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Strategies to Improve Adherence to Anti-Hypertensive Medications: a Narrative Review

Chigozirim Izeogu[1], **Jolaade Kalinowski**[2], **Antoinette Schoenthaler**[1]

[1]Department of Population Health, Center for Healthful Behavior Change, New York University Grossman School of Medicine, New York, NY, USA

[2]Department of Human Development and Family Sciences, University of Connecticut, Storrs, CT, USA

Abstract

Purpose of Review—Medication adherence is critical for effective management of hypertension, yet half of patients with hypertension are non-adherent to medications. In this review, we describe and critically evaluate medication adherence interventions published in the past 3 years for patients with hypertension.

Recent Findings—We identified 1593 articles and 163 underwent full review, of which 42 studies met the inclusion criteria. Studies were classified into eight categories: simplification of medication regimen (e.g., fixed dose combination pills); electronic Health (eHealth) tools (e.g., text messaging reminders); behavioral counseling (e.g., motivational interviewing); healthcare system changes (e.g., patient-centered medical home); patient education; multicomponent chronic disease management program; home blood pressure monitoring; and financial incentives. Studies utilizing strategies to simplify medication regimens, eHealth tools, patient education, and behavioral counseling were most likely to report positive findings.

Summary—Interventions targeting patient behavior were more likely to be associated with improvements in medication adherence compared to those targeting providers or the healthcare system. eHealth tools show promise for augmenting behavioral interventions. A major limitation of included trials was short study duration and use of self-report measures of medication adherence. Future research should explore how complex interventions that utilize a combination of evidence-based strategies and target multiple adherence behaviors (e.g., both day-to-day medication taking and long-term persistence) may be efficacious in improving medication adherence.

Keywords

Medication adherence; Hypertension; Intervention; Review

✉Antoinette Schoenthaler, Antoinette.Schoenthaler@nyulangone.org.

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Introduction

Hypertension is a major risk factor for cardiovascular disease (CVD), the leading cause of death worldwide [1, 2]. Hypertension affects approximately one-third of individuals in the United States (US) and approximately 1 billion individuals worldwide [2]. Recent data utilizing the 1999–2018 US National Health and Nutrition Examination Survey, showed that more than half of patients with hypertension (56.3%) have uncontrolled blood pressure [3]. Medication adherence is at the cornerstone of effective treatment and management of hypertension. Patients with high adherence (defined as medication possession ratio [MPR] 80–100%) to antihypertensive medications are 45% more likely to achieve blood pressure control than those with medium (50–79%) or low adherence (< 50%) [4]. The economic benefit of improved medication adherence parallels that of the reduced disease burden on the health of the US population. High patient adherence levels are associated with lower hospitalizations [5], reduced cardiovascular events [6], and the cost savings are significant [7].

Medication adherence is commonly defined using the World Health Organization's description as "the extent to which a person's behavior-taking medications, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider" [8]. More recently, the definition has evolved to emphasize the distinction between three key phases of medication adherence known as the ABC taxonomy: (1) initiation of the prescribed regimen, which entails the initial uptake of the prescribed medication; (2) implementation of the recommended treatment plan, which is the extent to which the patient engages in taking the medication appropriately and in accordance with the prescribed dose; and (3) persistence with medication-taking behavior, which encompasses the length of time the patient takes the medication [9•, 10].

Despite research that has been dedicated to improving medication adherence in patients with hypertension, rates remain suboptimal [11]. Prior systematic reviews indicate that intervention approaches that use multiple strategies to improve medication non-adherence are more effective than singular approaches [12]. For example, efficacious multicomponent strategies include the use of electronic health (eHealth) applications and technology [13–15], family and peer support [16], nurse or pharmacist-led behavioral counseling, [13, 17], and partnerships with community-based organizations [18]. Despite the efficacy of these approaches, there is lack of understanding of interventions that can effectively target the complex and dynamic nature of medication adherence.

The aim of this review is to synthesize and critically review the updated literature (2017–present) to facilitate greater understanding of efficacious intervention strategies that could lead to sustainable changes in medication adherence among patients with hypertension.

Methods

Selection of Studies

In consultation with a medical librarian, we searched the PubMed, OVID Medline, EMBASE, Web of Science, and Cochrane Central databases for results from January 1, 2017

to March 17, 2020. Additional strategies included searching the bibliographies of eligible articles and searching other systematic reviews and meta-analyses for relevant articles. The concepts for medication adherence, hypertension, and prospective or cohort study designs were included in the search with keyword synonyms. Studies were limited to adults at least 18 years of age and publications written in English. For a full search strategy, see Appendix A.

Studies were eligible if they met the following criteria: (1) participants that had a diagnosis of high blood pressure or hypertension or if they were taking an antihypertensive medication; (2) there was an outcome assessment of adherence to antihypertensive regimens; and (3) primary studies designed to increase medication adherence in adult subjects with a diagnosis of hypertension. Both randomized and nonrandomized studies (e.g., did not report control groups but did compare post-intervention adherence to baseline) were included. Single and multicomponent intervention strategies as well as those that target different levels of influence (e.g., individual or organization) were also eligible for inclusion. Intervention strategies employed in the included articles were categorized using frameworks outlined in previous reviews [19] of medication adherence. Studies with varied measures of medication adherence (e.g., via self-report, pill count, electronic monitoring device, pharmacy refill data) were included. Articles were excluded if they did not specify measures used to assess medication adherence, or changes in adherence due to the intervention was not reported. We excluded studies with cross-sectional designs, as we were interested in determining the causal relationships between the intervention and medication adherence.

Two authors independently reviewed all titles and abstracts from the search. Each retrieved citation was categorized as potentially relevant, not relevant, or as having insufficient information to make a judgment. All authors independently reviewed the included articles. The authors discussed any disagreements about inclusion in the review, with all differences resolved by consensus. The primary author independently extracted data on study design, methods, participant characteristics, study groups, and outcomes from the selected articles using a [20–27] structured data collection form. Two of the authors independently reviewed the extracted data for completeness before summarizing the included studies.

Results

In total, 1593 articles were identified, of which 163 were extracted for full review. One hundred twenty-one of these articles were excluded for the following reasons: the study was cross-sectional, medication adherence was not assessed, adherence outcomes were not reported specifically for patients with hypertension (e.g., outcomes were combined with other chronic disease), there was no English translation available, and the publication was limited to a conference abstract or a protocol paper. Thus, 42 studies were included in this review. Table 1 shows the characteristics of the included trials. The most common study designs included randomized controlled trials ($n = 24$) [14, 28, 29, 30••, 31, 32••, 33–46] and retrospective and prospective cohort studies ($n = 11$) [47–55]. One-third ($n = 14/42$) of the studies were conducted in the US [14, 18, 20–22, 35, 36, 40, 45, 47, 48, 55–57]. The number of individuals per study varied widely ranging from 10 to 2,169,845 (median: 299). The duration of follow-up ranged from 1 month–5 years (median: 6 months).

Assessment of Medication Adherence

Medication adherence was commonly operationalized as the mean change in adherence score between the pre- and post-intervention period. As shown in Table 1, the majority of studies (57%; $n = 24/42$) used a patient self-report measure of medication adherence to assess the primary outcome. While the validated Morisky Medication Adherence Scale (MMAS) was the most commonly used measure (54%; $n = 13/24$), five studies (21%) utilized novel self-report measures that were created for the purposes of their study [30••, 41–43, 46]. Fourteen studies (33%) utilized pharmacy refill records to assess medication adherence [22, 32••, 39, 47–51, 53–55, 57, 58, 60••]. Medication adherence assessed via pharmacy records was operationalized using either the MPR or the proportion of days covered (PDC) metric. Three studies (7%) utilized an electronic monitoring device [33, 40, 56] and one (2%) used pill count [37]. Only three studies used a combination of assessments (e.g., a self-report questionnaire plus pharmacy refill data) [32••, 40, 60••].

Overview of Intervention Approaches

About three-quarters ($n = 29/42$; 78%) of the interventions utilized a combination of strategies to improve medication adherence. Eight categories of interventions were examined across the 42 studies: nine studies (21%) tested an eHealth tool (e.g., text messaging reminders; education delivered via a smartphone app) [14, 21, 32••, 33–36, 56, 59]; eight studies (19%) tested the effectiveness of simplifying the medication regimen (e.g., using fixed-dose combination pills) [30••, 31, 50–55]; eight (19%) tested behavioral counseling strategies (e.g., motivational interviewing) [22–27, 37, 38]; five (12%) targeted changes in the healthcare system (e.g., patient-centered medical home) [20, 40, 47, 48, 60••]; four (10%) utilized patient education as the primary strategy [18, 28, 29, 46]; three (7%) tested a multicomponent chronic disease management program [41, 42, 44]; three (7%) utilized financial incentives to promote adherence [39, 49, 57]; and two (5%) utilized home blood pressure monitoring. [43, 45]. Of these studies, 30 (71%) reported statistically significant improvements in medication adherence attributable to the intervention [14, 18, 22–24, 26–29, 30••, 31, 33, 34, 36–38, 41, 42, 46, 47, 49–55, 59]. Studies utilizing strategies to simplify medication regimens, eHealth tools, patient education, and behavioral counseling were most likely to report positive findings. Almost half ($n = 19/42$; 45%) of control groups were characterized as usual care. Below, we review the studies and the impact on medication adherence grouped by intervention category.

Simplification of the Medication Regimen

All studies reported a statistically significant improvement in medication adherence as a result of simplifying patients' anti-hypertensive regimen. Seven studies (78%) assessed medication adherence using electronic pharmacy records (i.e., MPR, PDC). The most common intervention strategy was changing patients' antihypertensive regimen to a fixed-dose combination pill to reduce the number of pills taken per day. All five studies examining the effectiveness of a fixed-dose combination pill reported a positive effect on medication adherence, as compared to the control group (i.e., single pill combination or multiple pill regimen), regardless of the method of adherence assessment. One additional study compared the combined effect of a low-cost pillbox organizer that was equipped with an alarm plus

two health education classes versus usual care on self-reported medication adherence among 518 patients with hypertension [30••]. At 6 months, patients in the intervention group reported small but significantly better medication adherence as compared to the control group (mean difference 0.23, $p = 0.005$).

eHealth Tools

Seven of the nine studies (78%) that tested the effectiveness of an eHealth intervention reported significant improvements in medication adherence, as compared to a control condition, regardless of the type of adherence assessment [14, 32••, 33, 34, 36, 56, 59]. Five of the intervention strategies used a multicomponent Smartphone application (app); two sent text messages that included educational content as well as medication reminders; and one tested an ingestible sensor that contained the co-encapsulated antihypertensive medicines. Most of the studies (83%) testing Smartphone apps reported significantly better medication adherence in the intervention group. However, these studies also paired the app with additional evidence-based strategies (e.g., nurse case management), making it difficult to tease out the independent effect of the app on changes in medication adherence. For example, Chandler et al. [36] tested the effectiveness of the SMASH app, which included electronic medication trays with reminder signals, Bluetooth-enabled blood pressure monitors, and motivation and reinforcement text messages to improve adherence among 54 Latino adults with uncontrolled hypertension. As compared to the attention control condition, (text messages that contained links to education and brief video clips on lifestyle behaviors) participants randomized to the SMASH app exhibited greater improvements in self-reported medication adherence (assessed through the 8-item MMAS) across the 9-month study (mean change: 2.98, $p < 0.001$).

Behavioral Counseling Strategies

Seven of the eight (88%) studies that evaluated behavioral counseling strategies for improved medication adherence reported positive findings [22–24, 26, 27, 37, 38]. The individuals delivering the counseling differed across these studies; four interventions were led by nurses, three by pharmacists, and one by a community health worker (CHW). Three studies tested the effectiveness of home-based counseling for improved medication adherence, of which all reported positive effects using both self-report measures (i.e., MMAS) and pill count [23, 26, 37]. For example, a nurse-led intervention showed that monthly home visits, which included health education and counseling on healthy lifestyle behaviors and medication adherence led to higher self-reported medication adherence at 6-months when compared to usual care (78.5% vs. 48.7%) [23]. Similarly, bimonthly home visits by CHWs, which consisted of blood pressure measurements, medication adherence counseling, physician-directed dose-escalation, and scheduling of clinic appointments resulted in a significant increase in the percentage of patients taking their medications at 12 months, as compared to the control condition (PDC: 74.9%, 95% confidence interval [95 CI]: 70.2%–79.0% vs. 61.4%, 95% CI 56.14–66.41%, $p = .001$) [37]. The remaining positive studies utilized several evidence-based strategies in combination with nurse- or pharmacist-led motivational interviewing to improve adherence including the distribution of adherence aids (e.g., pillboxes), text messages reinforcing counseling content, inclusion of family support, and regular check-in calls to monitor patient adherence behaviors.

While one of the pharmacist-led interventions did not result in improved self-reported adherence (assessed through the Medication Adherence Report Scale-5) in the total sample, significant differences emerged when limiting the population to participants who reported ≥ 3 barriers during the first counseling session (mean difference 0.84 [95% CI: 0.03 to 1.65], $p = 0.04$) [25].

Health System Changes

Two of the five (40%) studies that tested the effectiveness of changes to the health system reported a positive effect on medication adherence, as assessed by the PDC metric [47, 60••]. The studies varied greatly in their approaches to change the health system. In one study, receiving care in patient-centered medical homes (PCMH, e.g., use of patient tracking, care management, self-management, and electronic prescribing) was associated with significantly higher medication adherence among patients initiating medications for hypertension than in non-PCMH sites (mean difference: 3.2% [95% CI: 2.2 to 4.2%]) [47]. Adoption of the chronic care model in primary care practices that also included subsidies for out-of-pocket payments, health education and counseling services, and a community campaign to encourage early detection and treatment of hypertension led to greater persistence with anti-hypertensive medications over a 12-month period among older adults with hypertension (mean increase of 2.2 days with medications per month in intervention versus control sites) [60••]. Alternatively, there was no effect on medication adherence among patients receiving care in accountable care organizations in the Medicare Shared Savings Program. [48] Two studies that utilized electronic health record-based medication management tools and counseling by ancillary clinic staff (i.e., nurses, medical assistants) also reported no effect on medication adherence [20, 40].

Patient Education

All four studies that utilized patient education as the primary intervention strategy reported a positive effect on medication adherence [18, 28, 29, 46]. A common feature of the studies was tailoring the intervention content to meet the needs of the participants. For example, Harvin et al. [18] developed a faith-based self-management education curriculum that included prayer, Scripture reading, and journaling. In another study, Delavar et al. [28] developed a self-management education curriculum that was personalized to the participant's level of health literacy. Another common feature was the inclusion of face-to-face educational sessions that were supported by additional sessions delivered via telephone or email. It is important to note all four studies assessed medication adherence using a self-report measure and had an average study duration of seven weeks.

Chronic Disease Management Program

Two of the three studies (67%) that evaluated the effectiveness of chronic disease management programs for hypertension control reported statistically significant improvements in medication adherence [41, 42]. In one study, patients in the intervention condition designated a family member to supervise their medication taking and provide reminders to regularly take their blood pressure as well as attend healthcare appointments [41]. Patient-family pairs also attended health education sessions at the clinic and could receive educational text messages on hypertension control and prevention. At the 12-month

follow-up, patients in the intervention group were almost twice as likely to report being adherent to their medications than those in the usual care group (odds ratio [OR]: 1.7 (95% CI: 0.9–3.3). The other positive trial included a multi-component chronic disease management program comprised of tailored hypertension care management, blood pressure monitoring, stress reduction activities, and referral to a dietician [42]. At 6-months, patients in the intervention group reported better mean adherence (3.77 ± 1.19) than those in the usual care group (5.80 ± 2.43, $p < 0.001$; note: lower scores indicate better adherence). A main difference between the positive trials and the trial reporting no effect was the inclusion of an enhanced control group in the latter group. In the negative trial, patients in the control group received access to free antihypertensive medications, home blood pressure monitoring, and to the extended healthcare team (e.g. Dietician, Nurse) potentially diluting any intervention effect [44].

Home Blood Pressure Monitoring

None of the studies that examined home blood pressure monitoring (HBPM) as the primary intervention strategy were associated with improvements in medication adherence. This included studies that utilized HBPM alone as well as those that included HBPM in combination with patient education. A common design feature among these studies was the inclusion of an enhanced usual care condition (e.g., receipt of education pamphlets), which may have limited the ability to detect differences between the study groups.

Financial Incentives

One of the three (33%) studies that tested the effectiveness of financial incentives reported positive effects attributable to the intervention [49]. In this study, a multilevel intervention consisting of copayment reductions and physician incentives resulted in significant improvements in medication adherence (assessed using the MPR metric) and persistence with antihypertensive medications (assessed as the receipt of medication refills within a specified period) at 12 months (6.3% and 8.3% increase in adherence and persistence respectively, $p < .001$) [49]. Alternatively, implementation of a value-based formulary resulted in significantly lower member expenditures for antihypertensive medications (−$4 per member per month [95% CI: −5 to −3]) among individuals enrolled in an employer-sponsored health plan but it had no effect on medication adherence [57]. Similarly, a clinical decision support (CDS) tool [7] that was designed to prompt provider's selection of cost-effective antihypertensive medications had no effect on medication adherence in patients with newly diagnosed hypertension (intervention PDC: 57.7%; control PDC: 52.8%; $p = 0.70$) or those with established hypertension (intervention PDC: 72.1%; versus control PDC: 70.7% $p = 0.36$), as compared to a basic CDS tool that did not recommend medications based on cost-effectiveness [39].

Conclusions

The implementation of the recent blood pressure guidelines has led to an increase in the prevalence of hypertension from 72.2 million to an estimated 103.3 million US adults [1]. In addition to this increase in prevalence, the changes resulted in an increase of 11.0 million Americans who are recommended for antihypertensive medications [1]. Given the

high proportion of patients with hypertension who exhibit poor medication adherence, [61] identifying effective strategies to improve adherence will be especially critical for reducing the clinical and economic burden of CVD.

The aim of this review was to provide a synthesis and critical review of recent interventions targeting medication non-adherence in patients with hypertension. We reviewed 42 articles published between 2017 and 2020, and identified eight categories of interventions: (1) simplification of the medication regimen; (2) eHealth tools; (3) behavioral counseling strategies (4) health care system transformation; (5) patient education; (6) chronic disease management; (7) HBPM; and (8) financial incentives to promote adherence. Similar to previous reviews, our findings indicate that tailored intervention strategies as well as those that simplify patients' antihypertensive regimen and utilize evidence-based behavioral counseling approaches were associated with improvements in medication adherence, regardless of the type of adherence measure. eHealth interventions that incorporated other evidence-based strategies (e.g., adherence reminders, educational and motivational messaging) were also effective in improving medication adherence. Alternatively, intervention strategies that targeted healthcare providers or the broader health system, utilized HBPM, and chronic disease management programs were less effective at improving medication adherence.

While not a new intervention approach, the largely positive results of utilizing a fixed-dose combination pill to improve medication adherence are not surprising. Previous studies have noted the multiple benefits of using fixed-dose combination pills as it represents a simple and cost-effective intervention strategy that is also acceptable to patients with hypertension [62, 63].The three major challenges to widespread use of this approach are decreased availability, inability to quickly and easily titrate medications for patients who are not reaching their blood pressure goal, and the out of pocket costs for the patients [64]. Despite these limitations, fixed-dose combination pills offer several significant advantages for clinical outcomes because of their positive effect on medication adherence. For example, one of the included studies found that patients receiving combination pills had significantly lower rates of mortality and hospitalization for heart attack, heart failure, or stroke than those prescribed single pills due to better medication adherence [22].

Tailored interventions and those that use behavioral counseling strategies aimed at educating or motivating patients to improve medication adherence have been well described in the literature [19, 65, 66]. While there was significant heterogeneity both across and within all eight intervention categories included in this review, a vast majority of trials utilized some form of behavioral counseling that was conducted by a nurse, medical assistant, CHW, or a pharmacist. Like previous studies, many of these counseling strategies were aimed at educating patients about hypertension and adopting self-management behaviors, as well as addressing barriers to adherence to antihypertensive medications. While not all the counseling-based interventions reported significant effects on medication adherence, common characteristics of the positive trials included utilizing face-to-face encounters, motivational interviewing, and addressing patient-specific barriers to medication taking.

Individualized instruction and tailored self-management support were additional key features in many of the trials, especially those utilizing patient education or an eHealth tools as their primary intervention. The patient education interventions, while varied, were all positive and went beyond providing written material to patients. Notably, among the 42 interventions in our review, only one trial utilized a classroom-based educational format [29]. Instead, the included interventions utilized a variety of efficacious strategies such as *Teach Back* to enhance comprehension. The trials also utilized a variety of methods to deliver tailored education and counseling to patients including one-on-one in-person meetings, via telephone, eHealth tools, and were conducted in both community-based and home settings.

The success of eHealth tools in improving medication adherence in our review stems from the ability of Smartphone apps to tailor the intervention to the patient and easily incorporate co-interventions such as HBPM, counseling, reminders, and motivational and educational text messages. The benefits of the traditional models of hypertension management based on the provider and clinic visit are now augmented by the use of telemedicine delivered through eHealth tools. This synergistic approach to hypertension management was best demonstrated through the intervention by Zare et al. [59], which utilized a Smartphone app in combination with case management to significantly improve adherence in patients with hypertension.

The role of the provider in improving medication adherence was addressed in few trials in our review. Interventions focused on changing provider behavior around medication selection, transforming health care systems, and implementing chronic disease management programs such as the chronic care model. These interventions were not as successful as the interventions that were more closely associated with changing patient behavior. The majority of interventions that used financial incentives such as a value-based formulary or copayment reduction did not have positive findings. A possible reason for the mixed results may be that the actual behavior changes patients needed to make in order to be adherent to their medications were too far downstream from the intervention itself.

Despite our comprehensive search strategy, there are limitations that should be considered. First, our review was limited to articles written in English language that were published between 2017 and 2020. While we conducted an extensive search of the literature, it is possible that we did not identify all articles that described an experimental study whose main goal was to improve medication adherence among hypertensive patients. Finally, the included studies used a variety of methods for measuring and reporting medication adherence therefore, our findings may not be generalizable to all populations.

This review highlights potential areas for future research. Reasons for non-adherence are often multifactorial and patients' adherence patterns may change in the short and long-term. A major limitation of many of the trials included in our review was the narrow conceptualization of medication adherence. Most interventions treated medication adherence as a singular behavior by either dichotomizing the outcome using an arbitrary threshold of 80% or reporting a mean score to a self-report survey [67]. This falls short of the recent guidelines, which recommends use of the ABC taxonomy for the measurement and reporting of medication adherence in clinical trials [68••]. Without this comprehensive assessment, it

is difficult to understand the mechanisms by which interventions are increasing medication adherence. Prior research has shown that even short periods of non-adherence can affect clinical outcomes. For example, one study demonstrated that fluctuations in the time antihypertensive medications were taken within a 7-day period in addition to short-term lapses in adherence behaviors had significant negative effects on blood pressure readings [69].This study underscores the importance of designing targeted interventions that address the multiple behaviors that comprise patients' use of and persistence with taking antihypertensive medications. Future research endeavors should prioritize exploring these behavioral fluctuations and potential mechanisms further.

The broad application and positive effects of behavioral counseling strategies in the current review shows a continued acceptance and adoption of this approach. This growing evidence-base supports the widespread dissemination of behavioral counseling across a variety of settings and methods of delivery. Evaluating the cost-effectiveness of this approach will be vital to widespread use and sustainability; however, none of the included studies examined cost-related outcomes related to behavioral counseling for improving adherence.

Development and refinement of eHealth tools that prioritize bridging the gap between patients and providers is another potential area for improving the quality of hypertension care through the delivery of tailored adherence messages and support. The ongoing challenge of eHealth tools rests in developing ways to seamlessly deliver these technologies in an inclusive manner, so that even the most vulnerable groups can take advantage of its benefits [70]. It is expected that as technology becomes ubiquitous in the delivery of healthcare, medication adherence interventions will be able to provide more tailored solutions that support patients across all three phases of medication adherence.

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Appendix A.: Review Search Strategy

(((“hypertension”[MeSH Terms] OR hypertension[Text Word]) OR blood pressure[Text Word]) OR (“blood pressure”[MeSH Terms] OR “blood pressure determination”[MeSH Terms] OR “arterial pressure”[MeSH Terms])) AND (“Medication Adherence”[Mesh] OR “medication adherence”[tw] OR “medication nonadherence”[tw]) AND (((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]))

"Medication Adherence" [Mesh] OR adherence[tw] OR nonadherence[tw] OR … adherence, adherent, compliance, compliant, noncompliant, noncompliance, nonadherence, nonadherent

AND ((((((((((hypertension[MeSH Terms]) OR hypertension[Text Word]) OR blood pressure[Text Word]) OR blood pressure[MeSH Terms])

AND (((((Prospective Studies[MeSH Terms]) OR Cohort Studies[MeSH Terms]) OR Followup Studies[MeSH Terms]) OR Longitudinal Studies[MeSH Terms]) AND Cross Sectional Studies[MeSH Terms])

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018;392(10159):1736–88. 10.1016/S0140-6736(18)32203-7 [PubMed: 30496103]
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206–52. [PubMed: 14656957]
3. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, et al. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. JAMA. 2020;324(12):1190–200. 10.1001/jama.2020.14545. [PubMed: 32902588]
4. Bramley TJ, et al. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. J Manag Care Pharm. 2006;12(3):239–45. [PubMed: 16623608]
5. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43(6):521–30. [PubMed: 15908846]
6. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8. [PubMed: 23907142]
7. Dragomir A, Côté R, Roy L, Blais L, Lalonde L, Bérard A, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Med Care. 2010;48(5):418–25. [PubMed: 20393367]
8. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
9•. Kronish IM, Thorpe CT, Voils Cl. Measuring the multiple domains of medication nonadherence: findings from a Delphi survey of adherence experts. Transl Behav Med. 2019;ibz133. 10.1093/tbm/ibz133.This paper describes the three phases of medication adherence that should be applied in clinical research.
10. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44–7. [PubMed: 18237359]
11. Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019;124(7):1124–40. [PubMed: 30920917]
12. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi

C, Haynes RB. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;2014(11):CD000011. 10.1002/14651858.CD000011.pub4.

13. Crilly P, Kayyali R. A systematic review of randomized controlled trials of telehealth and digital technology use by community pharmacists to improve public health. Pharmacy (Basel). 2020;8(3):E137.
14. Morawski K, Ghazinouri R, Krumme A, Lauffenburger JC, Lu Z, Durfee E, et al. Association of a Smartphone application with medication adherence and blood pressure control: the MedISAFE-BP randomized clinical trial. JAMA Intern Med. 2018;178(6):802–9. [PubMed: 29710289]
15. Sartori AC, Rodrigues Lucena TF, Takáo Lopes C, Picinin Bernuci M, Yamaguchi MU. Educational Intervention Using WhatsApp on Medication Adherence in Hypertension and Diabetes Patients: A Randomized Clinical Trial. Telemed J E Health. 2020. 10.1089/tmj.2019.0305.
16. Turner BJ, Hollenbeak CS, Liang Y, Pandit K, Joseph S, Weiner MG. A randomized trial of peer coach and office staff support to reduce coronary heart disease risk in African-Americans with uncontrolled hypertension. J Gen Intern Med. 2012;27(10):1258–64. [PubMed: 22570108]
17. Zhai P, Hayat K, Ji W, Li Q, Shi L, Atif N, et al. Efficacy of text messaging and personal consultation by pharmacy students among adults with hypertension: randomized controlled trial. J Med Internet Res. 2020;22(5):e16019. [PubMed: 32432556]
18. Harvin LA, Winter DM, Hoover EL, Lewis LM. A faith-based intervention to improve hypertension management among African Americans. J Christ Nurs. 2020;37(1):38–15. [PubMed: 31809379]
19. Kini V, Ho PM. Interventions to improve medication adherence: a review. Jama. 2018;320(23):2461–73. [PubMed: 30561486]
20. Persell SD, Karmali KN, Lazar D, Friesema EM, Lee JY, Rademaker A, et al. Effect of electronic health record-based medication support and nurse-led medication therapy management on hypertension and medication self-management: a randomized clinical trial. JAMA Intern Med. 2018;178(8):1069–77. [PubMed: 29987324]
21. Persell SD, Peprah YA, Lipiszko D, Lee JY, Li JJ, Ciolino JD, et al. Effect of home blood pressure monitoring via a smartphone hypertension coaching application or tracking application on adults with uncontrolled hypertension: a randomized clinical trial. JAMA Netw Open. 2020;3(3):e200255. [PubMed: 32119093]
22. Abughosh S, Wang X, Serna O, Esse T, Mann A, Masilamani S, et al. A motivational interviewing intervention by pharmacy students to improve medication adherence. J Manag Care Special Pharm. 2017;23(5):549–60.
23. Bolarinwa O, Juni MH, Nor Afiah MZ, Salmiah MS, Akande TM. Mid-term impact of home-based follow-up care on health-related quality of life of hypertensive patients at a teaching hospital in Ilorin, *Nigeria*. Niger J Clin Pract. 2019;22(1):69–78. [PubMed: 30666023]
24. Sheilini M, Hande HM, Prabhu MM, Pai MS, George A. Impact of multimodal interventions on medication nonadherence among elderly hypertensives: a randomized controlled study. Patient Prefer Adherence. 2019;13:549–59. [PubMed: 31114169]
25. van der Laan DM, et al. Effectiveness of a patient-tailored, *Pharmacist-Led Intervention Program to Enhance Adherence to Antihypertensive Medication: The CATI Study*. Front Pharmacol. 2018;9:1057. [PubMed: 30319409]
26. Mirniam AA, Habibi Z, Khosravi A, Sadeghi M, Eghbali-Babadi M. A clinical trial on the effect of a multifaceted intervention on blood pressure control and medication adherence in patients with uncontrolled hypertension. ARYA Atheroscler. 2019;15(6):267–74. [PubMed: 32206070]
27. Amer M, et al. Impact of pharmacist's intervention on disease related knowledge, medication adherence, HRQoL and control of blood pressure among hypertensive patients. Pak J Pharm Sci. 2018;31(6 (Supplementary):2607–16. [PubMed: 30587468]
28. Delavar F, Pashaeypoor S, Negarandeh R. The effects of self-management education tailored to health literacy on medication adherence and blood pressure control among elderly people with primary hypertension: a randomized controlled trial. Patient Educ Couns. 2020;103(2):336–42. [PubMed: 31451361]

29. Yazdanpanah Y. Effect of an educational program based on health belief model on medication adherence in elderly patients with hypertension. Evid Based Care J. 2019;9(1):12.

30••. Shen Y, et al. Effectiveness of low-cost reminder package combined with case-based health education to improve hypertensive patients' medication adherence: a clustered randomized controlled trial. Patient Prefer Adherence. 2019;13:1083–92. [PubMed: 31371926] This study demonstrated the importance of using multicomponent strategies that include family members to improve medication adherence in patients with hypertension.

31. Tan BY, et al. Assessment of medication adherence and the costs associated with a calendar blister pack intervention among hypertensive patients in Malaysia: a randomized controlled trial. SAGE Open Med. 2017;5:2050312117709189. [PubMed: 28839933]

32••. Sarfo FS, et al. Phone-based intervention for blood pressure control among Ghanaian stroke survivors: a pilot randomized controlled trial. Int J Stroke. 2019;14(6):630–8. [PubMed: 30465630] This study demonstrates the efficacy of a multicomponent intervention that combines innovative tools (Smartphone app) with traditional methods (nurse case management) to improve medication adherence.

33. Márquez Contreras E, Márquez Rivero S, Rodríguez García E, López-García-Ramos L, Carlos Pastoriza Vilas J, Baldonedo Suárez A, et al. Specific hypertension smartphone application to improve medication adherence in hypertension: a cluster-randomized trial. Curr Med Res Opin. 2019;35(1):167–73. [PubMed: 30431384]

34. Varleta P, Acevedo M, Akel C, Salinas C, Navarrete C, García A, et al. Mobile phone text messaging improves antihypertensive drug adherence in the community. J Clin Hypertens. 2017;19(12):1276–84.

35. Buis L, Hirzel L, Dawood RM, Dawood KL, Nichols LP, Artinian NT, et al. Text messaging to improve hypertension medication adherence in African Americans from primary care and emergency department settings: results from two randomized feasibility studies. JMIR Mhealth Uhealth. 2017;5(2):e9. [PubMed: 28148474]

36. Chandler J, et al. Impact of a culturally tailored mHealth medication regimen self-management program upon blood pressure among hypertensive Hispanic adults. Int J Environ Res Public Health. 2019;16(7):1226. [PubMed: 30959858]

37. Joshi R, Agrawal T, Fathima F, Usha T, Thomas T, Misquith D, et al. Cardiovascular risk factor reduction by community health workers in rural India: a cluster randomized trial. Am Heart J. 2019;216:9–19. [PubMed: 31377568]

38. Kim M. Effects of customized long-message service and phone-based health-coaching on elderly people with hypertension. Iran J Public Health. 2019;48(4):655–63. [PubMed: 31110975]

39. Tamblyn R, Winslade N, Qian CJ, Moraga T, Huang A. What is in your wallet? A cluster randomized trial of the effects of showing comparative patient out-of-pocket costs on primary care prescribing for uncomplicated hypertension. Implement Sci. 2018;13(1):7. [PubMed: 29321043]

40. Schoenthaler A, de la Calle F, Pitaro M, Lum A, Chaplin W, Mogavero J, et al. A systems-level approach to improving medication adherence in hypertensive Latinos: a randomized control trial. J Gen Intern Med. 2020;35(1):182–9. [PubMed: 31625041]

41. Shen Y, Peng X, Wang M, Zheng X, Xu G, Lü L, et al. Family member-based supervision of patients with hypertension: a cluster randomized trial in rural China. J Hum Hypertens. 2017;31(1):29–36. [PubMed: 26911532]

42. Ozpancar N, Pakyuz SC, Topcu B. Hypertension management: what is the role of case management? Rev Esc Enferm USP. 2017;51 :e03291. [PubMed: 29562041]

43. Muhammad J, Jamial MM, Ishak A. Home blood pressure monitoring has similar effects on office blood pressure and medication compliance as usual care. Korean J Fam Med. 2019;40(5):335–13. [PubMed: 30636386]

44. da Silva Mattei ÂT, et al. Nursing case management for people with hypertension in primary health care: a randomized controlled trial. Res Nurs Health. 2020;43(1):68–78. [PubMed: 31710134]

45. Cuffee YL, Sciamanna C, Gerin W, Lehman E, Cover L, Johnson AA, et al. The effectiveness of home blood pressure on 24-hour blood pressure control: a randomized controlled trial. Am J Hypertens. 2019;32(2):186–92. [PubMed: 30371759]

46. Aghakhani N, Parizad N, Soltani B, Khademvatan K, Rahimi Z. The effect of the blended education program on treatment concordance of patients with hypertension: a single-blind randomized, controlled trial. J Vasc Nurs. 2019;37(4):250–6. [PubMed: 31847979]
47. Lauffenburger JC, Shrank WH, Bitton A, Franklin JM, Glynn RJ, Krumme AA, et al. Association between patient-centered medical homes and adherence to chronic disease medications: a cohort study. Ann Intern Med. 2017;166(2):81–8. [PubMed: 27842386]
48. McWilliams JM, Najafzadeh M, Shrank WH, Polinski JM. Association of changes in medication use and adherence with accountable care organization exposure in patients with cardiovascular disease or diabetes. JAMA Cardiol. 2017;2(9):1019–23. [PubMed: 28700790]
49. Kim J-A, Kim E-S, Lee E-K. Evaluation of the chronic disease management program for appropriateness of medication adherence and persistence in hypertension and type-2 diabetes patients in Korea. Medicine. 2017;96(14):e6577. [PubMed: 28383439]
50. Bartlett LE, Pratt N, Roughead EE. Does a fixed-dose combination of amlodipine and atorvastatin improve persistence with therapy in the Australian population? Curr Med Res Opin. 2018;34(2):305–11. [PubMed: 28945105]
51. Ho CT, Tung YC, Chou SH, Hsiao FC, Lin YS, Chang CJ, et al. Clinical outcomes in hypertensive patients treated with a single-pill fixed-dose combination of renin-angiotensin system inhibitor and thiazide diuretic. J Clin Hypertens (Greenwich). 2018;20(12):1731–8. [PubMed: 30375168]
52. Fleig SV, Weger B, Haller H, Limbourg FP. Effectiveness of a fixed-dose, single-pill combination of perindopril and amlodipine in patients with hypertension: a non-interventional study. Adv Ther. 2018;35(3):353–66. [PubMed: 29498018]
53. Kim SJ, Kwon OD, Cho BL, Oh SW, Lee CM, Choi HC. Effects of combination drugs on antihypertensive medication adherence in a real-world setting: a Korean Nationwide study. BMJ Open. 2019;9(6):e029862.
54. Vemra AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: a population-based retrospective cohort study. PLoS Med. 2018;15(6):e1002584. [PubMed: 29889841]
55. Doshi JA, et al. Synchronized prescription refills and medication adherence: a retrospective claims analysis. Am J Manag Care. 2017;23(2):98–104. [PubMed: 28245653]
56. Moorhead P, et al. Efficacy and safety of a medication dose reminder feature in a digital health offering with the use of sensor-enabled medicines. J Am Pharm Assoc (2003). 2017;57(2):155–161.e1. [PubMed: 28159505]
57. Yeung K, Basu A, Marcum ZA, Watkins JB, Sullivan SD. Impact of a value-based formulary in three chronic disease cohorts. Am J Manag Care. 2017;23(3 Suppl):S46–s53. [PubMed: 29648740]
58. Tan BY, Shafie AA, Hassali MAA, Saleem F, Muneswarao J. Improving medication adherence through calendar packaging: results of a randomized controlled trial among hypertensive patients. J Pharm Health Serv Res. 2017;8(2):115–22.
59. Zare S, Rezaee R, Aslani A, Shirdeli M, Kojuri J. Moving toward community based telehealth services using mHealth for hypertensive patients. Int J Technol Assess Health Care. 2019;35(5):379–83. [PubMed: 31547890]
60••. Son K-J, et al. A community-based intervention for improving medication adherence for elderly patients with hypertension in Korea. Int J Environ Res Public Health. 2019;16(5):721. [PubMed: 30823383] This study describes a multilevel intervention strategy that combines approaches at the level of the health system with that of the community to make an impact on patient medication adherence.
61. Vrijens B, et al. Current situation of medication adherence in hypertension. Front Pharmacol. 2017;8:100. [PubMed: 28298894]
62. Salam A, et al. Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens. 2019;37(9):1768–74. [PubMed: 30986788]
63. Hong SH, Wang J, Tang J. Dynamic view on affordability of fixed-dose combination antihypertensive drug therapy. Am J Hypertens. 2013;26(7):879–87. [PubMed: 23512697]

64. DiPette DJ, et al. Fixed-dose combination pharmacologic therapy to improve hypertension control worldwide: clinical perspective and policy implications. J Clin Hypertens. 2019;21(1):4–15.

65. Conn VS, Ruppar TM, Chase JAD, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. Curr Hypertens Rep. 2015;17(12):94. [PubMed: 26560139]

66. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: systematic review and meta-analysis. Prev Med. 2017;99:269–76. [PubMed: 28315760]

67. Schroeder K, Fahey T, Ebrahim S, Peters TJ. Adherence to long-term therapies: recent WHO report provides some answers but poses even more questions. J Clin Epidemiol. 2004;57(1):2–3. [PubMed: 15019004]

68••. De Geest S, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med. 2018;169(1):30–5. [PubMed: 29946690] This paper outlines the reporting guidelines all researcher should employ when conducting research and publishing findings related to medication adherence.

69. Rose AJ, et al. Effects of daily adherence to antihypertensive medication on blood pressure control. J Clin Hypertens (Greenwich, Conn). 2011;13(6):416–21.

70. van der Kleij R, Kasteleyn MJ, Meijer E, Bonten TN, Houwink EJF, Teichert M, et al. SERIES: eHealth in primary care. Part 1: concepts, conditions and challenges. Eur J Gen Pract. 2019;25(4):179–89. [PubMed: 31597502]

Table 1

Summary of Clinical Trials, by Intervention Type

Study Reference	Country	Study Design	Study Duration	Sample Size	Intervention Details	Comparison Group	Adherence Measure	Outcome
Patient Education								
Aghakhani et al, [46]	Iran	RCT[a]	4 weeks	60	Blended education consisting of face-to-face education and online education via emails	Traditional face-to face education	Novel self-report questionnaire	46.7% of intervention group reported good medication adherence vs. 0% of control group at 4 weeks. (P < .001)
Delavar et al, [28]	Iran	RCT	1 month	118	Health literacy tailored self-management education utilizing teach back method and delivered face-to-face and by telephone	Usual care	MMAS-8	50% of participants in the intervention groups reported moderate or good medication adherence vs 21% of the control group at 1 month (P=0.002)
Yazdanpanah et al, [29]	Iran	RCT	1 month	60	Community-based educational sessions based on Health Belief Model	Usual Care	MMAS-8	Mean MMAS change was higher in the intervention group (2.6 ±0.8) vs the control group score (−0.1±0.1) at 1 month (P<0.001)
Harvin et al [18]	USA	Pre-post test	4 months	10	Faith-based self-management education program guided by the Understanding and Controlling Your High Blood Pressure booklet	N/A	HTN Self-Care Activity Level Effects Scale (H-scale)	There was a 30% increase in the number of participants who reported being adherent to their antihypertensive medications at 4 months (P=0.034)
Simplification of Medication Regimen								
Doshi et al [55]	USA	Retrospective cohort study	12 months	11,452	Synchronized refill schedule of all maintenance drugs	Non-synchronized refills	PDC[c]	Adherence was higher in the intervention group (92%) vs control group (86%) at 12 months (P<0.01)
Verma et al, [54]	Canada	Retrospective cohort study	5 years	13,350	Fixed Dose Combination (FDC) pill	Multiple-pill combination (MPC)	PDC Time to 1st Discontinuation	Adherence was higher in the intervention group (70%) vs control group (42%) at 5 years (P< 0.01); Time to 1st discontinuation was 41 days longer in the intervention group vs control group (P< 0.01)
Kim et al, [53]	Korea	Retrospective cohort study	5 years	116,677	Single Pill Combination (SPC)	MPC Angiotensin Receptor Blocker (ARB)-only Calcium Channel Blocker (CCB)-only	MPR[d]	Adjusted MPR was higher in combination therapy (89.7% in SPC, 87.2% in MPC) than monotherapy (81.6% in ARB, 79.7% in CCB), and MPR of SPC (89.7%, 95% CI 89.3 to 90.0) was higher than MPR of MPC (87.2%, 95% CI 86.7 to 87.7) (p<0.05).
Shen et al, [30••]	China	RCT	6 months	518	Low-cost reminder package (28 compartment pill box w/alarm)	Usual care	Novel self-report questionnaire	Mean scores were higher in the intervention group vs the control group with a difference

Study Reference	Country	Study Design	Study Duration	Sample Size	Intervention Details	Comparison Group	Adherence Measure	Outcome
					combined with two case-based health education session			in change of (0.287; [0.103, 0.471] P=0.002)
Fleig et al, [52]	Germany	Prospective cohort study	12 weeks	1814	FDC pill	MPC	Hill-Bone Medication Adherence scale	In previously treated patients, adherence increased from 20.6% to 43.4% (P<0.0001)
Ho et al, [51]	Taiwan	Retrospective cohort study	12 months	17,568	FDC pill	MPC	PDC	FDC pill was associated with better medication adherence (58%) vs than MPC (47%) at 12 months (P <0.001)
Tan et al, [58]	Malaysia	RCT	7 months	73	Calendar blister packaging	Normal blister packaging	MPR Percentage of on-time refills	Mean MPR for the interventions group was 0.99 and 0.98 for the control group (P=0.012); percentage of on-time refills was 0.99 for the intervention and 0.93 for the control (P=0.001)
Bartlett et al, [50]	Australia	Retrospective cohort study	12 months	26,848	Fixed-dose Combination pill	Separate pill combination (SePC)	Cessation of combination therapy (persistence)	Cessation rates at 12 months were lower in in the SePC group (40%) vs FDC (44%); following adjustment for differences in age, safety-net and prior antihypertensive, the risk of cessation was higher in those that initiated the SePC: hazard ratio (95%CI)-1.15 (1.11, 1.21)
Electronic Health Tool								
Zare et al [59]	Iran	Matched control	8 weeks	120	Smartphone app with educational self-care information and BP monitoring 2x/week combined with case management	Usual care	Hill-Bone hypertension self-care questionnaire	Mean adherence scores were higher in the intervention group (4.21) vs the control group (3.09) at 8 weeks (P ⩽0.001)
Morawski et al, [14]	USA	RCT	12 weeks	411	Smartphone app with reminder alerts, adherence reports, and optional peer support	Usual care	MMAS-8	Mean MMAS scores were higher in the intervention group (6.3) vs the control group score (5.7) at 12 weeks; Mean MMAS change scores were higher in the intervention group (0.4) vs the control group score (−0.1) at 12 weeks (P<0.01)
Sarfo et al, [32••]	Ghana	RCT	9 months	60	Smartphone app with Bluetooth enabled BP device for home BP monitoring (HBPM) and reporting medications; and motivational text messages based upon levels of adherence	SMS messages about healthy lifestyle behaviors but not medication adherence	MPR MMAS-8	MPR was higher in the intervention group (0.88) than the control group (0.64) at 3 months (P=0.03); however, this difference was not sustained as MPR for the intervention group (0.95) than the control group (0.98) at 9 months (P=0.56); MMAS-8 was 13 in both groups (P=0.94)
Marquez Contreras et al, [33]	Spain	RCT	12 months	154	Smartphone app with reminder alarms, BP measurement records and recommended BP levels,	Usual care	Global adherence via Medication Event Monitoring Systems (MEMS),	Global adherence was higher in the intervention group (93%) vs the control group (75%) at 6 months (P<0.01). Adherence decreased in the control group to

Study Reference	Country	Study Design	Study Duration	Sample Size	Intervention Details	Comparison Group	Adherence Measure	Outcome
					doctor's advice about the prescribed treatment and posology; and calendar of appointments or events		defined as percentage between ≥80% of all doses taken	63% at 12 months whereas the intervention group stayed relatively consistent (92%) (P<0.01)
Varleta et al, [34]	Chile	RCT	6 months	314	SMS text messages related to medication adherence and healthy lifestyle practices	Usual care	MMAS-4	Mean adherence scores were higher in the intervention group vs the control group at 6 months (62.3% vs. 51.4%, P<0.01)
Buis et al, [35]	USA	RCT	1 month	123	Daily medication reminders and two educational text messages per week based upon the Health Belief Model	Usual care	MMAS-8	Intervention group had greater mean change on the MMAS (0.9) compared to the control group (0.5) (P=.26)
Chandler et al, [36]	USA	RCT	9 months	54	Smartphone app with a Bluetooth enabled BP monitor for HBPM, as well as an electronic medication and reminder text messages	Text messages with links to PDFs and video clips with lifestyle tips	MMAS-8 Medication tray time-stamped data	Mean adherence scores were higher in the intervention group (9.81) vs the control group (6.84) at 9 months with a change in difference of 2.971 (P<0.001)
Moorhead et al, [56]	USA	Post hoc analysis	12 weeks	57	Co-encapsulated, ingestible, sensor-enabled medication with dose reminder within 30 minutes of the scheduled dose	Usual care	Mean daily adherence and mean difference in proportion of medications taken after seeing and not seeing the dose reminder	Reminder messages were associated with a 16 ± 16% increase in medication adherence; impact was larger on patients who have lower overall adherence (<60%)
Persell et al, [21]	USA	RCT	6 months	333	Conversational smartphone app using artificial intelligence and cognitive behavioral therapy to coach and promote HBPM and lifestyle behavior changes	Blood pressure tracking app plus HBPM	4-day recall	The percentage of participants with full adherence was 80.6% in the intervention group and 81.7% in the control group at 6 months (P=0.99)
Behavioral Counseling Strategies								
Abughosh et al, [22]	USA	RCT	6 months	743	Pharmacy-led telephone motivational interviewing using Ask-Provide-Ask approach	Usual Care	PDC (adherence = PDC ≥ 0.80) Discontinuation	Patients receiving 2 or more calls were more likely to become adherent (OR: 1.53; P = 0.009) and less likely to discontinue (OR: 0.29; P < 0.001) during the 6 months following initial calls compared with those who did not receive calls
Bolarinwa et al, [23]	Nigeria	RCT	6 months	299	Nurse-led health education and counseling on healthy lifestyle behaviors and medication adherence delivered in the home	Usual care	MMAS-8 Low= <6 Medium= 6-7.99 High= 8	Percentage of participants with high medication adherence was higher in the intervention group (78.5%) vs control group (48.7%) at 6 months. (P<0.001)

Study Reference	Country	Study Design	Study Duration	Sample Size	Intervention Details	Comparison Group	Adherence Measure	Outcome
van der Laan et al, [25]	Netherlands	RCT	9 months	170	Two pharmacist-led consultations to identify participants' barriers to medication adherence and counseling to overcome these barriers.	Usual care	MARS-5	No significant between group differences in the total sample. A significant intervention effect was found in participants with ≥ 3 barriers identified during the first consultation at 9 months (mean difference 0.84 [95CI: 0.03 to 1.65], p = 0.04)
Sheilini et al, [24]	India	RCT	6 months	160	Nurse-led individualized education; medication reminder boxes; and reminder calls	Usual care	MMAS-8	Mean adherence scores were higher in the intervention group (8.00) vs the control group (7.70) at 6 months (F(1.75,214.30)=4.24, p=0.02)
Mimiam et al, [26]	Iran	RCT	4 weeks	72	Nurse-led motivational interviewing and educational sessions, use of a medication reminder box, family support, and weekly phone calls with patient and family	Usual care plus a medication reminder box and educational training booklet	MMAS-8	Mean change in MMAS score was higher in the intervention group (2.91 ± 1.64) than the control group (−0.36) at 4 week (P < 0.001)
Amer et al, [27]	Pakistan	RCT	3 months	384	Face-to-face pharmacist-led educational session and interview addressing adherence, lifestyle choices, and barriers	Usual care	MMAS	Mean MMAS scores were higher in the intervention group (5.89 ± 1.90) vs the control group (3.89 ± 1.19) at 3 months (P<0.001)
Kim et al, 2019 [38]	Korea	RCT	2 months	124	Face-to-face nurse-led health coaching 30 minutes once a week. Tailored text messages delivered up to two times a day Combination intervention of face-to-face nurse-led health coaching and tailored text messages	Usual Care	MMAS	Mean MMAS score was significantly higher in the combination group (2.87 ± 1.11), as compared to face-to-face health coaching (2.503 ± 1.22), text-message delivered health coaching (1.87 ± 1.38), and usual care (0.87 ± 1.08) at 2 months (P<0.001)
Joshi et al, [37]	India	RCT	12 months	1164	CHW-delivered advice on reduction of risk factors with household visits every 2 months	Usual Care	Proportion of consumed to prescribed number of pills	Adherence to antihypertensive drugs was greater in the intervention (74.9%) vs control households (61.4%) at 12 months (P=0.001)
Financial Incentives								
Yeung et al, [57]	USA	Interrupted time series	3 years	3436	Value-based formulary that used cost-effectiveness analysis to inform medication co-payments.	Similar plans without any changes in pharmacy benefits	PDC	No between group differences in medication adherence (P=.279). Member expenditures decreased ($4 per member per month (PMPM); P <.001), health plan expenditures increased ($5 PMPM; P <.001).
Kim et al, [49]	Korea	Retrospective cohort study	12 months	3908	Multilevel chronic disease management program including copayment	Usual care	MPR: (0.8–1.1) Persistence: 12-	Pre-post change in MPR adherence improved +6.0% (P <0.001) and 12-month

Study Reference	Country	Study Design	Study Duration	Sample Size	Intervention Details	Comparison Group	Adherence Measure	Outcome
					reduction and physician incentives		month cumulative persistence rate	cumulative persistence improved +6.5% (P <0.001).
Tamblyn et al, [39]	Canada	RCT	12 months	3592	Decision support tool to help providers select the most cost-effective drug, as well as tools to monitor blood pressure (BP) targets and medication compliance	Medical record system with no out-of-pocket expenditure module	PDC	Mean adherence was higher in the intervention group for both incident (intervention 57.7%; control 52.8%; P=0.70) and prevalent patients (intervention 72.1%; control 70.7%; P=0.36)
Healthcare System Changes								
Schoenthaler et al, [40]	USA	RCT	6 months	119	Systems-level intervention that used the electronic health record to identify patients with uncontrolled hypertension and refer them to Medical Assistant-led health coaching based on motivational interviewing	Standard health coaching (provision of patient education)	EMD[e] MMAS	EMD-measured adherence declined in both groups; mean change in EMD adherence rates in the intervention group was −9.6% vs control group −6.6% at 6 months (p=0.66) Mean change in MMAS scores was higher in the intervention group (1.98) vs control group (1.26) at 6 months (p=0.03)
McWilliams et al, [48]	USA	Retrospective cohort study	12 months	2,169, 845	Accountable care organization contracts/ Medicare Shared Savings Program	Non- Medicare Shared Savings Program	PDC	No significant differential changes in PDC among beneficiaries with at least 1 prescription fill, except for slight increase in the PDC for β-blockers in the 2012 entry (adjusted differential change, 0.3 percentage point; 95% CI, 0.1-0.5 percentage points; or 0.4% of the mean PDC [82.3%]; P = .003)
Lauffen-burger et al, [47]	USA	Retrospective cohort study	12 months	4660	Providers caring for patients using the patient-centered medical home (PCMH) model	Non-PCMH primary care practices	PDC	Medication adherence was higher in PCMH than non-PCMH practices (mean difference: 3.2% [95CI: 2.2% to 4.2%]) at 12 months
Son et al, [60••]	Korea	Non-equivalent control group design	12 months	2685	Adoption of chronic care model in primary care practices including a community-based chronic disease management program	Usual care	Dispensation per prescription (DPP) Dispensation days per patient (DDPP)	DPP and the DDPP in the intervention region increased by approximately 11% and 2.2 days on average by month, respectively, compared to those in the control region
Persell et al, [20]	USA	RCT	12 months	794	EHR medication management tool (medication review sheets at check-in, lay medication information sheets printed after visits) with and without a nurse-led education intervention	Usual care	4-Day Recall	Compared with usual care, the EHR tools alone and EHR plus education interventions did not improve medication adherence (OR, 0.9; 95%CI,0.6-1.4 for both)
Chronic Disease Management Program								
Shen et al, [41]	China	RCT	12 months	554	Family based care management with	Usual Care	Novel self-report questionnaire	Better adherence in the intervention group vs control group at 6 months (OR 3.82;

Study Reference	Country	Study Design	Study Duration	Sample Size	Intervention Details	Comparison Group	Adherence Measure	Outcome
					educational text messages and medication reminders			P<0.001); however, this was not sustained at 12 months (OR 1.74; P=0.097)
Ozpancar et al, [42]	Turkey	RCT	6 months	60	Case Management Model that included a hypertension care protocol, dietician and individualized hypertension education	Usual care	Scale for Adherence to Antihypertensive Medications (SAAM)	Mean scores were lower in the intervention group (i.e., better adherence, 3.77±1.19) vs the control group score (5.80±2.43) at 12 6 months; (P<0.001)
Mattei da Silva et al, [44]	Brazil	RCT	12 months	94	Nurse case management model with individual care plans, tailored health education, home visits, and telephone calls for re-evaluations and reminders every 2 months	Usual care with free medications, HBPM and access to extended healthcare team (e.g., Nurse, dietician)	Questionnaire on Adherence to Treatment of Systemic Hypertension	No between group differences in medication adherence at 12 months; slight increase in medication adherence within the intervention group with absolute difference in treatment adherence as 4.8 [3.1; 6.4] (P<.001) vs the control group −1.1 [−2.9; 0.6] (P=0.206)
Home Blood Pressure Monitoring (HBPM)								
Muhammad et al, [43]	Malaysia	RCT	2 months	88	HBPM with instructions to take daily readings and reminder phone call made at 1 month	Usual care	Novel self-report questionnaire: Mean Adherence Survey (MAS)	No significant between group difference in the intervention and control groups at 2 months (1.5 (0.9–2.1) vs 1.3 (0.6–1.9), P=0.77)
Cuffee et al, [45]	USA	RCT	3 months	213	Home blood pressure monitor and 5 educational pamphlets from NHLBI Home blood pressure monitor and computer-based education modules	Usual Care + 5 educational pamphlets Usual care + computer-based education modules	MMAS-4	No significant difference between intervention group mean change in score −0.18 (−0.45, 0.09) and the control group mean change in score −0.53 (−0.78, −0.28) (P = 0.068)