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Modes of delivery for interventions to improve cardiovascular medication adherence: Review

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Abstract

Objectives—To determine the optimal modes of delivery for interventions to improve adherence to cardiovascular medications.

Study Design—Systematic Review

Methods—We conducted systematic searches of English-language peer-reviewed publications in MEDLINE and EMBASE, 1966 through 12/31/2008. We selected randomized controlled trials of interventions to improve adherence to medications for preventing or treating cardiovascular disease or diabetes. Articles were classified based on mode of delivery of the main intervention as (1) person-independent interventions (mailed, faxed or hand-distributed; or delivered via electronic interface) or (2) person-dependent interventions (nonautomated phone calls, in-person interventions).

Results—We identified 6550 articles; 168 were reviewed in full, 51 met inclusion criteria. Among person-independent interventions (56% successful), electronic interventions were most successful (67%). Among person-dependent interventions (52% successful), phone calls showed low success rates (38%). In-person interventions at hospital discharge were more effective (67%) than clinic interventions (47%). In-person pharmacist interventions were effective when held in a pharmacy (83% successful), less effective in clinics (38%).

Conclusions—Future medication adherence studies should explore new electronic approaches and in-person interventions at the site of medication distribution. Identifying times of increased patient receptivity to the adherence message such as hospital discharge will also be important.

Background

Non-adherence to essential chronic medication therapy for cardiovascular disease and diabetes is common, leading to substantial morbidity, mortality, and health care costs[1-3]. Evidence-based efforts to improve adherence are needed. Previous studies have demonstrated the effectiveness of reduced dosing demands and complex, multi-factorial interventions[4-5], but there is little evidence available comparing modes of delivery for adherence interventions.

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Evidence-based information on modes of delivery would enhance the construction of adherence interventions in several domains: the communication channel (e.g. written, electronic, phone, in-person), the purveyor of information, (e.g. lay person, pharmacist, physician), and the optimal setting (hospital, home, pharmacy, clinic). The mode of delivery is closely linked to an intervention's cost and therefore to its long-term viability. A careful consideration of the comparative efficacy and intensity of different approaches is therefore needed to develop evidence-based strategies.

We conducted a systematic review of interventions that seek to improve adherence to medications for cardiovascular disease and diabetes, a cardiovascular disease equivalent. We focused on the mechanism of information transfer to patients. By evaluating the effects of (1) the purveyor of information; (2) the channel of information; and (3) the setting of transfer, we offer to payors, providers and policymakers additional guidance on the development of adherence interventions.

Methods

We performed a systematic search of articles published in peer-reviewed health-care related journals between 1966 and December 31, 2008. The search was performed 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., "adherence" OR "compliance" OR "medication adherence" or "treatment adherence") 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 3 of the main categories (study type AND adherence AND either drug OR disease) met criteria for the title/abstract review (see Appendix).

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 (age ≥18) in either the outpatient setting or at the inpatient/outpatient transition. Data was gathered on outpatient adherence for all patients. Studies were excluded if they described an intervention characterized by regimen simplification (either unit-of-use packaging or changes in dose frequency or formulation), as they could not be placed into the study categorization, and previous studies have demonstrated their effectiveness[4]. Studies were excluded if they were written in a language other than English. Those with duration less than 24 weeks were excluded, since cardiovascular medications typically require long-term adherence.

After exclusions, 51 articles (see figure 1) were classified by the mode of delivery of the intervention. Person-independent interventions included (1) mailed, faxed or hand-distributed interventions and (2) interventions delivered via electronic system. Person-dependent interventions included (1) interventions delivered via non-automated phone calls and (2) in-person interventions (classified based on site of delivery, i.e. home, worksite, pharmacy, clinic, or hospital). Person-dependent interventions were further classified based

on the level of training required of the person administering the intervention, i.e. (a) trained lay person; (b) nurse; (c) pharmacist; (d) physician; or (e) not specified.

For those studies that incorporated two or more modes of intervention, we assigned categories based on what appeared to be the main mode of intervention. Where categories appeared to be equivalent, we assigned priority in the following order: person-dependent (in person, followed by phone); person-independent (electronic system, followed by mailed, faxed or hand-distributed).

Data extraction

Data were extracted by 2 investigators (S.C. and W.S.) 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, characteristics of intervention, methods used to measure medication adherence, clinical outcomes, and medication adherence outcomes. We report confidence intervals when available and p values when no confidence intervals are available.

Results

Our search retrieved a total of 6550 articles, of which 168 were reviewed in full and 51 articles met inclusion criteria[6-56] (see figure 1; Tables 1, 2). The majority (55%) of interventions were aimed at subjects with hypertension. Other patient populations studied included those with diabetes (8%); coronary artery disease (8%); congestive heart failure (14%); dyslipidemia (10%); 6% of the studies evaluated patients with a mix of cardiovascular and noncardiovascular diseases.

Person-independent interventions: mailed, faxed or hand-distributed material

There were three studies[6-8] in which the main intervention was delivered via mail, fax or hand-distribution of paper or video information; one[6] was successful. Smith followed 907 patients after discharge from a hospital stay for myocardial infarct; 2 letters sent to patients and to primary care providers describing the importance of beta-blocker use yielded improved adherence as measured by pharmacy claims data. Patients receiving mailings were 17% more likely to have 80% of days covered (RR 1.17; 95% CI 1.02-1.29). The two unsuccessful studies described direct patient mailings of written information on hypertension[7] or video information on one of four medications (2 blood pressure agents, an antihyperlidemic, and transdermal estrogen)[8]; Takala defined adherent patients as those still under treatment after two years and Powell studied mean medication possession ratios.

Person-independent interventions: electronic systems

There were 6 studies[9-14] that examined a range of electronic interventions including use of electronic pill boxes with programmable reminders, automated phone calls with interactive components, computer-generated individualized interventions, and home automatic blood pressure monitoring. Overall, this group included more positive studies than the mailed/faxed/hand-delivered group (four out of six showed improved adherence).

Rosen[14] studied 33 people with diabetes with baseline adherence < 80%. This study tested use of electronic pill caps with a time display and programmable beeper compared to electronic pill caps alone. Participants with programmable beeper pill caps showed improved adherence (80% intervention vs. 60% control, p=0.017).

Friedman[10] and Piette[13] studied the effect of automated phone calls. Friedman followed 299 hypertensive patients, randomizing patients to an interactive computer-based home

telemonitoring system vs. usual care. Patients called in weekly, shared information by phone regarding automated blood pressures and adherence, and received targeted education and motivational counseling (all automated) with responses forwarded to doctors. Adherence, measured by pill count, was not significantly different between groups in unadjusted analysis; adjustment for age, sex, and baseline adherence yielded significant differences (17.7% adherence in intervention vs. 11.7% control, p=0.03). Piette randomized 280 patients to biweekly automated interactive phone calls with structured messages that were adjusted based on patient responses, followed by targeted nurse calls vs. usual care. Differences from Friedman's intervention include outgoing calls to patients (Friedman required patients to call in) and limited non-automated phone follow-up. Piette found that intervention patients were "substantially less likely to report adherence problems" (based on self-report using modified Morisky scale) (p=0.003, no adherence percentages given) but did not provide baseline adherence (56% reported "any medication problem" at baseline).

Johnson[11] followed 404 adults, describing the impact of a computer program designed to mimic the reasoning and problem-solving of humans based on an integrative model of behavioral change (the Transtheoretical Model) and incorporating an individualized computer-generated report mailed to patients. Johnson found an improvement in adherence at 18 months (OR 2.86, $p<0.05$). Emmett[9] studied 217 patients newly diagnosed with hypertension who were randomized in a factorial manner to a computerized decision analysis intervention, mailed video and leaflet, both or neither. Neither the decision analysis nor the mailed video resulted in significant improvement. Marquez-Contreras[12] examined use of home automatic blood pressure monitoring (along with a phone call with instructions on use) in 250 patients with uncontrolled or newly diagnosed hypertension. At the end of 6 months, 92% of the intervention group had adherence > 80% (assessed using electronic pill boxes) compared to 74% of the control group ($p<0.05$).

Person-dependent interventions: nonautomated phone calls

Eight studies described the use of non-automated phone calls to improve adherence. Calls were made by trained lay people[15-16]; nurses[17]; pharmacists[18-19]; or by a nonspecified caller[20-22]. Overall, five of these studies showed a nonsignificant improvement in adherence, one[20] showed significant improvement but did not clearly define its adherence outcome measure, and two showed significant improvement with clearly defined outcomes.

Neither phone calls by trained lay people nor calls by a nurse yielded significant improvements in adherence. Pharmacist calls showed mixed results. Faulkner[18] described twelve weeks of weekly phone calls from a pharmacist for patients after cardiac surgery or angioplasty, and found a significant improvement in adherence as measured by pharmacy refills (60% adherence for phone call group vs. 27% control at 2 years for lovastatin). Mehos[19] evaluated the effect of monthly pharmacist phone calls in conjunction with home blood pressure monitoring in a group of hypertensive patients who all received direct clinical services from a pharmacist and found no significant improvement.

Three studies did not specify the identity of the caller. Antonicelli[20] described a home telemonitoring intervention managed by a specialized congestive heart failure team that included doctors and nurses, without specifying the actual caller. The study reported significant improvement in adherence (91% intervention group vs. 46%, $p<0.03$), but did not adequately define how adherence was measured. Sclar[21] used phone calls in which adherence was reinforced and monthly mailings delivered to patients with previously treated and newly-diagnosed hypertension, and found statistically significant improvements in both intervention groups (previously treated, 82% adherence intervention vs. 48% control; newly treated 93% vs. 52%; $p<0.05$ for both). Guthrie[22] used phone reminders along with mailings

to patients with elevated cholesterol and finds no significant difference in self-reported pravastatin use.

Person-dependent interventions: in-person meetings

We identified 34 in-person interventions[23-56] (see Table 2). These interventions included those conducted in the home[23-26], at work-sites[27-29], at pharmacies[30-35], and at medical facilities[36-56]. Overall, in-person interventions were more likely (56%) than phone calls (38%) to show significant improvement.

Morisky[25] examined the effect of a trained lay person, (a health educator) visiting the home of a patient in order to provide education to family members in addition to patients, and found a significant improvement in self-reported adherence scores. Saunders[23] also incorporated trained lay person visits. This study sent reminder letters to patients with hypertension and used patient-recorded blood pressure and medication records, adding fieldworker home visits after 2 reminder letters went unanswered, but did not find significant improvement. Kirscht[26] applied a factorial design to multiple educational and behavioral strategies (Table 2) and found a significant improvement in adherence among patients who received nurse-administered home visits aimed at a support person along with the patient (adherence 65% vs. control 55%, $p<0.05$). Johnson[24] examined monthly home visits with or without home blood pressure monitoring (the training of the home visitor was not identified) and found no significant improvement. Both effective in-home interventions incorporated family member involvement, as compared to the two unsuccessful interventions.

The three work-site interventions provided hypertension care by a nurse[27-28] or physician[29]; improvement was shown only in the study in which a nurse was acting with relative autonomy[27]. Logan[27] examined the effect of hypertension care for 457 patients administered by a specially-trained nurse at the worksite. All aspects of blood pressure management were handled directly by the nurse, and the intervention demonstrated improved adherence (68% vs. 49% had at least 80% of medications consumed by pill count).

We identified 6 interventions[30-35] that were conducted in pharmacies, all administered by pharmacists. All but one study in this group showed success at improving adherence. Although methods of measuring adherence differed between studies, the successful interventions improved adherence by 7% to 27% (Table 2). Interventions in this group were similar, involving an in-person meeting with a pharmacist in which patient-centered medication histories were obtained, medication knowledge was elicited and expanded upon, and disease and lifestyle teaching was conducted, sometimes with accompanying written information. All six studies lasted between 6 and 12 months.

Lee[30] made use of blister packaging in addition to clinical pharmacist meeting and medication education for 159 patients with hypertension, hyperlipidemia, and other diseases, and found 96% adherence at 6 months in intervention patients compared to 69% in controls ($p<0.001$). Murray[31] found an adherence improvement of 11 % (95% CI 5%, 17%) among 314 patients with hypertension over 12 months but noted that the difference declined to a nonsignificant level after the intervention was discontinued. Blenkinsopp[32] followed 282 patients with hypertension from community pharmacies over 6 months (63% intervention vs. 50% control, $p<0.05$). Bouvy[35] followed 152 patients with congestive heart failure, defining non-adherence as <80% of days without opening the electronic pill bottle, and found all patients in the intervention group took pills >80% of days, while 86% in the control reached that threshold (RR 0.5, CI 0.4-0.6). Vrijens[33] followed 392 patients with hyperlipidemia and found that intervention patients at follow-up had higher adherence (96% vs. 89, $p<0.001$). Jaffray's study[34] of patients with coronary artery disease used a self-

reported score to measure adherence (making a comparison to other studies difficult) and reported very high baseline and follow-up adherence scores. For this reason, the nonsignificant findings in this study may not be representative of the group of pharmacist interventions.

We identified 15 in-person studies[36-50] that were conducted in a clinic setting. Among in-person clinic interventions conducted by a lay person or nurse[36-39], 50% of studies showed significant improvement over control (Table 2). Whereas in-person pharmacist interventions showed high success rates when conducted in a pharmacy, in-person pharmacist interventions in clinics[40-47] showed the lowest rate of success among clinic interventions (38% compared to 50-67% for other in-clinic interventions). All three successful clinic interventions [41, 46-47] were carried out at clinics that also had medication dispensing capabilities. The five unsuccessful clinic interventions[40, 42-45] were carried out at primary care offices and neighborhood clinics that did not dispense medications.

Three in-person clinic interventions were carried out by physicians[48-50]. Although two of these studies were successful[49-50], neither used a rigorous method of assessing adherence. Yilmaz[49] studied the impact of verbal advice on statin benefits from an “expert physician”. At the end of the study there was an increased likelihood of being on continuous statin therapy (63% intervention vs. 46% control) but the authors do not define the outcome or the data source. Avanzini[50] studied 1771 patients with hypertension, randomized to care by doctors who (1) had the opportunity to educate themselves extensively on hypertension and (2) then designed and implemented hypertension management guidelines compared to care by doctors without this experience. At follow-up, 4% of intervention vs. 10% of controls “admitted poor compliance” but the authors give no further information on how this outcome was calculated. Birtwhistle[48] randomized patients with hypertension to every 3 vs. every 6 month physician follow-up and found no significant difference in adherence. In-person interventions for patients at the point of hospital discharge[51-56] (67% successful) showed lower success rates than interventions carried out in a pharmacy (83%) but higher success than those carried out in a clinic setting (47%). However, while four out of six showed significant improvement in adherence[52, 54-56], two of the successful studies had unclear definitions of adherence.

Of the six studies, four recruited in-hospital patients exclusively and followed them after discharge while two studies recruited patients from both in-hospital sites and outpatient clinics.

Tsuyuki[51] found a non-significant effect of educational meetings with a research assistant prior to hospital discharge, accompanied by adherence aids, phone and mail follow-up. Krantz[52] found a significantly higher rate of beta blocker utilization (96% intervention vs. 48% control) after predischarge nurse counseling and outpatient nurse follow-up, but the term “utilization” was not clearly defined. Two of the three pharmacist interventions[54-55] showed significant improvement although Sadik[54], who evaluated pharmacist education for congestive heart failure, did not clearly define the way self-reported adherence was calculated. Varma’s study[55], a successful pharmacist intervention which defined adherence as 80-120% of all congestive heart failure drugs taken at 12 months, found a significant effect (77% intervention vs. 30% control). Edworthy[56] followed 2643 cardiac patients after hospitalization, giving in-hospital counsel on medications and medical conditions by nurses and pharmacists along with video, printed material, and phone follow-up by both a nurse and a pharmacist. Significant improvement in adherence was seen for both beta-blocker (intervention 89% vs. control 80%, $p<0.01$) and lipid-lowering agents (intervention 83% vs. control 78%, $p<0.05$).

Discussion

Our review of interventions to improve adherence to cardiovascular and diabetes medications yielded a highly diverse group of interventions. Several themes arose regarding the effectiveness of different approaches that may inform future intervention development.

Among person-independent interventions, those that used electronic interventions showed promise. Effective electronic interventions included those that were designed to be individualized using either computer-generated algorithms or hierarchically structured messages, and one study effectively combined hierarchical phone messages and targeted phone follow-up by a nurse. Home automatic blood pressure monitoring and programmable pill caps with reminder cues also demonstrated promising results. Adherence interventions delivered via paper or video showed minimal effectiveness unless targeted at a group (in this case hospitalized patients post-myocardial infarct) that was especially likely to be sensitive to the message.

Among person-dependent interventions, the results of phone call interventions were not encouraging. Only a minority were effective. These interventions targeted groups at a time in their lives when they should have been particularly sensitive to the message (e.g., immediately post bypass surgery, percutaneous intervention or hospitalization for congestive heart failure, or after a new diagnosis of hypertension).

In-person interventions yielded some interesting patterns. Home visits, an expensive intervention, were only effective in half the studies identified; both of the effective studies sought to target a family member as support person, while neither of the ineffective studies did so. The data on worksite interventions were limited and no recent studies were identified. Interventions carried out in the pharmacy (all by pharmacists) were almost uniformly effective and were a fairly homogenous group in both the nature of the services rendered and in duration of follow-up. Interestingly, when we looked at the group of interventions carried out in the clinic by pharmacists, only three out of eight were effective. All three of these were carried out in clinics that also had dispensing abilities and therefore may have been more similar to the group of in-person pharmacy interventions. Interventions that targeted patients at the point of hospital discharge were more effective than those that focused on clinic patients, though the lower number of in-person hospital studies should be noted (6 compared to 15 clinic studies).

Person-dependent administration of an adherence intervention can be costly, whether carried out by a lay person, nurse, pharmacist or physician. We found the success rate of person-dependent interventions comparable or lower than that of person-independent interventions. We interpret this result cautiously, given the presence of fewer person-independent interventions overall.

The wide heterogeneity of the adherence intervention studies we identified should prompt us to interpret all comparisons with caution. We included studies with differing populations (patients from different countries and with different cardiovascular diseases; nonadherent vs. all patients; hospitalized vs. outpatient) and we encountered a wide variety of study designs, including some with idiosyncracies that limited their generalizability. In addition, while a detailed discussion of comparative adherence measurement methods is outside the scope of this paper, we found inconsistencies in methods of adherence measurement across the studies reviewed, demonstrated most clearly in our tables. Direct comparison of the magnitude of intervention effect is complicated by this heterogeneity. While we were able to consider some aspects of healthcare setting in our analysis, stratification by health care facility size was not possible due to inconsistencies in reporting. Finally, although over 40%

of studies identified showed no significant improvement, publication bias may also be playing a role in our findings.

We suggest that future research focus on (1) the life-events causing increased patient receptiveness to the adherence message (i.e. hospital stays, particularly after a serious cardiac event); (2) the psychological factors present during an acute illness and hospital stay as they relate to a patient's willingness to modify adherence behavior; (3) in-person pharmacist counsel delivered at the site of medication dispensing (so that arriving for an appointment to discuss adherence can be combined with retrieving the medication); (4) new and innovative ways to take advantage of electronic technologies.

We saw few interventions that capitalized on lay-person social networks, either electronic or in-person. Research on adherence to other medically recommended behaviors including cancer screening has indicated that this may be a promising direction[57], and the same may be true for medication adherence interventions.

In conclusion, among interventions to improve adherence to cardiovascular medications, electronic interventions, in-person pharmacist interventions held at a site of medication dispensing, and in-person interventions targeted to patients at the point of hospital discharge showed the highest rates of success. Future studies should explore new electronic approaches and in-person interventions at the site of medication distribution. A focus on identifying times of increased patient receptivity to the adherence message will also be important.

Appendix. Pubmed search term

("compliance"[tiab] OR "patient compliance"[mesh] OR "patient adherence"[tw] OR "patients adherence"[tw] OR "patient compliance"[tw] OR "medication adherence"[tw] OR "medication compliance"[tw] OR "treatment compliance"[tw] OR "Treatment Refusal"[mesh] OR "patient dropouts"[mesh] OR "treatment refusal"[tw] OR "patient dropout"[tw] OR "patient dropouts"[tw] OR "patient dropped"[tw] OR "drug adherence"[tw] OR "drug compliance"[tw] OR "persistence"[tw] OR (("compliance"[tw] OR "adherence"[tw]) NOT medline[sb])) AND ("drug therapy"[mesh] OR "drug therapy"[sh] OR "Pharmaceutical Services"[mesh] OR "Medication systems"[Mesh] OR "Drug Utilization Review"[mesh] OR "pharmacies"[mesh] OR "Pharmaceutical Preparations"[mesh] OR "prescription drugs"[tw] OR "prescription drug"[tw] OR "drug therapy"[tw] OR "drug treatment"[tw] OR (("drug"[tw] OR "drugs"[tw] OR "medicine"[tw] OR "medicines"[tw] OR "medication"[tw] OR "medications"[tw]) NOT medline[sb]) OR "Cardiovascular Agents/therapeutic use"[Mesh] OR "Hypoglycemic Agents/therapeutic use"[Mesh] OR "Antihypertensive agents/therapeutic use"[Mesh] OR "Antilipemic Agents/therapeutic use"[Mesh]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR "randomized controlled trials as Topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "single-blind method"[MeSH Terms] OR ("random allocation"[TIAB] NOT Medline[SB]) OR "random allocation"[MeSH Terms] OR "controlled"[TIAB] OR "Evaluation Studies as Topic"[Mesh] OR random*) AND (("Cardiovascular Diseases"[Mesh] OR "Myocardial Revascularization"[Mesh] OR ("cardiovascular"[tw] NOT medline[sb]) OR "Heart failure"[tw] OR "Myocardial Failure"[tw] OR "Heart Decompensation"[tw] OR "Cardiac Failure"[tw] OR "Ischemic Heart Disease"[tw] OR "Ischemic Heart Diseases"[tw] OR "Myocardial Ischemia"[tw] OR "Myocardial Ischemias"[tw] OR "Coronary Disease"[tw] OR "Coronary Diseases"[tw] OR "Coronary Heart Disease"[tw] OR "Coronary Heart Diseases"[tw] OR "Platelet Aggregation Inhibitors"[Mesh] OR "Diuretics"[Mesh] OR "Diuretics"[Pharmacological Action] OR "Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic beta-Antagonists"[Pharmacological Action] OR "Angiotensin-Converting Enzyme Inhibitors"

[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors “[Pharmacological Action] OR “Vasodilator Agents”[mesh] OR “Vasodilator Agents “[Pharmacological Action] OR “Cardiovascular Agents”[Mesh] OR “Cardiovascular Agents “[Pharmacological Action]) OR (“Diabetes Mellitus”[Mesh] OR “diabetes”[tw] OR “Insulin”[Mesh] OR “insulin”[tw] OR “hypoglycemic agents”[Mesh] OR “hypoglycemic agents”[pa] OR “hypoglycemic agent”[tw] OR “antidiabetic”[tw] OR “hypoglycemic drug”[tw] OR “hypoglycemic agents” [tw] OR “antidiabetics”[tw] OR “hypoglycemic drugs”[tw]) OR (“Antihypertensive agents” [Mesh] OR “Antihypertensive Agents”[pa] OR “hypertension”[MeSH Terms] OR “Blood Pressure”[Mesh] OR “high blood pressure”[tw] OR “high blood pressures”[tw] OR antihypertensive[tw] OR hypertension[tw]) OR (“Hyperlipidemias”[Mesh] OR “Antilipemic Agents”[Mesh] OR “Antilipemic Agents”[pa] OR “Hyperlipidemia”[tw] OR “Hyperlipemia”[tw] OR “Hyperlipemias”[tw] OR “Lipidemia”[tw] OR “Lipemia”[tw] OR “Lipemias”[tw] OR “Hyperlipidaemia”[tw] OR “Hyperlipaemia”[tw] OR “Hyperlipaemias” [tw] OR “Lipidaemia”[tw] OR “Lipaemia”[tw] OR “Lipaemias”[tw] OR “Hypercholesterolemias”[tw] OR “Hypercholesteremia”[tw] OR “Hypercholesteremias”[tw] OR “statin*”[tw] OR “Anticholesteremic”[tw] OR “antilipidemic”[tw] OR “antilipemic” [tw] OR “cholesterol lowering”[tw])) AND English[lang]

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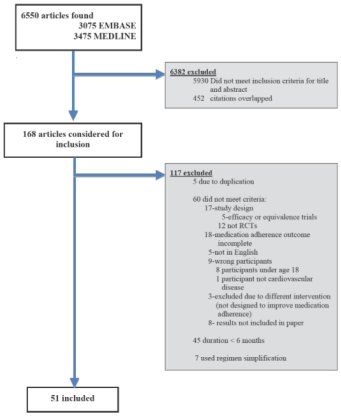

Figure 1.
Study Selection Criteria

Table 1

Person-Independent Interventions

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
Paper information: mailed, faxed or handed out				
Smith, 2008 U.S. urban centers	907 patients at hospital discharge post-MI, with β-blocker prescriptions 9 months	2 mailings to patients, PCP's addressing importance of β-blockers, guidelines.	% of patients with ≥80% of days covered in the 9 months after 1st mailing; pharmacy claims and other electronic data.	Treatment patients were 17% more likely to have 80% of days covered (RR 1.17; CI 1.02 -1.29)
Takala, J, 1983 Southwest Finland	147 untreated HTN patients 2 years	Mailed information on HTN	2 years after intervention, asked if "still under treatment after 2 years."	Adherent: I: 90% C: 79% P=NS
Video information: mailed or handed out				
Powell, KM, 1995	4246 patients on benzapril, metoprolol, simvastatin or estrogen. 9 months	Mailed 1 of 4 educational videotapes	MPR; pharmacy claims	No significant between-group differences in mean MPRs.
Electronic system				
Emmett, CL, 2005 Bristol, England.	217 newly diagnosed HTN patients, primary care practices 3 years	**1** Decision analysis (DA) **2** Video and leaflet **3** DA and video, leaflet vs.Usual care	Proportion of patients who report taking all their medications.	DA: 90% Adjusted OR 1.56, CI 0.49-4.96, p=0.45 Video plus leaflet: 94% Adjusted OR 0.53, CI 0.15 -1.84, p=0.32
Friedman, 1996 Boston	299 HTN patients. 6 months	Interactive computer-based home monitoring. Patient self-BP checks, weekly calls to counsel on adherence.	MPR (expressed as percent); home pill count	Mean Δ adherence, unadjusted: C: -0.4% I: +2.4% p=0.29 Adjusted for baseline adherence: I: 17.7% C: 11.7% p =0.03
Johnson, SS, 2006 Massachusetts and Rhode Island	404 adults with hyperlipidemia. 18 months	Population-based, computer-generated individualized intervention; report mailed to patient	Responses to 5 questions (on Likert scale) summed to create a continuous measure. Calculated Odds of appropriate adherence; Self-report	Adherence as continuous measure: 6 months OR 2.03 p>0.05 18 months OR 2.86 p<0.05
Marquez-Contreras, 2006 Spain	250 HTN patients from primary care centers 6 months	Home automatic BP monitoring	MPR (expressed as %); Adherent is >80%; MEMS	% of adherent patients I: 92 (SD 14.2) C: 74 (SD 18.1) P = 0.0007
Piette, 2000	280 DM patients on hypoglycemic medications. Included Spanish-speaking patients. 12 months	Biweekly automated assessment/ education calls: hierarchically structured messages (positive feedback for adherence, questions on adherence barriers, advice); targeted nurse follow-up calls.	Abbreviated Morisky Index. Patients considered nonadherent if they sometimes forgot or stopped taking medication. Phone interviews, self-report.	I: "substantially less likely" to report adherence problems (P=0.003).

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
Rosen, 2004 Connecticut	33 DM patients on metformin with <80% adherence 28 weeks	Cue-dose training: given electronic pill caps programmed to beep, instruction on other cues.	Mean MPR (doses needed to be taken on time); electronic pill bottles	16 weeks of intervention: I: 80% C: 60% p = 0.017 No numbers given for 28 weeks (graph provided)

Controls received usual care unless otherwise specified. Duration indicates time until last follow up in which adherence is measured. Confidence interval (CI) is 95% unless otherwise specified.

Unless country is otherwise indicated, study took place in United States.

HTN = hypertension; BP = Blood pressure; CHF = Congestive heart failure; MI = Myocardial Infarct; MEMS = Medication Electronic Monitoring System; PCP = Primary Care Practitioner; MPR = Medication Possession Ratio, medication doses taken divided by doses prescribed. “Morisky scale” has 4 questions: 1 pt for every ‘yes” response. 1.Do you ever forget to take your medication? 2.Are you careless at times about taking your medication? 3. When you feel better, do you sometimes stop taking your medication? 4. Sometimes if you feel worse when you take your medication, do you stop taking it? I = Intervention group; C=control group

Table 2

Person-dependent Interventions

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
Phone call (non-automated)				
Call by lay person				
Stewart, A, 2005 Johannesburg, S. Africa.	83 HTN patients, majority indigent. 36 weeks	Support of physiotherapist and family member by phone.	Self-described as adherent to medications	I: 82.4% C: 86.7% P = 0.56
Schectman, G, 1994 Milwaukee	162 patients with hyperlipidemia. 6 months	Weekly phone counsel in 1st month of therapy by medical assistant. Each group also randomized to niacin vs bile acid sequestrants	MPR; pharmacy claims	% Adherence, bile acid sequestrants: I: 88 (SD 4) C: 82 (SD 4) P = 0.32 Adherence, Niacin I: 90 (SD 2) C:84 (SD 3) P = 0.07
Call by nurse				
Hamet, P, 2003 Canada	4864 patients with essential HTN on irbesartan. 12 months	Behavioral modification program: phone nurse counsel, reminder letters, BP diaries, mailed education brochures.	"Are you taking your Avapro every day?" (no = nonadherent); self-report	% nonadherent patients I: 25.4% (CI 23.7-27.2) C: 25.5% (CI 23.8 -27.3) Between group difference: -0.1% (-2.6 to 2.3) p=0.94
Call by pharmacist				
Faulkner, MA, 2000 Omaha, Nebraska	30 patients post CABG, PTCA or both (7-30 days) 2 years	Weekly phone contact for 12 weeks. All received lovastatin daily and colestipol twice daily	Patients returning more than 20% of prescribed pills, and those failing to fill 80% or more of scripts at 1 and 2 years were considered nonadherent; pharmacy records	% adherent patients: Lovastatin: I: 1 year: 67% 2 year: 60% C: 1 year: 33% 2 year: 27% p<0.05 for all values (Colestipol findings similar, not shown here)
Mehos, 2000 Colorado	36 HTN patients from clinic in which pharmacist provides direct clinical services. 6 months	Home BP monitors, diary for BP and missed doses. Pharmacist evaluated BP by phone monthly.	MPR (mean), expressed as %; pharmacy refill data	I: 82% C: 89% p=0.29
Caller not specified				
Antonicelli, 2008 Italy	57 hospitalized CHF patients, age >70 12 months	home telemonitoring managed by specialized CHF team	% adherent patients (no further definition)	I: 91% C: 46% p<0.03
Sclar, DA, 1991 Delaware, Texas and Wisconsin.	453 HTN patients on atenolol. 180 days	On refill, educational material given. Phone contact, refill reminder, mailings. (4 arms. Each group divided: previously treated/newly diagnosed)	MPR: Multiplied the number of requested atenolol refills by 30 and dividing by 180	MPR (SD) Previously treated C: 0.48 (0.06) I: 0.82 (0.04) Newly diagnosed C: 0.52 (0.06) I: 0.93 (0.05) P<0.05
Guthrie, RM, 2001 Ohio	13,100 patients with elevated total cholesterol 6 months	Postal, phone reminders about coronary risk reduction and medication adherence	Taking pravastatin as prescribed per self-report: yes/no.	Taking as prescribed I: 79.7%, C: 77.4% Authors conclude: "no meaningful difference"
In person				

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
Home				
Lay person				
Saunders, LD, 1991 Soweto, S Africa	115 HTN patients 6 months	Appointment reminders sent; patient-retained BP and medication records. Targeted fieldworker home visit follow-up.	MPR based on clinic instructions Adherent: ≥80% consumed	I: 31%, C: 15% P= 0.19
Johnson, 1978 Hamilton, Ontario, Canada.	140 people with persistently elevated DBP 6 months	2×2 factorial: I1-self-recording BP I2-monthly home visits I3-self-recording and home visits C-control (neither)	% adherence estimated by comparing pills on hand with prescription records; self-report, pill count	Mean Δ adherence (SD): I1-self-recording BP: 11.8% (4.5%) I2-monthly home visits: 2.2% (5.6%) I3-self-recording + home visits: 10.1% (4.9%) C: 1.0% (7.0%) P=NS
Morisky, DE, 1985 Baltimore, Maryland.	290 HTN patients 18 months	Family support: Home interview, training with family member	Scale: 0-4 (1 point per yes answer) (4 = lower compliance); self-report	Intervention group had improved scores (0.876 vs 1.932, p<0.01)
Nurse				
Kirscht, JP, 1981 Tecumseh, Michigan	417 patients with HTN 3 year	Assigned to 4 interventions in a factorial design: 3×2×3×2 **1** Printed messages **2** Nurse phone reminder and reinforcement **3** Self-monitoring with charts **4** Nurse worked with support person	MPR; pharmacy records Averaged over the set of HTN medications.	Printed information:* I: 0.689 C: 0.684 Nurse phone contact:** I:0.749 C:0.690 Self-monitoring* Charts: 0.683 BP: 0.665 C: 0.665 Nurse support:** I:0.654 C: 0.545 *Between group: NS **Between group P<0.05
Work-site				
Nurse				
Logan, 1979 Toronto, Canada	457 HTN patients selected from various work-sites. 6 months	I: Work-site care: nurse working under physician supervision managed all aspects of HTN.	Adherence: ≥ 80% of prescribed medications were consumed (pill count) and patient claimed to be taking the medication as instructed (self-report)	% of Adherent patients: I: 67.6% C: 49.1% p<0.005
Logan, 1983 Toronto	194 HTN patients 1 year	I: Worksite care by physician plus nurse. Nonadherents: counseled on medication diary, tailored regimen, home BPs; increased visit frequency.	% adherent patients (≥80% of prescribed medication taken); Home pill count	I: 55.4% C: 55.7% P = NS
Doctor				
Sackett, 1975 Hamilton, Ontario	230 Canadian steelworkers with HTN detected on screening. 6 months	Augmented convenience(AC) HTN treated by worksite doctor. Additional education (AE): program on HTN, pill-taking reminders C: no AC, no AE	Adherence: MPR in 6th month; pill count. Adherent is MPR ≥ 0.8	% compliant at 6 months AC: 54% No AC: 51% AE: 50% No AE: 56% AE: with AC: 48% without AC: 53% No AE: with

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
		I-1: AC, no AE I-2: no AC, AE I-3: AC, AE		AC: 62% without AC: 48% Nonsignificant difference
Pharmacy				
Pharmacist				
Lee, JK, 2006 Walter Reid Army Medical Center	159 patients with HTN, Hyperlipidemia, other diseases. 6 months	Pharmacy care (education, blister packs, meeting with clinical pharmacist).	Mean MPR for all chronic diseases; pill count	Mean (SD) I: 95.5%(SD 7.7%) C: 69.1%(SD 16.4%) p<0.001
Murray, 2007 Indianapolis, Indiana	314 HTN patients from inner-city practice. 12 months	Pharmacist medication history, knowledge assessment, verbal, written education	% of prescribed medication taken; MEMS	During intervention: I: 78.8% C: 67.9% Difference: 10.9% CI: 5.0 16.7% Post-intervention difference: 3.9% CI: -2.8 -10.7
Blenkinsopp, 2000 England	282 HTN patients from community pharmacies. 6 months	Pharmacist counsel: structured, questions, medication advice, HTN teaching	% Adherent patients; Modified version of Horne's Medication Adherence Report Scale (MARS) used.	I: 62.9% C: 50.0% p<0.05
Vrijens, B, 2006 Belgium	392 patients with hyperlipidemia on atorvastatin. 12 months	I:Pharmacy program: medication history educational reminders, written information. C: Written information	% of days that medication container opening was recorded; MEMS	I: 95.89% (CI 90.28 - 98.66) C: 89.37 (CI 69.70 -96.33) P<0.001
Jaffray, 2007 England	1493 CAD patients from primary care organizations.	Community pharmacist assessed therapy, adherence, lifestyle, social support.	Adherence score (12-60) based on 12 questions; self-report	I: 59 (57-60 IQR) C: 59 (57-60 IQR) OR =1.0, 95% CI: 0.61-1.65 p=0.99
Bouvy, 2003 The Netherlands	152 CHF patients, inpatient and outpatient. 6 months	Community pharmacist: structured interview using computerized record, discussed medications, nonadherence.	Adherence based on % of days without opening pill bottle. Nonadherence defined as <80% of days; MEMS	% nonadherent patients I: 0% C: 14% RR 0.5 CI 0.4-0.6
Clinic				
Lay person				
Ogedegbe, G, 2008 New York, NY.	190 HTN patients, African-Americans, most women 12 months	Motivational interviewing with patient-centered counseling by research assistants.	MPR, expressed as %; MEMS	I: 60% C: 47% p=0.054 intent-to-treat analysis showed model-predicted rates: I: 57% C:43% p=0.027
Haynes, RB, 1976 Canada	39 noncompliant HTN patients (pill count <80% at baseline) 12 months	Visits every 2 weeks with research assistant. Home BP self-checks, medication and BP charting; tailoring regimen	Proportion of prescribed pills removed from their containers.	Mean (SD): I: 65.8% (8.2) Within group p = 0.001 C: 43.2(10.1) Within group p=NS Between groups p=0.025
Nurse				
Schroeder, K, 2005 Avon, UK	245 HTN patients 6 months	Nurse-led adherence support sessions	MPR (expressed as %); MEMS, used for 1 medication only	I: 95.6 (SD 16.4) C: 95.6 (SD 15.7) p=0.76

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
Rudd, 2004 California	150 patients on medication for HTN. 6 months	I: Physician-directed, nurse-managed algorithm-based home HTN management, based on self-BP checks.	Adherence: average % of days on which the correct number of doses were taken; electronic pill monitors	Mean (SD) I: 80.5% (23.0%) C: 69.2% (31.1%) p=0.03
Pharmacist				
Vivian, EM, 2002 Philadelphia, Pennsylvania	56 male HTN patients, majority African-American. 6 months	Monthly pharmacist counseling: changed drugs, adjusted doses.	Nonadherence = failure to refill within 2 weeks of scheduled refill date or missing > 3 doses in 1 week; pharmacy records:	% of adherent patients I: 85% C: 93% p>0.42
Phumipa-morn, S, 2008 Krabi Province, Thailand.	135 Muslim DM patients. 8 months	Pharmacist meeting day of doctor visit. Visit reminder 3 days prior. Given refills, lifestyle and medication education.	MPR (expressed as %); pill count	Mean difference (CI): I: + 6.8% (2.1,11.4) P= 0.005 C: -2.8(-7.31,1.7) p= 0.29 Between-group mean difference p=0.004
Hunt, 2008 Oregon	463 uncontrolled HTN patients 12 months	Pharmacists managed HTN in PCP office with physician input.	% with high adherence, categorized by Morisky scale; Self-report	I: 67% C: 69% p = 0.77 Change in I: p=0.08 Change in C: p=0.52
Taylor, 2003 Alabama	81 patients with ≥3 diseases (HTN, dyslipidemia, DM were most common) 1 year	Pharmacy care medical history, medication review and education; monitoring. Simplified regimens, devised reminders.	Estimated MPR;self-report Mean compliance score calculated from scores for each medication.	12 month: I: 100% C: 88.9% (6.3) p=0.115
Hawkins, 1979	200 HTN patients on a diuretic +/- methyldopa. 29 months	I: Clinical pharmacist managed HTN in place of physician	% of adherent patients (MPR > 0.80 considered adherent); pharmacy records	Diuretic only: I: 60.5%, C: 52.9%, p≤0.7 Diuretic plus Methyldopa: I: 84.6%, C: 65.4%, p≤0.2
Odegard, 2005 Seattle, Washington	77 subjects with HgA1c≥9 taking DM medication. 12 months	Pharmacist developed care plan, regular pharmacist-patient communication on DM care, medication problems.	Adherence based on 2 questions: “Do you ever find it difficult to remember to take (medication name)?” If yes, “How many times over the last 2 weeks have you missed a dose?”	Control showed better adherence than intervention throughout study (p=0.003)
Sookaneknun 2004 Urban and rural Thailand	235 HTN patients from pharmacy and primary care. 6 months	Research pharmacist consult: assessed medication understanding, adherence, counseled on use, lifestyle. Educational leaflets, diary.	Calculated MPR, expressed as % ≥ 80% necessary to be considered adherent	% of adherent patients: I: 63.64%, C: 55.56% p=0.014
Solomon, 1998 Multiple sites	133 HTN patients. 6 months	Standardized pharmacy care: patient assessment, regular interventions for disease management and education.	Adherence score based on 4- point Morisky scale; self-report	I: 0.23(0.054) C: 0.61(0.094) p<0.05 compared within and between groups.
Doctor				
Birtwhistle, 2004 Urban, rural Canada	614 HTN patients. 36 months	3 month vs 6 month physician follow-up	Morisky scale questions including: Ever forget blood pressure pills?; self-report	I-3 month: 30% I-6 month:27% Difference: 2.96% (SE 3.92) 90%CI(-3.48 - 9.41)
Yilmaz, MB, 2005 Ankara, Turkey.	202 patients on statin for secondary prevention. 15 months	Education which included physician conversation on statins	Odds of being on continuous statin (after	I: more likely to be on continuous

Author, Year, Site	Participants, Duration	Intervention	Adherence Measures	Outcomes
			median of 15 months); Self-report	statin, OR 1.977 (CI 1.127-3.468)
Avanzini, 2002 Italy	1771 treated HTN patients 1 year	Physicians treating intervention group wrote guidelines on HTN management. Control: patients of non-guideline writing physicians.	% of patients with poor adherence; self-report. (not defined further)	I: 3.8% C: 9.5% p=0.004
Hospital (or combination of Hospital and Clinic)				
Lay person				
Tsuyuki, RT, 2004 Canada	276 patients with CHF discharged from hospital. 6 months	Education; adherence aids (organizer, schedule), phone, mail follow-up C: pamphlet	MPR for ACE inhibitor, expressed as %; pharmacy records	I: 83.5% (SD 31.2) C: 86.2% (SD 29.0) P=0.691
Nurse				
Krantz, 2008 Denver, Colorado	64 CHF patients with ejection fraction <40% 6 months	Pre-hospital discharge carvedilol inititation and nurse counseling with outpatient nurse management	Beta-blocker “utilization.” On medication (yes/no); pill count	Beta-blocker utilization: C: Hospital discharge: 9.4% 6 months: 47.8% I: Hospital discharge: 96.9% 6 months: 96.2% Utilization significantly higher in intervention group at all time periods, p<0.001.
Pharmacist				
Lopez Cabezas, C, 2006 Barcelona, Spain	134 hospitalized patients with CHF 1 year	Pharmacist program: educational interview with patient and caregiver at discharge, follow up phone calls	Adherent: 95-100% of prescribed doses taken	% of adherent patients at 1 year: I: 85.0% C: 73.9% P = NS
Sadik, 2005 Al-Ain, United Arab Emirates	221 CHF patients. 12 months	Structured pharmacist counsel (in clinic or hospital); CHF and medication education, booklet; self-monitoring: 1-month card (told to bring to PCP).	“Patient self-report on missing dose or taking extra doses without medical advice”, no further definition.	Number of compliant patients I: 85, C:35; P<0.05
Varma, 1999 Northern Ireland	83 elderly CHF patients followed after hospital discharge. 12 months	Pharmacist counseling on CHF medications, adherence, lifestyle. Dose simplification. symptom monitoring.	Adherence defined as 80-120% of medications taken for all CHF drugs assessed; pharmacy records	% of adherent patients: I: 76.9% C: 30% p=0.039
Nurse-pharmacist team				
Edworthy, 2007 Calgary, Alberta. Canada.	2643 cardiac patients after hospitalization. 19 months	In-hospital individual and group counseling on medications and medical conditions. Videos, printed materials; Developed longterm medication plans.	% of adherent patients (not further defined); self-report Data on medication use collected by: I: Nurses C: Nonmedical staff	Beta blockers I: 89% C: 80% p<0.01 Lipid lowering agents I: 83% C: 78% p<0.05

Controls received usual care unless otherwise specified. Duration indicates time until last follow up in which adherence is measured. Confidence interval (CI) is 95% unless otherwise specified.

Unless country is otherwise indicated, study took place in United States.

HTN = hypertension; BP = Blood pressure; CHF = Congestive heart failure; MI = Myocardial Infarct; MEMS = Medication Electronic Monitoring System; PCP = Primary Care Practitioner; MPR = Medication Possession Ratio, medication doses taken divided by doses prescribed. “Morisky scale” has 4 questions: 1 pt for every ‘yes” response. 1.Do you ever forget to take your medication? 2.Are you careless at times about taking your

medication? 3. When you feel better, do you sometimes stop taking your medication? 4. Sometimes if you feel worse when you take your medication, do you stop taking it? I = Intervention group; C=control group

Table 3

Modes of delivery for adherence interventions and associated success rates

Study Type	# of studies	# showing improved adherence (%)
Person-Independent: Mailed, faxed or hand-distributed information		
Paper	2	1 (50%)
Video	1	0
Electronic system	6	4 (67%)*
All (person-independent)	9	5 (56%)
Person-dependent		
Phone call by:		
lay person	2	0
nurse	1	0
pharmacist	2	1 (50%)
caller not specified	3	2 (67%)
All (phone calls)	8	3 (38%)
In person visit (by site)		
Home		
lay person	3	1 (33%)
nurse	1	1 (100%)
Work-site		
nurse	2	1 (50%)
doctor	1	0
Pharmacy		
pharmacist	6	5 (83%)
Clinic		
lay person	2	1 (50%)**
nurse	2	1 (50%)
pharmacist	8	3 (38%)
doctor	3	2 (67%)
Hospital		
lay person	1	0
nurse	1	1
pharmacist	3	2 (67%)
nurse-pharmacist team	1	1 (100%)
All (in person)	34	19 (56%)
All (person-dependent)	42	22 (52%)

* Friedman et al showed nonsignificant improvement in unadjusted analyses and we classify this study as unsuccessful; however adjustment for age, sex, baseline adherence did show significant improvement.

** Ogedegbe et al showed nonsignificant improvement in analysis of study completers and we classify this study as unsuccessful; however, intent-to-treat analysis does predict significant improvement in intervention group adherence.