methods are used to measure medication adherence, ranging from patient self-reporting to sophisticated electronic monitoring. These measures are generally grouped into three categories: subjective (eg, patient interviews), direct (eg, analysis of drug levels in bodily fluids), and indirect (eg, pill counts, prescription refills, electronic monitoring of medication use). Subjective evaluations, such as the four-item Morisky Medication Taking Behavior Scale,⁷ are simple and practical approaches to determining medication adherence. In that study, for example, patients who answered “yes” to questions such as “Do you ever forget to take your medicine?” and “Are you careless at times about taking your medicine?” were less likely to have their BP under control. An eight-item instrument that could be easily administered to identify problems with medication-taking behavior has since been developed by Morisky et al (manuscript in development), and was found to have good concurrent and predictive

validity. However, self-reporting of medication adherence may often be inaccurate because of difficulties with patient recall, attempts to please the healthcare provider, or a combination of these factors.⁸ Physicians also tend to overestimate medication adherence in their patients, with one early study reporting poor correlation between the physician estimate of adherence and objective pill counts.⁹ Moreover, studies have demonstrated that the physician’s judgment on patients’ adherence has low sensitivity (<40%) but good specificity (~90%), suggesting that physicians are good at detecting good adherence but not poor or partial adherence.^{10,11}

For some drugs, such as antiepileptic agents, adherence may be determined from the measurement of drug levels in bodily fluids (eg, blood, urine, saliva). This approach is generally considered to be more reliable than subjective measures of medication adherence¹² but is not feasible in most practice settings and tests can be costly. Moreover, interpretation is complicated by drug pharmacokinetics; if the patient takes the dose just before a physician visit, for example, the results may be misleading. Interindividual differences in drug absorption and metabolism can also lead to differences in drug levels among those who show similar medication adherence. Finally, drug assays are unable to show whether the patient took the appropriate dose at the proper time as prescribed.

Indirect methods are the most common approach to measuring medication adherence. For example, counting the number of unused pills remaining after a given time, and subtracting this from the original quantity dispensed, is a simple and practical method of estimating the quantity of medication presumably used by the patient. However, patients may have discarded some tablets, and counting inaccuracies are common; therefore pill counting can often result in an overestimation of medication adherence.¹³ In addition, important information such as the pattern of missed doses is not captured using this approach. Other indirect methods include the analysis of prescription refill data from pharmacy database records. One technique involves calculation of the medication possession ratio, defined as the number of days’ supply of drug obtained during a specific time period.¹⁴ For example, if the patient’s prescription was for 30 days of therapy but the subsequent prescription was not filled for another 7 days, then the medication possession ratio would be 0.81 (ie, 30/37). Pharmacy refill data can also be used to measure medication persistence, in terms of the time between initiation and discontinuation of therapy. However, prescription refill records are only a valid source of information about medication-taking behavior when the database is complete; if the patient uses a pharmacy not linked to the database, then it can lead to incomplete and erroneous calculations.

Electronic monitoring devices, such as the Medication Event Monitoring System ([MEMS] Apex Corporation, Fremont, CA), can be used to provide accurate and detailed information on medication-taking behavior.^{15,16} Al-

Table 1. Potential reasons for poor medication-taking behavior during antihypertensive therapy

Physician and patient factors
Cost of medication and related care
Instructions not clear to patient
Failure of physician to increase or change therapy to achieve blood pressure goals
Inadequate or no patient education
Lack of involvement of patient in treatment plan
Therapy factors
Side effects of medication
Complexity of dosing regimen

though expensive and therefore generally restricted to the research setting, an advantage of these devices is that the actual dates and times of events are recorded; this information can subsequently be retrieved and interpreted by the healthcare provider during consultation with the patient. In turn, electronic monitors can help to address problems with medication-taking behavior.^{17–19} Although there is no certainty about the actual intake of the medication by the patient, these devices have been shown to have superior sensitivity compared with other methods of determining medication adherence.¹⁶

Medication-Taking Behavior During Antihypertensive Therapy

Numerous large-scale clinical trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)²⁰ and the Hypertension Optimal Treatment (HOT) trial,²¹ have demonstrated the benefits of BP control to reduce cardiovascular mortality and morbidity in patients with hypertension. In the HOT trial, for example, which involved 18,790 patients with hypertension, the lowest incidence of major cardiovascular events was found to occur when antihypertensive therapy decreased diastolic BP to an average of 82.6 mm Hg.²¹ Yet there is still a large discrepancy between results from clinical trials and the low rates of BP control within the community.^{22–25} This gap between everyday clinical practice and clinical trials is probably largely explained by differences in medication-taking behavior, in that clinical trials tend to select for highly motivated patients whose medication adherence and persistence is closely monitored.^{11,26} Indeed, medication-taking behavior can vary considerably in the hypertensive patient population routinely encountered. Results from a systematic review of electronic monitoring studies, for example, indicated that 9% to 37% of patients had inadequate adherence to antihypertensive medication,²⁷ whereas a study based on self-reported medication intake found that 35% of patients were nonadherent.²⁸ Others have reported nonadherence rates in the range of 15% to 47% (mean 24%).²⁹ The wide range of adherence rates in published studies is presumably a reflection not only of the range of methodologies

and antihypertensive agents that have been used but also of the number and complexity of reasons for poor medication-taking behavior³⁰ (Table 1).

Persistence with antihypertensive therapy is also problematic in routine care. In one study that analyzed pharmacy refill data, persistence decreased in the first 6 months after antihypertensive therapy was started and continued to decline over the next 4 years. Among patients with newly diagnosed hypertension, for example, 78% were persistent at 1 year and only 46% at 4.5 years; patients with established hypertension generally showed higher persistence rates (97% and 82%, respectively)³¹ (Fig. 2). Bovet et al³² reported that among newly diagnosed hypertensive patients in a developing country, the percentage of patients who had good adherence (as determined by electronic monitoring) decreased from 46% to 26% between 1 month and 12 months of follow-up. Other studies show that, within 1 year, up to half of patients are no longer taking their antihypertensive medication.³³ Barriers to good medication-taking behavior clearly tend to occur early in the therapeutic course of antihypertensive therapy, emphasizing the need for regular reinforcement of the adherence message by facilitators such as the following: 1) use of reminders (as patient forgetfulness can be a frequent reason for poor medication-taking behavior); 2) knowledge about hypertension treatment and complications; and 3) having social support and good doctor–patient communication.^{34,35}

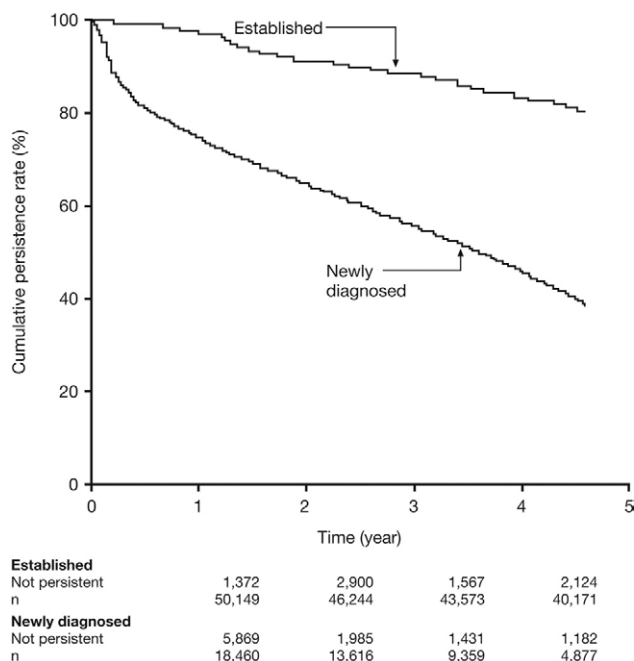


FIG. 2. Cumulative rate of persistence with antihypertensive therapy, according to whether patients had established hypertension or were newly diagnosed. Reproduced with permission from Ref. ³¹

Consequences of Poor Medication-Taking Behavior During Antihypertensive Therapy

Clearly, patients need to engage in good medication-taking behavior during antihypertensive therapy to achieve good control of their BP and decreased risk of cardiovascular outcomes, a link that was established more than 40 years ago.³⁶ Some investigators have since suggested that poor medication-taking behavior may not necessarily be associated with resistance to antihypertensive treatment.^{27,37} For example, Nuesch et al³⁷ reported that poor adherence was no more prevalent among patients with poor BP control than in patients without treatment resistance, leading to the conclusion that other factors independent of a patient's medication-taking behavior were more relevant in explaining poor BP control. However, these investigators made no mention of the potential influence of treatment side effects that may independently influence medication-taking behavior, and they did not emphasize the improvement in BP control upon monitoring of adherence in their patients. The study by Wetzels et al,²⁷ which reviewed adherence findings reported in 30 studies of antihypertensive medication treatment, also showed that the relationship between medication-taking behavior and BP control can be difficult to establish. The latter authors restricted their analysis to studies that used electronic monitoring, and in the majority of studies the patients were aware that their adherence was being monitored. This may have contributed to a trend toward higher adherence rates and, in turn, better BP control, than in other studies. Indeed, several authors reported that BP control was improved (without changes in therapy) when a group of patients with resistant hypertension were told that their medication adherence was going to be electronically measured.^{18,19} In addition, in a recent study of 62 patients with uncontrolled hypertension, use of MEMS was associated with a significantly greater proportion of patients achieving target systolic BP after 4 months compared with patients whose adherence was monitored according to usual care.³⁸ If the majority of patients achieve a high rate of adherence, a direct correlation between BP control and medication-taking behavior may be difficult to show. It is also important to note that difficulties exist in studying patient adherence without informing patients that their adherence is being monitored.

Elsewhere, most of the evidence suggests a correlation between medication-taking behavior during antihypertensive therapy and BP control, as highlighted by the study of Elzubier et al,³⁹ in which only 18% of nonadherent patients (as determined by returned tablet counts) achieved good control of BP v 92% of those with good medication adherence. Other studies have provided similarly convincing evidence. DiMatteo et al⁴⁰ reported that patients who adhered to their antihypertensive medication were three times more likely to achieve good BP control than those who were nonadherent. More recently, Halpern et al eval-

uated the impact of medication-taking behavior on BP outcomes during treatment with the angiotensin receptor blocker (ARB) valsartan.⁴¹ Overall, patients with $\geq 90\%$ medication adherence (as determined by the medication possession ratio) had lower average systolic BP and were significantly more likely to achieve target BP goals than patients with $< 90\%$ adherence (96% v 81%; $P < .0001$). Not surprisingly, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has identified poor medication-taking behavior (specifically, adherence) as one of the main causes of failure to control BP in patients with hypertension.²⁵ In turn, these patients remain at high risk for cardiovascular disease⁴² including a higher risk of stroke,⁴³ and can be expected to account for a significant cost burden through avoidable hospital admissions, premature deaths, work absenteeism, and reduced productivity.^{44,45} For example, a study of noninstitutionalized Medicaid patients with hypertension found that those with poor adherence consumed an additional \$873 per patient in healthcare costs during the first year (1994 values), primarily because of increased hospital expenditures.⁴⁶ Consequently, adherence-based savings in medical costs are driven primarily by reductions in hospitalization rates at higher levels of medication adherence.⁴⁷ Others have shown that poor medication adherence causes an average loss of 3.5 workdays per year in patients with hypertension⁴⁸ and can double the cost per quality-adjusted life-year gained,⁴⁹ which emphasizes the economic impact of poor adherence. Improving medication-taking behavior during antihypertensive therapy could therefore represent an important potential source of health and economic improvement.⁵⁰ Further research is warranted.

Improving Medication-Taking Behavior During Antihypertensive Therapy

Improving medication-taking behavior requires consideration of factors relating to patients, physicians and therapy, the influences of which are not necessarily mutually exclusive.

Patient and Physician Factors

No single intervention can robustly enhance medication-taking behavior because many variables affect the patient's decision to take or not take a drug. There is an urgent need, therefore, for comprehensive interventions that use cognitive, behavioral, and affective strategies tailored to the patient's particular needs and based on objective and reliable assessments of medication-taking behavior.^{51–53} In this regard, and based on the integral role of healthcare professionals in patient education and self-management of other diseases, education programs delivered by academic nurse-counselors in a primary care setting may encourage hypertensive patients in their quest to attain and maintain

target BP goals. For example, diabetes educators partner with patients and their families to teach diabetes self-management and help patients to gain control of their disease,⁵⁴ highlighting the benefits that can be achieved through better communication between patients and healthcare providers. For example, addressing the patient's inability to perceive a benefit from the use of therapy for an asymptomatic disease overcomes a powerful stimulus for poor medication-taking behavior⁵⁵; studies show that patients with hypertension who believe in the necessity of medication are more likely to comply with their therapy than those who do not.⁵⁶ Multifaceted and tailored interventions appear to be the most effective methods of improving medication-taking behavior during antihypertensive therapy because they address the multiple factors associated with the problem.⁵⁷ However, these techniques tend to be complex, expensive, and labor-intensive,⁵⁸ and they are not always effective in terms of optimizing BP control.^{59,60}

Although the emphasis has been on the patient's role in adherence and persistence issues, it is necessary to consider physician-related factors that may also influence medication-taking behavior. DiMatteo et al⁶¹ noted that the behavior of the physician was a crucial element in patients' willingness and ability to follow treatment advice, as was closer attention to regular follow-up. This finding is in agreement with earlier studies, which recognized the importance of giving patients time and confidence to ask their physician any questions about their therapy and to discuss any problems relating to their medication, as a means of overcoming barriers to poor medication-taking behavior.⁶²

Therapy Factors

It has been suggested that the complexity of the dosage regimen and side effects are the therapy-related factors that probably have the greatest influence.^{1,63} Indeed, a review of studies that measured adherence using electronic monitoring (across multiple indications) confirmed the inverse relationship between adherence and the prescribed number of doses per day,⁶⁴ a relationship that is apparent in the hypertension setting as well.^{37,65} Indeed, antihypertensive agents that are dosed once daily are taken more regularly than drugs that have to be taken more than twice daily.⁶⁶

Patient surveys, which have attempted to determine the reasons for poor medication-taking behavior, have repeatedly demonstrated that side effects associated with antihypertensive drugs are also important in determining adherence rates. Richardson et al,⁶⁷ for example, noted that fear of adverse effects, particularly among younger patients and those in the early stages of treatment, was a major barrier to good medication-taking behavior during antihypertensive treatment. This threat to adherence occurs when patients decide that the accompanying burden of side effects outweighs the potential future benefits. The risk of dose-dependent side effects, and the consequences

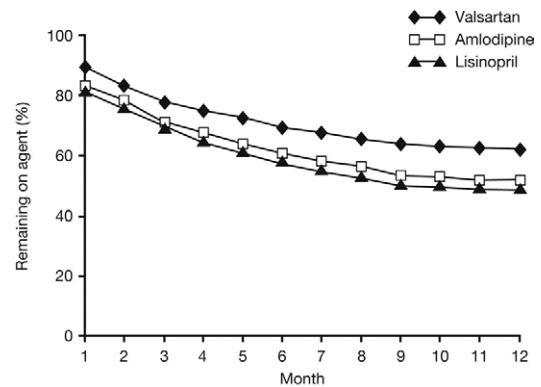


FIG. 3. Persistence with antihypertensive therapy in a usual-care setting. Reproduced with permission from Ref. ⁷³

for medication-taking behavior, is also probably one of the important reasons for acceptance of inadequate BP control by physicians. Indeed, studies show that physicians often accept inadequate BP control to minimize, via the use of low doses that carry a lower risk of side effects, the threat of patient non adherence with the treatment regimen.⁶⁸ Consequently, less frequent dosing regimens (ideally once daily) combined with a favorable tolerability profile results in better medication-taking behavior.^{69–71} Indeed, the availability of antihypertensive agents such as ARB, which have proven efficacy and excellent tolerability, has demonstrated that the selection of drugs with more favorable side effect profiles results in improved medication-taking behavior. Data from a large pharmacy database in the United States, for example, showed that patients treated with ARB had greater medication persistence rates at 1 year than those treated with other classes of antihypertensive agents.⁶⁹ Similar findings were apparent in a more recent analysis of German prescriptions claims data, in which persistence and adherence rates were significantly higher for ARB such as valsartan compared with all other drug classes.⁷² In another pharmacy system database study of nearly 143,000 patients, significantly more patients taking valsartan remained persistent on therapy at 12 months (63%) compared with patients taking amlodipine (53%) or lisinopril (50%) ($P < .001$)⁷³ (Fig. 3). The benefits of ARB for improving medication-taking behavior have been confirmed in other studies^{74–76} and are presumably explained by the combination of favorable tolerability and once-daily dosing provided by these agents. It is important to note that treatment choice is also dependent on other key factors specific to each patient.

Conclusion

Treatment efficacy alone is not sufficient if patients do not take their medications properly and consistently—in the case of hypertension, most likely for the rest of their lives. Patients with hypertension who have poor medication-taking behavior remain largely unrecognized and the development of programs to detect these individuals and

support long-term adherence is an important issue. On the basis of current literature and clinical experience, it appears that an effective, convenient drug regimen that is relatively free of side effects, combined with a positive and supportive approach to treatment, will therefore yield the best results in terms of facilitating adherence and persistence with antihypertensive therapy.

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