A Randomized Trial of Special Packaging of Antihypertensive Medications

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This article reports a randomized controlled trial designed to test the effects of special packaging of antihypertensive medication on compliance and blood pressure control. One hundred eighty subjects who had exhibited elevated blood pressure greater than 90 mmHg in the two years prior to the study were recruited from patients receiving care at a community hospital-based family medicine practice.

After completing preenrollment interviews and blood pressure measurements, subjects were randomly assigned to receive their antihypertensive medications either in the usual vials or in special unit dose-reminder packaging. Follow-up interviews, pill counts, and blood pressure measurements were performed at three-month intervals. There were no statistically significant differences between the control and experimental groups with regard to age, sex, race, employment, education, marital status, insurance coverage, or blood pressure regimens. Prior to the intervention, the experimental group had slightly lower diastolic blood pressures and reported better compliance than the control group.

Analyses performed on 165 subjects completing the first follow-up visit revealed no significant improvements in blood pressure control or compliance for patients receiving special medication packaging. While some patients found it easy to remember to take pills packaged using this format, they also found the packages somewhat more difficult and inconvenient to use. In contrast to previously reported work, this study did not demonstrate any significant improvement in compliance with special packaging of antihypertensive medications.

Hypertension is one of the most significant problems managed by the primary care physician. It affects more than 60 million Americans,[1] increasing their risks of thrombotic stroke[2] and coronary artery disease.[3,4] Drug therapy for hypertension has been shown to reduce cardiovascular mortality and to provide protection against stroke, left ventricular hypertrophy, congestive heart failure, and coronary disease.[5-9] Much of the efficacy of antihypertensive therapy is lost, however, because of patient noncompliance. Only about one third of hypertensive patients who begin treatment take enough of their prescribed medication to achieve blood pressure control.[10-14] While many methods of improving patient compliance have been suggested, few have been shown to be effective in well-designed clinical trials.[15,16] Studies that have included long-term follow-up have usually found that improvements in compliance are not likely to be sustained unless the intervention is continued.[16]

Rudd[17] has reviewed the potential advantages of special packaging of medication as a compliance-building intervention. Because it does not require time and ongoing input from health professionals, packaging may prove less expensive to implement for a large population of patients with hypertension than would many of the more complex interpersonal strategies reported in the literature. Packaging may facilitate patient self-motivation by giving patients more responsibility for medication compliance. Any positive effects of packaging on compliance should be long lasting, since the intervention can be applied consistently and need never be removed. On the other hand, special packaging could lead to poorer compliance if the

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package proved cumbersome or inconvenient to use.[18]

The aim of the present study was to determine the effects of a special medication packaging intervention on both blood pressure control and compliance as measured by pill counts and self-report. Each patient was followed for up to one year to determine both the short-term and the long-term effectiveness of the intervention. This paper reports the results of the three-month follow-up period and patient opinions about special packaging as recorded at the final visit.

METHODS

The study was carried out in the ambulatory practice center of the Department of Family Practice and Community Health of Temple University School of Medicine. Approximately 6,000 patients make 12,000 outpatient visits per year to the center. Included in the study were patients aged between 20 and 80 years who were already taking medication for previously diagnosed hypertension. All patients had demonstrated poor blood pressure control (diastolic blood pressure greater than 90 mmHg) on at least one visit during the two preceding years. Patients who had significant visual, auditory, or mental problems that could interfere with their compliance were excluded.

Eligible patients, identified by a chart review of all patient records, were contacted at their next regularly scheduled visit and invited to participate in the study. Patients who agreed were randomly assigned into either the experimental or the control group. Patients in the experimental group received all their antihypertensive medications in the special packaging format. Patients in the control group received all their antihypertensive medications in traditional pill vials.

The special packaging of medications was done at the hospital pharmacy using a commercially available system. All pills to be taken together at one time were enclosed in a single plastic blister sealed with a foil backing on which was printed the day of the week and the time of day in which the medication in the blister was to be taken. Each medication package contained 28 foil-backed blisters, representing 28 consecutive doses of medication. The packets were perforated so that it was possible for patients, if they wished, to separate one or more doses from the larger packet.

Patients in the control group received each of their antihypertensive medications in a separate vial that was labeled with the drug name, the dosage, the medication instructions, and the physician's name.

Antihypertensive medications were provided free of charge to patients in both groups to ensure that patients would receive all of their antihypertensive medication in the special format specified by this study.

Basic demographic data and a history of blood pressure control over the preceding two years were obtained from a review of patient charts. At the time of the patient's next visit to the center (the preenrollment visit), the study was explained and informed consent obtained. More detailed demographic data, a history of hypertension, a detailed medication history, and self-reports of compliance were obtained at this time. At the next regular clinic visit (the baseline visit) additional preintervention data were collected, including the completion of a questionnaire concerning important compliance-related variables such as health locus of control, affective status, satisfaction with medical care, and family and social history. At this visit the first three months' supply of medication was dispensed, either in special or regular packaging depending on the group to which the patient had been randomly assigned. The patients were then followed every three months at regular clinic visits for up to one year.

All data collection was done by a nurse research assistant immediately before a regular office visit. Physicians caring for these patients were aware that a compliance study was in progress but were not told the aims of the study or informed of whether any individual patient was in the experimental or control group. Physicians were encouraged to make any changes in antihypertensive medications they felt were indicated, using a stepped-care approach. At the time of each follow-up visit, blood pressure was measured and self-reports of compliance and pill count measures were obtained.

At the final follow-up visit, patients were asked to give their opinions about the usefulness and desirability of the packaging format in which they obtained their medications.

Three different outcome measures (self-reports of compliance, pill counts, and blood pressure measurements) were used to provide a more valid and sensitive indication of noncompliance than would be possible with a single indicator. Self-reports of compliance have been shown to have acceptable validity in other studies.[19] Patients were asked a nonthreatening, nonjudgmental question about their compliance behavior. Those who admitted less than perfect compliance with physician's instructions about taking any one of their antihypertensive drugs were considered noncompliant. Although it was not possible to do pill counts at the initial visit, patients were asked to bring in all remaining medication to each follow-up visit, and pill counts were done in an unobtrusive fashion. Patients were considered compliant if they had taken 80 percent or more of their prescribed medications. Blood pressure was taken three times at each visit. The first measure was discarded, and the average of the second and the third was used as the blood pressure measurement for that visit. Blood pressure control was defined as a diastolic blood pressure of less than 90 mmHg. In addition to this dichotomous measure, blood pressure was treated as a continuous variable, and the mean diastolic pressures in each group were compared at each visit. An additional outcome variable was the hybrid rule suggested by Inui et al.[19] Using this rule, any patient who admitted noncompliance or who had a

TABLE 1. BLOOD PRESSURE CONTROL AND COMPLIANCE AT PREENROLLMENT, BASELINE, AND THREE-MONTH FOLLOW-UP VISITS

	Group	No.*	Percentage "Compliant" Preenrollment Visit	Baseline Visit	First Follow-up Visit
Diastolic blood pressure <90 mmHg	Special	86	61.6	66.3	72.1
	Regular	85	45.9	54.1	55.3
Diastolic blood pressure <100 mmHg	Special	86	84.9	94.2	93.0
	Regular	85	77.6	85.9	83.5
Self-report of compliance	Special	84	53.6	—	56.0
	Regular	85	50.6	—	54.1
Self-report plus diastolic blood pressure <100 mmHg	Special	84	47.6	—	51.2
	Regular	85	41.2	—	42.4
>80% of pills taken	Special	81	—	—	84.0
	Regular	77	—	—	75.3

Sample sizes vary slightly because of missing data

blood pressure reading of greater than 100 mmHg but denied noncompliance was assumed to be noncompliant. Patients with blood pressures reading below 100 mmHg whose self-reports indicated that they were compliant were defined as compliant by this measure.

Statistical analysis was done using the unpaired Student's *t* test and chi-square test methods. Multiple regression analysis was also done using follow-up blood pressure as the dependent variable with initial blood pressure at the time of enrollment included in the independent variables.

RESULTS

Patients enrolled were primarily middle-aged black women. Less than 20 percent were employed, and most had not completed high school. Study patients had been diagnosed as hypertensive for an average of 13 years and had been taking antihypertensive medication for an average of 11 years. Most were taking more than one medication on a regular basis. The maximum number of different medications was 13; the median was 3.5. Not all these drugs were prescribed for hypertension; 61 percent of the patients were taking only a single antihypertensive medication, and no patient took more than three different antihypertensive medications. Hydrochlorothiazide was the antihypertensive most frequently prescribed, followed by alphamethyldopa and propranolol.

Fifteen of the 180 patients enrolled did not complete the study. Most of these patients did not show up for appointments and could not be contacted by telephone. Other reasons for dropouts included death (1 patient) and discontinuation of antihypertensive medications (1 patient). No patients indicated that problems with the medication packaging were involved in their reasons for dropping out, although one patient requested that she be removed from the study because she was "sick of answering questions."

Patients in the study were well aware of the importance of hypertension as a health risk and of the potential benefits of therapy. Most had received some additional instruction in nonpharmacologic antihypertensive measures. All patients had at least one diastolic blood pressure greater than 90 mmHg recorded during the two years prior to enrollment (an eligibility criterion for the study). More than two thirds had at least one diastolic blood pressure greater than 100 mmHg. Forty-eight percent of the patients reported perfect compliance with antihypertensive medications.

At the time of enrollment in the study, there were no significant differences between the special packaging and regular packaging group on any of the demographic variables or on the health belief variables measured. However, even though assignment was random, the special packaging group reported slightly better compliance and had better blood pressure control at the beginning of the study (Table 1).

At the time of the first follow-up visit both groups showed slightly improved compliance on all measures (Table 1). The smallest amount of change was seen in the self-reports of compliance. The improvement in control of diastolic blood pressure was somewhat greater, with approximately 10 percent more compliant patients at the first follow-up visit than at the preenrollment visit. A great deal of this improvement in blood pressure control, however, actually occurred between the preenrollment and baseline visit (that is, after patients were informed that they were to be enrolled in the study, but before medication had been

TABLE 2. AVERAGE DIASTOLIC BLOOD PRESSURES AT THREE STUDY VISITS

	Preenrollment Visit	Baseline Visit	Three-Month Follow-up Visit
Special packaging (n = 86)	88.5	86.3	85.3
Regular packaging (n = 85)	91.6	89.6	88.8
Significance (2-tailed *t* test)	NS	NS	NS

TABLE 3. REGRESSION ANALYSIS OF DIASTOLIC BLOOD PRESSURE AT THREE-MONTH FOLLOW-UP VISIT (N = 171)

Variable	B	R^2	F	P
Baseline diastolic blood pressure	.39	.359	31.7	<.001
Preenrollment diastolic blood pressure	.27	.447	18.7	<.001
Age	−.18	.473	8.7	<.005
Packaging group	1.45	.477	1.2	.259

provided in the special packages). The combination measure of self-report and measured diastolic blood pressure showed very little change in either group between the preenrollment and follow-up visit. There were no statistically significant differences between the experimental and control group at the follow-up visit on any of the compliance measures—pill count, self-reports, or the combination of self-report and diastolic blood pressure. Sackett et al[20] have suggested that a medium effect size should be considered clinically effective in studies of hypertension compliance. For this study, the power of the statistical test in detecting a medium effect is 0.90 for an alpha level of 0.01.

Table 2 summarizes the change in diastolic blood pressure between the preenrollment visit and the first follow-up visit for patients in the two groups. Blood pressures actually increased between these two visits for 28 patients in the special packaging group and for 35 in the regular packaging group. Although the average decline was slightly greater in the study group than in the control group, the difference is not statistically significant, and the mean differences in both groups are too small to have clinical significance. Given the sample size used in this study, the power of the statistical test in detecting a 10 mmHg or larger difference is over 0.99 for an alpha level of 0.01.

To adjust for the difference in blood pressure between patients in the two groups at the time of enrollment into the study, the diastolic blood pressure at the first follow-up was analyzed using multiple regression, with the patient's age, preenrollment diastolic blood pressure, and baseline diastolic blood pressures as independent variables, and with the group assignment as a dummy variable. Independent variables were allowed to enter the equation in stepwise fashion depending on their F values. The results are shown in Table 3. Diastolic blood pressures at the preenrollment and baseline visit were the most powerful predictors of diastolic blood pressure at the follow-up visit. Age of the patient was also significant, with older patients having lower diastolic blood pressures at follow-up. Between them, these three variables accounted for 47.3 percent of the variance in follow-up blood pressure. By contrast, the assignment to the special packaging group was not associated with significantly lower diastolic blood pressures. The regression coefficient for the dummy variable is 1.45, indicating that only an estimated 1.45-mmHg drop in diastolic pressure is attributable to the special packaging format.

When asked for their opinions, patients in the special packaging group considered their packaging more difficult and less convenient to use than did patients who received their medication in the regular format. Special packages did appear to make it somewhat easier for patients to remember taking their medications.

DISCUSSION

Other investigators have shown improvements in compliance when medications were dispensed in a special packaging format. Rehder et al[21] found that patients receiving special packaging alone or counseling plus special packaging were more likely to take 95 percent of prescribed medication. These higher pill counts were accompanied by a fall in diastolic blood pressure only for the groups receiving both packaging and counseling. Blood pressures rose slightly for patients receiving the special packaging intervention alone. Eshelman and Fitzloff[22] found higher urine thiazide levels in patients receiving their once-daily thiazide tablets in a special dispenser. They found no differences, however, when pill counts were used as the measure of compliance. Diastolic blood pressure measurements were not reported in the Eshelman and Fitzloff study. As can be seen, both studies could be interpreted to show either an effect or no effect for special packaging, depending on the compliance measure chosen. Furthermore, the study results differ from one another when pill counts (the only compliance measure used in both studies) are compared. Given these inconsistencies between and within studies, it is not particularly surprising that no signifi-

cant compliance improvements were evident in the special packaging group over a three-month period in the present study.

Both studies cited above had a large proportion of patients who dropped out before any outcome data could be collected. Ramsay[23] has commented on the biases involved when compliance studies include only the more compliant patients in a sample. The present study included aggressive attempts to get patients to return for follow-up visits, including free medication, reminders by telephone or by mail that appointments were imminent, and follow-up telephone or mail contacts for missed appointments. The resulting low dropout rate (8.3 percent) makes it likely that this study suffers less from compliance bias than previous studies.

Aggressive patient follow-up and provision of free medications, along with other study procedures, represent cointerventions that may have had their own effects on compliance. The magnitude of this cointervention effect is suggested by the increase (Table 1) in the proportion of patients in both groups whose diastolic blood pressure was controlled between the time of the preenrollment and the baseline visit (ie, before the special packaging intervention was initiated). This cointervention appears to have affected both groups equally and is thus unlikely to have biased the results. As shown in Table 3, the effect of study procedures on average diastolic blood pressure was rather small—resulting in a drop of only 2 mmHg, suggesting that any effect of special packaging, which may have been obscured by the effects of study cointerventions, was also small and of questionable clinical significance.

Patients' subjective feelings about special packaging were also negative. Although they found it easier to remember to take pills packaged in this format, some of them found the packages difficult and inconvenient to use. Thirty-nine percent expressed a preference for more traditional packages.

The special packaging format used in this study is not the only style of special packaging that is possible, and these findings may not be applicable to other new technologies designed to assist patients in taking their medicines faithfully. Future studies might compare different forms of the more streamlined and convenient packaging now becoming available. Another potential approach would be to study special packaging as an intervention for only those patients who admit to some difficulty in remembering to take their pills or remembering which pills have been taken. Based on the present study findings, however, it is not possible to recommend the use of special packaging for general hypertensive populations or to the physicians who provide medical care to them.

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