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Interventions to Improve Medication Adherence in Hypertensive Patients: Systematic Review and Meta-analysis

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Abstract

This systematic review applied meta-analytic procedures to synthesize medication adherence interventions that focus on adults with hypertension. Comprehensive searching located trials with medication adherence behavior outcomes. Study sample, design, intervention characteristics, and outcomes were coded. Random-effects models were used in calculating standardized mean difference effect sizes. Moderator analyses were conducted using meta-analytic analogues of ANOVA and regression to explore associations between effect sizes and sample, design, and intervention characteristics. Effect sizes were calculated for 112 eligible treatment-vs.-control group outcome comparisons of 34,272 subjects. The overall standardized mean difference effect size between treatment and control subjects was 0.300. Exploratory moderator analyses revealed interventions were most effective among female, older, and moderate- or high-income participants. The most promising intervention components were those linking adherence behavior with habits, giving adherence feedback to patients, self-monitoring of blood pressure, using pill boxes and other special packaging, and motivational interviewing. The most effective interventions employed multiple components and were delivered over many days. Future research should strive for minimizing risks of bias common in this literature, especially avoiding self-report adherence measures.

Keywords

hypertension; medication adherence; patient compliance; meta-analysis

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Introduction

About half of people with hypertension (HTN) have uncontrolled blood pressure [1]. A significant cause of poor blood pressure control is inadequate medication adherence [2–7]. Adherence to antihypertensive medications drops after initiating treatment, with about 10% of patients missing a dose on any given day and around half of HTN patients stopping medication by one year after prescription [8]. Among patients with presumed resistant HTN, 43% to 65.5% of them are medication nonadherent [4, 9]. Patients with poor adherence to anti-hypertensives are at greater risk for coronary disease, cerebrovascular disease, and chronic heart failure [10]. Poor medication adherence is associated with higher nondrug medical costs and constitutes a major barrier in reducing cardiovascular mortality [11, 12].

The problem of poor medication adherence (henceforth, adherence) has prompted investigators to conduct clinical trials testing interventions to improve medication taking among adults with HTN. The proliferation of these primary intervention trials has prompted a number of reviews that summarize and synthesize parts of this extant research. Some of these reviews are limited because they include only a few primary studies [13–16] or they synthesize blood pressure outcomes but do not directly analyze adherence [17]. Some reviews restrict their analysis of intervention effects to a specific type of adherence measurement method [3]. Other reviews have restricted their focus to specific types of interventions, for example, including only interventions conducted by specific clinic personnel [18, 19]. The present report attempts to provide a more comprehensive analysis of primary intervention studies aimed at increasing medication adherence in hypertensive patients. To accomplish this, multiple search strategies were employed to permit synthesis of adherence outcomes across as large a sample of primary studies as possible.

The following questions were addressed in this report: 1) What is the overall average effect of interventions designed to increase adherence among subjects with HTN? 2) Do effects of interventions vary depending on sample and study characteristics? 3) Do the effects vary depending on intervention features? 4) What risks of bias are present in studies, and what influence do they have on effect sizes?

Methods

Widely accepted systematic review and meta-analysis methods were used to conduct the project, and PRISMA guidelines were followed in preparing this report [20, 21].

Eligibility Criteria

Studies eligible for inclusion were those testing interventions designed to increase adherence among adults with HTN and reported adherence as an outcome measure. Adherence was defined as the extent to which medication taking behavior is consistent with health care provider recommendations [22]. This project focused on implementation adherence (how accurately patient follows prescribed dosing regimen) because primary studies rarely reported persistence (continued administration over the intended course of therapy) [23]. The meta-analysis included primary studies with varied adherence measures (e.g., electronic

bottle cap devices, pharmacy refill data, pill counts, self-report) because meta-analysis methods convert primary study outcomes to unitless indices [24, 5].

Studies with varied research methods were included, and risk of bias related to study design was assessed as described below [21]. Small-sample studies, which may be underpowered to detect differences in outcomes, were eligible for inclusion because meta-analyses do not rely on *p* values to determine effect sizes [24]. Effect sizes were weighted so larger studies had more influence on aggregate findings. Both published and unpublished studies were eligible for inclusion because the most consistent difference between published and unpublished research is the statistical significance of the findings [25, 26]. This article does not contain any studies with human or animal subjects performed by the any of the authors for this meta-analysis.

Search Strategies and Information Sources

Multiple search strategies were employed to avoid bias that can result from narrow searches [26–28]. An expert health sciences librarian conducted searches in the following electronic databases: MEDLINE, PsycINFO, PUBMED, EBSCSO, Cochrane Central Trials Register, CINAHL, Cochrane Database of Systematic Reviews, EBM Reviews, PDQT, ERIC, INDMed, International Pharmaceutical Abstracts, and Communication and Mass Media. The primary MeSH terms used in constructing search strategies were *patient compliance* and *medication adherence*. *Patient compliance* was used to locate studies published before 2009, and *medication adherence* was used to locate studies published after 2008, when medication adherence MeSH term was introduced. Other MeSH terms used in search strategies were: *drugs, dosage forms, generic, prescription drugs*, and *pharmaceutical preparations*. Text words used in searches were: *adherence, adherent, compliance, compliant, noncompliant, noncompliance, nonadherence, nonadherent, advocate, improve, promote, enhance, encourage, foster, influence, incentive, ensure, remind, optimize, increase, decrease, address, impact, prevent, prescription(s), prescribed, drug(s), medication(s), pill(s), tablet(s)*, and *regimen(s)*.

Searches were also completed in 19 grant databases and clinical trials registries [29, 30]. Journal hand searches were conducted for 57 journals [31]. Abstracts from 48 conferences were evaluated for eligible studies. Author searches on eligible studies were used to extend the search. Ancestry searches on primary studies and extant reviews were conducted.

Study Selection

Potentially eligible studies identified through the various searching methods were imported into bibliographic software, and custom fields and term lists were used for study tracking and management. Figure 1 shows how potentially eligible studies flowed through the project [21]. Final eligibility was determined by at least two investigators. If primary studies contained inadequate data to calculate effect sizes, additional publications about the same project were sought or authors were contacted to secure the information. To ensure independence of the data, names of authors on each eligible study were compared against the author names of other eligible studies. Studies with authors in common were examined

closely for possible sample overlap [32]. If uniqueness of samples was not clear from examination of the written reports, corresponding authors were contacted for clarification.

Data Collection

A coding frame to extract study data was created based on previous related meta-analyses and the research team's expertise [33, 34]. This coding frame was pilot tested on 20 studies before implementation in the larger project. The coding frame was designed to capture report level features, participant demographics, intervention characteristics, study design attributes, and data to calculate adherence effect sizes. Year of distribution, publication status, and funding were recorded as report level features. Participant characteristics that were coded included gender, ethnicity, socio-economic status, age, number of prescribed medications, and whether subjects were selected because of poor adherence.

Intervention characteristics coded from studies included: theoretical basis of intervention; intervention delivery site (e.g., pharmacy, ambulatory care setting); delivery medium (e.g., face-to-face, telephone); interventionist profession (e.g., pharmacist, physician); days over which the intervention was delivered; and dose (i.e., duration of sessions and number of sessions). The intervention recipient (i.e., patient, health care provider) was recorded. Whether the intervention targeted adherence behavior alone or also included other health behaviors (e.g., physical activity) was coded.

The content of each intervention was coded in detail. Examples of coded content included specific strategies to address barriers to adherence, medication administration calendar, decisional balance activities, feedback about adherence, feedback about blood pressure, habit analysis and linking adherence with habits, improving health care provider communication with patients, increasing integration of care, motivational interviewing, special packaging of medications (e.g., blister packs, pill boxes), problem solving strategies, self-monitoring adherence behavior, self-monitoring blood pressure, social support for adherence, and written instructions. Other types of intervention content were coded but were reported too infrequently for analyses.

Study design features that were coded included random vs. nonrandom assignment to groups, allocation concealment, comparison group management (i.e., true control group or attention control group), data collector masking, intention-to-treat analyses, and percent attrition [21]. The method used to measure adherence (e.g., electronic medication event monitoring, pharmacy refills, pill counts, self-report) was recorded [5]. Outcome data coded included baseline and outcome sample sizes, means, measures of variability, change scores, t statistics, and success rates. All data used in the calculation of effect sizes were independently verified by a doctorally prepared researcher. If more than one report was available about the same samples, all reports were used in order to code as many details about studies as possible.

Summary Measures and Statistical Analysis

Standardized mean difference effect sizes (d) were calculated for each comparison [24, 35]. This represents the post-intervention difference between treatment and control participants divided by the pooled standard deviation for treatment vs. control two-group comparisons. A

positive value for d indicates higher adherence for the treatment group compared to the control group. Pooled effect size estimates were obtained using random-effects models to acknowledge that variation in effect sizes results not only from participant-level sampling error but also from study-level sources of variation due to methodological and other differences [36, 37]. Individual effect sizes were weighted by the inverse of variance to give larger studies more influence in meta-analysis findings [35, 38]. Corresponding 95% confidence intervals were constructed for each effect size and the overall mean effect size.

Single-group pre-post overall mean effect sizes were also calculated for both treatment and control groups, but they were analyzed and reported separately from two-group treatment vs. control comparisons. The single-group analyses should be considered ancillary information to the more valid treatment vs. control comparisons. All effect size outcomes reported in this paper are for treatment vs. control comparisons unless otherwise specified.

Heterogeneity was expected because it is common in behavioral research [39]. This anticipated heterogeneity was managed in four ways: 1. random-effects models were used because they take into account heterogeneity beyond that which can be explained by moderator analyses; 2. both location and extent of heterogeneity were reported; 3. possible sources of heterogeneity were explored using moderator analysis, and 4. findings were interpreted in the context of discovered heterogeneity [39].

Cochran's test of the conventional heterogeneity statistic Q was used to determine whether between-studies sampling error was statistically significant [40], and I^2 was computed to quantify the extent of heterogeneity beyond within-studies sampling error [40, 24].

Exploratory moderator analyses were conducted to detect patterns among studies related to sample, intervention, and methodological characteristics. Dichotomous moderators were tested by between-group heterogeneity statistics ($Q_{between}$) using a meta-analytic analogue of ANOVA [24]. Continuous moderators were analyzed by testing unstandardized regression slopes in a meta-analytic analogue of regression [24].

Risk of Bias

To avoid introducing bias by including only easy-to-locate studies that may have larger effect sizes, comprehensive search strategies were employed [25, 41, 42]. This strategy permitted identification of eligible unpublished as well as published studies, which minimized inflation of overall effect sizes due to publication bias. To detect the presence of publication bias, funnel plots of effect sizes vs. sampling variance were visually examined [25]. Begg's test using Kendall's method was conducted to determine whether detected associations between effect size and variance were greater than might be expected due to chance [25].

To assess risk of bias due to study quality, common indicators of methodological strength (random assignment, allocation concealment, data collector masking, use of attention controls, intention-to-treat analysis, low attrition) were examined via moderator analyses as a form of sensitivity analyses [21]. For all analyses, effect sizes were weighted so more precise estimates from larger sample sizes exerted proportionately more influence on

findings[24], but they were not weighted by overall quality scores because existing quality instruments lack validity [43–45]. Effect sizes of control group baseline vs. outcome comparisons were also analyzed to determine whether subjects' mere participation in a study could have biased the estimated overall treatment effect.

Results

Comprehensive searching located 101 eligible primary study reports [46–146]. Twenty-five additional papers were located that reported on the same studies; these were used as companion papers to enhance coded data. Five reports in Spanish were included. Eighty-eight reports were published articles, ten were dissertations, two were conference presentations, and one was an unpublished report. Seventy papers were published in 2000 or more recently; only 20 reports were published prior to 1990. The earliest article was published in 1973. Thirty-one reports did not report funding for studies.

The primary study reports provided information for 112 treatment vs. control comparisons, 48 treatment pre- vs. post-intervention comparisons, and 32 control baseline vs. outcome comparisons (k indicates the number of comparisons). Some reports had more than one treatment group; eight reports included two comparisons and six reports had three comparisons. All subsequent results are based on comparisons.

Table 1 provides descriptive characteristics of the included treatment vs. control comparisons. Median treatment and control group sample sizes were 56 and 51 participants, respectively. Median attrition rates were 8.1%. Women were well represented in samples. Only $k = 9$ comparisons reported the number of prescribed medications taken by participants; for these comparisons, the median number of prescribed medications was 5.1.

Overall Effects of Interventions on Adherence Outcomes

Overall effect sizes for treatment vs. control and single-group pre-post comparisons are presented in Table 2. Effect sizes could be calculated for 112 treatment vs. control comparisons involving 34,272 subjects, but four comparisons were excluded as outliers from the pooled analysis. The estimated overall standardized mean difference effect size for the remaining 108 comparisons was $d = 0.300$. With the outliers included, the effect size was 0.421 (CI: 0.322, 0.520; $Q = 1429.559$). Exclusion of the two largest studies involving more than 2000 participants resulted in an overall mean effect size of 0.341 (CI: 0.257, 0.425; $Q = 673.440$).

We calculated effect sizes for 47 treatment group pre-post comparisons involving 5,703 participants and for 32 control pre-post comparisons involving 4,603 participants. Three outliers each were excluded from the pooled analysis of the treatment pre-post comparison and control group pre-post comparisons. For treatment outcome vs. baseline comparisons, the overall mean effect size was 0.378, and for control group pre-post comparisons, the overall effect size was 0.096.

Analysis of Q statistics showed significant heterogeneity across studies for all three types of comparisons. The proportion of variation due to between-studies heterogeneity ranged from 78 to 87%.

Report and Sample Characteristics Moderator Analyses

Moderator analysis was conducted to determine whether effect sizes were linked to study attributes or participant demographics. With respect to study attributes, those studies conducted more recently reported larger effect sizes than older studies ($p < .001$). Effect sizes were larger for unfunded studies ($d = 0.454$, $k = 30$) than funded studies, ($d = 0.253$, $k = 78$), but the difference was not statistically significant.

Although effect sizes were not linked to study attributes, they were affected by participant demographics. Larger effect sizes were associated with higher mean participant age ($p = .009$, $k = 85$) and with higher proportions of women in the sample ($p = .001$, $k = 93$). There was no association between effect size and the proportion of participants in the sample belonging to underrepresented ethnic/racial groups ($p = .974$, $k = 44$). Effect sizes were lower for studies reporting inclusion of low-income participants ($d = 0.133$, $k = 18$) than studies not reporting low income participants ($d = 0.327$, $k = 90$); this difference was statistically significant ($Q_b = 7.294$, $p = .007$).

The difference in effect sizes for studies of subjects recruited specifically because they had adherence problems ($d = 0.479$, $k = 13$) and studies that did not target such subjects ($d = 0.282$, $k = 95$) was not statistically significant ($Q_b = 2.059$, $p = .151$). The number of medications patients were prescribed was not analyzed as a moderator because only nine studies provided this information.

Moderator Analyses of Intervention Delivery Attributes

Moderator analyses were conducted on specific intervention delivery attributes reported by at least seven primary studies. Results of the analysis are shown in Table 3. Similar effect sizes were found regardless of whether interventions targeted adherence exclusively ($d = 0.318$) or addressed additional health behaviors ($d = 0.292$). Interventions delivered to health care providers teaching them how to elicit adherence behavior change in their patients were significantly less effective ($d = 0.107$) than interventions delivered directly to patients themselves ($d = 0.316$). Effects on interventions were similar whether delivered by physicians ($d = 0.356$) or pharmacist ($d = 0.369$), but neither were significantly more effective than interventions delivered by other personnel. Interventions delivered in ambulatory care facilities were similar in effect to interventions delivered in other settings (0.272 vs. 0.282). Although interventions delivered in pharmacies were somewhat more effective than interventions delivered in other settings (0.432 vs. 0.290), this difference did not achieve statistical significance. Interventions delivered face-to-face were not significantly more effective than mediated interventions (0.335 vs. 0.284).

Moderator analysis of theory-based interventions relative to studies not based in theory showed no difference in overall effect size (0.335 vs. 0.284). Effect size was 0.560 for the health promotion model ($k = 3$), 0.366 for social cognitive theory ($k = 7$), 0.152 for the health belief model ($k = 3$), and 0.118 for the transtheoretical model ($k = 6$). Given the small

number of samples contributing to each of the pooled effect sizes, these findings should be regarded with caution.

Intervention dose was poorly reported. Only 29 comparisons reported a mean duration of intervention sessions; the median of those means was 20 minutes. A median of four intervention sessions was reported across 71 comparisons. The total duration of intervention sessions in minutes could be calculated from data reported in 26 studies, but regression analyses revealed no relationship between total minutes of intervention and effect size ($p = .534$). The median of the mean period of time over which interventions were delivered was 183 days. Interventions delivered over a longer time frame improved adherence more than those delivered over a shorter one ($p < .001$).

Intervention Content Moderator Analyses

Moderator analysis was conducted to determine whether effect size was influenced by specific types of intervention content. A pooled effect size for studies incorporating a particular intervention component was compared to the pooled effect size of studies lacking that component. Results of the moderator analyses are shown in Table 4.

Meta-regression showed that studies with more intervention components had larger effect sizes than studies with fewer components ($p <.001$). Among the 15 individual intervention components tested as moderators, two were found to have statistically significant influences on effect size. Studies that focused on increasing integration of a patient's care across health care providers ($d = 0.185$) reported lower effect sizes than studies without integration ($d = 0.344$). Primary research that used adherence problem-solving strategies reported significantly smaller effect sizes ($d = 0.152$) than studies lacking this component ($d = 0.334$).

Self-monitoring of blood pressure is a common recommendation made by health care providers to patients with hypertension. Studies that incorporated blood pressure self-monitoring into interventions had slightly greater effect sizes than interventions lacking a self-monitoring component, but the difference was not significant (0.381 vs. 0.216, $p = .160$). Having patients self-monitor their medication taking also did not result in significantly greater effect sizes (0.381 vs. 0.280, $p = .508$). Studies in which patients received feedback about their blood pressure did not have significantly great effect sizes than studies that did not incorporate blood pressure feedback (0.298 vs. 0.296, $p = .974$). Although effect sizes were larger for studies in which patients received feedback about their adherence compared to studies in which no adherence feedback was given (0.500 vs. 0.280), the difference was not statistically significant ($p = .140$).

Larger effects sizes were found for studies that linked patient habits with medication taking, employed motivational interviewing, or provided medication in special packaging or pill boxes, but the differences from studies lacking these components also failed to achieve statistical significance. The small number of studies available for analysis for some intervention components may have limited the statistical power of the tests to detect true differences, so findings should be regarded as exploratory.

Risk of Bias Sensitivity Analyses

Several risks of bias were identified in the studies included in the meta-analysis sample: lack of random assignment of subjects ($k = 34$), allocation not concealed ($k = 90$), data collectors not masked to group assignment ($k = 79$), and absence of intention-to-treat analysis ($k = 85$). Moderator analysis determined that adherence effect size was not linked to any of these risks (Table 5). Effect sizes were also not significantly associated with attrition rates ($p = .201$). Moderator analysis could not be conducted to assess for control bias because only two comparisons used attention control groups.

The method used to measure adherence is an important area of potential bias in this area of science. The largest effect sizes were reported among studies with electronic event monitoring adherence ($d = 0.621$) followed by pharmacy refill data ($d = 0.299$) and pill counts ($d = 0.299$). The smallest effect was found among studies using self-report measures of adherence ($d = 0.232$).

The effect size for published studies was 0.310 compared to an effect size of 0.230 for unpublished reports. To further assess whether publication bias might be present, funnel plots of effect sizes vs. sampling variance were examined. Asymmetry in the distribution suggested publication bias, and this was confirmed by Begg's test ($p = .030$). The funnel plot for treatment group pre-post comparisons also showed evidence for publication bias that was confirmed by Begg's test ($p = .002$). No evidence of publication bias was detected in funnel plots of control group pre-post comparisons, and Begg's test was not significant ($p = .333$).

Discussion

This project provides the first comprehensive review and meta-analysis of medication adherence intervention outcomes among adults with HTN. Multiple search strategies were employed to locate as large a sample of studies as possible. The overall mean effect size of 0.300, which was calculated across 108 treatment vs. control comparisons, documents that treatment subjects had significantly better medication adherence outcomes than control subjects. This value was comparable to effect sizes reported in meta-analyses of adherence interventions conducted in general populations ($d = 0.18$ to 0.37) [147, 148]; among older adults ($d = 0.33$) [149]; adults with coronary artery disease ($d = 0.229$) [150]; adults with heart failure ($d = 0.29$) [151]; patients with adherence problems ($d = 0.301$) [152]; and in targeted populations of underrepresented racial/ethnic groups ($d = 0.211$) [153].

The 0.300 effect size is consistent with treatment subjects taking 4% more of their prescribed daily doses than control subjects at outcome, a difference that may be clinically significant. Cardiovascular risk and outcomes are influenced by the extent of blood pressure control, which in turn is related to adherence to anti-hypertensive medications. Higher adherence rates to HTN medications are correlated with reduced risk for the development of congestive heart failure [154], cardiovascular disease [155], and acute cardiovascular events [156, 157]. Lowy and colleagues (2011) showed an increase in adherence for prescribed HTN medication with similar pharmacokinetics improves the reduction in 10-year cardiovascular disease risk [155]. Thus, modest increases in medication adherence can help reduce cardiovascular disease risk through improved blood pressure control.

The modest effect sizes found in this report and previous meta-analyses demonstrate the difficulty in changing adherence behavior. Health care providers need to understand the challenges in changing adherence behavior and make this a priority in providing care. The findings that interventions delivered over more days were more effective than shorter interventions suggests that improved adherence behavior typically will not be achieved in a single visit or with a short-term intervention. Rather, health care providers will be more successful if they repeatedly address adherence across multiple clinic visits.

The drawback of interventions of longer duration is that they may require health policy changes to permit reimbursement for providers' delivery of health behavior change intervention activities. However, the cost savings to the health care system in terms of prevented disease and reduced illness-related hospitalizations would offset the cost of reimbursing providers for helping patients to improve medication adherence [158, 159].

The moderator analyses of intervention characteristics provide promising directions for future work. The larger effect size for interventions having more components suggests providers need to use multiple strategies in their attempts to improve adherence. This increases the likelihood of an intervention component addressing the reasons for nonadherence for any given patient. Few interventions have attempted to tailor intervention approaches to patients' reasons for nonadherence. Future intervention research will need to explore the potential benefits of tailored interventions, based either on patients' type of nonadherence (e.g. intentional vs. unintentional; implementation vs. persistence), and preferences for intervention delivery (e.g., face-to-face vs. technology-mediated).

The finding that mediated delivery of interventions was as effective as face-to-face delivery suggests mediated interventions such as text messaging could be tried. The results also suggest that interventions can target multiple health behaviors without adversely affecting adherence outcomes [150]. This is important information for hypertensive populations in which other health behaviors affecting cardiovascular health such as diet and exercise must also be addressed.

Interventions delivered directly to patients were more effective than those delivered to health care providers [152, 151]. Interventions to increase integration of care were less effective than interventions with other characteristics. Regarding specific content of interventions, exploratory findings suggest future attention to habit-based interventions, adherence feedback to patients, patients self-monitoring blood pressure, special packaging such as pill boxes, and motivational interviewing approaches [160, 152]. These moderator analyses indicated differences in effect sizes, but the differences did not reach statistical significance, likely due to too few studies using these approaches. In contrast, this meta-analysis found no support for specifically addressing adherence barriers or problem solving, medication administration calendars, decisional balance activities, and social support interventions.

The overall effect size reflects aggregate changes. Some individual patients likely experienced little or no adherence improvement while other others ended studies with much higher adherence levels. The sample characteristic moderator analyses suggested interventions were more effective for older, female, and middle- or upper-income subjects.

These findings suggest different interventions need to be developed for men, younger subjects, and adults with limited income [161].

Project limitations inherent to meta-analyses and specific to this topic must be considered. Some primary research may not have been retrieved despite comprehensive searching. Effect sizes were significantly heterogeneous, which was expected given the methodological variations among studies. Intervention content may have been incompletely coded due to lack of information provided in study reports. Inadequate description of interventions in some primary studies is a common problem in behavior sciences research reporting [162, 11, 163]. This project did not link adherence with blood pressure outcomes. The scarcity of information regarding the mean number of medications is a serious limitation in this area of science because adherence may be related to the numbers of medications taken or medication regimen complexity [149].

The primary intervention studies located for this meta-analysis focused exclusively on implementation adherence. Given evidence that persistence may be more important than implementation adherence for blood pressure control [164], future research should include persistence measures and consider separate reporting of implementation adherence and persistence outcomes.

Disparities in treatment and control of hypertension are related to the often intertwining influences of socioeconomic status, educational level (which may also be, at times, a proxy for health literacy), and race/ethnicity. Improved reporting in primary studies regarding of socioeconomic and racial/ethnic attributes of participants would permit more precise estimation of these factors in meta-analysis. This meta-analysis found income-associated differences intervention effectiveness, but moderator analysis of the effect of educational level on adherence was not conducted because too few studies reported on the educational demographics of participants. Future comparative effectiveness research to identify interventions most suitable for individuals within specific socioeconomic and racial/ethnic groups would allow for improved blood pressure control across a more diverse spectrum of patient populations.

Potential sources of bias in primary studies diminish confidence in study findings [21]. More than half the studies in this meta-analysis failed to report the use of allocation concealment, data collector masking, or intention-to-treat analysis. Although moderator analysis found no linkage to effect size, the results should still be interpreted within the context of these methodological limitations. Publication bias was detected in this meta-analysis, suggesting calculated overall effect sizes overestimate true effects. Location of more unpublished studies might provide a truer estimate of overall effects of interventions on medication adherence.

Despite documented concerns about the validity of self-report measures in assessing adherence [2, 11], 43% of the primary studies relied on self-report to measure adherence. The smallest effect sizes were among studies with self-report adherence measures (d = 0.232), while the largest effects were among studies with electronic event monitoring adherence measures (d = 0.621). The low cost and ease of collecting self-report adherence

data may be less important than collecting adherence data with adequate sensitivity to detect intervention effects. Improving methodological rigor in future research will enhance the quality of evidence provided by trials. New measures should be developed that combine the low cost of self-report, with the greater sensitivity of electronic monitoring to improve the validity of clinical trial data as well as the potential usage of adherence assessment in clinical practice as part of adherence-enhancing intervention efforts.

Conclusion

This comprehensive meta-analysis of interventions documented significant but modest post intervention improvements in medication adherence among hypertensive patients. These improvements were comparable to findings of previous meta-analyses that examined effects of interventions on medication adherence in diverse chronic illness populations. Interventions to improve ant-hypertensive medication adherence were most effective among female, older, and moderate- or high-income participants. Clinicians should consider interventions that incorporated multiple different components and are delivered over many days. Promising intervention components include linking adherence behavior with daily habits, providing adherence feedback to patients, self-monitoring blood pressure, special packaging of medications, and motivational interviewing. Future research designs should strive to incorporate fewer threats of bias, especially avoiding self-report adherence measures.

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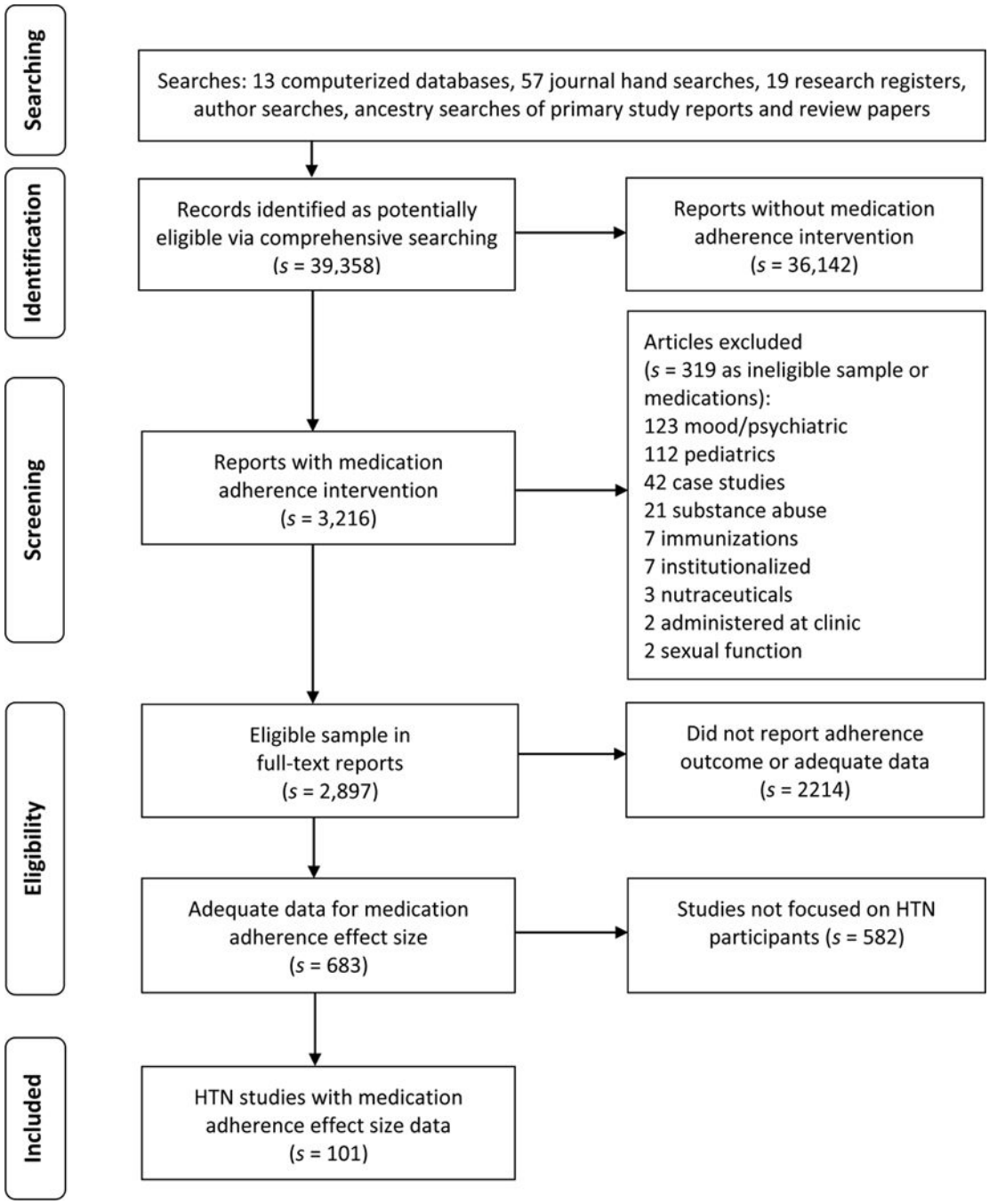

Fig. 1. Flow of potentially eligible primary research reports through review process
Note: *s* indicates the number of research reports

Table 1

Characteristics of Treatment vs. Control Comparisons Included in Medication Adherence Meta-analysis

Characteristic	k	Min	Q_1	Mdn	Q_3	Max
Total number of treatment subjects at outcome	112	8	30	56	154	3407
Total number of control subjects at outcome	112	5	26	51	144	3406
Percentage attrition across treatment & control subjects	93	0	0	8.1	23.1	82.2
Percentage from underrepresented ethnic/racial groups in North America, Europe, and Australia studies	45	5	52.7	75	100	100
Percentage female	98	0	45	57	66	100
Mean age (years)	90	39	54.5	59.2	63.8	77.4
Mean number of prescribed medications	9	1.93	3.1	5.1	5.5	6.93
Number of intervention sessions	71	1	2	4	8	52
Minutes per intervention session	29	6	12	20	35	90
Days over which the intervention was delivered	94	1	84	183	224	732

Note. Includes all studies that contributed at least one effect size to primary analyses.

*k d*enotes number of comparisons providing data on characteristic.

Min=minimum, Q_1=first quartile, Mdn=median, Q_3=third quartile, Max=maximum.

Table 2

Random-effects Medication Adherence Outcome Effect Size Estimates and Heterogeneity Statistics

	k	Effect size	*p* (ES)	95% Confidence interval	Standard error	I^2	*Q*	*p* (*Q*)
Treatment vs. control comparisons	108	0.300	<.001	0.222, 0.379	0.040	86.696	804.255	<.001
Treatment pre- vs. post-comparisons	44	0.378	<.001	0.293, 0.464	0.043	84.147	271.706	<.001
Control pre- vs. post-comparisons	29	0.096	.023	0.013, 0.179	0.042	77.808	126.172	<.001

k denotes number of comparisons, effect size is standardized mean difference, *Q* is a conventional homogeneity statistic, I^2 is the percentage of total variation among studies' observed ES due to heterogeneity.

Table 3

Moderator Analyses of Intervention Characteristics

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Behavior target				0.087	.768
Intervention exclusively targeted adherence behavior	41	0.318	0.073		
Intervention targeted multiple health behaviors including adherence	67	0.292	0.046		
Intervention delivered to health care providers vs. patients				4.722	.030
Health care providers received intervention	7	0.107	0.086		
Patients received intervention	101	0.316	0.043		
Pharmacist interventionist				0.960	.327
Present	28	0.356	0.063		
Absent	80	0.277	0.050		
Physician interventionist				0.361	.548
Present	14	0.369	0.166		
Absent	94	0.267	0.032		
Ambulatory care delivery site				0.006	.938
Present	25	0.272	0.118		
Absent	83	0.282	0.035		
Intervention delivered in pharmacy				0.692	.405
Present	9	0.432	0.166		
Absent	99	0.290	0.042		
Intervention delivery				0.709	.400
Face-to-face delivery	81	0.319	0.053		
Mediated delivery (e.g., telephone, mail)	27	0.259	0.048		
Theory used to design intervention				0.350	.554
Any theory used to design intervention	29	0.335	0.072		
No theory used to design intervention	79	0.284	0.048		

k denotes number of comparisons, effect size is standardized mean difference, *Q* is a conventional heterogeneity statistic.

Table 4

Specific Intervention Content Moderator Analyses

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Specifically address barriers to adherence				2.383	.123
Present	14	0.161	0.094		
Absent	94	0.321	0.044		
Medication administration calendar				0.509	.476
Present	10	0.232	0.086		
Absent	98	0.301	0.043		
Decisional balance activity				0.004	.952
Present	7	0.292	0.157		
Absent	101	0.301	0.042		
Habit analysis and linking adherence behavior with habits				1.083	.298
Present	9	0.412	0.109		
Absent	99	0.290	0.042		
Motivational interviewing				1.118	.290
Present	10	0.482	0.190		
Absent	98	0.277	0.038		
Packaging				1.159	.282
Present	10	0.439	0.135		
Absent	98	0.287	0.042		
Adherence problem solving				5.032	.025
Present	21	0.152	0.066		
Absent	87	0.334	0.047		
Social support				0.272	.602
Present	15	0.201	0.188		
Absent	93	0.301	0.039		
Written instructions				1.105	.293
Present	37	0.352	0.061		
Absent	71	0.269	0.050		
Improve provider communication with patients				0.105	.746

Moderator	*k*	Effect size	Standard error	$Q_{between}$	p ($Q_{between}$)
Present	7	0.217	0.246		
Absent	101	0.298	0.038		
Increase integration among health care providers				5.366	.021
Present	25	0.185	0.040		
Absent	83	0.344	0.056		
Self-monitoring medication administration				0.438	.508
Present	16	0.381	0.148		
Absent	92	0.280	0.040		
Self-monitoring blood pressure				1.974	.160
Present	36	0.381	0.072		
Absent	72	0.261	0.047		
Feedback about subjects adherence scores				2.180	.140
Present	14	0.500	0.143		
Absent	94	0.280	0.042		
Feedback about blood pressure				0.001	.974
Present	14	0.298	0.069		
Absent	94	0.296	0.044		

k denotes number of comparisons, effect size is standardized mean difference, *Q* is a conventional heterogeneity statistic.

Table 5

Risk of Bias Moderator Analyses

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Allocation to treatment groups				1.322	.250
Randomization of individual subjects	74	0.267	0.047		
Subjects not individually randomized	34	0.363	0.069		
Allocation concealment				0.080	.777
Allocation concealed	18	0.328	0.112		
Did not report allocation concealed	90	0.362	0.048		
Data collector masking				2.930	.087
Data collectors masked to group assignment	29	0.210	0.057		
Did not report data collectors masked to group assignment	79	0.340	0.500		
Intention-to-treat approach				0.061	.805
Reported intention-to-treat approach	23	0.277	0.098		
Did not report intention-to-treat approach	85	0.304	0.044		
Publication status				0.417	.518
Published articles	96	0.310	0.043		
Dissertations, presentations, unpublished reports	12	0.230	0.116		
Adherence measured with medication event monitoring system				2.925	.087
Medication event monitoring system	10	0.621	0.202		
Did not use medication event monitoring system	98	0.269	0.038		
Adherence measured with pharmacy refill data				0.001	.974
Pharmacy refill data	13	0.299	0.090		
Did not use pharmacy refill data	95	0.303	0.046		
Adherence measured with pill counts				0.001	.979
Pill counts	23	0.299	0.078		
Did not use pill counts	85	0.297	0.046		
Adherence measured by self-report				2.349	.125
Self-report adherence data	46	0.232	0.059		
Did not use self-report data	62	0.352	0.052		

k denotes number of comparisons, effect size is standardized mean difference, *Q* is a conventional heterogeneity statistic.