HHS Public Access

Author manuscript

Curr Med Res Opin. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Curr Med Res Opin. 2015 January ; 31(1): 145–160. doi:10.1185/03007995.2014.978939.

Packaging interventions to increase medication adherence: systematic review and meta-analysis

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Abstract

Objective—Inadequate medication adherence is a widespread problem that contributes to increase chronic disease complications and health care expenditures. Packaging interventions using pill boxes and blister packs have been widely recommended to address the medication adherence issue. This meta-analysis review determined the overall effect of packaging interventions on medication adherence and health outcomes. In addition, we tested whether effects vary depending on intervention, sample, and design characteristics.

Research design and methods—Extensive literature search strategies included examination of 13 computerized databases and 19 research registries, hand searches of 57 journal, and author and ancestry searches. Eligible studies included either pill-boxes or blister packaging interventions to increase medication adherence. Primary study characteristics and outcomes were reliably coded. Random-effects analyses were used to calculate overall effect sizes and conduct moderator analyses.

Results—Data were synthesized across 22,858 subjects from 52 reports. The overall mean weighted standardized difference effect size for two-group comparisons was 0.593 (favoring treatment over control), which is consistent with the mean of 71% adherence for treatment subjects compared to 63% among control subjects. We found using moderator analyses that

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Previous presentations: None

Declaration of financial/other relationships: The authors report no conflicts of interest.

interventions were most effective when they used blister packs and were delivered in pharmacies, while interventions were less effective when studies included older subjects and those with cognitive impairment. Methodological moderator analyses revealed significantly larger effect sizes in studies reporting continuous data outcomes instead of dichotomous results and in studies using pharmacy refill medication adherence measures as compared to studies with self-report measures.

Conclusions—Overall, meta-analysis findings support the use of packaging interventions to effectively increase medication adherence. Limitations of the study include the exclusion of packaging interventions other than pill boxes and blister packs, evidence of publication bias, and primary study sparse reporting of health outcomes and potentially interesting moderating variables such as the number of prescribed medications.

Keywords

medication adherence; meta-analysis; intervention; medication compliance

Introduction

Inadequate medication adherence (MA) is a pervasive global hidden epidemic with devastating health and economic consequences[1, 2]. The cost of nonadherence has been estimated at over €25 billion in the European Union and $100 billion yearly in the United States[3–5]. Overall, MA is suboptimal, estimated at around 50%[1, 6–8]. Between 20% and 25% of prescriptions are never filled, and another 20% of prescriptions are filled, but are not consumed due to patient-initiated drug holidays[9]. Rates of MA have not improved over the decades[10, 11]. Considering these findings, it is not surprising that the World Health Organization (WHO) calls poor adherence a “worldwide problem of striking magnitude”[1].

The consistent evidence of widespread inadequate MA, as well as the importance of the issue, has led to considerable research testing diverse interventions to remedy the problem. Packaging interventions have long been recommended[12–17], and several trials have tested various packaging types with inconclusive results. A few small reviews of six to twelve primary studies have attempted to summarize the effectiveness of packaging interventions[12–16, 18]. Very limited meta-analyses have been reported across two, three, and six primary studies[15, 16, 18]. These reviews have been hampered by narrow searches and very small numbers of primary studies. Moderator analysis, which examines the associations between study characteristics and MA behavior outcomes, is a strength of meta-analytic work. Previous reviews have retrieved too few studies to conduct moderator analyses to determine sample, design, and intervention characteristics linked to better MA outcomes.

Primary studies testing packaging interventions have not been adequately synthesized, which seriously impedes research progress and effective practice. This project aimed to provide the most comprehensive integration of scientific knowledge about packaging interventions to increase MA. This meta-analysis addressed the following research questions: 1) What are the overall effects of packaging interventions on MA? 2) Do the effects of packaging interventions on MA outcomes vary depending on intervention characteristics? 3) Do the effects of packaging interventions on MA outcomes vary

depending on study design or sample characteristics? 4) What are the overall effects of packaging interventions on health outcomes?

Methods

We used standard meta-analysis review methods to identify and secure potential studies, assess eligibility, code data from primary study reports, meta-analyze results across studies, and interpret findings[19].

Search Strategies

Multiple search strategies were employed to ensure a comprehensive search, move beyond previous narrow reviews, and limit the bias associated with limited searches[20, 21]. An experienced health sciences reference librarian performed searches in PubMED, MEDLINE, PsychINFO, 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 *Patient Compliance* and *Medication Adherence. Patient Compliance* was used to locate studies published prior to 2009 because the term 'medication adherence' was not in MeSH usage until that year. *Medication adherence* (MeSH term) was used to locate studies published after 2008. Other MeSH terms used in constructing search strategies were: *pharmaceutical preparations, dosage forms, drugs, generic, or prescription drugs*. Keywords used in searches were: *medication(s), regimen(s), prescription(s), prescribed, drug(s), pill(s), tablet(s), agent(s), compliant, compliance, adherent, adherence, noncompliant, noncompliance, nonadherent, nonadherence, improve, promote, enhance, encourage, foster, advocate, influence, incentive, ensure, remind, optimize, increase, impact, prevent, address, decrease.* Other potential MA search terms, such as persistence, were not used because they are not MeSH terms and *medication adherence* and *patient compliance* are broader terms. Nineteen research registers were searched (e.g., Research Portfolio Online Reporting Tool). Hand searches were conducted in 57 journals where multiple eligible studies in the parent project were published. Author searches were conducted for authors of more than one eligible primary study in the parent project. Ancestry searches were conducted on all eligible studies and review papers. We retrieved abstracts from forty-eight conferences that contained, or led to, includable reports. Final searching was completed in 2013.

Inclusion Criteria

We included reports of packaging interventions to increase MA among adult subjects. MA refers to the extent to which patient medication-taking behavior is consistent with health care provider recommendations[1, 6].

Packaging interventions provide a physical assembly of medications into an object that indicates the day and/or time medications should be administered[16]. Examples of packaging interventions include professionally prepared single-use sealed containers of medications, which are called blister packs, unit-packaging, unit-of-use systems, unit-of-dose packaging,

and monitored dosage systems in the literature[14–16]. Blister packs provide correct medications in containers because they are filled by professionals. Pill boxes, reusable multi-compartment containers with designated spaces for medications to be consumed at a particular time, are another common type of packaging[16]. Unlike blister packs, pill boxes do not require professional action: they may be filled by patients, informal caregivers, or health care providers. While this may reduce costs, pill boxes may contain incorrect medications because they may be filled by patients or informal caregivers. Both blister packs and pill boxes may be recommended for aging adults with multiple chronic diseases. Possible cognitive limitations in this population could increase the incidence of incorrect medications in pill boxes. Other types of medication container changes such as replacing child-resistant caps, placing medications in envelopes instead of bottles, changing labels on medication containers, or instituting individual electronic medication containers caps which display the last medication administration time, were excluded from this review because they were functionally dissimilar to pill boxes and blister packs.

Studies of incarcerated or institutionalized persons were excluded because of institutional control over medication administration. Subjects with psychiatric (e.g., schizophrenia, major clinical depression) or substance abuse problems (e.g., nicotine, alcohol) were excluded because patients often deliberately decide to omit or cease medications. Contraceptive and sexual dysfunction medications were excluded because they are voluntary medications were patient decisions about consuming medications are expected. Although packaging interventions might be beneficial for these patients, the reasons for poor MA may differ significantly from the typical reasons for inadequate MA among persons with acute and chronic physical diseases. Nutraceuticals were excluded because they are food-focused instead of medication-focused.

Since only studies with adequate data to calculate an effect size (ES) were included, strategies to ensure adequate data were used. For reports without adequate data, author searches were completed to locate other reports about the same sample which might include the necessary information such as a measure of variability. Corresponding authors were contacted to secure ES data when such data were not provided in reports nor found in companion papers. Procedures that meta-analysts use for missing ESs are to exclude the study from the analysis, set the ES to 0 for studies reporting lack of statistically significant effect, estimate possible ESs from studies with sample size and direction of effect information, or estimate the ES magnitude derived from other studies with nonsignificant or significant findings. Using 0 may result in underestimating the ESs and distorting estimates of heterogeneity, if the treatment is effective but the primary study exhibited low statistical power. Imputing values from other studies requires assumptions that may not be justified. We excluded from the meta-analysis studies without sufficient ES information.

Both unpublished and published studies were included to reduce potential publication bias[22, 23]. Small-sample and pre-experimental studies were included[19]. Non-English studies were included if research specialists or investigators were fluent in that language. Studies distributed from 1960 until 2013 were eligible for inclusion. The flow of potential primary studies through the project is displayed in Figure 1.

Data Coding and Evaluation

A coding frame was developed from elements in previous related meta-analyses by this research team, suggestions from MA and meta-analysis experts, and a preview of 50 studies with diverse MA interventions. The coding frame includes source, participant, methodology, and intervention characteristics as well as MA outcome data. Extensive pilot testing was used to fine-tune the coding frame. The year of distribution, dissemination medium (e.g. journal article, dissertation), and presence of funding were recorded as source information. Participant characteristics included gender, age, ethnicity, chronic diseases, cognitive impairment, number of prescribed medications, and whether the subjects were selected because of poor MA.

Intervention characteristics coded included whether the intervention was a pill box or blister pack. For pill boxes, we coded whether the device was given to subjects or if subjects were told to obtain a pill box on their own. We also coded other packaging intervention details including cycle (i.e., duration in days that the current packaging lasts before subjects must obtain additional packages or refill the device) and the number of compartments. We recorded other intervention characteristics, such as information about MA intervention components in addition to the packaging, location of intervention delivery, and the professional background of the interventionist.

We coded a wide variety of aspects of how researchers conducted their studies. Of primary interest were MA data necessary for calculating effect sizes: baseline and outcome means, measures of variability, success rates, and sample sizes. If studies reported multiple MA outcome data, we preferentially selected the data from the most distal time point with the largest number of subjects using the most valid MA measure (e.g., coded pharmacy refill data when self-report data were also available). We noted the type of MA measure as an additional indicator of methodological quality in MA research. In addition, methodological features we coded included sample size, attrition rates, random vs. nonrandom assignment of participants to groups, allocation concealment, data collector masking, intention-to-treat analyses, and days between receiving the intervention and MA outcome measurement. Each attribute was analyzed as a potential moderator variable. This sensitivity analysis was used to determine if findings were robust to variations in methodological quality.

All data were independently coded by two extensively trained coders. Every variable was compared between coders to achieve 100% agreement[24, 25]. A doctorally-prepared coder further verified effect size data. To obtain sample independence, author lists on every study were cross checked with author lists of all other studies to identify and resolve any potentially overlapping samples. Senior authors were contacted when necessary to clarify the uniqueness of samples in their research. When multiple reports about the same sample were located, we kept these ancillary reports and used them to enhance the detail of coding.

Statistical Analysis

Analyses were conducted using Comprehensive Meta Analysis software. The main analyses in this project compared treatment and control groups after interventions. Supplementary analyses examined treatment group pre- versus post-intervention scores. A similar single-

group analysis was conducted for control subjects. Unless otherwise stated, all analyses and results in the report address the treatment versus control post-intervention comparisons.

Data calculations were handled by meta-analytic standardized mean difference (*d*) ES[26]. For treatment versus control comparisons, a standardized mean difference is the difference between treatment group versus control group post-intervention means divided by the pooled standard deviation. For single group ES, the *d* represents the outcome scores minus the baseline scores divided by the baseline standard deviation. A positive *d* reflects more favorable outcomes for treatment groups or following interventions. The ESs were weighted by the inverse of variance to give larger sample studies more influence and adjust for bias[27]. To acknowledge that ESs vary both from subject-level sampling error and other sources of study-level error such as participant or method variations, random-effect models were used to calculate ESs[26]. ES confidence intervals were constructed. Homogeneity was assessed using a conventional heterogeneity statistic (*Q*) and computing the I^2 index of heterogeneity beyond within-study sampling error[26]. Since clinical and statistical heterogeneity is common in behavior change research[28], the expected heterogeneity was managed in four ways. Random-effects models were used for analyses because they take into account heterogeneity beyond that explained by moderator analyses. Potential heterogeneity was explored with moderator analyses. Heterogeneity was quantified, along with the location parameter. Finally, the interpretation of findings considered the context of discovered heterogeneity.

Potential outliers were detected by examining the externally standardized residuals of ESs. Potential publication bias was explored using funnel plots of ES against sampling variance[26]. Larger samples typically yield less sampling error in observed ESs. Observed ESs should be symmetrical around the overall average ES regardless of sample size in the absence of publication bias. Begg's and Egger's tests were used to assess publication bias.

We conducted exploratory moderator analyses to examine the association between study characteristics and ESs[26]. Continuous moderator analyses consisted of testing effects through an unstandardized regression slope, which is a meta-analytic analogue of regression. Dichotomous moderators were examined by testing effects of between-group heterogeneity statistics ($Q_{between}$), which is a meta-analytic analogue of ANOVA.

Results

We identified 52 eligible primary study reports with a total of 22,858 subjects[29–80]. Eight additional articles reported on the same studies and were used as companion papers for additional coding information[81–88]. One Spanish language study was included[58]. One study was included by using ESs data obtained directly from the author because the published article lacked sufficient ES data[47]. These reports yielded ES data for 51 comparisons for treatment vs. control at outcome, 19 treatment pre- vs. post-intervention, and 7 control baseline vs. outcome comparisons.

Primary Study Characteristics

Most comparisons were disseminated as journal articles (*k*=50); two dissertation comparisons were included (*s*=number of reports, *k*=number of comparisons). The numbers

of studies that have examined packaging interventions have increased in recent years. Nine reports were disseminated before 1990, and 31 were disseminated in 2000 or after. Table 1 shows descriptive statistics across the all primary studies. Most studies (*k*=32) received funding. The median of mean sample size was 104.5 subjects. Attrition was modest and similar between treatment (median=3.45%) and control (2.74%) groups. The mean length of follow-up was 12 weeks, with a range from 1 to 52 weeks. The median value for mean age was 54.4 years. Among the studies that reported gender distribution (*s*=33), almost half the subjects were women. Ethnicity was very poorly reported; only four comparisons provided this information. Among the seven studies that reported the mean number of medications prescribed to subjects, the median of mean value was 5.94 medications. Length of follow-up was poorly reported, it ranged from one week to one year.

Tables 2 and 3 contain information about individual treatment vs. control comparisons which were included in the meta-analysis. Among the two-group comparisons, 28 were conducted in North America, 9 in Europe, 5 in Asia, 4 in Africa, and 2 in Australia. No studies conducted in South America were retrieved. Eleven studies included samples with diverse chronic diseases. Twenty studies focused on infectious diseases, including eight studies with HIV subjects. Six of the nine studies focused on cardiovascular populations recruited samples with hypertension.

Most interventions targeted MA behavior exclusively, ten interventions focused on multiple health behaviors. Packaging interventions were combined with other MA intervention components in 33 comparisons.

Risk of bias was poorly reported in many primary studies. For example, 36 comparisons did not report whether allocation was concealed. Data collector masking is a common risk of bias measure which could be difficult to implement in this research, 38 studies did not report masking data collectors. Most studies randomly assigned subjects to treatment and control conditions, 14 did not.

Overall Effects of Packaging Interventions on Medication Adherence Outcomes

Overall MA ESs are presented in Table 4. We calculated ESs for 48 treatment-vs.-control-group outcome comparisons of 21,944 subjects. The overall standardized mean difference ES was 0.593. For two-group comparisons, three ESs were excluded as outliers (the ES with outliers included was 0.757). The positive ES documents that treatment subjects had significantly better MA outcomes than were reported for control subjects. The 0.593 ES is consistent with the finding of 71% adherence rate among treatment subjects compared to 63% adherence rate among control subjects. The forest plot in Figure 2 includes ES for individual studies which compared treatment and control groups.

Subgroup analyses were conducted for primary studies that reported continuous outcome data and those that reported dichotomous outcome data[16]. The overall ES for continuous data was 1.160. The overall ES for dichotomous data studies was significantly smaller at 0.535.

We calculated ESs for 19 treatment group pre-post comparisons of 1,757 subjects and for 7 control pre-post comparisons with 844 subjects. No outliers were found for treatment or control group pre-post comparisons. For treatment baseline vs. outcome comparisons, the overall ES was 0.540. In contrast to treatment subjects, control group subjects did not have improved MA outcomes from participating in studies, the overall ES was 0.002, which was not significantly different from zero.

Treatment vs. control and treatment pre- vs. post-intervention comparisons were significantly heterogeneous (based on Q statistics) with I^2 from 79 to 92. The funnel plots of ES vs. sampling variance suggested possible evidence of publication bias among treatment vs. control group comparisons which was confirmed with Begg's test ($p = .021$) but not by the Egger's test ($p = .324$). The funnel plot for treatment group pre-post comparisons displayed evidence of publication bias which was confirmed by the Begg's test ($p = .010$) but not by the Egger's test ($p = .235$). No publication bias was evident for the control group pre-post comparisons as confirmed by both the Begg's ($p = .368$) and Egger's ($p = .529$) tests. (Funnel plots are available from the corresponding author.)

Moderator Analyses

Tables 5 and 6 display dichotomous and continuous moderator analyses. Many additional potential moderators could not be analyzed because they occurred too infrequently or were poorly reported (e.g., ethnicity). Moderator analyses are exploratory and should be interpreted with caution given the small number of studies in some analyses.

Intervention Moderators—Studies that used blister packs reported significantly larger ESs (0.802) than studies that used pill boxes (0.384). There was no difference in ESs between studies that gave pill boxes to subjects and studies where interventionists merely recommended that subjects acquire a pill box. Medication refill cycle was recorded as the number of days before participants would be required to refill pill boxes or obtain new blister packs. Studies with longer cycles reported slightly lower MA ES than studies with shorter cycles ($\hat{\beta_1} = -0.006$).

Packaging was the sole intervention in 15 studies while other researchers ($k = 33$) combined packaging with other MA interventions. The ESs did not differ between trials with exclusively packaging interventions and studies with packaging as one component of multiple MA interventions. None of the studies combined packaging with telemedicine interventions.

ESs were significantly smaller for studies with physician intervention delivery (0.269) as compared to interventions not delivered by physicians (0.641). The same pattern was present for nurse delivered interventions; studies with nurse interventionists had significantly smaller ESs (0.295) than studies with interventions not delivered by nurses (0.661). While the trend for interventions to be more effective when delivered by pharmacists (0.782) as compared to interventions without pharmacists (0.475) did not achieve statistical significance, interventions delivered in pharmacies reported significantly larger ESs (0.945) than interventions administered elsewhere (0.485). Interventions were less effective when delivered while patients were hospitalized (0.194) than when not delivered in an inpatient

setting (0.704). ESs were also smaller for interventions delivered in ambulatory care settings (0.334) than for interventions delivered elsewhere such as subjects' homes or pharmacies (0.710).

Report and Sample Moderators—The ESs did not differ between published and unpublished studies. Studies completed more recently reported slightly larger ESs than studies distributed earlier ($\hat{\beta_1}$ =0.018). The ESs did not differ between studies conducted in North America and studies conducted in Asia, Australia, Africa or Europe. Neither the presence of funding for the research nor the source of funding (for-profit vs. not-for-profit) was a significant moderator.

Studies with younger subjects reported larger ESs than studies with older samples ($\hat{\beta_1}$ = −0.022). The reported socio-economic status of participants was unrelated to ESs. Studies with more female subjects reported slightly larger ESs than studies with fewer female participants ($\hat{\beta_1}$ = 0.006). Interventions were much less effective in samples with cognitive impairment (0.074) as compared to samples without reported cognitive impairment (0.649). The ES difference between samples recruited because of medication nonadherence (0.835) and studies that did not target nonadherent subjects (0.568) was not statistically significant. The number of chronic illnesses and prescribed medications were too infrequently reported for moderator analyses.

Potential Sources of Bias: Design and Methods Moderators—Studies with larger sample sizes reported slightly larger ESs than studies with smaller samples. Allocation of subjects to treatment groups, individually randomized vs. some other allocation, was not related to ESs. The difference between ESs of studies with allocation concealment (0.276) and studies without concealment (0.636) did not achieve statistical significance. Studies with masked data collectors reported significantly smaller ESs (0.289) than studies that did not report masking (0.625). There was no difference in ESs between studies that reported intention-to-treat analyses and those that did not report such analyses.

Studies with lower attrition rates reported significantly higher MA ESs ($\hat{\beta_1}$ = −0.795). Studies with longer follow-up, days between completion of the intervention and MA outcome measurement, reported slightly higher MA ES ($\hat{\beta_1}$ = 0.004).

Primary studies reported either continuous data (e.g., means and measures of variability) or dichotomous data such as success rates. Studies that reported continuous data outcomes had significantly larger ESs (1.160) than studies that reported dichotomous outcomes (0.535). The largest ESs were reported among studies that measured MA with pharmacy refills (1.044) as compared to studies with pill counts (0.628), drug metabolites (0.418), and self-report (0.247). No studies used electronic monitoring to assess MA.

Overall Effects of Packaging Interventions on Health Outcomes

Health outcomes findings should be considered exploratory and interpreted with caution given the small number of comparisons for each health outcome (see Table 4). ESs ranged from 0.102 to 0.591: quality of life (ES=0.226), diastolic blood pressure (ES=0.318), systolic blood pressure (ES=0.416), knowledge (ES=0.456), mood (ES=0.591), and HIV

viral load (ES=0.102). ESs were significantly heterogeneous for quality of life and both systolic and diastolic blood pressure.

Discussion

The completed meta-analyses of 48 comparisons between treatment groups receiving packaging interventions and control groups without packaging interventions provided valuable new information not available in the previous meta-analyses of two to six primary studies[15, 1618]. The moderate effect sizes that we found document that packaging interventions significantly improve MA.

There are several reasons packaging interventions may be effective at producing good MA. Packaging interventions provide a mechanism for patients to self-monitor medication consumption. Difficulty remembering whether a certain dose had been consumed may be an important aspect of forgetting medications: the most often patient-reported reason for nonadherence[14, 16]. Packaging interventions also allow third parties, such as informal and home-visiting formal caregivers, to monitor dose removal from the device[12].

Packaging interventions may be especially effective for medications that should be consumed at different times of day[16], because patients do not need to make decisions about which medications to consume at different times. The number of prescribed medications has been positively linked to lack of MA[16], and packaging interventions may be useful for this particular issue, because patients do not need to open multiple containers for each administration. Unfortunately, primary studies rarely reported the number of prescribed medications, so no moderator analyses could be conducted on this possibly relevant variable. Future research should examine possible interactions between the number of medications and effectiveness of packaging interventions.

Most MA interventions, such as pharmacist counseling, are time limited[16]. Pill boxes are a more persistent intervention than programs that are designed to last a discrete period of time[17]. The moderator analyses of this study documented improved MA over time using packaging interventions. This contrasts with MA behavior following most MA intervention with a reveal a pattern of diminished MA over time. Since persisting MA is important to achieve positive health outcomes, this is an important benefit of packaging interventions. Future research should continue follow-up months or years after interventions to determine long-term benefits from packaging interventions.

Another benefit of pill boxes is that they do not require much health care provider labor, unless they are filled by providers during home or clinic visits. In contrast, blister packs require pharmacist effort[17]. The low cost of pill box interventions make them especially attractive for widespread use.

Packaging interventions have limitations. Packaging interventions can be useful for non-intentional nonadherence, but not for intentional nonadherence[12, 16]. Some packaging may not be child resistant[17]. A further limitation is that pill boxes and blister packs do not provide feedback to tell patients the time when previous doses were consumed. Packaging

interventions may be less useful when patients make voluntary decisions about consuming medications, such as for some psychiatric and substance abuse medications.

The exploratory moderator analyses showed that blister pack interventions were significantly more effective than pill boxes. Because blister packs are prepared by pharmacists, they are more likely to contain the appropriate medications than pill boxes, which are often filled by patients or caregivers. We noted that the observed pattern of interventions being the most effective when delivered in pharmacies (as compared to in-patient or ambulatory care settings) by pharmacists (as compared to physicians and nurses) was not entirely due to pharmacists preparing blister packs; 12 of the comparisons with pharmacist interventionists did not involve blister packs and 8 of the pharmacist-delivered interventions were not located in pharmacies.

Although blister packs are more expensive than pill boxes, because they require pharmacist activity and special technology, the gains in MA may make such expenditure reasonable in light of reducing health care costs arising from disease complications. Unfortunately, none of the packaging primary studies provide data about cost-effectiveness. This is an important limitation in existing primary research. It is crucial that future research examine the cost-benefit of using these interventions. Without such cost-benefit information, policy changes will be difficult to secure.

The blister pack interventions included in this meta-analysis involved medications dispensed by pharmacists in blister packs, rather than medications sold in blister packs. Regulations vary by country regarding the approvals needed for pharmaceutical manufacturers to utilize blister packs, as opposed to other forms of medication packaging. In the U.S., manufacturers must have packaging methods approved by the Food and Drug Administration as part of new drug applications, or as an equivalent change to approved packaging methods[89, 90]. The European Union has guidelines for plastic packaging; blister packs are regulated separately by each country[91]. In the U.S., repackaged blister packs are used almost exclusively in long-term care settings, while in other countries such practices are more common.

We found two surprising results analyzing pill box interventions. Pill box interventions in which pill boxes were just suggested to the patient were as effective as interventions that actually provided them to patients. Other studies found that patients are receptive to using pill boxes as descriptive research has documented that 35% to 77% of surveyed adults use pill boxes[47, 9293]. Also, MA interventions that exclusively used packaging interventions were as effective as interventions that combined packaging with other MA interventions. The effectiveness and very low cost of recommending pill boxes to patients are sufficient rationale for health care providers to incorporate this minute step into their treatment programs.

We did find circumstances when packaging interventions were not effective. Packaging interventions did not help MA in in primary research studies among patients with documented cognitive impairments as much as in studies that reported samples without cognitive limitations. Perhaps packaging interventions do not provide stimulus to take medications for cognitively impaired adults. Cognitive impairment could also affect

accuracy in filling pill boxes. Older subjects also benefited less from packaging interventions than younger subjects. One possible explanation for this finding could be the increased number of medications among older adults and the additional burden that a heavy medication load imposes on MA. Unfortunately, too few studies reported the numbers of medications to explore this possibility through moderator analyses. It is also possible that opening blister packs may be an obstacle among older subjects with greater dexterity problems.

Common methodological weaknesses in primary research on packaging interventions include the infrequent application of steps such as random allocation to groups, concealed allocation, masked data collectors, and intention-to-treat analyses. Poor reporting, such as baseline MA values, prevented analyses controlling for baseline values or determining if baseline MA differed between pill boxes and blister packs. The moderator analyses revealed some lower ESs among studies with stronger methodological features. MA outcome measurement using self-report is a significant methodological weakness associated with significantly lower ES outcomes, leading us to think that intervention effectiveness may be masked by imprecise measurement of MA. Overall, the largest ESs among these primary studies was for research using pharmacy refill data to assess MA. Because this study focused on packaging interventions, electronic medication cap monitoring device data were not available for measuring MA[94]. In the future, new packaging technology, such as devices that accept blister packs, use an audible cue for dose administration, record administration, and display when previous pills were administered, will provide alternative MA interventions and measures[95].

MA is not a unitary construct. Aspects of MA, such as initiation, implementation, and persistence, may be influenced by different MA adherence interventions. Lack of conceptual clarity may have contributed to the scant primary research which has evaluated different aspects of MA. The primary studies in this project examined implementation as the proportion of prescribed drugs which were consumed. As future primary research examines different dimensions of MA, meta-analyses may find variations in effectiveness for initiation, implementation, and persistence.

MA outcomes reported as a dichotomous variable (i.e., success rates of treatment and control groups) is another significant weakness in the MA primary research. In studies that reported dichotomous outcomes, continuous data about MA behavior were recorded and researchers categorized individual subjects as adherent or non-adherent. Significant information about the size of the effect is lost when these continuous data are transformed to dichotomous data. Furthermore, a criterion value for acceptable levels of MA has not been established for most medications, so establishing a cut-off point for success is somewhat arbitrary. Moderator analyses confirmed a larger ES for studies that reported continuous data as compared to those that reported dichotomous data. Future primary research should include continuous data MA outcomes.

This meta-analysis encountered a few factors that could have limited the robustness of the results. We were unable to assess potentially interesting variables that were poorly reported, such as the numbers of medications and chronic illnesses. Another limitation of the project

was the dearth of primary studies with health outcomes. Although all of the present health outcomes had overall positive ESs, the scant amount of primary study data limits confidence in these findings. Additional reporting of intermediate and clinical health outcomes in MA research would be very valuable[14]. Also, although extensive searching was completed, it is possible the investigators missed some potentially eligible studies. This study used a specific operational definition of packaging interventions consistent with extant research. Other aspects of interventions related to packaging, such as labeling, were not examined.

This meta-analysis is the most comprehensive quantitative synthesis of packaging interventions to improve MA to date. Interventions were moderately effective across most populations. Blister packs were more effective than pill boxes, although pill boxes remain an attractive intervention due to low cost. Future research should include pharmacy refill or other objective measures of MA over self-report data. Furthermore, studies should report outcomes as continuous data instead of converting continuous data to dichotomous outcomes. Finally, we recommend that more MA studies report health and health care cost outcomes to fully evaluate the importance of MA interventions.

Acknowledgement

None

Funding: The project described was supported by Award Number R01NR011990 (Conn-PI) from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors have no financial support or personal connection which could be perceived to bias their work.

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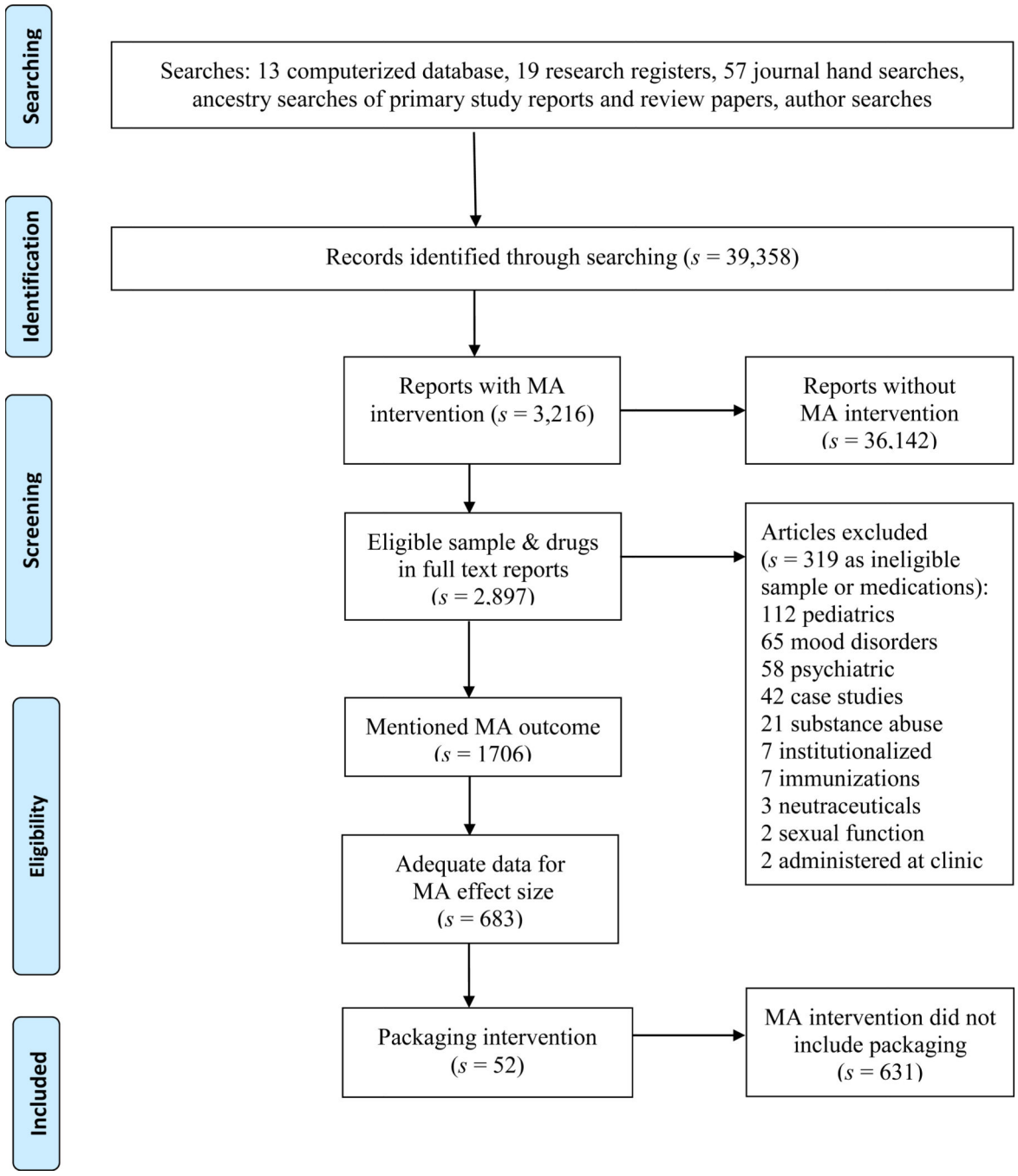

Figure 1.
Flow diagram

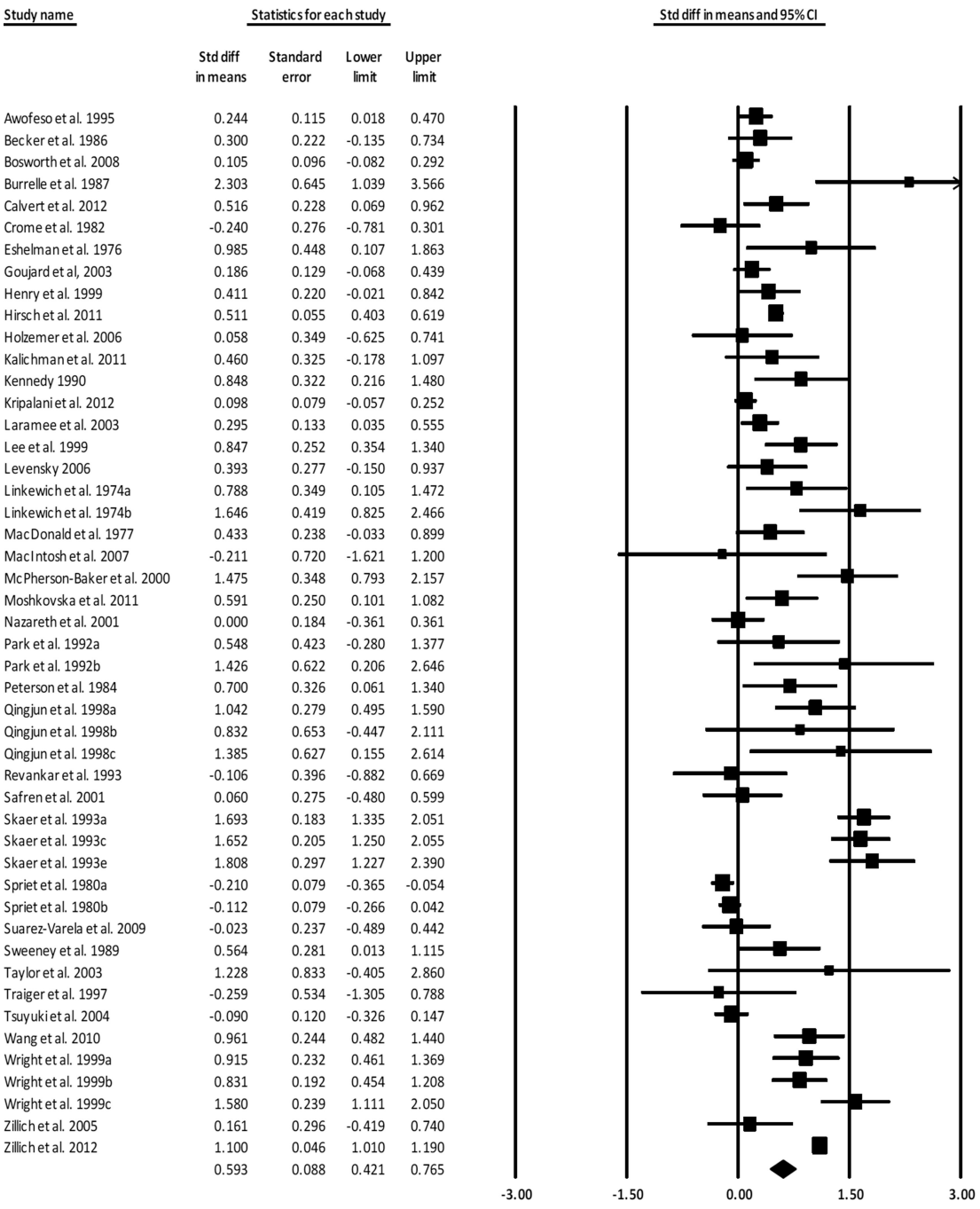

Figure 2.
Forest plot for treatment vs. control comparisons

Table 1

Characteristics of Primary Studies Included in Medication Adherence Meta-analyses

Characteristic	*s*	Min	Q_1	*Mdn*	Q_3	Max
Mean age (years)	31	26.8	43.5	54.4	69.85	85
Total post-test sample size per study	48	16	53	104.50	183.75	12969
Percentage attrition treatment group	32	0	0	3.45	20.10	81.36
Percentage attrition control group	32	0	0	2.74	24.31	68
Percentage female	36	0	27.28	43.5	64	92
Percentage ethnic minority	4	4.6	24.4	59.55	89.2	92.5
Mean number of prescribed medications	7	2.04	4.45	5.94	6.00	8.09

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

s=number of reports providing data on characteristic; Q_1=first quartile, Q_3=third quartile.

Table 2

Characteristics and Quality Indicators of Pill Box Intervention Primary Studies.

Study & location	Sample	Random assignment	Allocation concealed	Bundled intervention	Behavior target	Masking	Attrition	Intention to treat	Adherence measure
Bosworth et al. (2008) North America	N = 636 hypertension	yes	NR	yes	MA +	NR	0%	yes	self-report
Burrelle et al. (1987) North America	N = 16 hypertension	yes	NR	yes	MA	NR	0%	no	pill counts
Calvert et al. (2012) North America	N = 143 cardiac diseases	yes	yes	yes	MA	yes	27%	no	pharmacy refills
Goujard et al. (2003) Europe	N = 367 HIV	no	NR	yes	MA	NR	35%	no	self-report
Henry et al. (1999) Australia	N = 119 infections	yes	NR	yes	MA	NR	2%	yes	combined measures
Holzemer et al. (2006) North America	N = 240 HIV	yes	NR	yes	MA +	no	25%	no	combined measures
Kalichman et al. (2011) North America	N = 40 HIV	yes	yes	yes	MA	yes	3%	yes	self-report
Kennedy (1990) North America	N = 65 chronic diseases	yes	NR	yes	MA	yes	34%	no	pill counts
Kripalani et al. (2012) North America	N = 862 chronic diseases	yes	no	yes	MA	yes	25%	yes	self-report
Laramee et al. (2003) North America	N = 287 heart failure	yes	NR	yes	MA +	NR	20%	no	self-report
Lee et al. (1999) North America	N = 125 infections	yes	yes	yes	MA	NR	0%	yes	pill counts
Levensky (2006) North America	N = 54 HIV	yes	NR	yes	MA +	NR	2%	yes	pill counts
MacDonald et al. (1977) Europe	N = 74 chronic diseases	no	NR	yes	MA	NR	0%	no	combined measures
MacIntosh et al. (2007) North America	N = 25 cancer	yes	NR	no	MA	NR	4%	no	pill counts
McPherson-Baker et al. (2000) North America	N = 42 HIV	no	NR	yes	MA	NR	0%	no	pharmacy refills
Moshkovska et al. (2011) Europe	N = 84 gastrointestinal	yes	yes	yes	MA	NR	0%	yes	drug level
Nazareth et al. (2001) Europe	N = 362 chronic diseases	yes	NR	yes	MA	yes	NR	no	self-report
Park et al. (1992) North America	N = 31 chronic diseases	yes	NR	no	MA	NR	0%	no	combined measures
Park et al. (1992) North America	N = 31 chronic diseases	yes	NR	no	MA	NR	0%	no	combined measures
Peterson et al. (1984) Australia	N = 27 epilepsy	yes	NR	yes	MA	NR	NR	no	drug level
Saafren et al. (2001) North America	N = 56 HIV	no	NR	yes	MA	NR	5%	no	self-report
Suarez-Varela et al. (2009) Europe	N = 182 chronic diseases	yes	NR	no	MA	NR	0%	no	self-report
Sweeney et al. (1989) Europe	N = 103 chronic diseases	no	no	yes	MA	no	34%	no	pill counts
Taylor et al. (2003) North America	N = 81 chronic diseases	yes	NR	yes	MA	NR	15%	no	self-report
Traiger et al. (1997) North America	N = 41 organ transplant	no	NR	yes	MA	NR	12%	no	self-report
Tsuyuki et al (2004) North America	N = 276 heart failure	yes	NR	yes	MA +	NR	0%	yes	pharmacy refills

Study & location	Sample	Random assignment	Allocation concealed	Bundled intervention	Behavior target	Masking	Attrition	Intention to treat	Adherence measure
Wang et al. (2010) Asia	N = 116 HIV	yes	NR	yes	MA +	NR	16%	no	self-report
Zillich et al. (2005) North America	N = 125 hypertension	no	NR	yes	MA +	NR	6%	no	self-report

NR: not reported

Some reports contained multiple comparisons of different treatment groups compared to control groups.
Bundled interventions include packaging plus other medication adherence enhancing interventions.
Behavioral target: MA studies focused exclusively on MA. MA + studies targeted MA and other health behaviors such as diet, exercise, etc.
Masking refers to masking of data collectors regarding group assignment.
Combined MA measure indicates primary studies that reported MA outcomes from combined measures. Conn et al. did not combine measures.

Table 3

Characteristics and Quality Indicators of Blister Pack Intervention Primary Studies included in Meta-Analysis.

Study & location	Sample	Random assignment	Allocation concealed	Bundled intervention	Behavior target	Masking	Attrition	Intention to treat	Adherence measure
Awofeso et al. (1995) Africa	N = 294 infections	no	NR	yes	MA	NR	0%	no	drug level
Becker et al. (1986) North America	N = 171 hypertension	yes	NR	no	MA	NR	8%	no	pill counts
Crome et al. (1982) Europe	N = 78 chronic diseases	yes	NR	no	MA	NR	NR	no	pill counts
Eshelman et al (1976) North America	N = 100 hypertension	yes	NR	no	MA	NR	35%	no	drug level
Hirsch et al. (2011) North America	N = 2234 HIV	no	NR	yes	MA	NR	0%	no	pharmacy refills
Linkewich et al. (1974) North America	N = 46 infections	yes	NR	yes	MA	NR	NR	no	pill counts
Linkewich et al. (1974) North America	N = 51 infections	yes	NR	yes	MA	NR	NR	no	pill counts
Qingjun et al. (1998) Asia	N = 342 malaria	yes	NR	no	MA	NR	0%	no	self-report
Qingjun et al. (1998) Asia	N = 59 malaria	yes	NR	no	MA	NR	0%	no	tracers
Qingjun et al. (1998) Asia	N = 65 malaria	yes	NR	no	MA	NR	0%	no	tracers
Revankar et al. (1993) Asia	N = 189 infections	no	NR	no	MA	NR	0%	no	drug level
Skaer et al. (1993) North America	N = 163 hypertension	yes	NR	yes	MA	NR	0%	no	pharmacy refills
Skaer et al. (1993) North America	N = 131 type 2 diabetes	yes	NR	yes	MA	NR	0%	no	pharmacy refills
Skaer et al. (1993) North America	N = 64 hypertension	yes	NR	yes	MA	NR	0%	no	pharmacy refills
Spriet et al. (1980) Europe	N = 842 neurological	yes	yes	no	MA	NR	0%	no	pill counts
Spriet et al. (1980) Europe	N = 833 neurological	yes	yes	yes	MA	NR	0%	no	pill counts
Wright et al. (1999) Africa	N = 143 STD	no	no	no	MA +	no	NR	no	pill counts
Wright et al. (1999) Africa	N = 162 STD	no	no	no	MA +	no	NR	no	pill counts
Wright et al. (1999) Africa	N = 142 STD	no	no	no	MA +	no	NR	no	pill counts
Zillich et al. (2012) North America	N = 12969 chronic diseases	no	NR	yes	MA	NR	0%	yes	pharmacy refills

NR: not reported

Some reports contained multiple comparisons of different treatment groups compared to control groups.
Bundled interventions include packaging plus other medication adherence enhancing interventions.
Behavioral target: MA studies focused exclusively on MA. MA + studies targeted MA and other health behaviors such as diet, exercise, etc.
Masking refers to masking of data collectors regarding group assignment.

Table 4

Random-Effects Medication Adherence and Health Outcome Estimates and Tests

	k	Effect size	p (ES)	95% Confidence interval	Standard error	I^2	*Q*	p (*Q*)
Medication Adherence Outcomes								
Treatment vs. control all studies[a]	48	0.593	<.001	0.421, 0.765	.088	91.940	583.090	<.001
Treatment vs. control continuous data studies	18	1.160	<.001	0.699, 1.621	.235	96.186	445.729	<.001
Treatment vs. control dichotomous data studies	33	0.535	<.001	0.327, 0.742	.106	92.052	402.636	<.001
Treatment subjects pre- vs. post-comparisons	19	0.540	<.001	0.374, 0.705	.084	79.338	87.117	<.001
Control subjects pre- vs. post-comparisons	7	0.002	.995	−0.181, 0.184	.093	49.981	11.995	.062
Health Outcomes[b]								
Quality of life	5	0.226	.168	−0.112, 0.645	.193	80.502	20.515	<.001
Diastolic blood pressure	5	0.318	.159	−0.125, 0.762	.226	86.951	30.653	<.001
Systolic blood pressure	4	0.416	.092	−0.068, 0.900	.247	86.335	21.954	<.001
Knowledge	3	0.456	.082	−0.058, 0.970	.262	72.843	7.364	.025
Mood	2	0.591	.011	0.135, 1.047	.233	46.093	1.855	.173
HIV viral load	2	0.102	.476	−0.178, 0.381	.143	15.921	1.189	.275

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

[a]Three comparisons were excluded as outliers. The overall effect size with inclusion of outliers was .757 (SE = .099, CI: .563, .952).

[b]Health outcomes were calculated for treatment vs. control comparisons.

Table 5

Dichotomous Moderator Results for Medication Adherence: Treatment vs. Control at Outcome

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Report Moderators					
Publication status				0.000	.996
Published articles	46	0.592	0.090		
Dissertations	2	0.591	0.225		
Location of primary research				2.493	.114
Europe, Asia, Africa, Australia	20	0.444	0.113		
North America	28	0.699	0.115		
Presence of funding for research				2.024	.155
Funded	32	0.655	0.101		
Unfunded	16	0.420	0.131		
Source of funding for research				1.672	.196
Funding from for-profit source	8	0.948	0.257		
Funding from not-for-profit source	22	0.583	0.117		
Research Methods Moderators					
Allocation to treatment groups				0.003	.958
Randomization of individual subjects	34	0.595	0.102		
Subjects not individually randomized	14	0.586	0.132		
Allocation concealment				3.807	.051
Allocation concealed	6	0.276	0.161		
Did not report allocation concealed	42	0.636	0.090		
Data collector masking				4.088	.043
Data collectors masked to group assignment	5	0.289	0.136		
Did not report data collectors masked to group assignment	43	0.625	0.096		

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Intention-to-treat approach				0.804	.370
Reported intention-to-treat approach	9	0.429	0.210		
Did not report intention-to-treat approach	39	0.636	0.097		
Outcome data					
Continuous outcome data in primary report	18	1.160	0.235		
Dichotomous outcome data in primary report	33	0.535	0.106		
Medication adherence measure: pharmacy refill				7.522	.006
Pharmacy refill data	8	1.044	0.201		
Study did not use pharmacy refill data	40	0.455	0.075		
Medication adherence measure: pill count				0.069	.792
Pill count data	15	0.628	0.167		
Study did not use pill counts to measure medication adherence	33	0.577	0.100		
Medication adherence measure: drug metabolite				1.167	.280
Drug metabolite data	5	0.418	0.149		
Study did not use drug metabolite data	43	0.609	0.095		
Medication adherence measure: self-report				11.692	.001
Self-report data	12	0.247	0.080		
Study did not use self-report to measure medication adherence	36	0.715	0.111		
Sample Characteristic Moderators					
Sample socio-economic status				0.388	.533
Reported low socio-economic status	6	0.737	0.245		
Did not report low socio-economic status	42	0.574	0.093		
Sample with cognitive impairment				15.682	<.001
Reported subjects had cognitive impairment	5	0.074	0.115		
Did not report cognitively impaired subjects	43	0.649	0.088		
Sample selected for poor medication adherence				0.719	0.396

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Reported sample selected for poor medication adherence	6	0.835	0.301		
Did not report targeting subjects with poor medication adherence	42	0.568	0.093		
Intervention Feature Moderators					
Pill boxes vs. blister packs				6.255	.012
Pill boxes	28	0.384	0.072		
Blister packs	20	0.802	0.151		
Packaging recommended to patients vs. given to patients				0.300	.584
Recommended to patients	6	0.379	0.153		
Given to patients	17	0.483	0.112		
Intervention exclusively packaging vs. other interventions				0.019	.890
Medication intervention exclusively packaging	15	0.573	0.192		
Intervention included packaging and other strategies	33	0.602	0.101		
Interventionist: physician				5.992	.014
Physician interventionist	9	0.269	0.121		
Study did not report physician interventionist	39	0.641	0.093		
Interventionist: pharmacist				3.126	.077
Pharmacist interventionist	18	0.782	0.146		
Study did not report pharmacist interventionist	30	0.475	0.095		
Interventionist: nurse				4.734	.030
Nurse interventionist	10	0.295	0.135		
Study did not report nurse interventionist	38	0.661	0.101		
Intervention location: inpatient				13.930	<.001
Intervention delivered while subjects was an inpatient	10	0.194	0.089		
Study did not report inpatient location	38	0.704	0.104		
Intervention location: ambulatory care clinic				6.838	.009
Intervention delivered in ambulatory care clinic	19	0.334	0.095		

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Study did not report clinic as location for intervention	29	0.710	0.108		
Intervention location: pharmacy				4.326	0.038
Intervention delivered in pharmacy	11	0.945	0.103		
Study did not report intervention delivered in pharmacy	37	0.485	0.196		

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

Table 6

Continuous Moderator Results for Medication Adherence: Treatment vs. Control at Outcome

Moderator	*k*	Slope	Standard Error	Tau^2	Q_{model}	p (slope)
Report Moderator						
Year of publication	48	0.018	0.002	.253	100.976	<.001
Method Moderators						
Sample size	48	<.001	0.000	.209	217.352	<.001
Attrition proportion	32	−0.795	0.202	.237	15.466	<.001
Days between intervention completion and outcome measurement	24	0.004	0.000	.276	99.876	<.001
Sample Attribute Moderators						
Age	31	−0.022	0.002	.207	90.021	<.001
Percent women	36	0.006	0.001	.263	21.015	<.001
Intervention Feature Moderator						
Cycle (days when subjects must take action to refill/receive packaging)	28	−.0.006	0.003	.518	5.985	.014

k denotes number of comparisons, *Q* is a conventional homogeneity statistic, Tau^2 is the between-study variance.