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Medication Adherence Interventions That Target Subjects with Adherence Problems: Systematic Review and Meta-analysis

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Abstract

Background—Inadequate medication adherence is a pervasive, under-recognized cause of poor health outcomes. Many intervention trials designed to improve medication adherence have targeted adults with adherence problems. No previous reviews have synthesized the effectiveness of medication adherence interventions focused on subjects with medication adherence difficulties.

Objective—This systematic review and meta-analysis synthesized findings from medication adherence intervention studies conducted among adults with medication adherence difficulties.

Methods—Primary research studies were eligible for inclusion if they tested an intervention designed to increase medication adherence among adults with documented adherence difficulties and reported medication adherence behavior outcomes. Comprehensive search strategies of 13 computerized databases, author and ancestry searches, and hand searches of 57 journals were used to locate eligible primary research. Participant demographics, intervention characteristics, and methodological features were reliably coded from reports along with medication adherence outcomes. Effect sizes for outcomes were calculated as standardized mean differences, and random effects models were used to estimate overall mean effects. Exploratory dichotomous and continuous variable moderator analyses were employed to examine potential associations between medication adherence effect size and sample, intervention, and methodological characteristics.

Results—Data were extracted from 53 reports of studies involving 8,243 individual primary study participants. The overall standardized mean difference effect size for treatment vs. control subjects was 0.301. For treatment pre- vs. post-intervention comparisons, the overall effect size was 0.533. Significantly larger effect sizes were associated with interventions incorporating prompts to take medications than interventions lacking medication prompts (0.497 vs. 0.234). Larger effect sizes were also found for interventions that linked medication taking with existing habits compared to interventions that did not (0.574 vs. 0.222).

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Effect sizes were largest among studies that measured adherence by pill counts or electronic event monitoring systems. Analysis of study design features identified several potential risks of bias. Statistically significant publication bias was detected, but adherence effect sizes were not significantly associated with other risks of bias.

Conclusions—These findings document that interventions targeting individuals with medication adherence problems can have modest but significant effects on medication-taking behavior. The findings support the use of behavioral strategies such as prompts and linking medications to habits to increase medication adherence in adults with adherence challenges. Face-to-face interventions appear to be critical for patients who have experienced past problems with medication adherence.

Keywords

Medication adherence; intervention; meta-analysis; systematic review

Introduction

Medication adherence is an important component in the effective treatment of many acute and chronic diseases. Consequences of inadequate medication adherence include not only poor clinical outcomes with attendant increased morbidity and mortality but also diminished quality of life, decreased work and personal productivity, and increased health care costs.[1–3] Poor medication adherence is a pervasive and long-standing problem; rates around 50% have been reported for decades.[1,4–8] Inadequate medication adherence constitutes a global epidemic with estimated annual costs to the health care system of $100 billion in the US and €25 billion in the European Union.[1,3,6,7]

The problem of poor medication adherence (henceforth, adherence) has prompted many trials testing interventions to improve medication-taking behaviors.[1,2] A number of these studies have intentionally recruited subjects who have difficulty with adherence.[9–61] Targeting subjects who have adherence problems allows for potentially larger improvements in adherence scores than subjects who have good adherence at study entry.[62] These larger increases in adherence may also result in concomitantly greater improvements in health outcomes.[63]

The present review and meta-analysis were conducted to assess the overall effectiveness of adherence interventions in subjects who have difficulties with medication taking. As such, this research fills a knowledge gap because no previously published meta-analyses have used subject baseline adherence level as a selection criterion.[64–66] Focus in previous meta-analyses has been on specific types of medication adherence interventions,[67–72] on populations with specific clinical conditions,[69,72–76] or on specific demographic groups.[77–79]

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

Material and Methods

Widely accepted systematic review and meta-analysis methods, including PRISMA guidelines, were used.[80–82] This study is part of a larger parent project consisting of a series of meta-analyses of medication adherence intervention trials. The protocol was not registered. This review emphasizes comparisons of adherence behavior outcomes between treatment and control subjects.

Eligibility Criteria

Eligible studies for the analysis were primary intervention studies designed to increase medication adherence in adult subjects recruited specifically because they had problems with adherence to prescription medications. For purposes of inclusion in the meta-analysis, adherence was defined as the extent to which medication consumption is consistent with professional health care provider recommendations.[8] What constituted an adherence problem was defined by primary investigators. Small-sample studies with questionable statistical power were included because meta-analyses do not rely on *p* values to determine effect sizes.[83,84] The project focused on treatment andcontrol group comparisons. Both randomized and nonrandomized studies were included in the meta-analysis. Subject allocation was examined as part of risk of bias assessment, which is described below.[80,84–88] Pre-experimental studies were included in an analysis of single-group studies. These studies did not report control groups but instead compared post-intervention adherence to baseline values. All analyses were conducted separately for single-group and two-group comparisons. The single-group findings are reported only as ancillary information to the more valid two-group results.

To avoid bias, both unpublished and published studies were included because the most consistent difference between published and unpublished research is the statistical significance of the results.[89–94] Although investigators used diverse methods to measure adherence, the method of measurement was not used as a selection criterion because in meta-analysis, primary study outcomes are converted to unitless indices.[80]

Only studies with adequate data to calculate effect sizes were included.[95–97] When the data necessary for effect size calculation were lacking, author searches were conducted to locate other papers that might contain the necessary information. When the information could not be located in the literature, it was requested from corresponding authors. In the parent project, 2,897 potentially eligible primary studies were located that included a medication adherence intervention and mentioned medication adherence behavior outcomes. Adequate medication adherence behavior statistical information to calculate effect sizes was absent in 2,214 reports, so they were excluded from meta-analyses (see Figure 1).

Strategies do exist for including studies that do not have adequate data for effect size determination, such as setting the effect size to 0, estimating possible effect sizes from other studies with significant or nonsignificant findings, or estimating effect size magnitude from similar studies reporting sample size and direction of effect information. However, none of these strategies were employed in the present study because they can distort estimates of heterogeneity and because imputing values requires assumptions that may not be justified.

This study focused on medications prescribed to prevent or treat acute or chronic physical disease. The project excluded primary research focused on subjects being treated for psychiatric conditions (e.g., schizophrenia) or substance abuse (e.g., alcohol) because decisions to skip or cease medications may be a consequence of patients' impaired psychological status or addicted state.

Studies of patients who were prescribed contraceptive and sexual dysfunction medications were also excluded. These medications are most often prescribed for health promotion or as "lifestyle" medications, and patient decision-making about consuming such medications is expected. For example, contraceptives may be discontinued when a woman intends to become pregnant. Medications for sexual dysfunction are typically taken in an episodic, rather than a scheduled, regimen, which changes the conceptualization of adherence and adherence measurement for these medications. Different interventions would be needed for patients with major psychiatric diseases or for patients expected to modify consumption to meet personal goals. Thus, none of these medication classes fit the inclusion criteria for treating acute or chronic disease.

Studies of adherence to any of the following medications were also excluded: vitamins, supplements, or nutraceuticals not prescribed by a provider; medications administered by health care providers in clinical settings. Studies of institutionalized or incarcerated adults were not included in the meta-analysis sample because of institutional control over medication administration.

Information Sources and Search Strategies

Multiple search strategies were used to avoid potential bias resulting from narrow searches.[93,98–104] An expert health sciences librarian conducted searches in PubMed, MEDLINE, PsycINFO, EBSCO, PDQT, ERIC, Cochrane Database of Systematic Reviews, Cochrane Central Trials Register, CINAHL, Communication and Mass Media, EBM Reviews, IndMED, and International Pharmaceutical Abstracts.[100] The primary MeSH search terms were *patient compliance* for studies published before 2009 and *medication adherence* for studies published after 2008, the year *medication adherence* was introduced as a MeSH term. Other MeSH and text word search terms included *compliant, compliance, adherent, adherence, noncompliant, noncompliance, nonadherent, nonadherence, prescription drugs, pharmaceutical preparations, drugs, dosage forms, or generic, prescription(s), prescribed, drug(s), medication(s), pill(s), tablet(s), regimen(s), improve, promote, enhance, encourage, foster, advocate, influence, incentive, ensure, remind, optimize, optimize, increase, impact, prevent, address,* and *decrease.* Searches for the parent project were completed in 2013 to allow time for coding and analyses in 2014.

Several other methods were used to find additional potentially eligible studies. Authors having more than a single study in the parent project were contacted to solicit additional published or unpublished research.[105,106] Abstracts from 48 conferences were examined. Searches were conducted in 19 research registers (e.g., Research Portfolio Online Reporting Tools), and investigators were contacted to obtain research reports of those studies.[94,107,108] Hand searches were conducted in 57 journals where multiple eligible papers in the parent project were published.[109,110]

Study Selection

Potentially eligible studies were imported into bibliographic software and subsequently tracked with study-specific custom fields and terms. Studies were selected by extensively trained research specialists with graduate degrees and the principal investigator (VC). Each final eligibility decision was made by at least two research specialists. The 39,358 studies identified via comprehensive searching were examined using a multi-staged eligibility determination process. First, titles and abstracts were examined for visual heralds.[111] Second, reports were examined for an intervention to increase adherence.[112] Third, the sample and medications were examined for eligibility. Fourth, potentially eligible studies were assessed to determine whether adequate data were available for effect size calculation. If necessary, additional publication searches or author contacts were used to secure data for effect size calculations. To prevent sample overlap among coded studies and therefore ensure independence of data, author names of each potential study were checked against an author list of previously coded studies, and all potentially related studies were compared side by side.[113] When necessary, corresponding authors were contacted to clarify the uniqueness of sample. Finally, primary studies were examined to determine if the sample was composed entirely of participants with adherence problems.

Data Items and Collection

The coding frame was based on the research team's previous experience conducting meta-analyses.[114,115] Medication adherence-specific content was incorporated using suggestions from medication adherence and meta-analysis experts, examining adherence review articles, and by previewing 50 primary studies for the parent project.[86,115,116] The coding frame included information about study source, study design and methods, participant characteristics, intervention features, plus outcome data and descriptive statistics.[86,114,117] Type of study (e.g., journal article or dissertation), presence and type of funding, and year of distribution were coded as source attributes. Assignment to groups, allocation concealment, type of control group (i.e., attention control or true control), data collector masking, attrition, intention-to-treat analyses, and type of adherence measurement (e.g., electronic medication event monitoring, pharmacy refills, pill counts, or self-report) were coded as methodological features. Participant characteristics that were coded included the mean age and the gender and ethnic composition of the sample populations.

Intervention features coded included dose (i.e., number of sessions and duration of sessions), days over which the intervention was delivered, theoretical basis of intervention, delivery medium (e.g., face-to-face, telephone), and whether the intervention targeted adherence behavior alone or other health behaviors in addition to adherence (e.g., diet, exercise). Specific intervention content was coded including: prompts/cues to administer medications; self-monitoring of medication administration; self-monitoring of disease symptoms; written instructions; rewards for increased adherence; increased communication between providers and patients; providing feedback to participants about their adherence; goal setting about adherence; habit assessment/modification; and problem solving about adherence challenges.

Data coded for effect size determinations included sample sizes, means, measures of variability, and success rates. Whenever multiple reports were available about the same

subjects, all were used to code study information. Two extensively trained research specialists independently coded all data from each study.[114,115] Coders compared all data and discussed discrepancies to achieve 100% agreement.[114] Data collected for effect size calculations were further verified by a doctorally prepared coder.

Summary Measures and Statistical Analysis

A unitless standardized mean difference effect size (*d*) was calculated for each treatment vs. control comparison.[82,84,118,119] This effect size is the difference between treatment and control subjects divided by the pooled standard deviation. A better outcome for treatment than control participants is denoted by a positive effect size. Effect sizes were adjusted for bias, and each effect size was weighted by the inverse of its variance to give more weight to larger samples.[84,120] Externally standardized residuals of effect sizes were examined to detect potential outliers, which were excluded from the calculation of the overall mean difference effect size.[120] Although this review emphasizes treatment vs. control comparisons, effect sizes for treatment group pre-post comparisons and control group pre-post comparisons were additionally calculated.

Clinical and statistical effect size heterogeneity is common in behavior change research.[121] To address heterogeneity in the sample, four strategies were employed. First, a random effects model was used to acknowledge that effect sizes vary due to both subject-level sampling error and study-level sources of error such as variations in methods and participant demographics.[122–125] Second, the conventional heterogeneity statistic *Q* was calculated to test for the presence of heterogeneity,[126] and the index of heterogeneity I^2 was computed to determine the proportion of variation due to heterogeneity.[82,126] Third, moderator analyses were used to explore potential sources of heterogeneity. Finally, findings were interpreted in the context of discovered heterogeneity.

To aid in interpretation, the overall standardized mean difference effect sizes for treatment vs. control comparisons was converted to an original adherence metric.[84] To accomplish this, studies using identical adherence metrics were selected, and the individual reported baseline means and standard deviations were used to calculate a pooled mean and standard deviation of the baseline adherence. Adherence at outcome was calculated by multiplying the pooled baseline standard deviation by the effect size and adding this product to the pooled baseline mean.[84]

To explore whether adherence effect sizes were associated with specific intervention characteristics, exploratory moderator analyses were conducted for treatment vs. control comparisons. Dichotomous moderators were tested with between-group heterogeneity statistics ($Q_{between}$) using a meta-analytic analogue of ANOVA. Continuous moderators were tested by analysis of unstandardized regression slopes using meta-regression.[82]

Risk of Bias Management and Assessment

Efforts were made to minimize the introduction of bias into effect size estimates. Comprehensive searching helped avoid bias related to using easy-to-locate primary research with larger effect sizes.[89,90,96,105] Publication bias was addressed to the extent possible by

including both unpublished and published studies.[93] Small-sample studies, which may be underpowered, were included because meta-analyses do not utilize *p* values for determining effect sizes.[82] Sample size variations were managed by statistically weighting effect sizes so more precise effect sizes from studies with larger sample sizes had proportionately more influence in the calculation of the overall effect size.[82]

To minimize bias related to preferential selection of outcome data when studies reported multiple methods of measuring medication adherence, decisions were made *a priori* regarding which outcomes to use for effect size calculations.[127–129] To address design bias, effect sizes for treatment vs. control comparisons were analyzed separately from those for treatment group pre-post comparisons. Outliers detected by examination of externally standardized residuals of effect sizes were excluded from the calculation of overall effect sizes.

To determine if publication bias was present, funnel plots of study effect size vs. sampling variance were constructed.[89,93,130] Plots were visually assessed for asymmetry suggestive of an association between effect size and variance.[89] Begg's test using Kendall's method was conducted to determine whether associations between effect size and variance were greater than might be expected due to chance.[89]

To explore potential bias related to subjects' mere participation in a trial, control group pre-post comparison effect sizes were calculated. To investigate risks of bias related to study design, moderator analyses of potential associations between methodological features and effect sizes were conducted as a form of sensitivity analysis.[81,127] Indicators of methodological strength in treatment vs. control comparisons such as allocation concealment, random assignment of participants, control group management, data collector masking, and intention-to-treat analyses were analyzed as dichotomous moderators, whereas sample size and attrition were analyzed as continuous moderators.[81] Risk of bias related to the technique used to measure adherence was also assessed by dichotomous moderator analysis.

Quality rating scales were not used to weight effect sizes because of problems with the scales.[88,126,127,131–134] The scales have questionable validity, and they don't adequately distinguish report from study design quality. Quality scales combine distinct aspects of quality and methodology into a single score that might obscure important differences among studies. Different aspects of quality may influence effect sizes in different ways. Finally, quality scales do not assess the measurement of medication adherence, which is an important methodological variation in this area of science.

Results

Study Selection and Characteristics

Comprehensive search strategies located 39,358 potentially eligible reports. The flow of these studies through the screening and selection process is depicted in Figure 1. From these citations, 53 reports of studies were identified that specifically targeted subjects with adherence problems.[9–61] The eligible primary studies involved 8,423 individual participants.

Forty of these reports, which involved 8,017 participants, were included in the meta-analytic sample for treatment vs. control comparisons. One study contributed two treatment groups compared to a single control group for a total of 41 comparisons in the meta-analytic sample. The pre-post treatment group meta-analytic sample consisted of 38 comparisons found in 37 reports involving 1,265 participants. The pre-post control sample consisted of 24 comparisons involving 842 participants.

The majority of studies were published since the year 2000. Forty-five reports were published in 2000 or later; five were published prior to 1990. Most reports were published journal articles ($s = 43$) (s indicates the number of reports; k denotes the number of comparisons). The sample included nine dissertations and one unpublished report.

Descriptive statistics for all the primary studies included in any meta-analysis are shown in Table 1. The median study sample size was 42 participants. The median of mean age of participants was 53 years. Women were well-represented in samples. In the studies reporting race/ethnicity of subjects, a median of 70% of participants were non-Caucasian. Median attrition rates were modest at 0.8%. All further results are about the treatment vs. control group comparisons, unless otherwise specified.

Information about individual primary studies reporting treatment vs. control group outcomes is shown in Table 2. Thirty-two studies were conducted in the United States and three in Canada. The other studies were conducted in Australia, Hong Kong, Ireland, Netherlands, Switzerland, and the United Kingdom. Twenty comparisons reported specific criteria for determining subjects' eligibility in relation to their adherence. The most common inclusion criterion was whether patients' adherence fell below a threshold value of 80% ($k = 9$). Only eight studies reported the number of prescribed medications subjects were taking. The most common chronic diseases targeted by primary studies included HIV ($k = 16$) and hypertension ($k = 10$). Several studies possessed mixed samples of subjects having different diseases.

Overall Effects of Interventions on Adherence Outcomes

Overall adherence effect sizes are presented in Table 3. For treatment vs. control comparisons, the overall standardized mean difference effect size for was 0.301. (Analysis of treatment vs. control effect size residuals revealed one outlier, and that effect size was excluded from estimation of the overall effect size. The overall mean effect size with the outlier included was 0.423). The effect size represents the degree of difference between treatment and control groups. The 0.301 effect size is consistent with mean adherence rates at outcome of 65% for treatment subjects and 57% for control subjects.

The overall mean effect size for treatment group pre- vs. post-intervention comparisons was 0.533 (mean effect size with two outliers included was 0.618). By contrast, the control group pre- vs. post-intervention adherence effect size was 0.011, which was not significantly different from zero. Chisquared tests of the heterogeneity statistic Q indicated significant between-studies variation for all three effect size estimates.

Moderator Analyses of Study and Sample Characteristics

Study attributes of publication status and fiscal support were investigated as dichotomous moderators (Table 4), and the year of dissemination was investigated as a continuous moderator (Table 5). Continuous moderator analysis was also conducted to examine the influence on effect size of participant age, percentage of women, and the proportion individuals belonging to underrepresented ethnic/racial groups (Table 5). Although published studies tended to have larger effect sizes than unpublished investigations (0.346 vs. 0.097), this difference did not achieve statistical significance. Effect size was also not related to whether studies received grant or other financial support. Studies that were conducted more recently had slightly smaller effect sizes than older studies (Table 5). No association was found between effect size and any of the three participant demographic variables analyzed (Table 5).

Because certain interventions might be more effective for some disease conditions than others, such as due to the nature and complexity of the medication regimen, exploratory analysis was conducted to determine effect sizes for studies focusing on specific diseases. The two most frequent disease conditions in the meta-analysis sample were hypertension and HIV infection. Similar effect sizes were found for studies composed entirely of hypertensive subjects ($d = 0.307$, SE = 0.152, $p = .044$) and subjects with HIV ($d = 0.303$, SE = 0.093, $p < .001$). Other specific health problems were too infrequently reported to assess their potential as moderators of effect size.

An important potential moderator of effect size was the threshold adherence level used to determine subject eligibility. However, analysis of this moderator was precluded by a lack of variation in the sample; 14 of the 20 studies reporting an adherence inclusion criterion used <80–90% adherence for determination of eligibility.

Study Design Moderators and Risks of Bias

Several potential risks of bias related to study design attributes were identified in the meta-analysis sample: nonrandom assignment of subjects to treatment groups, nonconcealment of subject allocation, comparison group bias (attention control vs. true control), nonmasking of data collectors, on-treatment rather than intent-to-treat analysis, subject attrition, and small sample size. With the exception of study sample size, no evidence was found linking effect size to the design features analyzed. Treatment fidelity was not analyzed as a potential moderator because it was only reported by one primary study.

The method used to measure medication adherence was also investigated as a potential moderator of effect size (Table 4). Researchers used varied methods to measure adherence, including pill counts, electronic event monitoring systems, pharmacy refill data, and self-report questionnaires. The largest effect sizes were reported for studies using pill counts (0.636) and electronic event monitoring systems (0.449). Effect sizes were significantly larger for studies with electronic monitoring systems than for studies employing other types of adherence measures (0.449 vs. 0.227, $p = .044$). Studies using pharmacy refills to measure adherence reported significantly smaller effect sizes than studies using other methods (0.112 vs. 0.358, $p = .026$). Effect sizes for studies using self-report instruments to assess adherence

were smaller than for studies using other methods (0.198 vs. 0.357), but this difference was not statistically significant.

Funnel plot analysis of treatment vs. control comparisons revealed evidence of possible publication bias that was confirmed with Begg's test ($p = .02$). Publication bias was also detected for treatment group pre-post comparisons and confirmed by a statistically significant Begg's test ($p = .03$). The presence of publication bias suggested studies with small or negative effect sizes were not available for inclusion. In contrast, control group baseline vs. outcome effect sizes showed no evidence of publication bias.

Moderator Analyses of Intervention Characteristics

The results of moderator analyses to determine the impact of intervention characteristics on effect size are shown in Table 6. Interventions were significantly more effective if they were delivered face-to-face than if they were delivered through a medium such as telephone or email (0.411 vs. 0.182, $p = .050$). Effect size was not significantly impacted by whether medication adherence interventions were delivered alone or in conjunction with other health behaviors (0.318 vs. 0.282, $p = 0.752$).

Whether theory-based interventions were more effective in increasing adherence could be assessed only for studies employing Motivational Interviewing and Social Cognitive Theory. No other theories were sufficiently represented in the sample to permit a moderator analysis. Effect sizes were lower for interventions using Motivational Interviewing theory/approaches compared to those that did not (0.186 vs. 0.336). Likewise, effect sizes were lower for interventions based on the Social Cognitive Theory than interventions that were not (0.086 vs. 0.356). Neither of these differences achieved statistical significance, owing in part to the small number of studies in the sample that used these theoretical approaches; only nine studies employed Motivational Interviewing and only six studies were grounded in Social Cognitive Theory.

With regard to intervention components that required patients to make specific changes in their behaviors, studies that employed prompts or cues for taking medications had larger effect sizes than studies that did not (0.497 vs. 0.234, $p = .034$). Typical prompts might include cell phone alarm reminders, locating medications in a particular location to cue medication taking such as on the kitchen table for medication to be consumed with meals, or placing reminders in strategic locations such as a note on the bathroom mirror. Habit-focused interventions in which participants' daily habits were linked to taking medications were also effective in increasing medication adherence relative to interventions lacking this component (0.574 vs. 0.222, $p = .007$). Interventions directing participants to set medication adherence goals were not significantly more effective than those lacking a goal-setting component (0.121 vs. 0.363, $p = .082$).

Other intervention components that had no moderating influence on effect size included helping patients manage medication side effects, improving provider patient communication, providing rewards for adherence, and giving patients feedback on their adherence levels.

Discussion

This project was the first comprehensive review and meta-analysis of interventions specifically directed at individuals who have problems with medication adherence. For treatment vs. control comparisons, the statistically significant overall mean effect size of 0.301 documented that interventions do improve medication-taking behaviors in patients with adherence challenges. Although the magnitude of the effect was relatively modest, it was nevertheless comparable to the effects found in previous meta-analyses of medication adherence interventions conducted in general populations (d = 0.18–0.37).[64,65] Effects were also comparable to those found in meta-analysis of interventions directed at targeted populations of underrepresented racial/ethnic groups (d = 0.211)[135] and older adults (d = 0.33).[79]

Whether any given improvement in medication adherence translates into clinical improvements is difficult to assess because the level of adherence necessary to achieve therapeutic goals likely varies across diseases and among the medications used to treat any specific condition.[136] In some situations, even a modest increase in adherence may be sufficient to realize a therapeutic effect, whereas in others, very high levels of adherence must be achieved.

Although participants with adherence problems may have more to gain in health benefits from improved adherence, it may be more difficult to induce behavior change in these individuals compared to those having fairly high adherence at baseline. It is plausible that individuals who have a history of adherence problems may lack confidence in their ability to become adherent. The overall modest effect size may reflect the inherent difficulty in changing adherence behaviors. Alternatively, it may indicate that, on average, the interventions were not adequately addressing the underlying reasons for participants' nonadherence. A better understanding of patients' past and current problems surrounding adherence could lead to increased intervention impact.

Analysis of Q statistics documented considerable heterogeneity among study effect sizes, indicating that some interventions were more effective than others or that intervention effectiveness might be related to sample characteristics. The exploratory moderator analyses of intervention characteristics provide direction for future research and interventions. Although mediated delivery of interventions may be attractive to increase the numbers of people who may be reached, the findings document that face-to-face delivery is more effective for people with adherence problems. The costs of face-to-face interventions may be less than the costs of nonadherence. The results also suggest that interventions can target multiple health behaviors without adversely affecting adherence outcomes. This is useful information given that clinical improvements can be achieved for some chronic conditions by changing additional health behaviors such as diet and physical activity.

The moderator analyses identified some intriguing intervention characteristics that were strongly associated with improved adherence. Especially effective interventions were those employing prompts or cues for medication-taking, such as signs on refrigerator doors or placing medication containers where meals are eaten. Habit-based interventions that

examined the participants' daily routines and then linked medication administration to those routines were also particularly effective. Unlike many adherence interventions that attempt to change subjects' knowledge, attitudes or beliefs[79], these types of intervention focus on behaviors.

The typical health care provider focus on educating patients about medications may have limited effectiveness because lack of knowledge may not be an underlying reason for poor adherence. Educating patients about medications may still be a necessary component of interventions, but for reasons not directly related to increasing adherence. Patient education may be important for patient safety. Patient education may also help patients make informed decisions about their medications such as when to see their health care provider for potential medication side-effects. People with adherence challenges may not need to be persuaded of the importance of taking their medications but rather may require strategies to help them remember to take them. The relatively greater effectiveness of behavioral interventions compared to cognitive interventions has been demonstrated for other health behaviors.[137–139]

Another possible explanation for the strength of prompt- and habit-based interventions is their greater sustainability relative to education-based interventions. Interventions that focus on educating patients about medications occur once or over a limited period of time, so the impact on behavior may fade once the formal intervention period is completed. In contrast, setting up prompts or linking medication administration to existing habits provides an ongoing intervention.

The results provided no support for interventions that ask participants to self-monitor their disease symptoms or medication-taking behaviors. Interventions that included providing patients strategies to manage medication side effects, giving them feedback about their medication adherence, or having them set goals were also not effective methods for increasing medication adherence. Increased provider communication also was not an effective means of increasing medication adherence in patients with adherence problems. Future research should focus on other strategies and on novel ways of implementing effective strategies.

The findings from these studies did not support the use of Social Cognitive Theory or Motivational Interviewing to increase adherence among adults with adherence problems. This finding should be interpreted considering the implementation of theories in intervention research. Specifically, theories are often incompletely operationalized in interventions. The link between theory constructs and intervention content is in general poorly reported in primary research. Theory-linked medication adherence interventions often include multiple components, some of which may not be based on specific theories. Also, theory-linked intervention studies rarely measure mediating constructs, such as self-efficacy, that would provide information about change in theory constructs.

The moderator analyses revealed that intervention effectiveness was not related to sample age, sex, or racial/ethnic composition. Future research that tests interventions specifically designed for certain populations, such as adults from racially and ethnically

underrepresented groups, may be useful to determine if these tailored interventions are more effective than standard interventions. Intervention effectiveness may be related to regimen complexity. Unfortunately, very few studies reported the number of medications patients were taking or other attributes of regimen complexity. Intervention effectiveness might also vary across health conditions. Future meta-analyses could compare intervention effectiveness across disease health conditions. This analysis found no evidence for a Hawthorne effect in which control subjects improve adherence by virtue of being enrolled in a trial, as has been reported in some primary investigations.[15]

Primary study investigators rarely reported whether participants' lack of adherence was intentional or not. Very different kinds of interventions are necessary for patients who deliberately do not take medications.[140] Future research should specify whether nonadherence was intentional or unintentional.

Risks of methodological bias were common in these studies.[81] Although there was no significant association between most methodological attributes and effect sizes, the results nevertheless should be interpreted in the context of these methodological limitations. Some methodological difficulties, such as treatment integrity problems, were rarely addressed in primary studies.

Moderator analyses of the methods used to measure medication adherence suggested electronic event monitoring systems and pill counts may have better sensitivity to detect differences in adherence following interventions than other methods. Self-report measures are less expensive to administer but may lack accuracy and sensitivity. The most accurate methods for adherence measurement remain controversial.[141,142]

This study has limitations inherent to all meta-analysis research and specific to this project. Despite comprehensive searching, some eligible studies may have been missed. It is possible some potentially eligible studies were not included because the authors did not report that subjects were recruited because of adherence problems. The results should also be interpreted in the context of discovered publication bias.

The findings are limited to studies that targeted participants with adherence challenges. Other kinds of interventions may be more effective for patients without documented adherence challenges, such as patients starting new medication regimens. All of the moderator analyses should be considered exploratory and hypothesis generating. Those analyses performed with limited numbers of comparisons should be interpreted with particular caution.

Some potentially interesting variables were too infrequently reported to permit moderator analysis. For example, the number of medications patients were taking was rarely reported, so it was not possible to assess whether effectiveness of interventions was related to medication burden. Intervention effectiveness might be related to disease condition and should be explored in future research. Interventions may be differentially effective for subjects with intentional nonadherence compared to those with unintentional nonadherence. Likewise, specific intervention content is necessary for subjects with cognitive impairment, and the cognitive status of subjects is rarely reported in primary studies. Increased reporting

of study details such as the number of medications prescribed to subjects would permit more complete analyses of moderators of intervention effectiveness.

Several gaps in knowledge were identified during this systematic review and meta-analysis. The relationship between effect size and regimen complexity needs to be further explored. More research is needed to test the effectiveness of newer delivery technologies such as text messaging and various social media platforms. Studies are necessary to compare the effectiveness of different intervention strategies among subjects who possess particular characteristics, such as similar health conditions. Another area that has been inadequately investigated is identifying which interventions are most effective when nonadherence is intentional vs. unintentional. Research directly comparing behavior-focused interventions to cognitively-focused interventions would clarify to what extent each component contributes to changing adherence behaviors.

Future investigations should fully implement theoretical frameworks and provide explicit information about intervention content linked with theories to allow for a robust assessment of the effectiveness of theory-linked interventions. Because subjects' level of adherence at study entry can potentially influence effect size, more emphasis should be placed by authors on analyzing and reporting potential links between baseline adherence and intervention effectiveness. Finally, greater emphasis by investigators to design studies so as to minimize the risk of bias would enhance confidence in primary study findings.

Conclusion

Inadequate medication adherence contributes substantially to patient morbidity and mortality. Nonadherent patients have a significantly higher risk of hospitalization, often resulting in increased health care costs. This comprehensive systematic review and meta-analysis documented that interventions can result in modest but statistically significant improvements in medication-taking by patients with a history of adherence problems. The findings support face-to-face interventions for patients with adherence difficulties and behavioral interventions such as linking medication administration with existing habits or using cues for medication administration may be most effective in this population.

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- We meta-analyzed adherence interventions among adults with adherence problems.
- The overall standardized mean difference effect size was 0.301.
- Interventions that included prompts to take medications were effective.
- Interventions that linked medication to daily habits were effective.

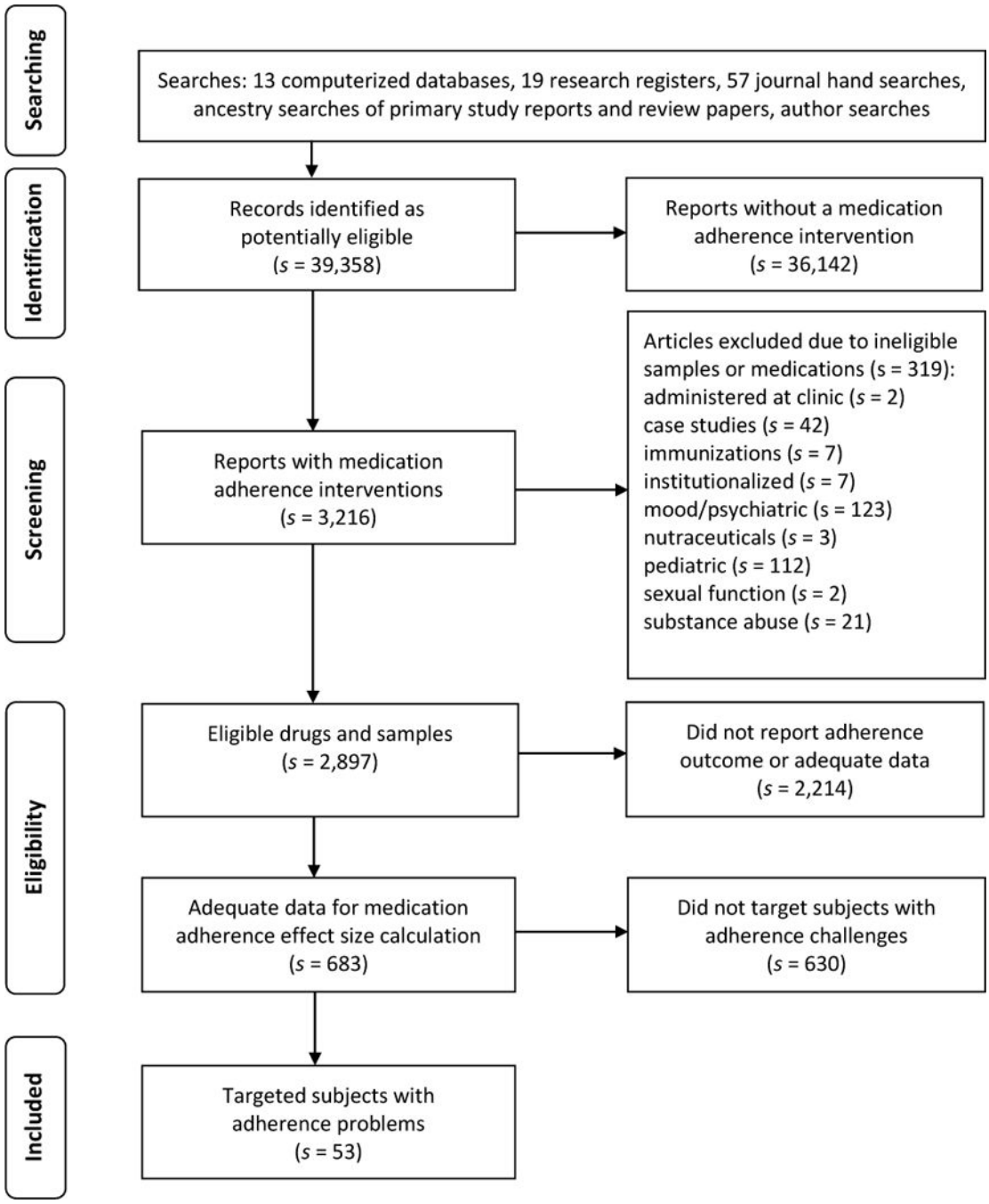

Figure 1.

Flow of potentially eligible studies through review process

Note: *s* indicates the number of research reports

Table 1

Descriptive statistics for primary studies Included in medication adherence meta-analyses

Characteristic	*k*	*Min*	Q_1	*Mdn*	Q_3	*Max*
Total post – test sample size per study	53	5	16	42	91	2,032
Percentage attrition	36	0	0	0.8	13.2	67.7
Percentage female	50	0	18.2	42.05	56.18	100
Percentage non-Caucasian subjects	38	5	40	70	92.5	100
Mean age (years)	49	26.3	44.08	52.9	60.5	77.76
Percent adherence cutoff criterion for inclusion	27	<50	<80	<80	<90	<100

Note: Includes studies that contributed to primary analyses at least one effect size for any type of comparison.

k denotes number of comparisons providing data on characteristic. Q_1=first quartile, Q_3=third quartile.

Table 2

Individual primary study information for treatment vs. control comparisons

Study & Location	Sample	Methods	Intervention	Effect Size
Alhalaiqa et al., 2012[9] Great Britain	*N*: 136 *Mean meds:* 3.3 *Health:* 100% HTN *% female:* 53.7 *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized*: Yes *Allocation concealed:* Yes *Blinded:* Yes *% Attrition:* 0 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Pill counts	*Theory:* NA *Interventionist:* NA *Content:* Drug education, problem solving, thought restructuring *Target:* Medication adherence (MA) only *Delivery:* Face-to-face *Dose:* 7 sessions, 20 min each	3.293
Austin, 1986[11] United States	*N*: 30 *Mean meds:* 3.1 *Health:* 100% HTN, 30% diabetes, 13% cardiac, 10% kidney disease, 3% gallbladder disease, 10% stroke, 17% other *% female:* 57 *% non-Caucasian:* 100 *% MA criterion:* 80	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* No *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory:* Social Cognitive Theory *Interventionist:* Registered nurse *Content:* Improve self-management skills, self-monitoring of MA and BP, feedback about MA and BP, habit linking, rewards, social support *Target:* MA and additional health behaviors *Delivery:* Face-to-face *Dose:* 3 sessions, 45 min each	0.277
Burrelle, 1986[13] United States	*N*: 16 *Mean meds:* 5.94 *Health:* 100% HTN *% female:* 75 *% non-Caucasian:* 75 *% MA criterion:* NA	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Pill counts	*Theory:* NA *Interventionist:* Nurse, pharmacist, social worker *Content*: Medication-taking calendar, disease/drug education, pill boxes *Target:* MA only *Delivery:* Face-to-face, written materials *Dose:* 1 session	2.303
Cook et al., 2010[14] United States	*N:* 10 *Mean meds:* NA *Health:* 100% glaucoma *% female:* 42 *% non-Caucasian:* 58.3 *% MA criterion:* 80	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 16.7 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory*: Motivational interviewing *Interventionist:* Person other than *HCP* *Content:* Motivational interviewing, barriers management, problem solving education/counseling *Target:* MA only materials, drug *Delivery:* Face-to-face, telephone, written *Dose:* 3 in-person sessions, 30–45 min each, 3 telephone contacts, 5–10 min each	1.295
De Geest et al., 2006[15] Switzerland	*N:* 13 *Mean meds:* NA *Health:* 100% kidney transplant *% female:* 21.4 *% non-Caucasian:* NA *% MA criterion:* 98	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* No *% Attrition:* 28 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* NA *Interventionist:* Nurse *Content:* Drug education, monitoring MA by device with feedback about MA, goal setting, problem solving, habit linking, patient empowerment, self-efficacy enhancement, self-management education *Target:* MA only *Delivery:* Face-to-face, telephone *Dose:* 4 sessions	0.047
Freedman, 2007[17] United States	*N*: 16 *Mean meds:* NA *Health:* 100% HIV *% female:* 81.3 *% non-Caucasian:* 75 *% MA criterion:* NA	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory*: NA *Interventionist:* NA *Content:* Disease/drug education, improve patient communication with provider, goal setting, problem solving, stress management, investigator-formed support group *Target:* MA and additional health behaviors *Delivery:* Face-to-face, written materials *Dose:* 8 sessions, 90 min each	0.386
Gamble et al., 2011[18] Ireland	*N*: 18 *Mean meds:* NA	*Randomized:* Yes *Allocation concealed:* NA	*Theory*: Cognitive-behavioral Theory, motivational interviewing,	1.431

Study & Location	Sample	Methods	Intervention	Effect Size
	Health: 100% asthma *% female:* 85 *% non-Caucasian:* NA *% MA criterion:* 50	*Blinded:* NA *% Attrition:* 10 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Prescription refills	Transtheoretical Stages of Change Model *Interventionist:* Nurse *Content:* Motivational interviewing, behavior modification, disease/drug education *Target:* MA only *Delivery:* Face-to-face *Dose:* 8 sessions	
Glanz et al., 2012[19] United States	*N:* 246 *Mean meds:* NA *Health:* 100% glaucoma *% female:* 37.5 *% non-Caucasian:* 90.7 *% MA criterion:* NA	*Randomized:* No *Allocation concealed:* No *Blinded:* No *% Attrition:* 5 *ITT:* NA *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Prescription refills	*Theory*: NA *Interventionist:* Automated delivery *Content:* Disease/drug education, barriers management, problem solving *Target:* MA only *Delivery:* Telephone, mail *Dose:* 12 phone calls, 12 mailings	−0.031
Harper, 1984[21] United States	*N*: 59 *Mean meds:* 5.25 *Health:* 100% HTN, 70% osteoarthritis, 55% cardiac disease, 45% diabetes *% female:* 100 *% non-Caucasian:* 100 *% MA criterion:* NA	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 1.7 *ITT:* NA *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Pill counts	*Theory*: Orem's Self-care Theory, General System Theory *Interventionist:* Nurse *Content:* Drug education, rewards, habit linking, cues/prompts, special labelling, side effects management *Target:* MA and additional health behaviors *Delivery:* Face-to-face *Dose:* 4 sessions	1.047
Haynes et al., 1976[22] Canada	*N*: 38 *Mean meds:* NA *Health:* 100% HTN, mean 3.4 other chronic illnesses *% female:* 0 *% non-Caucasian:* NA *% MA criterion:* 80	*Randomized*: Yes *Allocation concealed:* No *Blinded:* Yes *% Attrition:* 2.6 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Pill count	*Theory:* NA *Interventionist:* Person other than HCP *Content:* Drug reminder chart, habit linking, self-monitoring of medication taking, symptoms, cues/prompts *Target:* MA and additional health behaviors *Delivery:* Face-to-face *Dose:* 13 sessions, 30 min each	0.569
Kalichman et al., 2011[25] United States	*N:* 39 *Mean meds:* NA *Health:* 100% HIV *% female:* 35.0 *% non-Caucasian:* 92.5 *% MA criterion:* 95	*Randomized*: Yes *Allocation concealed:* Yes *Blinded:* Yes *% Attrition:* 2.5 *ITT:* Yes *Comparison:* Attention control *Tx fidelity:* 99% *MA Measure:* Self-report	*Theory*: Self-regulation Theory, Self-management Theory *Interventionist:* Person other than HCP *Content:* Improve self-management skills, barriers management, goal setting, problem solving, pill boxes, cues/prompts, habit linking, disease/drug education, drug counseling, diary to self-monitor MA, feedback about MA *Target:* MA only *Delivery:* Face-to-face, telephone *Dose:* 5 sessions	0.460
Kogos, 2004[26] United States	*N*: 30 *Mean meds:* NA *Health:* various unspecified chronic illnesses *% female:* 0 *% non-Caucasian:* 27.0 *% MA criterion:* NA	*Randomized*: No *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* Attention control *Tx fidelity:* NA *MA Measure:* Pill counts	*Theory*: Health Belief Model *Interventionist:* Person other than HCP *Content:* Barriers management, contracting, goal setting, problem solving, self-monitor medication taking, self-management education, intervention delivered in both group and individual contexts *Target:* MA and additional health behaviors *Delivery:* Face-to-face, written materials *Dose:* 5 sessions, 60 min each	−0.312
Levensky, 2006[29] United States	*N*: 53 *Mean meds:* NA *Health:* 100% HIV *% female:* 15 *% non-Caucasian:* 22 *% MA criterion:* 90	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 1.9 *ITT:* Yes *Comparison:* True control	*Theory*: Motivational interviewing, Theory, Problem-solving Theory Social Cognitive *Interventionist:* Nurse, unspecified other HCP, person other than HCP	0.393

Study & Location	Sample	Methods	Intervention	Effect Size
		Tx fidelity: NA *MA Measure:* Pill counts	*Content:* Motivational interviewing, behavior modification, self-efficacy enhancement, contracting/commitment to increased MA, barriers management, problem solving, goal setting, rewards, pill boxes, habit linking, diary o self-monitor MA, disease/drug education, drug counseling, simplifying medication regimen, side effects management, improve patient communication with health care provider, teach provider skills to improve communication with patient and promote MA; improve integration of health care *Target:* MA and additional health behaviors *Delivery:* Face-to-face, telephone, written materials *Dose:* 3–4 sessions depending on patient needs	
Matteson, 2011[31] United States	*N*: 5 *Mean meds:* NA *Health:* 100% inflammatory bowel disease *% female:* 42.1 *% non-Caucasian:* NA *% MA criterion:* 85	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* Attention control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory*: Continuous Self-improvement Framework *Interventionist:* Advanced practice nurse *Content:* Behavior modification, personal system change, habit linking, feedback about MA, drug education *Target:* MA only *Delivery:* Face-to-face *Dose:* 1 session averaging 32.5 min	1.821
McPherson-Baker et al., 2000[32] United States	*N*: 42 *Mean meds:* NA *Health:* 100% HIV *% female:* 0 *% non-Caucasian:* 88.1 *% MA criterion:* NA	*Randomized*: No *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Prescription refills	*Theory*: Health BeliefModel *Interventionist:* Pharmacist *Content:* Disease/drug education, barriers management, problem solving, behavior rehearsal, modeling medication-taking behaviors, improve self-management skills *Target:* MA only *Delivery:* Face-to-face *Dose:* 5 sessions, 20–25 min each	1.475
Migneault et al., 2012[33] United States	*N*: 337 *Mean meds:* 5.1 *Health:* 100% HTN, 37% diabetes, 7.7% history of stroke *% female:* 70.4 *% non-Caucasian:* 100 *% MA criterion:* NA	*Randomized*: Yes *Allocation concealed:* Yes *Blinded:* No *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory*: Motivational interviewing, Social Cognitive Theory, Transtheoretical Stages of Change Model *Interventionist:* Automated delivery *Content:* Motivational interviewing, drug education/counseling, self-monitoring of BP, feedback about MA *Target:* MA and additional health behaviors *Delivery:* Telephone *Dose:* 8 contacts	0.233
Mitchell, 1993[34] United States	*N*: 109 *Mean meds:* NA *Health:* 100% HTN *% female:* 61 *% non-Caucasian:* 5 *% MA criterion:* NA	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* NA *% Attrition:* NA *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* self-report	*Theory*: Health Promotion Model, Social Cognitive Theory *Interventionist:* Advanced practice nurse *Content:* Self-efficacy enhancement, value clarification, goal setting, problem solving, barriers management, monitoring MA by device with feedback about MA *Target:* MA and additional health behaviors *Delivery:* Face-to-face, telephone *Dose:* 4 sessions	−0.315
Moitra et al., 2011[35] United States	*N*: 10 *Mean meds:* NA *Health:* 100% HIV *% female:* 7.7	*Randomized:* yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 67.7	*Theory*: Acceptance and Commitment Theory *Interventionist:* Person other than HCP	0

Study & Location	Sample	Methods	Intervention	Effect Size
	% non-Caucasian: 84.6 *% MA criterion:* NA	*ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Content:* Acceptance and commitment therapy, goal setting, self-re-evaluation, disease/drug education, drug counseling, investigator-formed support group *Target:* MA only *Delivery:* Face-to-face, written materials *Dose:* 4 sessions, 60 min each	
Murphy et al., 2002[37] United States	*N*: 33 *Mean meds:* NA *Health:* 100% HIV *% female:* 12.0 *% non-Caucasian:* 64 *% MA criterion:* NA	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 36.5 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory:* Cognitive-behavioral Theory, Social Cognitive Theory *Interventionist:* Nurse, person other than HCP *Content:* Behavior and cognitive modification, disease/drug education, cues/prompts, barriers management, goal setting, problem solving, relapse prevention, improve patient ability to communicate with provider, social support via experimenter-formed group *Target:* MA and exercise *Delivery:* Face-to-face, written materials *Dose:* 5 sessions	0.795
Murphy et al., 2007[38] United States	*N:* 141 *Mean meds:* NA *Health:* 100% HIV *% female:* 17.6 *% non-Caucasian:* 70.4 *% MA criterion: NA*	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* NA *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* Cognitive-behavioral Theory, Social Cognitive Theory *Interventionist:* Nurse, person other than HCP *Content:* Behavior and cognitive modification; disease education, cues/prompts, barriers management, problem solving, rewards, diary to self-monitor MA, improve patient ability to communicate with provider, social support via investigator-formed group *Target:* MA only *Delivery:* Face-to-face *Dose:* 5 sessions, 90 min + 4 sessions, 60 min	0.249
Nietert et al., 2009[39] United States	*N*: 2,032 *Mean meds:* NA *Health:* 56.4% HTN or heart failure, 11.3% diabetes, 17.4% hyperlipidemia, 14.2% depression *% female:* NA *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* No *% Attrition:* 0 *ITT:* Yes *Comparison:* NA *Tx fidelity:* NA *MA Measure:* Prescription refills	*Theory*: NA *Interventionist:* Pharmacist, person other than HCP *Content:* Drug education, telephone prompts to remind patient to refill prescriptions, barriers management, problem solving *Target:* MA only *Delivery:* Telephone *Dose:* NA	−0.012
Nietert et al., 2009[39] United States	*N*: 2,030 *Mean meds:* NA *Health:* 56% HTN or heart failure, 11.3% diabetes, 17.3% hyperlipidemia, 14.9% depression *% female:* NA *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* No *% Attrition:* 0 *ITT:* Yes *Comparison:* NA *Tx fidelity:* NA *MA Measure:* Prescription refills	*Theory:* NA *Interventionist:* None *Content:* Patient prescription refill information faxed to physician along with written prompts for physicians to encourage patients' medication persistence *Target:* MA only *Delivery:* FAX sent to patients' physicians *Dose:* NA	−0.061
Okeke et al., 2009[41] United States	*N*: 66 *Mean meds:* NA *Health:* 100% glaucoma *% female:* 45.5 *% non-Caucasian:* 62.1 *% MA criterion:* 75	*Randomized*: Yes *Allocation concealed:* Yes *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory*: NA *Interventionist:* NA *Content:* Disease/drug education, barriers self-management, problem solving, cues/prompts, habit linking, drug reminder chart, diary to monitor MA, social support *Target:* MA only *Delivery:* Face-to-face, telephone, video	0.844

Study & Location	Sample	Methods	Intervention	Effect Size
			Dose: 10 sessions	
Oser, 2008[42] United States	*N*: 22 *Mean meds:* NA *Health:* 100% HTN *% female:* 0 *% non-Caucasian:* 54.5 *% MA criterion:* 80	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Pill counts	*Theory*: Cognitive-behavioral Theory, motivational interviewing *Interventionist:* NA *Content:* Motivational interviewing, behavior modification, decisional balance activities, thought restructuring, self-re-evaluation, barriers management, problem solving, goal setting, habit linking, rewards, diary to self-monitor MA, relapse prevention, improve patient communication with provider, drug education, social support *Target:* MA and additional health behaviors *Delivery:* Written materials *Dose:* 1 contact	0.405
Ramirez Canada-Garcia & Cote, 2012[43]	*N*: 44 *Mean meds:* NA *Health:* 100% HIV *% female:* 9.8 *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* NA *% Attrition:* 13.7 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory*: Social Cognitive Theory, Persuasion Theory *Interventionist:* Nurse *Content:* Self-efficacy enhancement, thought restructuring, problem solving, goal setting, improve patient communication with provider, social support, drug education, side effects management *Target:* MA only *Delivery:* Face-to-face, written materials *Dose:* 4 sessions, 60 min each	−0.411
Remien et al., 2005[44] United States	*N:* 115 *Mean meds:* NA *Health:* 100% HIV *% female:* 46 *% non-Caucasian:* 86 *% MA criterion:* 80	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* Yes *% Attrition:* 0 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* Ewart's Social Action Theory *Interventionist:* Advanced practice nurse *Content:* Cognitive modification, behavior modification, disease/drug education, barriers management, problem solving, social support *Target:* MA and additional health behaviors *Delivery:* Face-to-face *Dose:* 4 sessions, 45–60 min each	0.184
Rosen et al., 2007[45] United States	*N*: 56 *Mean meds:* NA *Health:* 100% HIV *% female:* 41 *% non-Caucasian:* 59 *% MA criterion:* 80	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* NA *Interventionist:* Person other than HCP *Content:* Monitoring MA by device with feedback about MA, payment for taking medications, cues/prompts *Target:* MA and additional health behaviors *Delivery:* Face-to-face *Dose:* 16 sessions	0.507
Ruppar, 2010[46] United States	*N*: 15 *Mean meds: NA* *Health: 100% HTN* *% female:* 73 *% non-Caucasian:* 33 *% MA criterion:* 85	*Randomized*: Yes *Allocation concealed:* Yes *Blinded:* No *% Attrition:* 0 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory*: Self-Regulation Theory *Interventionist:* Advanced practice nurse *Content:* Disease/drug education, habit linking, BP self-monitoring, MA self-monitoring using electronic device, feedback about BP and MA, goal setting, pill boxes, special medication labels *Target:* MA only *Delivery:* Face-to-face *Dose:* 5 sessions	1.039
Russell et al., 2010[47] United States	*N:* 13 *Mean meds:* NA *Health:* 100% kidney transplant *% female:* 53 *% non-Caucasian:* NA	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 13.3 *ITT:* No	*Theory:* Continuous System Improvement *Interventionist:* Advanced practice nurse *Content:* Personal system change; habit linking, goal setting, problem solving,	1.3682

Study & Location	Sample	Methods	Intervention	Effect Size
	% MA criterion: 85	*Comparison:* Attention control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	monitoring MA by device with feedback about MA *Target:* MA only *Delivery:* Face-to-face, written materials *Dose:* 6 sessions	
Safren et al., 2001[50] United States	*N*: 53 *Mean meds:* NA *Health:* 100% HIV *% female:* 13 *% non-Caucasian:* 49 *% MA criterion:* 100	*Randomized:* No *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 5.4 *ITT:* No *Comparison:* True control *Tx fidelity: NA* *MA Measure:* Self-report	*Theory*: Cognitive-behavioral Theory, motivational interviewing, Problem solving Theory *Interventionist:* Person other than HCP *Content*: Motivational interviewing, cognitive and behavior modification, disease/drug education, habit linking, cues/prompts, pill boxes improved patient communication and shared decision-making with health care provider, problem solving, thought restructuring, guided imagery, side effects management *Target:* MA only *Delivery:* Face-to-face, telephone, videotape *Dose:* 2 sessions	0.060
Safren et al., 2003[48] United States	*N*: 44 *Mean meds:* NA *Health:* 100% HIV *% female:* 20 *% non-Caucasian:* 47 *% MA criterion:* 90	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* NA *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* NA *Interventionist:* NA *Content:* Pager system for medication taking reminders *Target:* MA only *Delivery:* Telephone *Dose:* NA	0.470
Sorensen et al., 2007[51] United States	*N*: 66 *Mean meds:* NA *Health:* 100% HIV *% female:* 41 *% non-Caucasian:* 44 *% MA criterion:* 80	*Randomized*: Yes *Allocation concealed:* Yes *Blinded:* NA *% Attrition:* 0 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* Behavioral Modification *Interventionist:* Person other than HCP *Content:* Behavior modification, payment for taking medication *Target:* MA only *Delivery:* NA *Dose:* 24 contacts	0.485
Stewart et al., 2008[52] Australia	*N*: 343 *Mean meds:* NA *Health:* 100% HTN, 73.5% cardiovascular disease, including stroke, cardiac disease, 35.5% diabetes, 34.5% depression *% female:* 48.9 *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized*: No *Allocation concealed:* Yes *Blinded:* NA *% Attrition:* 13.2 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory*: Motivational interviewing *Interventionist:* Pharmacist *Content:* Motivational interviewing, medication review for appropriate prescription, self-monitor of symptoms/ signs with feedback, drug education, pill boxes, cues/prompts to refill prescriptions, health care provider improved skills to enhance patient MA, health care integration *Target*: MA and additional health behaviors *Delivery:* Face-to-face, telephone, text messages, mail, written materials *Dose:* NA	0.122
Taylor, et al., 2003[53] United States	*N*: 69 *Mean meds:* 6 *Health:* 76.8% HTN, 55% hyperlipidemia, 42% diabetes, 14.5% anti-coagulant therapy, 12% osteoarthritis *% female:* 68.1 *% non-Caucasian:* NA *% MA criterion: NA*	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 14.8 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure: Self-report*	*Theory*: NA *Interventionist:* Pharmacist *Content:* Disease/drug education, medication review and reduction in number of prescriptions to increase MA, problem solving, pill boxes, teach skills related to administering medications and self-monitoring of signs *Target:* MA only *Delivery:* Face-to-face, written materials	1.223

Study & Location	Sample	Methods	Intervention	Effect Size
			Dose: Number of sessions determined by frequency of clinic visits, 20 min each	
Van Servellen et al., 2005[55] United States	*N*: 69 *Mean meds:* NA *Health:* 100% HIV *% female:* 9.9 *% non-Caucasian:* 100 *% MA criterion:* NA	*Randomized:* Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 18.8 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	*Theory:* NA *Interventionist:* Advanced practice nurse, person other than HCP *Content:* Disease/drug education, increase health literacy, motivational interviewing, empower patients to improve communication with providers; problem solving, barriers management, stress management, social support *Target:* MA and additional health behaviors *Delivery:* Face-to-face, telephone, videotape, written materials *Dose:* NA	0.074
Vervloet et al., 2012[56] Netherlands	*N:* 104 *Mean meds:* NA *Health:* 100% Type 2 diabetes *% female:* 45.2 *% non-Caucasian:* NA *% MA criterion:* 80	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 12.6 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory:* NA *Interventionist:* Automated delivery *Content:* Real-time electronic monitoring of medication-taking with transmission of short text-message reminders *Target:* MA only *Delivery:* Text messages *Dose:* NA	0.544
Villeneuve et al., 2010[57] Canada	*N*: 225 *Mean meds:* NA *Health:* 100% hyperlipidemia, 64% HTN, 43% diabetes *% female:* 38 *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized:* No *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 0 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Prescription refills	*Theory*: NA *Interventionist:* Physician, pharmacist *Content:* Organizational improvement; improved integration of health care, teach provider skills to improve communication with patient and promote MA, patient/provider concordance, drug education, feedback to patients on symptoms/signs, goal setting *Target:* MA and additional health behaviors *Delivery:* Face-to-face, written materials *Dose:* NA	0.105
Wall, et al., 1995[58] United States	*N*: 25 *Mean meds:* 3.0 *Health:* 100% HIV *% female:* 48 *% non-Caucasian:* 68 *% MA criterion:* NA	*Randomized*: Yes *Allocation concealed:* NA *Blinded:* NA *% Attrition:* 7.4 *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Electronic event monitoring device	*Theory*: NA *Interventionist:* Registered nurse *Content:* Self-administration program with directly observed therapy, distance-to-pharmacy barriers management, charting MA as a clinical parameter, feedback about MA and clinical signs *Target:* MA only *Delivery:* Face-to-face *Dose:* 40 contacts	0.175
Watakakasol, 2010[59] United States	*N*: 42 *Mean meds:* NA *Health:* 100% HIV *% female:* 40.5 *% non-Caucasian:* 7.1 *% MA criterion:* 95	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* Yes *% Attrition:* 0 *ITT:* Yes *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Patient medication administration diary	*Theory*: Motivational interviewing, Transtheoretical Stages of Change Model *Interventionist:* Person other than HCP *Content:* Motivational interviewing, decisional balance and decision-making activities related to MA, problem solving, rewards, intervention targeted to subject's stage of change *Target:* MA only *Delivery:* Telephone *Dose:* 1 session, 60 min	−0.199
Wu et al., 2006[60] Hong Kong, China	*N*: 442 *Mean meds:* 6 *Health:* various unspecified chronic illnesses *% female:* 51	*Randomized:* Yes *Allocation concealed:* Yes *Blinded:* No *% Attrition:* 0 *ITT:* Yes	*Theory*: NA *Interventionist:* Pharmacist *Content:* Drug education, telephone conversations to encourage MA and	0.607

Study & Location	Sample	Methods	Intervention	Effect Size
	% non-Caucasian: NA *% MA criterion:* 80	*Comparison:* True control *Tx fidelity:* NA *MA Measure:* Self-report	self-monitoring of symptoms/side effects *Target:* MA and additional health behaviors *Delivery:* Telephone *Dose:* 7 contacts, 5–10 min each	
Zuckerman et al., 2004[61] United States	*N:* 1,675 *Mean meds:* NA *Health:* 100% coronary artery disease *% female:* NA *% non-Caucasian:* NA *% MA criterion:* NA	*Randomized*: No *Allocation concealed:* NA *Blinded:* NA *% Attrition:* NA *ITT:* No *Comparison:* True control *Tx fidelity:* NA *MA Measure:* Prescription refills	*Theory*: NA *Interventionist:* NA *Content:* Teach physicians skills to enhance patient MA *Target:* MA only *Delivery:* Written materials mailed to patients' physicians *Dose:* NA	0.134

Abbreviations and definitions: BP, blood pressure; HCP, health care provider; HTN, hypertension; MA, medication adherence; NA, not addressed; N, total number of subjects at outcome assessment ; % MA criterion, maximum adherence level for eligibility; Blinded, data collectors masked to group assignment; ITT, intention-to-treat analysis; Tx fidelity, treatment fidelity; Target, intervention focused on MA exclusively or MA plus other health behaviors; Effect size, standardized mean difference effect size.

Table 3

Random effects medication adherence estimates and tests

	k	Effect size	*p* (ES)	95% Confidence interval	Standard error	I^2	*Q*	*p*(*Q*)
Treatment vs. control comparisons[a]	40	0.301	<.001	0.186, 0.415	0.058	68.472	123.701	<.001
Treatment subjects pre-post comparisons[b]	36	0.533	<.001	0.404, 0.663	0.066	70.189	117.403	<.001
Control subjects pre-post comparisons	24	0.011	.861	−0.115, 0.138	0.064	59.535	56.840	<.001

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

[a]One comparison excluded as an outlier. The overall effect size with inclusion of outlier was 0.423 (SE = 0.079, 95% CI: 0.277, 0.587).

[b]Two comparisons excluded as outliers. The overall effect size with inclusion of outliers was 0.618 (SE = 0.084, 95% CI: 0.454, 0.783).

Table 4

Dichotomous moderator analysis of medication adherence effect size: Report and study design characteristics

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Report Moderators					
Publication status				3.244	.072
Published articles	32	0.346	0.066		
Unpublished reports	8	0.097	0.121		
Presence of funding for research				0.024	.878
Funded	31	0.306	0.062		
Unfunded	9	0.274	0.196		
Design Moderators					
Allocation to treatment groups				2.621	.105
Randomization of individual subjects	33	0.360	0.073		
Subjects not individually randomized	7	0.156	0.103		
Allocation concealment				0.424	.515
Allocation concealed	13	0.247	0.103		
Did not report allocation concealed	27	0.329	0.072		
Comparison group				0.414	.520
True control group	36	0.293	0.059		
Attention control group	4	0.557	0.407		
Data collector masking				0.425	.514
Data collectors masked to group assignment	4	0.218	0.131		
Did not report data collectors masked to group assignment	36	0.312	0.063		
Intention-to-treat approach				2.847	.092
Reported intention-to-treat approach	15	0.205	0.077		
Did not report intention-to-treat approach	25	0.404	0.089		
Adherence measured with electronic event monitoring system				4.042	.044

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Electronic event monitoring system data	13	0.449	0.088		
Other measure of adherence	27	0.227	0.066		
Adherence measured with pharmacy refill information				4.954	.026
Pharmacy refill data	7	0.112	0.084		
Other measure of adherence	33	0.358	0.071		
Adherence measured with pill counts by research staff				1.993	.158
Pill count data	6	0.636	0.265		
Other measure of adherence	34	0.253	0.057		
Adherence measured with subjects' self-report				1.673	.196
Self-report data	13	0.198	0.099		
Other measure of adherence	27	0.357	0.073		

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

Table 5

Continuous moderator analysis of medication adherence effect size

Moderator	*k*	Slope	Standard Error	τ^2	Q_{model}	*p* (Slope)
Report Moderator						
Year of publication	40	−0.017	0.005	0.055	10.773	.001
Sample Attribute Moderators						
Age	36	−0.003	0.004	0.080	0.746	.388
Percent women	37	0.002	0.002	0.088	1.379	.240
Percent non-Caucasian adults	27	−0.003	0.002	0.099	2.936	.087
Method Moderators						
Sample size	40	0	0	0.041	33.396	<.001
Attrition proportion	36	0.712	0.462	0.080	2.373	.123

k denotes number of comparisons. *Q* is a conventional heterogeneity statistic. τ^2 is the between-studies variance.

Table 6

Dichotomous moderator analysis of medication adherence effect size: Intervention characteristics

Moderator	*k*	Effect size	Standard error	$Q_{between}$	p ($Q_{between}$)
Intervention delivery medium				3.845	.050
Face to-face	29	0.411	0.093		
Mediated delivery (e.g., telephone, mail)	11	0.182	0.071		
Behaviors targeted with intervention				0.1	.752
Medication adherence exclusively targeted	24	0.318	0.081		
Multiple behaviors including medication adherence	16	0.282	0.091		
Motivational interviewing theory/approach				2.142	.143
Present	9	0.186	0.074		
Absent	31	0.336	0.070		
Social Cognitive Theory				3.590	.058
Present	6	0.086	0.126		
Absent	34	0.356	0.067		
Subjects self-monitoring adherence behavior				0.651	.420
Present	8	0.382	0.105		
Absent	32	0.283	0.065		
Subjects self-monitoring signs of disease				0.943	.331
Present	5	0.213	0.073		
Absent	35	0.309	0.066		
Strategies to manage/reduce medication side effects				0.026	.873
Present	5	0.255	0.265		
Absent	35	0.299	0.060		
Prompts or cues to administer medications				4.481	.034
Present	10	0.497	0.107		
Absent	30	0.234	0.063		

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Rewards or consequences for increased adherence				0.189	.663
Present	6	0.365	0.165		
Absent	34	0.288	0.062		
Habit assessment and linkage for adherence				7.237	.007
Present	12	0.574	0.116		
Absent	28	0.222	0.061		
Adherence goal setting				3.024	.082
Present	13	0.121	0.121		
Absent	27	0.363	0.068		
Improve communication between patients and providers				0.943	.332
Present	8	0.204	0.107		
Absent	32	0.326	0.066		
Feedback to patients about adherence levels				0	.992
Present	10	0.303	0.143		
Absent	30	0.305	0.065		

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