The Safety and Effectiveness of Mail Order Pharmacy Use in Diabetes Patients

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Abstract

Background—Research suggests mail order pharmacy use is associated with greater medication adherence and CVD risk factor control. However, no research has examined the potential impact of mail order pharmacy use on patient safety and utilization.

Objective—To compare safety and utilization outcomes in patients using mail order vs. local pharmacies.

Subjects—17,217 Kaiser Permanente Northern California (KPNC) adult diabetes patients prescribed new cardiometabolic medications in 2006.

Research Design—Cross-sectional, observational study.

Measures—Outcomes included any all-cause and preventable hospitalizations and emergency department (ED) visits; laboratory tests for monitoring persistent medications; and overlapping days' supply of contraindicated medications. Multivariate logistic regression results were stratified by patient age and converted to adjusted predicted percentages.

Results—Overall, there were few differences in outcomes between mail order and local pharmacy users. Patients < 65 using mail order had fewer ED visits (34.0% vs. 40.2%; p<.001); preventable ED visits (7.8% vs. 9.6%; p<.01); and serum creatinine laboratory monitoring tests after ACE/ARB or diuretic initiation (41.4% vs. 47.2%; p<.01). Among patients 65, mail order users had fewer preventable ED visits (13.4% vs. 16.3%; p<.01); but more occurrences of overlapping days' supply of contraindicated medications (1.1% vs. 0.7%; p<.01).

Conclusions—Mail order pharmacy use is not associated with adverse outcomes in most diabetes patients, and is associated with lower ED use. Interventions to increase mail order pharmacy use may be an important strategy for improving care; however, these interventions should employ a patient-centered approach that is sensitive to primary and preventive care access.

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Introduction

Mail order pharmacies are widely used to deliver medications in the U.S., with up to 1/3 of chronic illness medications delivered by mail.[1–2] Research suggests a positive association between mail order pharmacy use and greater adherence to diabetes and antihypertensive medications, [3–6] and with better LDL-C control.[7] These favorable outcomes may reflect improved access to medications with mail order pharmacy use,[8] which may be of particular value to patients with disabilities, time constraints, or limited transportation (Figure 1).[3,8] However, there may be unintended consequences to using mail order pharmacies. When medical offices and pharmacies are in the same location, patients who use mail-order pharmacies may be less likely to access preventive care services. This may increase the risk of hospitalizations and emergency department (ED) visits that are sensitive to preventive care quality.[9,10] Diabetes patients, who often take multiple medications, may be particularly at-risk for exposure to contraindicated medications;[11–12] mail order pharmacy users may miss face-to-face consultations with pharmacists and physicians designed to prevent contraindicated medication use. Finally, many medications require laboratory monitoring to reduce the risk of potential adverse drug events:[13] mail order pharmacy use may inadvertently reduce the likelihood such tests are ordered by physicians and completed by patients. The purpose of this study is to examine the relationship of mail order pharmacy use with safety and healthcare outcomes in diabetes patients, and whether effects vary by key patient characteristics.

Methods

Study Population and Setting

This study was conducted within Kaiser Permanente Northern California (KPNC), an integrated health system providing comprehensive medical care to over three million members. Patients were included in the study if they had diabetes, were 18 years of age by January 1, 2006, and had been prescribed a new (no use in the past 24 months) antiglycemic, antihypertensive, or lipid-lowering medication from January 1 – May 31, 2006. If patients were prescribed multiple new cardiometabolic medications during this period, the earliest prescription was defined as the "index medication." We excluded the small proportion (<5%) of members who lacked KPNC drug benefits during the study period.

KPNC maintains a mail order pharmacy distribution system in coordination with over 120 local "walk-in" KPNC pharmacies located within outpatient clinics and hospitals.[3,7] The first fill of a medication is typically at a local KPNC pharmacy, and includes a pharmacist consultation. Patients may then refill existing prescriptions either by mail or at any KPNC local pharmacy. Mail delivery of medications, with free shipping, can be requested by phone or online. While KPNC members also have the option of filling prescriptions at non-KPNC pharmacies, the cost of these fills are not covered by the patient's pharmacy benefit. Pharmacists are available via telephone to answer medication-related questions regardless of the mode of delivery. There is no proscribed days' supply of pills required for mail delivery; KPNC typically dispenses 100-day supplies through both mail order and local pharmacies. Some patients have a financial incentive to use mail order in the form of a lower co-payment for the same days' supply. For this analysis, patients were defined as local KPNC pharmacy

users if they never used the mail order pharmacy to fill the new index medication in the 12 months post-initiation, and as a mail-order pharmacy user if they filled the index medication at least once via mail during that timeframe.

Outcome Variables

All-cause hospitalizations, preventable hospitalizations, all-cause ED use, and preventable ED use were defined as zero vs. one or more episodes in the 3 years post-index medication initiation date. Hospitalizations and ED visits were defined as 'preventable' using validated lists geared towards sensitivity to primary care access.[9,10,14]

Among patients whose index medication was an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or diuretic, we examined whether there was an appropriate potassium or serum creatinine lab test within 30 days post-index date.[13,15] These tests monitor for the possibility of electrolyte abnormalities or decreased renal function in patients new to these medications.

Potential for serious medication interaction was defined using a published list of contraindicated medications,[16] and operationalized as two or more occurrences of overlapping days' supply of contraindicated drugs (*e.g.*, anti-coagulants and thyroid hormones) for one or more days in the 15 months post-index date.

Statistical Analysis

We estimated separate logistic regression models to examine the relationship between mail order pharmacy use and each outcome variable. In each analysis, we adjusted for age; sex; race/ethnicity; neighborhood deprivation score calculated with geocoded census socioeconomic data; [17–18] number of comorbidities; smoking status; use of non-formulary medications, antidepressants, or insulin; whether the index medication was generic or brand name; length of therapy with the index medication, days' supply of the first refill; and medical facility. Detailed definitions of these variables has been published previously.[3] Patients with missing covariates (n=85) were excluded from the analysis. Models included interaction terms for mail order use with age, race/ethnicity, and deprivation score to assess whether different groups of patients might be more vulnerable to potential safety concerns with using the mail order pharmacy. Since the age interaction was the only interaction term that was significant, we present the results as adjusted percentages from models stratified by age <65 vs. age 65 plus.

Omitted (unmeasured) variable bias, or self-selection, may be of particular concern when studying the impact of mail order pharmacy use on outcomes; it is possible that patients who use the mail order pharmacy are different from those who do not in ways we are unable to measure (*e.g.*, patient motivation). We employed health econometric techniques, specifically a bivariate probit (BVP) model incorporating an instrumental variable, to assess whether our estimates from the logistic regression predicting safety outcomes may be subject to such bias.[19] We used distance from the patient's home to their nearest local KPNC pharmacy as our instrumental variable, based on both empirical and theoretical considerations.[3,20–21] An instrumental variable is required to be related directly to exposure (in this case, mail order

pharmacy use), but not directly to the outcomes of interest.[22] We found greater distance to a local pharmacy was associated with mail-order pharmacy use in unadjusted analyses (X^2=78.48, p<0.001), but was not independently associated with our outcomes. The likelihood-ratio test for endogeneity in the BVP models were all non-significant (p-values 0.08–0.93, data not shown), suggesting no evidence of omitted variable bias; therefore we report results from the more efficient logistic regression analyses.

All analyses were performed using Stata Version 10.1. The study protocol was approved by the KPNC Institutional Review Board.

Results

A total of 17,217 diabetes patients met study eligibility criteria. Of these, 5,890 (34.1%) used the mail order pharmacy at least once to refill their new cardiometabolic medication during the study period (Table 1). Mail order pharmacy users were more likely to be white (56.7% vs. 37.1%, p<.001) and to live in census tracts with higher socioeconomic status (p<.001).

Table 2 shows the adjusted predicted percentages of patients experiencing each outcome, stratified by age. After adjustment for demographic, clinical and census-block characteristics, patients < 65 using the mail order pharmacy were less likely to have an all-cause ED visit (34.0% vs. 40.2%, p<.001); less likely to have a preventable ED visit (7.8% vs. 9.6%, p<.01); and less likely to receive a serum creatinine lab test within 30 days if their index medication was an ACE, ARB, or diuretic (41.4% vs. 47.2%; p<.01). Among patients 65, those using mail order were less likely to experience a preventable ED visit (13.4% vs. 16.3%; p<.05) and slightly more likely to experience two or more occurrences of overlap in days' supply of contraindicated medications (1.1% vs. 0.7%; p<.01).

Discussion

This is the first study to examine the relationship between mail order pharmacy use and patient safety and utilization outcomes. We found that mail order use was not negatively associated with patient safety outcomes overall, suggesting mail order use does not serve as a barrier to receiving primary and preventive care services for most patients. Patients < 65 using the mail order pharmacy did have slightly lower rates of serum creatinine testing with ACE, ARB, or diuretic use (41.4% v. 47.2%, p<.01). While there was no statistically significant difference in potassium laboratory testing in this group, or for any lab testing in patients 65, our findings suggest that in-person pharmacy refills may increase opportunities for monitoring of persistent medications in settings where laboratories and pharmacies are co-located.

Our study also found that patients 65 had slightly higher rates of two or more occurrences of overlapping days' supply of contraindicated medications. While these rates were extremely low for both mail order and local pharmacy users (1.1% and 0.7%, respectively), our analysis adds to the evidence suggesting older patients using multiple medications may require additional monitoring for adverse events.[12,13] It is important that pharmacies provide

increased access to chronic illness medications while also maintaining appropriate systems for preventing contraindicated medication use.

We found mail order pharmacy use was associated with lower overall ED use in patients <65, as well as lower preventable ED use in patients in all age groups. Previous studies have shown mail order use is associated with greater medication adherence [3–6] and LDL-C control.[7] Since good medication adherence and CVD risk factor control are associated with reduced hospitalizations and better outcomes,[23–25] mail order use may lead to lower preventable utilization over time.

Mail order pharmacy services, which are provided at the health care delivery system level rather than the physician or practice level, can be considered a structural or system-level intervention for improving access to chronic illness medications.[3,7] While this study and others [3–7] suggest using mail order pharmacy services may improve outcomes, our study also suggests that certain patients may be more sensitive to any potential negative impact of mail order pharmacy use on health care access. System-level efforts to promote mail order use should preserve patient choice in pharmacy services and maintain a patient-centered approach to meeting an individual's overall healthcare needs. Future research should continue to address the important issue of how to appropriately target and promote mail order pharmacy services while preserving the benefits of in-person interaction with pharmacists and other care providers.

This study has several limitations. Observational studies cannot entirely control for differences between patients who use mail order pharmacy services and those that do not. While we used instrumental variable analyses to test for the evidence of such biases, it is possible that were unable to completely control for these differences. Future research should leverage randomized controlled trial designs to examine the impact of mail order pharmacy use on intermediate outcomes, healthcare utilization, and patient safety.

We were unable to ascertain pharmacy utilization at non-KPNC pharmacies. However, we limited our analyses to members with a drug benefit, which is only recognized at KPNC pharmacies. This under-ascertainment should be minimal, as previous research suggests that diabetes patients with drug benefits report extremely low use of non-KPNC pharmacies.[26]

This study was conducted in an integrated delivery system where patients access prescription medications differently than in many other settings. Use of "brick and mortar" pharmacies to fill prescriptions is primarily limited to KPNC local pharmacies; KPNC's mail order and local pharmacies do not differ in the standard days' supply of pills issued; and mail order pharmacy does not require physician enrollment of the prescription. KPNC local pharmacies are primarily 'co-located' with medical offices and laboratories, which is often not the case in other settings. It is therefore possible that the use of mail order pharmacy services in KPNC has a different impact on outcomes than in other settings.

Conclusion

Mail order pharmacy use is not associated with adverse events in most diabetes patients, and may be associated with improved health outcomes. System-level interventions to increase

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mail order pharmacy use may be an important strategy for improving processes and outcomes of care for patients with chronic illness; however, these interventions should employ a patient-centered approach that does not increase risk in older patients and others who may be sensitive to primary and preventive care access.

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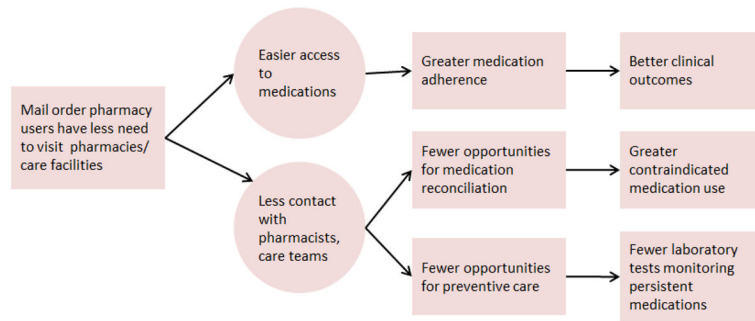**Figure 1.**
Potential Impact of Mail Order Pharmacy Use on Outcomes

Table 1

Patient Characteristics

	Entire Sample (n=17,217)	Mail-Order Pharmacy Users (n=5,890)	Local Pharmacy Users (n=11,327)
Female (%)	46.4	46.0	46.7
Mean age (in years) (SD)	62 (11.9)	63 (11.7)	62 (12.0)[***]
Race/ethnicity			
White, non-Latino (%)	43.8	56.7	37.1[***]
African American, non-Latino (%)	9.1	4.7	11.4[***]
Latino (%)	8.8	6.0	10.2[***]
Asian (%)	10.9	9.5	11.6[***]
Native American (%)	1.7	1.9	1.6
Mixed-race (%)	11.0	9.2	12.0[***]
Missing race (%)	14.7	11.9	16.1[***]
Socioeconomic deprivation			
1st quartile (least deprived) (%)	20.5	25.8	17.8[***]
2nd quartile (%)	28.9	30.0	28.3[*]
3rd quartile (%)	26.3	23.3	27.8[***]
4th quartile (most deprived) (%)	17.9	12.0	21.0[***]
SES Missing	6.5	9.0	5.2[***]
Mean number of comorbidities (SD)	0.81 (1.1)	0.83 (1.0)	0.80 (1.1)[*]
Smoker (%)	7.7	7.0	8.0[*]
History of medication for depression (%)	22.1	24.0	21.1[***]
History of insulin use (%)	19.1	17.8	19.8[***]
History of nonformulary medication use (%)	6.0	6.4	5.8
New medication is brand-name (%)	22.3	24.0	21.4[***]
Medication days' supply			
1–30 Days (%)	5.2	5.0	5.3
31–60 Days (%)	5.4	5.5	5.4
61–90 Days (%)	5.7	6.1	5.4
>90 Days (%)	83.7	83.3	83.9
Mean # of Days from 1st Fill to Last Fill (SD)	349 (100)	362 (87)	342 (106)[***]

[*]
p<.05 difference between groups

[**]
p<.01 difference between groups

[***]
p<.001 difference between groups

Table 2

Predicted Percentages of Patients Experiencing Safety And Utilization Outcomes[†]

Outcome	AGE<65 (n=9,851)		AGE>=65 (n=7,281)	
	Local Pharmacy Users	**Mail-order Pharmacy Users**	**Local Pharmacy Users**	**Mail-order Pharmacy Users**
At Least 1 Hospitalization – All Cause	12.2%	11.2%	23.0%	22.5%
At Least 1 Hospitalization – Preventable[†]	1.9%	1.4%	4.3%	3.7%
At Least 1 ED Visit – All Cause	40.2%[***]	34.0%[***]	52.3%	49.7%
At Least 1 ED Visit – Preventable[†]	9.6%[**]	7.8%[**]	16.3%[**]	13.4%[**]
Had Potential Serious Medication Interaction	0.5%	0.4%	0.7%[**]	1.1%[**]
	(n=2,553)		(n=2,026)	
Had Potassium Lab Test within 30 days	43.4%	39.7%	50.5%	55.0%
Had Serum Creatinine Lab Test within 30 days	47.2%[**]	41.4%[**]	52.6%	56.1%

[†]Adjusted for age; sex; race/ethnicity; neighborhood deprivation score; number of comorbidities; smoking status; use of non-formulary medications, antidepressants, or insulin; whether the index medication was generic or brand name, length of therapy with the index medication, and medical facility.

[*]p<0.05

[**]p<0.01

[***]p<0.001