Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients

Philip J. Schneider, John E. Murphy, and Craig A. Pedersen

Abstract

Objective: To evaluate medication adherence and treatment outcomes in elderly outpatients using daily-dose blister packaging (Pill Calendar) compared with medications packaged in bottles of loose tablets.

Design: Randomized controlled trial.

Setting: Ambulatory care clinics at Ohio State University Medical Center, Columbus; University of Arizona Health Science Center, Tucson; and Riverside Methodist Hospital Family Medicine Clinic, Columbus, Ohio, from July 1, 2002, to December 31, 2004.

Patients: 85 individuals 65 years of age or older being treated with lisinopril for hypertension.

Intervention: Patients were randomly assigned to receive lisinopril in either daily-dose blister packaging (Pill Calendar) or traditional bottles of loose tablets.

Main outcome measures: Adherence was assessed by prescription refill regularity and medication possession ratio (MPR). Treatment outcome and use of medical services were assessed by medical record review of blood pressure and morbidity associated with poorly controlled hypertension.

Results: Patients receiving lisinopril in the daily-dose blister packaging (Pill Calendar) refilled their prescriptions on time more often ($P = 0.01$), had higher MPRs ($P = 0.04$), and had lower diastolic blood pressure ($P = 0.01$) than patients who had their medications packaged in traditional bottles of loose tablets.

Conclusion: Providing medications in a package that identifies the day each dose is intended to be taken and provides information on proper self-administration can improve treatment regimen adherence and treatment outcomes in elderly patients.

Keywords: Medication packaging, adherence, blood pressure.

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Improving treatment outcomes requires more than good medications and a sound plan of pharmacotherapy; plan implementation is also necessary. Treatment failure and adverse outcomes can result if a sound plan is not implemented. This principle was recognized more than 40 years ago with the medication error studies of Barker et al.,[1] which led to better medication-use systems in hospital settings, including unit–dose drug distribution and intravenous admixture systems. These systems increased the likelihood of implementing treatment plans and reduced medication errors by as much as 10-fold. Similar systems based on improved packaging and distribution of medications in long-term care facilities have reduced medication errors to the extent that the Centers for Medicare & Medicaid Services requires no significant medication errors and an overall medication error rate of 5% or less as a condition for participation in the Medicare program.[2] Considerably more medications are administered in the outpatient setting, with ample evidence of nonadherence and errors, yet similar systems approaches using improved packaging and distribution have not been rigorously studied or widely adopted.

At a Glance

Synopsis: This study of older patients (n = 85; age, 65 years of age or older) with hypertension shows that those who received lisinopril in adherence-aiding daily-dose blister packaging were statistically significantly more likely to refill their prescriptions on time and to have a higher medication possession ratio and lower diastolic blood pressures, compared with patients receiving lisinopril in traditional bottles of loose tablets. The blister packaging, marketed as Pill Calendar and containing 28 days of therapy arranged in weekly rows, was labeled with medication-specific instructions and the day of the week on which the dose was to be taken. Unlike packaging used in some older studies, the Pill Calendar is a single card that does not allow separation of individual doses, and it therefore provides an ongoing visual record of doses taken or missed.

Analysis: *Previous research has shown special blister packaging to have either a positive effect on adherence (particularly combined with counseling) or no benefit because of patient difficulty opening the packaging. The current study used streamlined packaging that increased not only ease of handling for the pharmacist but also ease of use for the patient. As a result, better treatment outcomes (i.e., improved blood pressure values) were demonstrated. The blister package used here identified the day on which each dose was to be taken and effectively ensured proper self-administration in an elderly patient population.*

Adherence packaging has been used with oral contraceptives, corticosteroids, and antibiotics but is not widely used for medications to treat chronic diseases. Adherence-aiding packaging has also been used for short-term therapy but not necessarily for older patients, who are most likely to need help remembering to take their medications. With the implementation of the Medicare prescription drug benefit, even more patients will be treated for chronic diseases with medications. Getting the full benefit from an investment in drug therapy will be enhanced by a system of medication use that improves the likelihood of implementing the treatment plan as intended. Improved packaging is one method for accomplishing this on a widespread basis.

Objective

The purpose of this study was to examine the impact on adherence and clinical outcomes of an adherence medication package, the Pill Calendar.

Methods

Population and setting

Patients 65 years of age or older with a diagnosis of essential hypertension from three centers in Ohio and Arizona were eligible for enrollment in the study, which was conducted from July 1, 2002, to December 31, 2004.

Design

This was a randomized controlled trial of an antihypertensive medication (lisinopril) packaged in a daily-dose adherence package (Pill Calendar, Philadelphia; Figure 1) in patients aged 65 years or older with hypertension. Patients were eligible if they were taking lisinopril for hypertension or starting on lisinopril as part of study enrollment. Lisinopril doses could be changed during the study period, and other antihypertensive agents could be added or discontinued. Patients were not enrolled if, according to the assessment of their physician, they exhibited cognitive impairment (e.g., psychoses or Alzheimer's disease), had visual impairment or severe arthritis, or had terminal illness that might result in death or impairment during the study. Because packaging was the dependent variable, patients were dropped from the study and lost to follow-up if they did not have prescriptions filled after signing informed consent or if they had fewer than six prescriptions filled during the study period. Approval for this study was obtained from the human subjects committee at each center, and written informed consent was obtained from each patient before enrollment.

Patients were randomly assigned by the dispensing pharmacist at each site to a study group that received an antihypertensive medication (lisinopril) in a daily-dose adherence package or a control group that received their antihypertensive medications in traditional bottles of loose tablets. Four tablet strengths available for lisinopril were used: 5, 10, 20, and 40 mg. The dosage of lisinopril was determined by the prescribing physician, and the proper package or combination of packages was dis-

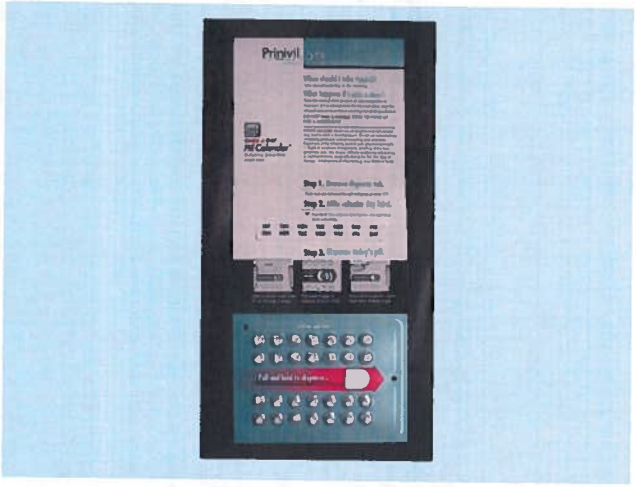

Figure 1. Daily-dose adherence package (Pill Calendar)

pensed by the pharmacist. A patient randomization assignment log was developed for the three participating pharmacies (two in Ohio and one in Arizona). Pharmacist investigators assigned patients to the study or control groups using randomization logs provided by the Department of Biostatistics at the Ohio State University and therefore were not blinded to the study assignment. Physicians who provided care to the patients were not provided information on study assignment by the investigators, and patients were instructed not to discuss their study group assignment with their physician or physician's staff (e.g., nurses working in physician's office).

Intervention

The daily-dose adherence package was blister packaged with four rows of seven tablets, allowing patients to see if the dose had been taken each day. The packaging also provided more space for patient information, including what to do if a dose is missed. The potential impact of this daily-dose adherence package was assessed by evaluating patient adherence and treatment outcome. After a baseline assessment, patients were scheduled to visit the study pharmacist and obtain refills every 28 days during the 12 months that each patient was enrolled in the study. At each visit, the pharmacist investigators recorded the time between prescription refills for the hypertension medication and recorded any study-related problems among study patients. At enrollment and 6 and 12 months after enrollment, the patients visited their physician for blood pressure measurement; the occurrence of morbidity in the prior 6 months, including angina, myocardial infarction (MI), and stroke; and any medical services required in the prior 6 months, including hospitalizations and emergency department visits. Medical charts were reviewed by two pharmacists to collect this information.

Description of the outcome variables

The following comparisons were made to assess patient adherence: percentage of times that patients had their prescriptions refilled on time, which was defined as being within 5 days before or after the due date, and medication possession ratio (MPR), which was defined as the sum of the day's supply for all prescriptions received during the study (except for the last refilling of the prescription) divided by the number of days between the dates of the first and last prescription dispensing.[3,4]

The following comparisons were made to assess treatment outcome: blood pressure at baseline, 6 months, and 12 months; number of patients who experienced morbidity during the study period; and number of hospitalizations and emergency department visits during the study period.

Description of the covariates

The continuous covariates were age, blood pressure, and serum creatinine (SCr). The categorical covariates were gender, prior MI, and stroke.

Statistical analysis

Baseline demographic characteristics were examined to determine whether the study and control groups were comparable. For the continuous covariates, summary measures of the group distributions were calculated and two-sample t tests or nonparametric Wilcoxon rank-sum tests were applied. For the categorical covariates, χ^2 tests or Fisher's exact tests were used.

To assess adherence, the percentage of refills on time and MPR in the two groups were compared using nonparametric Wilcoxon rank–sum tests. Analysis of covariance was then applied to assess the percentage of refills on time and MPR for both the study and control groups.

Mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and SCr for each group were calculated at the 6- and 12-month physician visits. Simple group comparisons at baseline and each of the two follow-up visits were performed using Wilcoxon rank–sum tests. Longitudinal models were then applied to the data to assess the change in blood pressure and SCr over time; SBP and DBP were modeled separately. Baseline (initial) blood pressure value, visit month, and group (i.e., control or study) were included as covariates in the model. In addition, the presence of other significant predictors of blood pressure (such as gender and age) was assessed.

All analyses were conducted using STATA version 7.0 (Stata, College Station, Tex.) and SAS version 8.0 (SAS Institute, Cary, N.C.).

Results

A total of 112 patients were evaluated for eligibility and signed informed consent in their physician's office. Of these, 19 patients did not have prescriptions filled—9 in the study group and 10 in the control group. Of those having prescriptions filled, eight (four in the study group and four in the control group) had fewer than six prescriptions filled during the 12 months that they were enrolled in the study and were excluded from data analysis. A total of 85 patients met the criteria for inclusion in the study

and data analysis. Daily-dose adherence packages (Pill Calendar) were provided to 47 study patients, and 38 control patients received their medication in a traditional bottle of loose tablets. Data from all 85 patients were used in the analyses. At baseline, no significant differences between the study and control groups were observed for any of the medical or demographic information, such as age, gender, SBP, DBP, total number of medications currently being taken, prior stroke, or emergency department visits in the previous 6 months (Table 1).

Adherence

The percentage of on-time refills was significantly higher for the study group than the control group (Table 2). Adjusting for age and gender (using analysis of covariance) did not alter the results; the percentage of on-time refills was 13.7% higher in the study group than the control group.

MPR was significantly higher for the study group than the control group (Table 2), though the absolute difference was small (6%). After adjusting for age and gender using a statistical model, a significant difference remained in MPR between the two groups, with the mean MPR for the study group being 6.2% higher than the control group.

Clinical outcomes

Wide variation in both DBP and SBP occurred at baseline, 6 months, and 12 months. As noted, no significant differences were observed in DBP or SPB at baseline between study and control patients (Table 1).

At 6 months, the mean (± SD) DBP was 73.2 ± 8.8 mm Hg in study patients compared with 77.7 ± 10.2 mm Hg in control patients. This difference was statistically significant (P = 0.0367). SBP at 6 months was 132.7 ± 17.3 mm Hg in study patients and 138.2 ± 22.2 mm Hg in control patients. This difference was not significant (P = 0.2143). At 12 months, DBP was 72.0 ± 11.0 mm Hg in study patients and 75.2 ± 10.1 mm Hg in control patients. SBP at 12 months was 130.9 ± 18.1 mm Hg in study patients and 136.5 ± 17.3 mm Hg in control patients. These differences were not significant. Absolute change in both SBP and DBP at 6 and 12 months is reported in Table 2. DBP was 2.6 mm Hg lower at 6 months and 5.7 mm Hg lower at 12 months in the study group, compared with the control group. These differences were not statistically significant. Differences in SBP were also not significant at 6 and 12 months.

Twelve patients (48%) in the study group had a lower DBP by the 12-month visit, compared with 4 patients (18.2%) in the control group (P = 0.0313; Table 2), despite the wide variation in DBP seen throughout the study. Adjusting for initial DBP and visit in a longitudinal model, the average decrease over time in DBP was significantly lower in the study group than in the control group (P = 0.0104). Based on the longitudinal model with initial SBP as a covariate, the estimated average SBP for the study group was consistently lower at each visit. However, this difference was not statistically significant.

No significant differences were observed between the two groups in any of the long-term outcome measures (i.e., angina, MI, renal function, emergency department visits, hospitalization) for the 6- and 12-month visits.

Several patients reported some difficulty with opening the packaging, but no one dropped out of the special-packaging group because of this difficulty. No other study-related problems were noted among the participants.

Discussion

Improved adherence to treatment plan and clinical outcomes were demonstrated in this randomized controlled trial comparing outpatient use of daily-dose blister packaging and traditional packages of loose tablets. Several other studies have investigated the impact of packaging on adherence in patients with hypertension, some of which were either not randomized controlled trials or did not evaluate the impact of packaging on

Table 1. Comparison of patient characteristics at baseline

Characteristic	Study group (adherence package) (n = 47)	Control group (traditional bottle) (n = 38)	*P* value
Mean age (± SD)	71.6 ± 5.9	72.3 ± 5.2	0.21
Mean no. medications (± SD)	5.0 ± 2.8	5.3 ± 3.0	0.61
Gender			0.23
Men	26	16	
Women	21	22	
Prior ED visits, last 6 months (%)	2 (4.3)	0	0.34
Prior hospitalizations, last 6 months (%)	3 (6.5)	3 (7.9)	1.00
Renal impairment (SCr > 1.2 mg/dl) (%)	3 (6.5)	1 (2.6)	0.62
Prior MI	0	1 (2.6)	0.45
Prior stroke	0	0	—
SBP (mm Hg) (± SD)	137.8 ± 19.7	141.4 ± 19.2	0.40
DBP (mm Hg) (± SD)	74.2 ± 11.6	76.3 ± 11.1	0.41
SCr (mg/dL) (± SD)	1.1 ± 0.3	1.1 ± 0.3	0.45

Abbreviations used: ED, emergency department; MI, myocardial infarction; SCr, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Impact of daily-dose adherence package

Outcome	Study group (adherence package) (n = 47)	Control group (traditional bottle) (n = 38)	*P* value
Adherence	Mean (± SD)	Mean (± SD)	
% Patients who had prescriptions refilled on time	80.4 (± 21.2)	66.1 (± 28.0)	0.012
MPR	0.93 (± 11.4)	0.87 (± 14.2)	0.039
Blood pressure			
Patients with reduced blood pressure	No. patients (%)	No. patients (%)	
DBP at 6 months	21 (46.7)	13 (37.1)	0.393
DBP at 12 months	12 (48.0)	4 (18.2)	0.031
SBP at 6 months	22 (48.9)	22 (62.9)	0.213
SBP at 12 months	14 (46.0)	9 (40.9)	0.312
Absolute change in blood pressure	Mean (± SD)	Mean (± SD)	
DBP at 6 months	−0.8 (± 12.4)	1.8 (± 9.1)	0.287
DBP at 12 months	−3.0 (± 11.6)	2.7 (± 10.7)	0.125
SBP at 6 months	−4.2 (± 21.5)	−4.2 (± 20.9)	0.992
SBP at 12 months	−2.7 (± 16.5)	−1.3 (± 17.8)	0.669

Abbreviations used: MPR, medication possession ratio; DBP, diastolic blood pressure; SBP, systolic blood pressure.

treatment outcome. Eshelman and Fitzloff[5] examined the impact of providing chlorthalidone in a "Compliance PAK," compared with traditional prescription vials. While the study package was not described in the publication, it was designed to "help them remember to take their medication." Using a urinalysis to assess adherence, patients who received their antihypertensive medication in the adherence packages were significantly more adherent than control patients. However, in contrast to the present study, the effect on blood pressure control was not measured. Our study was also designed to evaluate adherence and treatment outcome, both of which were positively affected.

Rehder et al.[6] studied the impact of patient counseling and use of "special medication containers" on adherence among 100 patients with hypertension. Patients were divided into four groups: control, counseling only, medication container only, and medication container with counseling. The special medication container was a 7 × 4 box with 28 sections for doses to be placed by day of the week, up to 4 times per day. The pharmacist loaded four of these containers per patient for each 28-day refill cycle. The group receiving counseling kept more appointments than the control group or the group receiving medications in special medication containers. When adherence to medications was compared, counseling and the special medication container had an additive effect. Patients receiving medications in the special medication container experienced a statistically significant decrease in DBP. The authors concluded that a special medication container that was loaded by the pharmacist helped patients follow prescribed regimens more closely, particularly if patients were counseled by a pharmacist. Our study evaluated a package given to patients without additional counseling that unlike the special container studied by Rehder could be made commercially available and not require extra work by a pharmacist to fill.

In contrast, Becker et al.[7] conducted a randomized trial of "special packaging" of antihypertensive medications to test the effect on adherence and blood pressure control. The special packaging allowed all doses that were to be taken at the same time to be placed in a single package. The special packaging of the medications was done at the hospital pharmacy using a commercially available system. All tablets and capsules that were to be taken together were enclosed in a single plastic blister sealed with a foil backing on which was printed the day of the week and time of day the doses were to be taken. Each medication package contained 28 foil-backed blisters representing 28 consecutive doses of medication. The packets were perforated, allowing patients to separate one or more doses from the larger packet. No significant improvements in blood pressure control or adherence were found between the special packaging group and the group receiving medications in regular prescription vials. Patients in this study found that the "special package" was more difficult and less convenient to use than regular packaging. The authors suggested that "future studies might compare different forms of the more streamlined packages now becoming available."[6] Our study was designed to evaluate a different type of package that was easier for pharmacists to dispense and patients to use.

The daily-dose blister packaging (Pill Calendar) used in our study was different from the package studied by Becker et al. in that it contained a single medication in a single 6.25 × 5-inch card labeled with medication-specific instructions and the day of the week on which the dose was to be taken. It could not be separated by the patient; therefore, the package provided an ongoing visual record of doses taken or omitted (Figure 1). Thus, the design of the package may have influenced the effectiveness of this strategy to improve adherence. Although some studies have only examined and demonstrated the impact of special packaging on a single drug, blister packaging has been

shown to improve adherence with more complex treatment regimens (e.g., for sexually transmitted diseases).[8]

This single-blind, randomized, controlled study was designed to measure the impact of a single intervention: packaging. Finding significant differences in blood pressure can be difficult in a population of patients because of the wide variation typical in hypertension. Of note, in addition to showing improved adherence to medication regimens, the current work demonstrated significant differences in DBP between the study and control groups. This simple strategy of improving the packaging of prescription medications could help large numbers of patients, including elderly patients and those with memory deficits, take their medications more reliably with better treatment outcomes. Furthermore, Sokol et al.[9] demonstrated that improving medication adherence in patients with chronic disease substantially decreases other health care costs, such as hospital care. While this is not the only way to address problems with adherence, other more individualized and time-consuming strategies for improving adherence, such as patient counseling and self-monitoring, can be built upon this foundation.

Improvements in adherence and treatment outcome in elderly patients with a chronic disease such as hypertension are desirable. Achievement of treatment goals has been shown to reduce the morbidity and mortality resulting from untreated and poorly treated hypertension.[10] Developing a simple way to improve blood pressure in patients with hypertension is therefore desirable.

Limitations

This study was limited by the relatively small number of patients, the tracking of only one disease, and the short time frame relative to some of the long-term outcomes measured. The study patients may not reflect a typical Medicare population. Nevertheless, improvements were noted in both adherence measures and the intermediate outcome measure (DBP).

Conclusion

Providing medications in a package that identifies the day each dose is intended to be taken and provides information about proper self-administration can improve adherence to treatment regimen and treatment outcomes in elderly patients being treated for hypertension. Incorporation of this durable strategy could also lead to improvements in medication-related outcomes in elderly patients with other chronic diseases. Considering the potential effect of the new Medicare prescription benefit on the U.S. health care system, further research into the benefits of durable strategies in various patient groups on health and economic outcomes is important. Because benefits have already been demonstrated with adherence-aiding packaging, such packaging should be made increasingly available for long-term medications. Better packaging may be used for medications as a way to create an improved system of care that results in better adherence to treatment regimens and enhanced treatment outcomes.

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