Impact of Bubble Packaging on Adherence to Long-Term Oral Medications Used to Prevent Cardiovascular Disease

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Abstract

Background: Adherence to long-term pharmacotherapy is problematic in the United States. Bubble packaging of medications has been touted to improve patients' use of medications. Scant research has assessed bubble packaging's impact on adherence to multiple medications. **Objective:** To compare medication adherence between patients receiving medications to address cardiovascular disease risk factors in bubble packages to those receiving medications in pill bottles. **Methods:** This retrospective cohort study utilized prescription dispensing records from an independent pharmacy. Patients receiving statins, β -blockers, angiotensin-converting enzyme inhibitors, or oral hypoglycemic agents were identified and grouped into those who received medications in bubble packages and those received medications in pill bottles. Adherence was assessed with medication possession ratios. Patients were classified as adherent if their medication possession ratio was 80% or more. **Results:** Receiving medications in bubble packaging was significantly associated with greater adherence compared to pill bottles ($P < .001$). In adjusted models, greater numbers of medications filled ($P = .024$) and increasing patient age ($P = .018$) were significantly associated with low adherence, while bubble packaging was not ($P = .13$). Stratified analyses revealed that bubble packaging was significantly associated with greater adherence when 4 or fewer medications are filled ($P = .012$) and for patients between 18 and 44 years of age ($P = .023$). **Conclusion:** Bubble packages can improve medication adherence. However, they may not resolve complex issues contributing to the problem of nonadherence, especially for older patients and those prescribed multiple medications.

Keywords

adherence, cardiovascular drugs, ACE inhibitors, antihypertensive, β -adrenergic blockers

Introduction

Cardiovascular disease (CVD) is one of the leading causes of mortality in the United States, accounting for more than 385 000 deaths annually.¹ Hypertension, diabetes, and dyslipidemia are major risk factors of cardiovascular conditions.² Therapies must target these risk factors in an effort to prevent major cardiovascular events.³ Statins, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, and oral hypoglycemic agents are effective in the management of these CVD risk factors.^{4,5} However, the effectiveness of these medications can be suboptimal due to poor adherence.^{6,7}

Patients with CVD-related conditions often have problems adhering to medication regimens.⁸ Researchers have found low rates of continuation and adherence for statins, β -blockers, ACE inhibitors, and oral hypoglycemic agents.^{9–11} Newby et al reported that persistent use of β -blockers and statins was very low in patients with coronary artery diseases.¹² In addition, nonadherence to statins,

β -blockers, and ACE inhibitors may lead to poor outcomes such as increased emergency room visits, hospitalization, and costs.^{12–14} Diabetes is also associated with increased CVD risk.¹⁵ The incidence of myocardial infarction or stroke is 2-fold higher in diabetic patients, and there is a 2-fold increase in death rates.¹⁶ A review conducted by Cramer found that patients with diabetes are often nonadherent with their treatment, which could lead to poor health outcomes.¹⁷

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Patients with CVD are often treated with more than one medication. In order to derive maximal benefit from adherence to all guideline-recommended drug classes (statins, β -blockers, and ACE inhibitors), identifying strategies to improve long-term, multi-medication adherence is critical.¹⁸⁻²⁰ Medications dispensed in special packages, commonly known as bubble packaging, is often used in clinical trials to help patients adhere to their medication regimens.²¹⁻²³ These special packages help patients address recall problems that hinder adherence, especially in the case of long-term, multiple medication regimens. In addition, some common nonadherence behaviors such as failure to refill prescription, taking the wrong dose of medications, at the wrong time, or in the wrong amount may be addressed by bubble packaging.

The majority of the studies have demonstrated a positive impact of bubble packaging on adherence with antihypertensives.²³⁻²⁵ For example, Dupclay et al showed that patients who received medications in bubble packages had greater medication adherence in comparison to patients who received medications in regular pill bottles.²¹ However, there is a paucity of research assessing the impact of bubble packaging on adherence among patients who use multiple medications to address CVD risk. There is a need for further examination of bubble packaging's impact on patients' medication use due to the role adherence plays in the prevention of major cardiovascular events. The goal of this study was to compare medication adherence between patients who received medications used to address CVD risk factors in bubble packages to those who received medications used to address CVD risk factors in pill bottles.

Methods

Study Design and Data Source

This study used a retrospective cohort design to evaluate 1 year of pharmacy prescription data obtained from an independent pharmacy located in Augusta, Georgia. The pharmacy averages about 4000 prescriptions per week and all patients were offered bubble packaging *free of charge*. De-identified prescription dispensing records for medications dispensed in bubble packages and regular pill bottles were provided by the pharmacy. The data contained the following information: medication information (name, strength, days' supply, and fill dates) and patient sociodemographics (age, gender, and type of insurance). The institutional review board approved this study.

Sample Selection

Patients receiving any of the following drug therapies—statins, β -blockers, ACE inhibitors, and oral hypoglycemic agents—between January 1, 2013, and December 31, 2013,

Figure 1. Bubble packaging.

were identified in the data. The date of the first medication received during this study period was assigned as index date, while the date of the last medication received during this study period was assigned as end date. Patient data were included in the analyses if they had at least 2 prescriptions filled and no medication changes during the study period, and were 18 years or older.

Description of Bubble Packages

The bubble package (Figure 1) is a packaged container with 31 single-use dose compartments (ie, bubbles) that can contain medications. Depending on the size of the medication, each bubble of the pack could contain up to 20 tablets. The bubbles are limited to a maximum of 16 individual products due to labeling requirements. The bubble packages containing all the medications for the month were prepared by pharmacy staff and checked by a pharmacist. Each compartment of the pack is marked for each day, time of day and dose, and contains all the medications needed at that specific date/time (ie, one or more medications). A note to order medications was also printed on the bubble packages to remind patients to refill their medications before the end of each monthly regimen.

Table 1. Patient Baseline Characteristics.

Characteristics	Bubble Pack Users (n = 140)	Regular Pill Bottle Users (n = 1705)	P
Overall age, mean ($\pm$ SD)	67.67 (15.15)	62.05 (15.28)	.862
Age groups, n (%)			
18-44 years	21 (15%)	194 (11.38%)	.065
45-54 years	14 (10.0%)	305 (17.89%)	
55-64 years	35 (25.0%)	452 (26.51%)	
65 years and older	70 (50.0%)	754 (44.22%)	
Number of medications, mean ($\pm$ SD)	10 (3.8)	6 (3.6)	.046
Gender, n (%)			
Males	53 (37.86%)	717 (42.05%)	.063
Females	87 (62.14%)	988 (57.95%)	
Medication classes, n (%)			
Statins	64 (45.71%)	857 (50.26%)	.074
Oral hypoglycemic	24 (17.14%)	262 (15.37%)	
Beta-blockers	29 (20.71%)	227 (13.31%)	
ACE inhibitors	23 (16.43%)	359 (21.06%)	
Insurance type, n (%)			
Public	79 (56.43%)	698 (40.94%)	.019
Private	59 (42.14%)	913 (53.55%)	
Other ^a	2 (1.43%)	94 (5.51%)	

Abbreviations: SD, standard deviation; ACE, angiotensin-converting enzyme.

^aThe "other" category consisted of patients who had no clearly specified insurance type specified.

Measures

Medication possession ratios (MPR) were calculated to assess the medication adherence of patients using bubble packages and regular pill bottles. MPR was calculated as the ratio of sum of days' supply of medication during the study period to the total number of days between the first and last prescriptions. For multiple medications, an average MPR across all medications for each patient was calculated and a group mean was generated for both the groups. For example, if a patient was dispensed 2 different medications, then an MPR was calculated for each medication and then averaged to get the overall MPR for that patient. Patients were considered adherent if their MPR was 80% or more.^{19,21,26-28} Previous studies have determined that MPR $\geq 80\%$ is associated with improved clinical outcomes.²⁹⁻³¹

Statistical Analyses

Descriptive statistics were calculated for all study variables. A 2-sample test of proportions was conducted to compare the proportion of patients who were adherent (MPR $\geq 80\%$) as well as average medication adherence (MPR) by drug therapies between patients receiving bubble packaging and pill bottles. Multivariate regression analyses were used to compare the medication adherence (MPR) of patients who received medications in bubble packages with those who received medications in regular pill bottles adjusting for covariates including age, gender, insurance, and number of

medications filled (included oral medications only). Insurance was categorized as public (such as Medicare or Medicaid), private (employer sponsored or plans not provided by federal or state government), and others (patients who had unspecified insurance types). In addition to addressing potential endogeneity, we conducted this analysis using a propensity scoring approach and found similar results. Therefore, we present the results of the regression for ease of interpretation.

In addition, stratified analyses were conducted to assess the impact of the number of medications filled and patient age on the effectiveness of bubble packaging. For the stratified analyses, the number of medications were dichotomized to represent low (≤ 4) and high (≥ 5) medication use based on the definition of polypharmacy,³² and the age groups were modeled categorically (in years) as 18 to 44, 45 to 54, 55 to 64, and 65 and older. All analyses were conducted using SAS version 9.4.

Results

The sample included 140 patients in the bubble package group and 1705 in the regular pill bottle group. Table 1 presents the baseline characteristics of the patients. The average age in the bubble package group was approximately 68 years, while the average age was 62 years in the regular pill bottle group. The majority of individuals in both groups were women (62.14% and 57.95% in the bubble package

Table 2. Overall Medication Possession Ratio and by Medication Classes.

Category	Bubble Pack Users (n = 140)	Regular Pill Bottle Users (n = 1705)	P
Overall MPR, mean (SD)	83.78 (19.83)	78.67 (26.18)	<.001
MPR by medication class, mean (SD)			
Statins	82 (17.83)	74.66 (23.59)	.0024
Oral hypoglycemic	82.8 (13.87)	80.30 (25.64)	.0003
Beta-blockers	81.8 (15.99)	77.86 (27.58)	.003
ACE inhibitors	86.10 (15.75)	80.70 (21.83)	<.001

Abbreviations: MPR, medication possession ratio; SD, standard deviation; ACE, angiotensin-converting enzyme.

Figure 2. Proportion of patients with medication possession ratio (MPR) $\geq 80\%$ for the medication classes in both groups.

and regular pill bottles group, respectively). Almost half of the patients in both the groups were 65 years and older (50% and 44.22% in the bubble package and regular pill bottles group, respectively) and filled prescription for statins (45.71% and 50.26% in the bubble package and regular pill bottles group, respectively). The majority of the patients in the bubble package group had public insurance (56.43%), while the majority of the patients in the regular pill bottle group had private insurance (53.55%).

Table 2 presents the results from the 2 sample test of proportions that compared overall MPR and MPR by medication classes in both groups. The overall MPR in the bubble package group was significantly higher than the overall MPR in the regular pill bottle group (83.78% vs 78.67%, $P < .001$). Overall, a significantly higher percentage of patients who received medication in bubble packaging were adherent (MPR $\geq 80\%$) compared to patients who used pill bottles (67.14% vs 53.2%, $P < .001$). Significant differences were found in adherence rates by medication classes between both cohorts (Figure 2). The bubble package group had significantly higher MPR ($P < .05$) for all the medication classes (statins, oral hypoglycemic agents, β -blockers, and ACE inhibitors) as compared to regular pill bottle group. In the adjusted analysis, the number of medications filled ($\beta = -0.31$, $P = .024$) and patient age ($\beta = -0.35$, $P = .018$) were significantly associated with MPR, while bubble packaging was not ($\beta = 0.005$, $P = .13$).

The MPR for the bubble pack users with 4 or fewer medications was 87.9%, and the MPR for the bubble pack users with 5 or more medications was 79.1%. The MPR for the pill bottle users with 4 or fewer medications was 78.9%, and the MPR for the pill bottle users with 5 or more medications was 80.3%. Stratified analyses revealed that bubble packaging was significantly associated with medication adherence ($\beta = 0.42$, $P = .012$) when the number of medications filled was restricted to 4 or fewer. When the number of medications filled exceeded this threshold (≥ 5), bubble packaging was not significantly associated with adherence ($\beta = -0.024$, $P = .069$). Among the various age groups, bubble packaging was only significantly associated with medication adherence ($\beta = 0.32$, $P = .023$) when the data were restricted to the age group of 18 to 44 years.

Discussion

Nonadherence to medication regimens continues to be problematic for patients managing multiple chronic conditions. Strategies are needed to help patients use medications safely and appropriately to achieve maximal benefit. Results from this study suggest that some individuals with CVD risk factors who received their medications in bubble packages have greater adherence to medication regimens in comparison to those who received their medications in pill bottles. However, bubble packaging may not resolve the complex problem of nonadherence, especially for older patients and those who are prescribed multiple medications.

Our results align with previous studies that compared adherence among patients who used bubble packs to those who used regular pill bottles.^{21-23,25,33} These previous studies examined the impact of bubble packaging in ambulatory and clinical trial settings, or through pharmacy claims obtained from chain pharmacies or mass merchandise.^{21-23,25} Dupclay et al assessed the use of antihypertensive drugs received in reminder packaging (RP; ie, bubble packs) and found that adherence was significantly higher in the RP cohort compared with the non-RP cohort (MPR, RP 80% vs non-RP 73%).²¹ Huang et al showed that blister packs (ie, bubble packs) improved patients' adherence to vitamin

supplements.²² Our study contributes to the literature by showing bubble packaging's impact on adherence across several medications classes used to address CVD risk in an independent community pharmacy setting.

Study findings also showed that the number of medications dispensed and age were negatively associated with adherence. In a review of 76 studies, Claxton et al found an inverse relationship between adherence and the complexity of dosing regimen.³⁴ Researchers also conclude that as the population ages and face more chronic conditions, it becomes difficult to remain adherent to medication regimens.³⁵ In addition, results from our study indicated that bubble packaging, in comparison to pill bottles, was not associated with greater adherence in patients who received 5 more medications. Previous researchers have suggested that patients who receive more than 5 medications (ie, polypharmacy) are at high risk for drug-related problems (eg, side effects, drug-drug interactions) that may lead to deviations from medication regimens.^{32,36} Patients in this study who used 5 or more medications may have encountered problems that go beyond recall, and thus the use of bubble packaging for these individuals may be a moot point.

Similar to previous research, our findings suggest that older adults and those with complex regimens may deal with issues that hinder adherence to medication regimens. To address these issues, interventions tailored to specific individuals may be needed. Since there could be several issues faced by the patient, any one approach or intervention may not address the underlying issue contributing to nonadherence. Targeted multiple interventions addressing patient's specific barriers may be needed.³⁷ Further research is needed to design and explore the impact of other interventions such as patient counseling and imparting knowledge along with the use of bubble packs on adherence. However, the improvements in adherence with these personalized interventions must be balanced against their higher costs; hence, research is warranted before its wide scale implementation.

One interesting finding from this study was the small number of patients who chose to receive their medications in bubble packaging (140 vs 1705), even though the pharmacy offered this service free of charge. One plausible reason for the low uptake of bubble packaging could be the perceived usability of the units. Muhlfeld et al suggest that older adults may struggle with the opening mechanism and/or force needed to access the stored medications.³⁸ A previous study comparing pill organizers and blister packs found better adherence with blister packs in comparison to pill organizers, thereby reflecting the importance of blister packs and providing tailored interventions.²² To address these issues associated with opening mechanisms, pharmacists could counsel patients regarding the proper techniques of retrieving medications from the packaging. Other possible reasons for the small number of patients using bubble

packaging include more familiarity with pill bottles and a lack of awareness regarding availability or potential benefits of using bubble packaging.³⁸ To support use of bubble packs, pharmacists could actively promote the use of bubble packaging and educate patients about the possible benefits of using bubble packs such as helping synchronize medications, maintaining prescribed dosing scheduling, providing a visual record of when they last took their medications.³³ In addition, future research could be conducted to gain insight into patients' experiences and future expectations with bubble packaging. Findings from these studies may help improve the features of bubble packs and lead to greater effectiveness.

Recent changes in health policy highlight the need for high quality care, and foster reimbursement models based on outcomes rather than process. Many Part D pharmacy benefit managers are evaluated on the "star rating," which includes evaluation of medication adherence. Community pharmacies are incentivized through preferred contracts to improve medication adherence, and this study helps examine the impact of bubble packing on medication adherence, which could directly relate to improve reimbursement.

Limitations

Our study has limitations that warrant mentioning. We used pharmacy claims data to assess adherence. Although patients received their medications from the pharmacy, they may not actually take the medications. Thus, MPR may overestimate adherence in these instances. Second, there was no information available on various factors that might influence medication adherence such as alarm systems or help from caregivers, free samples, multiple prescribers, multiple pharmacies and multiple health systems, and hospital admission. The differences in MPR could be due to some of these factors, which we could not account for due to the retrospective nature of our study. Next, patients who chose bubble packaging may be more concerned about their health or more proactive in their health care in comparison to those who opted not to use bubble packaging. This might have led to an issue of selection bias, which could not be addressed due to limitations with the available data. We attempted to account for biases that may occur due to the observational design by using propensity score weighing method (analyses not shown). Results from the propensity score analyses showed the same findings. In addition, we were unable to differentiate inappropriate behaviors (eg, overuse, early refills) from appropriate behaviors (eg, adhering to prescriber changes in drug regimens, multiple dispensing to achieve a specific dosage). However, this is equally likely in both the groups and may not bias our study findings. Finally, we used data from only one independent pharmacy in the southeastern region of the United States, and we focused on only 4 medication classes. Therefore, our findings may not

be generalizable to the entire US population, and for those individuals who use other medications.

Conclusion

Adherence to medications for hypertension, dyslipidemia, and diabetes plays an important role in the prevention of CVD. Our study presents evidence to support the assertion that bubble packaging assists with medication adherence, which could possibly reduce CVD risk. However, study results also suggest that bubble packaging may not address all issues that may lead to poor adherence such as complex medication regimens (5 or more medications) and increasing age. In addition, findings indicate that bubble packaging may not be acceptable to many patients. Future research could examine factors that mediate/moderate bubble packaging's impact on patients' adherence to complex medication regimens to bolster bubble packaging's utility. In addition, researchers should explore the attributes of bubble packaging that may influence its adoption.³⁹

Authors' Note

This study was presented as a poster at the American Pharmacists Association meeting held in San Diego, California, between March 27 and 30, 2015.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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