Effect of a Pharmacy Care Program on Medication Adherence and Persistence, Blood Pressure, and Low-Density Lipoprotein Cholesterol

A Randomized Controlled Trial

Jeannie K. Lee, PharmD

Karen A. Grace, PharmD

Allen J. Taylor, MD

ADHERENCE TO CHRONIC PHARmacological therapies is poor,[1-3] leading to worsening disease severity and increased costs associated with higher hospital admission rates.[4,5] Barriers to medication adherence are numerous, but include the prescription of complex medication regimens, treatment of asymptomatic conditions, and convenience factors.[6] These factors are particularly prevalent among the elderly population, placing them at increased risk for medication nonadherence. Because approaches to improve adherence can be complex and labor intensive,[7] there are no accepted, fully effective strategies in widespread clinical use. Moreover, in elderly patients, effective strategies to improve adherence have not been investigated, and an effect on meaningful health outcomes has not been identified.

The Federal Study of Adherence to Medications in the Elderly (FAME) was a multiphase, single-center study of the efficacy of a comprehensive pharmacy care program, which included patient education and an adherence aid (medications custom-packaged in blister packs) to improve medication adherence among military health care beneficiaries aged 65 years

Context Poor medication adherence diminishes the health benefits of pharmacotherapies. Elderly patients with coronary risk factors frequently require treatment with multiple medications, placing them at increased risk for nonadherence.

Objective To test the efficacy of a comprehensive pharmacy care program to improve medication adherence and its associated effects on blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C).

Design, Setting, and Patients A multiphase, prospective study with an observational phase and a randomized controlled trial conducted at the Walter Reed Army Medical Center of 200 community-based patients aged 65 years or older taking at least 4 chronic medications. The study was conducted from June 2004 to August 2006.

Intervention After a 2-month run-in phase (measurement of baseline adherence, BP, and LDL-C), patients entered a 6-month intervention phase (standardized medication education, regular follow-up by pharmacists, and medications dispensed in time-specific packs). Following the intervention phase, patients were randomized to continued pharmacy care vs usual care for an additional 6 months.

Main Outcome Measures Primary end point of the observation phase was change in the proportion of pills taken vs baseline; secondary end points were the associated changes in BP and LDL-C. Primary end point of the randomization phase was the between-group comparison of medication persistence.

Results A total of 200 elderly patients (77.1% men; mean [SD] age, 78 [8.3] years), taking a mean (SD) of 9 (3) chronic medications were enrolled. Coronary risk factors included drug-treated hypertension in 184 patients (91.5%) and drug-treated hyperlipidemia in 162 (80.6%). Mean (SD) baseline medication adherence was 61.2% (13.5%). After 6 months of intervention, medication adherence increased to 96.9% (5.2%; $P<.001$) and was associated with significant improvements in systolic BP (133.2 [14.9] to 129.9 [16.0] mm Hg; $P=.02$) and LDL-C (91.7 [26.1] to 86.8 [23.4] mg/dL; $P=.001$). Six months after randomization, the persistence of medication adherence decreased to 69.1% (16.4%) among those patients assigned to usual care, whereas it was sustained at 95.5% (7.7%) in pharmacy care ($P<.001$). This was associated with significant reductions in systolic BP in the pharmacy care group (−6.9 mm Hg; 95% CI, −10.7 to −3.1 mm Hg) vs the usual care group (−1.0 mm Hg; 95% CI, −5.9 to 3.9 mm Hg; $P=.04$), but no significant between-group differences in LDL-C levels or reductions.

Conclusions A pharmacy care program led to increases in medication adherence, medication persistence, and clinically meaningful reductions in BP, whereas discontinuation of the program was associated with decreased medication adherence and persistence.

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Author Affiliations: Departments of Pharmacy (Drs Lee and Grace) and Cardiology (Dr Taylor), Walter Reed Army Medical Center, Washington, DC.
Corresponding Author: COL Allen J. Taylor, MD, MC, USA, Chief, Cardiology Service, Walter Reed Army Medical Center, 6900 Georgia Ave NW, Bldg 2, Room 4A34, Washington, DC 20307-5001 (allen.taylor@na.amedd.army.mil).

or older who were prescribed at least 4 chronic medications per day. We further tested the impact of this program on blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C), biomarkers of the efficacy of pharmacotherapy to lead to optimal cardiovascular health outcomes.

Figure 1. Flow of Patients Through the Study Protocol

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┌─────────────────────────────────┐
│ 208 Eligible Patients Approached │
│         for Consent              │
└─────────────────────────────────┘
            │
            │   ┌──────────────────────┐
            ├──►│ 8 Excluded (Refused to│
            │   │    Participate)       │
            │   └──────────────────────┘
┌─────────────────────────────────┐
│ 200 Enrolled in Run-in Phase     │
│        (Months 1-2)              │
└─────────────────────────────────┘
            │   ┌──────────────────────┐
            │   │ 26 Withdrew           │
            │   │   6 Moved Out of      │
            │   │     the Area          │
            │   │   4 Moved Into        │
            │   │     Assisted Living   │
            │   │   6 Uncomfortable     │
            ├──►│     About Using       │
            │   │     Blister Pack      │
            │   │   4 Unable to Make    │
            │   │     Every 2-Month Visit│
            │   │   1 Withdrew Before   │
            │   │     Completing        │
            │   │     Baseline          │
            │   │   4 Personal Reasons  │
            │   │   1 Died              │
            │   └──────────────────────┘
┌─────────────────────────────────┐
│ 174 Enrolled in Phase 1          │
│ Prospective Observational        │
│      Study (Months 3-8)          │
└─────────────────────────────────┘
            │   ┌──────────────────────┐
            │   │ 15 Withdrew           │
            │   │   8 Moved Out of the  │
            │   │     Area              │
            ├──►│   3 Moved Into        │
            │   │     Assisted Living   │
            │   │   1 Uncomfortable     │
            │   │     About Using       │
            │   │     Blister Pack      │
            │   │   3 Died              │
            │   └──────────────────────┘
┌─────────────────────────────────┐
│ 159 Enrolled in Phase 2          │
│      Randomized Trial            │
│        (Months 9-14)             │
└─────────────────────────────────┘
            │
       ╭──────────────────╮
       │ 159 Randomized   │
       ╰──────────────────╯
         │            │
┌──────────────┐  ┌──────────────────┐
│ 76 Assigned  │  │ 83 Assigned to   │
│  to Usual    │  │ Continued        │
│   Care       │  │ Pharmacy Care    │
└──────────────┘  └──────────────────┘
┌──────────────┐  ┌──────────────────┐
│ 7 Withdrew   │  │ 6 Withdrew       │
│  1 Moved Out │  │  2 Moved Out of  │
│    of the    │  │    the Area      │
│    Area      │  │  2 Moved Into    │
│  1 Moved Into│  │    Assisted      │
│    Assisted  │  │    Living        │
│    Living    │  │  2 Died          │
│  5 Died      │  │                  │
└──────────────┘  └──────────────────┘
┌──────────────┐  ┌──────────────────┐
│ 76 Included  │  │ 83 Included in   │
│ in Primary   │  │ Primary          │
│  Analysis    │  │ Analysis         │
└──────────────┘  └──────────────────┘
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METHODS
Study Population
The FAME trial follows the specifications of the revised CONSORT criteria.[8] This trial was a single-center study conducted at the Walter Reed Army Medical Center, a university-affiliated, suburban, tertiary care US military medical center. Eligible patients were recruited from the outpatient general medicine service and the Armed Forces Retirement Home, an affiliated retirement home of approximately 900 independently living military health care beneficiaries located in Washington, DC, and were elderly men and women (≥65 years) taking 4 or more chronic medications daily, a population selected as being at increased risk for medication nonadherence. Patients were excluded if they did not live independently (assisted living or nursing home residents were excluded) or in the presence of any serious medical condition for which 1-year survival was expected to be unlikely.

The Walter Reed Army Medical Center Department of Clinical Investigation, which is composed of the Clinical Investigation Committee, Human Use Committee, and the Central Investigative Regulatory Office, approved the study. Among 208 eligible patients approached for written informed consent, 200 patients volunteered to participate and 8 refused. Study patients were observed at the pharmacy clinics at both the Walter Reed Army Medical Center and Armed Forces Retirement Home. Study enrollment began on June 30, 2004, and was completed on July 6, 2005. The last follow-up visit occurred on August 30, 2006.

Study Design
The FAME study consisted of 3 phases (run-in phase, phase 1 [prospective, observational study], and phase 2 [randomized controlled trial]), with a follow-up period of 14 months. The flow of patients through the trial is shown in **FIGURE 1**. The intent was for all volunteers to participate in all 3 phases of the study.

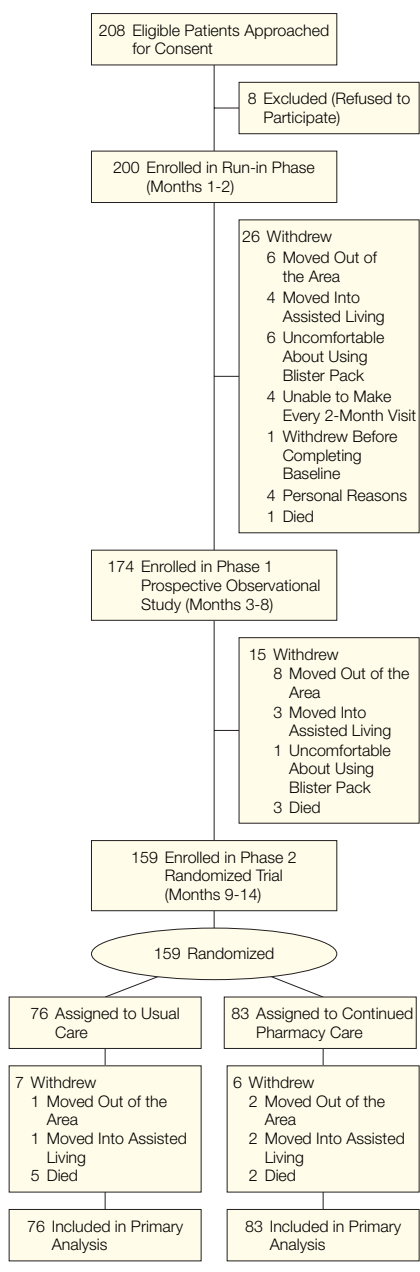During the run-in phase (initial visit through 2 months), data collection included baseline demographics, self-

reported race according to categories of the US Census Bureau (for descriptive purposes), medication lists, measurement of baseline medication adherence (measured at both 1 and 2 months), BP (initial visit and 2 months), and LDL-C (initial visit and 2 months). Baseline medication adherence during the run-in phase was assessed for all chronic medications using pill counts, expressed as the percentage of pills taken relative to the number of pills that should have been taken.

During the run-in phase, no specific educational or adherence interventions were performed. Baseline medication adherence was defined as the mean value of the 1- and 2-month adherence assessments.

Baseline BP and LDL-C levels were measured twice (initial visit and 2 months), with the mean representing the baseline value for subsequent comparisons. For all time points (run-in phase, phase 1, and phase 2), the clinical pharmacist meeting with the patient used a calibrated, automated sphygmomanometer to obtain the BPs. Blood pressure was measured 3 times, each 2 minutes apart, in the seated position. Measured BP was calculated as the mean of the second and third BP values. Serum, collected for the measurement of LDL-C, was processed at a single laboratory located in Walter Reed Army Medical Center using a direct assay, eliminating the need for fasting. Other lipid values were not defined end points of our study and therefore were not measured. The rationale for this was the prevalent use of statins in clinical practice as the principle mode of therapy for hyperlipidemia aimed at reducing LDL-C.

Following successful completion of the run-in phase, all patients entered phase 1 (3-8 months), a prospective, observational study of a comprehensive pharmacy care program. The comprehensive pharmacy care program consisted of 3 elements, including individualized medication education (using standardized scripts), medications dispensed using an adherence aid (blister packs) (**FIGURE 2**), and regular fol-

low-up with clinical pharmacists every 2 months. Individualized educational interventions were performed to teach participants their drug names, indications, strengths, adverse effects, and usage instructions during each visit. The initial visit was scheduled for 1 hour. Subsequent visits (including adherence assessments, education as needed, and prescription refills) were scheduled for 30 minutes.

At the start of this phase, all pill bottles were confiscated and discarded. Thereafter, all medications were provided to patients in customized blister packs (Figure 2) filled by pharmacy technicians at the main outpatient pharmacy using a commercially available system and checked by clinical pharmacists. Each blister pack, with 31 numbered blisters, was labeled using a customized computer program to meet the standards of the prescriptions. Two blister packs per dosing time (a 2-month supply) were dispensed at each study visit. Patients were instructed to tape any medications not taken back into the blister pack, to account for any selective adherence.

During follow-up visits, blister-packed medications were counted, including medications not taken (taped back into the blister pack). Study personnel did not adjust medications or their dosages. At 3 times during this phase (4, 6, and 8 months), pill counts were performed, using the blister packs, for all participants. At the end of this phase (study month 8), repeat measurements of BP and LDL-C of the participants were performed.

Patients successfully completing phase 1 entered phase 2, a 6-month randomized clinical trial evaluating the relationship between the method of medication administration and sustained medication adherence (persistence). Patients were randomized in a 1:1 ratio to either a return to usual care or continued pharmacy care. Usual care was defined as returning to their baseline (prestudy) status of medication provision; however, medi-

Figure 2. Sample Blister Pack of Medications for Morning

The multidose adherence package enables clear packaging and labeling of multiple medications in a disposable, punch card format. The translucent blister facilitates visual verification of the card content. This medication packaging organizes the patients' pills according to the daily dosing time and prevents them from working with multiple medication bottles. Patients received combinations of morning, noon, evening, or bedtime blister packs according to their regimen. Patients took the numbered blister that matched the day of the month.

cation education and blister-packed medications were not provided. At the end of phase 1, participants had none of their chronic medications. For the usual care group in phase 2, all medications were provided in new pill bottles with a 90-day supply and 1 refill prescription. Participants were directly provided their medications by study personnel; therefore, there was exact accounting of the prescription fill date. The proportion of pills taken, using these pill bottles, was assessed at the end of the study at 14 months when the patients randomized to the usual care group returned for the final study visit.

Patients randomized to the pharmacy care group continued to meet with clinical pharmacists every 2 months, as previously performed in phase 1 of the study, and were provided blister-packed medications and also continued

medication education as needed. An assessment of the proportion of pills taken was measured using the blister packs at 10, 12, and 14 months for patients randomized to the continued pharmacy care group. Blood pressure and LDL-C were measured at the conclusion of phase 2 (study month 14) to note the associated changes in these outcome markers with the changes in medication adherence observed between the 2 randomized groups.

Randomization

Patients were randomized to either usual care or continued pharmacy care in a 1:1 ratio using a computer-generated random number sequence. Allocation was concealed to both patients and the study personnel who enrolled participants by central control of the randomization sequence. Patients were randomized in blocks

based on the level of baseline medication adherence (above or below 55% baseline adherence).[9] The randomization assignment was revealed to the participants at the 8-month study visit (end of phase 1) after completing the end point data collection. Because of the nature of the intervention, it was not possible to blind either the participants or the clinical pharmacists assessing the outcomes to the study group assignment.

Table 1. Baseline Characteristics of the Elderly Patients*

| Characteristic | Baseline (n = 200) | Phase 2: Randomization | | P Value† |
		Usual Care Group (n = 76)	Continued Pharmacy Care Group (n = 83)	
Age, mean (SD), y	78 (8.3)	78 (6.2)	77 (10.5)	.45
Men	155 (77.1)	56 (73.7)	62 (74.7)	.51
Race				
White	128 (63.7)	43 (56.6)	51 (61.4)	.24
Black	65 (32.3)	31 (40.8)	29 (34.9)	
Education				
<High school	15 (7.5)	9 (12.9)	3 (3.7)	
High school graduate	68 (33.8)	27 (38.6)	26 (32.1)	
Some college	63 (31.3)	21 (30.0)	32 (39.5)	.11
College graduate	43 (21.4)	13 (18.6)	20 (24.7)	
Unknown‡	11 (5.5)	6 (7.9)	2 (2.4)	
Drug-treated hypertension	184 (91.5)	69 (90.8)	77 (92.8)	.43
Drug-treated hyperlipidemia	162 (80.6)	61 (80.3)	69 (83.1)	.40
Having ≥4 health problems	115 (57.2)	38 (50.0)	52 (62.7)	.07
Taking tricyclic antidepressant, selective serotonin reuptake inhibitor, or both	33 (16.4)	6 (7.9)	17 (20.5)	.03
Taking medication for memory problems	13 (6.5)	2 (1.3)	6 (3.8)	.28
Medication practice at study entry				
Taking multiple doses (≥3 per d)	78 (38.8)	27 (35.5)	31 (37.3)	.47
Receiving help with taking medications	34 (16.9)	12 (15.8)	19 (22.9)	.18
Using pill box	117 (58.2)	37 (48.7)	51 (61.4)	.07
Using medication chart or list	40 (19.9)	10 (13.2)	22 (26.5)	.03
No. of chronic medications, mean (SD)	8.7 (3.1)	8.3 (2.8)	9.1 (3.2)	.12
Baseline medication adherence at completion of run-in phase (n = 179), mean (SD)	61.2 (13.5)	61.1 (14.1)	61.4 (13.0)	.88
Medications				
β-Blocker	95 (47.3)	43 (56.6)	48 (58.5)	.46
ACE inhibitor	101 (50.2)	39 (51.3)	55 (67.1)	.03
Calcium channel blocker	74 (36.8)	31 (40.8)	36 (43.9)	.41
Angiotensin II receptor blocker	22 (10.9)	13 (17.1)	7 (8.5)	.08
Clonidine	9 (4.5)	5 (6.6)	4 (4.9)	.45
Thiazide diuretic	52 (25.9)	24 (31.6)	25 (30.5)	.51
Furosemide	44 (21.9)	19 (25.0)	20 (24.4)	.54
Other antihypertensive agents§	31 (15.4)	11 (14.5)	18 (22.0)	.16
Statin	160 (80)	61 (80.3)	68 (81.9)	.79
Niacin	8 (4.0)	1 (1.3)	7 (8.5)	.04
Fibrate	1 (0.5)	1 (1.3)	0	.48
Ezetimibe	4 (2.0)	1 (1.3)	3 (3.7)	.34
Other antilipid agents‖	9 (4.5)	4 (5.3)	5 (6.1)	.55
Systolic BP, mean (SD), mm Hg	134.2 (18.6)	135.0 (20.3)	133.4 (17.6)	.60
Diastolic BP, mean (SD), mm Hg	71.4 (10.0)	71.4 (10.6)	71.7 (9.1)	.85
LDL-C, mean (SD), mg/dL	92.8 (30.4)	98.4 (33.6)	91.6 (30.5)	.18

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.
SI conversion: To convert LDL-C to mmol/L, multiply by 0.0259.
*Data are presented as number (percentage) unless otherwise specified.
†Usual care group vs continued pharmacy care group.
‡Patient refused to disclose.
§Hydralazine, doxazosin, and terazosin.
‖Fish oil and bile acid sequestrants.

Outcome Measures and End Points

The prespecified primary end point of phase 1 was the change in medication adherence from run-in to the 8-month adherence assessment. The prespecified secondary end points were the associated changes in BP and LDL-C from run-in to the 8-month point within subgroups of patients with either pharmacologically treated hypertension or hyperlipidemia. The prespecified primary end point of the phase 2 randomized trial was the persistence of mean medication adherence between the usual care and continued pharmacy care groups.

Statistical Analyses

Mean medication adherence was calculated as the proportion of medications taken for all chronic medications. Baseline characteristics between the usual care and continued pharmacy care groups were compared using t test or a χ^2 test, as appropriate. Changes in medication adherence, BP, and LDL-C for phase 1 were compared using paired t tests.

For the primary end point of phase 2, analyses were performed according to the intention-to-treat principle. Mean medication adherence between the 2 study groups (usual care and continued pharmacy care) were compared by using a t test for independent groups. Patients who did not complete the randomized trial (because of death or withdrawal) were analyzed by the imputation method of last observation carried forward, using the medication adherence level at the conclusion of phase 1.

To control for baseline differences between study groups, a multivariable analysis was performed for the randomized trial (phase 2) primary end point. The dependent variable for this analysis was the change in medication adherence between the end of phase 1 and the conclusion of phase 2. The independent variables were those baseline characteristics that had between-group comparisons with $P<.20$, in addition to the randomized trial group assignment and the baseline (run-in phase) medication adherence. As a pre-

specified analysis in phase 2, we tested the change in BP and LDL-C between the usual care and continued pharmacy care groups.

All analyses were conducted using SPSS version 13.0 (SPSS Inc, Chicago, Ill) by an investigator (A.J.T.). $P \leq .05$ was considered statistically significant, except for the dual primary end points (phase 1 and phase 2) for which statistical significance was set at $P \leq .025$ to correct for multiple comparisons.

RESULTS

Of the 200 study patients, 1 did not provide complete baseline assessments; therefore, 199 contributed to the data analysis (Figure 1). The mean (SD) age of the study patients was 78 (8.3) years (**Table 1**). Cardiovascular risk factors were prevalent, including drug-treated hypertension in 184 patients (91.5%) and drug-treated hyperlipidemia in 162 patients (80.6%). The patients took a mean (SD) of 9 (3) different chronic daily medications.

Mean (SD) baseline medication adherence at completion of run-in phase was 61.2% (13.5%). After initiation of the 6-month pharmacy care program, there was improvement in medication adherence (**Figure 3**) noted at the 4-month pharmacy visit. At 4, 6, and 8 months, medication adherence was 96% or higher. At the conclusion of phase 1 (8 months), the primary end point was met with a mean (SD) medication adherence of 96.9% (5.2%), representing an absolute change in adherence of 35.5% (95% confidence interval [CI], 31.2%-38.5%; $P<.001$). The proportion of patients in whom all chronic medications were taken with an adherence rate of at least 80%, a commonly accepted cut point for defining an acceptable level of medication adherence, increased from 5.0% to 98.7% ($P<.001$) (**Table 2**).

Improved adherence was associated with improvements in both secondary end points (BP and LDL-C). Among patients with drug-treated hypertension (n=184), mean (SD) systolic BP was reduced from 133.2 (14.9) mm Hg to 129.9 (16.0) mm Hg

Figure 3. Box Plot of Medication Adherence Across Time in Months of the Run-in Phase and Phase 1
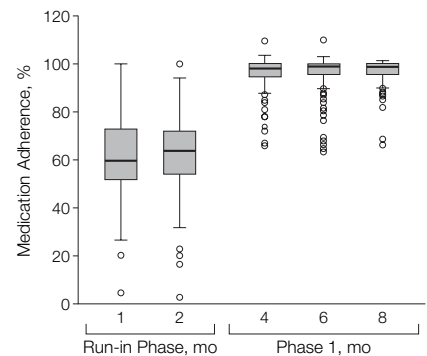
The run-in phase includes months 1 and 2. Phase 1 is pharmacy care including education and blister-packed medications for months 4, 6, and 8. The heavy horizontal line represents the mean, the box represents interquartile range, whiskers represent 95% confidence intervals, and circles represent outliers. Medication adherence may exceed 100% when patients mistakenly take more medications than they should (duplicate consumption of medications).

($P=.02$). Diastolic BP was not significantly reduced. There was no change in the number of antihypertensive agents taken from baseline to the end of phase 1 (mean [SD], 2.52 [1.15] vs 2.55 [1.23]; $P=.68$). Among patients with drug-treated hyperlipidemia (n=162), mean (SD) LDL-C decreased from 91.7 (26.1) mg/dL (2.38 [0.68] mmol/L) to 86.8 (23.4) mg/dL (2.25 [0.61] mmol/L) ($P=.001$).

Following successful completion of phase 1 (n=159), patients were randomized to either continued pharmacy care (n=83) or were returned to their previous (baseline) method of medication administration (usual care; n=76). The characteristics of the 2 groups were similar with respect to age, sex, baseline medication adherence, and other baseline characteristics (Table 1).

For the primary end point of the randomized clinical trial (**Figure 4**), the continued pharmacy care group showed sustained mean (SD) medication adherence (95.5% [7.7%]), whereas medication adherence declined in the usual care group (69.1% [16.4%]; $P<.001$) (Table 2). However, medication adherence at the conclusion of phase 2 for the

usual care group was modestly higher than at study entry (run-in phase, 66.5% [14.0%] vs 61.1% [14.1%]; *P* = .02). At the end of the study, those elderly patients assigned to usual care had a similar frequency (compared with their baseline method of medication administration) of receiving help with their medications (11.6% vs 15.9%; *P* = .58) and using a pillbox (62.3% vs 49.3%; *P* = .09), but were more likely to use a medication chart (65.2% vs 13.0%; *P* < .001).

Multiple linear regression analysis controlling for baseline differences (*P* < .20) in the study groups showed that the assignment to usual care (β = .81; *P* < .001) and taking medications for psychiatric or memory problems (β = .15; *P* = .007) were independently related to the change in medication adherence during phase 2. A prespecified analysis of the associated changes in BP and lipid levels in the continued pharmacy care group showed significant reductions in systolic BP (–6.9 mm Hg; 95% CI, –10.7 to –3.1 mm Hg; *P* = .04 vs usual care) and diastolic BP (–2.5 mm Hg; 95% CI, –4.9 to –0.2 mm Hg; *P* = .39 vs usual care). The mean (SD) number of antihypertensive agents used was similar between treatment groups (continued pharmacy care vs usual care: 2.60 [1.23] vs 2.61 [1.14]; *P* = .93). The LDL-C was not further reduced from 9 to 14 months in the continued pharmacy care group and was not different between study groups.

Patients who did not complete the run-in phase, phase 1, and phase 2 were comparable with those patients who completed each phase with respect to all baseline characteristics as shown in Table 1, except dropouts after phases 1 and 2 were more likely to be men. Among patients who completed the study, compliance with study visits was 100% in that the study was the source of refill medications.

COMMENT

The National Council on Patient Information and Education has aptly termed medication nonadherence "America's other drug problem."[10] Furthermore, the problem of medication nonadherence poses an even greater risk among elderly patients in the United States,[11,12] among whom poor medication adherence is common, morbid, costly, and difficult to treat. Among the elderly, polypharmacy, the use of multiple medications resulting in complicated drug regimens, is an important barrier to medication adherence.[11]

The FAME study sought to investigate the effect of a comprehensive pharmacy care program composed of clinical pharmacist education and blister-packed medications on medication adherence in the elderly population and to associate this intervention to improved control of BP and LDL-C, 2 surrogates of clinical risk for cardiovascu-

Table 2. Outcomes at 2 Months, 8 Months, and 14 Months

Outcomes	2 Months (Run-in Phase)	8 Months (End of Phase 1: Intervention)	*P* Value*	14 Months (End of Phase 2: Randomization) Usual Care Group	14 Months (End of Phase 2: Randomization) Continued Pharmacy Care Group	*P* Value†
All patients	(n = 179)	(n = 159)		(n = 76)	(n = 83)	
Medication adherence, % Mean (SD)	61.2 (13.5)	96.9 (5.2)	<.001	69.1 (16.4)	95.5 (7.7)	<.001
Median (range)	61.7 (4.0-92.0)	99.1 (66.0-100.0)		67.9 (33.0-97.0)	99.1 (47.0-100.0)	
≥80% Adherence to all medications, %	5.0	98.7	<.001	21.7‡	97.4‡	<.001
Patients with drug-treated hypertension	(n = 184)	(n = 142)		(n = 62)	(n = 73)	
Systolic BP, mm Hg Mean (SD)	133.2 (14.9)	129.9 (16.0)	.02	133.3 (21.5)	124.4 (14.0)	.005
Difference (95% CI)§		–3.3 (–6.0 to –0.6)		–1.0 (–5.9 to 3.9)	–6.9 (–10.7 to –3.1)	.04
P value‖				.69	.001	
Diastolic BP, mm Hg Mean (SD)	70.5 (9.2)	69.7 (10.5)	.30	68.6 (10.5)	67.5 (9.9)	.54
Difference (95% CI)§		–0.8 (–2.3 to 0.7)		–1.2 (–3.7 to 1.2)	–2.5 (–4.9 to –0.2)	.39
P value‖				.30	.04	
Patients with drug-treated hyperlipidemia	(n = 162)	(n = 122)		(n = 57)	(n = 64)	
LDL-C, mg/dL Mean (SD)	91.7 (26.1)	86.8 (23.4)	.001	88.4 (21.0)	87.5 (24.2)	.84
Difference (95% CI)§		–4.8 (–7.8 to –1.9)		–5.8 (–11.0 to –0.6)	–2.8 (–8.1 to 2.5)	.85
P value‖				.03	.30	

Abbreviations: BP, blood pressure; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.
SI conversion: To convert LDL-C to mmol/L, multiply by 0.0259.
*Run-in phase vs end of phase 1 (intervention).
†Usual care group vs continued pharmacy care group.
‡For usual care group, 15 of 69 patients adhered to at least 80% of all medications; for continued pharmacy care group, 75 of 77 patients adhered.
§Compared with 2 months (run-in phase).
‖Either usual care group or continued pharmacy care group vs run-in phase.

lar outcomes. This study is the first clinical trial to specifically address medication nonadherence in the elderly population and is one of few randomized controlled studies to demonstrate improvement in both adherence and health outcomes with the use of reminder packing in a comprehensive pharmacy care program. These findings of marked improvements in rates of medication adherence to levels consistently at 96%, associated with reduced BP and LDL-C, and the requirement of continued pharmacy intervention for persistence of these changes provide a template for optimal delivery of complex medication regimens to elderly individuals for maximal benefit of prescribed pharmacological therapy.

Medication nonadherence among older adults is a prevalent and costly problem. Among adults aged 65 years or older, the prevalence of patients with 2 or more chronic health problems is high (65%)[13] and leads to frequent use of multiple medications.[14,15] Predictably, the complexity of these regimens promotes medication nonadherence. Medication nonadherence is particularly problematic for asymptomatic conditions, such as hypertension and hyperlipidemia, despite a favorable tolerability profile of many medications used in their treatment. In a retrospective study[16] of 4053 patients aged 65 years or older prescribed medications for hypertension and hyperlipidemia, the adherence to both classes of medication decreased rapidly to 40.5% at the 3-month interval, and then to 32.7% at 6 months and thereafter stabilized.

Low adherence rates lead to increased adverse health outcomes, including increased ambulatory care visits, emergency department visits, and hospitalizations. In a claims database analysis, patients who were adherent and who had either hypertension or hyperlipidemia showed up to 50% lower all-cause hospitalization risks.[5] This problem may be magnified in the treatment of cardiovascular conditions, in which up to 50% of cardiovascular ad-

Figure 4. Box Plot of Medication Adherence During the Randomized Trial (Phase 2) for the Continued Pharmacy Care and Usual Care Groups From Baseline and Final Medication Adherence Assessment
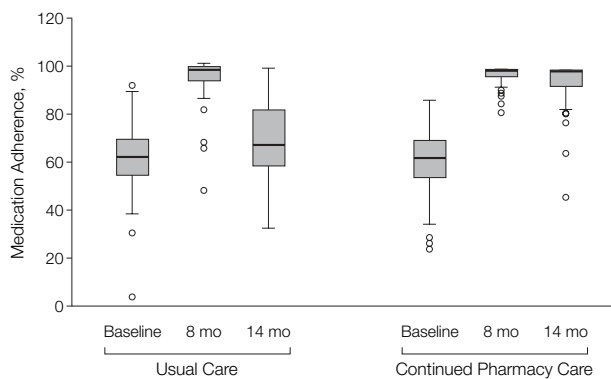
Baseline was at the end of the run-in phase (2 months), end of phase 1 was at 8 months, and final medication adherence assessment was at 14 months. The heavy horizontal line represents the mean, the box represents interquartile range, whiskers represent 95% confidence intervals, and circles represent outliers.

missions may be attributable to nonadherence.[4] Furthermore, although drug costs for adherent patients are higher, overall health care costs related to fewer hospital admissions are substantially lower in patients who are adherent.[5,17]

In contrast with the extensive existing literature on the effectiveness of pharmacological interventions, few prospective trials of adherence interventions have been conducted, and evidence from randomized trials is scant.[18] These trials have provided little evidence to date that medication adherence can be consistently and durably improved within the resources typically available in clinical settings,[19-22] and that such interventions lead to improved health outcomes. In general, multicomponent interventions, including cognitive and behavioral characteristics, are believed to be most effective.[7] These recommendations are relevant to the study design of FAME, which included the provision of external cognitive supports involving education strategies (patient education and counseling) and a behavioral component focused on the mechanics of medication delivery (blister packs).

Patient education, regarded as an essential initial step to ensure medication adherence, has only a marginal and

nondurable effect on medication-taking behavior.[19,20,22] Convenience packaging alone has not been adequately studied as an adherence aide. A meta-analysis of unit-of-use packaging suggested slight increases in medication adherence, but of 13 trials, only 7 reported statistically significant results[23] and most were of short duration (months). In comparison with simple studies of convenience packaging alone, 2 studies of complex intervention programs, involving provision of care at the worksite, special pill containers, reminders, self-monitoring, support groups, feedback, and reinforcement, reported positive effects on both adherence and clinical outcomes in patients with hypertension.[24,25]

We used a strategy of education, tailored medication provision, and the convenience of blister-packed medications, which led to a marked and sustained increase in medication adherence from 61% to 96%. The proportion of individuals who achieved a pill count exceeding 80% for all of their medications increased by 16-fold (from 5.0% to 98.7%), and these changes were associated with clinically meaningful reductions in BP and LDL-C.

The randomized controlled trial phase of FAME provides insight into the

required duration of a pharmacy care adherence program. Despite receiving 6 months of pharmacy care education and enculturation of medication adherence through the use of blister-packed medications, the initial marked increase in medication adherence did not persist in the group randomized to resume "usual care" for 6 months, although there was a modest increase over baseline adherence levels. In comparison, the group randomized to continued pharmacy care sustained high medication adherence and had further improvements in BP. These findings are consistent with the known transient effect of medication education and imply that the continued provision of blister-packed medications was a key component of the medication adherence program.

Based on our experience and consistent with the recommendations of others,[26] we suggest that medication adherence interventions should follow the FAME strategy of addressing underlying reasons for nonadherence, educating patients, providing serial follow-up, and promoting convenience through reminder packaging. In our experience, pharmacists are essential health care professionals in this process of evaluation and follow-up, underscoring the need for a teamwork approach to the problem of medication adherence.[26]

There are practical limitations to the wide-scale implementation of a comprehensive pharmacy care program that must be recognized and overcome to ensure its effectiveness for improving medication adherence. For the pharmacist, education, medication organization, and oversight of blister packing are all time intensive. Blister packing is particularly time-consuming due to the absence of automated systems to facilitate this key component of the program; therefore, the development of accurate, technological-based blister-packing systems is needed before such programs could be disseminated on a wide-scale basis. Moreover, given the pervasive and morbid effects of medi-

cation nonadherence, health care professionals, health systems, third-party payers, governmental agencies, and policy makers are all stakeholders in promoting greater emphasis on not simply the prescription or provision of medications, but also on medication adherence.[27]

Several limitations to our study are acknowledged. The generalizability of our results is limited to elderly patients taking multiple chronic medications and may not apply to specialized populations, such as elderly individuals in assisted living or those with memory problems. Our study did not evaluate formal measures of cognitive function. Our study design provides evidence on its global impact on adherence, BP, and LDL-C, but cannot distinguish the individual impact of its components (education vs blister packs). Although factorial design trials could provide such data, presently available data have been summarized and indicate that comprehensive programs are more effective than limited ones.[7] On a practical level, patient knowledge on the indications and proper use of medications plausibly should promote the beneficial impact of convenience aides like blister packs.

We studied BP and LDL-C as accepted surrogate clinical outcomes known to be associated with cardiovascular events. Practical performance of clinical outcome studies to measure the effect of adherence programs on hard clinical events (death, myocardial infarction, or stroke) are likely to be limited by large sample sizes and long durations.

The relationship between BP and LDL-C control and clinical outcomes has been established through both epidemiological and clinical treatment trials. For example, a 3-mm BP reduction, observed at the end of phase 1 of the FAME study, has been associated with a 5% reduction in coronary deaths and an 8% reduction in stroke deaths.[28-31] Each mg/dL reduction in LDL-C has been associated with an approximately 1% relative risk reduction for cardiovascular events.[30-32] Ac-

cordingly, among elderly, at-risk populations with high absolute event rates, the absolute population impact of improved BP and LDL-C control simply through improved medication adherence could be substantial.

Our study was conducted in a population of elderly US citizens eligible for health care at military medical treatment facilities as a federal health care benefit and who were treated with 4 or more chronic medications. This is consistent with survey data from older community living populations showing that 4 chronic medications is an average medication burden.[33,34] Thus, we think that our results should be generalizable to other elderly populations. However, within the military health care system, all medications are provided at no cost to the patient, thereby removing financial constraints as a barrier to adherence. This characteristic of the military health care system created an optimal environment for this study, but potentially limits the generalizability of our findings to clinical populations in which financial barriers to medication acquisition are present. In such populations, generic formulations and coverage plans such as the Medicare drug plan should be leveraged to remove financial barriers to adherence.[27] Alternatives to pill counts for adherence monitoring include systems such as electronic pill caps. Such systems provide a time and date stamp to bottle opening but are generally not widely available, are not available in our system, and are only considered an adjunct to pill counts.[35] Lastly, because of the nature of the intervention studied in this trial, blinding of participants and the research personnel was not possible.

CONCLUSIONS

In this study, a comprehensive pharmacy program composed of patient education and custom blister-packed medications was associated with substantial and sustained improvements in medication adherence among elderly patients receiving complex medication regimens. The association of improved medication adherence with re-

duced levels of BP and LDL-C suggests that such a program could lead to meaningful improvements in health outcomes. The results of the FAME study call for greater emphasis within health care delivery systems and policy organizations on the development and promotion of clinical programs to enhance medication adherence particularly among the at-risk elderly population.

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