Physician Effectiveness in Interventions to Improve Cardiovascular Medication Adherence: A Systematic Review

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BACKGROUND: Medications for the prevention and treatment of cardiovascular disease save lives but adherence is often inadequate. The optimal role for physicians in improving adherence remains unclear.
OBJECTIVE: Using existing evidence, we set the goal of evaluating the physician's role in improving medication adherence.
DESIGN: We conducted systematic searches of English-language peer-reviewed publications in MEDLINE and EMBASE from 1966 through 12/31/2008.
SUBJECTS AND INTERVENTIONS: We selected randomized controlled trials of interventions to improve adherence to medications used for preventing or treating cardiovascular disease or diabetes.
MAIN MEASURES: Articles were classified as either (1) physician "active"—a physician participated in designing or implementing the intervention; (2) physician "passive"—physicians treating intervention group patients received patient adherence information while physicians treating controls did not; or (3) physicians noninvolved. We also identified studies in which healthcare professionals helped deliver the intervention. We did a meta-analysis of the studies involving healthcare professionals to determine aggregate Cohen's D effect sizes (ES).
KEY RESULTS: We identified 6,550 articles; 168 were reviewed in full, 82 met inclusion criteria. The majority of all studies (88.9%) showed improved adherence. Physician noninvolved studies were more likely (35.0% of studies) to show a medium or large effect on adherence compared to physician-involved studies (31.3%). Among interventions requiring a healthcare professional, physician-noninvolved interventions were more effective (ES 0.47; 95% CI 0.38–0.56) than physician-involved interventions (ES 0.25; 95% CI 0.21–0.29; $p<0.001$). Among physician-involved interventions, physician-passive interventions were marginally more effective (ES 0.29; 95% CI 0.22–0.36) than physician-active interventions (ES 0.23; 95% CI 0.17–0.28; $p=0.2$).
CONCLUSIONS: Adherence interventions utilizing non-physician healthcare professionals are effective in improving cardiovascular medication adherence, but further study is needed to identify the optimal role for physicians.

KEY WORDS: medication adherence; pharmaceutical care; doctor–patient relationships; preventive care; systematic reviews.
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BACKGROUND

Non-adherence to essential, chronic medications is common[1,2], with profound consequences. Medication non-adherence has been shown to be a critical source of morbidity[3] and mortality[4], with annual costs in the U.S. estimated in excess of $100 billion[5]. As a result, increasing attention is being directed at developing interventions to improve adherence to chronic therapy. Rigorous analyses of these interventions can be used to better understand characteristics of adherence interventions that predict success, to evaluate their comparative effectiveness and costs, and to develop best-practices to encourage appropriate medication-taking.

While several systematic reviews of adherence interventions indicate that multi-factorial strategies are more effective than simple ones[6,7], there is little data to compare the effectiveness of specific characteristics of adherence interventions. Specifically, little is known about who is best able to deliver adherence interventions, and what role should be assumed by the physician. Considering the high cost of physician time as compared to some other health professionals, a better understanding of the effectiveness of interventions provided by physicians can help guide intervention development.

We conducted a systematic review of interventions to improve adherence to medications for cardiovascular disease and diabetes, a cardiovascular disease equivalent[8]. We explored the effectiveness of interventions that utilized physicians and compared them to interventions that relied on other healthcare professionals or no professionals at all. Using existing evidence, our goal was to evaluate the physician's role in improving medication adherence.

METHODS

We performed a systematic search of articles published in peer-reviewed health-care related journals between 1966 and December 31, 2008 using MEDLINE and EMBASE with the help of a professional librarian. We limited our search to randomized controlled trials.

We used search terms related to the type of study (randomized controlled trial), adherence (i.e. "compliance" OR "adherence" OR "medication adherence" or "treatment compliance"), prescription drugs (i.e. "drug," OR "medication" OR "antihypertensive" OR "antihyperlipidemic" OR "hypoglycemic agents") and cardiovascular disease and diabetes (myocardial infarction, coronary heart disease, heart failure; hypertension; hyperlipidemia; and diabetes.) Articles with at least 1 search term in all three of the main categories (study type AND adherence AND either drug OR disease) met criteria for the title/abstract review.

Search terms and parameters were adjusted for both databases while maintaining a common overall architecture. Search results from MEDLINE and EMBASE were combined and screened for duplicate entries.

Study Selection

Studies were included if they reported the results of randomized controlled trials studying interventions to improve adherence to medications used for the prevention or treatment of cardiovascular disease or diabetes. Studies were limited to adult subjects only (age $\geq$18) with adherence measured in the outpatient setting (i.e. take place exclusively in the outpatient setting or bridge the inpatient/outpatient transition with data gathered on outpatient adherence). Studies were excluded if they were written in a language other than English. We assigned each to 1 of 5 categories: Remind/Reinforce, Education, Behavioral, Simplify Regimen, and Complex/Combination. Complex/Combination interventions were those that (1) did not clearly fall into one of the previous four categories because they combined two or more of these categories or (2) those requiring the ongoing involvement of a health professional (nurse, pharmacist, or physician) in a manner that could not be clearly classified into one of the above four categories. For this review, we excluded those interventions characterized solely by regimen simplification.

The remaining 82 articles (see Fig. 1) were classified as either (1) physician "active"—a physician participated in designing and/or implementing the intervention; (2) physician "passive"—physicians treating the intervention group potentially received different medication adherence information about their patients than physicians treating the control group; or (3) physicians uninvolved in the intervention.

To compare the effectiveness of health care professionals as purveyors of the intervention and to limit the heterogeneity of studies included, we divided the 82 studies into those involving a health professional (nurse, pharmacist, or physician) and those that did not and performed a meta-analysis on the 44 studies involving healthcare professionals.

Data Extraction

Data were extracted by one investigator (SLC) and checked by a second (WS) with disagreements resolved by consensus. We assessed a number of variables related to the organization and outcome of studies including: the study design, setting, characteristics of population studied, the number of participants, the mean age (or age range) of participants, characteristics of intervention, level of physician involvement in intervention, methods used to measure medication adherence, clinical outcomes, medication adherence outcomes, and listed source of funding.

For the meta-analysis we identified those randomized controlled trials where means and standard deviations for medication adherence outcomes were presented. We combined these studies using Cohen's D statistics which can be calculated for outcomes that are either binary (e.g. survey responses or predefined adherence cutoffs) or continuous (e.g. proportion of days covered)[9,10]. The effect sizes compare the difference in effect between the study groups divided by the standard deviation of this difference[11]. When standard deviations were not reported we derived them from the p-value or t statistic. We performed a meta-regression using study estimates of the Cohen's D. The method involved maximum likelihood estimation of the treatment difference from a weighted least-squares regression predicting the Cohen's D from physician involvement category. Weights were specified as the precision of the estimated Cohen's Ds.[12]

We considered an effect size of less than 0.2 to be very small, an effect size of 0.2 to 0.5 to be small, an effect size of 0.5 to 0.8 to be medium, and an effect size of greater than 0.8 to be large. This measure is independent of the measurement used, the sample size, and the standard deviation of the outcome measure. It therefore allowed us to aggregate different end points across studies to obtain effect sizes with 95% CIs for each category of physician involvement (i.e. physician-active; physician-passive; physician-non-involved.) In the meta-analysis, we derived combined summary estimates for physician-active, physician-passive, and physician-non-involved groups. We also derived a combined summary estimate for all physician-involved vs. all physician non-involved interventions.

RESULTS

Our search retrieved a total of 6550 articles, of which 168 were reviewed in full and 82 articles met inclusion criteria (see Online Tables 1[13–25], 2[26–45], 3[46–68], and 4[69–94]).

There were few adherence improvement trials published before 1990 that involved physicians; physician-involved adherence interventions were reported with increased frequency only in the past ten years. Years of publication for all studies ranged from 1976 through 2008, with 50% of all studies published in or after 2003.

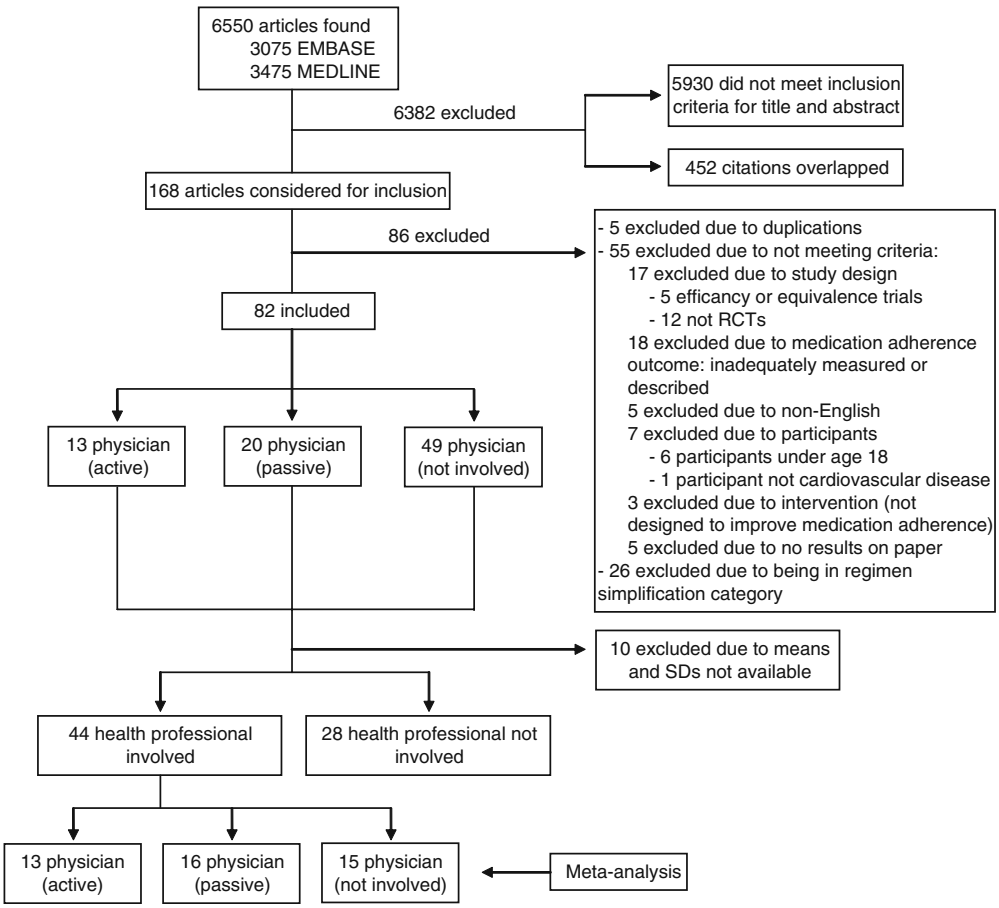

Figure 1. Article selection.

The majority (56.1%) of all interventions were aimed at subjects with hypertension. Other patient populations studied included those with diabetes (8.5% of all interventions); coronary artery disease (9.8%); congestive heart failure (11.0%); or dyslipidemia (7.3%). Additionally, 7.3% of the studies evaluated patients with a mix of cardiovascular and noncardiovascular diseases.

PHYSICIAN-ACTIVE INTERVENTIONS

Interventions characterized as physician-active were described in 13 articles. The mean age of patients included in these studies ranged from 53 to 68 years, for those studies in which a mean age was available.

Physician-active interventions were generally characterized by moderate time investment on the part of the physician and could be grouped into four categories. These articles described (1) physicians receiving additional education (physicians wrote hypertension guidelines, took intensive classes on hypertension management, or were mailed information reminding them of appropriate treatment regimen); (2) physicians recruited as agents of intervention via cues (all intervention physicians sent prompts urging medication regimen assessment); (3) physicians varying their own exposure to patients (changing frequency of follow up visits or ceding primary care of patients to a pharmacist); or (4) physicians directly involving themselves in delivery of intervention (physicians giving educational lectures or distributing pamphlets, or physicians reviewing patient data and approving various strategies for improving adherence).

Articles in the first three categories consistently demonstrated very small or small effects on adherence. For those articles in which physicians directly involved themselves in delivery of an intervention, results were mixed and difficult to interpret. The intervention studied by Logan et al. had a nonsignificant negative impact on adherence, worsening adherence slightly[22]. In this study, the physician's role was to approve compliance-improving strategies after reviewing blood pressure and compliance information gathered by an occupational health nurse. Hunt et al. also found a negative impact on adherence[20]. In this study, the role of the physician was to approve and co-sign pharmacist recommendations, and also to discuss treatment plans for hypertension as part of a collaborative pharmacist protocol. Four studies in this category showed medium to large improvement on adherence (Gonzalez-Fernandez[21], Kelly[19], Yilmaz[25], Antonicelli[24]), but two of these were of short duration (2–8 weeks); it is possible that their effect might have been attenuated if patients were followed for longer duration. In addition, one of these studies (Kelly[19]) examined the impact of a directly observed test dose of sublingual nitroglycerin administered in the physician's office. The adherence outcome assessed in this study was use of the medication at least once before the

second office visit. It is likely that this intervention and adherence outcome measure are not easily generalizable to most chronic cardiovascular medications.

PHYSICIAN-PASSIVE INTERVENTIONS

Interventions characterized as physician-passive were described in 20 articles. For those studies in which a mean age was available, mean ages ranged between 46 and 76 years.

Articles in which the physician was passively involved required minimal time commitments from the physician. In cases where no adherence problems were identified, such interventions were often designed to minimize or completely avoid using the physician's time. These interventions fell into four categories describing (1) pharmacist-initiated physician contact (i.e., in order to communicate clinical or adherence data, the pharmacist contacted the physician by phone, issued a report, entered data into medical records, sent recommendations or referred the patient to the physician); (2) nurse-initiated physician contact (i.e. for the same reasons and in the same ways, nurses initiated contact); (3) patient-initiated contact (i.e., patient prompted to speak to a physician based on patient self monitoring and algorithm); or (4) data sent directly to the physician, to be communicated subsequently to patients.

Almost all the articles describing nurse-initiated contact, patient-initiated contact or data sent directly to the physician demonstrated a very small or small impact on adherence, with only one exception. Johnson et al. examined the impact of monthly home visits, self-monitoring of blood pressure, or both on patient compliance and found a large effect (Cohen's D 1.51, CI 0.96, 2.05)[45].

Articles describing pharmacist-initiated contact were the most common (14 articles, n=4536) and displayed a range of effect sizes. They were the only group of articles displaying a negative impact on adherence (n=109) and were also the only group to include a significant number of interventions (n=829) with medium to large effects on adherence.

In our meta-analysis limited to those interventions requiring a healthcare professional (Fig. 2), physician-passive interventions were marginally more effective (pooled Cohen's D=0.29, CI 0.22, 0.36) than physician-active interventions (pooled Cohen's D=0.23, CI 0.17, 0.28). This difference was not statistically significant (p=0.2).

PHYSICIAN-NONINVOLVED INTERVENTIONS

Interventions characterized as physician-noninvolved were described in 49 articles. For those studies in which a mean age was available, mean ages fell between 49 and 85 years.

Articles in which physicians were not involved were grouped into four categories. These articles described (1) educational interventions aimed at patients; (2) reminders or reinforcement of adherence aimed at patients; (3) behavioral interventions aimed at patients; (4) complex/combination interventions, requiring involvement of a healthcare professional or combining two or more of the above categories.

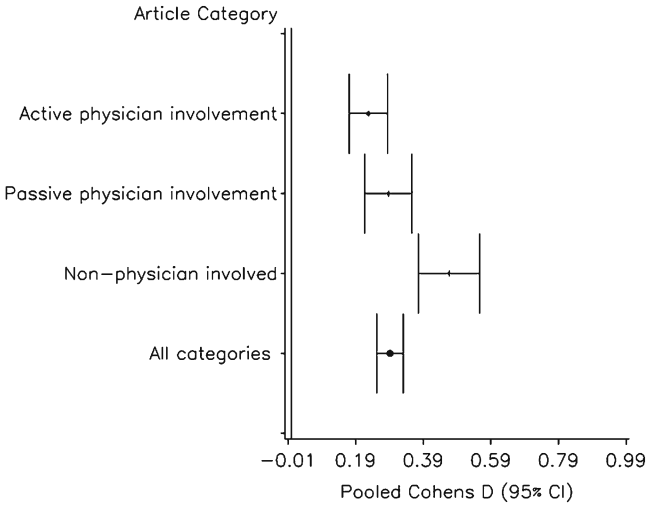

Figure 2. Meta-analysis of studies involving a health professional.

The most successful category of intervention was the complex/combination category, which had a majority of interventions (n=9284) yielding medium to large effects (pooled Cohen's D=0.49, CI 0.41, 0.57); compared to pooled behavioral interventions, Cohen's D=0.13, CI 0.01, 0.26); pooled educational interventions, Cohen's D=0.10, 0.04, 0.16); and pooled remind/reinforce interventions, Cohen's D=0.18, CI 0.13, 0.23).

Two studies in the complex/combination category had small negative effect sizes. Tsuyuki et al.[86], combined patient education, adherence aids, phone follow-up and a monthly newsletter; Vivian et al.[87] provided monthly pharmacist counseling.

Five interventions were characterized as primarily educational. The majority (4) of these had a very small or small effect, while one educational intervention (Morisky et al.[66]), a randomized factorial intervention providing hypertension education and training to both patients and family members, yielded a large effect.

Sixteen interventions used reminder or reinforcement techniques. The majority of these showed very small or small effects while three yielded large effects. McKenney et al.[53] tested the effect of timepiece pill bottle caps along with pocket cards for recording blood pressure while Skaer et al.[57,58] examined the effect of mailed refill reminders, unit of use packaging or the combination on patients with hypertension[57] and in diabetic patients[58].

The majority (88.9%) of all studies for which Cohen's D values could be calculated showed improved adherence (Cohen's D >0). Physician-noninvolved studies showed a higher rate of a medium or large effect (35.0% of studies) on adherence compared to physician-involved studies (31.3%). Similarly, only 7.5% of physician-noninvolved studies displayed a negative effect or lack of any effect compared to 15.6% of physician-involved studies. Physician-passive studies were slightly more likely to have a medium or large effect (31.6%) compared to physician-active studies (30.8%) and similarly likely (15.8% vs. 15.4%) to negatively impact adherence.

In our meta-analysis limited to interventions requiring involvement of a healthcare professional (Fig. 2), physician-non-involved

interventions were substantially more effective (pooled Cohen's D=0.47, CI 0.38–0.56) than physician-involved interventions (combined physician-involved pooled Cohen's D=0.25, CI 0.21–0.29; p<0.001).

DISCUSSION

Our findings demonstrate that existing physician-based adherence interventions have been less effective than strategies relying on other healthcare professionals. Healthcare professionals with specialized skills in pharmaceutical counseling or with expertise in behavioral interventions may be better equipped to address medication adherence challenges, and may be able to do so in more cost-effective ways.

Although small, the positive effect of physician-involved interventions must not be overlooked. While primary responsibility for time-intensive adherence interventions may not be ideally suited for physicians, it is still essential that we identify the most effective components of the physician adherence intervention. The strength in a physician-involved adherence intervention may lie, for example, in a patient's perception of the physician's expertise or in the trust built through long-term relationships. Referral networks that link physicians to other adherence experts could take advantage of the strengths of the physician-involved adherence intervention while limiting demands placed on a physician's time.

Our review identified a number of areas in which well-designed studies were lacking. Few studies provided physicians with quantitative real-time adherence information, though several did describe interventions in which pharmacists or nurses provided the physician with ongoing medication information. Future interventions providing real-time quantitative adherence data might improve doctor–patient communication about medication adherence, though we need to consider whether the physician is the healthcare professional best-equipped to invest large amounts of time in such communication. In addition, few studies provided information on the cost of interventions. Future trials should provide estimates of the cost of their intervention so that comparisons can be made on this basis.

Our review was limited to published randomized controlled trials. Best practices have not yet been developed for adherence interventions, and future studies may better identify effective roles for physicians to improve patient behavior. The trials included in this evaluation were heterogeneous. While Cohen's D effect sizes provide a means for standardizing, the clinical significance of these effect sizes may be hard to interpret. It is possible that there was publication bias in the studies we included in this review; however, we do not expect that publication bias should disproportionately affect any of the categories we used to differentiate interventions. It is possible that the chosen measure of adherence may have impacted the outcomes. However, if self-report yields a higher estimate of adherence compared to more objective measures[16], the presence of a higher number of self-reported adherence outcomes in the physician-involved studies would over-estimate the effectiveness of this group, and our findings would be conservative. Several studies identified in our review followed subjects for short periods of time (less than 6 months). Given the long-term commitment necessary in the case of most cardiovascular medications, these studies may not be as readily generalizable.

As we continue to strive for evidence-based approaches to improve adherence to essential medications, we must also consider who is best able to deliver interventions that are both effective and cost-effective. Our results suggest that non-physician healthcare professionals such as pharmacists and nurses can play an important role in improving adherence. Existing studies have not provided a compelling evidence-base to support large investments in interventions that are delivered by physicians. Further study is needed to better understand the role of the physician in improving patient adherence in a cost-effective manner and how physicians should collaborate best with other healthcare professionals.

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