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HYPERTENSION (S TALER, SECTION EDITOR)

Adherence to Antihypertensive Medications: Current Status and Future Directions

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Abstract Elevated blood pressure (BP) accounts for the largest global proportion of disease burden and is largely treatable through the use of antihypertensive medications. Adherence to antihypertensive medication may be defined as the extent to which patient behavior coincides with recommendations agreed upon by the health-care provider and the patient and encompasses initiation, implementation, and discontinuation. Despite the proven clinical efficacy of antihypertensive medications to control BP, approximately half of treated patients are nonadherent. Nonadherence to antihypertensive medications is a multifactorial concern. Barriers to antihypertensive medication adherence are numerous and include patient-related (e.g., beliefs about medication, motivation, mental health), provider-related (e.g., patient-provider communication, failure to appropriately escalate treatment), therapy-related (e.g., an asymptomatic disease, side effects, complexity of regimens), and system-related (e.g., medication cost, health literacy, uncoordinated delivery of services) influences. Several techniques to improve adherence to antihypertensive medications have been identified, with sufficient supporting evidence from randomized trials to inform clinical practice recommendations. This review summarizes the current understanding of the prevalence and impact of the failure to adhere to the medical management of hypertension. Factors linked to improved adherence and studies that assessed strategies to improve adherence are also summarized.

Keywords Adherence · Persistence · Compliance · Antihypertensive medication · Hypertension · Blood pressure

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Introduction

Elevated blood pressure (BP) is the leading risk factor for cardiovascular disease and global mortality and accounts for the largest global proportion of disease burden [1]. Over the past several decades, there have been advances in the diagnosis and control of hypertension. Among hypertensive patients, BP control rates have risen to more than 50 % in the USA and more than 65 % in Canada [2]. Notwithstanding these advances, there is a significant discrepancy between current levels of BP control and levels that could be achieved given the current scientific understanding regarding effective treatments. Controlled clinical trials with rigorous attention to study protocols and careful patient monitoring indicate that BP control rates in excess of 80 % can be obtained [3]. Behavioral factors are increasingly being recognized as a key component accounting for the gap between current BP control rates and those that are achieved in careful clinical trials. These behavioral factors are both health-care provider-centered (i.e., relating to therapeutic inertia) and patient-centered (i.e., relating to nonadherence).

The management of hypertension is complex. While the effective treatment of hypertension incorporates the adoption of good health behaviors, pharmacotherapy remains a key

component to management in most patients. Drug therapy is effective in reducing hypertension-related complications. Five classes of drugs—angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, and beta-blockers (in younger patients)—have proven effective in lowering BP and reducing associated risk of morbidity and mortality [4–6]. Randomized trial data has consistently demonstrated that the use of BP-lowering drugs reduces cardiovascular morbidity and mortality by as much as 46 %, independent of pretreatment BP, history of cardiovascular disease[5, 4], or age[7]. Despite the proven clinical efficacy of antihypertensive medications in lowering BP and associated risk, many patients prescribed antihypertensive medications do not adhere to their hypertension management plan (both in terms of health behaviors and drug therapy) [8]. Using the World Health Organization (WHO) definition, adherence is referred to as the extent to which patient behavior coincides with recommendations agreed upon by the health-care provider and the patient [9]. The term adherence encompasses three aspects of medication administration: initiation of prescribed medication, implementation of the dosing regimen, and discontinuation [10•]. Adherence is a significant clinical concern as the average patient prescribed antihypertensive treatment has a medication possession ratio (MPR) of less than 50 %, and only 21 % of patients have sufficiently high adherence (i.e., MPR≥80 %) to receive the benefits expected based on observations from clinical trials [11].

Poor patient adherence to antihypertensive medications is particularly concerning given that the failure to take antihypertensive medication as prescribed has been identified as an important factor contributing to poor BP control [12–14], hospitalization, and mortality [15, 16]. A meta-analysis of prospective epidemiological studies reported that relative to good adherence (i.e., taking more than 80 % of prescribed medication), poor adherence to antihypertensive medication was associated with a 19 % increase in the likelihood of developing cardiovascular disease and a 29 % increase in the likelihood of all-cause mortality [17••]. It has been estimated that 89,000 premature deaths in the USA could be prevented annually if adherence to antihypertensive medications were higher [18]. Further, one study using electronic monitoring of dose histories reported that approximately half of patients presumed to have treatment-resistant hypertension turned out to be nonadherent to antihypertensive medication [19]. Acknowledging the link between adherence and BP control, the American Heart Association (AHA) recommends measuring medication adherence as an important first step for managing patients with treatment-resistant hypertension [20].

This review summarizes the current understanding of the prevalence and impact of the failure to adhere to the medical management of hypertension. Factors linked to improved adherence and studies that assessed strategies to improve adherence will be summarized.

What Proportion of Patients Are Adherent to the Pharmacological Treatment of Hypertension?

A meta-analysis of observational trials examining adherence to seven classes of medication that prevent cardiovascular disease in an international sample of 376,162 hypertensive patients with and without CHD reported a mean adherence of 57 % as measured by prescription refill data over a median treatment period of 24 months [21••]. Different rates of adherence were found for different classes of antihypertensive medications (see also [22]). Adherence rates to angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel blockers were 56, 44, and 48 % when used in primary prevention and 70, 62, and 76 % when taken for secondary prevention, respectively. Patients were 61 % adherent to angiotensin receptor blockers and 42 % adherent to diuretics when taken for primary prevention (no studies reported rates for secondary prevention for either of these drug classes). Reported rates of adherence were similar in a second meta-analysis [17••] of nearly two million patients, where only 59 % of patients exhibited good adherence (defined as >80 %) to antihypertensive medications.

Point prevalence estimates of adherence reported in meta-analytic reviews may not adequately capture the longitudinal nature of patient adherence which is a dynamic process with atemporal pattern that relates directly to time since initiation of medication. For example, antihypertensive medication adherence data from 16,907 patients (the majority of whom were European) with a heterogeneous set of conditions (e.g., hypertension, angina, heart failure) reported in 95 studies [23•] highlighted temporal differences in adherence and nonpersistence. Approximately 4 % of patients did not initiate treatment by filling their first prescription. By day 100, 20 % of patients stopped taking their medication and 12 % of patients did not properly adhere to the dosing recommended by their health-care provider. Close to half of patients discontinued treatment within the first year of therapy. The same trend was observed when this database was used to examine adherence to different classes of antihypertensive medications [24]. The latter study also reported that the typical patient omitted about 10 % of doses on any single day and that medication holidays (i.e., a sequence of three or more days during which no medication was taken) were common. Further, an observational study of 60,685 patients prescribed antihypertensive medication monotherapy in the USA reported that between 31 and 44 % of patients took a 60-day medication holiday within the 1-year observation period [25].

The use of an 80 % cutoff above which a patient is considered to exhibit "good" adherence is increasingly recognized as arbitrary and problematic. These cutoff values are often of little clinical interest because such values can be achieved in many different ways (e.g., frequently missing a single dose or infrequently taking a medication holiday), and the impact will

depend on the dosing schedule and the pharmacological characteristics of the prescribed medication [26]. For instance, twice-daily medications have been reported to maintain a therapeutic window more effectively than once-daily medications, offering the patient better omission forgiveness [27]. Thus, future investigations into medication adherence may be best served by selecting a method of measurement that is tailored to capture the dynamic nature of medication adherence which includes initiation, implementation, and discontinuation. For example, analysis of chemical markers for medication exposure can indicate initiation at therapeutic levels, electronic pill counts can indicate dose administration timing or implementation, and prescription refill records can indicate discontinuation. Methods to measure medication adherence have been reviewed in more detail elsewhere [10•].

Factors Influencing Adherence to Antihypertensive Medication

As is the case with hypertension, nonadherence to medication is particularly problematic for chronic diseases in which lifetime daily therapy is required, and where the benefit is not immediately apparent (in contrast to conditions such as diabetes and asthma). There are multiple reasons why a patient would not adhere to their antihypertensive medication as prescribed, and these reasons have been generally classified into two categories: intentional nonadherence and unintentional nonadherence [28]. Intentional nonadherence is an active process where the patient chooses to deviate from the treatment regimen, perhaps after weighing the benefits of treatment against the risks of side effects, or due to distorted or unrealistic disease or treatment beliefs. Unintentional nonadherence is where a well-intended patient is ambivalent, careless, or forgetful about their medication regimen [29]. The WHO further developed five categories to classify potential reasons for nonadherence, including patient-centered, condition-centered, therapy-centered, socioeconomic, and health-care system-related factors (Table 1) [30, 8]. These categories can be more parsimoniously described as patient-related, provider-related, and system-related. Some risk factors are nonmodifiable, while others are modifiable and offer a means for improving adherence.

Nonmodifiable Risk Factors

Characteristics such as age, sex, race, and severity of medical comorbidity are risk factors for poor adherence. For example, younger age, female sex, higher copayment, and lower chronic disease score were associated with medication nonadherence in a sample of 625,620 US citizens who were prescribed antihypertensive medications and were enrolled in a national pharmacy benefits program [31]. Further, it is well documented that adherence to antihypertensive medication is lower among ethnic minority patients [32, 33], a finding which is associated with perceived discrimination and stress [34]. These risk factors are outside of the patient's control and cannot be substantially modified; however, their presence may serve as indicators to utilize additional practices to target them for interventions. We will focus on modifiable risk factors that are more amenable to intervention and have been the predominant focus in the development of strategies to improve adherence.

Modifiable Risk Factors

Patient Knowledge

Patient knowledge is critical for medication adherence. If a patient is to adhere to their prescribed medication schedule, they should have a fairly comprehensive understanding of their treatment, including the medications they take, how to follow prescribed behaviors, and the importance of adherence. Most interventions to improve medication adherence include a prominent education component with the goal of improving patient knowledge about cardiovascular risk and their perceptions regarding the importance of medication adherence. A recent systematic review reported that education interventions with behavioral support have the most voluminous and consistent

Table 1 Influences of medication nonadherence

Influence	Nonadherence	Adherence
Patient-centered	Minority status; cognitive impairment; younger age; inaccurate beliefs about disease or medication	Adherence self-efficacy
Condition-centered	Asymptomatic; mental health disorder (e.g., depression); low perceived risk	
Therapy-centered	Complexity of regimens; side effects; polypharmacy	
Socioeconomic	Low literacy; higher medication costs; low social support	
Health system-related	Poor patient-provider relationship; poor communication; little continuity of care	Strong patient-provider working alliance; early follow-up after initiation

Adapted from Ho et al. [29]

evidence for improving adherence to self-administered medication, including antihypertensive medication [35••].

To ensure uptake and implementation, education content must be appropriately matched to the patient's level of health literacy. Health literacy refers to a set of skills needed to function effectively in the health-care system (e.g., to read and understand text, locate and interpret information in documents) [36]. An assessment of more than 300 studies suggested that patients may be incapable of understanding the health information they receive [37]. One systematic review of six good or fair quality studies reported moderate evidence that supported an association between medication adherence and health literacy [38]. Low health literacy was associated with lower medication adherence. Further, a meta-analysis [39] reported a small but significant positive association between health literacy and adherence. On an encouraging note, a 6-month pilot intervention provided preliminary evidence that health literacy can be manipulated to improve patient adherence to cardiovascular medications [40••].

Not all patients with hypertension are naturally motivated to adhere to antihypertensive medication. Rather, patients may be located at different points along a continuum of "readiness to change" [41, 42]. Education content should be tailored to the patient's readiness in order to optimize treatment gains and avoid offering intervention resources to patients who are not ready to receive them. Attesting to this, hypertensive patients randomized to receive three individualized reports and a manual matched to their stage of readiness to take their antihypertensive medication as prescribed self-reported higher adherence to medication than patients randomized to a usual care control group at 12 and 18 months postintervention [43].

While necessary, patient knowledge is not sufficient for optimizing adherence. A Cochrane review of largely education-based interventions to improve adherence to medication concluded that even the most effective educational interventions did not lead to large improvements in adherence and treatment outcomes [44]. Even the most knowledgeable patients may fail to adhere to medical advice if they lack motivation and confidence to do so.

Patient Autonomy, Motivation, and Self-Efficacy

Patients are most likely to engage in health behavior change, such as taking medication as prescribed, when they are engaged in the process, motivated to do so, and have confidence in their abilities [45, 46]. Evidence indicates that medication adherence depends on a strong therapeutic relationship and informed collaborative choice (i.e., shared decision-making) [47, 48], two important ingredients when fostering autonomy and self-efficacy. A recent meta-analysis reported that patient self-efficacy (or confidence in one's ability to implement their medication regimen) is one of the most common patient-reported barriers to adherence with antihypertensive medications [49]. Similarly, autonomous motivation for adherence, defined as the extent to which patients experience participation in treatment as a freely made choice emanating from themselves, mediated the association between patient perception of physicians' autonomy support and medication adherence in a sample of 126 adults prescribed medication for a variety of chronic health conditions [50]. Further attesting to the importance of patient motivation, a motivational interviewing intervention was reported to improve adherence and reduce BP in a sample of hypertensive African Americans [45].

A variety of strategies can be used to improve patient autonomy, motivation, and self-efficacy in order to improve adherence [51•, 52]. Patients can be helped to believe in the efficacy of the treatment. Negative attitudes toward treatment can be elicited, listened to, and discussed. The role of the patient's social system in supporting or contradicting elements of the regimen can be determined. The patient can be helped to build commitment to adhere and to believe that they are capable to do so.

Patient-Provider Communication

Increasing recognition is being paid to the impact of health-care system factors on patient adherence to prescribed medication. For example, the quality of the patient-provider relationship, including the way the provider communicates and builds trust, is associated with favorable medication adherence patterns [53, 54•, 55, 56]. A meta-analysis assessing the association between patient-physician communication and treatment adherence in 106 studies (87 of which reported on medication adherence) reported that the risk for nonadherence was 19 % higher in patients whose physicians communicated poorly compared to patients whose physician communicated well [57]. Similarly, patient perceptions of poorer communication with their health-care provider were associated with a significant 4–6 % reduction in adherence to cardiometabolic medications in a sample of 9,377 primary care patients with diabetes [54•]. Moreover, physicians report that their weakest area of training is in communication [58], and an evidence review [51•] suggests that training physicians in communication skills may be an effective method for improving patient adherence to treatment recommendations. A meta-analysis of 21 trials reported a 12 % greater risk that a patient would be nonadherent to treatment recommendations if their physician had not received communication skills training [57]. Another meta-analysis reported that a majority of doctors (83 %) could be trained in motivational interviewing and that such training improved patient clinical outcomes [59]. A systematic review of ten studies using motivational interviewing training for general health-care practitioners reported that a median of 9 h of training generated positive outcomes on many aspects of the practitioners' daily practice [60]. While these results

suggest that communication skills training is important, additional research is needed to establish the content, contact duration and frequency, and dose of communication skills intervention that leads to the best long-term patient outcomes.

Patient Mental Health

Increasing attention is being paid to the effects of mental health on patient adherence to prescribed medication. A 12-month prospective observation of 178 patients initiating antihypertensive drug therapy reported that patients with mild depressed mood and mild anxious mood were 2.48 and 1.59 times less likely to be adherent (defined as MPR>80 % assessed using pill counts) [61]. This report is consistent with a meta-analysis of 12 studies that reported a negative association between depression and compliance with medical advice, including medication adherence [62]. Patients with depressed mood were three times less likely to adhere to medical advice. The effect of depressed mood on adherence to antihypertensive medication was reported to be fully mediated by low self-efficacy in a sample of 167 hypertensive African Americans [63], suggesting that interventions that improve patient self-efficacy may be particularly beneficial among patients with depressed or anxious mood.

Patient Self-Monitoring

Self-monitoring is an important tool to improve adherence and inform the health-care team about patient behavior and needs. New technologies can facilitate self-monitoring (e.g., automatic pill dispensers, electronic pill caps, smartphone applications synced with electronic pill dispensers). These data could provide patients with direct feedback regarding their success or challenges and offer health-care providers insight into potential effective intervention ingredients.

While no empirical evidence directly supports an association between self-monitoring and medication adherence, the use of home BP monitors has been reported to lower BP and reduce clinical inertia [64]. Further, while the evidence was mixed, some evidence suggests that there is a positive association between home BP monitoring and medication adherence [65]. It may be that self-monitoring increases autonomy and self-efficacy for health behavior management.

Regimen Complexity

The majority of hypertensive patients require a combination of antihypertensive medications to achieve optimal BP control [66, 67]. The chance of forgetting to take one medication increases as the number of doses per day or number of prescribed medications increases [68]. Simplifying antihypertensive regimens using fixed dose combination pills (i.e., the use of a single pill that combines two or more antihypertensive agents), blister packing, or a Dosette improves patient adherence [69–71]. A meta-analysis reported that the use of single pill combination drugs significantly increased adherence to antihypertensive medications by 29 % (OR=1.29 [95 % CI 1.11 to 1.50]) with a trend toward lowering BP and adverse side effects [71].

Side Effects

Antihypertensive medications may produce a variety of side effects, depending on the specific agent, including frequent urination, fatigue, erectile dysfunction, muscle weakness, and sleep disruption. While specific side effects of antihypertensive drugs (e.g., fatigue with beta-blockers, cough with angiotensin-converting enzyme inhibitors, peripheral edema with dihydropyridine calcium channel blockers) remain a factor in patient nonadherence, perceived side effects (i.e., adverse effects that cannot be reasonably associated with a specific drug) are probably as important. Perceived side effects of antihypertensive medications can be common within the first few months of treatment, occurring in as many as 50 % of patients [72]. Yet, it is not yet clear whether the association between perceived side effects and nonadherence is one of causation or a yet unknown third variable. For instance, patients who are more likely to report perceived side effects may also be less likely to take antihypertensive drugs as prescribed.

Health-Care Provider Counseling

Most patients find it difficult to remember their medical recommendations and have trouble identifying the medications they take and the specific purpose of each [49]. Utilizing a variety of health-care providers can provide practical supports to improve patient adherence with their antihypertensive medication, the absence of which is a potent predictor of medication nonadherence [73].

Pharmacists are one of the most likely health-care providers to lead interventions and offer patient counseling. Results from a review and meta-analysis reported that pharmacist interventions to improve adherence to antihypertensive medication offered some improvement [74] with 7 out of 16 (43.8 %) pharmacist interventions resulting in improved adherence. These studies varied in their sample size (from 40 to 1,341), study attrition (from 3 to 366), method for measuring adherence (e.g., pill count, self-report, prescription refill data), number of sessions administered (from 3 to 10+), frequency of contact (from biweekly to bimonthly), intervention delivered (e.g., education, reminders, blister packing, counseling), and duration of follow-up (from 2 weeks to 12 months). While less than 50 % of interventions were associated with improvements in medication adherence, all interventions that significantly improved adherence to antihypertensive medication

also reported improvements in systolic blood pressure (SBP) and diastolic blood pressure (DBP). In general, complex interventions that incorporated several intervention elements were more effective at improving patient adherence.

Clinical Inertia

Health-care providers play an important role in initiating or intensifying treatment appropriately to achieve risk factor control. This includes implementing nationally published recommendations [75] to improve antihypertensive medication adherence among patients with low adherence. The term clinical inertia is used to describe when a health-care provider fails to initiate or intensify treatment appropriately in order to achieve risk factor control [76]. Clinical inertia involves failure to initiate treatment, failure to titrate treatment to goal, underestimation of patient need, failure to identify and manage comorbid conditions such as depression, insufficient time, and reactive rather than proactive care [77]. Failure of health-care providers to employ effective tactics to improve the likelihood of effective drug taking habits required to maintain risk factor control may be an important contributor to the nonadherence epidemic and poor BP control [78]. For example, Okonofua et al. reported that hypertensive patients being treated at clinical practices in the lowest quintile of clinical inertia were 33 times more likely to have their BP controlled than patients being treated at practices in the highest quintile of clinical inertia [79].

Preliminary evidence suggests that adherence rates improve when health-care providers modify and escalate treatment appropriately. Tamblyn et al. reported that appropriate modification of drug dosage or class of antihypertensive medication prescribed was associated with a 55 % reduction in the risk of nonadherence in a sample of 13,205 Canadian patients with hypertension [56]. Further, high physician clinical decision-making skills reduced the risk of patient nonadherence by 15.8 %. Of interest, the health-care provider's decision to escalate treatment for risk factor management depends on the characteristics of the patient. One recent US-based study of 27 physicians and 158 patients reported that physicians were 40 % less likely to escalate treatment of patients with uncontrolled hypertension when patients suffered from comorbid depression [80]. It would appear that some more complex patients who would benefit most from an escalation of their treatment may be most likely to experience health-care provider clinical inertia. For example, poor patient self-management behavior was reported to increase therapeutic clinical inertia in a sample of patients with type 2 diabetes [81]. Future research is needed to place an exact figure on the magnitude of clinical inertia for empirically supported strategies to improve adherence to antihypertensive medication and to assess the effectiveness of interventions aimed at reducing clinical inertia for medication adherence.

Prescription Cost and Socioeconomic Status

Out-of-pocket costs for medication and socioeconomic status clearly affect adherence to antihypertensive medication. Medications can be prohibitively expensive, and patients are more likely to take their medications as prescribed when the costs are low [82–86] and when market availability is high [87]. Similarly, patients are more likely to adhere to prescribed medications if they are of higher socioeconomic status. A meta-analysis of 51 studies including approximately 4.8 million patients reported that patients classified at high socioeconomic status were 11 % more likely to adhere to antihypertensive medication than patients classified at low socioeconomic status [88]. Socioeconomic status was typically based on income or income-related measures (e.g., prescription drug benefits, copayments).

Sliding scale coverage systems that are tailored to the patient's unique financial situation may be needed in order to improve medication adherence related to socioeconomic circumstances. Other successful cost reduction approaches include reducing patient out-of-pocket costs, reduced copayments, and refill assistance [89, 35••]. Regardless of the specific strategy, increasing access to prescribed medication by reducing costs is an important strategy for improving adherence to antihypertensive medication. It should be acknowledged that adherence to antihypertensive medication remains a problem even in countries where cost is less of an issue such as in Canada where prescription medications are usually covered or reimbursed [90], highlighting the need for multifaceted interventions.

Recent Interventions to Improve Adherence to Antihypertensive Medication

We conducted a review of the literature to identify recent articles reporting on interventions to improve adherence to antihypertensive medications. PubMed and PsycInfo were searched for articles published between January 01, 2012 and February 15, 2014 using the terms adherence or concordance or convergence or nonadherence or "non adherence" or noncompliance or "non compliance" or persistence AND "blood pressure" or hypertens$. This review returned 1,015 abstracts. Seven studies were identified that used interventions to improve adherence to antihypertensive medications. Characteristics of each study can be found in Table 2. Three studies sought to improve patient adherence by having pharmacists or nurses deliver education and counseling in community settings [91, 92•, 93]. Relative to usual care, a single education session where information was tailored to help patients overcome self-reported barriers that was delivered by community pharmacists in Spain resulted in an improvement in adherence

Table 2 Description of intervention trials to improve adherence to antihypertensive medications

Trial	Sample size	Sample characteristics	Methods	Results
Crowley et al. [93]	359	African Americans with T2DM	Parallel group RCT with a 12-month follow-up CG: TAU + education (n=177) IG: monthly education + counseling sessions delivered by a nurse over the phone + medication management delivered every 3 months (n=182)	8.0 % attrition IG patients were 4.4 times more likely to self-report medication adherence using the MMAQ at 12 months Hard outcomes did not differ between groups
Fikri-Benbrahim et al. [91]	176	Spanish patients treated for hypertension and recruited from 13 community pharmacies	Parallel group RCT with a 20-week follow-up CG: Usual pharmacy care (n=89) IG: 1 pharmacy-delivered education session tailored to patient barriers (n=87)	15.8 % attrition Adherence increased in the IG relative to CG (11.6 %). Further, patients in the IG were more likely to be adherent (pill count ≥80 %) at follow-up (+11.6 %) (OR=4.07)
Ho et al. [98••]	253	Patients admitted to Department of Veterans Affairs medical center with acute coronary syndrome	Parallel group RCT with a 12-month follow-up CG: TAU (n=119) IG: multifaceted intervention, including pharmacist-led medication tailoring, education, collaborative care, and voice messaging reminders (n=122)	4.7 % attrition More patients in the IG were adherent to statins (+21.9 %), ACE-I/ARB (+12.4 %), and clopidogrel (+16.1 %) at 12 months, but not to beta-blockers (+3.3 %)
McGillicuddy et al. [94••]	20	Hypertensive kidney transplant patients identified as nonadherent and prescribed 3 or more medications	Parallel group RCT with 3-month follow-up CG: TAU IG: mobile health smartphone application that integrated data from an electronic medication tray and delivered reminders	5 % attrition Adherence increased (+37.1 % using electronic monitoring) and SBP decreased (−16 mmHg) in the IG relative to the CG at 3 months
Ogedegbe et al. [96••]	256	Hypertensive African American patients prescribed antihypertensive medication	Parallel group RCT with 12-month follow-up CG: culturally tailored education control with bimonthly attention phone calls (n=131) IG: workbook emphasizing positive emotions to overcome barriers, bimonthly positive affect phone calls, and mailed gifts (n=125)	10.9 % attrition Adherence was higher in the IG (+6 % using electronic monitoring) at 12 months, but there was no difference in SBP or DBP
Patel et al. [95]	50	High-risk African American (96 %) primary hypertension patients prescribed 2 or more antihypertensive medications	Single group 3-phase (3-month run-in, 3-month intervention, 3-month follow-up) intervention testing the Pill Phone application on a smartphone. Pill Phone app provides information and medication reminders	Adherence (assessed using pharmacy refill records and MMAQ) increased when the phone app was on (+4 %) and decreased when the phone app was off (−12 %)
Svarstad et al. [92•]	576	Hypertensive African American patients	Observational trial with 6-month intervention and 6-month follow-up CG: usual care + handout (n=21 %) IG: 6 pharmacist-led scheduled visits. Pharmacists were provided a toolkit to measure adherence, assess barriers, and tailor feedback. Patients were given a toolkit containing self-monitoring tools and education (n=79 %)	IG showed improved adherence (assessed using prescription refill records) at 6 months (+26 %) that were sustained at 12 months. IG had lower SBP (−7.31 mmHg) at 6 months but not at 12 months

CG control group, *DBP* diastolic blood pressure, *IG* intervention group, *MMAQ* Morisky Medication Adherence Questionnaire, *SBP* systolic blood pressure, *TAU* treatment as usual

to antihypertensive medication of 11.6 % assessed using pill counts [91]. Relative to usual care plus an information brochure, randomizing African American patients to receive 1 to 6 (mean 4.25) pharmacist counseling sessions resulted in an improvement in adherence of 26 % with a concomitant 7.31-mmHg reduction in SBP [92•]. Adherence outcomes were sustained at 12 months following intervention. Counseling included the provision of individually tailored educational information and pharmacist and patient toolkits that contained easy assessment devices and monitoring aids. Finally, African American patients randomized to receive 12 monthly education counseling sessions delivered by a nurse over the telephone were 4.4 times more likely than control patients to self-report medication adherence using the Morisky Medication Adherence Scale [93]. Counseling consisted of delivering education information using a motivational technique that was adapted to the patient's level of readiness to engage in health behavior change. These interventions attest to the importance of using a variety of health-care providers to educate patients and engage them in the process.

Two proof-of-concept investigations suggested that electronic aids such as smartphone applications can remind patients to take medications and improve adherence [94••, 95]. The use of a mobile health smartphone application that integrated data from an electronic medication tray increased adherence by 37.1 % and reduced SBP by 16 mmHg in a sample of 20 hypertensive kidney transplant patients identified as nonadherent (adherence score <85 % following a 1-month observation period) [94••]. The effects reported in this trial are atypically large, and replication is needed with a large and diverse sample of patients with hypertension. The second study used a three-phase crossover with an ABA design and reported that smartphone application reminders improved adherence in a sample of African American patients with primary hypertension [95]. It should be noted that improvements in adherence were small at 4 %.

In a novel approach, one trial sought to improve adherence to antihypertensive medication in a sample of 256 hypertensive African Americans using a positive affect intervention [96••]. Patients in both groups received an education workbook relevant to the clinical focus of the study, a behavioral contract, and bimonthly telephone calls to assist with overcoming barriers. In addition, patients in the intervention group received small gifts and were encouraged to incorporate positive, self-affirming thoughts into their daily lives and use such thoughts to overcome barriers to medication adherence during bimonthly phone calls. Relative to education control, a 6 % improvement in adherence was reported for patients who received the positive affect approach; however, improvements in adherence did not translate to improvements in BP. This study was limited in that there was no attempt to measure possible mechanisms through which the intervention worked, nor was maintenance of change assessed. From a theoretical perspective, positive affect interventions may operate through fostering self-efficacy and assisting patients to internalize the value and requisite skills for effective medication taking behavior [97].

One truly multifactorial trial to improve adherence to cardiovascular medications was located through the literature search. Two hundred fifty-three patients from four Department of Veterans Affairs medical centers in the USA admitted with acute coronary syndrome were randomized to usual care or a multifactorial intervention that involved medication management, patient education, coordinated care, and patient reminders [98••]. Delivery of the intervention resulted in a mean 7 % improvement in all cardiovascular medication adherence and a higher portion of adherent patients by 15 % by 12 months postdischarge. The results were not universally observed. For example, patient adherence improved for ACE-I/ARBs but not for beta-blockers. Further, no concomitant changes were observed in BP, although there was a near significant 8-mmHg reduction in SBP. This trial lends

Table 3 Strategies to improve patient adherence to antihypertensive medication recommended by the Canadian Hypertension Education Program (CHEP)

Assist your patient to adhere by:	• Tailoring pill taking to fit patients' daily habits
	• Simplifying medication regimens to once-daily dosing
	• Replacing multiple pill antihypertensive combinations with single pill combinations
	• Using unit-of-use packaging (of several medications to be taken together)
	• Supporting patients' adherence to therapy via a multidisciplinary team approach
Assist your patients in getting more involved in their treatment by:	• Encouraging greater patient responsibility/autonomy in monitoring blood pressure and adjusting prescriptions
	• Educating patients and patients' families about their disease and treatment regimens
Improve your management in the office and beyond by:	• Assessing adherence to pharmacologic and nonpharmacologic therapy at every visit
	• Encouraging adherence with therapy by out-of-office contact (either by phone or mail), particularly during the
	• First 3 months of therapy
	• Coordinating with pharmacists and work-site health caregivers to improve monitoring of adherence with pharmacologic and lifestyle modification prescriptions
	• Using electronic medication compliance aids

support for the use of multifaceted interventions to improve adherence to prescribed medication while reiterating that even the most complex and effective interventions do not always lead to large improvements in adherence to prescribed medications [44].

Summary and Conclusions

Adherence to antihypertensive medication is a prevalent concern that has been researched for decades, but an understanding of the issue along with evidence of what constitutes successful interventions has increased only modestly. A strong knowledge base of effective techniques for improving adherence is developing but further research is needed into how techniques can be combined for optimal patient gains.

Several techniques to improve adherence to antihypertensive medication have been identified with sufficient supporting evidence from randomized trials to inform clinical practice recommendations. For example, the Canadian Hypertension Education Program (CHEP) is a Canadian initiative to improve awareness, treatment, and control of hypertension through the education of health-care professionals that publishes annual recommendations for the assessment and treatment of hypertension in Canada [99]. Consistent with Appraisal of Guidelines, Research and Evaluation (AGREE-II) [100], recommendations are graded according to the strength of their underlying evidence, ranging from grade A (strongest evidence, based on high-quality randomized clinical trials) to grade D (weakest evidence, based on low power, imprecise studies or expert opinion alone). CHEP advocates for the use of several techniques to improve patient adherence and recommends a multipronged approach for assisting patients to improve adherence to antihypertensive medication (Table 3) [75].

While conceptually important techniques are recommended, their manipulation usually leads to modest success at improving adherence. There remains little consensus regarding what techniques work and for which individuals under given circumstances. Circumstances do not seem to have changed since Haynes' Cochrane review of interventions to improve adherence to medication where data from 70 unbiased randomized controlled trials were used to conclude that less than half of interventions resulted in improvements to adherence and even the most effective interventions did not lead to large improvements [44].

It may be unrealistic to expect to achieve enduring health behavior change with a simple adjustment of one or two elements of a complex treatment regimen embedded within a complex human life. The reasons for medication nonadherence are multifactorial and necessitate multipronged interventions that adopt several proven strategies in order to improve the situation. Yet, large, multifaceted interventions do not always improve adherence to antihypertensive medications [98••]. Such observations support the opinion that no universal set of strategies will improve adherence to antihypertensive medication in all settings [101]. *Rather than adopting a one-size-fits-all approach, evidence-based strategies that have been used to successfully improve adherence to antihypertensive medication should be selected to address each patient's specific barriers to nonadherence*. Unfortunately, sufficient evidence is not yet available to guide choices among the considerable array of intervening components [35••]. This is likely due to the lack of data about mediating relationships through which effective strategies operate and the lack of data about which strategies are most effective for the three aspects of adherence (i.e., initiation, implementation, and discontinuation).

Conclusion

Nonadherence to antihypertensive medication is a prevalent and clinically important concern. Despite evidence of their effectiveness in lowering BP and reducing risk of cardiovascular morbidity and mortality, there are a variety of patient-related (e.g., knowledge, motivation, mental health), provider-related (e.g., regimen complexity, patient-provider communication, clinical inertia), and system-related (e.g., prescription cost) factors that influence the initiation of prescribed medication, the development of effective drug taking habits, and/or drug discontinuation. There may be no impending pharmaceutical discovery, surgical innovation, or governmental policy change with greater potential for reducing rates of disease than increasing the percentage of treatment plans that patients carry out as prescribed. Several techniques to improve adherence to antihypertensive medications have been developed; however, large multifaceted interventions often result in less than anticipated improvements to adherence. As full adherence remains a barrier in achieving the full benefits of antihypertensive medication, the development of a framework for flexibly tailoring proven treatment strategies to address patient barriers in adhering to the medical management of hypertension and that can be easily translated to clinical practice should be considered a priority.

Compliance with Ethics Guidelines

Conflict of Interest Ross Feldman has no conflicts of interest. Kim Lavoie worked as a consultant for Abbvie, Takeda, Boehringer Ingelheim, and Kataka Medical Communication. Lavoie received a grant from Abbvie; payment for a motivational communication program for Canadian Dermatology Association; and payment for motivational communication programs for Kataka Medical Communication.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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