Medication Adherence and Persistence in Hypertension Management

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ABSTRACT

• **Objective:** To discuss barriers to adherence and persistence and present strategies for improving medication adherence and persistence in the management of hypertension.

• **Methods:** Review of the literature.

• **Results:** Despite the use of antihypertensive medication, blood pressure remains uncontrolled in a substantial percentage (46%) of patients with hypertension. One important cause of refractory hypertension is medication-taking behavior (ie, poor adherence and persistence to medication regimens). Rates of nonadherence to antihypertensive medications range from 9% to 37%, while nonpersistence has been found to occur at even higher rates (30% to 50%) in patients 12 months after the initiation of antihypertensive therapy. Modifiable factors for these medication-taking behaviors include high pill burden, drug tolerability, and drug costs. Selection of medications that are better tolerated, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, results in improved adherence and lower drug discontinuation rates compared to the use of the older, more poorly tolerated agents, diuretics and \( \beta \) blockers. Once-daily medications and fixed-dose combinations are strategies that can be considered to lessen the pill burden in patients with hypertension. Coordination of medication initiation in hypertensive patients with concomitant illness also increases adherence in these patients.

• **Conclusion:** Clinicians should consider and implement strategies that address the modifiable factors that contribute to low adherence and persistence with hypertension treatment.

Hypertension affects nearly 1 in 3 adults in the United States [1]. Uncontrolled high blood pressure is known to lead to severe debilitating complications, such as stroke and coronary artery disease [2]. In the United States, more than 40% of treated hypertensive patients do not have their blood pressure under control [1].

Poor compliance with prescribed medications can contribute to suboptimal hypertension control rates. Compliance may include both medication adherence and medication persistence. Medication adherence refers to the appropriate use of therapy as recommended by a health care provider, whereas medication persistence refers to the continued use of therapy [3]. In a systematic review, rates of nonadherence to antihypertensive medications ranged from 9% to 37% [4]. Several recent studies showed that 27% to 66% of patients discontinued their antihypertensive medications after 12 months [5,6]. Persistence with antihypertensive medications has been shown to significantly decline over time, particularly over the first 4 years after a patient receives the diagnosis of hypertension [7]. Good medication-taking behavior has been associated with improved blood pressure control rates [8] and improved clinical outcomes [9–12].

This article will review barriers to medication adherence and persistence as well as strategies for improving adherence and persistence in the management of hypertension.

**BARRIERS TO ADHERENCE AND PERSISTENCE**

Both modifiable and nonmodifiable factors have been associated with poor medication-taking behavior in patients with hypertension. Nonmodifiable factors include age, gender and race. Modifiable factors include high pill burden, drug adverse effects, and drug costs.

**Age**

Several studies have evaluated the effect of age on medication adherence and persistence in patients with
hypertension; however, the results of these studies are conflicting. Although a few studies have shown that older hypertensive patients are less adherent than their younger counterparts, other studies have shown that younger patients are least adherent to their antihypertensive medications. An Italian study involving 7626 patients who were taking antihypertensive drugs found that younger age was significantly associated with poor adherence rates [13]. In a survey completed by 1432 individuals receiving antihypertensive drugs, 57%, 37%, and 32% of respondents aged 18–34 years, 35–44 years, and 45–54 years, respectively, reported having difficulty in taking these medications [14]. When compared with individuals in the oldest age group (≥65 years), those aged 18–44 years and 45–54 years were 2.8 and 1.6 times more likely to have difficulty in taking their antihypertensive medications (P < 0.001 for both comparisons). Similarly, in a high-risk Medicaid population, those younger than 40 years were significantly less likely to be adherent to their antihypertensive regimen compared with individuals older than 60 years (P = 0.01) [15]. However, a prescription claims database study showed that older patients were significantly less likely to fill a first prescription for an antihypertensive medication within 30 days after the prescription order date compared with patients who were 10 years younger (P = 0.016) [16].

Younger patients have also been shown to have difficulty with persistence with their antihypertensive medications. Based on data from NHANES III, individuals younger than 30 years were more than 12 times more likely to be nonpersistent with their antihypertensive medications (ie, did not use these medications during the 30 days prior to the survey) compared with those aged 50 years or older (P < 0.001) [17]. In a Medicaid population, antihypertensive discontinuation rates were progressively lower after the age of 40 years, with a marked reduction in these rates occurring in those older than 60 years of age [18].

Gender

The results of studies evaluating the effect that gender may have on medication adherence and persistence among hypertensive patients have also been conflicting. While men have been shown to be more adherent to antihypertensive medications than women, they have also been shown to have less medication persistence than women. In a nested case-control study within a cohort of new users of antihypertensive drugs, nonadherence was higher in women (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.37–1.94) than in men (OR, 1.14; 95% CI, 0.94–1.40) [19]. Women were less adherent to antihypertensive medications regardless of the duration of therapy, whereas in men, nonadherence was apparent only when the duration of antihypertensive therapy exceeded 6 months. Compared with women, men have also been shown to be more likely to fill their first-time antihypertensive prescription within 30 days after the prescription order date [14]. However, nonpersistence has been shown to be 31% more likely in men than in women (P = 0.01) [17].

Race

African Americans have been shown to be less adherent to their antihypertensive medications. In a Medicaid population, African Americans were approximately 50% less likely to be adherent to antihypertensive drug therapy than were Caucasians (P < 0.05) [15]. In another study involving 569 hypertensive veterans, African Americans were significantly more likely to be nonadherent to their antihypertensive medications than were Caucasians (OR, 1.81; 95% CI, 1.28–2.58) [20]. Nonadherence to antihypertensive medications has also been shown to be prevalent among Hispanics. In a cross-sectional analysis of data from the Health and Retirement Study, antihypertensive use was significantly lower in Hispanic adults (53%) compared with Caucasian adults (64%) and African American adults (73%) (P < 0.001) [21]. In this particular study, the lower rate of medication use in the Hispanic population could not be attributed to differences in demographics, socioeconomic status, health insurance coverage, health status, or health risk behaviors. Rates of nonpersistence with antihypertensive medications have also shown to be significantly higher in African Americans (OR, 1.40; 95% CI, 1.11–1.75) and Hispanics (OR, 1.75; 95% CI, 1.19–2.56) compared with Caucasian patients [17].

High Pill Burden

High pill burden has historically been associated with medication nonadherence. As with other disease states, many individuals with hypertension receive multiple medications. In fact, most patients with hypertension require at least 2 antihypertensive drugs to achieve their blood pressure goals [2]. Several studies have been con-
ducted to evaluate whether the number of prescription medications taken by hypertensive patients (ie, polypharmacy) has an impact on adherence. In a retrospective cohort study involving 5759 patients, the rates of adherence to antihypertensive and lipid-lowering therapies decreased from 35% to 20% when the patients went from taking 1 medication to 10 or more medications [22]. In another retrospective cohort study involving 4052 patients aged 65 years and older, the likelihood of medication adherence decreased as the number of prescription medications increased, with the adjusted OR for 2, 3 to 5, and 6 or more medications being 0.67 (95% CI, 0.56–0.79), 0.56 (95% CI, 0.48–0.64), and 0.43 (95%, CI 0.36–0.50), respectively [23].

Over the years, fixed-dose combination pills have been developed to help improve adherence and persistence rates in many disease states, including hypertension. In the Medicaid population, the adherence rate was significantly higher with the use of fixed-dose antihypertensive combination regimens (31%) than with the separate agents (22%) (P = 0.016) [15]. In another study, adherence rates were significantly higher with 2-pill antihypertensive regimens (either valsartan + amlodipine [75%] or valsartan/hydrochlorothiazide [in a fixed-dose combination] + amlodipine [73%]) than with a 3-pill regimen (valsartan + hydrochlorothiazide + amlodipine [61%]) (P = 0.005) [24]. Among these therapies, persistence rates were the lowest with the 3-pill regimen at each of the designated time points related to a gap of 80%, 120%, and 160% of day’s supply of the medication. In another study, patients taking the fixed-dose combination regimen of an angiotensin II receptor blocker (ARB) and hydrochlorothiazide were significantly more adherent than those who received the 2-pill combination regimen consisting of the individual components [25]. Additionally, patients receiving the fixed-dose combination regimen were more persistent than those in the 2-pill regimen group at both 180 days (73% vs 28%, respectively) and 365 days (54% vs 19%, respectively). In this particular study, persistence rates decreased over time regardless of whether patients took a 1-pill fixed-dose combination regimen or a 2-pill free-dose combination regimen.

**Drug Adverse Effects (Tolerability)**

Adverse effects associated with antihypertensive agents may be another important barrier to adherence. Drugs that are poorly tolerated have higher discontinuation rates than those that are associated with fewer adverse effects [26,27]. Several studies have demonstrated that adverse effects associated with antihypertensive agents contribute to premature discontinuation of drug therapy. In a German multicenter study involving 1603 patients who experienced a change in antihypertensive therapy within the previous 6 months, achieving inadequate blood pressure control was cited as the most common reason for changing their antihypertensive therapy; however, drug adverse effects (50.1%) was the next most common reason for making medication changes [28]. Similar results were observed among a cohort of 401 hypertensive patients, with 32% and 25% of men and women, respectively, reporting that they were nonadherent to their antihypertensive therapies because of adverse effects [29].

Adherence and persistence rates appear to be higher with newer antihypertensive therapies, such as the angiotensin-converting enzyme (ACE) inhibitors, ARBs, and calcium channel blockers (CCBs), compared with older agents such as β blockers and diuretics. In a Canadian retrospective cohort study involving 4561 hypertensive patients, diuretics were associated with significantly lower rates of adherence (51%) compared with β blockers (60%), CCBs (64%), ACE inhibitors (65%), and ARBs (65%) (P < 0.01 for diuretics vs. other antihypertensives) [30]. Similar results were seen in a retrospective cohort study based in the United States that evaluated 242,882 patients who had been initiated on antihypertensive therapy [31]. After 1 year, ARBs (39%) and ACE inhibitors (39%) had significantly higher adherence rates compared with CCBs (32%), β blockers (33%), and diuretics (24%) (P < 0.001). In addition, patients receiving ARBs were more persistent with their therapy at 1 year (52%) compared with those receiving ACE inhibitors (48%), β blockers (40%), CCBs (38%), or diuretics (30%). Additionally, diuretics had the highest rate of discontinuation compared with each of the other classes of antihypertensive medications (P < 0.001) and differences were seen as early as 30 days.

**Drug Costs**

Drug costs associated with various antihypertensive regimens may also contribute to nonadherence. In a retrospective study that evaluated pharmacy claims data of 528,969 patients, the doubling of copayments
required under prescription drug benefit plans was associated with a 26% reduction in use of antihypertensives, including ACE inhibitors, ARBs, CCBs, β-blockers, and diuretics [32]. In 1 study that evaluated health care claims data from 45 large employers, adherence to antihypertensive therapy was significantly more likely to occur with copayments of $0 compared with copayments of $1 to $9 [33]. In another study, copayments of $10 or less were associated with higher first-fill prescription rates for antihypertensive medications (87%) compared with copayments greater than $10 (72%; \( P < 0.001 \)) [16]. Additionally, in logistic regression models, copayment was found to be an independent predictor of first-fill rates, with patients having copayments of $10 or less being almost 2.5 times more likely to fill their prescription than those with copayments greater than $10. This study also noted that ARBs were also associated with lower first-fill rates, which could be attributed to several factors, such as higher tier copayments or step-therapy requirements recommending that patients try an ACE inhibitor first.

Antihypertensive medication persistence rates have also been evaluated in relation to drug costs. A retrospective study evaluating claims data of 23,047 hypertensive patients who were new users of antihypertensive therapy showed that persistence rates improved significantly when the drug coverage was average or better than average [34]. In this study, the authors concluded that less generous drug coverage appeared to be a risk factor for poor persistence among this group of individuals who were new users of antihypertensive therapies.

**STRATEGIES FOR IMPROVING ADHERENCE AND PERSISTENCE**

**Drug Costs**

Drug cost and insurance coverage can play a role in a patient’s decision to fill a prescription [32–34]. If a patient expresses concern over the cost of their antihypertensive medication, consideration should be given to substituting with a generic medication. In addition, for patients with prescription drug benefit coverage, selecting antihypertensive drugs from the plan’s preferred list will help to minimize costs associated with copayments.

**Drug Tolerability and Pill Burden**

Once-daily antihypertensive medications with minimal adverse effects should be considered over medications that are less well tolerated or dosed multiple times per day. Although considered first-line agents for many individuals, diuretic agents have been shown to be the most poorly tolerated class of antihypertensive agents compared with ACE inhibitors, β-blockers, ARBs, and CCBs. In a retrospective analysis of the prescription records of patients who recently started antihypertensive therapy, the percentage of patients who were persistent with initial ARB therapy at 12 months was much higher than that of patients who were persistent with ACE inhibitors, CCBs, and ARBs. This study noted that additional studies are needed to determine which factors—tolerability, financial incentives, newness of the products, selection bias—may have influenced patient refill behavior. Also, when prescribing multiple antihypertensive medications, health care providers should consider that fixed-dose combination pills may be an ideal option for selected patients.

Since patients with hypertension often have concomitant disease states, such as dyslipidemia or diabetes, it is quite probable that these individuals will be receiving multiple medications for the treatment of these conditions. There are some data to suggest that concomitantly initiating antihypertensive and lipid-lowering medications may be associated with an improvement in adherence. A retrospective cohort study evaluating the prescription records and claims of 15,400 patients showed that those who started a lipid-lowering medication and an antihypertensive medication at the same time (defined as having prescriptions filled for both agents on the same day) were significantly more likely to be adherent over a 12-month period than those who had either agent filled before the other (\( P < 0.001 \)) [36]. Another study with similar findings evaluated the prescription records and claims of 4052 Medicare-eligible enrollees and found that patients were more likely to be adherent if antihypertensive and lipid-lowering medications were initiated closer together (within 0–30 days of each other) rather than further apart (within 61–90 days of each other); however, these results were not considered statistically significant (\( P = 0.056 \)) [23]. Therefore, initiating antihypertensive and lipid-lowering medications as close to concurrently as possible may be another strategy to improve patient adherence.
Collaboration Among Health Care Professionals

Collaboration among health care professionals is being emphasized to improve patient outcomes. The American Society of Hypertension published a position paper discussing the importance of adherence and persistence to antihypertensive medications to improve blood pressure control [37]. This document highlights the role of a patient-centered team approach to health care as well as the importance of improving physician-patient communication in managing patients with hypertension. There are several studies that have shown that physician-pharmacist collaboration programs, such as medication therapy management or pharmacy care programs, have improved antihypertensive medication adherence and persistence as well as blood pressure control [38–43]. In one of these studies, patients were randomized to usual care or an intervention group [43]. Patients randomized to the intervention group met with a pharmacist every 3 months in addition to their usual care for medication adherence counseling and patient education regarding hypertension. Patients in the intervention group experienced a significant improvement in both medication adherence (74.5% vs. 57.6%, \(P = 0.012\)) and blood pressure control (66.0% vs. 41.7%, \(P < 0.001\)) compared to the control group (usual care). Blood pressure control was based on the goals set forth in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment Of High Blood Pressure (JNC 7) [2]. Additionally, this study used a questionnaire that had previously been validated to assess medication adherence [44]. Overall, collaboration with pharmacists as part of the patient-centered team approach should be considered to improve medication adherence and persistence as well as blood pressure control in patients with hypertension.

Education and Communication

Additional strategies for improving antihypertensive adherence and persistence may also include patient education as well as enhanced communication with the patient. Both education and communication are always critical components of the physician-patient interaction. As previously noted, the American Society of Hypertension highlighted the importance of physician-patient communication as a way to improve blood pressure control [37]. Studies have shown that nonadherence is multifactorial. A lack of patient education regarding the disease state, the long-term complications of uncontrolled hypertension, the benefits of taking antihypertensive medications as prescribed, and Medicare Part D plans in the Medicare-eligible population have all been associated with nonadherence with medication regimens [45–48]. A lack of collaboration between patients and physicians has also been associated with a statistically significant reduction in adherence in patients with hypertension [49].

Furthermore, patients who had a positive perception about the way in which health care providers communicated with them had improved adherence to antihypertensive medications [46,49,50]. In the study by Roumie et al, health care providers’ communication skills had the strongest association with medication adherence [50]. Patients included in this study were evaluated using the short-form Primary Care Assessment Survey (PCAS) [51]. This survey is a 14-point validated questionnaire that is completed by the patient and is designed to measure 7 elements of primary care: access, continuity, comprehensiveness, integration of care, clinical interactions (including both communication and exam skills), interpersonal treatment, and trust [50]. This study found that as PCAS scores increased, medication adherence increased as well (relative risk, 3.18 [95% CI, 1.44–16.23]; \(P = 0.001\)).

While improving patient education may not have a great impact on medication adherence or persistence, this strategy should not be downplayed. Some methods for improving patient education include distributing patient education handouts, providing increased one-on-one patient counseling, or engaging in motivational interviewing.

Face-to-face counseling has been shown to improve medication adherence in patients with hypertension. In one particular randomized controlled trial, patients with hypertension were allocated to usual care or adherence therapy [52]. In the adherence therapy group, patients received a 20-minute individual counseling session once a week for 7 weeks. As determined by pill count, patients in the intervention group were significantly more adherent to their antihypertensive regimen compared with those in the usual care group (97.2% vs. 70.6%; \(P < 0.01\)). Motivational interviewing, a directive, patient-centered behavioral counseling approach, has also been shown to maintain medication adherence in hypertensive African Americans over
time compared with the reduced adherence rates over a 12-month period that otherwise occur [53].

CONCLUSION

Uncontrolled blood pressure despite taking antihypertensive medications is a common problem. Medication adherence is a multifactorial issue that should be evaluated in all hypertensive patients, especially those who are not at targeted blood pressure goals despite antihypertensive therapy. Modifiable factors that impact medication adherence, such as drug costs, pill burden, adverse effects, and coordinating initiation of antihypertensive medications with other therapies when applicable, should be considered prior to initiating antihypertensive therapy. Additional strategies for improving antihypertensive medication adherence and persistence may include patient education, enhanced communication with the patient, and collaboration with pharmacists.

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REFERENCES

40. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA 2006;296:2563–71.