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J Clin Outcomes Manag. Author manuscript; available in PMC 2009 May 6.

Published in final edited form as:
J Clin Outcomes Manag. 2008 December 1; 15(12): 595–606.

Optimizing Medication Adherence in Older Patients: A Systematic Review

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Abstract

Objective: To review the literature on strategies to optimize medication adherence in community-dwelling older adults and to make recommendations for clinical practice.

Methods: A systematic literature search was conducted using the MEDLINE, CINAHL, PsycINFO, International Pharmaceutical Abstracts, and EMBASE databases for randomized controlled trials examining strategies to optimize medication adherence in patients aged 65 or older prescribed long-term medication regimens. Additional studies were found by examining the reference lists of systematic reviews and selected papers. 34 papers reporting on 33 studies met the eligibility criteria and were included in this review.

Results: Improvement in adherence was mixed across the studies examining educational interventions, with only 12 of the 28 studies showing improvement in adherence; most were delivered by pharmacists. Effect sizes for the statistically significant educational interventions ranged from Cohen's d = 0.14 to 4.93. Four of the 5 interventions using memory aids and cues, some in conjunction with newer technologies, improved adherence. Effect sizes for the statistically significant interventions using memory aids and cues ranged from Cohen's d = 0.26 to 2.72.

Conclusion: The evidence from this review does not clearly support one single intervention to optimize medication adherence in older patients. Future studies should explore suggestive strategies, such as tailored interventions involving ongoing contact, and should endeavor to correct methodologic weaknesses found in the literature.

Patient nonadherence to medical recommendations is an important clinical problem. Adherence (sometimes called compliance) is defined as the extent to which a person's behavior corresponds to medical or health advice [1] and is considered independent of the patient's decision to follow a specific treatment regimen [2]. Adherence is presumably important for achieving high-quality outcomes, yet studies indicate that approximately 50% of patients across gender, age, and ethnic cohorts and with various medical disorders fail to follow their prescribed medication regimens [3].

The health consequences of medication nonadherence can be severe. Patients who are nonadherent can experience disease complications or progression from failing to take their

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Author contributions: conception and design, EAS, LMB, SE; analysis and interpretation of data, EAS, LMB, LAG, SE; drafting of article, EAS, LMB, LAG, MLK, SE; critical revision of the article, EAS, LMB, LAG, SE; statistical experience, EAS, SE; collection and assembly of data, EAS, LAG, MLK, SE.

Financial disclosures: None.

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medication, experience untoward side effects from taking their medicine incorrectly, and often require emergency department visits and readmission to the hospital for disease exacerbations [4,5]. DiMatteo [6] has estimated the total annual costs of medication nonadherence, including the cost of lost productivity and early mortality, to be $300 billion.

Medication nonadherence is particularly problematic in older adults who often must self-manage complex medication regimens for multiple chronic disorders [7]. With a rapidly growing U.S. population of adults over 65 years of age [8] and with 93% of adults aged 65 years and older residing in traditional community settings [9], it is imperative to apply effective strategies to address the problem of medication nonadherence in older patients. The purpose of this paper was to review the literature on strategies to optimize medication adherence in community-dwelling older adults and to make recommendations for clinical practice.

Methods

We searched for English-language papers published between 1996 and 2006 inclusive that met the following criteria:

1. Used a randomized controlled trial design
2. Evaluated an intervention designed to improve medication adherence
3. Used medication adherence as an outcome
4. Patients were prescribed a long-term medication regimen that required ongoing medical care or supervision
5. Patients lived in the community
6. Patients had a mean age of ≥ 65 years, or at least 40% ≥ 65 years, or subgroup analyses on participants ≥ 65 years

Studies were identified by searching the MEDLINE, CINAHL, PsycINFO, International Pharmaceutical Abstracts, and EMBASE databases. The searches were completed in September 2007. Search strategies were based on those used by Haynes et al [15] and are described in the Appendix.

A total of 3874 published papers (including 18 systematic reviews) were returned from the electronic search. A hand search of the systematic reviews [10-27] was done to identify additional articles of interest, which yielded 198 new articles. From this list of 4072, 1751 pertinent papers were identified based on their titles and abstracts and retrieved for more detailed evaluation. Of the 1751 papers, 60 met the inclusion criteria. After elimination of duplicate papers (n = 26), 34 papers reporting on 33 studies remained for review. Each of the included papers was reviewed by 2 of the authors, who reported the results in tabular format summarizing the design, sample characteristics, intervention, adherence outcome, findings, and effect sizes. Because the focus was on interventions to optimize adherence and there was inconsistent and variable measurement of clinical outcomes, data on clinical outcomes were not reported.

Because definitions and measurements of adherence varied across the studies and the methods used to report adherence were inconsistent across the studies, a meta-analysis was not done. However, when sufficient data were reported, effect sizes using Cohen's d were computed for the studies. Cohen's d was calculated using formulas recommended by Lipsey and Wilson [28] and Rosenthal [29]. Cohen's d is a measure of the strength of the relationship between the intervention and the adherence outcome and is an indicator of the effectiveness of the intervention. Cohen [30] suggested the following as a guide to interpreting effect sizes: small is d = 0.20, medium is d = 0.50, and large is d = 0.80.

Results

Two major types of strategies to optimize medication adherence emerged from the literature review: (1) educational interventions and (2) memory aids and cues.

Educational Interventions

Twenty-eight studies examining the impact of educational interventions on medication adherence were identified [31-58] (Table 1). The nature of the educational interventions was variable and while most focused exclusively on the patient, 1 study examined provider education, provider education combined with electronic alerts, and provider education combined with electronic alerts and mailed patient educational materials [48], which showed nonsignificant differences between groups. The samples in most of these studies were not limited to individuals with specific chronic disorders. In the studies examining patients with a specific disorder, the disorders were heart disease, hypertension, hyperlipidemia, diabetes mellitus, depression, osteoporosis, chronic obstructive pulmonary disease (COPD), and overactive bladder. Definitions of adherence varied widely among the studies as did method of measuring adherence. Three used electronic event monitoring (EEM), 1 used pill count, 5 used pharmacy refill, and the remaining 19 used patient self-report. Follow-up ranged from 1 to 24 months.

Nineteen studies identified as educational interventions utilized pharmacists as the interventionists [31-35,37-39,43-45,47,50,52-56,58], with 10 demonstrating that education and counseling by pharmacists significantly improved medication adherence compared with usual care [32-35,44,45,50,52,54,58]. Effect sizes for the statistically significant educational interventions by pharmacists ranged from Cohen's d = 0.14 to 4.93. The largest effect size in this subset of educational interventions with statistically significant findings was observed in the hypertension arm in the study by Solomon et al [50]. Interestingly, there was no statistically significant difference in medication adherence between the treatment and control groups in the COPD arm; the authors attributed this to greater motivation among COPD patients, who might be more likely to take their medication as prescribed because COPD is symptomatic while hypertension is not.

Among the 9 reports on educational interventions delivered by pharmacists in which education and counseling did not significantly improve medication adherence, 5 did not report a power analysis or were powered on outcomes other than medication adherence [39,43,53,55,56]. Four of these studies attributed nonsignificant differences in medication adherence to highly motivated and adherent subjects, which limited the impact of the intervention on adherence [31,37,38,47].

One study found that monthly small-group lay health mentoring to improve cardiovascular disease and medication adherence resulted in a statistically significant improvement in medication adherence as compared with usual care [36], with an effect size of Cohen's d = 0.28. Another study augmented nurse-delivered education with a computer educational session and found a statistically significant improvement in medication adherence at 1 month compared with nurse-delivered education alone with an effect size of Cohen's d = 0.43, but the effect was not sustained at 6 months [51].

In the remaining 6 educational interventions, patient education materials were used alone or in combination with interviews by nurses, care managers, and physicians; none of these interventions showed a statistically significant difference in medication adherence compared with usual care [40-42,46,49,57]. Five of these studies were characterized by either small sample sizes without a power analysis reported [41,46] or brief interventions [40,42,49].

Williams et al [57] reported that their self-report measure showed ceiling effects for medication adherence, which could contribute to nonsignificant group differences.

Memory Aids and Cues

Five studies tested memory aids and cues [59-64] (Table 2). One study reported in 2 separate papers examined a telephone-linked computer system for automated patient monitoring and counseling [60,61], 2 used video telephone technology [59,62], 1 investigated time-specific blister packs [63], and 1 studied a voice-activated message and automatic dispenser [64]. Three of the 5 studies investigated interventions in older adults with hypertension, heart failure, or cardiovascular risk factors. Three studies assessed medication adherence by pill count, 1 by EEM, and 1 by self-report. Follow-up ranged from 2 to 14 months.

Four of the 5 studies showed that interventions using memory aids and cues, some in conjunction with newer technologies, improved adherence [59-61,63,64]. Jerant et al's [62] pilot study of real-time, interactive, video-based home telecare by a nurse, which incorporated a video conferencing device and an integrated electronic stethoscope, resulted in no significant differences between groups, perhaps owing to the small sample size. However, the results were in the expected direction with effect sizes of Cohen's d = 0.46 and 0.37 for telecare and telephone versus control, respectively. Effect sizes for the statistically significant interventions using memory aids and cues ranged from Cohen's d = 0.26 to 2.72. The largest effect size was observed for time-specific blister packs combined with education and pharmacist follow-up [63].

Discussion

This review of randomized controlled trials of interventions to optimize medication adherence in patients aged 65 years or older found only 28 educational interventions and 5 interventions of memory aids and cues meeting selection criteria. The studies were implemented in a variety of settings, such as primary care clinics, pharmacies, and patient homes, and included samples of older adults with specific chronic disorders as well as generally healthy older adults prescribed a variety of medications.

The evidence from this review does not clearly support one single intervention to optimize medication adherence in older patients. In general, educational interventions did not consistently improve medication adherence in older adults. Among the educational interventions, tailored interventions that involved ongoing contact with health care professionals, primarily pharmacists, or lay health mentors as well as an interactive computer-based educational session, seemed more effective than interventions with mailed patient educational materials or brief interactions. Interventions that used memory aids and provided cues to improve adherence were somewhat effective, but studies were few in number and additional research is needed. While some strategies, such as time-specific blister packs, could be easily implemented, other strategies involving newer computer-based technologies need to be replicated to be generalizable. These results are consistent with those of previous systematic reviews of interventions to improve medication adherence in older adults [18,24,27].

The studies included in this review had a number of methodologic weaknesses, which limits our ability to draw firm conclusions. First, all of the samples were chosen by convenience, so sampling bias was likely, making the results less generalizable to other samples of older adults. Indeed, a few investigators acknowledged that their samples tended to be highly motivated and adherent at baseline. Second, many studies did not report a power analysis and were underpowered to find statistically significant differences between groups. Other studies reported a power calculation for their sample size using an outcome other than adherence, suggesting that nonsignificant results for adherence may be related to lack of power. Third, because of the nature of the interventions, the investigators were not able to blind the participants and interventionists to group assignment, which could produce Hawthorne, novelty, and experimenter effects in the intervention group subjects. Fourth, an intention-to-treat analysis was not consistently used in the studies, which makes the results less generalizable to clinical practice. Fifth, dropout rates were not routinely reported across the studies and dropout rates that were reported ranged widely, greater in studies with longer follow-up periods and samples prone to worsening health conditions. Sixth, adherence rates to the intervention by the subjects were not reported. Seventh, intervention integrity was a problem in a few studies due to lack of time and motivation by the pharmacists [33,52,56], which limits generalizability of these interventions. Lastly, measurement of adherence was primarily by self-report, which tends to overestimate adherence as a result of recall bias and a desire to please the investigator. Further, assessing adherence at baseline and follow-up could potentially sensitize subjects to their adherence, producing a measurement effect and artificially inflating adherence.

EEM is one method increasingly used to assess medication adherence. EEM consists of a medication cap fitted with a microprocessor above the inner liner of the cap that records the date and time that the cap is removed from a standard medication vial. Each presumptive medication-taking event is recorded at the time of occurrence. Unlike other medication adherence measures, EEM shows patterns of adherence, timing of doses, extra doses, and nonadherence episodes that might otherwise be missed [65,66]. EEM also overcomes recording problems that might be associated with memory, willingness to report accurately, and failure to maintain records or return pills for pill counts. A disadvantage is that EEM can only document that the vial was opened and not that the medication was consumed at that time and that the prescribed dose was consumed. Further, EEM may underestimate medication adherence in patients who pocket dose their medications to be taken throughout the day [67]. Also, the cost of EEM may be prohibitive for large clinical trials as well as routine clinical care.

Our review has several limitations. Non-English language papers and literature over a decade old were excluded, so it is possible that some articles were not included in the review. Despite the careful literature search and appraisal, it is possible that some articles were overlooked.

Recommendations for future research include continuing to explore tailored interventions with ongoing contact. Future studies need to rectify the methodologic weaknesses evident in the extant literature and consistently provide complete statistical reports of adherence, specifically, means and standard deviations, proportions with exact frequencies as well as percentages, statistical values, and exact *P* values. Dropout rates should be reported within treatment groups at all time points. Future studies should clearly define adherence and use EEM when possible to enhance measurement accuracy as well as consistently report clinical as well as adherence outcomes. Consistent clinical outcomes, such as blood pressure in participants with hypertension, glycosylated hemoglobin in subjects with diabetes, serum cholesterol in those with hyperlipidemia, and hospitalizations in older adults with heart failure, would permit future meta-analyses to examine the impact of these interventions on clinical and adherence outcomes in older patients.

Acknowledgements

Funding/support: This paper was supported in part by the National Institutes of Health, National Institute of Nursing Research (P30 NR003924) and the National Institute on Aging (P30 AG024827).

Appendix. Search Strategies

MEDLINE

(patient compliance.sh.OR patient dropouts.sh.OR treatment refusal.sh.OR patient compliance.ti,ab.OR adherence.ti,ab.OR treatment persistence.ti,ab.OR noncomplian$.ti,ab) AND (exp Drug Therapy.sh.OR medicat$.ti,ab.OR drug regimen$.ti,ab.OR medication regimen$.ti,ab.OR treatment.ti,ab.) AND (exp Aged OR elderly.ti,ab.OR geriatric$.tw.OR gerontolo$.tw.) AND (clinical and trial.ti,ab.OR exp Clinical Trials.sh.OR clinical trial.pt.OR randomized controlled trial.pt.OR random$.ti,ab.OR random allocation.sh.)

CINAHL

(patient compliance.sh.OR patient dropouts.sh.OR treatment refusal.sh.OR medication compliance.sh.OR self administration. sh.OR patient compliance.ti,ab.OR adherence.ti,ab.OR treatment adj persistence.ti,ab.OR noncomplian$.ti,ab.) AND (exp Drug Therapy.sh.OR medicat$.ti,ab.OR drug regimen$.ti,ab.OR medication regimen$.ti,ab.OR treatment.ti,ab.) AND (Exp Aged. sh.OR elderly.ti,ab.OR geriatric$.ti,ab.OR gerontolo$.ti,ab.) AND (exp Clinical Trials OR clinical and trial.ti,ab.OR clinical trial.pt.OR random$.ti,ab.OR random.hw.)

PsycINFO

(treatment compliance.sh.OR treatment dropouts.sh.OR treatment refusal.sh.OR drug self administration.sh.OR treatment adj compliance.ti,ab. OR adherence.ti,ab.OR treatment persistence. ti,ab.OR treatment dropout$.ti,ab.OR treatment adj refusal$.ti,ab.) AND (exp Drug Therapy OR exp DRUGS OR drug.ti,ab.OR treatment.ti,ab.OR regimen$.ti,ab.) AND (random$.ti,ab.OR clinical trial$.ti,ab.OR treatment outcome$.ti,ab.OR control$.ti,ab.) AND (limit to middle age <age 40 to 64 yrs> OR aged <age 65 yrs and older> OR very old <age 85 yrs and older>)

International Pharmaceutical Abstracts

(patient education interventions.sh.OR interventions patient education .sh.OR interventions patient information.sh.OR interventions patients.sh.OR interventions.hw.OR education.hw.) AND (compliance. hw.OR compliance.fs.OR noncomplian$.tw.OR nonadheren$. tw.OR treatment persistence.tw.) AND limit to journal articles

EMBASE

(randomization/de OR clinical trial/exp OR controlled trial/exp OR controlled study/exp OR random* OR control*) AND (‘drug therapy’/ exp OR medicat* OR ‘drug regimen’) AND(patient compliance/de OR treatment refusal/de OR illness behavior OR patient dropout OR medication compliance OR medication adherence OR patient compliance OR treatment persistence OR noncomplian*) AND (aged/exp OR elderly OR geriatric* OR gerontolog*) AND (intervention* OR outcome* OR treatment outcome/exp OR education)

exp = explode; .fs. = floating subheading; py = publication year; .sh. and /de = subject heading; .ti,ab. = title and abstract; $ and * = truncation symbols.

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Table 1

Studies of Educational Interventions to Optimize Medication Adherence

Study	Design/ Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
Begley et al (1997) [32]	RCT/UK	190 men and women, mean age ≥ 75 yr (*n*'s for intervention and controls not reported)	Pharmacist completed 5 home visits over 12 mo for counseling on correct use and storage of drugs vs. Attention Control with 5 home visits but no counseling vs. Usual Care	Taking ≥ 85% of drug doses measured by pill count	At 12 mo, mean percentage adherence was Intervention: 86% (SD = 19) Attention Control: 75% (SD = 21) Usual Care: 69% (SD = 29) $P < 0.001$	0.58
Bernsten et al (2001) [33]	Cluster RCT/ 7 European countries	190 pharmacies Intervention: $n = 104$ with 1290 men and women, mean age 74 (8) yr Control: $n = 86$ with 1164 men and women, mean age 74 (8) yr	Pharmacist assessed patients individually to identify actual and potential drug problems and formulated an intervention and monitoring plan vs. Usual Care	Never experiencing aspects of nonadherence measured on a 4-item, 4-point Likert self-report scale	At 18 mo, proportion who changed from being non- adherent to adherent was Intervention: 15.2% (107/704) Control: 12.2% (77/636) $P = 0.028$	0.14
Bouvy et al (2003) [34]	RCT/ Netherlands	152 men and women with heart failure Intervention: $n = 74$, mean age 69.1 (10.2) yr Control: $n = 78$, mean age, 70.2 (11.2) yr	Pharmacist met with patients monthly over 6 mo for counseling on drug use, reasons for nonadherence, and reinforcement of adherence vs. Usual Care	Days with dosing during scheduled dosing measured by EEM	At 6 mo Intervention: 140/7656 days without diuretic Control: 337/6196 days without diuretic, RR = 0.33 (95% CI, 0.24–0.38)	0.49
Clifford et al (2006) [35]	RCT/UK	492 men and women ≥ 75 yr Intervention: $n = 255$ Control: $n = 237$	Pharmacist telephoned patients 2 wk after starting a new medication for a chronic disorder to identify medication-related problems and information needs and provide advice, information, and reassurance vs. Usual Care	Not missing any doses in the last 7 days measured by self-report	At 1 mo, proportion nonadherent was Intervention: 9% (16/185) Control: 16% (31/194) $P = 0.032$	0.37
Coull et al (2004) [36]	RCT/UK	319 men and women with heart disease Intervention: $n = 165$, mean age 67.7 yr Control: $n = 154$, mean age 67.4 yr	Monthly small group lay health mentoring on cardiovascular disease including medication adherence vs. Usual	Perceived change in taking medication measured by self-report on 5-point Likert scale	At 12 mo, adherence improved more in intervention than control subjects	0.28

Study	Design/ Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
		(SDs not reported)	Care		$P < 0.01$	
Grant et al (2003) [37]	RCT/US	120 men and women with type 2 diabetes Intervention: $n = 62$, mean age 64 (12) yr Control: $n = 58$, mean age 69 (10) yr	Pharmacist telephoned patients for tailored education on drug use, help with appointment referrals, and electronic summary to medical record and physician vs. Usual Care	Not missing any doses of any diabetes-related medication in the last 7 days measured by self-report	At 3 mo, mean improvement from baseline was Intervention: $n = 61$, 0.1 days (SD = 1.0) Control: $n = 54$, 0.1 days (SD = 0.4) $P = 0.80$	0.00
Grymonpre et al (2001) [38]	RCT/ Canada	135 men and women Intervention: $n = 69$, mean age 76.9 (8.4) yr Control: $n = 66$, mean age 77.2 (8.8) yr	Pharmacist completed a medication history, provided counseling and written information to patients, made recommendations to physician, and followed up as needed vs. medication history and referral to usual pharmacist for Usual Care	Percentage of prescribed doses taken measured by pharmacy refill	At 12 mo, mean adherence by drug was Intervention: $n = 309$ drugs, 86.7% (SD = 46.0) Control: $n = 280$ drugs, 85.1% (SD = 41.1) $P = 0.895$	0.04
Hanlon et al (1996) [39]	RCT/US	208 men and women, mean age ≥ 65 yr Intervention: $n = 105$ Control: $n = 103$	Pharmacist met with patients during all scheduled clinic visits to evaluate their drug regimens and make recommendations to them and their physicians vs. Usual Care	Proportion of medications for which the patient's response agreed with the directions for their use on the profile measured by self-report	At 12 mo, mean adherence was Intervention: $n = 86$, 77.4% Control: $n = 83$, 76.1% $P = 0.88$	0.02
Herschorn et al (2004) [40]	RCT/ Canada	84 men and women with overactive bladder Intervention: $n = 39$, mean age 65.7 (14.5) yr Control: $n = 45$, mean age 63.1 (15.7) yr	3 information sheets on overactive bladder, behavioral modification, and tolterodine with 3- to 5-min review by physician or study nurse vs. Usual Care	Taking the medication as prescribed measured by self-report	At 4 mo, proportion adherent was Intervention: $n = 34$, 39% Control: $n = 31$, 31% $P > 0.05$	0.22
Higgins et al (2004) [41]	RCT/UK	19 men and women with depression and new prescription for antidepressant, mean age ≥ 65 yr Intervention: $n = 10$ Control: $n = 9$	Concordance therapy by a psychiatrist over 3–4 sessions with cognitive behavioral therapy and motivational interviewing, which included medication information vs. Usual Care	Omission and dosage alteration measured on a self-report scale where maximum score of 50 = 100% adherence	At 3 mo, no significant group differences	Unable to compute

Study	Design/ Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
Hunt et al (2004) [42]	RCT/US	312 men and women with hypertension Intervention: n = 162, mean age 69.2 (12.4) yr Control: n = 150, mean age 69.3 (12.3) yr	2 mailed educational packets 3 months apart from primary care providers vs. Usual Care	Adherence measured on a 4-item dichotomous self-report scale	At 12 mo, mean adherence was Intervention: 0.35 Control: 0.35 $P > 0.05$	Unable to compute
Lim et al (2004) [43]	RCT/ Singapore	126 men and women Intervention: n = 64, mean age 79.6 (7.7) yr Control: n = 62, mean age 80.5 (8.1) yr	Pharmacist met with patients to review medical records for existing medication regimens and to counsel patients on medication knowledge and proper administration and use vs. Usual Care	Not forgetting to take medication as prescribed measured by self-report	At 2 mo, no significant group differences Unadjusted OR, 1.50 (90% CI, 0.73–3.08); $P = 0.36$ Adjusted OR, 2.52 (90% CI, 1.09–5.83); $P = 0.07$	0.22 0.51
Lowe et al (2000) [44]	RCT/UK	161 men and women Intervention: n = 77, mean age 77.5 yr Control: n = 84, mean age 75.0 yr (SD not reported)	Pharmacist met with patients 3 times for medication review and education vs. Usual Care	Percentage of prescribed doses taken measured by self-report and pill count	At 1 mo, mean adherence was Intervention: n = 73, 91.3% (95% CI, 88.7–93.9) Control: n = 79, 79.5% (95% CI, 74.7–84.3) $P < 0.001$	0.65
Naunton and Peterson (2003) [45]	RCT/ Australia	121 men and women Intervention: n = 57, mean age 74 yr Control: n = 64, mean age 77 yr	Pharmacist visited patients 5 days after hospital discharge to provide education about medications, encourage adherence, assess for drug-related problems, intervene when appropriate, and communicate findings to health care providers vs. wait list control	Never missing medication measured by single-item self-report	At 3 mo, proportion adherent was Intervention: 87% (47/55) Control: 44% (26/59) $P < 0.001$	1.28
Oakley and Walley (2006) [46]	RCT/UK	33 women on bisphosphonates, mean age 77 years Intervention: n = 16 Control: n = 17	Osteoporosis workshop; decision aid that included information booklet, audiocassette, and worksheet on personal lifetime risk of hip fracture, family health issues, and personal values;	Percentage of prescribed doses taken measured by pharmacy refill	At 4 mo, no significant group differences Intervention: median, 100% Control: median, 100% $P = 0.80$	0.08

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Study	Design/ Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
			consultation with physician 2 wk later vs. Usual Care			
Peterson et al (2004) [47]	RCT/ Australia	81 men and women with hyperlipidemia Intervention: n = 39, mean age 65.5 (11.0) yr Control: n = 42, mean age 63.5 (12.1) yr	Pharmacist assessed patients monthly in their homes regarding lipid therapy and lifestyle modifications vs. Usual Care	Frequency of forgetting to take medications measured by self-report	At 6 mo, no significant group differences	Unable to compute
Roumie et al (2006) [48]	Cluster RCT/US	1341 men and women with hypertension, mean age 65 (12) yr, and 182 health care providers Provider education: n = 324 Provider education and alert: n = 547 Provider education and alert and patient education: n = 470	Provider education about hypertension vs. Provider education and electronic alerts to re-evaluate antihypertensive regimen vs. Provider education and electronic alerts and mailed patient educational material	Adherence measured by pharmacy refill	At 12 mo (n = 948), mean adherence was Provider education: 0.89 (SD = 0.14) Provider education and alert: 0.89 (SD = 0.14) Provider education and alert and patient education: 0.88 (SD = 0.16) P = 0.71	0.02
Rozenfeld et al (1999) [31]	RCT/US	33 men and women Intervention: n = 17, mean age 66 (12) yr Control: n = 16, mean age 65 (10) yr	Pharmacist counseling at VAMC cardiology clinic with medication history, recommendations to cardiologists, medication counseling, drug information, therapeutic drug monitoring and follow-up, and continuity of care vs. Usual Care at VAMC outpatient pharmacy	Therapeutic coverage with optimal ≥ 80%, partial 20% to 80%, and poor < 20% measured by EEM	At 1 mo Intervention: 83.2% (SD = 19.9) Control: 78.0% (SD = 25.5) P = 1.00	0.24
Schroeder et al (2005) [49]	RCT/UK	245 men and women with hypertension Intervention: n = 128, mean age 67.9 (10.3) yr Control: n = 117, mean age 68.2 (9.4) yr	20-min nurse-led educational intervention and 10-min follow-up 2 mo later vs. Usual Care	Percentage days correct number of doses of prescribed doses taken on time measured by EEM	At 6 mo, mean percentage adherence was Intervention: 87.2% (SD = 20.1) Control: 90.2% (SD = 16.2) P = 0.63	0.16
Solomon et al (1998) [50]	RCT/US	133 men and women with hypertension Intervention: n = 63, mean age 66.3 (10.0) yr	Pharmacy resident met 5 times for recommendations to physicians, patient education and counseling, patient	Adherence measured by 4-item dichotomous self-report scale (lower score is better adherence)	At 6 mo, in hypertension arm mean adherence was Intervention: 0.23 (SD = 0.054)	4.93 Unable to compute

Study	Design/ Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
		Control: *n* = 70, mean age 67.3 (11.0) yr 98 men with COPD Intervention: *n* = 43, mean age 69.3 (5.9) yr Control: *n* = 55, mean age 69.3 (9.2) yr	assessment and follow-up vs. Usual Care		Control: 0.61 (SD = 0.094) $P < 0.05$ In COPD arm, no significant group differences	
Stromberg et al (2006) [51]	RCT/ Sweden	154 men and women with heart failure Intervention: *n* = 82, mean age 70 (10) yr Control: *n* = 72, mean age 70 (11) yr	45-min interactive computer educational session plus Usual Care (educational session with a heart failure clinic nurse) vs. Usual Care	How often a dose of diuretics was skipped measured on a 1-item, 3-point self-report scale	At 1 mo, adherence improved more in intervention subjects ($n = 72$) than control subjects ($n = 65$); $P = 0.01$ At 6 mo, no significant group differences	0.43 Unable to compute
Sturgess et al (2003) [52]	Cluster RCT/UK	10 pharmacies Intervention: *n* = 5 with 110 men and women, mean age 73.1 (5.0) yr Control: *n* = 5 with 81 men and women, mean age 74.2 (6.3) yr	Pharmacist assessed patients individually to identify actual and potential drug-related problems during home visits vs. Usual Care	Adherence measured by self-report	At 18 mo, proportion adherent was Intervention: *n* = 75, 47.3% Control: *n* = 35, 14.7% $P < 0.05$	0.98
Taylor et al (2003) [53]	RCT/US	69 men and women Intervention: *n* = 33, mean age 64.4 (13.7) yr Control: *n* = 36, mean age 66.7 (12.3) yr	Pharmacist provided medical record review, medication history review, pharmacotherapeutic evaluation, patient education and monitoring vs. Usual Care	≥ 80% of prescribed doses taken in the previous week/month measured by self-report	At 12 mo, proportion adherent was Intervention: 100% Control: 88.9% $P = 0.115$	0.38
Varma et al (1999) [54]	RCT/UK	83 men and women with heart failure Intervention: *n* = 42, mean age 75.50 (6.44) yr Control: *n* = 41, mean age 76.36 (7.12) yr	Pharmacist provided education on heart failure, its treatment, and life-style changes to control symptoms; encouraged monitoring of symptoms and adherence with prescribed medication therapy vs. Usual Care	Using a minimum of 6 mo continuous data, adherence defined as 80%–120% of prescribed doses taken measured by pharmacy refill Underadherence: < 80% Overadherence: > 120%	At 12 mo, adherence with at least 1 heart failure drug was Intervention: 77% (10/13) Control: 30% (3/10) $P = 0.039$	1.26
Vivian (2002) [55]	RCT/US	56 men with hypertension Intervention: *n* = 27, mean age 64.0 (10.9) yr	Pharmacist at VAMC hypertension clinic met with patients monthly for appropriate changes in prescribed drugs,	Refilling drugs within 2 wk of the scheduled refill date measured by pharmacy refill	At 6 mo, proportion adherent was Intervention: 85% (22/26)	−0.43

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Study	Design/ Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
		Control: n = 29, mean age 65.5 (7.8) yr	adjustments in dosages, and drug counseling vs. Usual Care		Control: 93% (25/27) $P > 0.42$	
Volume et al (2001) [56]	Cluster RCT/ Canada	16 pharmacies Intervention: n = 8 with 159 men and women, mean age 73.89 (6.09) yr Control: n = 8 with 204 men and women, mean age 73.18 (6.11) yr	Pharmacist spoke with patients in person or by telephone to assess, plan, and document actions related to pharmaceutical care vs. Usual Care	Adherence measured on a 4-item dichotomous self-report scale	At 12 mo Intervention: 0.56 (SD = 0.75) Control: 0.47 (SD = 0.69) $P > 0.05$	Unable to compute
Williams et al (2004) [57]	RCT/US	417 men and women with depression and diabetes Intervention: n = 205, mean age 70.1 (6.9) yr Control: n = 212, mean age 70.3 (7.1) yr	Depression care management program with care manager providing education, problem-solving treatment, and support vs. Usual Care	Taking diabetes medication as prescribed measured on a 5-point self-report scale	At 12 mo, mean adherence was Intervention: n = 193, 1.16 (SD = 0.53) Control: n = 200, 1.19 (SD = 0.50) $P > 0.20$	0.06
Wu et al (2006) [58]	RCT/ Hong Kong	442 men and women Intervention: n = 219, mean age 71.2 (9.4) yr Control: n =223, mean age 70.5 (11.1) yr	Pharmacist assessed patients individually via a telephone call between clinic visits vs. Usual Care	Adherence defined as 80%–120% of prescribed doses taken measured by self-report	At 24 mo, proportion nonadherent at enrollment who remained nonadherent was Intervention: 7% (7/102) Control: 18% (19/104) $P < 0.001$	0.58
					At 24 mo, proportion adherent at enrollment who remained adherent was Intervention: 81% (95/117) Control: 58% (69/119) $P = 0.038$	0.68

CI = confidence interval; COPD = chronic obstructive pulmonary disease; EEM = electronic event monitoring; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; VAMC = Veterans Affairs Medical Center.

*Number in parentheses is standard deviation.

Table 2

Studies of Memory Aids and Cues to Optimize Medication Adherence

Study	Design/Setting	Sample*	Intervention	Definition of Adherence	Results	Effect Size (Cohen's d)
Friedman et al (1996) [60] Friedman (1998) [61]	RCT/US	267 men and women with hypertension, mean age 76.0 yr (SD not reported) Intervention: $n = 133$ Control: $n = 134$	Telephone-linked computer system vs. Usual Care	≥ 80% of prescribed doses taken measured by pill count	At 6 mo, mean improvement in adherence was Intervention: 17.7% Control: 11.7% $P = 0.03$	0.26
Fulmer et al (1999) [59]	RCT/US	50 men and women, mean age 74.2 (6.8) yr Video telephone: $n = 17$ Telephone: $n = 15$ Control: $n = 18$	Daily video telephone call reminder for 6 wk vs. daily telephone call reminder for 6 wk vs. Usual Care	Percentage of prescribed doses taken measured by EEM	At 2 mo, mean adherence was Video telephone: 84% Telephone: 74% Control: 57%, $F(2,34) = 4.08$; $P < 0.05$	0.90
Jerant et al (2003) [62]	RCT/US	37 men and women with heart failure Telecare: $n = 13$, mean age 66.6 (10.9) yr Telephone: $n = 12$, mean age 71.3 (14.1) yr Control: $n = 12$, mean age 72.7 (11.4) yr	Interactive video-based home telecare by nurse vs. telephone calls by nurse vs. Usual Care	> 75% of prescribed doses taken measured by self-report	At 2 mo, proportion adherent was Telecare: 92% (12/13) Telephone: 91% (10/11) Control: 83% (10/12) $P = 0.75$	Telecare vs. Control 0.46 Telephone vs. Control 0.37
Lee et al (2006) [63]	Multiphase, prospective study with run-in phase of 2 mo, observational phase of 6 mo, and RCT of 6 mo/US	159 men and women with cardiovascular risk factors Intervention: $n = 83$, mean age 77 (10.5) yr Control: $n = 76$, mean age 78 (6.2)yr	Time-specific blister packs, medication education, and pharmacist follow-up vs. Usual Care	≥ 80% of prescribed doses taken measured by pill count	At 14 mo, proportion adherent was Intervention: 97.4% (75/77) Control: 21.7% (15/69) $P < 0.001$ At 14 mo, mean adherence was Intervention: 95.5 (SD = 7.7) Control: 69.1 (SD = 16.4) $P < 0.001$	2.72 2.10
Winland-Brown and Vallante (2000) [64]	RCT/US	61 men and women, mean age 87 yr (SD not reported) Voice-activated: $n = 24$ Medication box: $n = 16$ Control: $n = 21$	Voice-activated message and automatic dispenser vs. prefilled medication box vs. Usual Care	Adherence measured by pill count	After 6 mo, mean number of missed doses was Voice-activated: (1.7) Medication box: (15.1) Usual Care: (19.7) $F(2,59) = 20.28$; $P < 0.001$ Voice activated was better than Medication box ($P < 0.01$) and Usual Care ($P < 0.01$)	−1.83

EEM = electronic event monitoring; RCT = randomized controlled trial.

* Number in parentheses is standard deviation.