Targeting cardiovascular medication adherence interventions

Sarah L. Cutrona, Niteesh K. Choudhry, Michael A. Fischer, Amber D. Servi, Margaret Stedman, Joshua N. Liberman, Troyen A. Brennan, and William H. Shrank

Abstract

Objectives: To determine whether adherence interventions should be administered to all medication takers or targeted to nonadherers.

Data sources and study selection: Systematic search (Medline and Embase, 1966–2009) of randomized controlled trials of interventions to improve adherence to medications for preventing or treating cardiovascular disease or diabetes.

Data extraction: Articles were classified as (1) broad interventions (targeted all medication takers), (2) focused interventions (targeted nonadherers), or (3) dynamic interventions (administered to all medication takers; real-time adherence information targets nonadherers as intervention proceeds). Cohen's *d* effect sizes were calculated.

Data synthesis: We identified 7,190 articles; 59 met inclusion criteria. Broad interventions were less likely (18%) to show medium or large effects compared with focused (25%) or dynamic (32%) interventions. Of the 33 dynamic interventions, 6 used externally generated adherence data to target nonadherers. Those with externally generated data were less likely to have a medium or large effect (20% vs. 34.8% self-generated data).

Conclusion: Adherence interventions targeting nonadherers are heterogeneous but may have advantages over broad interventions. Dynamic interventions show promise and require further study.

Keywords: Medication adherence, cardiovascular disease, diabetes.

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Medications for preventing and treating cardiovascular disease can reduce morbidity and mortality, but nonadherence limits their benefits. Nonadherence is widely recognized as a major public health concern that contributes to patient morbidity, mortality, and health care costs.[1,2] Recent estimates indicate that nonadherence to essential chronic medications may contribute as much as $290 billion in excess costs to the U.S. health care system annually.[3] Improving adherence to therapy should be a priority for our health care system.

Despite broad recognition of the importance of medication adherence, little consensus exists about how to best change behavior and support appropriate use.[4] Studies show that multifactorial interventions tend to be more effective than simple ones[4]; however, the best manner in which to target these interventions remains unknown. Specifically, whether interventions should be targeted to nonadherers only or to all medication takers is unclear. Nonadherence may be improved more effectively if the patients most likely to benefit are targeted. Alternatively, waiting for nonadherence to occur may introduce missed opportunities if the optimal moment for intervention has already passed.

Objective

We conducted a systematic review of interventions to improve adherence to cardiovascular and diabetes medications, in order to explore what is known about how to target interventions. We evaluated existing evidence regarding delivery of interventions (1) exclusively to nonadherent patients, (2) to all patients regardless of adherence behavior, or (3) to all patients but using real-time adherence information during the intervention to identify nonadherers and thereby target resources.

At a Glance

Synopsis: Medline and Embase were searched for articles on medication adherence interventions classified as broad interventions (targeting all medication takers), focused (targeting nonadherers), or dynamic (administered to all medication takers, with real-time adherence information targeting nonadherers as intervention proceeded). Broad interventions were less likely (18%) to show medium or large effects compared with focused (25%) or dynamic (32%) interventions. Targeting nonadherent patients may lead to better adherence; however, data are limited and studies in the literature are highly heterogeneous.

Analysis: *Focused interventions allow limited resources to be directed toward fewer, higher-risk patients, and dynamic interventions share this advantage when the more costly portion of the intervention is reserved for identified nonadherers. However, attention must be paid to the method of identifying nonadherers. None of the focused interventions identified here used pharmacy claims data to identify nonadherence. Dynamic interventions were overwhelmingly dependent on self-generated adherence data (often requiring intensive interaction with a health provider), and very few used any form of external data. The accuracy, cost, and reproducibility of methods for identifying target populations must be a central consideration in future studies.*

Methods

A systematic search of peer-reviewed journals between 1966 and 2009 was performed using Medline and Embase. We limited our search to randomized controlled trials. Our search terms related to the type of study (randomized controlled trial), adherence (i.e., *adherence*, *compliance*, *medication adherence*, *treatment adherence*), prescription drugs (i.e. *drug*, *medication*, *antihypertensive*, *antihyperlipidemic*, *hypoglycemic*), and cardiovascular disease and diabetes (i.e., *myocardial infarction*, *coronary heart disease*, *heart failure*, *hypertension*, *dyslipidemia*, *diabetes*.) Articles with at least one search term in three of the main categories (study type and adherence and either drug or disease) met criteria for review. Search terms and parameters were adjusted for both databases (Medline and Embase) while maintaining a common overall architecture. Search results then were screened for duplicate entries.

Study selection

Studies were included if they reported results of randomized controlled trials studying interventions to improve adherence to medications used for preventing or treating cardiovascular disease or diabetes. Studies were limited to adult patients (age ≥18 years). We included only studies that reported long-term outpatient medication adherence. 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 one of our prespecified study strata (described below), and previous studies have demonstrated their effectiveness.[4] Non-English studies and those with a follow-up period of less than 24 weeks also were excluded.

Study classification

After exclusions, 59 articles (Figure 1) were classified based on the target of the main intervention as (1) focused interventions (targeted exclusively to nonadherers), (2) broad interventions (targeted to the entire population of medication takers), or (3) dynamic interventions (administered to all medication takers but using real-time adherence information to identify and target nonadherers). To meet criteria for classification as a dynamic intervention, interventions were required to report that information was gathered on adherence and acted on before the conclusion of the study in a way that would differentiate adherers from nonadherers (i.e., an adherence feedback loop). Ongoing measurements of clinical outcomes (e.g., blood pressure) were not considered substitutes for real-time measurements of adherence. However, we considered patient self-reported adherence to be an acceptable measure (as in a situation where a patient discussed adherence challenges with a pharmacist in the absence of calculations of a numerical adherence outcome).

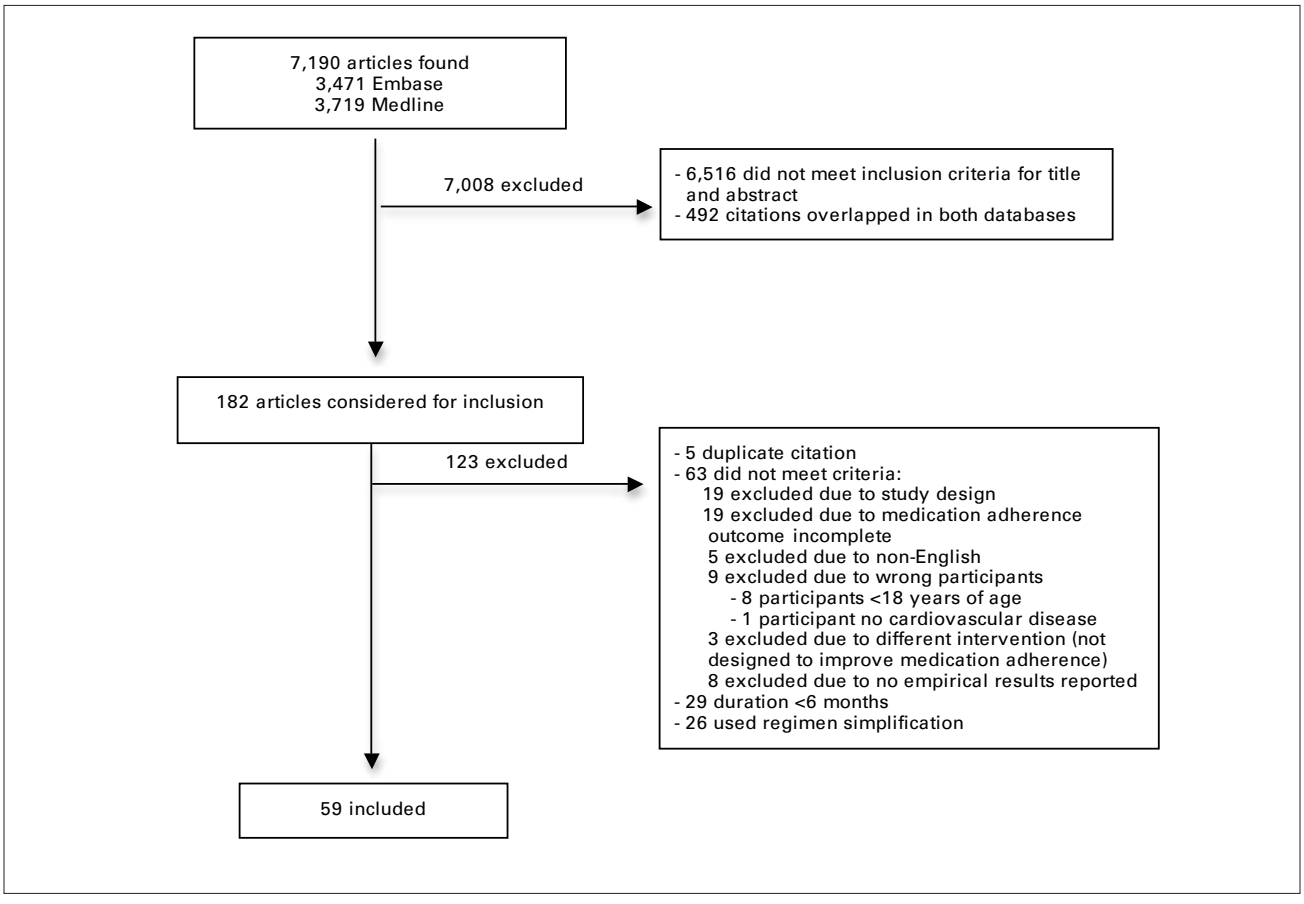

Figure 1. Included and excluded articles

We further classified dynamic studies based on the type of adherence data used in the adherence feedback loop: (1) self-generated data alone or (2) external data (either alone or as a supplement to self-generated data). Self-generated data feedback loops were those in which the intervention was tailored on the basis of patient self-reported nonadherence. For example, in a pharmacist counseling session in which the pharmacist does not have access to pharmacy records, a patient could report nonadherence and that would stimulate additional patient contact to support appropriate use. External data feedback loops were those in which information such as medication possession ratio derived from pharmacy records or other external sources was used to tailor the intervention. Authors were required to explicitly state that external data were accessed in real time before a study was characterized as using an external data feedback loop. We did not consider patient-controlled sources such as medication diary cards to be external data but did consider a pill count conducted by someone other than the patient to meet this criterion.

This classification was often distinct from the way adherence was ultimately measured as the study outcome. For example, patients might describe themselves as nonadherent in a pharmacist counseling session and receive appropriate interventions, while adherence outcomes were measured with claims data. In this scenario, we would classify the feedback loop as using self-generated adherence information.

Data extraction

Data were extracted by two investigators (S.L.C. and W.H.S.) with disagreements resolved by consensus. We assessed a number of variables related to the organization and outcome of studies, including study design, setting, characteristics of study population, number of participants, mean age (or age range) of participants, characteristics of intervention, methods used to measure medication adherence, clinical outcomes, medication adherence outcomes, and source of funding. CIs are reported when available and *P* values when no CIs were available. The methodological quality of studies was assessed using the five-point Jadad scale.[5] Because the overwhelming majority of adherence interventions identified in this study were not able to be double blinded, Jadad scores tended to be low. For this reason, we chose not to use a cut-off value and did not ultimately consider Jadad scores to be a useful means of ascertaining study quality. Jadad scores and funding sources for all studies are presented in Appendix 1 (electronic version of this article, available online at www.japha.org).

We identified randomized controlled trials in which means

and SDs for medication adherence outcomes were presented. A wide range of adherence outcome measures were observed, including binary (e.g., survey responses or predefined adherence cutoffs) and continuous measures (e.g., proportion of days covered), making interpretation of absolute changes difficult. To compare studies with differing outcomes, we used Cohen's *d* statistics, which can be calculated for outcomes that are either binary or continuous.[6,7] The effect sizes (ESs) compare the difference in effect between the study groups divided by the SD of this difference.[8] When SDs were not reported, we derived them from the *P* value or *t* test statistic.

Using standard methods, we considered an ES less than 0.2 to be very small, 0.2 to less than 0.5 small, 0.5 to less than 0.8 medium, and 0.8 or greater large. We used this categorization to simplify interpretability for readers so that magnitude of effect is more intuitive. We assumed that the estimated Cohen's *d* statistics were independent of scale, sample size, and the SD of the outcome studied.

We attempted a fixed-effects meta-analysis in which ESs were pooled. We performed an analysis of statistical heterogeneity in the intervention groups with at least 10 studies (broad intervention, dynamic self-generated intervention), and after finding high statistical heterogeneity in these groups (broad heterogeneity = 4.1, dynamic heterogeneity = 2.6), we removed outlying and influential studies and performed the analysis again. Heterogeneity measures remained high (broad heterogeneity = 1.7, dynamic heterogeneity = 1.8). Heterogeneity statistics above 1.5 indicate high heterogeneity.[9] Based on this finding and the clinical heterogeneity of the identified studies, we did not feel that presenting summary estimates was appropriate.

Results

Focused interventions

We found only four focused interventions[10–13] (Table 1), with mean participant ages ranging from 62 to 67 years. Adherence was measured differently in each study, and none of the studies made use of pharmacy claims data to determine inclusion criteria. One study showed a medium ES; the other three showed small ESs.

Haynes et al.[10] identified 39 nonadherent hypertensive patients from an initial group of 245 patients found to be hypertensive during workplace screening and advised home blood pressure self-checks, biweekly home visits by research assistants, and tailoring of the regimen. They found a medium ES by pill count at 6 months (0.73 [CI 0.07–1.39]).

Of an initial group of 79 patients with diabetes, Rosen et al.[11] selected 33 patients on metformin with poor adherence measured with electronic pill bottles. These patients were randomized to 16 weeks of programmable electronic pill caps versus nonprogrammable electronic caps. Although Rosen et al. described significantly improved adherence at 16 weeks based on medication possession ratio (80% intervention vs. 60% control, $P = 0.017$; ES 0.43 [CI –0.27 to 1.14]), the study provides only a graphic representation of outcomes at 28 weeks (both groups declined). Saunders et al.[12] identified a group of hypertensive "infrequent attenders" to a medical clinic in Soweto, South Africa, where medications were dispensed at the clinic appointment. They identified 109 nonadherent patients, 72 of whom were included in the analysis. Appointment reminders, patient-retained records, and targeted home visits yield significant improvement in the intervention group (68% vs. 37% control, $P = 0.009$) with a small calculated ES.

Taylor et al.[13] randomized 81 patients at high risk for medication events and analyzed 69 of them. Inclusion criteria included (but were not limited to) patient- or physician-reported nonadherence. Intervention patients received 20-minute counseling session at the pharmacy before physician office visits. Baseline data for the study indicated that 84.9% of the intervention patients and 88.9% of control patients had self-reported mean adherence scores between 80% and 100%. At 12 months, self-reported mean adherence scores showed a small ES difference between the intervention (100% adherence) and control (88.9%) groups. High initial adherence rates (or artificially inflated self-reports of adherence) may render this study less representative of a focused intervention than the previous three.

Broad interventions

We identified 25 broad interventions[14–38] (Table 2) and calculated ESs in all but three cases.[22,25,32] Mean ages of participants ranged from 46 to 76 years. We found medium to large effects on adherence in 18.2% of studies; 68.2% had very small or small effects and 13.6% had no effect or negative effects. The vast majority of interventions (19 of 25 studies) examined hypertensive patients; others addressed patients with diabetes (2 studies), dyslipidemia (1), congestive heart failure (1), myocardial infarction (1), and both cardiac and noncardiac diseases (1).

A total of 13 studies described interventions dependent on involvement of a health professional: physician mediated,[14,15,17,25,29,32,38] pharmacist mediated,[20,22] or nurse mediated.[19,22,23,31] Among these studies, ESs could be calculated for 10 studies, with 7 showing small or very small ESs, 1 a medium effect, and 2 negative or null effects. Yilmaz et al.,[38] who showed an ES in the medium range, implemented a primarily educational intervention. The study involved comprehensive education on statins but allowed for consultation as needed with a physician and showed that intervention patients were more likely to adhere to statins (odds ratio [OR] 1.98) than control patients, based on self-report. The study with an ES of zero (Hamet et al.[19]) involved nurse counseling by phone combined with reminder letters and mailed education brochures, with adherence measured using a single-question self-report.

Six studies described the introduction of an electronic resource including computerized decision aid,[18] electronic monitor with reminder,[16] or home blood pressure monitor.[21,26,27,37] We calculated ESs for all six of these studies, and all but one showed very small or small effects on adherence. Johnson et al.[21] conducted a 2×2 factorial study combining self-recorded blood pressure values with monthly home visits, with a calculated ES of 1.51 (CI 0.96–2.05). We identified six stud-

Table 1. Focused interventions: Targeted to nonadherers

Author, year, site	Participants; duration[a]	Intervention[b]	Method of targeting intervention group nonadherers	Adherence measures	Outcomes, Cohen's *d* ES (95% CI)[c]
Haynes, 1976, Canada	39 hypertensive patients identified as nonadherent (pill count <80%) after 6 months of treatment, also not at goal diastolic BP; 12 months	I: Home BP self-checks, medication and BP charting reviewed at 2-week intervals by research assistant during home visit, tailoring of regimen	Positive reinforcement for perfect adherence, reasons for nonadherence sought and attempts at problem solving through tailoring of regimen for nonadherence	Proportion of prescribed pills removed from containers.	Mean ± SD: I, 65.8% ± 8.2%, within-group $P = 0.001$; C: 43.2% ± 10.1%, within-group P = NS; between-group $P = 0.025$; ES 0.73 (0.07–1.39)
Rosen, 2004, Connecticut	33 diabetes patients on metformin with <80% adherence after 4-week baseline; 28 weeks	I: Cue-dose training: given electronic pill caps programmed to beep, instruction on other cues	Adherence data given monthly to providers; providers contacted before appointments, urged to discuss adherence data	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 only); ES 0.43 (–0.27 to 1.14)
Saunders, 1991, Soweto, S. Africa	Hypertensive patients divided into newly treated (115, not shown here) and nonadherent (109); 6 months	I: Appointment reminders sent; patient-retained BP and medication records; medications obtained at clinic visits	Targeted fieldworker home visit follow-up if no response to two callback letters	MPR based on clinic instructions; adherent if 80% consumed	Nonadherent: I, 68%; C, 37%, $P = 0.009$; ES 0.39 (–0.20 to 0.97)
Taylor, 2003, Alabama	81 patients[d] at high risk for medication events due to polypharmacy, nonadherence (per medical record, self-report, or refill history), other; 1 year	I: Pharmacy care: 20-minute in-person meetings before physician office visits, included medical history, medication review, education, and monitoring	Pharmacist review, advice to physician (spoken or via medical record) and to patient; suggestions for nonadherers included simplified regimen, pill boxes, minimizing adverse effects, consolidating regimens, devising reminders	Estimated MPR: self-report; mean adherence score calculated from scores for each medication	12 month: I, 100%; C, 88.9% ± 6.3%, $P = 0.115$; ES 0.38 (–0.11 to 0.87)

Abbreviations used: BP, blood pressure; C, control group; ES, effect size; I, intervention group; MPR, medication possession ratio; NS, nonsignificant.

[a]Duration indicates time until last follow-up at which adherence was measured.

[b]Control patients received usual care unless otherwise specified.

[c]95% CI unless otherwise specified.

For all studies where means (±SD) for adherence outcomes were available, Cohen's *d* statistics were calculated. The ESs compare the difference in effect between the study groups divided by the SD of this difference. We considered an ES <0.2 to be very small, 0.2–0.5 small, 0.5–0.8 medium, and >0.8 large.

[d]All patients in this study had three or more diseases, with hypertension, dyslipidemia, and diabetes being most common.

Table 2. Broad interventions (targeted to all medication takers) designed to improve adherence to cardiovascular medications

Author, year, site	Participants; duration[a]	Intervention[b]	Adherence measures	Outcomes, Cohen's *d* ESs (95% CI)[c]
Avanzini, 2002, Italy	1,771 treated hypertensive patients; 1 year	Patients followed by physicians who wrote guidelines for hypertension management	% of patients with poor adherence; self-report (not defined further)	Poor adherence: I, 3.8%; C, 9.5%, P = 0.004; ES 0.20 (0.13–0.27)
Birtwhistle, 2004, urban and rural Canada	614 hypertensive patients; 36 months	3- 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% ± 3.92% (mean ± SE); 90% CI (–3.48 to 9.41); ES 0.24 (0.07–0.42)
Christensen, 2010, Poland	784 hypertensive patients on telmisartan; 1 year (6 months per crossover arm)	Electronic adherence monitoring with audiovisual reminder device	Self-report: number of days in past week taking medication as prescribed; mean for population given as percent	12 months: I, 86.3%; C, 88.4%, P = 0.812; ES 0.06 (0.01–0.12)
Düsing, 2009, multiple sites in Germany	206 hypertensive patients newly diagnosed or untreated for 1 year; 34 weeks	Structured physician–patient interaction, printed hypertension information, reminder stickers, home timer, and BP measurements	Daily intake of medication at correct time; MEMS	For overall study duration: adherence for I is greater than C; P = 0.186; ES 0.08 (0.21–0.37)
Emmett, 2005, Bristol, U.K.	217 newly diagnosed hypertensive patients, primary care practices; 3 years	(1) In-person administration of decision aid on hypertension, cardiovascular risk; (2) video and leaflet; (3) decision analysis and video, leaflet vs. usual care	Proportion of patients who report taking all their medications	Decision analysis: 90%, adjusted OR 1.56 (0.49–4.96), P = 0.45; video plus leaflet: 94%, adjusted OR 0.53 (0.15–1.84), P = 0.32; ES 0.15 (–0.12 to 0.42)
Hamet, 2003, Canada	4,864 patients with essential hypertension 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% (23.7–27.2); C, 25.5% (23.8–27.3); between-group difference, –0.1% (–2.6 to 2.3), P = 0.94; ES 0 (–0.61 to 0.62)
Hawkins, 1979, Texas	200 hypertensive patients on a diuretic with/without methyldopa; 29 months	Clinical pharmacist managed hypertension in place of physician	% of adherent patients (MPR >0.80 considered adherent); pharmacy records	Diuretic only: I, 60.5%; C, 52.9%, $P \leq 0.7$; diuretic plus methyldopa: I, 84.6%; C, 65.4%, $P \leq 0.2$; ES 0.45 (–0.07 to 0.97)
Johnson, 1978, Hamilton, Canada	140 people with persistently elevated diastolic BP; 6 months	2 × 2 factorial: (1) self-recording BP, (2) monthly home visits, (3) self-recording and home visits; 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; ES 1.51 (0.96–2.05)
Kirscht, 1981, Tecumseh, MI	417 patients with hypertension; 3 years	Assigned to four 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 hypertension medications	Printed information: I, 0.689; C, 0.684, between-group P = NS; nurse phone contact: I, 0.749; C, 0.690, between-group P < 0.05; self-monitoring: charts, 0.683; BP, 0.665; C, 0.665, between-group P = NS; nurse support: I, 0.654; C, 0.545, between-group P < 0.05; ES unable to calculate

Table 2 continued

Logan, 1979, Toronto, Canada	457 hypertensive patients selected from various worksites; 6 months	Worksite care: nurse working under physician supervision managed all aspects of hypertension	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%, $P < 0.005$; ES 0.38 (0.13–0.63)
Lopez Cabezas, 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; ES 0.28 (–0.26 to 0.81)
Mann, 2009, New York	150 diabetes patients from primary care centers; 6 months	In-person review of statin risks and benefits with primary care provider, using statin decision aid at provider's discretion	Adherence assessed via 8-item Morisky adherence scale; does not define "good adherence"	80% of participants reported good adherence in both groups; P = NS; ES unable to calculate
Marquez-Contreras, 2006, Spain	250 hypertensive patients from primary care centers; 6 months	Home automatic BP monitoring	MPR (expressed as %); adherent is >80%; MEMS	% of adherent patients (mean ± SD): I, 92 ± 14.2); C, 74 ± 18.1, P = 0.0007; ES 0.29 (0.00–0.58)
Mehos, 2000, Colorado	36 hypertensive patients (with pharmacist providing 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; ES 0.35 (–0.32 to 1.02)
Morisky, 1985, Baltimore, MD	290 hypertensive patients; 18 months	Family support: home interview, training with family member	Self-report: scale 0–4 (1 point per yes; 4 = low adherence)	Intervention group had improved scores (0.876 vs. 1.932, $P < 0.01$); ES 0.87 (0.63–1.11)
Mullan, 2009, Minnesota	85 diabetes patients (randomized 40 clinicians); 6 months	Decision aid reviewing 5 diabetes drugs used during in-person clinician visit vs. control: educational pamphlet	Proportion of days covered,%; pharmacy records	% (range): I, 97.5 (0.0–100); C, 100 (73.9–100); adjusted mean difference, –8.88 (–13.6 to –4.14); ES –0.09 (–0.14 to –0.04)
Powell, 1995, midwest U.S.	4,246 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; ES 0.04 (–0.02 to 0.10)
Rudd, 2004, California	150 patients on medication for hypertension; 6 months	Physician-directed, nurse-managed, algorithm-based home hypertension 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; ES 0.41 (0.07–0.76)
Sackett, 1975, Hamilton, Canada	230 Canadian steelworkers with hypertension detected on screening; 6 months	AC hypertension treated by worksite physician; AE: program on hypertension, pill-taking reminders; C: no AC, no AE; I1: AC, no AE; I2: no AC, AE; I3, AC, AE	Adherence: MPR in 6th month; pill count; adherent is MPR ≥0.8	% adherent at 6 months: AC, 54%; no AC: 51%; AE, 50%; no AE, 56%; AE: with AC, 48%; without AC, 53%; no AE: with AC, 62%; without AC, 48%; nonsignificant difference; ES unable to calculate
Sclar, 1991, Delaware, Texas, and Wisconsin	453 hypertensive 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 divided by 180	MPR (mean ± 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; ES 7.42 (6.34–8.51)
Smith, 2008, U.S. urban centers	907 patients at hospital discharge post-MI, with beta blocker prescriptions; 9 months	Two mailings to patients, PCPs addressing importance of beta 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 [1.02–1.29]); ES 0.09 (–0.23 to 0.42)

Table 2 continued

Stewart, 2005, Johannesburg, S. Africa	83 hypertensive 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%, $P = 0.56$; ES –0.12 (–0.85 to 0.61)
Takala, 1983, southwest Finland	147 untreated hypertensive patients; 2 years	Mailed information on hypertension	2 years after intervention, asked if "still under treatment after 2 years"	Adherent: I, 90%; C, 79%, $P = NS$; ES 0.28 (–0.14 to 0.69)
van Onzenoort, 2009, the Netherlands	228 hypertensive patients; 1 year	Home self-BP measurement	% of days with correct dosing; MEMS	Median (IQR): I, 92.3% (86.9–94.4); C, 90.9% (82.9–93.7), $P = 0.043$; ES 0.07 (0.04–0.18)
Yilmaz, 2005, Ankara, Turkey	202 patients on statin for secondary prevention; 15 months	Education including physician conversation on statins	Odds of being on continuous statin (after median of 15 months); self-report	I, more likely to be on continuous statin, OR 1.977 (1.127–3.468); ES 0.53 (0.25, 0.82)

Abbreviations used: AC, augmented convenience; AE, additional education; BP, blood pressure; C, control group; CHF, congestive heart failure; ES, effect size; I, intervention group; IQR, interquartile range; MEMS, medication event monitoring system; MI, myocardial infarction; MPR, medication possession ratio; NS, nonsignificant; OR, odds ratio; PCP, primary care provider; RR, rate ratio.

[a] Duration indicates time until last follow-up at which adherence was measured.

[b] Control patients received usual care unless otherwise specified

[c] 95% CI unless otherwise specified.

For all studies where means (±SD) for adherence outcomes were available, Cohen's *d* statistics were calculated. The ESs compare the difference in effect between the study groups divided by the SD of this difference. We considered an ES <0.2 to be very small, 0.2–0.5 small, 0.5–0.8 medium, and >0.8 large.

ies[28,30,33–36] that assessed the impact of family support and education interventions, all of which had calculable ESs. As with previous groups of broad interventions, the majority were classified as having very small or small effects (three studies). This is a particularly hard group about which to generalize because an additional two studies yielded large effects[28,33] and one showed a negative effect.[35]

Although broad interventions did not incorporate adherence feedback loops, more than one-third of these studies[15–17,19,20,22,24,25,29,31,35] gathered adherence data at multiple time points. Several of these studies considered avoidance of a feedback loop to be an intentional part of the design. Christensen et al.,[16] who used electronic adherence monitoring with an audio-visual reminder device, explicitly stated that "treating physicians had no access to the questionnaire data during the study to avoid social desirability bias." Rudd et al.,[31] describing an intervention in which project staff downloaded data from electronic medication monitors at 3 and 6 month clinic visits, stated that they "provided no feedback on drug adherence to patients, physicians, or nurse care managers." For many others, the lack of a feedback loop appeared to be mediated by a separation between the person administering the intervention and those gathering data.

Dynamic interventions

We found 30 dynamic interventions[39–68] (Table 3), 28 of which had ESs that could be calculated.[47,68] Mean ages of participants ranged from 49 to 78 years. Of those with calculated ESs, 32.1% of studies had medium or large effects, 50.0% very small or small effects, and 17.9% no effect or negative effects. When examining the percentage of studies yielding medium or large ESs across all groups, dynamic interventions (32.1%) compared favorably with broad (18.2%) or focused (25%) interventions.

The majority of interventions (12 of 30) examined hypertensive patients; others addressed patients with diabetes (3), dyslipidemia (5), congestive heart failure (6), cardiac disease (3), and mixed diseases (1).

Use of self-generated data in adherence feedback loop. We identified 24 articles (Table 3) that described adherence feedback loops based on self-generated data, and all but 1 had calculable ESs. Of those with calculated ESs, 34.8% yielded medium or large effects, 43.5% very small or small effects, and 21.7% negative or no effects.

All eight studies[39–41,43,53,54,57,58] found to have a medium or large effect were dependent on the involvement of health professionals, and in all but one case,[39] the professional was a pharmacist. Antonicelli et al.[39] studied the effect of home telemonitoring managed by a specialized heart failure team and did not specify the training of the person making the phone calls. Adherence feedback loops were initiated in these studies when a pharmacist (or in the case of Antonicelli et al., a caller whose training was not specified) inquired about medication adherence either in person or by phone. This often occurred multiple times during the intervention. When a patient self-identified as nonadherent, an individualized intervention was

Table 3. Dynamic[a] medication adherence interventions: Classified by type of adherence data used in adherence feedback loop[b]

Author, year, site	Participants, duration[c]	Intervention[d]	Method of targeting intervention group nonadherers	Adherence measures[e]	Outcomes, Cohen's *d*ESs (95% CI)[f]
Self-generated adherence data only					
Antonicelli, 2008, Italy	57 hospitalized CHF patients, age >70 years; 12 months	I: home telemonitoring managed by specialized CHF team	Weekly calls by CHF team collecting information on symptoms, adherence. Regimen adjustment based on feedback	% adherent patients (no further definition)	I: 91%; C: 46%, $P < 0.03$; ES 1.12 (0.52–1.69)
Blenkinsopp, 2000, U.K.	282 hypertensive patients from community pharmacies; 6 months	I: Pharmacist counsel: structured questions, medication advice, hypertension teaching, every 2 months	Pharmacist gave advice (verbal or written); pharmacist might refer to GP or speak directly with GP	% adherent patients; modified version of Horne's medication adherence report scale used	I: 62.9%; C: 50.0%, $P < 0.05$; ES 0.56 (0.29–0.84)
Bouvy, 2003, the Netherlands	152 CHF patients, inpatient and outpatient; 6 months	I: Community pharmacist: structured interview using computerized medication record at initial encounter, discussed medications, nonadherence	Monthly pharmacist contact; discussion of reasons for nonadherence and reinforced adherence	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; ES 0.57 (0.14–1.00)
Edworthy, 2007, Calgary, Canada	2,643 cardiac patients after hospitalization; 19 months	I: In-hospital individual and group counseling on medications and medical conditions; videos, printed materials; developed long-term medication plans; follow-up contact by pharmacist once and monthly by nurse	Nurses and pharmacists identified and addressed medication problems; community pharmacists counseled intervention patients	% 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%, $P < 0.05$; ES 0.04 (–0.07 to 0.14)
Faulkner, 2000, Omaha, NE	30 patients post-CABG, PTCA, or both (7–30 days); 2 years	I: Weekly pharmacist calls (12 weeks); all received lovastatin daily and colestipol twice daily	Weekly phone call to check on adherence, medication issues, and costs; asked about specific reasons for nonadherence.	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 years: 60%; C: 1 year: 33%; 2 years: 27%, $P < 0.05$ for all values (colestipol findings similar, not shown here); ES 0.54 (–0.19 to 1.27)
Friedman, 1996, Boston	299 hypertensive patients; 6 months	I: Interactive computer-based home monitoring. Patient self-BP checks, weekly calls to counsel on adherence	Automated phone counseling on adherence; data collected weekly and transmitted to PCP	MPR (expressed as percent); home pill count; adherers: MPR ≥80%	Mean Δ adherence, unadjusted: I: +2.4%; C: –0.4%, $P = 0.29$; adjusted for baseline adherence: I: 17.7%; C: 11.7%, $P = 0.03$; ES 0.13 (–0.12 to 0.37)
Guthrie, 2001, Ohio	13,100 patients with elevated total cholesterol; 6 months	I: Postal, phone reminders about coronary risk reduction and medication adherence	Directly reported pravastatin adherence to their physicians (along with lifestyle changes, adverse events) at 3 months	Taking pravastatin as prescribed per self-report: yes/no	Taking as prescribed: I: 79.7%; C: 77.4%; authors conclude "no meaningful difference"; ES 0.06 (–0.02 to 0.13)

Table 3 continued

Hunt, 2008, Oregon	463 uncontrolled hypertensive patients; 12 months	I: Community pharmacists managed hypertension in PCP office (had PCP input)	Individualized pharmacist counseling including identification of adherence barriers; follow-up interval varied	% 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: $P = 0.52$; ES –0.04 (–0.29 to 0.20)
Jaffray, 2007, U.K.	1,493 CAD patients from primary care organizations; 12 months	Community pharmacist assessed therapy, adherence, lifestyle, social support	All participants got initial consult; further consults at pharmacist discretion based on assessed adherence and other needs	Adherence score (12–60) based on 12 questions; self-report	I: 59 (IQR 57–60); C: 59 (57–60); OR 1.0 (95% CI 0.61–1.65), $P = 0.99$; ES: unable to calculate
Krantz, 2008, Denver, CO	64 CHF patients with ejection fraction <40%; 6 months	Prehospital discharge carvedilol initiation and nurse counseling with outpatient nurse management	2 weeks after discharge, met with nurse manager, then every 2 weeks until deemed stable; counseling, including on adherence	Beta-blocker utilization; on medication (yes/no); pill count	Beta-blocker utilization: at discharge: C: 9.4%; I: 96.9%; 6 months: C: 47.8%; I: 96.2%; utilization significantly higher for I at all time periods ($P < 0.001$); ES 0.30 (–0.29 to 0.89)
Logan, 1983, Toronto, Canada	194 hypertensive patients; 1 year	I: Worksite care by physician plus nurse	Nonadherent patients counseled on medication diary, tailored regimen, home BP; increased visit frequency; nurse home phone call for missed visits	% adherent patients (≥80% of prescribed medication taken); home pill count	I: 55.4%; C: 55.7%, P = NS; ES –0.01 (–0.31 to 0.29)
Odegard, 2005, Seattle, WA	77 participants with A1C ≥9% taking diabetes medication; 12 months	I: Primary care pharmacist developed care plan, in-person or phone meetings (weekly, then monthly)	Adherence assessed at baseline, 6 months, and 12 months; pharmacist gave regular advice to patient and provider where needed; addressed diabetes 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?"	C showed better adherence than I throughout study ($P = 0.003$); ES –0.73 (–1.25 to –0.21)
Ogedegbe, 2008, New York	190 hypertensive patients, black race/ethnicity, most women; 12 months	I: Motivational interviewing with patient-centered counseling by research assistants who elicited adherence barriers, discussed solutions	Assessments every 3 months based on patient verbally discussing adherence barriers; MEMS data are downloaded but not used at those visits	MPR, expressed as %; MEMS	I: 60%; C: 47%, $P = 0.054$; intent-to-treat analysis showed model-predicted rates: I: 57%; C: 43%, $P = 0.027$; ES 0.13 (–0.01 to 0.27)
Piette, 2000, California	280 diabetes patients on hypoglycemic medications; included Spanish-speaking patients; 12 months	I: Biweekly automated assessment/education calls: hierarchically structured messages with targeted nurse follow-up calls	In automated calls, patients given positive feedback and reinforcement; nonadherers were asked about barriers, given automated advice with targeted, prioritized nurse phone follow-up; nurse called those who rarely responded to automated calls	Abbreviated Morisky index; patients considered nonadherent if they sometimes forgot or stopped medication; phone interviews, self-report	I: "Substantially less likely" to report adherence problems ($P = 0.003$); ES 0.38 (0.12–0.63)

Table 3 continued

Planas, 2009, Oklahoma	52 diabetes and hypertensive managed care patients; 9 months	I: Monthly in-person community pharmacist counseling; identified and addressed medication problems, lifestyle counseling	Pharmacist assesses and encourages adherence, communicates problems to PCP via note	Used MPR based on prescription claims data from managed care organization; only included prescriptions with ≥3 consecutive refills in the 9 months before or after baseline visit	Mean adherence (%): I: 87.5 (CI 82.1–93.0); C: 78.8 (CI 69.7–87.9); ES 0.54 (0.13–1.21)
Sadik, 2005, Al-Ain, United Arab Emirates	221 CHF patients; 12 months	I: Structured pharmacist counsel (in clinic or hospital); CHF and medication education, booklet	Pharmacist visits with counseling every 3 months; self-monitoring: 1-month card (pharmacist reviewed regularly, told to bring to PCP); pharmacist spoke with PCP as needed	"Patient self-report on missing dose or taking extra doses without medical advice"; no further definition	Number of adherent patients: I: 85; C: 35, $P < 0.05$; ES 1.26 (0.99–1.54)
Schectman, 1994, Milwaukee, WI	162 patients with dyslipidemia; 6 months	I: Weekly phone counsel in 1st month of therapy by medical assistant; each group also randomized to niacin vs. bile acid sequestrants	Information on medication adherence and problems gathered by phone and at 2-month clinic visits; medical assistant offered advice on adverse effects, arranged pharmacist or physician phone contact as needed	MPR; pharmacy claims	% adherence (mean ± SD): bile acid sequestrants (mean ± SD): I: 88 ± SD 4; C: 82 ± 4, $P = 0.32$; niacin: I: 90 ± 2; C: 84 ± 3, $P = 0.07$; ES 0.41 (–0.05 to 0.86)
Schroeder, 2005, Avon, U.K.	245 hypertensive patients; 6 months	I: Nurse-led adherence support sessions	Reinforcement consult 2 months after randomization: nurse spoke to patients about adherence challenges but had no access to MEMS data at that time	MPR (expressed as %); MEMS, used for 1 medication only	Mean ± SD: I: 95.6 ± 16.4; C: 95.6 ± 15.7, $P = 0.76$; ES 0.06 (–0.24 to 0.35)
Solomon, 1998, multiple sites	133 hypertensive patients; 6 months	I: Standardized pharmacy care: monthly patient assessment, disease management, and education	Monthly pharmacist adherence assessment, includes development of adherence aid as needed	Adherence score based on 4-point Morisky scale; self-report	Mean ± SD: I: 0.23 ± 0.054; C: 0.61 ± 0.094, $P < 0.05$ compared within and between groups; ES 0.57 (0.21–0.93)
Sookaneknun, 2004, urban and rural Thailand	235 hypertensive patients from pharmacy and primary care; 6 months	I: Research pharmacist consult: assessed medication understanding, adherence, counseled on use, lifestyle; educational leaflets, diary	Regular pharmacist visits (appear to be monthly) to identify and address medication problems; recommendations given to physicians by letter and by note in medical record	Calculated MPR, expressed as %; ≥80% necessary to be considered adherent	% of adherent patients: I: 63.64%; C: 55.56%, $P = 0.014$; ES 0.60 (0.33–0.87)

Table 3 continued

Stacy, 2009, Massachusetts	497 new statin users; 6 months	I: Interactive voice response telephone technology providing tailored medication counseling; mailed letters	Interactive voice response provided tailored messages reinforcing adherence based on patient responses	6-month point prevalence persistency: possession of statin at end of 180-day period based on claims records; also provide MPR	Point prevalence persistency: I: 70.4%; C: 60.7%, $P < 0.05$; MPR >80%: I: 47.0%; C: 38.9%, $P < 0.10$; ES 0.08 (0.01–0.17)
Tsuyuki, 2004, Canada	276 patients with CHF discharged from hospital; 6 months	I: Phone call at 2 weeks, 4 weeks, then monthly; education; adherence aids (organizer, schedule), phone, mail follow-up; C: pamphlet	Research coordinator called patients to assess ACEI use, reinforced adherence; advised patients to consult physician for ACEI dose change, medication problems	MPR for ACE inhibitor, expressed as %; pharmacy records	% adherence (mean ± SD): I: 83.5 ± 31.2; C: 86.2 ± 29.0, $P = 0.691$; ES –0.09 (–0.33 to 0.15)
Varma, 1999, Northern Ireland	83 elderly CHF patients followed after hospital discharge; 12 months	I: In-person community pharmacist counseling on CHF medications, adherence, lifestyle; dose simplification; symptom monitoring	Every 3 months: assessed adherence with prescribed drugs, including review of drug diary cards	Adherence defined as 80–120% of medications taken for all CHF drugs assessed; pharmacy records	% of adherent patients: I: 76.9; C: 30, $P = 0.039$; ES 0.30 (–0.29 to 0.89)
Vivian, 2002, Philadelphia	56 male hypertensive patients, majority black; 6 months	I: Monthly pharmacist counseling; changed drugs, adjusted doses	Adherence assessment and counseling at each visit	Nonadherence meant 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, $P > 0.42$; ES –0.26 (–0.81 to 0.29)
External adherence data (alone or in combination with self-generated data)					
Johnson, 2006, Massachusetts and Rhode Island	404 adults with dyslipidemia; 18 months	I: Population-based, computer-generated individualized intervention assessing stage of change (precontemplation, contemplation, preparation, action, maintenance) via questionnaire	Written report mailed to patient (within 1 week of assessment) providing feedback: (1) at baseline (comparison with others trying to change adherence behavior) and (2) at two follow-up points (comparison with group and with individual's past responses)	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-month OR 2.03, $P > 0.05$; 18-month OR 2.86, $P < 0.05$; ES 0.18 (–0.08 to 0.45)
Murray, 2007, Indianapolis, IN	314 hypertensive patients from inner-city practice; 12 months	I: Pharmacist medication history, knowledge assessment, verbal, written education; both in-person and monthly phone contact	Pharmacist adherence counseling included option to review MEMS plot with patient, engage patient in problem solving	% of prescribed medication taken; MEMS	During intervention: I: 78.8%; C: 67.9%; difference: 10.9% (CI 5.0–16.7); postintervention difference: 3.9% (CI: –2.8 to 10.7); ES 0.08 (–0.89 to 1.06)

Table 3 continued

Phumipa-morn, 2008, Krabi Province, Thailand	135 Muslim diabetes patients; 8 months	I: Pharmacist meeting day of physician visit; visit reminder 3 days prior; given refills, lifestyle and medication education	Research pharmacist refilled medications, checked pill count, and advised on medications before usual PCP visit (every 4–8 weeks).	MPR (expressed as %); pill count	Mean difference (CI): I: +6.8% (2.1–11.4), $P = 0.005$; C: –2.8 (–7.31 to 1.7), $P = 0.29$; between-group mean difference $P = 0.004$; ES 0.50 (0.15–0.86)
Robinson, 2010, Tampa, FL	376 patients on hypertension medications with uncontrolled BP; 7–12 months	I: Monthly (or more frequent) in-person pharmacist counseling includes lifestyle, medication adherence education	Pharmacist gives tailored adherence improvement strategies, bases feedback on self-report and use of refill history to obtain estimated rate of adherence	MPR (mean adherence rate); pharmacy records	1–6 month period (mean ± SD): I: 0.91 ± 0.15; C: 0.78 ± 0.30, $P = 0.02$; 7–12 month period: I: 0.91 ± 0.15; C: 0.83 ± 0.28, $P = 0.09$; ES 0.36 (0.15–0.86)
Tamblyn, 2009, Montreal and Quebec, Canada	2,293 patients on lipid-lowering or hypertension medications; 6 months	I: Computerized complete drug profile with graphic displays, refill adherence calculation, and adherence alerts as part of computerized medical record used by primary care physicians; C: computerized medication list alone (usual care)	Gaps in graphically displayed medication profile (or numerical data) inform physician of nonadherence; if adherence <80%, physician got alert when opening medical chart, told to check drug profile	Mean refill adherence: proportion of days covered; accessed via daily retrieval of computerized dispensing information; real-time updates of records	I: 73.5%; C: 72.9%; Δ mean adherence ± SD: I: –6.2 ± 24.1; C: –6.4 ± 24.1, $P = 0.90$; ES 0.01 (–0.08, 0.09)
Vrijens, 2006, Belgium	392 patients with dyslipidemia on atorvastatin; 12 months	I: Pharmacy program: medication history educational reminders, written information; C: written information	Pharmacist sits with patient and reviews electronically compiled dosing history of past months; patient taught to read MEMS graphics	% of days that medication container opening was recorded; MEMS	I: 95.89% (CI 90.28–98.66); C: 89.37 (69.70–96.33), $P <$ 0.001; ES: unable to calculate

Abbreviations used: A1C, glycosylated hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; C, control group; CAD, coronary artery disease; CHF, congestive heart failure; ES, effect size; GP, general practitioner; I, intervention group; IQR, interquartile range; MEMS, medication event monitoring system; MPR, medication possession ratio; NS, nonsignificant; OR, odds ratio; PCP, primary care provider; PTCA, percutaneous transluminal coronary angioplasty; RR, rate ratio.

[a] Dynamic interventions are first administered to all medication takers, then real-time adherence information is used to further target nonadherers.

[b] An adherence feedback loop is created whereby adherence data are generated and then fed back into the intervention. Adherence feedback loops use either (1) self-generated data alone or (2) external data alone or along with self-generated data. Self-generated data feedback loops were those in which the tailoring of the intervention was based entirely on patient self-report of nonadherence. External data feedback loops were those in which information such as MPR derived from pharmacy records or other external sources was used to tailor the intervention.

[c] Duration indicates time until last follow-up in which adherence is measured.

[d] Control patients received usual care unless otherwise specified.

[e] MPR: medication doses taken divided by doses prescribed. Morisky scale has four questions (1 point 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?

[f] 95% CI unless otherwise specified.

For all studies where means (±SD) for adherence outcomes were available, Cohen's *d* statistics were calculated. The ESs compare the difference in effect between the study groups divided by the SD of this difference. We considered an ES <0.2 to be very small, 0.2–0.5 small, 0.5–0.8 medium, and >0.8 large.

delivered based on the patient's unique situation, incorporating components such as regimen adjustment, reinforcement, education, lifestyle counseling, advice on contacting physicians, and, in some cases, direct contact of primary physicians by the pharmacist.

A total of 10 studies yielded very small or small effects. Of these, four[42,48,56,61] relied on health professionals. These four interventions had similar feedback structures to those described above, although nurses played the main role, with only one intervention mediated primarily by a pharmacist.[61] Two interventions[51,55] were carried out by lay persons including research assistants who conducted motivational interviews[51] and medical assistants who provided medication counseling by phone.[55] Three interventions[44,52,59] made use of electronic systems including interactive computer-based home monitoring,[44] interactive phone technology with tailored messages,[59] and automated calls with structured messages and targeted nurse follow-up.[52] One study in this group[45] consisted mainly of postal and phone reminders but had patients reporting adherence directly to physicians at 3 months. There was no prespecified physician response to nonadherence; in this case, we assumed that discussion occurred or medication changes were administered if patients reported nonadherence directly to the physician.

Similar to the most effective group, the five studies that showed no improvement in adherence[23,46,50,60,62] were almost all conducted by health professionals. Hunt et al.[46] reported the effect of pharmacist-managed hypertension, and Logan et al.[23] described worksite hypertension management carried out by a nurse with physician support. Both had ESs very close to zero, as did Tsuyuki et al.,[60] who examined the effect of lay person (research coordinator) phone calls in which adherence was reinforced and patients were referred to their physicians for questions or adherence concerns.

In contrast, Vivian[62] studied monthly pharmacist counseling, including regimen adjustments as needed, and found a small negative effect. Odegard et al.[50] described the effect of a diabetes care plan developed by a primary care pharmacist along with follow-up meetings and calls but followed a group in which control patients showed better adherence than intervention patients.

Use of external data in adherence feedback loop. We identified six articles[63–68] that described adherence feedback loops reliant on externally generated data; for one of these,[68] an ES could not be calculated. Of those with calculated ESs, 20% (one study) yielded medium or large effects and 80% (four studies) very small or small effects.

The study of Phumipamorn et al. [65] was the only dynamic intervention to yield a medium to large ES while using an external adherence data feedback loop, and this study did not rely on automated adherence data. Research pharmacists meeting with patients with diabetes on the day of their physician visit conducted pill counts and provided counseling along with refills.

The four dynamic interventions with very small or small effects included three in which a health professional (pharmacist or physician) had access to electronic adherence data during the patient interaction. Robinson et al.[66] studied the effect of pharmacist adherence counseling using both self-reported adherence and pharmacy refill history.

Murray et al.[64] described pharmacist adherence counseling in which pharmacists had the option to review electronic pillbox adherence data with patients and engage in problem-solving based on these data. Pillbox data were reported to be available in plot form for ease of communication; however, such a review was at the pharmacist's discretion and not conducted with every patient. Tamblyn et al.[67] described an intervention in which computerized complete drug profiles with graphic displays were made available to primary care physicians, incorporating refill adherence calculation and adherence alerts as part of an electronic medical record already in use by physicians. One of the more complex systems for delivery of external adherence data directly to physicians, this study had a small and likely clinically insignificant ES (0.01 [CI –0.08 to 0.09]), although physicians overwhelmingly requested to have access to the graphics at the conclusion of the trial.

Johnson et al.[21] used a computer-generated intervention assessing stage of change with respect to adherence behavior based on a questionnaire administered to patients.[21] The external data in this feedback loop were a computerized interpretation of patients' readiness to change adherence behaviors that was delivered with patient-appropriate recommendations via a mailed written report to patients. The authors found that the odds of appropriate adherence were improved in the intervention group (OR 2.86) with a small ES (0.18 [–0.08 to 0.45]).

Discussion

Compared with broadly administered interventions, those that targeted nonadherers (either exclusively or in a dynamic fashion) tended to have a larger effect on medication adherence. In addition to the statistical heterogeneity reflected in our analyses, we found considerable clinical heterogeneity among the studies identified. Adherence measures differed between studies both as an outcome and a means of defining a target group. This heterogeneity prevented us from pursuing a meta-analysis and prompted us to interpret all findings with caution. Our findings highlight the need for standardized approaches to adherence measurement.

With respect to dynamic interventions, our findings support further attention to the unique components of the self-generated dynamic intervention. Possible mechanisms for the relative success we found among individuals participating in self-generated adherence feedback loops included an increased ability to provide tailored medication advice in real time and the requirement that patients have at least a degree of insight into their nonadherent behaviors.

Vrijens et al.[68] called for increased use of health information technology to identify "patients for whom poor medication adherence may undermine clinical goals and patients who could benefit from interventions aimed at achieving optimal medication use." Despite this emphasis on health information technology, our study did not find any advantage to using externally generated data for dynamic feedback loops. Although

we acknowledge the heterogeneity of the studies and our difficulty drawing firm conclusions on that basis, our findings do not support widescale implementation of automated electronic adherence feedback at this time. Further study in this regard is needed to demonstrate incremental benefit of this approach.

Focused interventions identify nonadherers before starting the intervention. This group provides very limited data, and the studies that exist do not consistently make use of reproducible, standardized methods for identifying nonadherers. This is an area that would benefit from additional studies, particularly ones in which better methods for identifying the focused population are presented.

Broad interventions appear to be least effective. Such interventions aim to prevent nonadherence by educating and motivating patients to adhere to treatment. Although many of these interventions were effective, their benefits were likely diluted because of the small effect of the intervention on patients already inclined toward adherence. Moreover, without the benefit of identifying patients and their specific barriers to nonadherence, these interventions may have been too general to motivate individual patients to meaningfully change their behavior. In a resource-constrained health care system, broad interventions without a feedback loop may not provide the best return on investment.

The current results have important implications. Broad interventions are the least effective and potentially the most expensive; research is needed to more fully evaluate focused and dynamic interventions. Focused interventions allow limited resources to be directed toward fewer, higher-risk patients, and dynamic interventions share this advantage when the more costly portion of the intervention is reserved for identified nonadherers. Attention must be paid, however, to the method of identifying nonadherers. None of the focused interventions that we identified made use of pharmacy claims data to identify nonadherence. Focused studies were administered after a baseline period in which adherence data were gathered from a larger group of patients, or ascertainment of nonadherent status was based more loosely on a combination of physician documentation, self-report, and refill history. Dynamic interventions were overwhelmingly dependent on self-generated adherence data (often requiring intensive interaction with a health provider), and very few used any form of external data. The accuracy, cost, and reproducibility of methods for identifying target populations must be a central consideration in future studies.

Based on our findings, we recommend further investigation of targeted adherence improvement efforts aimed at patients who are nonadherent. Methods for identifying nonadherence should be defined in advance as clearly as possible and evaluated for cost, validity, and reproducibility. As electronic pharmacy data become increasingly available, external adherence data should be explored as a means of focusing interventions from the outset and informing dynamic feedback loops; however, we must keep in mind the limited effectiveness demonstrated to date.

Limitations

Limitations of our review included the substantial clinical and statistical heterogeneity of the identified studies, thereby preventing meta-analysis estimates from being presented. Other limitations included the variable quality of study methodology, the possibility for publication bias, the paucity of available information on intervention costs, and the lack of standardized methods to study this issue. Heterogeneous adherence outcome measures prompted us to translate adherence outcomes into Cohen's *d* ESs, allowing for between-study comparison but possibly providing a less direct measure of adherence improvement. Because variability existed in the degree of detail offered on the adherence interventions, we may have misclassified some interventions, although we do not expect that this would have occurred in a biased manner. Our decision to exclude studies characterized by regimen simplification limits our ability to comment on this important group of adherence interventions. Success rates seen in focused interventions may reflect their exclusion of already-adherent patients, for whom any intervention would yield little additional improvement. Because dynamic and broad interventions measure improvements in adherence for the whole population, we were unable to directly compare the impact of dynamic, broad, and focused interventions on each group's subset of nonadherent patients. Thus, considerable gaps remain in the existing evidence base for targeting medication adherence interventions.

Conclusion

Targeting patients who are nonadherent to their cardiovascular medications may lead to better adherence; however, data are limited and studies are highly heterogeneous. With cost an ever-present consideration, future efforts to improve adherence may best be directed at patients who demonstrate that they do not adhere to therapy.

References

1. Institute of Medicine. 100 initial priority topics for comparative effectiveness research. Accessed at www.iom.edu/~/media/Files/Report%20Files/2009/ComparativeEffectivenessResearch-Priorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx, June 8, 2010.
2. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007;297:177–86.
3. New England Healthcare Institute. Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease. Accessed at www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease, May 27, 2010.
4. Kripalani S, Yao X, Haynes R. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Arch Intern Med. 2007;167:540–50.
5. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.

6. Cohen J. Statistical power analysis for the behavioral sciences. New York: Lawrence Erlbaum Associates; 1988.
7. Dunlap W, Cortina J, Vaslow J, Burke M. Meta-analysis of experiments with matched groups or repeated measures designs. Psychological Methods. 1996;1:170–7.
8. Hedges L, Olkin I. Statistical methods for meta-analysis. San Diego, CA: Academic Press; 1985.
9. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.
10. Haynes RB, Sackett DL, Gibson ES, et al. Improvement of medication compliance in uncontrolled hypertension. Lancet. 1976;1:1265–8.
11. Rosen MI, Rigsby MO, Salahi JT, et al. Electronic monitoring and counseling to improve medication adherence. Behav Res Ther. 2004;42:409–22.
12. Saunders LD, Irwig LM, Gear JS, Ramushu DL. A randomized controlled trial of compliance improving strategies in Soweto hypertensives. Med Care. 1991;29:669–78.
13. Taylor CT, Byrd DC, Krueger K. Improving primary care in rural Alabama with a pharmacy initiative. Am J Health Syst Pharm. 2003;60:1123–9.
14. Avanzini F, Corsetti A, Maglione T, et al. Simple, shared guidelines raise the quality of antihypertensive treatment in routine care. Am Heart J. 2002;144:726–32.
15. Birtwhistle RV, Godwin MS, Delva MD, et al. Randomised equivalence trial comparing three and six months of follow up of patients with hypertension by family practitioners. BMJ. 2004;328:204.
16. Christensen A, Christrupa LL, Fabriciusb PE, et al. The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. J Hypertens. 2010;28:194–200.
17. Dusing R, Handrock R, Klebs S, et al. Impact of supportive measures on drug adherence in patients with essential hypertension treated with valsartan: the randomized, open-label, parallel group study VALIDATE. J Hypertens. 2009;27:894–901.
18. Emmett CL, Montgomery AA, Peters TJ, Fahey T. Three-year follow-up of a factorial randomised controlled trial of two decision aids for newly diagnosed hypertensive patients. Br J Gen Pract. 2005;55:551–3.
19. Hamet P, Campbell N, Curnew G, et al. Avapromise: a randomized clinical trial for increasing adherence through behavioural modification in essential hypertension. Exp Clin Cardiol. 2003;7:165–72.
20. Hawkins DW, Fiedler FP, Douglas HL, Eschbach RC. Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients. Am J Hosp Pharm. 1979;36:1321–5.
21. Johnson AL, Taylor DW, Sackett DL, et al. Self-recording of blood pressure in the management of hypertension. Can Med Assoc J. 1978;119:1034–9.
22. Kirscht JP, Kirscht JL, Rosenstock IM. A test of interventions to increase adherence to hypertensive medical regimens. Health Education Quarterly. 1981;8:261–72.
23. Logan AG, Milne BJ, Achber C, et al. Work-site treatment of hypertension by specially trained nurses: controlled trial. Lancet. 1979;2:1175–8.
24. Lopez Cabezas C, Falces Salvador C, Cubi Quadrada D, et al. Randomized clinical trial of a postdischarge pharmaceutical care program vs regular follow-up in patients with heart failure. Farm Hosp. 2006;30:328–42.
25. Mann DM, Ponieman D, Montori VM, et al. The statin choice decision aid in primary care: a randomized trial. Patient Educ Couns. 2010;80:138–40.
26. Marquez-Contreras E, Martell-Claros N, Gil-Guillen V, et al. Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. J Hypertens. 2006;24:169–75.
27. Mehos BM, Saseen JJ, MacLaughlin EJ. Effect of pharmacist intervention and initiation of home blood pressure monitoring in patients with uncontrolled hypertension. Pharmacotherapy. 2000;20:1384–9.
28. Morisky DE, DeMuth NM, Field-Fass M, et al. Evaluation of family health education to build social support for long-term control of high blood pressure. Health Educ Q. 1985;12:35–50.
29. Mullan RJ, Montori VM, Shah ND, et al. The diabetes mellitus medication choice decision aid: a randomized trial. Arch Intern Med. 2009;169:1560–8.
30. Powell KM, Edgren B. Failure of educational videotapes to improve medication compliance in a health maintenance organization. Am J Health Syst Pharm. 1995;52:2196–9.
31. Rudd P, Miller NH, Kaufman J, et al. Nurse management for hypertension: a systems approach. Am J Hypertens. 2004;17:921–7.
32. Sackett DL, Gibson ES, Taylor DW, et al. Randomized clinical trial of strategies for improving medication compliance in primary hypertension. Lancet. 1975;1:1205–7.
33. Sclar DA, Chin A, Skaer TL, et al. Effect of health-education in promoting prescription refill compliance among patients with hypertension. Clin Ther. 1991;13:489–95.
34. Smith DH, Kramer JM, Perrin N, et al. A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. Arch Intern Med. 2008;168:477–83.
35. Stewart A, Noakes T, Eales C, et al. Adherence to cardiovascular risk factor modification in patients with hypertension. Cardiovasc J S Afr. 2005;16:102–7.
36. Takala J. Screening, treatment and adherence to treatment for hypertension. Scand J Prim Health Care. 1983;1:114–9.
37. van Onzenoort HA, Verberk WJ, Kroon AA, et al. Effect of self-measurement of blood pressure on adherence to treatment in patients with mild-to-moderate hypertension. J Hypertens. 2010;28:622–7.
38. Yilmaz MB, Pinar M, Naharci I, et al. Being well-informed about statin is associated with continuous adherence and reaching targets. Cardiovasc Drugs Ther. 2005;19:437–40.
39. Antonicelli R, Testarmata P, Spazzafumo L, et al. Impact of telemonitoring at home on the management of elderly patients with congestive heart failure. J Telemed Telecare. 2008;14:300–5.
40. Blenkinsopp A, Phelan M, Bourne J, Dakhil N. Extended adherence support by community pharmacists for patients with hypertension: a randomised controlled trial. Int J Pharm Pract. 2000;8:165–75.

41. Bouvy ML, Heerdink ER, Urquhart J, et al. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. J Card Fail. 2003;9:404–11.
42. Edworthy SM, Baptie B, Galvin D, et al. Effects of an enhanced secondary prevention program for patients with heart disease: a prospective randomized trial. Can J Cardiol. 2007;23:1066–72.
43. Faulkner MA, Wadibia EC, Lucas BD, Hilleman DE. Impact of pharmacy counseling on compliance and effectiveness of combination lipid-lowering therapy in patients undergoing coronary artery revascularization: a randomized, controlled trial. Pharmacotherapy. 2000;20:410–6.
44. Friedman RH, Kazis LE, Jette A, et al. A telecommunications system for monitoring and counseling patients with hypertension: impact on medication adherence and blood pressure control. Am J Hypertens. 1996;9:285–92.
45. Guthrie RM. The effects of postal and telephone reminders on compliance with pravastatin therapy in a national registry: results of the First Myocardial Infarction Risk Reduction Program. Clin Ther. 2001;23:970–80.
46. Hunt JS, Siemienczuk J, Pape G, et al. A randomized controlled trial of team-based care: impact of physician-pharmacist collaboration on uncontrolled hypertension. J Gen Intern Med. 2008;23:1966–72.
47. Jaffray M, Bond C, Watson M, et al. The MEDMAN study: a randomized controlled trial of community pharmacy-led medicines management for patients with coronary heart disease. Fam Pract. 2007;24:189–200.
48. Krantz MJ, Havranek EP, Haynes DK, et al. Inpatient initiation of beta-blockade plus nurse management in vulnerable heart failure patients: a randomized study. J Card Fail. 2008;14:303–9.
49. Logan AG, Milne BJ, Flanagan PT, Haynes RB. Clinical effectiveness and cost-effectiveness of monitoring blood-pressure of hypertensive employees at work. Hypertension. 1983;5:828–36.
50. Odegard PS, Goo A, Hummel J, et al. Caring for poorly controlled diabetes mellitus: a randomized pharmacist intervention. Ann Pharmacother. 2005;39:433–40.
51. Ogedegbe G, Chaplin W, Schoenthaler A, et al. A practice-based trial of motivational interviewing and adherence in hypertensive African Americans. Am J Hypertens. 2008;21:1137–43.
52. Piette JD, Weinberger M, McPhee SJ, et al. Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? Am J Med. 2000;108:20–7.
53. Planas LG, Crosby KM, Mitchell KD, Farmer KC. Evaluation of a hypertension medication therapy management program in patients with diabetes. J Am Pharm Assoc. 2009;49:164–70.
54. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol. 2005;60:183–93.
55. Schectman G, Hiatt J, Hartz A. Telephone contacts do not improve adherence to niacin or bile-acid sequestrant therapy. Ann Pharmacother. 1994;28:29–35.
56. Schroeder K, Fahey T, Hollinghurst S, Peters TJ. Nurse-led adherence support in hypertension: a randomized controlled trial. Fam Pract. 2005;22:144–51.
57. Solomon DK, Portner TS, Bass GE, et al. Clinical and economic outcomes in the hypertension and COPD arms of a multicenter outcomes study. J Am Pharm Assoc. 1998;38:574–85.
58. Sookaneknun P, Richards RM, Sanguansermsri J, Teerasut C. Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. Ann Pharmacother. 2004;38:2023–8.
59. Stacy JN, Schwartz SM, Ershoff D, Shreve MS. Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: results of a randomized clinical trial in a managed care setting. Popul Health Manag. 2009;12:241–54.
60. Tsuyuki RT, Fradette M, Johnson JA, et al. A multicenter disease management program for hospitalized patients with heart failure. J Card Fail. 2004;10:473–80.
61. Varma S, McElnay JC, Hughes CM, et al. Pharmaceutical care of patients with congestive heart failure: interventions and outcomes. Pharmacotherapy. 1999;19:860–9.
62. Vivian EM. Improving blood pressure control in a pharmacist-managed hypertension clinic. Pharmacotherapy. 2002;22:1533–40.
63. Johnson SS, Driskell MM, Johnson JL, et al. Transtheoretical model intervention for adherence to lipid-lowering drugs. Dis Manag. 2006;9:102–14.
64. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. Ann Intern Med. 2007;146:714–25.
65. Phumipamorn S, Pongwecharak J, Soorapan S, Pattharachayakul S. Effects of the pharmacist's input on glycaemic control and cardiovascular risks in Muslim diabetes. Prim Care Diabetes. 2008;2:31–7.
66. Robinson JD, Segal R, Lopez LM, Doty RE. Impact of a pharmaceutical care intervention on blood pressure control in a chain pharmacy practice. Ann Pharmacother. 2010;44:88–96.
67. Tamblyn R, Reidel K, Huang A, et al. Increasing the detection and response to adherence problems with cardiovascular medication in primary care through computerized drug management systems: a randomized controlled trial. Med Decis Making. 2010;30:176–88.
68. Vrijens B, Belmans A, Matthys K, et al. Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin. Pharmacoepidemiol Drug Saf. 2006;15:115–21.

Author, Year, Site	Funding source	Jadad Score
From Table 1		
Haynes, RB, 1976 Canada	Grant no. MA-5159 from Medical Research Council of Canada, National Health Grant from Health and Welfare Canada, and a grant from Dominion Foundries and Steel company of Canada. One of authors is Physicians Services Inc. foundation fellow.	3
Rosen, 2004 Connecticut	VA Merit Review grant, an RO1 and the VISN1 . Not supported by any company making MEMS or related products.	3
Saunders, LD, 1991 Soweto, S Africa	Supported by the S. African Medical Research Council.	2
Taylor, 2003 Alabama	ASHP Research and Education Foundation	2
From Table 2		
Avanzini, 2002 Italy	Supported in part by an educational grant from Hoechst-Roussel and Du Pont Pharma Italia	2
Birtwhistle, 2004 Urban, rural Canada	Canadien Institute for Health Research and McKnight Fund for Queen's University	3
Christensen , 2010 Poland	Bang & Olufsen Medicom A/S and the Danish Ministry of Science, Technology and Innovation.	2
Düsing R 2009 multiple sites, Germany	Novartis Pharma GmBH, NÜrnberg, Germany	2
Emmett, CL, 2005 Bristol, England.	Royal College of General Practitioners Scientific Foundation Board, Training Fellowship in Health Services Research at MRC and Royal College of General Practitioners Scientific Foundation Board	2
Hamet, P, 2003 Canada	Bristol-Myers Squibb Canda and Sanofi Canada	3
Hawkins, 1979	DHEW public service grant	2
Johnson,	Health research grant from Ontario Ministry of Health	2

1978 Hamilton, Ontario, Canada.		
Kirscht, JP, 1981 Tecumseh, Michigan	Grant HL18401 from the National Heart Lung and Blood Institute.	2
Logan, 1979 Toronto, Canada	Grant from Ontario Ministry of Health	2
Lopez Cabezas,C, 2006 Barcelona, Spain	Health research Fund (Fonodo de Investigacion Sanitaria, FIS) and the European Regional Development Fund (ERDF).	2
Mann, 2009 New York	Not given	1
Marquez-Contreras, 2006 Spain	Novartis Farmaceutica, Spain	3
Mehos, 2000 Colorado	1998-99 Bristol-Myers Squibb Pharmacy Practice Hypertension Program grant from American Association of Colleges of Pharmacy	3
Morisky, 1985 Baltimore, Maryland.	NHLBI grants, NCHRS and BRSG grant from the Biomedical Research Support Grant Program, NIH.	2
Mullan, 2009 Minnesota	American Diabetes Association. Novo Nordisk, a maker of insulin, subsidized the ADA grant program but did not have direct contact with the investigators and idd not play any role in the awarding the grant to the research team	3
Powell, KM, 1995	Ciba Geigy Corp, Merck (education grants)	1
Rudd, 2004 California	Grant from CorSolutions, Inc (Buffalo Grove, IL)	3

Sackett, 1975 Hamilton, Ontario	Not specified	2
Sclar, DA, 1991 Delaware, Texas and Wisconsin.	grant from ICI Pharmaceuticals, Wilmington, Delaware	1
Smith, 2008 U.S. urban centers	"ccoperative agreement" from AHRQ	2
Stewart, A, 2005 Johannesburg, S. Africa.	Not specified	2
Takala, J, 1983 Southwest Finland	Not specified	2
van Onzenoort, 2009 The Netherlands	The Netherlands Organzation for Health Research and Development (Healthcare Efficiency Research Program; grant 945-01-043)	2
Yilmaz, MB, 2005 Ankara, Turkey.	Not specified	2
From Table 3		
Antonicelli, 2008 Italy	Grants from the Italian Ministry of Health	2
Blenkinsopp, 2000 England	(England) Dept of Health as part of its Community Pharmacy Wider Role Programme	2
Bouvy, 2003 The Netherlands	Unrestricted research grant from independent nonprofit foundation for efficient ues of eds (DGMN)	3
Edworthy, 2007 Calgary, Alberta. Canada.	Supported by grant from Merck Frost Canada	2

Faulkner, 2000 Omaha, Nebraska	Not specified	3
Friedman, 1996 Boston	grant from NHLBI	2
Guthrie, 2001 Ohio	Bristol-Myers Squibb Co, Princeton, NJ	2
Hunt, 2008 Oregon	grant from Boehringer Ingelheim	3
Jaffray, 2007 England	Dept Health for England and Wales managed by collaboration of Nat'l Pharm Assoc'n, Poyal Pharm Society of Great Britain, Company Chemist Assoc and Coop Pharmacy Technical Panel	3
Krantz, 2008 Denver, Colorado	Glaxo Smith Kline.	3
Logan, 1983 Toronto	Ontario Ministry of Health, Public Health grant CHS-R21	1
Odegard, 2005 Seattle, Washington	grant from Academic and Managed care Forum, Quality Care Research Fund	3
Ogedegbe, 2008 New York, NY.	NHLBI, NIH grants	3
Piette, 2000	Clinical research grants program o f the ADA and the Health Services Research and Devlopment Service and mental Health Strategic Health Group, Dept of VA	3
Planas, 2009	American Pharmacists Association Foundation, the American Society of Health-System Pharmacists Foundation, and USA Drug Stores	
Sadik, 2005 Al-Ain, United Arab Emirates	Not specified	3
Schectman, G,	HSR&D Grant from the VA and grant from Squibb-Bristol	2

1994 Milwaukee	company	
Schroeder, K, 2005 Avon, UK	Medical Research Council Trianing Fellowship in Health Services Research	3
Solomon, 1998 Multiple sites	Educational grant Novartis pharmaceuticals corp	2
Sookaneknun 2004 Urban and rural Thailand	Research grant from Chiang Mai University, Thailand	2
Stacy, 2009	Not available	3
Tsuyuki, RT, 2004 Canada	Unrestricted educational grant from Parke Davis Canada (now Pfizer Canada) and the U of Alberta Hospital Foundation	3
Varma, 1999 Northern Ireland	Not specified	3
Vivian, EM, 2002 Philadelphia, Pennsylvania	Supported by the Christian R and Mary F Lindback Foundation	2
External adherence data (alone or in combination with self-generated data)		
Johnson, SS, 2006 Massachusetts and Rhode Island	Grant from the National Heart. Lung and Blood Institute (grant no. R44 HL64504)	2
Murray, 2007	National Institutes of Health grants R01 AG19105 and R01 HL 69399 and AG01799	3

Indianapolis, Indiana		
Phumipa-morn, S, 2008 Krabi Province, Thailand.	Research grants from Graduate School, Prince of Songkla University and the Provincial Public Health Dept of Krabi Province, Thailand	3
Robinson, 2010 Tampa, FL	Pfizer unrestricted grant	1
Tamblyn, 2009 Montreal and Quebec, Canada	Canadien Institutes of Health Research and Pfizer Canada Inc	2
Vrijens, 2006 Belgium	Contract grant sponsor is Pfizer Belgium	1