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Meta-analyses of Theory use in Medication Adherence Intervention Research

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Abstract

Objective—This systematic review applied meta-analytic procedures to integrate primary research that examined theory- or model-linked medication adherence interventions.

Methods—Extensive literature searching strategies were used to locate trials testing interventions with medication adherence behavior outcomes measured by electronic event monitoring, pharmacy refills, pill counts, and self-reports. Random-effects model analysis was used to calculate standardized mean difference effect sizes for medication adherence outcomes.

Results—Codable data were extracted from 146 comparisons with 19,348 participants. The most common theories and models were social cognitive theory and motivational interviewing. The overall weighted effect size for all interventions comparing treatment and control participants was 0.294. The effect size for interventions based on single-theories was 0.323 and for multiple-theory interventions was 0.214. Effect sizes for individual theories and models ranged from 0.041 to 0.447. The largest effect sizes were for interventions based on the health belief model (0.477) and adult learning theory (0.443). The smallest effect sizes were for interventions based on PRECEDE (0.041) and self-regulation (0.118).

Conclusion—These findings suggest that theory- and model-linked interventions have a significant but modest effect on medication adherence outcomes.

Keywords

medication adherence; meta-analysis; theory

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INTRODUCTION

Medication adherence (MA) is an essential component for effectively treating many diseases. Nonadherence is a persistent and pervasive yet hidden epidemic with major health and economic consequences.¹⁻⁴ Although pharmacological therapeutics have advanced markedly, knowledge development regarding MA lags, despite 6 decades of research.⁵ Overall, MA is about 50%, 20% to 25% of prescriptions are never filled, 20% of patients take drug holidays after filling prescriptions, and frequent missed doses are common.^{3,6-8} The World Health Organization calls poor adherence a “worldwide problem of striking magnitude.”³

MA refers to the extent to which patient medication-taking behavior is consistent with health care provider recommendations.³ We use ‘medication adherence’, rather than other phrases in the literature, because it is the most widely accepted term.⁹ A previously used phrase, medication compliance, is considered paternalistic.¹⁰

Extensive research has tested interventions to increase MA. The proliferation of intervention trials has led to many attempts to summarize and synthesize extant research. Most previous reviews have not used meta-analysis. Many used restricted inclusion criteria such as diseases, drugs, ethnic/racial groups, geographic location, or publication year. Others focused on specific kinds of interventions such as reducing drug frequency, self-monitoring, packaging, patient-provider interactions, directly observed therapy, paying patients to consume medications, and pictorial aids. Most meta-analyses have synthesized narrow sets of primary research focused on patients with specific diseases;¹¹⁻¹³ patients with certain demographic characteristics such as ethnicity or age;^{14,15} interventionists such as pharmacists, physicians, or nurses;¹⁶⁻¹⁹ and types of interventions such as dosing frequency,²⁰⁻²² reminder systems,²³ and packaging.^{24,25} None of these focused meta-analyses nor the few broader meta-analyses²⁶⁻²⁸ have addressed the theories or models used to develop interventions.

The absence of synthesized information about the MA interventions’ theories or models is an important gap in knowledge. Theory and model constructs can be used to explain causal relationships.²⁹ Health behavior change theories and models provide a foundation for understanding and predicting intervention effectiveness.²⁹ Evidence supporting the efficacy of interventions based on particular theories or models could be especially useful in generalizing findings to other populations.^{30,31} Even evidence that MA interventions linked with some theories and models do not significantly improve MA could enhance development of future interventions based on alternative theories and models. Meta-analysis has been suggested as a useful approach for analyzing health behavior theory- and model-linked intervention research.³²

Review Questions

The project addressed the following research questions: (1) What theories and models have been used to design MA change interventions? (2) To what extent has primary research compared interventions linked with different theories and models? (3) How have researchers

used theory- and model-based potential mediating variables in MA intervention research?
 (4) What are the overall effects of interventions linked with theories and models on MA behavior after interventions?

METHODS

Standard systematic review and meta-analytic methods were used to conduct the project.³³ The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to provide transparent and clear reporting of the project.³⁴ The protocol is available from the corresponding author.

Eligibility Criteria and Primary Research Selection

Primary research with a theory- or model-linked intervention designed to increase MA and an outcome measure of MA behavior among adults was included. Intervention was defined as a planned and systematically applied set of actions, delivered at a specified time and place, and designed to elicit MA behavior change in the intervention's recipients.³⁵

Only primary research that measured MA behavior as an outcome was included. Research that reported clinical outcomes as indicators of MA was not included because the clinical outcomes for most diseases are influenced by factors other than MA. Primary research with adherence measured as dose administration, dose timing, persistence, and the like was included. Primary research with varied adherence measures (eg, pharmacy refills, electronic bottle cap devices) was included. Including different measures is possible because meta-analysis methods convert primary research outcomes to unitless standardized indices.³³ An a priori list of preferred MA measures was used to select adherence outcomes for primary research that reported multiple MA measures: electronic event monitoring medication bottle caps, pharmacy refill data, pill counts, and patient self-reports. Reports were evaluated for adequacy of MA outcome data such as sample size, means, and measures of variability or other data which could be converted to effect sizes using established formulae (eg, t statistic).³⁶ This project did not have access to individual participant information from primary research. Corresponding authors were contacted to secure effect-size data when reports did not provide them.³³

Primary research with varied established theories or models were included if the theory or model had been described in other publications. This project included interventions that were linked to theories as well as those that were linked to models because both are commonly used to develop behavioral interventions. Limiting the project to only interventions that were specifically identified as theory-based would have excluded considerable primary research. Of note is the fact that the distinction between theories and models is often ambiguous in intervention research. Motivational interviewing, PRECEDE-PROCEED, and health literacy are examples of this lack of clarity and some evolving use of terms. Although motivational interviewing was not initially described as a theory, a more recent paper by Miller and Rose described an emerging theory of motivational interviewing.³⁷ Investigators who use PRECEDE-PROCEED often discuss the model in the same way other researchers might discuss theories, such as social cognitive theory.^{38,39} Health literacy has been conceptualized as a framework for intervention design.⁴⁰ Health

literacy interventions may actually be based on communication theory and literacy theory, but the investigators describe the intervention as being based on health literacy. It would be inappropriate, however, for reviewers to make inferences about actual theoretical bases; thus we are limited to what is stated in the primary research reports.⁴¹

Primary research with investigator-developed theories or models for a specific project was excluded because these theories and models are not widely known or used for health behavior change research. Potential reports which mentioned concepts that might be found in some theories or models, but did not claim a theory or model were not included. Only reports which indicated theories and models were selected prior to designing interventions were included.

Both published and unpublished research was included because the single most consistent difference between published and unpublished projects is the statistical significance of results.⁴² Publication status is not an adequate proxy of methodological quality.^{43–47} Meta-analyses that include only published research may overestimate the magnitude of the true intervention effect because at least for some topics, effect sizes of published research are larger than effect sizes of unpublished research.^{45,46,48}

Small-sample projects, which often lack statistical power to detect treatment effects, were included because meta-analyses do not rely on p values to determine effects. Pre-experimental research, without control groups, was included in exploratory analyses. All analyses were conducted separately for single-group and 2-group comparisons. We report the single-group findings only as ancillary information to the more valid 2-group results. Although non-English language research was eligible, none meeting other eligibility requirements was located. Primary research reported in 1960 or more recently was eligible for inclusion. The inclusion date of 1960 was determined because it is difficult to access research conducted prior to 1960 due to electronic database construction. There is no watershed moment in medication adherence intervention history that would demark a definitive cutoff date for eligibility.

Intervention research conducted with healthy or physically ill adults was included. Since the project was focused on theories in MA interventions, the sample was not limited to particular physical diseases or drugs. Medications not prescribed by health care providers, such as vitamins, were excluded because administration of these drugs does not constitute MA to prescribed medications. Research among participants with psychiatric problems (eg, schizophrenia) was excluded because interventions to treat MA for these conditions would likely differ from interventions to treat physical diseases such as diabetes or heart disease. For these patients with mental illness, inadequate MA may reflect the disorder the medications were prescribed to treat. Research focused on sexual or reproductive function medications were excluded. Primary research with incarcerated or institutionalized persons was excluded because of institutional control over medication administration. Research targeting children was not included because of complete or partial parental control over medications.

Potential reports were imported into bibliographic software for tracking. Several selection criteria were applied in a staged eligibility process to obtain the sample: 1) reports were evaluated for the presence of an MA intervention, 2) reports were examined for eligible samples and medications, 3) reports were examined for adequate adherence outcome data, and 4) reports with theory- or model-linked interventions were selected for this project. Figure 1 shows how potential primary reports flowed through the project.

Information Sources and Search

Multiple search strategies were employed to limit the bias associated with limited searches.⁴² An experienced health sciences reference librarian performed searches in PubMed, MEDLINE, PsycINFO, EBSCO, CINAHL, PQDT, Cochrane Central Trials Register, Cochrane Database of Systematic Reviews, ERIC, IndMed, International Pharmaceutical Abstracts, EBM Reviews - Database of Abstracts of Reviews of Effects, and Communication and Mass Media. Broad search terms were used. For example, the primary MeSH terms upon which searches were constructed were *Medication Adherence* and *Patient Compliance*. The MeSH term *Medication Adherence*, which came into MeSH usage in 2009, was used to locate research published from that year and later. *Patient Compliance* was used to locate research published prior to 2009. The MEDLINE search strategies are located in the appendix. Ancestry searches were conducted on review papers and all eligible reports. Author searches were completed for authors of more than one eligible primary research report. Hand searches were conducted in 57 journals where multiple eligible reports were published. Nineteen research registers were searched (eg, Research Portfolio Online Reporting Tool). Abstracts from 48 conferences were retrieved and reviewed.

Data Collection

A coding frame to extract primary study characteristics and outcomes was developed using previous meta-analyses on related topics and the research team's previous meta-analyses. The coding frame was pilot tested with 20 comparisons prior to implementation. Theories and models were added to the codebook throughout the project to adequately capture the extant literature. Publication status, year of distribution, and presence of funding were coded as report features. Sample age and health conditions, sex and ethnicity distribution, and characteristics of medication regimens were coded from descriptions of samples. Methodological features that were coded included random vs. nonrandom assignment to treatment and control groups, allocation concealment, control group management (ie, attention control participants received attention unrelated to MA vs. true control participants who received no attention or intervention), masking, and attrition rates.³⁴ Outcome data coded included baseline and outcome sample sizes, means, measures of variability, change scores, t statistics, and success rates.

All data were independently coded by 2 extensively trained coders to achieve 100% inter-coder reliability.⁴⁹ A doctorally prepared coder further verified all outcome data. The principal investigator determined coding decisions that were not easily reconciled between coders. To ensure independence among samples, author lists were cross checked to identify reports that might contain overlapping samples. When necessary, senior authors were

contacted to clarify uniqueness of samples. Additional publications about the same participants were used to enhance coding completion.

Risk of Bias

This project used both common meta-analysis approaches to address quality: a priori inclusion criteria and post hoc procedures for considering quality as an empirical question.^{33,50} To partly deal with design bias, effect sizes were reported separately for treatment vs. control 2-group comparisons and for treatment pre vs. post single group comparisons. Control group pre vs. post single comparisons were reported to explore potential bias from project participation. The main analyses of comparisons with treatment and control groups are emphasized in findings.

Sample size variations were managed statistically. Effect size estimates were weighted so more precise estimates (eg, due to larger sample sizes) exerted proportionally more influence on our findings.⁴³

To address risk of bias, common indicators of methodological strength (eg, random assignment of participants to groups, measures of MA) were examined via moderator analyses as a form of sensitivity analyses.³⁴ Quality scores were not used to weight effect sizes because existing quality instruments lack validity.³⁴

To avoid the bias of including comparisons with larger effect sizes, which are often easier to locate, comprehensive search strategies were employed.⁵¹ Funnel plots of effect sizes against sampling variance were used to assess publication bias.⁴⁷

Data Analyses

A standardized mean difference (d) was calculated for each comparison.^{52,53} This represented the post-intervention difference between treatment and control participants divided by pooled standard deviation. Effect sizes were adjusted for bias. Random-effects models were used to calculate effect sizes to acknowledge that effect sizes vary not only from participant-level sampling error but also from other sources of study-level error such as methodological variations.⁵⁴ Effect sizes were also calculated for treatment pre vs. post and control pre vs. post single-group comparisons. Single-group comparisons should be considered ancillary information for the more valid 2-group comparisons. All effect size outcomes are reported for treatment vs. control comparisons unless otherwise specified. Treatment vs. control comparisons were calculated separately using each theory or model if at least 3 comparisons were available.

Heterogeneity was assessed with *Q* statistic to assess whether comparisons' true effect sizes were very similar or contain significant differences.⁴³ I^2 , a measure of the percentage of total variation among observed effect sizes that is due to heterogeneity rather than sampling, was calculated.⁴³ Heterogeneity was expected because it is common in behavioral sciences and in research with diverse interventions and methods. Three strategies were used to address the expected heterogeneity. First, a random-effects model was used because it assumes both participant-level sampling error and additional sources of study-level error. Second, a measure of variability was reported along with the location parameter. Third, findings were

interpreted in light of heterogeneity. Externally standardized residuals and graphical examination were used to detect potential outliers.

Potential associations between effect sizes and risk of bias were explored using moderator analyses. Continuous potential moderators were analyzed using unstandardized regression slopes in a meta-analytic analogue of regression.⁴³ Dichotomous moderators were tested by between-group heterogeneity statistics (Q_{between}) using a meta-analytic analogue of ANOVA.⁴³ Comprehensive Meta-Analysis software was used for all analyses.

Information about primary research will be available to other researchers after all manuscripts reporting data from the parent project have been published. Requests for information will require a description specifying research use of the data. Because data are from research reports and no individual participant identifiable information will be included, no additional procedures for de-identification of the data will be required.

RESULTS

Primary Research Selection and Characteristics

The search located 39,358 potential reports. Figure 1 includes a flow diagram of potential reports through the selection process. Titles and abstracts of potential reports were examined for visual heralds to suggest reports with potential interventions. Full reports were examined to confirm the presence of an MA intervention. This narrowed the pool to 3,216 reports. Excluding potential reports with ineligible medications or samples reduced the number to 2,897 reports. Of the 683 reports that provided adequate data for an MA effect size, 124 reported using a theory- or model-linked intervention.

The list of 124 primary reports is in electronic supplementary material. There were 19,348 individual participants in the primary study reports. Eleven reports had 2 treatment groups. Two reports included 3 treatment groups. One report included 8 treatment groups.

One hundred reports contributed one or more treatment vs. control comparison(s), and effect sizes were calculated from 117 comparison samples (17,216 participants). Eighty-eight samples from 77 reports with pre-post treatment group comparisons were used to calculate effect sizes (5,846 participants). Pre-post control effect sizes were calculated from 48 sample comparisons (5,655 participants).

Most reports were published articles ($S = 97$), 24 were dissertations, 2 were presentations, and 1 was an unpublished report (S indicates the number of reports). Seventy-seven were published in 2000 or more recently; only 11 reports were published prior to 1990. The earliest report was published in 1976. Thirty-seven reports did not acknowledge funding for projects.

Table 1 provides descriptive characteristics of the included comparisons. Median treatment and control group sample sizes were 32 and 34 participants, respectively. Sample sizes ranged from 10 to 3572 participants. Twelve primary study comparisons included over 300 participants, 42 reported fewer than 50 participants. Median attrition rates were modest at 2.2%. Women were well represented in samples. Only 33 comparisons included non-

Caucasian participants. Few comparisons ($K = 10$) reported the number of prescribed drugs, whose median was 5.38 (K indicates the number of comparisons). The most common chronic diseases targeted by primary study comparisons included hypertension ($K = 32$), HIV ($K = 29$), cardiac disease ($K = 26$), diabetes ($K = 21$), and asthma ($K = 9$). Other less common diseases included arthritis, eye diseases, gastrointestinal disorders, hyperlipidemia, pulmonary disease, renal disease, seizures, stroke, and vascular disease.

Intervention dose was not completely described for many comparisons: only 48 comparisons reported the number of minutes per session. The median was 45 minutes. A median of 5 intervention sessions were reported among the 116 comparisons with this information. The median number of days over which interventions were delivered was 84 days.

Theories and Models

The theories and models most often linked with MA interventions were motivational interviewing ($K = 34$), social cognitive theory ($K = 31$), health belief model ($K = 15$), transtheoretical model ($K = 14$), and self-regulation/common sense model ($K = 11$). Theories and models reported less often included cognitive theory ($K = 9$), information-behavior-skill model ($K = 8$), self-management theory ($K = 7$), behavior modification theory ($K = 7$), Orem's self-care theory ($K = 6$), problem solving theory ($K = 6$), adult learning theory ($K = 5$), PRECEDE/PROCEED ($K = 4$), and theory of planned behavior/reasoned action ($K = 3$).

Theories or models reported by fewer than 3 comparisons included chronic care model, decision theory, elaboration likelihood model, empowerment theory, health literacy, integrated care framework, learned resourcefulness model, prospect theory, protection motivation theory, Roy's adaptation theory, self-determination theory, and social marketing model. These comparisons were not included in theory- or model-specific effect size calculations but were included in the overall effect size estimates across theories and models.

Forty-four comparisons included multiple theories or models linked to MA interventions. Combinations reported by more than one comparison were motivational interviewing and transtheoretical model ($K = 4$); health belief model and motivational interviewing ($K = 2$); motivational interviewing and social cognitive theory ($K = 2$); motivational interviewing, social cognitive theory, and transtheoretical model ($K = 2$); and motivational interviewing and information-behavior-skill model ($K = 2$). Most combinations appeared in only one comparison.

None included comparisons between 2 interventions linked with different theories or models. Several comparisons reported that they measured theory- or model-related constructs. These included self-efficacy ($K = 19$), medication/disease knowledge ($K = 5$), perceived barriers to adherence ($K = 4$), stage of readiness for change ($K = 3$), motivation ($K = 2$), information-motivation-behavior skills ($K = 1$), personal control ($K = 1$), stage of change ($K = 1$), empowerment ($K = 1$), and self-regulation ($K = 1$).

Synthesis of Results

Synthesis of all theory- or model-linked comparisons—Table 2 shows the effects of interventions on MA outcomes. All comparisons with single or multiple theories or models linked with MA interventions were included in these analyses. Standardized mean difference effect sizes ranged from -0.68 to 6.87 for individual primary study comparisons. We found a mean effect size of 0.294 among the comparisons between treatment and control groups following intervention. Excluding the 5 largest samples (over 400 participants in each comparison) revealed an effect size of 0.316 ($K = 104$; $CI = 0.240, 0.382$; $Q = 250.600$). Treatment group pre- vs. post-intervention comparisons yielded an effect size of 0.342 . Effect sizes for treatment vs. control 2-group comparisons and treatment group pre-post comparisons were statistically significant. In contrast, the control participants' effect size documented no improvement in adherence. Findings from the single-group comparisons should be interpreted cautiously. The treatment vs. control 2-group comparisons and treatment pre- vs. post-intervention comparisons were heterogeneous (Q).

Synthesis of primary research with specific theories and models—We found a mean effect size of 0.323 for single-theory or single-model comparisons (Table 2). The effects of interventions linked with specific theories or models are presented in Table 3. Synthesis of these results should be interpreted cautiously, given the small number of comparisons in some cases (K in Table 3). Effect sizes ranged from 0.041 to 0.447 . Several effect sizes were between 0.3 and 0.4 (behavior modification theory 0.363 , motivational interviewing 0.392 , self-management model 0.334 , social cognitive theory 0.350 , transtheoretical model 0.334). The largest effect sizes were for health belief model (0.477) and adult learning theory (0.443). The smallest effect sizes were for PRECEDE (0.041), self-regulation model (0.118), and information-behavior-skill model (0.175). The effect sizes for adult learning theory, behavior modification theory, motivational interviewing, self-management model, and social cognitive theory were significantly different from zero. Four effect sizes were heterogeneous as indicated by significant Q values (adult learning theory, health belief model, motivational interviewing, Orem's self-care theory).

Synthesis of primary research with combinations of theories—Effect sizes were calculated for all comparisons with multiple theories or models (Table 2). The mean effect size was 0.214 . Only one combination of specific theories or models was reported by at least 3 comparisons for calculating an effect size. The effect size for the primary research that combined motivational interviewing with the transtheoretical model was 0.371 ($K = 4$), which was not significantly different from 0.

Risk of Bias

Exploratory moderator analyses examined possible associations between effect sizes and indicators of potential bias. Primary research with attention control groups reported a significantly smaller effect size than true control groups ($Q_{\text{between}} = 11.519$, $p = .001$; attention control: $d = 0.106$, $K = 10$; true control: $d = 0.321$, $K = 99$). Effect sizes were similar between comparisons with random assignment ($d = 0.303$, $K = 79$) and without random assignment ($d = 0.264$, $K = 30$). Primary research with allocation concealment reported a significantly smaller effect size than comparisons that did not report such

concealment ($Q_{\text{between}} = 8.812$, $p = .003$; concealment: $d = 0.134$, $K = 23$; no concealment: $d = 0.347$, $K = 86$). Comparisons without masked data collectors reported a significantly larger effect size than those reporting masked data collectors ($Q_{\text{between}} = 5.390$, $p = .020$; unmasked: $d = 0.338$, $K = 86$; masked: $d = 0.160$, $K = 3$). Effect sizes were similar between comparisons that reported intention-to-treat analyses ($d = 0.256$, $K = 34$) and those without such analyses ($d = 0.318$, $K = 75$). Comparisons with higher attrition ($Q_{\text{model}} = 4.875$, $p = .027$) and with larger sample sizes ($Q_{\text{model}} = 23.903$, $p < .001$) reported lower effect sizes.

Comparisons that measured MA with electronic event monitoring systems reported a significantly larger effect size ($Q_{\text{between}} = 6.799$, $p = .009$, $d = .504$, $K = 17$) than comparisons with other measures ($d = .255$, $K = 92$). Effect sizes were significantly smaller among comparisons with self-report ($Q_{\text{between}} = 12.477$, $p < .001$, $d = .176$, $K = 53$) than among comparisons with other MA measures ($d = .412$, $K = 56$). Effect sizes were similar between comparisons with pharmacy refill data ($d = .320$, $K = 11$) and comparisons without pharmacy refill data ($d = .291$, $K = 98$). Effect sizes were not significantly different between comparisons with pill counts ($d = 0.410$, $K = 10$) and comparisons with other measures ($d = 0.284$, $K = 99$).

Published primary research reported a significantly larger effect size than unpublished comparisons ($Q_{\text{between}} = 20.149$, $p < .001$; published: $d = 0.353$, $K = 82$; unpublished: $d = 0.079$, $K = 27$). The funnel plots for the treatment vs. control 2-group comparisons and for treatment pre-post comparisons suggested that comparisons with nonsignificant results are under-reported. The funnel plot for treatment vs. control comparisons is in Figure 2. In contrast, the funnel plot for control group effect sizes demonstrated no evidence of publication bias. Moderator analyses revealed no relationship between year of publication and effect size ($Q_{\text{model}} = 1.066$, $p = .302$).

DISCUSSION

The magnitude of theory- and model-linked interventions' effects on MA behavior was modest. Several explanations are possible for this finding. Many health behavior theories and models are designed to predict behavior but may not provide specific suggestions regarding how to change behavioral determinants.^{55–57} Other theories or models, such as motivational interviewing, are specific about intervention strategies. It is also possible that theories or models may not have been applied correctly or were incompletely operationalized in interventions.^{58,59}

Inappropriate theory or model selection is another possible reason for the limited effect of interventions. Some theories and models were not designed to change behavior.⁵⁶ The most commonly reported theories and models (motivational interviewing, social cognitive theory, health belief model, transtheoretical model) have been commonly applied in research addressing other health behaviors,^{60,61} but it is unclear if these are optimal for MA interventions.^{32,57} Extant primary research used theories and models that target individuals. Theories that locate MA behavior in families, health systems, and communities were not reported by primary research.^{55,58,62,63} The absence of primary research considering the social context of behavior and multiple influences on behavior may hamper intervention

effectiveness because health behavior occurs in a context beyond the individual.⁵⁸ For example, spouses or partners may become involved in obtaining medications, discussing medications with health care providers, or reminding patients to administer medications. Some influences on adherence may be outside individual control, such as fiscal resources for medications.⁵⁶ Most theories and models focused on cognitive factors such as knowledge, beliefs, perceptions, expectations, or attitudes. Primary research focused on habits was absent from extant research, although medication taking is a habitual behavior.⁶² Future MA intervention research should address both individual determinants and the social and environmental context of behavior, include theories which use both cognitive and behavioral components of interventions, and incorporate theories which address the formation and change of habitual behavior. Multi-level interventions may be necessary to successfully change adherence behavior.⁵⁶

A few comparisons used combinations of theories for designing interventions. Efforts to combine theories may reflect the limited variance in adherence behavior explained by single theories as well as acknowledge overlapping constructs among some theories and models.⁵⁷ For example, Rickels proposed an integrated model of concepts about perceived outcomes of adherence and adherence behavior from health belief, locus of control, learned helplessness, learned resourcefulness, and self-efficacy theory.⁵⁷ Future adherence research may be based on integrating multiple theories and models.⁵⁷

Examination of theory-predicted mediating variables is an important strategy for determining whether appropriate theories are being used.⁶⁴ Fewer than one-third of the primary comparisons in this review measured theory-based mediating variables. The scarcity of health behavior change research examining mediating variables is common for other health behaviors.^{65,66} Outcomes other than MA which match the theory-linked intervention may be appropriate for some theories.⁵⁶ For example, medication knowledge might be an important variable for interventions based on adult learning theory. Future intervention research should measure and report important mediating variables and outcomes consistent with theory focus, as well as MA behavior outcomes.

Interventions typically are compared against control groups and so provide no evidence about whether the theory linkage was important or whether an intervention without theory would be as effective.⁶⁴ Direct comparison between theory- or model-linked interventions is rare in health behavior change research.³² MA interventions are rarely designed to test theories, but instead are constructed to maximize impact on MA behavior. Testing theories is a different purpose, and it is most often accomplished in laboratory research where multiple independent variables may be manipulated.⁶⁴ Such research is not possible when addressing MA behavior. Comparing theories and model commonly applied to MA would be both useful and challenging. Theories and models often have overlapping constructs, though sometimes with varying labels.^{32,61,62} Thus, interventions linked to particular theories might be similar to interventions linked with other theories. The similarity in concepts may contribute to the tendency to link interventions with multiple theories and models.³² Multiple theories and models may be used in an effort to change MA behavior, which is resistant to significant improvement.²⁹

Other possible reasons for the modest effect size were not addressed in this project. The content of interventions may have inadequately addressed theory or model constructs but this review did not examine intervention content. Many important aspects of interventions other than theories could influence MA outcomes. For example, intervention dose was limited in this primary research. Inadequate dose, regardless of theory or model use, may have been contributed to modest improvements in adherence outcomes.

This project has limitations inherent in meta-analysis research and specific to this topic. Despite comprehensive searching, some primary research might have been missed. Comparisons with varied MA measures were included. Effect sizes differed among the MA measures. Common risks of bias included lack of attention control groups, allocation concealment, random assignment, masked data collection, and intention-to-treat analyses. Attrition was significant in some comparisons. Other factors which could influence findings such as treatment fidelity were so poorly reported they could not be analyzed.

Descriptions of linkages between theory and model constructs and selection of participants, development of interventions, and application of measures were inadequate to quantify the extent to which interventions were based on theories.⁶⁷ Nor was it possible to identify a dominant theory or model in papers with multiple theories. Theory and model descriptions in research reports are often inadequate. It is possible some interventions were based on theories or models but did not report this information. This project did not attribute interventions to unclaimed theories or models because such attribution would require questionable inference and assumptions. Scant descriptions of interventions are a common problem in behavioral intervention research.^{14,68} Recent effort to develop guidelines for reporting interventions such as the Template for Intervention Description and Replication (TIDieR) may improve the information about interventions in future research.⁴¹ Complete descriptions of interventions, theory linkages with specific intervention components, and theory-specified mediating variables are essential in future research. Future research testing theory-based interventions is important to add to the body of evidence in this field.

This project did not compare theory- or model-linked interventions to interventions not based on theories or models. This sort of comparison would require being able to determine that some interventions were not linked with theory or models. Investigators did not explicitly state that their interventions were not associated with any theory or model. Comparing those without named theories to those with claimed theories would require questionable assumptions about the interventions without named theories.^{41,67}

Only 18% of the MA interventions identified in comprehensive searching reported using a theory or conceptual framework for developing interventions. No extant research reports the proportion of MA interventions based on theories. There is some evidence in the literature that a similar proportion of physical activity behavior change interventions (17%–23%) use theoretical frameworks for interventions.^{69,70} It is possible that many MA intervention trials are designed and conducted by health care clinicians who recognize the clinical consequences of poor MA in their patient populations. Clinicians may have minimal background in behavioral sciences to prepare them to apply behavioral theories to intervention design. MA intervention research is a rapidly developing area of science with

mainly recent work. MA intervention research may move to theory-based interventions as the field matures. It is also plausible that authors of MA intervention research omit reporting theories in manuscripts and journal reviewers do not request this information.

This is the first systematic review and meta-analysis to examine theory- and model-linked MA interventions. Meta-analysis results confirmed that these interventions have a significant but modest effect on MA outcomes. The modest effect sizes could have resulted from inadequate implementation or from inappropriate selection of theories and models. Theories that locate MA behavior in family and social context were not implemented in extant research. Primary research comparing treatment groups based on different theories or models and examining theory- and model-linked mediating constructs is necessary to move knowledge forward.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Search Strategies used in MedLine (OVID)

Search strategy using “medication adherence” as a MeSH term (2009-current)

1. medication adherence/
2. ..l/ 1 lg=en
3. exp Vaccines/

4. immunization/ or immunization schedule/ or immunotherapy, active/ or vaccination/ or mass vaccination/
5. exp Contraceptive Agents/
6. Contraception Behavior/
7. exp Contraception/
8. (viagra or sildenafil).mp.
9. exp antipsychotic agents/
10. exp Mental Retardation/
11. exp “schizophrenia and disorders with psychotic features”/
12. exp Substance-Related Disorders/
13. Mental Disorders/
14. exp Psychiatry/
15. Probiotics/
16. disabled children/ or mentally disabled persons/ or mentally ill persons/
17. Prisoners/
18. group homes/ or exp nursing homes/
19. Institutionalization/
20. Military Personnel/
21. Disulfiram/
22. antabuse.mp.
23. antabuse.mp.
24. exp Methadone/
25. or/3-24
26. 2 not 25
27. limit 26 to “all adult (19 plus years)”
28. limit 26 to “all child (0 to 18 years)”
29. 27 or (26 not 28)
30. remove duplicates from 29

Search strategy: All years, but focus on prior to 2009

1. patient compliance/
2. 1 not medication adherence/

3. [excluded these because they were already covered in 2009 to date search]
4. medication adherence/
5. ..l/ 4 lg=en
6. exp Vaccines/
7. immunization/ or immunization schedule/ or immunotherapy, active/ or vaccination/ or mass vaccination/
8. exp Contraceptive Agents/
9. Contraception Behavior/
10. exp Contraception/
11. (viagra or sildenafil).mp.
12. exp antipsychotic agents/
13. exp Mental Retardation/
14. exp "schizophrenia and disorders with psychotic features"/
15. exp Substance-Related Disorders/
16. Mental Disorders/
17. exp Psychiatry/
18. Probiotics/
19. disabled children/ or mentally disabled persons/ or mentally ill persons/
20. Prisoners/
21. group homes/ or exp nursing homes/
22. Institutionalization/
23. Military Personnel/
24. Disulfiram/
25. antabuse.mp.
26. antabuse.mp.
27. exp Methadone/
28. or/6-27
29. ((improv\$ or promot\$ or enhanc\$ or encourag\$ or foster\$ or advocat\$ or influenc\$ or incentiv\$ or ensur\$ or remind\$ or optimiz\$ or optimis\$ or increas\$ or impact\$) adj5 (complan\$ or adheren\$)).mp.
30. ((prevent\$ or address\$ or decreas\$) adj5 (noncomplan\$ or nonadher\$ or non complian\$ or non adher\$)).mp.
31. 29 or 30

32. 2 not 28
33. (medicat\$ or regimen\$ or prescription\$ or prescribed or drug\$ or pill or pills or tablet\$ or chemotherap\$).mp.
34. dt.fs.
35. pharmaceutical preparations/ or exp dosage forms/ or drugs, generic/ or prescription drugs/
36. agents.hw.
37. meds.tw.
38. (regimen or regimens).tw.
39. (antihypertens\$ or antitubercul\$ or antiretroviral\$ or haart).mp.
40. or/33-39
41. 32 and 40
42. *patient compliance/
43. (complan\$ or adher\$ or noncomplan\$ or nonadher).ti.
44. (complan\$ or adher\$).ab./freq=2
45. 29 or 30 or 42 or 43 or 44
46. ..l/ 41 lg=en
47. limit 46 to “all adult (19 plus years)”
48. limit 46 to “all child (0 to 18 years)”
49. 47 or (46 not 48)
50. 49 and 45
51. remove duplicates from 50

Figure 1.
Flow diagram of potential studies through review process
Note: s indicates the number of research reports

Figure 2.
Funnel plot of standard error by standardized difference in means for treatment vs. control comparisons across all theories and models

Table 1

Characteristics of Primary Research Included in Medication Adherence Meta-Analyses (146 Possible Comparisons)

Characteristic	K	Min	Q ₁	Mdn	Q ₃	Max
Total number of treatment subjects at outcome	146	5	20	32	66.75	1046
Total number of control Ss at outcome	102	5	19	34	67.75	3022
Percentage attrition across treatment & control subjects	92	0	0	2.2	16.1	57.8
Percentage female	117	0	33	50	70	100
Percentage underrepresented group subjects	33	0	31	60.4	100	100
Mean age (years)	101	19.34	42.9	54.5	63	80.6
Mean number of prescribed medications	10	1.93	4.35	5.38	9.33	13.2
Number of intervention sessions	116	1	2	5	7	30
Minutes per intervention session	48	8	24	45	77	240
Days over which the intervention was delivered	141	1	28	84	183	732

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

K denotes number of comparisons providing data on characteristic

Min=minimum, Mdn=median, Max=maximum, Q₁=first quartile, Q₃=third quartile.

Table 2
Random-Effects Medication Adherence Outcome Estimates and Tests (146 Possible Comparisons)

Comparison	K	Effect size	p (ES)	95% Confidence interval	Standard error	I ²	Tau ²	Q	p (Q)
Treatment vs. control all theory comparisons	109	0.294	<.001	0.227, 0.361	0.034	60.768	0.057	275.288	<.001
Treatment pre- vs. post-comparisons all theories	86	0.342	<.001	0.263, 0.421	0.040	77.697	0.089	381.113	<.001
Control pre- vs. post-comparisons all theories	47	0.049	.211	−0.028, 0.125	0.039	62.960	0.033	124.189	<.001
Treatment vs. control single-theory comparisons	86	0.323	<.001	0.246, 0.400	0.039	62.206	0.061	224.902	<.001
Treatment vs. control multiple-theory comparisons	24	0.214	.002	0.079, 0.348	0.069	56.544	0.051	52.927	<.001
Treatment vs. control MI plus TM ^a	4	0.371	.381	−0.460, 1.202	0.424	76.552	0.526	12.794	.005

K denotes number of comparisons, ES is effect size, Q is a conventional homogeneity statistic, I² is the percentage of total variation among comparisons' observed ES due to heterogeneity.

^aComparisons that used both motivational interviewing and the transtheoretical model.

Random-Effects Medication Adherence Outcome Estimates and Tests for Treatment vs. Control Comparisons for Individual Theories and Models (109 Possible Comparisons)

	K	Effect size	p (ES)	95% Confidence interval	Standard error	I ²	Tau ²	Q	p (Q)
Adult learning theory	4	0.443	.011	0.101, 0.786	0.175	62.654	0.070	8.033	.045
Behavior modification theory	3	0.363	.004	0.118, 0.607	0.125	0	0	0.658	.720
Health belief model	7	0.477	.050	0, 0.954	0.243	85.656	0.324	41.829	<.001
Information-behavior-skill model	3	0.175	.201	-0.093, 0.444	0.137	0	0	1.019	.601
Motivational interviewing theory	12	0.392	.002	0.148, 0.637	0.125	84.346	0.126	70.268	<.001
Orem's self-care theory	5	0.261	.377	-0.318, 0.841	0.296	64.525	0.255	11.275	.024
PRECEDE	3	0.041	.902	-0.612, 0.694	0.333	56.741	0.189	4.623	.099
Self-management model	3	0.334	.007	0.092, 0.576	0.123	0	0	0.714	.700
Self-regulation model	8	0.118	.286	-0.099, 0.335	0.111	19.221	0.018	8.666	.278
Social cognitive theory	18	0.350	<.001	0.117, 0.524	0.008	36.761	0.049	26.882	.060
Translational model	5	0.334	.106	-0.072, 0.740	0.207	57.785	0.103	9.475	.050

K denotes number of comparisons, ES is effect size, Q is a conventional homogeneity statistic, I² is the percentage of total variation among studies' observed ES due to heterogeneity. Only comparisons with at least three treatment vs. control comparisons were included.