REVIEWS

Depression and Medication Adherence in the Treatment of Chronic Diseases in the United States: A Meta-Analysis

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OBJECTIVE: To conduct a meta-analysis of the association between depression and medication adherence among patients with chronic diseases. Poor medication adherence may result in worse outcomes and higher costs than if patients fully adhere to their medication regimens.
DATA SOURCES: We searched the PubMed and PsycINFO databases, conducted forward searches for articles that cited major review articles, and examined the reference lists of relevant articles.
STUDY ELIGIBILITY CRITERIA, PARTICIPANTS, AND INTERVENTIONS: We included studies on adults in the United States that reported bivariate relationships between depression and medication adherence. We excluded studies on special populations (e.g., substance abusers) that were not representative of the general adult population with chronic diseases, studies on certain diseases (e.g., HIV) that required special adherence protocols, and studies on interventions for medication adherence.
STUDY APPRAISAL AND SYNTHESIS METHODS: Data abstracted included the study population, the protocol, measures of depression and adherence, and the quantitative association between depression and medication adherence. Synthesis of the data followed established statistical procedures for meta-analysis.
RESULTS: The estimated odds of a depressed patient being non-adherent are 1.76 times the odds of a non-depressed patient, across 31 studies and 18,245 participants. The association was similar across disease types but was not as strong among studies that used pharmacy records compared to self-report and electronic cap measures.
LIMITATIONS: The meta-analysis results are correlations limiting causal inferences, and there is some heterogeneity among the studies in participant characteristics, diseases studied, and methods used.
CONCLUSIONS: This analysis provides evidence that depression is associated with poor adherence to medication across a range of chronic diseases, and we find a new potential effect of adherence measurement type on this relationship. Although this study cannot assess causality, it supports the importance that must be placed on depression in studies that assess adherence and attempt to improve it.

KEY WORDS: depression; adherence; chronic disease; meta-analysis.
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INTRODUCTION

Poor adherence to prescribed medication is a well-known problem. Estimates for levels of medication adherence in chronic disease range from 20% to 80%, [1–3] and poor outcomes due to non-adherence are well documented and result in added health care costs in the United States. [4,5] Recent studies confirm that poor adherence is associated with higher costs across a range of diseases including heart failure, [6] osteoporosis, [7,8] Parkinson's disease, [9] Crohn's disease, [10] cardiovascular disease, [11] kidney transplant, [12] and diabetes. [13] Non-adherence has been associated with higher rates of mortality in cardiovascular disease and diabetes. [14–16] Despite the obvious nature of the medication adherence problem, interventions to improve adherence have not been overwhelmingly successful, in part because of the lack of understanding about true barriers to adherence. [17,18]

Researchers report on a wide range of barriers to adherence, including health system, provider, and patient factors. [1,4,19–22] It has long been known that psychological distress can affect medical well being, [23] and the effect of depression on medication adherence may be one mechanism through which mood disorders affect health outcomes. Whether from lack of energy, motivation, social withdrawal, feelings of hopelessness, or changes in cognition and expectations about the benefits or harms of treatment, patients with depression have many risk factors that could contribute to non-adherence. Patients with depression may also have more difficulty with patient–provider communication and less satisfaction with their care [24].

Two prior meta-analyses examined the association between depression and adherence to treatment recommendations. [25,26] In a meta-analysis of studies from 1968 to 1998, DiMatteo et al. [25] included 12 studies of the association between depression and treatment adherence, but only five studies examined medication adherence with a total of 284 patients. In these five studies, the

odds of non-adherence were threefold greater in depressed patients compared to non-depressed patients. [25] In a more recent meta-analysis, Gonzalez et al. [26] reviewed 47 studies on diabetes treatment adherence, but only 14 of the studies focused on medication adherence. The association between depression and medication adherence for those 14 studies was similar to that observed by DiMatteo et al.

Conclusions about the association between depression and medication adherence from these two earlier reviews are limited by the number of studies and the types of diseases included. First, there is a risk of publication bias when analyzing a small number of studies. For example, Gonzalez reported a small fail safe number (n=24) for the medication adherence studies, suggesting that a relatively small number of unpublished studies with null results could change the outcome of the analysis. [27] Second, two common chronic conditions, hyperlipidemia and hypertension, were not included in either review. Third, the small number of studies precluded analysis of important potential moderators of the association such as disease type, measures of adherence (which are known to affect adherence rates [28,29]), measures of depression, and sample size. Finally, the barriers influencing adherence to medication differ from those affecting adherence to other therapies such as diet and exercise, [30] and a focus specifically on medication-related adherence is warranted. To address these important issues, we reviewed the recent literature on the association between depression and medication adherence across a range of chronic diseases, performed a meta-analysis to evaluate the strength and direction of this association, and conducted a series of key moderation analyses.

METHODS

Data Sources

We followed the example of previous researchers to conduct our systematic review. [25,26] We searched the PubMed and PsycInfo databases for English-language articles published from 1998 to April, 2009. Dissertations, conference proceedings, and book chapters were excluded, and publication types of "letters," "editorials," and "comments" were omitted. Specific articles [22,31–33] were the basis of an additional forward search (i.e., articles citing the selected articles) and a related-article search in the PubMed database.

We searched PubMed and PsycInfo using synonyms for the following terms: adherence (e.g., compliance, non-adherence, and refusal), depression (e.g., depressive disorder and mental health), barriers (e.g., predictors, determinants, and factors), and medication (e.g., drugs, drug therapy, pharmaceutical, and prescription). The complete list of search terms and the search strategy are available online in Appendix 1.

Study Selection

We included observational studies that examined depression as a barrier to medication adherence among U.S. adults, including studies that described "predictors," "facilitators," or "determinants" of medication adherence and those studies that examined the "relationship" between specific barriers and adherence. We included only U.S.-based studies, since the effect of depression on adherence is likely influenced heavily by culture and other factors of the healthcare system, and we aimed to focus our results to be most applicable to the US. [34] We included only studies of adults over age 18, since adherence barriers for children can be very different from those of adults.

Studies testing an intervention for medication adherence were excluded, as they have been in prior reviews. [25] We also excluded studies that did not define adherence or specify its method of measurement. We excluded any studies focused specifically on people who were homeless or substance abusers, patients with schizophrenia or other psychotic disorders, tuberculosis, or HIV, and studies examining injectable medication, because of the unique circumstances that surround medication adherence for each of these populations. HIV regimens in particular have required an exceptionally high level of adherence (>95%) to be effective, [35,36] have a unique side effect profile, and are prescribed in unique settings, which makes them not comparable to regimens for other chronic diseases of interest to this study. We also excluded studies focusing solely on adherence to antidepressants.

The principal outcome of interest was medication adherence, which was defined as taking medication as prescribed by a health care provider. The types of non-adherence in the review included the following: (a) non-fulfillment (primary non-adherence), where patients do not fill prescriptions written by providers (b) non-persistence, where patients discontinue taking a prescribed medication without being advised to do so by a provider, and (c) non-conforming (our term for what is typically referred to as "non-adherence"), where patients fail to take medications as prescribed, for example, by skipping doses or taking doses at the wrong time. There is no gold standard for assessing medication adherence, so a variety of methods were accepted for this review. These methods ranged from self-report (e.g., questionnaires or interviews) to more objective measures such as electronic cap event monitoring and examination of pharmacy or medical records.

Two researchers (WG, JG) independently reviewed all titles retrieved using the search strategies. Titles were excluded if it was clear that the topic was not relevant to the current review. Abstracts of the remaining articles were examined independently by the same two researchers for the inclusion criteria listed above, and full articles were retrieved for abstracts meeting the inclusion criteria. Data collected on the full articles (see data extraction below) were used to exclude articles that did not meet the study eligibility criteria. The two reviewers resolved differences between them by consensus.

Data Extraction

We developed a worksheet form to collect data from the articles based upon the objectives for the current review. Two authors (WG, JG) independently collected data from the studies and compared results. Discrepancies between the reviewers were resolved by discussing the relevant points with each other until a consensus was reached. We examined the data to identify duplicate studies in the review (i.e. comparing author names, study location, population characteristics, study dates, and sample sizes). We did not contact any authors for additional information.

The data collection form contained the following items: (a) study design (e.g., cross-sectional, prospective, or case control), (b) participant characteristics including percentage of males, seniors (65 and over), and ethnic/racial category, (c) study characteristics including study location, recruitment method, and sample size, (d) chronic disease studied, (e) medication adherence assessment type (non-fulfillment, non-persistence, non-conforming), and (f) method of medication adherence evaluation (self-report, pill count, electronic monitoring, pharmacy or medical records).

We collected data specific to depression from each study, including the instrument used to measure depression or depressive symptoms (e.g. Beck Depression Inventory), whether depression was assessed in the article using ICD-9 code or another tool to report a diagnosed condition versus measured using symptom scales, and assessment of comorbid conditions. In addition, we determined if the reliability and validity of the depression scale was documented in the article by the authors. Methodological quality of the articles was discussed, but no formal scales were used for assessment.

One author (JG) collected the specific variables required for the meta-analysis; this data was then checked by a statistical analyst. The data included the following: analysis types, number of participants, effect size (correlation coefficient, odds ratio, etc.), standard error, confidence interval, *P*-value, means or proportions of groups, and type of variables used to measure adherence and depression.

Statistical Analyses and Data Synthesis

Data extracted from studies that reported bivariate associations between depression and medication adherence were evaluated for pooling. We included multiple studies from a single article in the meta-analysis if the participant samples were collected independently. For studies that reported effect sizes for more than one measure of adherence or depression, we selected the one measure more likely to be objective (e.g., pharmacy records over self-report) or the one that used a continuous scale, which would provide more statistical power to detect effects than a scale that was dichotomized (e.g., adherent and non-adherent).

We followed methods previously used by DiMatteo et al. [25] and by Gonzalez et al. [26] to conduct the meta-analysis and used the correlation effect size (*r*). [27,37] In some cases, studies reported the correlation coefficient (*r*) between medication adherence and depression. When the effect size *r* was not reported, we calculated it from the *t* or χ^2 statistics and odds ratios. [27] In studies reporting only the regression coefficient between medication adherence and depression, we used the formula suggested by Gonzalez et al. [26] and Peterson to calculate the effect size. [38] For one study, [39] simulation was used to generate *r* from the reported adherence rate (mean and standard deviation) for each level of depression score. Using the mean and standard deviation, we drew randomly from a normal distribution for the number of observations in each group to obtain an estimated adherence rate for all patients in the sample. [40] We then used the correlation between these estimates and depression level as the effect size. Results reported as non-significant (i.e. $P > 0.05$) were assigned a conservative estimate of an effect size of 0.

We calculated summary statistics, including median and mean effect size, for *r* using Fisher's z transformation of *r*. The 31 studies were significantly heterogeneous ($P < 0.01$); thus we employed a random effects model to calculate the 95% confidence intervals for the weighted and unweighted mean effect sizes. Weighted and unweighted effect size *d* and an odds ratio are reported. [27,41] We calculated the risk difference and relative risk using the weighted effect size [42].

We performed random effect meta-regressions [43] to examine the effect of each covariate of interest on *r*. Covariates we examined included method of effect size calculation, sample size, disease type, depression as the focus of the study (versus an included covariate), medication adherence evaluation method and the use of a validated depression scale. In addition, we evaluated the selective publishing of significant results over non-significant results by calculating the overall "fail safe n" and tolerance level. [27] Stata 10.1 was used to conduct all analyses [44].

RESULTS

The literature search and reference mining returned 5,260 titles, and of these titles, we selected 582 for further review (see Fig. 1). One study from the DiMatteo et al. [25] review and four from the Gonzalez et al. [26] review met our inclusion criteria. A total of 42 articles met our eligibility requirements, but collection of effect size data determined that only 30 of the 42 articles included the bivariate association data required for pooling the results. Twenty-nine of the articles reported results for a single sample of participants, and one article [45] reported effect sizes for two independently collected samples. As a result, we analyzed 31 studies across the 30 articles.

The studies covered a range of diseases, with coronary heart disease, diabetes, hyperlipidemia, and hypertension comprising the bulk of the studies (see Table 1). Appendix 2, available online, presents all the data collected from these studies. A negative effect size indicates that a higher level of depression or depressive symptoms is related to lower levels of medication adherence.

Measures of adherence included self-report for 17 studies, electronic caps for eight studies, and pharmacy records for six studies. The association between depression and adherence was the focus of seven studies, and the remaining 24 studies focused on other barriers to adherence including depression as a potential confounder. Measures of depression included self-report scales for 28 studies and depression diagnosis on a medical chart for three studies. Among the instruments used to assess depression and depressive symptoms, the Center for Epidemiological Studies Depression Scale (CES-D) was the most common (eight studies), the Patient Health Questionnaire (PHQ) was second (six studies), the Beck Depression Inventory (BDI) was third (four studies) with the remaining studies using nine different scales. The study sample sizes ranged from 47 to 8,406, and the total number of participants included in this meta-analysis was 18,245.

The results of the meta-analysis presented in Table 2 show a significant association between depression and medication adherence. While the weighted mean effect is of modest size, it is negative and achieves statistical significance (r=−0.16, 95%

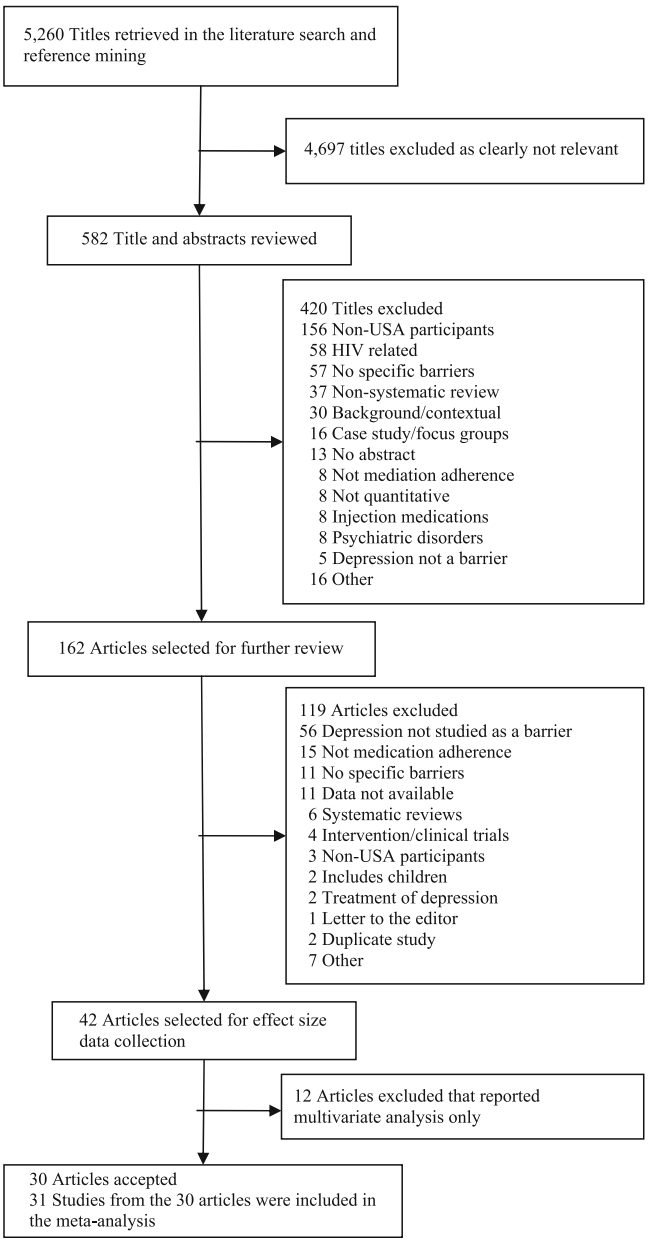

Figure 1. Flow diagram of study selection.

CI −0.20,−0.11, $P<0.001$). The estimated odds of a depressed patient being non-adherent are 1.76 times that of the odds of a non-depressed patient (weighted mean odds ratio). This corresponds to a risk difference in non-adherence between depressed and non-depressed patients of 16%. Figure 2 shows a forest plot of z-transformed correlation effect sizes with a graphic representation of the weighted confidence intervals for each study. The random effects pooled value is shown at the bottom of the figure.

Risk of Bias across Studies

The fail safe n for the weighted mean effect size is 1,613, indicating that 1,613 unpublished or unfound studies with non-significant findings (i.e. $P>0.05$) would be required to bring our effect to a non-significant level of $P=0.05$. This is almost 10 times the tolerance level of 165 studies [27].

We performed meta-regressions to evaluate potential moderators of the association between depression and medication adherence. The type of medication adherence measure had a statistically significant effect on the mean effect size such that studies using pharmacy records for obtaining medication adherence had a significantly smaller effect size than those studies using self-report (respectively, $r=-0.05$, $r=-0.21$; $P=0.006$). The mean effect size for studies using electronic monitoring devices was not significantly different from those using self-report ($r=-0.14$; $P=0.24$).

A number of other factors were not statistically significant predictors of the effect size across the studies. Diseases were grouped into three categories to increase the power to observe differences among the disease types (see Table 2). Diabetes was included as a unique category, hypertension and hyperlipidemia were combined as a category because they were often studied together, and the remaining studies were combined as a reference or baseline category. No statistically significant differences were observed among the categories: diabetes (six studies; $r=-0.17$; $P=0.91$), hyperlipidemia and hypertension (eight studies; $r=-0.16$; $P=0.98$), and other diseases (17 studies; $r=-0.16$; reference). There were no statistically significant differences in effect sizes among the types of bivariate analyses used across the studies. Sample size was not a statistically significant predictor of effect size ($P=0.21$). There was not a statistically significant difference whether a validated depression scale was used or not ($r=-0.18$ and -0.05 respectively; $P=0.08$) or if depression was the primary focus of the study or not ($r=-0.15$ and $r=-0.16$, respectively; $P=0.77$).

DISCUSSION

To our knowledge, this systematic review and meta-analysis is the first to focus specifically on the association between depression and medication adherence, analyze a sufficient number of studies to safely address the risk of publication bias, include studies of hypertension and hyperlipidemia, and investigate important potential moderators of the association. We found that depressed patients had 1.76 times the odds of being non-adherent compared to patients who were not depressed, across 31 studies and 18,245 participants.

These results were moderated by the method of adherence measurement. We found that using pharmacy records to assess medication adherence resulted in a significantly smaller

Table 1. Number of Articles Listed by Disease Studied

Disease	Number of Articles*	References
Anticoagulation therapy	1	[62]
Asthma	3	[31, 63, 64]
Coronary Heart Disease	4	[46, 65–67]
Diabetes	6	[68–73]
Glaucoma	1	[39]
Heart failure	1	[74]
Hemodialysis/Kidney transplant	1	[75]
Hyperlipidemia/ Hypertension	8	[76–83]
Systemic Lupus Erythematosus	1	[45]
Multiple Diseases or Not Specified	4	[22, 84–86]

* One article included two independent studies for a total of 31 studies across the 30 articles

Table 2. Summary of Meta-Analysis Results

Item	N	Heterogeneity Test (Q)	Median *r*	Mean *r* Un-weighted (95% CI)	Mean *r* Weighted (95% CI)	Cohen *d*	Odds Ratio (95% CI)	Risk Difference (%)	Relative Risk
All studies	31	$P<0.01$	−0.16	−0.16 (−0.47,0.19) $P=0.373$	−0.16 (−0.20, −0.11) $P<0.001$	−0.32, −0.31	1.76 (1.33,2.57)	16	1.33
By Disease:*									
Diabetes	6	$P= 0.22$	−0.17	−0.17 (−0.74,0.56) $P=0.682$	−0.16 (−0.22, −0.10) $P<0.001$	−0.34, −0.32	1.73 (1.24,2.87)	16	1.32
Hyperlipidemia/ Hypertension	8	$P=0.01$	–0.11	−0.13 (−0.68,0.51) $P=0.715$	−0.16 (−0.25, −0.07) $P<0.001$	−0.26,−0.32	1.79 (1.28,2.51)	16	1.34
Other diseases	17	$P<0.01$	−0.16	−0.17 (−0.57,0.29) $P=0.479$	−0.16 (−0.25, –0.06) $P=0.001$	−0.35,−0.32	1.80 (1.26,2.57)	16	1.34

* Notes: There were no significant differences in the weighted mean correlation coefficient (*r*) among the three categories of diseases. Abbreviations: *r* is the correlation coefficient (not the *z* transformed *r*); 95%CI is the 95% confidence interval; N is the number of studies; Cohen *d* estimate is reported for the unweighted and weighted effect sizes, respectively

correlation coefficient between depression and adherence compared to using self-report methods. The reason for this difference is not clear. Some have suggested that patients with depression may be more likely to self-report higher non-adherence than those without depression, in the setting of similar levels of actual medication-taking. [46,47] It is possible that pharmacy claims, which are objective measures of prescription filling, would not be subject to this reporting bias, although our analysis did not find any difference in the effect of depression between electronic monitoring studies and self-report. While pharmacy claims measure only the quantity of medications dispensed, it is also possible that self-reported

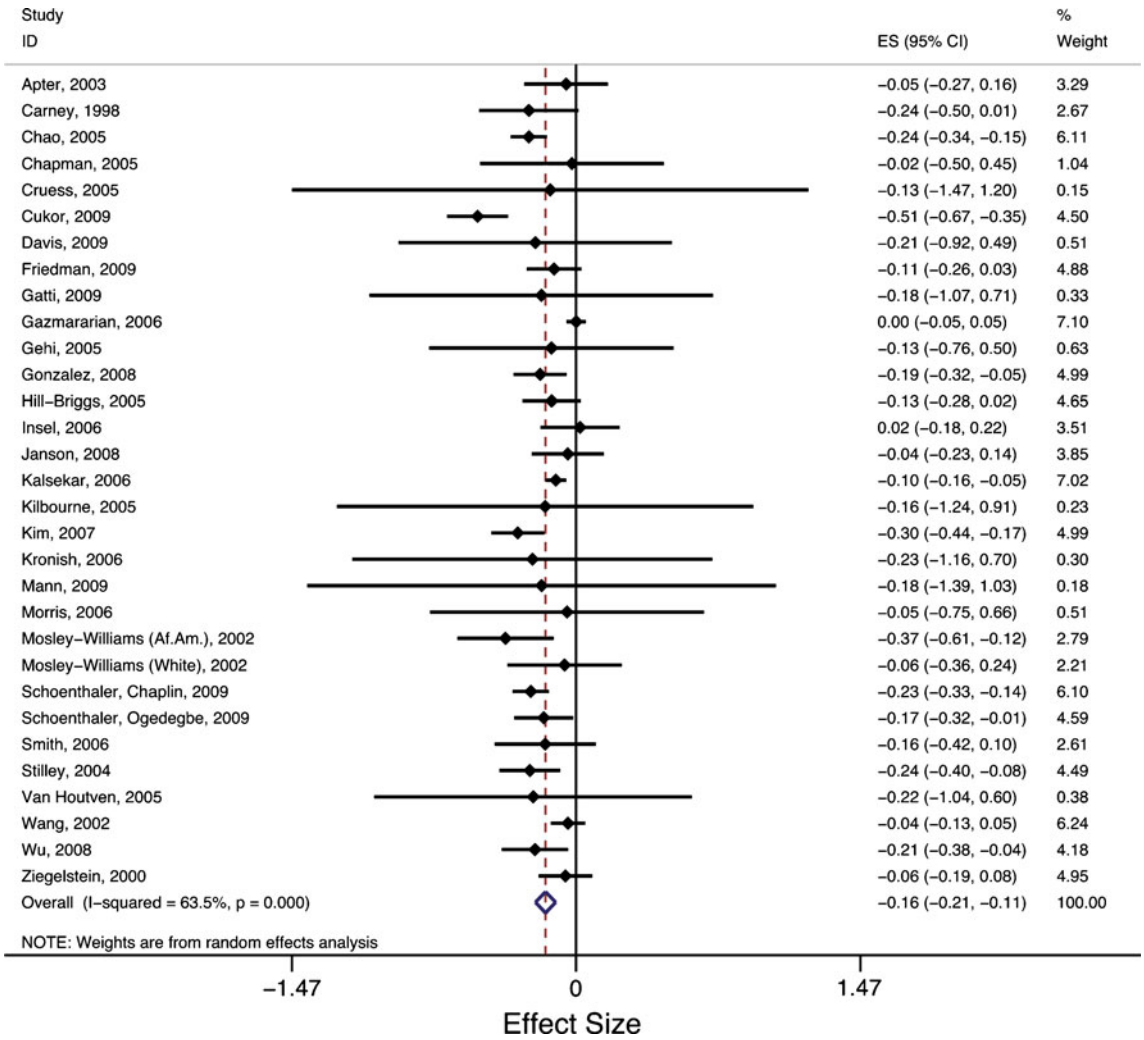

Figure 2. Forest Plot of Z-transformed Correlations. ES=Effect Size (z-transformed correlation) with 95% confidence interval.

adherence would capture other behaviors which may not be visible to claims and may be more susceptible to the effects of depression, such as incorrectly-timed doses or not ingesting filled medications. The variable concordance between the different measures of medication adherence, [28,48] and the heterogeneity of outcome measurement in these studies makes it difficult to draw firm conclusions; nonetheless, this finding suggests that future research in this area would benefit from including multiple methods of assessing adherence.

Other potential moderators did not reach statistical significance, including study size, depression assessment method, statistical methodology, or importantly, disease category (diabetes, hyperlipidemia/hypertension, and other). The consistent effect size across disease categories suggests that depression's effects on adherence could be independent of each chronic disease's treatment characteristics; while we are not able to draw definitive conclusions about how this finding might affect future research or interventions, lessons learned about the role of depression in adherence in diabetes, for example, could be applied to other chronic conditions.

The association between depression and medication adherence has important implications for clinical practice and quality of care for chronic diseases. Depression, as a diagnosis and as a set of symptoms, is extremely common in the US, with a 12-month national prevalence of approximately 6% and a lifetime prevalence of 13-16%. [49,50] Depression is common among those over age 65, who bear the burden of chronic diseases for which medication adherence is critical, [51] and there is evidence that depression is associated with adverse outcomes for several diseases, including coronary heart disease and diabetes. [52,53] Identifying depressed patients as being at high risk for medication non-adherence should be standard of care after decades of research. Alternatively, because the direction of the effect is not totally clear, medication non-adherence may be a marker for depression; suspected patient non-adherence would thus be an opportunity to screen for and discuss depression, which may be undiagnosed.

It is important to remember that depression is just one barrier known to affect medication adherence. Well-documented barriers include dose complexity and cost sharing. [54–56] Other barriers with research support include beliefs about medications, social support, side effects, and provider factors, among others. [57] Clinicians should be mindful of these barriers and be aware of recent reviews on interventions that may help improve adherence. [17,18,58,59] We are unable to comment on barriers to adherence for diseases excluded from this review such as HIV, although it should be noted that prior reviews have found depression to be a barrier to antiretroviral adherence [60,61].

There are several possible limitations in this study. First, meta-analysis results are correlational, providing limited opportunities to assess causality or identify confounders that could explain the apparent association between depression and poor adherence. A second limitation is the heterogeneity among the studies of assessment methodologies, participant characteristics, comparison groups, and statistical analyses methods. For example, patients with hypertension and hyperlipidemia constituted a large portion of the participants in the studies. Fortunately, however, our findings are supported by prior meta-analyses and our statistical methods partially account for the heterogeneity. A third limitation is the possibility of publication bias. In the current study, however, the number of unpublished studies with null effect would have to be quite large to change the outcome. The two largest included studies, in fact, found null effects, and yet the meta-analysis overall found a strong relationship between depression and adherence. Finally, it is possible that we missed some studies that have been published on medication adherence due to our selection of search terms.

CONCLUSIONS

This study confirms prior meta-analyses that show a statistically significant association between depression and medication adherence. More importantly, in two new findings, we show that depressed patients being treated for hypertension and/or hyperlipidemia are just as likely to be non-adherent as those being treated for diabetes or other chronic diseases, and that the observed relationship between depression and adherence may be different depending on the method of adherence measurement. Despite this new knowledge, the fundamental question remains whether treating depression can improve adherence. Several clinical trials are under way to address this important question. Regardless of the results of these trials, it is clear that clinicians should be asking about medication adherence in those with depression and should be asking about depression in those who are not adhering to their medications.

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Conflicts of Interest: *None disclosed.*

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