Medication Nonadherence: An Unrecognized Cardiovascular Risk Factor

Mark A. Munger, PharmD; Benjamin W. Van Tassell, PharmD; Joanne LaFleur, PharmD, MSPH
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Abstract

Nonadherence with prescribed drug regimens is a pervasive medical problem. Multiple variables affecting physicians and patients contribute to nonadherence, which negatively affects treatment outcomes. In patients with hypertension, medication nonadherence is a significant, often unrecognized, risk factor that contributes to poor blood pressure control, thereby contributing to the development of further vascular disorders such as heart failure, coronary heart disease, renal insufficiency, and stroke.

Analysis of various patient populations shows that choice of drug, use of concomitant medications, tolerability of drug, and duration of drug treatment influence the prevalence of nonadherence. Intervention is required among patients and healthcare prescribers to increase awareness of the need for improved medication adherence. Within this process, it is important to identify indicators of nonadherence within patient populations.

This review examines the prevalence of nonadherence as a risk factor in the management of chronic diseases, with a specific focus on antihypertensive medications. Factors leading to increased incidence of nonadherence and the strategies needed to improve adherence are discussed.

Medication nonadherence, defined as a patient's passive failure to follow a prescribed drug regimen, remains a significant concern for healthcare professionals and patients. On average, one third to one half of patients do not comply with prescribed treatment regimens.[1-3] Nonadherence rates are relatively high across disease states, treatment regimens, and age groups, with the first several months of therapy characterized by the highest rate of discontinuation.[3] In fact, it has recently been reported that low adherence to beta-blockers or statins in patients who have survived a myocardial infarction results in an increased risk of death.[4] In addition to inadequate disease control, medication nonadherence results in a significant burden to healthcare utilization -- the estimated yearly cost is $396 to $792 million.[1] Additionally, between one third and two thirds of all medication-related hospital admissions are attributed to nonadherence.[5,6]

Cardiovascular disease, which accounts for approximately 1 million deaths in the United States each year, remains a significant health concern.[7] Risk factors for the development of cardiovascular disease are associated with defined risk-taking behaviors (eg, smoking), inherited traits (eg, family history), or laboratory abnormalities (eg, abnormal lipid panels).[7] A significant but often unrecognized cardiovascular risk factor universal to all patient populations is medication nonadherence; if a patient does

not regularly take the medication prescribed to attenuate cardiovascular disease, no potential therapeutic gain can be achieved. Barriers to medication adherence are multifactorial and include complex medication regimens, convenience factors (eg, dosing frequency), behavioral factors, and treatment of asymptomatic conditions.[2] This review highlights the significance of nonadherence in the treatment of hypertension, a silent but life-threatening disorder that affects approximately 72 million adults in the United States.[7] Hypertension often develops in a cluster with insulin resistance, obesity, and hypercholesterolemia, which contributes to the risk imposed by nonadherence with antihypertensive medications. Numerous strategies to improve medication adherence are available, from enhancing patient education to providing medication adherence information to the healthcare team and will be discussed in this article.

Factors Contributing to Nonadherence With Antihypertensive Medication

Although a significant number of patients have cardiovascular disease, hypertension remains a silent and under treated risk factor. Only 59% of people with hypertension are receiving treatment, but -- most importantly -- only 34% of those receiving treatment achieve adequate control of blood pressure.[8] Patients with hypertension are at an increased rate for stroke, end-stage renal disease, and heart failure.[9-11] In addition, hypertension contributes to the prevalence of other cardiovascular risk factors, such as insulin resistance, lipid abnormalities, changes in renal function, endocrine abnormalities, obesity, left ventricular hypertrophy, diastolic dysfunction, and abnormalities in vascular structure and elasticity.[11] The clustering of these risk factors associated with the hypertensive state supports the importance of adherence with chronic treatment of hypertension. To this end, several studies of antihypertensive medication adherence have examined the effect of contributory factors, such as age, race and ethnicity, gender, and external factors, such as drug class, type of adverse effects, polypharmacy, and drug costs.[12-38]

Effect of Age

Studies of elderly patients (age ≥ 65 years) in Medicaid programs show that only 20% of patients exhibit "good adherence" (defined as 80% or more days that patients had antihypertensive medication available).[12] In these studies, adherence was greatest among patients taking angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (CCBs), compared with those taking beta-blockers or diuretics.[13,14] In general, blood pressure is more difficult to control with increasing age. A cross-sectional study of outpatients at a Veterans Health Administration site showed that concomitant use of more than 1 antihypertensive medication increases with patient age (up to age 80, after which it then decreases) and may have an impact on the patient's willingness or ability to comply with the overall regimen. Interestingly, the oldest patients (> 80 years of age), with the least favorable blood pressure control, in the Veteran's Health Administration study were treated less aggressively, with fewer medications, than those patients 60-79 years of age.[23] It is well recognized that uncontrolled hypertension and coronary heart disease together contribute to heart failure (HF) in the elderly; HF affects more than 5% of persons between 65 and 79 years of age and 10% to 20% of those

older than 80.[16] Medication nonadherence is the greatest risk factor associated with increased incidence of HF in the elderly.[16] A retrospective cohort study was conducted in the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) Program.[15] Logistic regression analysis showed that adherence with antihypertensives was consistently lower in elderly patients with asthma or chronic obstructive pulmonary disease (odds ratio [OR] = 0.43), depression (OR = 0.5), gastrointestinal disorders (OR = 0.59), and osteoarthritis (OR = 0.63), compared to elderly patients without these conditions (reference, OR = 1.0). The findings suggest that even noncardiovascular comorbidities negatively affect the use of antihypertensive medication in the elderly.[15]

Effect of Race and Ethnicity

Race and ethnicity may predispose certain patients to hypertension. For example, the National Health and Nutrition Examination Survey (NHANES) III study indicates that hypertension is more prevalent in African Americans (32.4% [age-adjusted]) than in Hispanics (22.6%) and whites (23.3%),[17] possibly attributed to the presence of the CYP3A5 genotype in African Americans.[18] In a study involving veterans with hypertension and minimal financial barriers, inadequate blood pressure control of hypertension was reported to be 63% in African Americans compared with 50% in whites ($P < .003$), and African Americans were more likely to be noncompliant with medication (OR = 1.81).[24] A comparative analysis demonstrated that antihypertensive use was even lower in Hispanic (52.5%) compared with African-American (72.6%) and white (63.6%) adults ($P < .001$ across all 3 groups).[25] This difference was not attributed to demographics, socioeconomic status, health insurance coverage, health status, or health risk behaviors.[25] Rather, language proficiency, cultural beliefs, and attitudes toward healthcare might have contributed to these results.[26] A population study from a multiethnic study of atherosclerosis also showed that the percentage of uncontrolled, treated hypertension was significantly higher in African Americans (35%, $P < .0001$), Chinese (33%, $P = .003$), and Hispanics (32%, $P = .0005$) than in whites (24%).[19] In addition, adherence with diuretic drug therapy was significantly lower in Chinese (22%) and Hispanics (32%) than in whites (47%, $P < .001$ for both comparisons).[19,20]

Effect of Gender

Although inconsistent across some ethnic backgrounds, women tend to exhibit more nonadherence than men. In a nested case-control study within a cohort of treatment-naive patients, nonadherence with antihypertensive medication was higher in women (OR = 1.64) than in men (OR = 1.14) and increased if the duration of treatment was longer than 6 months (adjusted ORs for men and women were = 1.71 and 1.88, respectively).[21] The PACE study of patients more than 65 years old also showed reduced adherence with antihypertensive medication in women.[15] A multiethnic study of premenopausal and perimenopausal women showed that goal blood pressure control was highest among white (43%) and Japanese (38.7%) women, but significantly lower among Hispanic women (11.4%; $P < .001$ vs non-Hispanic white subjects).[22]

Adverse Effects and Drug Tolerability

The incidence of adverse effects from antihypertensive treatment also contributes to nonadherence. Adverse effects vary according to antihypertensive class (Table 1).[39,40] For example, when the incidence of adverse effects was compared for each drug vs the pooled average incidences of the other drugs in the study, ACE inhibitors were associated with the highest incidence of dry cough (28% vs 8%, respectively; $P < .001$); dihydropyridine calcium channel blockers with the highest incidence of peripheral edema (22% vs 12%, respectively; $P < .001$); and beta-blockers with the highest incidence of sexual dysfunction (17% vs 10%, respectively; $P < .01$) and poor temperature perception in the extremities (26% vs 12%, respectively; $P < .001$).[27] Adverse effects reported with angiotensin receptor blockers (ARBs) were substantially lower than those reported for other classes of antihypertensives.[28] Additional studies also showed a significantly lower incidence of adverse effects in patients receiving losartan (adjusted OR = 1.0), an ARB, than the ACE inhibitors (OR = 1.78) or calcium channel blockers (OR = 2.65).[29] A 3-month cumulative study among first-time users of losartan, ACE inhibitors, and calcium channel blockers showed that the rates of perceived adverse effects were 52.5%, 60.2%, and 69.6%, respectively.[29] Users of calcium channel blockers had the highest probability of reporting an adverse effect after adjustments were made for sex, age, level of education, number of symptoms perceived before entering the study, insurance coverage, and duration of hypertension.[29] Collectively, the incidence of adverse effects can lead to adherence interruptions with antihypertensive medication.

Drugs with short durations of action, such as some alpha-blockers, ACE inhibitors, and dihydropyridines, may decrease blood pressure control when not taken in a consistent daily pattern.[30] In addition, interrupted adherence can lead to excessive adverse effects when the drug is reintroduced. Short-acting ACE inhibitors, beta-blockers, and clonidine (an alpha-agonist) have been shown to induce periods of rebound effects, such as enhanced beta-receptor responsiveness and increased risk for acute coronary syndrome event (relative risk [RR] = 4.60), with dosing interruptions.[30] Additionally, uncontrolled hypertension can lead to significant adverse sequelae, including increased incidence of chronic kidney disease, atherosclerosis, stroke, and diabetes.[41,42] These data point to the importance of patient drug counseling with both new and refill prescriptions.

The choice of drug treatment can also affect patient adherence with therapy for hypertension. A retrospective cohort study of Medicaid enrollees showed a lower refill rate among patients taking alpha-blockers (11%) than among those taking beta-blockers (30%), adrenergic agents (34%), calcium channel blockers (39%), ACE inhibitors (44%), direct vasodilators (45%), or thiazide diuretics (46%).[33] Furthermore, studies showed patients receiving initial therapy with ARBs showed greater adherence than those receiving other classes of drugs. Although definitions of adherence differed in these studies values ranged from 63% to 71% for patients treated with ARBs.[34-37]

Effect of Polypharmacy

Most patients with hypertension require 2 or more antihypertensive drugs to achieve effective blood pressure control,[8] and patients with hypertension may have 1 or more comorbidities, such as type 2 diabetes mellitus, that necessitate the use of additional medications.[38,43]

Many other studies on the effects of polypharmacy have involved patients with HIV infection. The management of HIV infection often involves complex regimens, requiring multiple medications and a high level of adherence to maintain virologic control. Studies of hypertensive patients with HIV have consistently found that medication adherence is suboptimal or poor in patients receiving polypharmacy, especially where regimens require greater than once-daily dosing frequency. Polypharmacy has a detrimental effect on adherence because many patients do not understand their complex regimens and have difficulty organizing their schedules to accommodate these regimens.[44-46] Healthcare professionals may be able to improve adherence by educating patients about the importance of adhering to their prescribed regimens,[47] simplifying regimens,[45,46] helping patients to improve their organizational skills,[46] and acquiring and using adherence aids.[45] Simplifying regimens can be accomplished by using combination products. One retrospective study of persistence with single-pill combination therapy compared to concurrent 2-pill therapy showed that as many as 20% more subjects continue to take prescribed medication for 12 months.[48]

Effect of Cost

Drug costs also provide another barrier to adherence with drug therapy. Although the high cost of drug acquisition can be an obstacle to adherence, results of a cross-sectional study of Medicaid recipients illustrates the detrimental effects of even modest tiered copayments on prescription fill rates.[49] Among patients who rated their health as fair, residents of states that require prescription copayments filled nearly 40% fewer prescriptions than their counterparts in non-copay states. Among those who rated their health as poor, the difference was 27%.[49]

The high cost of antihypertensive medications also contributes to nonadherence in developing countries. For example, 93% of patients in Ghana were noncompliant with their antihypertensive regimens, and 96% of these patients cited unaffordable drug prices as the main reason.[31] Ambrosioni and colleagues[32] suggest that low-dose combination therapy should be considered a cost-effective method to ensure universal improvements in tolerability, efficacy, and adherence with antihypertensive medication (a major global health economic burden). Another economic factor that can lead to nonadherence is the presence of restricted formularies, which may necessitate a switch to a cheaper but less well-tolerated antihypertensive agent within the same therapeutic class.[50]

Differential adherence to long-term antihypertensive drug therapy can translate to higher healthcare costs and increased healthcare needs.[51] Patients in a California Medicaid program who interrupted their antihypertensive treatment within the first year had higher

healthcare expenses centered around increased rates of hospitalization.[52] Sokol and colleagues[53] recently reported that increased adherence with antihypertensive medication can result in decreased healthcare utilization if treatment follows a guidelines-based therapy. In addition, a study in the United Kingdom of patients with newly diagnosed hypertension showed that switching and discontinuation of the initial therapy led to an excess expenditure of £ 26.9 million per year (approximately $53 million).[54] A similar analysis in a tertiary hypertension clinic showed that switching to an alternative drug treatment resulted in $1333 in additional medical care costs over the next 12 months.[51] Additional costs were accrued by blood pressure monitoring and laboratory costs.

Strategies for Promoting Adherence

Researchers have evaluated many strategies for promoting patient adherence to antihypertensive medications efforts to minimize adverse effects, simplification of dosing regimens, interventions to improve patient motivation, and patient education approaches. A recent Cochrane Collaboration review of studies across many chronic conditions concluded that the most effective interventions were complex, including combinations of these individual strategy types.[55] The more successful strategies to improve adherence among patients with hypertension are summarized below.

Proper Selection of Agents

Although not explicitly evaluated by researchers as a strategy to improve adherence, proper selection of antihypertensive drug therapy plays a key role because the adverse effects of these agents contribute to poor patient adherence. Strategies to improve adherence by minimizing these adverse effects are summarized in Table 2 and generally involve the appropriate selection of antihypertensive agents with a good tolerability profile. Overall, the selection of antihypertensive medication should involve a dynamic interaction between the healthcare practitioner and the patient to encourage patient involvement in treatment decisions that simplify the regimen and improve adherence.[56]

Use of Long-acting Drugs to Decrease the Frequency of Doses

As part of a review of 38 clinical trials testing 58 interventions, 7 of 9 trials demonstrated that the most effective method for improving compliance with antihypertensive regimens was to simplify dosing.[57] Simplified dosing regimens resulted in increasing adherence by between 8% and 19.6%. Longer acting therapeutics can also be used to achieve blood pressure control over a full 24-hour dosing interval.[58,59] This is critical for the prevention of cardiovascular events in patients with hypertension because stroke, myocardial infarction, congestive heart failure, and renal insufficiency are directly linked to elevated blood pressure.[59] Drugs with long half-lives (eg, amlodipine, nadolol, olmesartan, ramipril) stabilize blood pressure over time and minimize the loss of blood pressure control during periods of inconsistent medication compliance.[59]

Complex Interventions

Patient education alone is a largely unsuccessful strategy to improve adherence.[55] However, patient education combined with strategies aimed at decreasing dose frequency, improving tolerability of the regimen, and motivational approaches have been found to improve adherence as much as 41%.[55] A recent report of a complex intervention involving pharmacy care in a collaborative clinic setting was shown to improve mean adherence rates from 61% at baseline to 97% during 8 months of standardized medication education, regular pharmacist follow-up, and dispensing of medications in multidose blister packs.[60] These findings suggest that a multifaceted approach at improving adherence should be considered.

Improved Methods for Monitoring Adherence

Psychosocial variables provided by medical support staff can also encourage medication adherence through regular patient contact and individualized educational programs.[16, 39] Primary care physicians can contribute to better hypertension control among elderly patients by monitoring treatment, educating patients about the benefits of a healthy lifestyle, and assisting in lifestyle modifications.[61,62] Access to pharmaceutical care by a pharmacist-managed hypertension clinic has also been shown to improve blood pressure management through frequent follow-up care and patient education (81% vs 28% for pharmacist-managed and control groups, respectively; $P < .0001$).[63] Adherence may also be enhanced by direct communication between the healthcare provider and the patient's pharmacy regarding prescription refill rates. With the patient's approval, prescription refill data can be electronically forwarded from the pharmacy directly to the healthcare practitioner's office to provide constant monitoring of adherence. The practitioner, the pharmacist, or both, could use these data to engage the patient more directly in his or her own care. A multifactorial intervention program assessing the effect of provider and patient interventions showed that neither provider nor patient education alone was sufficient to increase adherence, suggesting the need for a more comprehensive interdisciplinary approach to adherence oversight.[64]

Another strategy, a home blood pressure monitoring program with an electronic monitoring device (monitoring events medication system [MEMS]), was able to improve adherence in patients with hypertension.[65] Use of these monitoring devices is limited by their high cost, but mean adherence rates were significantly increased in comparison with control groups monitored only by physicians (92% vs 74%, respectively; $P = .0001$). These strategies suggest that multiple methods to facilitate the monitoring and management of hypertension promote patient adherence and that patient education alone is not sufficient.[66]

New Drug Developments

Based on the prior discussion, increases in adherence may be gained by improving on drug characteristics such as symptom reduction, tolerability, and dosing schedule. Clinicians and researchers should be encouraged to identify and develop new pharmacologic targets for hypertension that meet these criteria. Such research will

undoubtedly require large investments of time and resources.

Summary

In summary, patient nonadherence is a universal significant risk factor for cardiovascular disease, thereby requiring a comprehensive intervention approach. For many patient populations, dynamic communication between the healthcare team and the patient is a key factor in fostering adherence with long-term medication regimens. Educational programs that inform patients about their disease and the importance of adherence, interdisciplinary approaches to monitoring adherence, and utilization of home-based technologies can also aid in increasing adherence. New therapeutic modalities to treat hypertension with increased efficacy and fewer adverse effects may also contribute to greater adherence.

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Table 1. Frequently Reported Adverse Effects of Available Antihypertensive Drugs Given as Monotherapy

Class of Drug	Adverse Effects
Angiotensin II receptor blockers	Dizziness, hypotension, hyperkalemia
Angiotensin-converting enzyme inhibitors	Dry cough, hyperkalemia, nausea, vomiting, constipation, rash, headache, dizziness, fatigue
Beta-blockers	Dizziness, headache, fatigue, nausea, urinary incontinence, postural hypotension
Alpha-blockers	Bradycardia, peripheral vasoconstriction, bronchospasm, gastrointestinal disturbances, fatigue, sleep disorders
Central alpha-2 agonists and other centrally acting drugs	Dry mouth, diarrhea, hepatotoxicity, fluid retention, depression, drowsiness, parkinsonism, inability to ejaculate
Calcium channel blockers (dihydropyridines and nondihydropyridines)	Peripheral edema, headache, diarrhea, nausea, flushing, dizziness
Diuretics (thiazide, loop, and potassium-sparing diuretics)	Impotence, decreased libido, lethargy, constipation, nausea, dizziness
Vasodilators	Tachycardia, fluid retention, nausea, vomiting,

	headache
Aldosterone receptor blockers	Upper respiratory tract infection, headache, nonspecific pain, hyperkalemia

See references 39, 40

Table 2. Strategies for Improving Adherence With Antihypertensive Drug Therapy

Factor Contributing to Nonadherence	Strategy for Improving Adherence
Adverse effects of drug(s)	Prescribe drug(s) with placebo-like tolerability
Periods of drug withdrawal	Use long-acting drugs that provide 24-hour blood pressure control (or longer)
Multiple-dosing regimen	Simplify the dosing regimen by prescribing a drug with high efficacy that can be taken once daily
Use of concomitant drugs	Prescribe low-dose combination therapy
Inadequate knowledge of drug	Improve patient monitoring Increase patient access to support staff Enhance patient education by scheduling follow-up visits and providing educational literature

See reference 2

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Mark A. Munger, PharmD, Professor, Departments of Pharmacotherapy and Internal Medicine, University of Utah, Salt Lake City, Utah

Benjamin W. Van Tassell, PharmD, Clinical Cardiovascular Experimental Pharmacology Fellow, Department of Pharmacotherapy, University of Utah, Salt Lake City, Utah

Joanne LaFleur, PharmD, MSPH, Research Assistant Professor, Department of Pharmacotherapy, University of Utah, Salt Lake City, Utah.

Author's email: mmunger@hsc.utah.edu

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