AJH 2006; 19:1190–1196

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.

Key Words: Medication adherence, persistence, hypertension, blood pressure control, medication-taking behavior.

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-

Received December 13, 2005. First decision March 17, 2006. Accepted April 15, 2006.

From the Service de Néphrologie et Consultation d'Hypertension, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.

Medical writing support was provided by ACUMED, funded by an educational grant from Novartis Pharma AG.

Address correspondence and reprint requests to Prof. M. Burnier, Service de Néphrologie et Consultation d'Hypertension, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 17, 1011 Lausanne, Switzerland; e-mail: michel.burnier@hospvd.ch

0895-7061/06/$32.00
doi:10.1016/j.amjhyper.2006.04.006

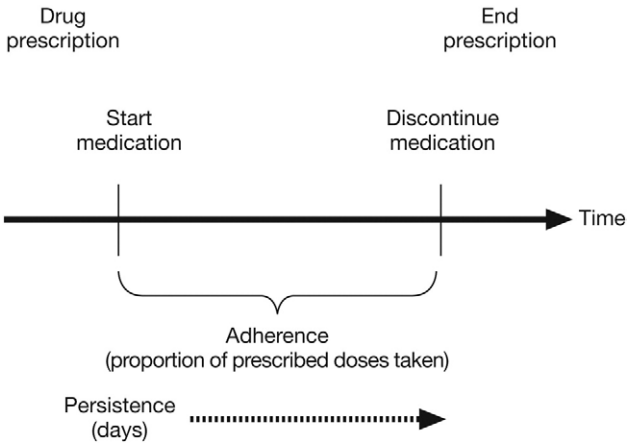


FIG. 1. Aspects of medication-taking behavior.

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 adherence[12] 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] Aprex 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

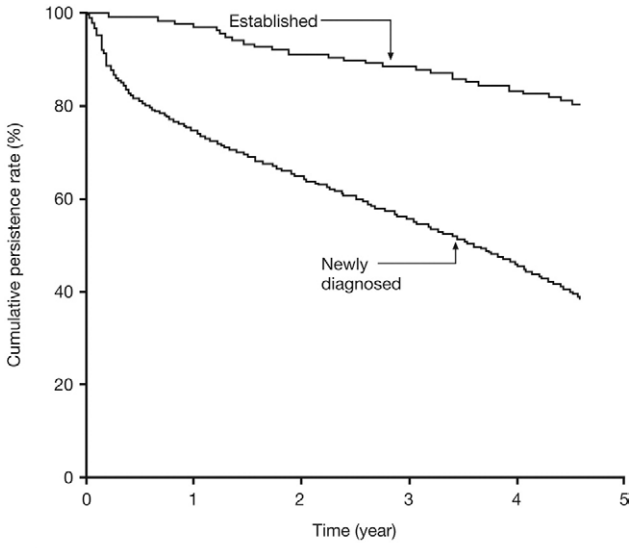
Physician and patient factors
Cost of medication and related care
Instructions not clear to patient
Failure of physician to increase or change therapy to achieve blood pressure goals
Inadequate or no patient education
Lack of involvement of patient in treatment plan
Therapy factors
Side effects of medication
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 behavior[30] (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 al[32] 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]



Established				
Not persistent	1,372	2,900	1,567	2,124
n	50,149	46,244	43,573	40,171
Newly diagnosed				
Not persistent	5,869	1,985	1,431	1,182
n	18,460	13,616	9,359	4,877

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 al[37] 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 al[40] 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 evaluated the impact of medication-taking behavior on BP outcomes during treatment with the angiotensin receptor blocker (ARB) valsartan.[41] Overall, patients with ≥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 disease[42] 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 hypertension[48] 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-counsellors 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 behavior[55]; 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 al[61] 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 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.

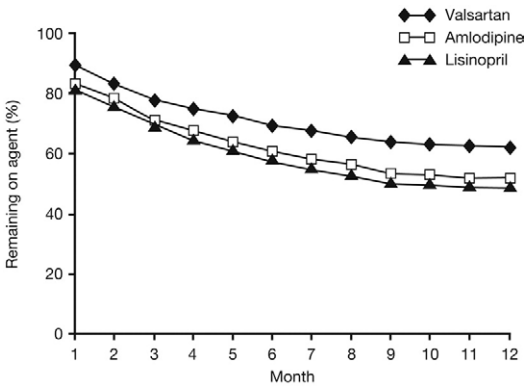


FIG. 3. Persistence with antihypertensive therapy in a usual-care setting. Reproduced with permission from Ref. [73]

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.

References

1. World Health Organization: Adherence to long-term therapies. Evidence for action. Geneva: World Health Organization, 2003. http://www.who.int/chronic_conditions/adherencereport/en/index.html. Last accessed May 1, 2006.
2. Hajjar I, Kotchen TA: Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. J Am Med Assoc 2003;290:199–206.
3. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodriguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F: Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. J Am Med Assoc 2003;289:2363–2369.
4. Mullen PD: Compliance becomes concordance. Br Med J 1997;314:691–692.
5. From compliance to concordance: achieving shared goals in medicine taking. Royal Pharmaceutical Society, London, 1997. http://www.rpsgb.org.uk. Last accessed May 1, 2006.
6. Cramer JA, Scheyer RD, Mattson RH: Compliance declines between clinic visits. Arch Intern Med 1990;150:1509–1510.
7. Morisky DE, Green LW, Levine DM: Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67–74.
8. Haynes RB, McDonald HP, Garg AX: Helping patients follow prescribed treatment: clinical applications. J Am Med Assoc 2002;288:2880–2883.
9. Roth HP, Caron HS: Accuracy of doctors' estimates and patients' statements on adherence to a drug regimen. Clin Pharmacol Ther 1978;23:361–370.
10. Gilbert JR, Evans CE, Haynes RB, Tugwell P: Predicting compliance with a regimen of digoxin therapy in family practice. Can Med Assoc J 1980;123:119–122.
11. Burnier M, Santschi V, Favrat B, Brunner HR: Monitoring compliance in resistant hypertension: an important step in patient management. J Hypertens 2003;21(Suppl 2):S37–S42.
12. Dowse R, Futter WT: Outpatient compliance with theophylline and phenytoin. S Afr Med J 1991;80:550–553.
13. Matsui D, Hermann C, Klein J, Berkovitch M, Olivieri N, Koren G: Critical comparison of novel and existing methods of compliance assessment during a clinical trial of an oral iron chelator. J Clin Pharmacol 1994;34:944–949.
14. Sclar DA, Chin A, Skaer TL, Okamoto MP, Nakahiro RJ, Gill MA: Effect of health education in promoting prescription refill compliance among patients with hypertension. Clin Ther 1991;13:495–498.
15. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL: How often is medication taken as prescribed? A novel assessment technique. J Am Med Assoc 1989;261:3273–3277.
16. Schwed A, Fallab CL, Burnier M, Waeber B, Kappenberger L, Burnand B, Darioli R: Electronic monitoring of compliance to lipid-lowering therapy in clinical practice. J Clin Pharmacol 1999;39:402–409.
17. McKenney JM, Munroe WP, Wright JT Jr: Impact of an electronic medication compliance aid on long-term blood pressure control. J Clin Pharmacol 1992;32:277–283.
18. Waeber B, Vetter W, Darioli R, Keller U, Brunner HR: Improved blood pressure control by monitoring compliance with antihypertensive therapy. Int J Clin Pract 1999;53:37–38.
19. Burnier M, Schnieder MP, Chiolero A, Stubi C, Brunner HR: Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens 2001;19:335–341.
20. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Am Med Assoc 2002;288:2981–2997.
21. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755–1762.
22. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D: Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305–313.
23. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, Moskowitz MA: Inadequate management of blood pressure in a hypertensive population. N Engl J Med 1998;339:1957–1963.
24. Knight EL, Bohn RL, Wang PS, Glynn RJ, Mogan H, Avorn J: Predictors of uncontrolled hypertension in ambulatory patients. Hypertension 2001;38:809–814.
25. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. J Am Med Assoc 2003;289:2560–2572.
26. Burnier M: Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? J Hypertens 2002;20:1251–1253.
27. Wetzels GEC, Nelemans P, Schouten JS, Prins MH: Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. J Hypertens 2004;22:1849–1855.
28. Peltzer K: Health beliefs and prescription medication compliance among diagnosed hypertension clinic attenders in a rural South African hospital. Curationis 2004;27:15–23.
29. Cramer JA: Consequences of intermittent treatment for hypertension: the case for medication compliance and persistence. Am J Managed Care 1998;4:1563–1568.
30. Oparil S, Calhoun DA: Managing the patient with hard to control hypertension. Am Fam Physician 1998;57:1007–1014, 1019–1020.
31. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD: Persistence with treatment for hypertension in actual practice. Can Med Assoc J 1999;160:31–37.
32. Bovet P, Burnier M, Madeleine G, Wäber B, Paccaud F: Monitoring one-year compliance to antihypertension medication in the Seychelles. Bull WHO 2002;80:33–39.
33. Morgan SG, Yan L: Persistence with hypertension treatment among community-dwelling BC seniors. Can J Clin Pharmacol 2004;12:e267–e273.
34. Düsing R, Weisser B, Mengden T, Vetter H: Changes in antihypertensive treatment—the role of adverse effects and compliance. Blood Press 1998;7:313–315.
35. Ogedegbe G, Harrison M, Robbins L, Mancuso CA, Allegrante JP: Barriers and facilitators of medication adherence in hypertensive African Americans: a qualitative study. Ethn Dis 2004;14:3–12.
36. Morisky DE, Levine DM, Green LW, Shapiro S, Russell RP, Smith CR: Five year blood pressure control and mortality following health education for hypertensive patients. Am J Public Health 1963;73:153–162.

37. Nuesch R, Schroeder K, Dieterle T, Martina B, Battegay E: Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study. Br Med J 2001;323:142–146.
38. Santschi V, Ruffieux C, Bugnon O, Burnier M: Electronic monitoring of drug adherence improves blood pressure control in hypertension: a randomized, controlled trial. J Hypertension 2005;23(Suppl 2):S75:P1.186.
39. Elzubier AG, Husain AA, Suleiman IA, Hamid ZA: Drug compliance among hypertensive patients in Kassala, eastern Sudan. East Mediterr Health J 2000;6:100–105.
40. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW: Patient adherence and medical treatment outcomes: a meta-analysis. Med Care 2002;40:794–811.
41. Halpern MT, Khan Z, Daley W, Stewart WF, Vincze G: Impact of compliance and Persistence of treatment with valsartan on hypertension clinical outcomes. Value in health 2005. 8(6):Abstract PCV52.
42. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS: The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. J Am Med Assoc 1990; 263:1653–1657.
43. Baune BT, Aljeesh YI, Bender R: The impact of non-compliance with the therapeutic regimen on the development of stroke among hypertensive men and women in Gaza, Palestine. Saudi Med J 2004;25:1683–1688.
44. Rizzo JA, Simons WR: Variations in compliance among hypertensive patients by drug class: implications for healthcare costs. Clin Ther 1997;19:1446–1457.
45. Hodgson TA, Cai L: Medical care expenditures for hypertension, its complications, and its comorbidities. Med Care 2001;39:599–615.
46. McCombs JS, Nichol MB, Newman CM, Sclar DA: The costs of interrupting antihypertensive drug therapy in a Medicaid population. Med Care 1994;32:214–226.
47. Sokol MC, McGuigan KA, Verbrugge, RR, Epstein RS: Impact of medication adherence on hospitalization risk and healthcare cost. Med Care 2005;43:521–530.
48. Rizzo JA, Abbott TA III, Pashko S: Labour productivity effects of prescribed medicines for chronically ill workers. Health Econ 1996; 5:249–265.
49. Drummond M, Coyle D: Assessing the economic value of antihypertensive medicines. J Hum Hypertens 1992;6:495–501.
50. Mar J, Rodriguez-Artalejo F: Which is more important for the efficiency of hypertension treatment: hypertension stage, type of drug or therapeutic compliance? J Hypertens 2001;19:149–155.
51. Haynes RB, McKibbon KA, Kanani R: Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. Lancet 1996;348:383–386.
52. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B: Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care 1998;36:1138–1161.
53. 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; 164:722–732.
54. Maryniuk MD, Bronzini BM, Lorenzi GM: Quality diabetes self-management education: achieving and maintaining ADA Education Program Recognition. Diabetes Educ 2004;30:467–475.
55. Conrad P: The meaning of medications: another look at compliance. Social Science Med 1985;20:29–37.
56. Ross S, Walker A, MacLeod MJ: Patient compliance in hypertension: role of illness perceptions and treatment beliefs. J Hum Hypertens 2004;18:607–613.
57. van Eijken M, Tsang S, Wensing M, de Smet PA, Grol RP: Interventions to improve medication compliance in older patients living in the community: a systematic review of the literature. Drugs Aging 2003;20:229–240.
58. McDonald HP, Garg AX, Haynes RB: Interventions to enhance patient adherence to medication prescriptions: scientific review. J Am Med Assoc 2002;288:2868–2879.
59. Woollard J, Burke V, Beilin LJ: Effects of general practice-based nurse-counselling on ambulatory blood pressure and antihypertensive drug prescription in patients at increased risk of cardiovascular disease. J Hum Hypertens 2003;17:689–695.
60. Schroeder K, Fahey T, Hollinghurst S, Peters TJ: Nurse-led adherence support in hypertension: a randomized controlled trial. Fam Pract 2005;22:144–151.
61. DiMatteo MR, Sherbourne CD, Hays RD, Ordway L, Kravitz RL, McGlynn EA, Kaplan S, Rogers WH: Physicians characteristics influence patients adherence to medical treatment. Results from a medical outcomes study. Health Psych 1993;12:93–102.
62. Stamler R, Stamler J, Civinelli J, Pritchard D, Gosch FC, Ticho S, Restivo B, Fine D: Adherence and blood pressure control to hypertension treatment. Lancet 1975;2;1227–1230.
63. Carter S, Taylor D, Levenson R: A question of choice—compliance in medicine taking. A preliminary review. London: Medicines Partnership, 2005. http://www.medicines-partnership.org/research-evidence/major-reviews/a-question-of-choice. Last accessed May 1, 2006.
64. Claxton AJ, Cramer J, Pierce C: A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296–1310.
65. Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, Hersich AL: Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther 2002;24:302–316.
66. Sica DA: Fixed dose combination antihypertensive drugs. Do they have a role in rational therapy? Drugs 1994;48:16–24.
67. Richardson MA, Simons-Morton B, Annegers JF: Effect of perceived barriers on compliance with antihypertensive medication. Health Educ Q 1993;20:489–503.
68. Moser M: Clarify the message, improve outcome in the management of hypertension. J Clin Hypertens (Greenwich) 2000;2:71–76.
69. Bloom BS: Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther 1998;20:671–681.
70. Hasford JM: A population-based European cohort study of persistence in newly diagnosed hypertensive patients. J Hum Hypertens 2002;16:569–575.
71. Burnier M, Hess B, Greminger P, Wäber B: Determinants of persistence in hypertensive patients treated with irbesartan: results of a postmarketing survey. BMC Cardiovascular Disorders 2005;5:13. Available at: www.biomedcentral.com/1471-2261/5/13. Last accessed May 1, 2006.
72. Höer A, Gothe H, Khan Z, Häussler B: Patients on ARBs (and valsartan as a representative) experience higher persistence and compliance (adherence) with therapy compared with other antihypertensive drug classes in a German sickness fund population [abstract]. ISPOR 8th Annual European Congress, 6–8 November, 2005, Florence, Italy.
73. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F: Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. J Managed Care Pharm 2003;9:424–429.
74. Conlin PR, Gerth WC, Fox J, Röhm JB, Boccuzzi SJ: Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. Clin Ther 2001;23:1999–2010.
75. Marentette MA, Gerth WC, Billings DK, Zarnke KB: Antihypertensive therapy persistence and drug class. Can J Cardiol 2002;18: 649–656.
76. Bourgault C, Sénécal M, Brisson M, Marantette MA, Gregoire JP: Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. J Hum Hypertens 2005;8:607–613.