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Impact of Interventions on Medication Adherence and Blood Pressure Control in Patients with Essential Hypertension: A Systematic Review by the ISPOR Medication Adherence and Persistence Special Interest Group

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ABSTRACT

Objectives: To systematically review the evidence on the impact of interventions to improve medication adherence in adults prescribed antihypertensive medications. **Methods:** An electronic search was undertaken of articles published between 1979 and 2009, without language restriction, that focused on interventions to improve antihypertensive medication adherence among patients (≥ 18 years) with essential hypertension. Studies must have measured adherence as an outcome of the intervention. We followed standard guidelines for the conduct and reporting of the review and conducted a narrative synthesis of reported data. **Results:** Ninety-seven articles were identified for inclusion; 35 (35 of 97, 36.1%) examined interventions to directly improve medication adherence, and the majority (58 of 97, 59.8%) were randomized controlled trials. Thirty-four (34 of 97, 35.1%)

studies reported a statistically significant improvement in medication adherence. **Discussion/Conclusions:** Interventions aimed at improving patients' knowledge of medications possess the greatest potential clinical value in improving adherence with antihypertensive therapy. However, we identified several limitations of these studies, and advise future researchers to focus on using validated adherence measures, well-designed randomized controlled trials with relevant adherence and clinical outcomes, and guidelines on the appropriate design and analysis of adherence research.

Keywords: hypertension, intervention, medication adherence, uncontrolled blood pressure.

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Introduction

Nonadherence to medications is well established as an important contributor to poorly controlled hypertension [1–4]. However, despite the convenience of once-daily dosing schedules of antihypertensives, the relative lack of adverse effects, and the many interventions developed to improve medicine taking [5], adherence to antihypertensives remains suboptimal, resulting in persisting rates of uncontrolled blood pressure (BP) among hypertensive patients (BP below 140/90 mmHg) [6,7]. In the United States, only 50% of the patients have good control of their BP [8]. Poor medication adherence has been widely identified as the main cause of failure to control hypertension [9].

A quarter of patients who are newly initiated on antihypertensive therapy fail to fill their first prescription [2,3]. During the first year of treatment, the average patient has possession of antihypertensive medications for only 50% of the time, and only one patient in five has sufficiently high adherence during this period to achieve the benefits observed in clinical trials [10]. Consequently, suboptimal implementation of a daily-dosing

regimen and a lack of adherence to antihypertensive agents [2,3,5,11,12] constitute major barriers to reductions in cardiovascular mortality [10,13]. A study by Nelson et al. [14] found that hypertensive patients who reported forgetting to take their medication were significantly more likely to experience a cardiovascular event or death than those who reported never forgetting to take their medication. In 2010, hypertension cost the United States \$93.5 billion in health care services, medications, and missed days of work [15]; improving adherence could represent a major source of health and economic improvement from a societal, institutional, and employers' perspective [16–19].

A significant proportion of nonadherence is intentional, and despite the existence of patient-centered behavioral theories and models developed to understand reasons for poor adherence [20–24], there has been limited work focusing on the doctor-patient relationship and patient health beliefs [18]. Interventions aimed at promoting adherence are variably effective [5], a likely consequence of large intraindividual variability in the factors that influence patients' behavior to take their medicines. An important criterion for any adherence-enhancing intervention is that it

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should be tailored to address the root causes of nonadherence [21–28].

While a Cochrane review has been previously published on interventions aimed at improving medication adherence in hypertension [29], it included randomized controlled trials (RCTs) published only up to 2002, of interventions directly geared at patients. The aims of this systematic review were to update previous reviews on examining interventions geared toward improving medication adherence in hypertension and to broaden the coverage of studies and interventions to be included. This latter aim was achieved by not restricting research designs or specifying for whom the intervention is to be directed. Our consideration of studies besides RCTs is aligned with the notion that different forms of evidence should be valued, in contrast to the traditional concept of an evidence hierarchy [30].

Definition of Adherence

For the purposes of this article, dichotomous and continuous measures of medication adherence are defined as the process by which patients take their medications as prescribed, composed of initiation, implementation, and discontinuation [12,31–34]. We also draw distinction between adherence and persistence according to Vrijens et al. [12], where persistence describes the length of time between initiation and the last dose immediately preceding discontinuation. This article will focus on adherence to antihypertensive medication only. Although medication adherence seems to be the more preferred term, patient compliance is recognized as a synonym for adherence provided the term is used to describe the process by which patients take their medications as prescribed [35]. Medication adherence will be operationally defined as dose taking in relation to what was prescribed [35].

Methods

Authors followed the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [36] guidelines that have also adopted the definitions of systematic reviews and meta-

analysis used by the COCHRANE collaboration [37]. Owing to the diverse nature of interventions and study designs considered, a meta-analysis (quantitative synthesis) was not conducted.

Literature Search

A literature search of articles published between January 1979 (when the first article on adherence research was published) and February 2009 was conducted using four electronic databases: CINAHL, EMBASE, all EBM reviews, and MEDLINE. Databases were selected on the basis of relevancy to the subject area (i.e., medicine and health) and available publication type (i.e., journal articles). The search strategy focused on four key elements: study design (e.g., RCTs, comparison study), sample (e.g., age of study population), measurements of adherence and BP (self-reporting, medication event monitoring systems), and findings (e.g., improvement in clinical outcomes). Search terms were determined by the research team's own expertise and by examining previous literature in the area. These were refined iteratively on the basis of a sample of articles identified previously as being suitable for inclusion (Table 1).

Relevant citations and abstracts were examined independently by eight reviewers (E.M., M.G., L.L., M.S., C.H., F.G.S., A.R.L., and S.G.). Studies were examined to determine whether the adherence-enhancing intervention 1) directly improved medication adherence, 2) indirectly improved medication adherence via the involvement of a single health care provider or a multidisciplinary team, or 3) indirectly improved adherence through an intervention directed at the health care provider of the multidisciplinary team. Interventions could constitute a number of different approaches, including behavioral change techniques, case management, counseling, disease management, family therapy, patient education, or reminders for patients or for health professionals.

Reviewers also hand-searched references found in included publications for additional articles of relevance. Any duplicate and redundant articles were flagged and eliminated from the review.

Study inclusion criteria

Studies that focused on interventions to improve medication adherence to antihypertensives in adult (≥ 18 years) patients with

Table 1 – Search strategy using PubMed, EMBASE, EBM reviews, and MEDLINE.

PubMed MeSH heading search strategy				
Patient adherence	AND	Disease	AND	Intervention
OR Patient adherence		Hypertension		Case management
OR Medication adherence				Counseling
OR Treatment refusal				Disease management
OR Patient dropout				Health promotion
OR				Family therapy
OR				Patient education
OR				Reminder system*
EMBASE, EBM reviews, and MEDLINE keyword search strategy				
Patient adherence	AND	Disease	AND	Intervention
Adherence		Hypertension		Behavior
OR Persistence				Behavior
OR				Communication
OR				Intervention

* The wildcard character.

essential hypertension were considered for review. Articles were considered with no language restrictions. Studies were included if 1) the intervention was adequately described, 2) the intervention aimed to improve adherence to hypertension medication, 3) adherence was measured as an outcome of the intervention, and 4) the study reported on how the measurement was achieved.

Study exclusion criteria

Studies that included the Medical Subject Headings (MeSH) terms child and adolescent, any comment OR editorial OR letter (publication type) were excluded. Similarly, articles that did not define an adult (≥ 18 years) population or patients with secondary hypertension were excluded from the review.

Coding and Data Management

To establish the eligibility of the study, we developed level 1, 2, and 3 data abstraction forms that ensured that relevant parameters were available for the review. Initial screening of titles and abstracts was performed independently and in duplicate, with a third reviewer judging any disagreements in view. The screening forms were developed from criteria previously used in the literature [5].

The full text of articles considered eligible for inclusion was retrieved and subjected to level 1 review; this level addressed the disease of interest, the year of publication, the intervention strategy (improved adherence directly or indirectly), and the outcomes of the study—specifically whether medication adherence was reported. Independent groups of two to three reviewers determined which abstracts met the initial screening criteria. An article that passed the screening phase advanced to level 2 review. Level 2 abstraction involved a review of the study design (e.g., RCT, quasi-RCT, cohort, or case-control). F.G.S. adjudicated discrepancies between reviewer groups prior to the data extraction phase (level 3) until consensus among all groups was reached. Data from eligible articles were extracted during level 3. These extractions related to the type of intervention used (e.g., behavioral, case management, counseling, disease management,

family therapy, health fairs, patient education, and reminder systems), the location of the intervention (country, clinic-based, hospital-based, home-based), whether the intervention was based on theory or was validated in any way, the mean adherence and SD of the intervention/control group (pre or post), the demographics of the population and sample size, the adherence and BP measurements used, the primary outcomes, and the statistical results of the study. We used commercial software to facilitate the review, data extraction, and compilation (SRS 4.0, Mobius Analytics, Ottawa, ON, Canada).

Results

Identification and Selection of Studies

The search of the databases yielded 138 citations. Of these, 41 were rejected following the initial screening, largely because the studies did not examine an adherence-enhancing intervention or provide a measure of medication adherence. In total, 97 articles met the inclusion criteria for the systematic review [38–134]. (Fig. 1)

Types of Studies and Sample Characteristics

The most common research design was RCTs including cluster and factorial designs (58 of 97, 59.8%) [39,41,44–49,58–61,65,67–72,76–78,81,82,84–88,90,92–94,97,98,100,104–108,110–118,121–124,126,127,131,133] followed by cohort designs, mainly prospective cohort studies, cross-sectional studies, and open-label designs (13 of 97, 13.4%) [38,55,64,66,73–75,83,101,117,118,125,132], hybrid design studies (10 of 97, 10.3%) [42,43,50,80,95,99,103,109,120,129], systematic or literature reviews (9 of 97, 9.3%) [40,52,54,56,57,62,79,89,120], and retrospective cohort studies (4 of 97, 4.1%) [38,55,74,75]. Sample sizes ranged from 2 [63] to 15,519 [56], with more than half the studies conducted in North America (United States = 51 of 97, 52.6% [38–41,44–47,49,52,54,56,57,59,62,63,67,72–79,82,90–94,97,98,100,103,106,108,109–113,118–120,122–125,129,130];

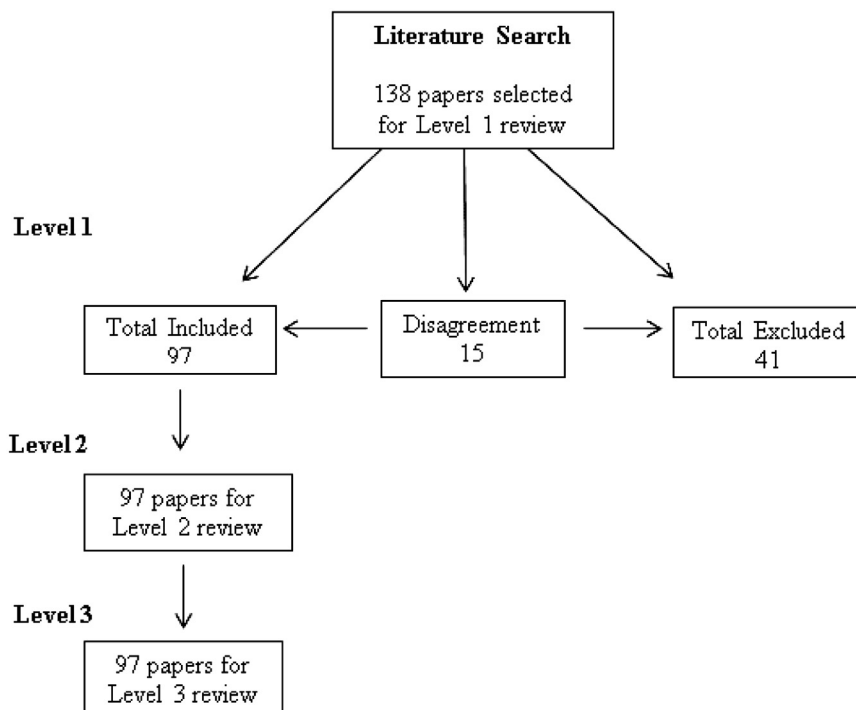


Fig. 1 – Flowchart of articles through the systematic review process.

Canada = 4 of 97, 4.1% [50,51,71,89]). Study participants were typically older (i.e., >45 years old), except one study that reported a mean age of 39 years [63]; the highest mean age was 76.4 years [109]. Population groups consisted of patients being treated with antihypertensive medication for newly diagnosed or existing grades of hypertension (with or without comorbidities). Demographics such as race (seven studies examined African-American/black populations) [42,46,55,94,100,116,130], location (five studies looked at adherence levels among rural dwellers) [43,65,85,118,128], and lifestyle habits (one study examined adherence in hypertensive patients who consumed excessive alcohol) [81] were also examined (see Table 2 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2013.03.1631>).

Interventions, Follow-Up, and Methods of Adherence Measurement

A variety of interventions were studied in the 97 articles (see Table 2 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2013.03.1631>). Interventions ranged from provider-directed strategies (providers included pharmacists, physicians, nurses, and paramedics) to multifaceted programs combining several adherence-enhancing strategies. One study by Morisky et al. [92] assessed a total of eight different combinations of interventions. Methods of intervention delivery included reminder messages, mailed packages, telephone contacts/counseling, special packaging, handouts, home visits, computer-/video-/audio-based education programs, medication time devices, and group and individual discussion/teaching sessions. The settings within which interventions were delivered varied among the studies. Interventions were most commonly delivered within a clinic setting (32 of 97, 33.0%) [38,39,44,45,49,59–61,67,70,71,76,78,80,85,86,90,91,96,98,103,106,107,110,119,121,125–129,132], followed by community pharmacies (6 of 97, 6.2%) [46,48,50,51,65,66].

Follow-up to interventions occurred once or over a number of sessions. The longest continuous study period spanned 14 years [64], with follow-ups for interventions ranging between 2 days [68] and 14 years [64] from baseline. Some studies did not report baseline data on adherence and/or BP measures (30 of 97, 30.9%) [39,43,50,66,69–71,76,80–82,87,88,90,93,94,97,101,105,108,111,112,114,116,119,122–125,128] or follow-up times (8 of 97, 8.3%) [78,80,82,84,101,108,119,128] (see Table 2 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2013.03.1631>).

Thirty-five of 97 (35 of 97, 36.1%) [38,39,53,55,59,60,63,64,66,71–76,83,85,87,88,91,98,101,107,111,112,114–116,118,119,122–125,130] articles sought to improve patient medication adherence directly, 46 (46 of 97, 47.4%) [41–51,58,61,65,68–71,77,78,80,84,86,90,94–96,99,100,102–106,108,109,113,117,121,126,127,129,131–134] sought to improve adherence through a health care provider or multidisciplinary health professional process, and 4 (4 of 97, 4.1%) [67,81,97,110] involved interventions to improve adherence indirectly through changing physician or pharmacist practice. Among interventions designed to directly improve patient adherence, 16 (16 of 35, 45.7%) [38,53,55,59,88,91,97,98,107,116,119,122–125,130] demonstrated a statistically significant impact on medication adherence and 5 (5 of 35, 14.3%) [87,111,115,125,130] on BP control. Among interventions aimed at improving adherence through a health care provider or health care team, 15 (15 of 46, 32.6%) [44,61,68–70,78,80,84,86,99,100,102,108,121,134] showed a statistically significant impact on adherence and 13 (13 of 46, 28.2%) [41,47,48,61,77,86,94,96,100,102,103,106,113] on BP control. Finally, among interventions to improve adherence indirectly through changing physician or pharmacist practice, 2 (2 of 4, 50.0%) [91,93] reported statistically significant improvements in adherence and 2 (2 of 4, 50.0%) [81,110] in BP control.

With respect to authors' justification for the interventions used, 20 studies (20 of 97, 20.6%) [43–45,47,50,51,59,69,71–73,77,90,109,

113,115,125,129,131,132] made explicit reference to the use of a theoretical framework to guide the research. Of these 20 studies, 6 (6 of 20, 30.0%) [45,59,69,73,115,125] demonstrated statistically significant improvements in medication adherence and 7 (7 of 20, 35.0%) [44,47,77,90,106,113,125] in BP control. A systematic review by Ficke and Farris [62] examined the application of the transtheoretical model on the prescribing and use of medications—the study found that evaluating medication taking on the basis of stage of change can predict adherence. The most common theoretical approaches reported were the collaborative model [43,47,77,90,115,129], the change model [71–73], the health decision model [44,45,59], and the PRECEDE-PROCEED model [51,59]. Other reported models included the social ecological model [109], the nurse management model [113,132], the structural model for determinants of adherence [125], Leventhal's self-regulatory model of illness [131], the cost-benefit model [59], and the health belief model [69].

Measures of adherence included self-report of medication utilization (46 of 97, 47.4%) [39,41,43–50,53,59,60,63,66–69,72,73,76–78,81,82,91–94,101–104,109,114–116,125–127,130,131–134], refill data or pharmacy records (18 of 97, 18.6%) [38,50,51,70,71,74,78,90,97,99,110,118,119,122–124,129,130], pill counts (16 of 97, 16.5%) [39,53,64,66,68,84–86,95,96,98,105,107,111,112,116], medication event monitoring systems (11 of 97, 11.3%) [58,80,83,87,88,100,111–113,115,121], and clinic visits (1 of 97, 1.0%) [116]. Sixteen studies (16 of 97, 16.5%) [39,50,53,64,66,68,78,111,112,116,119,122–125,130] used two or more measures of adherence; pill counts and self-reports were the most frequent combination of measures (7 of 16, 43.8%) [39,50,53,66,68,116,125]. Adherence self-reporting was often based on the Morisky Scale or its modifications (11 of 97, 11.3%) [44,45,47,50,53,76,77,91–94]. Other validated self-reporting measures were used such as the Brief Medication Questionnaire [48] and the validated Health Belief Model Questionnaire [49,69]. Theunissen et al. [131] used the validated 5-question Medication Adherence Rating Scale; however, this questionnaire is more specific to psychiatric as opposed to hypertensive populations. Mehos et al. [90] asked patients to fill out a diary to assist with adherence though information on adherence to writing in the diary was not reported. A total of 19 studies did not provide information on the validity or reliability of the self-reporting measure [43,46,63,66,68,72,73,81,82,101–104,114,126,127,130,132,133].

The majority of articles included in the review described nonpharmacological- based interventions (86 of 97, 88.7%) [39–62,64–72,74,76–82,84–100,102–110,113,114,116,117,119,129,130–131,134]; only two studies described pharmacological interventions (i.e., change in taste of tablet and monitoring intensity of pharmacotherapy) [63,83]. An intervention was deemed nonpharmacological if it involved patient or caregiver education (e.g., counseling, pamphlets), decision aids (e.g., consultation packages), special monitoring (e.g., vial caps, BP self-measurement), and/or motivation techniques (e.g., diaries, reminders, follow-up interviews) (see "Effectiveness of Interventions" section).

Although a recent study on adherence-enhancing interventions in HIV was able to categorize interventions according to determinants of adherence (i.e., knowledge, awareness, social influence, attitude, self-efficacy, intention formation, action control, maintenance, and facilitation) [135], the level of detail available in the hypertension studies was insufficient to provide the same level of granularity. Because most of the studies did not define behavioral change techniques, we were not able to further classify the methods of adherence improvement according to the determinant being addressed. We were, however, able to organize the interventions on the basis of their location and primary focus.

Effectiveness of Interventions

Close to half of all articles (47 of 97, 48.5%) [38,41,44–48,53,55,58,59,61,68,70,77,78,80,81,84,86–88,90,91,93,94,96,98,100,102,103,

106–108,110,113,115–117,119,122–125,130,133,134] reported statistically significant improvement in either adherence or BP. Of these 47 studies, 34 (34 of 47, 72.3%) [38,45,53,55,58,59,61,68,70,78,80,84,86–88,90,91,93,94,96,98,100,102, 107,108,115,116,119,122–125,130,133] demonstrated a statistically significant improvement in medication adherence (26 [26 of 34, 76.5%] [45,58,59,61,68,70,78,84,86–88,90,91,93,94,98,100,107,108,115, 116,119,122–124,133] were RCTs) and 24 (24 of 47, 51.1%) [41,44,46–48,61,77,81,86,87,90,91,96,100,102,103,106,110,113,115, 117,125,130,134] showed a statistically significant improvement in systolic and/or diastolic BP (18 [18 of 24, 75.0%] [41,44,46–48,61,77,81,86,87,90,91,100,106,110,113,115,117] were RCTs). Of the 18 RCTs that reported improvements in BP, only 10 (10 of 18, 55.6%) [47,48,61,77,81,86,87,100,110,113] adequately reported the level of medication adherence, and so limited conclusions could be drawn on the effect of adherence on BP control. The type of measures used may have also led to variations in the intervention effectiveness. For instance, while Kirscht et al. [78] achieved statistical significance of pharmacy refills when comparing the intervention to control, self-reported pharmacy refill was not significantly different between the two groups. Almost half of the interventions that reported statistical significance used self-reporting measures (22 of 47, 46.8%) [41,44–48,53,59,68,77,78,81,91,93,94,102,103,116,125,130,133,134], followed by prescription refill measures (8 of 47, 17.0%) [38,70,90,110,119,122–124] and pill counts (8 of 47, 17.0%) [53,84,86,96,98,107,108,116]. A lack of baseline data across all studies may have distorted the extent of impact of the intervention on adherence or BP.

The majority of interventions were based on one or a combination of the following strategies: education (25 of 97, 25.8%) [41,46,48,51,58,60,68,71,76,88,95,96,99,102,103,105,107,109,110,114,117,120,126,127,129], tele-management (18 of 97, 18.6%) [42,44,45,49,70,71,78,85,87,90,100,102,103,122,126–128,133], interviews/visits (15 of 97, 15.5%) [61,91,94,98,102,104,106,108,113,116,125–127,131,133], handouts/mail (14 of 97, 14.4%) [58,71,76,78,84,86,88,92,99,100,102,114,116,122], reminders (14 of 97, 14.4%) [43,53,58,71,78,85,86,94,100,110,116,122–124], self-monitoring (12 of 97, 12.4%) [41,49,50,58,72,78,87,90,95,100,105,117], provider-directed strategies (11 of 97, 11.3%) [47,58,59,65,67,69,77,80,81,97,110], packaging (10 of 97, 10.3%) [39,41,108,111,112,115,119,122–124], support groups (7 of 97, 8.2%) [59,78,82,89,91–93], pharmacy prescription profiles (5 of 97, 5.2%) [38,70,116,118,122], and diaries (2 of 97, 2.1%) [88,90]. Twelve out of the 25 (12 of 25, 48.0%) [41,46,48,58,68,88,96,102,103,107,110,117] education-based strategies reported statistically significant improvements in adherence or BP. Out of the 18 interventions that were based on (or incorporated) tele-management, 9 (9 of 18, 50.0%) [45,70,78,87,90,100,102,103,122] reported statistical significance. Finally, statistically significant improvements in either adherence or BP were reported for interventions that were based on (or included) interviews/visits (10 of 15, 66.7%) [61,91,94,98,103,106,108,113,116,125], handouts/mail (9 of 14, 64.3%) [58,78,84,86,88,100,102,116,122], reminders (11 of 14, 78.6%) [53,58,78,86,94,100,110,116,122–124], self-monitoring (7 of 12, 58.3%) [41,58,78,87,90,100,117], provider-directed strategies (7 of 11, 63.6%) [47,58,59,77,80,81,110], packaging (7 of 10, 70.0%) [41,108,115,119,122–124], support groups (5 of 7, 71.4%) [59,78,84,91,93], pharmacy prescription profiles (4 of 5, 80.0%) [70,116,118,122], and diaries (2 of 2, 100%) [88,90].

General trends and factors affecting adherence and BP control were explored by some investigators. Bailey et al. [38] found significant improvement in medication adherence with increasing age and provider visits, and reductions in multiple-dosing regimens and medication class. Social function, energy/fatigue, emotional well-being, and levels of glycohemoglobin were also found to significantly impact adherence behavior [73]. Bosworth et al. [44] was able to increase patients' confidence with

hypertension treatments leading to improved BP control; however, the reported results were not statistically significant. One study found a decrease in adherence with an increase in time between intervention and follow-up, emphasizing the importance of interventions to promote sustainable behavior change [58]. Overall, 56 of 97 (57.7%) [39,42,43,45,46,49,50,53,55,58–60,63–74,76,78,82–85,92,95,97–99,101,104–109,112,114,116,121–124,126–129,131–133] studies failed to show statistical improvements in BP that could be related to improved adherence.

Discussion/Conclusions

Our systematic review of the literature identified a broad range of interventions with plausible effectiveness. Multiple approaches for the delivery of interventions were described, in different settings of care.

We identified that interventions aimed at improving patients' knowledge of medications are of potential clinical value in improving adherence with antihypertensive therapy—these interventions included both patients and families through individual and small-group sessions and used a variety of media from informational pamphlets to personal communications. The results of these studies support the notion that improving the knowledge base and gaining an understanding of the long-term risk of hypertension are valid approaches to improving adherence. It is unclear, however, whether this improved knowledge translates to improvement in the control of hypertension, or how generalizable the results are to different settings of care.

Our review focused on hypertension, which is generally an asymptomatic disease, though long-term uncontrolled BP predisposes individuals to greatly elevated risk of cardiovascular and cerebrovascular morbidity and mortality. Because there are also some questions about the impact of adherence on BP control, we reviewed all articles to determine whether outcomes were collected and whether adherence did affect BP control. The location of the delivery of the intervention varied from mail outs, clinic-based, home-based, and managed care. Most interventions were delivered in a clinic (where nurses or other hypertension specialists delivered the intervention) or were based in a community pharmacy setting. Generally, most interventions conducted did not involve a multidisciplinary focus.

While other systematic reviews have looked at adherence-enhancing interventions across multiple diseases and found no effect [5,89,136], the present review focuses on a specific disease area. This degree of specificity is a major asset to adherence research because intervention effects cannot necessarily be generalized across therapeutic areas. Narrowing our lens to interventions to improve adherence to antihypertensive medication provides an important focus, given the burden of hypertension-related conditions, and scope for implementation of effective interventions.

We identified, however, several limitations in the studies that assessed the efficacy of adherence-enhancing interventions in hypertension. First, the development of such interventions was not guided routinely by conceptual models of the determinants of nonadherence, and many were not validated, thereby limiting the reproducibility of interventions that showed benefit. Many reasons for intentional (or deliberate) and nonintentional (e.g., due to forgetfulness) nonadherence have been described extensively [5,20–22,24–26,120,137,139,140]. Developers of adherence-enhancing interventions need to build on this knowledge about reasons for nonadherence to maximize the chances of establishing efficacy. In most cases, no information was provided about the rationale for including different adherence components (initiation, implementation, and discontinuation) of interventions [12]. Moreover, the semantics associated with characterizing the intervention was disparate. For example, a nonpharmacological

intervention could be conceptualized in many different ways depending on authors' interpretations. Second, most studies did not adequately define or describe their interventions, making it almost impossible to reproduce them in subsequent research. There is a need to provide guidance on the ontologies used to describe interventions so that findings can be reproduced by other researchers. Third, the quantification and measurement of medication adherence were inconsistent. The measurement varied from a qualitative measure of adherence (adherent vs. not) to a more quantitative, continuous measure, but based on some arbitrary threshold for adherence and nonadherence. Many studies often reported the proportion of patients who were adherent without an actual measurement. The distinctions between the various components of medication adherence were inadequately described [12]. Fourth, there was a lack of studies measuring BP control, other clinical biomarkers, and medication adherence, and, notably, the impact of adherence on BP regulation. This clinical deficiency places a limit on the potential inferences that can be made between adherence improvement and BP control. Furthermore, as hypertension requires chronic treatment, it would be worthwhile to evaluate the long-term effects of adherence interventions to improve BP control. Fifth, the methods for assessing adherence are inconsistent across studies—ranging from self-reports to electronic monitoring devices such as MEMSTM caps. Many self-reported measures have not been previously validated, thereby diminishing their utility. In addition, some studies examined multiple interventions, making it difficult to interpret the resulting benefits (i.e., Did benefits arise as a result of a single intervention despite and within a multiintervention framework? Or were the benefits an overall result of a combined multidimensional intervention?). Sixth, reporting of adherence rates and BP was poor. Where mean adherence scores were provided for RCTs, no information was available on the SDs, making it difficult to calculate effect size, which can be used as a comparative measure across studies. Without the use of validated interventions that could be replicated by others in the future, achieving consistent and incremental benefit in patients will be challenging. Finally, dropouts and loss to follow-up in individual studies may have affected the estimation of the treatment effect, the comparability of the treatment groups, and the representativeness of study samples in relation to the target population [141].

We have previously provided guidance on how to conduct research on medication adherence by using both retrospective and prospective designs [137,142]. To be clinically meaningful, future research aimed at improving adherence has to clearly define the interventions used, attempt to use a theoretical framework to justify the proposed mode of action, and finally measure both adherence and a clinical outcome by using evidence-based guidelines or validated methods. In the absence of large well-designed RCTs, this systematic review can serve as a valuable guide for clinicians to explore the impact of nonpharmacological interventions to improve adherence in the management of hypertension and to use these data to plan future studies. What is clear is that more well-designed studies are required to illustrate the effect of adherence on clinical outcomes such as BP control and cardiovascular health; these outcomes will form the cornerstone of evidence-based guidelines [143]. Well-designed RCTs of methods to support medication adherence are warranted to ensure that patients fully benefit from therapy. These studies should be based on conceptual models that provide a framework for the development of the interventions.

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Supplemental Materials

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