

Consequences of Intermittent Treatment for Hypertension: The Case for Medication Compliance and Persistence

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Abstract

Objective: To review patient compliance with once-daily antihypertensive medications and the impact of partial compliance on healthcare outcomes.

Data Sources: A MEDLINE search of the literature using the terms "patient compliance," "antihypertensive medications," and "hypertension" for the period 1976-1996 was conducted. In addition, papers cited in reference lists of source articles were reviewed.

Study Selection: Articles were selected if they described patterns of compliance, including rates for differing dosing regimens. Articles discussing once-daily dosing were selected only if they included information on the methodology for compliance assessment. Thirteen reports met these criteria.

Data Synthesis: Patterns of compliance vary, with only a partial relationship to dosing regimens. Overall compliance was 76% for once-daily antihypertensive medications, with a wide range found (53% to 85%). These data were comparable to the mean 75% compliance found for other medical disorders.

Conclusions: Persistence with treatment is necessary for reduction of long-term consequences of hypertension. Enhancing compliance with antihypertensive medications could thus have a profound impact on health outcomes. Once-daily dosing should be coupled with selection of a drug with long duration of action to overcome problems of missed doses. Widespread adoption of simple compliance enhancement methods could lead to decreased morbidity and mortality from cardiovascular disease and stroke.

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Uncontrolled hypertension is one of the most powerful contributors to cardiovascular disease, resulting in a fourfold risk of coronary artery disease and sevenfold risk of stroke, as compared with normotensive patients.^{1,3} Reduction of blood pressure with antihypertensive therapy decreases incidence of stroke, coronary events, and heart failure; progression of renal disease; progression to more severe hypertension; and all-cause mortality.^{4,5} Nonetheless, only half of treated hypertensive patients have their disease adequately controlled.⁶

Key underlying factors are compliance (ie, attempting to take the medication each day as prescribed) and persistence (ie, continuing to take the medication long-term).⁷ However, neither compliance nor persistence can be assumed among hypertensive patients or other groups of patients.^{6,8} The common reluctance of patients to participate in lifestyle modification⁹ leads physicians to prescribe antihypertensive medications that are considered to be well-tolerated and easy to manage in a once-daily regimen. Unfortunately, the majority of patients diagnosed with hypertension do not take medication as prescribed.¹⁰⁻¹² Studies in which dosing was carefully monitored found that patients take approximately three fourths of doses as prescribed, regardless of the specific medical disorder.⁸ Compliance with antihypertensive medication regimens is the link between disease management and attainment of the desired therapeutic result. When that link is broken, either sporadically or permanently, costly consequences ensue.^{13,14}

The objective of this article was to review overall compliance issues for antihypertensive medications and for a once-daily regimen. In addition, the case for improvement in treatment efficacy is examined with respect to investment in healthcare during the early, asymptomatic phase of hypertension to prevent severe and expensive long-term consequences.

... METHODS ...

A MEDLINE search, using the terms "patient compliance", "antihypertensive medications", and

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"hypertension" from 1976 to 1996 was augmented by review of papers cited in reference lists of source articles. Papers describing patterns of compliance were selected if they described rates for different dosing regimens. For the survey of once-daily dosing, papers were selected only if they provided data on rates of compliance with antihypertensive medication prescribed once a day and on the methodology for compliance assessment. Thirteen reports met these criteria. Eight of the reports were based on microelectronic monitoring that documented the number of days on which one dose was taken, and the number of days on which the dose was taken within the prescribed interval of 24 hours (± 6 to 12 hours). Three reports used prescription refill records to estimate compliance as the number of days between refills. One investigator counted the number of pills remaining, and one used patient interviews to estimate the number of days a dose was taken. Selection of reports of the consequences of poor compliance was made if the paper described short-term or long-term outcomes in hypertension.

The definition of partial compliance is taking less than the prescribed amount of antihypertensive med-

ication or taking the medication at inappropriate time intervals (hours between doses). Treatment persistence is defined as long-term continuation of antihypertensive treatment. Outcomes are defined as blood pressure measurements or sequelae of hypertension (eg, cardiovascular or cerebrovascular events).

... RESULTS ...

Patterns of Compliance

As a chronic disorder, hypertension requires long-term treatment. As an asymptomatic disorder, hypertension treatment does not produce an immediately recognizable benefit but often does diminish quality of life with adverse effects (eg, impotence, sedation).¹⁵ Rudd¹⁶ identified three types of patients: near-optimal compliers, partial compliers, and non-compliers. He estimated that approximately 50% to 60% of people were categorized as near-optimal compliers with antihypertensive regimens; 30% to 45% of patients are partial compliers who takes doses erratically or at a lower rate than the prescribed number of doses.¹⁷ Dosing can vary from day to day, leaving short and long periods without treatment¹⁷ or periods of overcompliance when extra doses are

Table 1. Compliance Rates for Once-Daily Antihypertensive Medication*

| Reference | Compliance Rate (%) [†] | Compliance Definition | Assessment Technique | Antihypertensive Medication |
|---|----------------------------------|-----------------------|----------------------|------------------------------------|
| Detry et al, 1995 ²³ | 85 | 1/d | Electronic | Amlodipine |
| Farmer et al, 1994 ²⁴ | 85 | No. days dispensed | Rx refill | Calcium channel blockers |
| Juncos, 1990 ²⁸ | 85 | >90% Doses taken | Interview | Enalapril |
| Kruse et al, 1994 ²² | 85 | 1/d | Electronic | Triamterene + hydrochlorothiazide |
| Eisen et al, 1987 ³¹ | 84 | 24 \pm 12 hours | Electronic | Hydrochlorothiazide chlorthalidone |
| Mallion et al, 1996 ²⁹ | 83 | >80% Doses taken | Electronic | Trandolapril |
| Sclar et al, 1991 ³³ | 83 | No. days dispensed | Rx refill | Atenolol |
| Mengden et al, 1993 ¹² | 78 | 1/d | Electronic | Amlodipine |
| Mallion et al, 1992 ²⁶ | 72 | 24 \pm 1 hours | Electronic | Nitrendipine |
| Guerrero et al, 1993 ²⁵ | 67 | 24 \pm 12 hours | Electronic | Isradipine |
| Haynes et al, 1976 ³⁴ | 66 | >80% Doses taken | Pill count | All |
| Skaer et al, 1993 ²⁷ | 56 | No. days dispensed | Rx refill | Verapamil |
| Vander Stichele et al, 1992 ²⁰ | 53 | 24 \pm 6 hours | Electronic | Lisinopril, atenolol |

Rx = prescription

*Based on 13 reports

[†]Mean, 76%; standard deviation, 11.6%; range, 53% to 85%

taken.^{18,19} In addition, 5% to 10% of patients are non-compliers who probably are not engaged in their diagnosis and need for treatment.

Cramer et al²⁰ described fluctuations in dosing as a response to medical intervention. Compliance was found to be significantly higher during 5-day periods before and after medical appointments, compared with 30 days after a visit. The anticipation of the visit probably increased compliance as part of enhanced health behavior that was maintained for a period after the visit.²¹ Fading of health behavior was associated with erratic compliance and the potential for medical problems because of underdosing.²⁰ Feinstein²² characterized this behavior as "white-coat compliance."

A review of 26 studies¹⁰ found that prescribing 1, 2, 3, or 4 doses a day gave diminishing returns as the number of doses increased to more than twice daily ($P < 0.05$). Overall compliance rates were 73%, 70%, 52%, and 42%, respectively. In a survey of nine reports in which medication compliance was assessed prospectively with microelectronic monitoring, Cramer⁸ found that patients take approximately 75% of doses as prescribed, across a wide variety of medical disorders.

Compliance with Once-Daily Dosing Regimens

The table describes 13 reports of compliance with antihypertensive medications prescribed once daily. The overall rate of compliance was 76%, with a wide range found (53% to 85%). Six investigations evaluated use of a calcium channel blocker,^{12,23,27} three studies included angiotensin-converting enzyme inhibitors,²⁸⁻³⁰ two included diuretics,^{31,32} and one study used a β -blocker.³³ One report described a variety of antihypertensive medications.³⁴

Eight studies used microelectronic monitoring that provides a computer-based record of the date and time of each container opening.⁷ MEMS[®] monitors (APREX, Menlo Park, CA) were used in seven studies,^{12,23,25,26,29,30,32} and another device (not commercially available) was used in one study.³¹ The mean compliance rate was the same (76%) for the studies using MEMS methodology as for the overall group of 13 studies (76%).

Three reports^{24,27,33} used prescription database records to identify the number of days between refills to determine the ratio of pills prescribed over the period of observation. Surreptitious counting of pills during home visits was the method used by Haynes et al.³⁴ Juncos²⁸ interviewed patients to assess who reported taking their medication more than 80% of the time.

Consequences of Poor Compliance with Antihypertensive Therapy

Risks related to poor compliance with β -blockers were defined by Psaty et al³⁵ in a case-controlled study of risk factors for coronary artery disease events related to hypertension. They examined the records of patients who were admitted to the hospital for an acute cardiac event to assess medication compliance before the event. Patients who took less than 80% of their antihypertensive medication were at a fourfold elevated risk for an event (relative risk, 4.5 to 6.5) than good compliers. Patients who had taken 80% to 99% of doses had a twofold-increased risk, suggesting that occasional missed doses also could have severe sequelae. This report demonstrates that dose omission is not always benign but could have serious consequences. Partial compliance with β -blockers might do more transient harm than the overall beneficial effect of treatment.

Abrupt discontinuation of nonintrinsic sympathomimetic activity blockers can also lead to rebound hypertension with elevated blood pressure.³⁶ These "demanding" drugs require regular daily dosing to maintain continuous drug action.³⁷ The danger of omitting doses of antihypertensive medication was defined in two simulation studies. Leenen et al³⁸ designed a study of calcium channel blockers with short and long elimination half-lives in which doses were purposely omitted to simulate noncompliance. Patients were randomized to diltiazem (short-acting) given twice daily or amlodipine (long-acting) given once daily. After 2 months of stabilization, 24-hour blood pressure monitoring was performed during 2 days of placebo treatment. In the diltiazem group, systolic and diastolic pressures and heart rate rose over the 2 days without treatment. Both systolic and diastolic pressures were maintained over 2 days for the amlodipine group.

A similar study design was used by Johnson et al³⁹ to evaluate patients receiving a β -blocker, either atenolol (half-life, 7 hours) or betaxolol (half-life, 14 to 22 hours) given once daily. Blood pressure and heart rate were observed during a full-dosing phase when diastolic blood pressure was <90 mm Hg and when placebo was substituted for active medication. Although both drugs provided similar efficacy when patients were taking daily doses, systolic and diastolic pressures increased significantly over 24 hours after a placebo dose replaced atenolol but not betaxolol. Both of these studies represent the conditions present when a patient misses doses for a day or two. The compliance scenario often is an abrupt discontinuation of treatment, followed by abrupt resumption. In the

study by Johnson et al, three patients developed rebound hypertension after missing one dose of atenolol, demonstrating the risk taken by patients during periods of noncompliance.

Maronde et al¹³ reviewed pharmacy records of medically indigent patients (who received medications at no cost) to evaluate underuse of antihypertensive medications and associated hospitalizations. Patients readmitted to the hospital because of uncontrolled blood pressure were found to have used significantly less medication than patients who were not readmitted (26% vs 9% of days without medications, $P = 0.003$). Vinson et al¹⁴ found that periods of noncompliance ("drug holidays") contributed to hospitalization. Similarly, Kruse et al⁴⁰ used continuous microelectronic dose monitoring to determine that consecutive days without diuretic therapy was followed by deterioration of congestive heart failure due to severe pulmonary congestion.

Target organ damage correlates with variability in arterial blood pressure independent of mean actual blood pressure. This concept is supported by the observation that myocardial infarction and sudden death most often occur between 8 AM and noon, when the rate of blood pressure change is greatest.³⁴¹ Cross-sectional evidence indicates that patients with hypertension who do not experience the usual nighttime dip in blood pressure are at increased risk for target organ damage, left ventricular hypertrophy, cerebrovascular damage, and cerebrovascular accident, as well as having a high incidence of atherosclerotic disease.⁴¹

... DISCUSSION ...

The studies described demonstrate that control of hypertension is an important goal for reduction in severe medical consequences and societal cost savings. Meta-analyses indicate that patients with mild-to-moderate hypertension can benefit significantly from even modest blood pressure reductions.⁴¹ A reduction of 5 mm Hg in diastolic pressure would reduce mortality from stroke by 40% and coronary heart disease by 14%.⁴³ The distribution of hypertension and morbidity/mortality reflects the predominance of much larger numbers of people (70% to 75%) with borderline or mild blood pressure elevations. Thus, notable associations of mild disease with stroke and coronary heart disease can be diminished with small reductions in blood pressure.

This survey (table) demonstrates that compliance is not perfect even for a once-daily regimen, with a mean of 76% of doses taken as prescribed. The clinical impli-

cation of these findings is that many patients have wide swings in blood pressure when doses are late or missed. Some antihypertensive medications with short half-lives have been shown to have extended duration of action with protection for approximately 24 hours. However, the difference in blood pressure between the time of maximum absorption of a dose and the terminal phase of activity can be pronounced. Antihypertensive medications with long half-lives that provide coverage for more than 24 hours not only provide smooth blood pressure control, but they also provide coverage for a period after a missed or late dose.^{17,44,45} Extended action is particularly important during the early morning period of high vulnerability,⁴¹ as well as to avoid cardiac events or rebound hypertension.³⁶

Because the difference in compliance rates between once- and twice-daily dosing is small,^{7,10} there is only modest incentive to select a drug based on the convenience of once-daily dosing as a pharmacokinetic variable. However, as these data demonstrate, the rationale for selecting a once-daily drug should be based on the continuity of action in case one or more doses are omitted. Simply reformulating a drug for slow release will not provide persistent therapeutic coverage after missed doses.³⁸ Given the propensity of individuals to forget doses, it is worthwhile for a physician to select an antihypertensive medication that is protective for more than 24 hours. Acknowledging that few patients are 100% compliant for long periods,⁷ the table shows that most patients with hypertension are at risk 24% of the time. Interruptions in pharmacodynamic action may compromise health.³⁴¹ Taking three fourths of doses as prescribed leaves a wide window for potential cardiac disaster. The immediate risk is a rebound phenomenon with precipitous fall in blood pressure when medication is restarted at full dose after a lapse in treatment.³⁸ Target organ damage occurs slowly, taking its inexorable toll over years or decades.

During the course of treatment, management of hypertension is complicated by partial or erratic compliance.²⁰ The physician is faced with a question: Did the drug fail or did the patient fail to comply?⁷ If the dose is increased, adverse effects could increase. If the medication is changed, the risks and costs of switching are incurred. How can physicians help patients to enhance compliance with their prescription for antihypertensive medications? Starting with the assumption that patients with a variety of medical disorders take approximately three fourths of medication as prescribed,⁸ physicians should look for poor compliance as a reason for ineffectiveness of a prescribed treatment. In addition, healthcare providers should be aware of the possibility of erratic compliance during long-term

follow-up.²⁰ As stated by former Surgeon General C. Everett Koop, "drugs don't work in patients who don't take them." Taking time to enhance patient compliance is a value-added role for physicians, both for the health of the patient and for the cost-savings to the community. In addition to prescribing antihypertensive medications with long duration of action that provide therapeutic coverage for far longer than 24 hours, healthcare providers could institute simple programs to foster compliance enhancement.^{46,47} Additional research is needed in this area of health services.

As medical care moves toward capitation, physicians face increasing responsibility for long-term outcomes for their patients. Talking about how to follow a prescribed plan takes time but that should be considered an investment toward management of uncontrolled hypertension or the potential for costly cardiovascular and cerebrovascular disasters. The American Heart Association has recommended use of strategies to enhance compliance with antihypertensive medications to decrease morbidity and mortality from cardiovascular disease and stroke.⁴⁸ The first task should be to help partial compliers develop better dosing habits. Use of longer acting medications and development of compliance cues may help to achieve this goal. In addition, physicians should look toward antihypertensive medications that control blood pressure for 48 to 72 hours to provide protection for patients who are, after all, only human and, by nature, forgetful.

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