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Scalable strategies for improving adherence in adults with hypertension—review

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Abstract

The global epidemic of hypertension remains largely uncontrolled and is a leading contributor to noncommunicable disease deaths worldwide. Failure to detect and to adequately treat hypertension is the largest contributor to uncontrolled hypertension. Yet, suboptimal adherence, which includes failure to initiate a prescription for antihypertensive pharmacotherapy, to take medications as often as prescribed, and to persist on pharmacotherapy long-term, is a well-recognized factor contributing to uncontrolled hypertension. A large body of research has identified several variables including patient, sociodemographic, comorbid medical and behavioral conditions, therapy-related, healthcare team, and are associated with nonadherence. Unfortunately, these factors individually and even in combination are typically only weakly related to adherence of individual patients. A two-fold strategy can be efficiently applied in the clinical setting to improve adherence. First, address major categories of adherence throughout the therapeutic journey for all patients from initiation of pharmacotherapy to titration, and maintenance. Efficient, scalable strategies in this category include teach back, clarity on treatment goals including the blood pressure range required to attain consistent control, initiation, and titration of single-pill antihypertensive combinations, limiting out-of-pocket expense, and refill consolidation. Second, objectively assess adherence when treatment goals are not attained with effective pharmacotherapy. Then, identify and address patient-specific barriers for individuals with suboptimal adherence. Given the multiple competing priorities and resultant time demands on clinicians and healthcare teams, effective, replicable, and scalable strategies to optimize adherence are important in attaining the evidence-based benefits of antihypertensive pharmacotherapy.

Keywords

Hypertension, adherence, persistence, single-pill combination, patient-centered

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Introduction

Hypertension, defined by systolic blood pressure (SBP, mmHg) ≥ 140 systolic or ≥ 90 diastolic blood pressure (DBP, mmHg) or antihypertensive treatment, impacts approximately 1.3 billion adults globally and is a leading contributor to non-communicable disease deaths [1]. Among the 1.3 billion adults with hypertension, roughly 700 million (54%) are on antihypertensive pharmacotherapy with an estimated 350 million controlled to < 140/< 90. In other words, among approximately 950 million adults with uncontrolled hypertension, ~600 million are untreated. Of those on antihypertensive pharmacotherapy, approximately half are on monotherapy, which is often insufficient to control blood pressure (BP) to < 140/< 90 in most adults. Consequently, untreated, and inadequately treated hypertension are major contributors to uncontrolled hypertension globally. While this review focuses on a treatment goal of < 140/< 90, the narrative is relevant for clinicians targeting < 130/< 80.

Estimating the global impact of perfect adherence to prescribed antihypertensive pharmacotherapy

Suboptimal adherence is also a significant contributor to uncontrolled hypertension. In the U.S., prescription fill data suggest that adults with hypertension take approximately 60% of their prescribed antihypertensive medication [2, 3]. Biochemical adherence monitoring in patients with uncontrolled and treatment resistant hypertension in various countries has identified non-adherence rates ranging from 26% to 66% [4–8]. If adherence among adults on antihypertensive pharmacotherapy improved from roughly 60% to 100%, control of hypertension would rise an estimated ten percentage points [2]. Assuming these estimates from U.S. data are relevant globally, then perfect adherence among the 700 million adults on antihypertensive pharmacotherapy would increase the number of adults with controlled hypertension from ~350 million to ~420 million. If we further assume a 25% decline in cardiovascular events (CVEs) from 2% (1.4 million CVEs) to 1.5% (1.05 million CVEs) annually among seventy million adults moving from uncontrolled to controlled hypertension [9], then roughly 350,000 CVEs globally would be prevented annually through perfect adherence. These crude estimates suggest that efficient, scalable strategies to improve antihypertensive medication adherence merit attention.

Definitions of key terms including adherence, persistence, and discontinuation

Medication adherence has been defined as the extent to which a person's behavior corresponds with taking a medicine optimally [10]. Adherence includes three components: (a) initiation or starting prescribed therapy, (b) implementation or the extent to which medications are taken in the amount and frequency prescribed, (c) continuation or the time therapy is sustained.

Persistence represents the time (e.g., days, months, years) over which a patient continues the treatment or the third component of adherence. Given that chronic conditions including hypertension typically require sustained adherence to derive ongoing benefit, it has been suggested that persistence is the relevant indicator of adherence [11]. Lack of persistence on treatment has been associated with adverse cardiovascular outcomes [12].

Adherence and outcomes

A note of caution is appropriate in attributing all clinical benefits of adherence to direct medication effects. For example, adherence to placebo is associated with better cardiovascular outcomes including approximately 30–35% lower cardiovascular mortality [13, 14]. These observations suggest benefits of adherence reflect behavioral or other traits associated with adherence in addition to direct medication effects. For example, adherent patients have a more positive attitude toward preventive health measures, which could have a favorable impact on outcomes [15, 16].

Factors associated with adherence

In the World Health Organization 2003 Report, "Adherence to long-term therapies: Evidence for action" [17], it was noted that "The ability of patients to follow treatments is frequently impeded by more than one barrier. Interventions to promote adherence often require several components to target these barriers, and

health professionals must follow a systematic process to assess all the potential barriers." While that advice is logical, it may be impractical, especially in primary care settings where estimates suggest that a clinician would require 27 hours each day to implement evidence-based guidelines [18]. Even with optimal team-based care, estimates suggest that more than 10 hours daily would be required to implement evidence-based guidelines. Thus, time constraints can limit clinicians' capacity to counsel patients on adherence, which highlights the value of team-based care [18–20].

Nevertheless, the five dimensions of adherence in the 2003 Report remain useful (Table 1) [17]. A conceptual understanding of these five dimensions can inform the assessment of factors contributing to suboptimal adherence and inform the design, implementation, and refinement of effective, replicable, and scalable multicomponent interventions to improve adherence and clinical outcomes.

Table 1. Adherence to pharmacotherapy is impacted by five categories of factors

Sociodemographic	Health team/system	Therapy-related	Condition-related	Patient-related
Health literacy	Access to and cost of care including co-pays	Adverse effects	Dementia	Alternative therapies
Housing status	Clinician burnout	Complex regimens	Drug/alcohol abuse	Deny diagnosis
Income	Communication	Refill consolidation	Major disability	Fear adverse effects
Minority status	Fail to detect clues	Refill frequency	Mental/behavioral health	Follow-up frequency
Social support	Financial incentives	Time to benefit	Multiple chronic conditions	Forget
Transportation	Knowledge/QI infrastructure	Treatment changes	Quality of life	Future discounting
War/disasters	Patient centeredness	Treatment duration	Symptom severity	Knowledge/understanding
Young, very old	Patient-clinician relationship	Treatment failure		Perception of illness severity/impact
	Team-based care			Perception of treatment efficacy

QI: quality improvement

Selected factors in each of the five categories impacting adherence

In some cases, related factors may be combined rather than presented in the category shown in Table 1.

Sociodemographic factors

Several factors in this group are associated with suboptimal adherence [15, 21–23]. However, a composite score developed from a basket of variables associated with adherence may not provide clinically useful discrimination, even for individuals from which the predictive model was developed [23]. Other evidence suggests that access to care and medications is more important than sociodemographic factors in mediating adherence and hypertension control [24, 25]. Rather than attempting to estimate adherence from sociodemographic factors, an alternative strategy is, to begin with, efficient scalable methods that support medication adherence for all patients. The clinician and care team can then use reliable methods to detect suboptimal adherence in individual patients who do not have the expected response to effective pharmacotherapy. Addressing the specific factors impacting adherence for those individuals allows a more focused and efficient use of time and resources.

War and disasters are among socioenvironmental factors impacting medication adherence. For example, the COVID-19 pandemic with mandates for social distancing and sheltering-in-place for extended periods of time had an adverse impact on adherence to antihypertensive medications and BP control [3, 26, 27]. Adherence to medications during the 6 months following guidance to distance and shelter was much more strongly associated with adherence in the 6 months prior to this guidance than age, sex, type of

healthcare insurance, several major comorbid conditions, and region of the country [3]. Our findings are consistent with other reports that past adherence is the strongest predictor of current or future adherence [28].

Healthcare system

In the U.S., most adults ≥ 65 years old have healthcare insurance as this age group qualifies for Medicare. Lack of healthcare insurance was more common among adults < 65 years old, especially in sociodemographic minorities and those with limited education and income status prior to the Affordable Care Act, with Medicaid expansion in 2014 [29]. From 1988 to 2010, adults < 65 years old without healthcare insurance in the U.S. did not have a significant improvement in hypertension control [24]. Despite sociodemographic characteristics similar to uninsured adults, those with public healthcare insurance, mainly Medicaid, had control rates similar to adults with private healthcare insurance, including a 22-percentage point absolute improvement from 1988 through 2010. Healthcare insurance, whether public or private, served as a proxy for access to healthcare and medications [24, 25].

Healthcare team

The relationship between the patient and clinician, the clinician's communication style, the extent of shared decision making, and the quality of team-based care can all impact patient adherence [15, 21, 22]. Trust is critical. Patients must be confident their clinician is competent and accounts for their interests in management decisions.

Communication style

Direct questioning such as 'Did you take your medication(s)?' or 'Why don't you take your medication?' is generally less effective at understanding the patient's perspective and promoting adherence than reflective questions such as 'Are you having any difficulties obtaining and taking your medications such as cost or side effects?'.

Shared decision making

Patients who participate in shared decisions on their medication regimens are more adherent than patients who are not engaged in the decision [30]. Racial-ethnic minorities are less often engaged in the decisions regarding their treatment than racial-ethnic majorities, which may be a contributing factor to lower adherence in the former [31].

Team-based care

Team-based care and well-functioning patient-centered medical homes are associated with better adherence and risk factor control than when these factors are not present [19–21, 32]. Clinician burn out can adversely impact patient adherence. Clinicians and staff are happier and more productive and have less burn out in an effective team-based care arrangement [20].

Red flags

Clinicians and staff may not recognize clues linked to suboptimal adherence, including missed appointments or prescription refills, or a poor therapeutic response to medications or combinations of medications that are usually effective. Identifying and addressing factors underlying 'red flags' can improve patient adherence and risk factor control [33].

Healthcare system issues

Including access to and cost of care and medications, impact adherence and clinical outcomes [19, 21, 22, 32]. Out-of-pocket costs account for roughly one-third of the variance in adherence, affecting adherence even in patients with the capacity to pay [34].

Therapy-related factors/interventions

Complex regimens with asynchronous dosing are barriers to adherence [10, 12, 14]. Fewer medications, and especially fewer pills, which can be implemented using once daily single-pill combinations (SPCs), are associated with better adherence and hypertension control [35, 36]. Patients who reach therapeutic targets more rapidly, who require fewer adjustments in their medication regimen, and who experience no or limited adverse effects are more likely to adhere than patients with a longer period to control, who often undergo multiple changes to their medication regimens, and experience adverse effects, are less likely to adhere to treatment [15, 21, 37, 38].

Condition-related factors/interventions

Adults with hypertension, especially older adults, often have multiple chronic conditions and polypharmacy [39]. Major depression and other psychoses, which are more prevalent among individuals with multiple chronic conditions, can adversely influence adherence as can drug or alcohol abuse and dementia [40, 41].

Patient-related factors/interventions

Some patients do not accept the diagnosis and related treatment. Other patients may not perceive potentially severe complications of a currently asymptomatic disease. If patients believe that prescription medications are ineffective in controlling hypertension or are associated with major adverse effects, then adherence is likely to be adversely impacted [42]. While education is often perceived to improve adherence, education alone often produces minimal change in adherence [15, 21, 43].

Forgetfulness is an important contributor to suboptimal adherence. Several interventions from pill organizers to electronic applications that provide timely and recurrent prompts can improve adherence [15, 21]. Low self-efficacy, or lacking confidence in one's ability to self-manage a condition or disease, is another documented barrier to adherence [15, 37, 44].

Patients who endorse alternatives to traditional or Western medicine are less adherent to prescription medications [45, 46]. Individuals who discount the future at higher rates are less likely to engage in preventive health behaviors [47–50]. For example, among 422 adults with hypertension receiving care in safety net clinics, their estimated future discount rate was approximately 44% annually [48]. Their discount rate suggested that events perceived to be two or more years in the future did not merit current attention. While these individuals knew that uncontrolled hypertension led to stroke, heart disease, and kidney disease, each 1% increase in the annual discount rate reduced the probability of getting BP checked by 3.5% and not following their doctor's treatment plan by 1.6%.

Detecting non-adherence

Among various cardiovascular medication classes, prescriptions of antihypertensive and lipid lowering drugs have the highest rates of non-initiation [50]. In some reports, only roughly half of the patients persisted in therapy two years later [21, 51]. Urine drug screening is a reliable method for detecting and addressing non-adherence that can be cost effective and even cost saving [7, 8, 52]. Unfortunately, simple, inexpensive, and highly reliable methods for assessing medication adherence are not readily available in many clinical settings. Universal availability of reliable, low-cost biochemical screening to detect antihypertensive drugs in body fluids would be helpful in detecting and addressing barriers to adherence.

Patient interview

While the patient interview is simple, studies suggest it is no better than tossing a coin for assessing adherence [21, 53]. Potential explanations include: (i) time available for the interview, (ii) communications skills of clinicians vary, (iii) inaccuracies in patient self-report as they tend to overstate their adherence either because they do not recall missing doses or because they want to please their clinicians, (iv) adherence is a variable and dynamic process [21, 54].

Direct observation

Another clinically useful method for detecting non-adherence is to measure the antihypertensive response to prescribed medication in the clinical setting [55]. With direct observation, patients are advised not to take medications before their clinical appointments.

Questionnaires

Questionnaires are rarely used in routine clinical practice due to time constraints. The relationship between adherence measured by questionnaires and more reliable methods is relatively weak, and questionnaires, like the patient interview, tend to over-estimate adherence [21, 56].

Pill count

Pill count is frequently used and provides a relatively good view of the medication taken by the patient over time. Among limitations of this method are included the fact that pills can be removed from their container but not taken, medication may be shared with another individual, and the patient may obtain medication from another source [21, 57].

Prescription refills

The percentage of days covered by prescriptions provides a rough estimate of drug adherence and persistence [24, 58, 59]. This approach is particularly useful when an electronic monitoring of drug prescriptions in pharmacies is available and assumes that patients take their drugs when therapy is available. Ideally, the data source for drug dispensation covers all sources of supply, which is not always the case.

Medication Electronic Monitoring System

A criticism of the Medication Electronic Monitoring System (MEMS) is that opening the pill container does not ensure medication was taken. Studies comparing MEMS data and drug concentrations have shown 97% concordance between the two methods, suggesting that when the pillbox is opened drugs are taken [21, 59, 60]. While MEMS is one the most reliable techniques for detecting poor adherence, availability outside research settings remains limited.

Measurement of drug levels

Most BP medications can be detected in urine or blood using high-performance liquid chromatography-tandem mass spectrometry [4, 5, 7, 21]. As noted previously, monitoring of drugs and metabolites is useful for detecting and addressing suboptimal adherence and can be cost effective to cost saving. Absence of medication typically indicates it has not been taken for several half-lives. Testing for antihypertensive drugs other than diuretics is limited in many clinical settings. However, even in these settings, if diuretics are prescribed in SPCs with other classes of antihypertensive medications, then adherence to other drugs in the combination can be indirectly assessed.

Efficient, scalable tactics to improve adherence

Prescribing-related tactics are among the most efficient for improving adherence

Another key advantage of prescribing-related tactics is the high degree of clinician-level control. This is not intended to discount effective team-based care and a well-aligned healthcare system or to suggest that physicians cannot provide guidance on pill organizers or applications to enhance adherence, especially for patients who occasionally forget to take their medications. Medications with longer half-lives including but not limited to amlodipine, telmisartan, and chlorthalidone can help sustain hypertension control on days when medications are forgotten.

SPCs

Prescribing SPCs represents a simple and effective, yet under-utilized strategy for improving adherence, hypertension control, and clinical outcomes. In a claims-based study, 17,465 adults with hypertension were

prescribed olmesartan or valsartan, amlodipine, and hydrochlorothiazide in one-, two-, or three-pill regimens [61]. Adherence assessed by at least 80% of days covered was roughly 50% lower with the two-pill regimen and 75% lower with the three-pill than one-pill regimen. Medication gaps of 60 days or greater were also significantly greater with the two- and three-pill than one-pill regimen.

In another, claims-based study, 28,999 adults with hypertension receiving SPCs and 28,999 adults receiving equivalent free-pill combinations (FPCs) were selected by propensity-score matching [62]. Several adverse clinical outcomes were reduced when patients received SPCs rather than equivalent FPCs, including myocardial infarction ~4–38%, coronary artery disease ~23–68%, stroke ~23–46%, and heart failure ~32–60%. The clinical outcomes advantage for SPCs over equivalent FPCs coincided with higher levels of medication persistence at one year with SPCs, which is consistent with greater adherence documented for SPCs [35]. Importantly, this and other claims-based studies showing improved outcomes with SPCs suggest that reducing pill counts represents a long-term strategy for improving adherence and clinical outcomes.

Days of supply

A greater number of days of supply with each prescription reduces refill frequency and improves adherence [63, 64]. In a claims-based analysis of 379,658 adults with hypertension, non-persistence during the last 90 days of a one-year period following treatment initiation was lower when 90 as compared to 30 days of medication were prescribed [65].

In some healthcare settings, access to SPCs of antihypertensive medications may be limited, costs may be higher than the separate medications, and coverage for 90- as compared to 30-day refills may be limited. In these settings, the preceding recommendations may not result in better adherence given limited access and financial barriers to SPCs and longer days of supply.

Refill consolidation

Most adults with hypertension require combination therapy, typically prescribed as FPCs. Moreover, patients with hypertension often have multiple chronic conditions requiring additional pharmacotherapy [66]. Pharmacy visits can be further reduced by consolidating refills, which improves persistence with anti-hypertensive and lipid lowering medications [67].

Teach back

Even when the patient agrees with the treatment plan, misunderstandings are common. A simple and efficient approach to ensuring the treatment regimen is understood, even when patient-centered and engaged, is to have the patient explain the treatment plan in their own words. Teach back has been associated with improvement in the response and outcomes from pharmacotherapy [68, 69].

Indirect evidence for the utility of these simple approaches to improving adherence

SPCs, increasing days of supply, refill consolidation, and teach back are standard components in training clinicians and healthcare teams to implement the American Medical Association's MAP™ (Measure accurately, Act rapidly, Partner with patients) Hypertension program. MAP Hypertension is associated with a 3–5 mmHg greater SBP response to adding an antihypertensive medication during the intervention than the baseline period [70, 71]. The effect of each component in this training package on the SBP response to treatment intensification has not been assessed.

Therapy-related factors/interventions

As noted earlier, patients who reach therapeutic targets more rapidly, who require fewer adjustments in their medication regimen, and who have few adverse effects are more adherent than patients experiencing these challenges [15, 21, 37].

Monthly clinical encounters until hypertension is controlled

To optimize this component, monthly clinical encounters are recommended until hypertension is controlled [71].

Therapeutic intensification when BP is not controlled

A majority of adults with uncontrolled hypertension are untreated or receive antihypertensive monotherapy when most require combination therapy to attain BP control [72, 73]. Upon verification that the uncontrolled BP values are accurate and represent usual BP, adding a single antihypertensive medication at half-standard, standard, or maximum recommended dose lowers SBP by ~7, 9, and 11 mmHg, respectively [74]. In contrast, doubling the dose of a single antihypertensive medication from standard to maximum recommended dose lowers SBP ~2–3 mmHg. Initiating therapy with half- or quarter-standard doses of two to four antihypertensive medications, then doubling the doses of all components concurrently is more efficient than initial monotherapy with a traditional stepped algorithm [75–77]. The initial SPC approach is generally well tolerated for patients who are not frail and have baseline SBP more than 10 mmHg from goal.

Adding a BP medication class for patients with verified uncontrolled hypertension is appropriate for most patients on less than three antihypertensive medications. When the patient is uncontrolled on three or more antihypertensive medications, then a management approach for apparent treatment resistant hypertension is appropriate [72, 73, 78].

Self-measured BP

Self-measured BP (SMBP) values relayed to the healthcare team, combined with timely advice from the healthcare team to the patient (advice), can be accomplished without an in-person healthcare visit. SMBP with support is effective for improving BP control [79] and lowering BP for patients with adverse social determinants of health [80]. Team-based care, which trains patients to measure their BP and guides them on actions to take for uncontrolled values, which is supported by efficient electronic transfer of SMBP readings, can provide an efficient, cost effective method for improving hypertension medication adherence and control [81, 82].

Healthcare system-related factors

Healthcare payment for volume of care and clinical documentation can be a barrier to supporting patient adherence and better BP control [83]. A study in the 1970s showed that reallocating time from clinical documentation to patient education and support improved adherence to antihypertensive medications and BP control [84].

A recent systematic review indicates that health insurance coverage, economic policies, and financial incentives can improve hypertension treatment and control [83], which impact multiple steps in the hypertension control pathway, including patient medication adherence. Thus, healthcare payment that compensates and incentivizes services and supports, including patient-centered, team-based care, which produces outcomes, is more effective than payment that reimburses primarily for the volume of services provided.

The limited focus of Table 2 is not intended to discount the value of other approaches, which may better align with available resources and patient needs.

Conclusions

Adherence is essential to deriving the substantial evidence-based benefits of pharmacotherapy for controlling hypertension and reducing multiple adverse cardiovascular outcomes. As with any sustained behavior, the perceived benefits must outweigh the perceived costs within a period relevant to the individual (recall future discounting). Reducing cost, complexity, and time to benefit is essential. The patient management-related approaches are intended to reduce the time to hypertension control, which is important to sustaining patient engagement. The healthcare system-related factors enable more efficient

Table 2. Stream-lined tactics for improving antihypertensive medication adherence and BP control

Prescribing related tactics (high-level clinician control)	Patient management (moderate clinician control)	Healthcare system, policy, and payment-related (limited clinician control)
SPCs for initial and long-term therapy	Rigorous measurement of office BP including AOBP with validated devices	Available and affordable SPC
Longer days of supply, especially for maintenance therapy (90 vs. 30 days)	SMBP training with relay of BP data to care team with patient advice and support	Infrastructure and payment for efficient SMBP with relay and advice/support
Rx intensification, especially adding BP med within an SPC or concurrent dose increase of 2–3 meds in SPC at encounters with uncontrolled BP	Monthly encounters until BP controlled	Patient-centered, team-based care with payment for quality
Refill consolidation, especially when multiple chronic conditions	Teach back, pill organizers, apps tailored to patient needs	Available and affordable objective measures of adherence

BP: blood pressure; SPCs: single-pill combinations; SMBP: self-measured BP; AOBP: automated office BP

and effective delivery of the prescribing and patient management-related tactics. Several efficient prescribing recommendations and system-related factors are included in successful ongoing programs to improve hypertension control [70, 71, 85, 86], which provides indirect support for their broad scalability and sustained effectiveness. Aligning healthcare policy and payment to support the tactics that facilitate effective prescribing for and management of hypertension represents important opportunities for healthcare system leaders and payers.

Abbreviations

BP: blood pressure

CVEs: cardiovascular events

FPCs: free-pill combinations

MAP: Measure accurately, Act rapidly, Partner with patients

MEMS: Medication Electronic Monitoring System

SBP: systolic blood pressure

SMBP: self-measured blood pressure

SPCs: single-pill combinations

Declarations

Disclaimer

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the American Medical Association.

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The author declares no conflicts of interest.

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