Examination of the Link Between Medication Adherence and Use of Mail-Order Pharmacies in Chronic Disease States

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ABSTRACT

BACKGROUND: Higher medication adherence is associated with positive health outcomes, including reduction in hospitalizations and costs, and many interventions have been implemented to increase patient adherence.

OBJECTIVES: To determine whether patients experience higher medication adherence by using mail-order or retail pharmacies.

METHODS: Articles pertaining to retail and mail-order pharmacies and medication adherence were collected from 3 literature databases: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and International Pharmaceutical Abstracts (IPA). Searches were created for each database and articles were compiled. Articles were screened for exclusion factors, and final articles (n=15) comparing medication adherence in patients utilizing mail and retail pharmacies were analyzed. For each study, various factors were identified including days supply, patients' out-of-pocket costs, prior adherence behavior, therapeutic class, measure of adherence, limitations, and results. Studies were then categorized by disease state, and relevant information from each study was compared and contrasted.

RESULTS: The majority of studies—14 out of the 15 reviewed—supported higher adherence through the mail-order dispensing channel rather than through retail pharmacies. There are a number of reasons for the differences in adherence between the channels. Study patients who used mail-order pharmacies were more likely to have substantially higher prior adherence behavior, socioeconomic status, and days supply of medicines received and were likely to be offered financial incentives to use mail-order. The few studies that attempted to statistically control for these factors also found that patients using mail-order services were more adherent but the size of the differences was smaller. The extent to which these results indicate an inherent adherence advantage of mail-order pharmacy (as distinct from adherence benefits due to greater days supply, lower copays, or more adherent patients selecting mail-order pharmacies) depends on how well the statistical controls adjusted for the substantial differences between the mail and retail samples.

CONCLUSIONS: While the research strongly indicates that consumers who use mail-order pharmacies are more likely to be adherent, more research is needed before it can be conclusively determined that use of mail-order pharmacies causes higher adherence.

J Manag Care Spec Pharm. 2016;22(11):1247-59

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What is already known about this subject

- Patient nonadherence to prescribed medications is high across the population and has been shown to decrease desired health outcomes and increase hospitalizations and medical costs.
- There have been many attempts to increase adherence, and several studies have compared patient adherence across dispensing channels.

What this study adds

- In this review, most studies found higher medication adherence in patients who used mail-order pharmacies.
- Patients who used mail-order pharmacies were more likely to have higher prior adherence behavior, socioeconomic status, and days supply of medicines received and were more likely to be offered financial incentives to use mail order than patients using retail pharmacies.
- The few studies that statistically controlled for prior adherence behavior, days supply of medicines, socioeconomic factors, and financial incentives also found that patients using mail-order pharmacies were more adherent, but the size of the differences was smaller.

Patient nonadherence to prescribed medications has been shown to decrease desired health outcomes and increase hospitalizations and medical costs.^{1,2} Medication adherence for treatment of chronic diseases is still poor across the population, with reports of less than 50% of patients taking their medications as prescribed.³⁻⁷ High medication costs, beliefs that medications are not necessary, transportation access, and unfavorable side effects are among the reasons that patients are not adherent to their medications. It is in the best interest of the health care community to determine ways to increase patient adherence in order to improve health outcomes and decrease hospital admissions and costs. There have been many attempts to increase adherence. Conn et al. (2015) summarized interventions to increase medication adherence, including introduction of medication therapy management (MTM) by educating patients on proper drug administration through provider counseling.⁸ Other attempts to increase adherence include (a) encouraging patients to self-manage, (b) use of medication calendars/diaries/pill boxes/drug reminders, (c) motivational interviewing to identify and correct barriers

TABLE 1 MEDLINE Search Results

#	Search	Results
1	("Medication Adherence"[Mesh]) OR (("adherence" OR "compliance" OR "medication adherence"))	145,744
2	("Postal Service"[Mesh]) OR (("postal service" OR "mail" OR " mail service"))	62,099
3	((("Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR "Pharmacy Service, Hospital"[Mesh] OR "Community Pharmacy Services"[Mesh] OR "Pharmaceutical Services, Online"[Mesh] OR "Pharmaceutical Services"[Mesh] OR "Insurance, Pharmaceutical Services"[Mesh])) OR ("community pharmacy" OR "retail pharmacy" OR "pharmacy services"))	44,528
4	(((((("Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR "Pharmacy Service, Hospital"[Mesh] OR "Community Pharmacy Services"[Mesh] OR "Pharmaceutical Services, Online"[Mesh] OR "Pharmaceutical Services"[Mesh] OR "Insurance, Pharmaceutical Services"[Mesh])) OR ("community pharmacy" OR "retail pharmacy" OR "pharmacy services")))) AND (("Medication Adherence"[Mesh]) OR ("adherence" OR "compliance" OR "medication adherence"))	3,933
5	(((((("Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR "Pharmacy Service, Hospital"[Mesh] OR "Community Pharmacy Services"[Mesh] OR "Pharmaceutical Services, Online"[Mesh] OR "Pharmaceutical Services"[Mesh] OR "Insurance, Pharmaceutical Services"[Mesh])) OR ("community pharmacy" OR "retail pharmacy" OR "pharmacy services")))) AND (("Postal Service"[Mesh]) OR ("postal service" OR "mail" OR " mail service"))	762
6	(((((("Postal Service"[Mesh]) OR ("postal service" OR "mail" OR " mail service")))) AND (("Medication Adherence"[Mesh]) OR ("adherence" OR "compliance" OR "medication adherence")))) AND (((("Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR "Pharmacy Service, Hospital"[Mesh] OR "Community Pharmacy Services"[Mesh] OR "Pharmaceutical Services, Online"[Mesh] OR "Pharmaceutical Services"[Mesh] OR "Insurance, Pharmaceutical Services"[Mesh])) OR ("community pharmacy" OR "retail pharmacy" OR "pharmacy services"))	86
7	(((((("Postal Service"[Mesh]) OR ("postal service" OR "mail" OR " mail service")))) AND (("Medication Adherence"[Mesh]) OR ("adherence" OR "compliance" OR "medication adherence")))) AND (((("Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR "Pharmacy Service, Hospital"[Mesh] OR "Community Pharmacy Services"[Mesh] OR "Pharmaceutical Services, Online"[Mesh] OR "Pharmaceutical Services"[Mesh] OR "Insurance, Pharmaceutical Services"[Mesh])) OR ("community pharmacy" OR "retail pharmacy" OR "pharmacy services"))	64

Note: MEDLINE was searched for various Medical Subject Headings (MeSH) and keywords pertaining to medication adherence and mail-order pharmacies as of June 29, 2015. The search was limited to English language and human subjects only.

and behavior by goal setting, (d) increasing communication with providers and social support, and (e) rewards including financial incentives for patients by doctors, insurance companies, and pharmacy benefit managers (PBMs).⁸⁻¹⁰ Aside from altering patient behaviors or incentives, several studies have compared patient adherence across dispensing channels.

Patients usually have the option to fill prescriptions through retail or mail-order pharmacies. Mail-order pharmacies provide patients with a number of advantages that could lead to greater adherence. Filling prescriptions through a mail-order pharmacy provides patients greater convenience by cutting out trips to retail pharmacies. This is especially advantageous for patients who have physical problems or lack of transportation that limits their ability to travel to pharmacies. Mail-order pharmacies also provide greater convenience by providing 90-day supplies of medications, rather than the 30-day supplies that are more commonly dispensed from retail pharmacies. Having medicines on hand and ease of refilling may both contribute to higher adherence.¹¹ Insurance companies and PBMs often provide financial incentives that make filling prescriptions via mail-order pharmacies less expensive for patients.¹²⁻¹⁴ Greater affordability may lead to greater adherence. Finally, mail-order may provide greater privacy in that the prescription is not filled in the community where the patient lives or is not picked up in a public place. This may be an important factor for patients on medicines for conditions that have social stigma. An advantage of retail is face-to-face interaction with a pharmacist. This may increase adherence through clarification of prescriptions

and more in-depth counseling on use of drugs for which patients may be less adherent.^{15,16} For example, Ratanawongsa et al. (2013) showed that increased communication and education about diabetic medications led to higher adherence.¹⁷ Additionally, Bauer et al. (2013) showed that patients with health literacy limitations had poorer adherence than those without such limitations.¹⁸

The primary goal of this systematic review was to identify whether patient adherence is related to dispensing channel. A second goal was to determine whether differences in adherence between channels were a result of inherent differences between the channels or the result of confounding factors such as days supply, financial incentives, or patient differences.

Methods

Literature Search

Literature searches were conducted in MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and International Pharmaceutical Abstracts (IPA) databases. Initially, a broad search strategy of relevant keywords was used to find evidence of patient medication adherence in retail and mail-order pharmacies. Search terms in the broad search included *medication adherence* and *mail* and *retail pharmacy*. Searches were built for each database to obtain all possible relevant articles.

Relevant subject headings for each of the 3 databases were determined and searches were constructed based on subject headings and key terms (Table 1 shows search results for MEDLINE).

FIGURE 1 Flow Diagram of Article Selection

CINAHL = Cumulative Index to Nursing and Allied Health Literature; IPA = International Pharmaceutical Abstracts.

Search results from MEDLINE, CINAHL, and IPA produced 124 articles after duplications were removed (Figure 1).

Following the PRISMA guidelines for reporting systematic reviews, 124 articles were screened by title and abstract for primary exclusion criteria.¹⁹ These included studies conducted outside of the United States; studies that examined adherence to medication after introduction of MTM or other programs to improve adherence, prescribing behaviors and adherence, technology advancement and adherence, insurance benefit or cost and drug utilization, and barriers to medication adherence; and review articles and letters to the editor or articles that did not examine medication adherence in mail and retail settings. Primary exclusion resulted in a total of 34 articles that were further analyzed.

The remaining articles were reviewed in depth for secondary exclusion criteria, which included articles mentioning mail-order pharmacies or adherence individually but not together, articles about interventions by prescribers to increase patient

adherence, and articles examining patients' internal motivations to be adherent. This resulted in a sample of 13 articles. Two additional articles were found as a result of reviewing the references in these articles. This resulted in a final total of 15 articles that examined the relationship between dispensing channel and medication adherence.

Data Extraction and Interpretation

For purposes of this review, articles were categorized by chronic disease. Articles were reviewed for factors that could account for differences in adherence across dispensing channels and relevant information was pre-determined, extracted, and summarized (Table 2). These factors included measures of adherence, days supply, out-of-pocket (OOP) costs, prior adherence behavior (PAB), and automatic prescription refills (auto-refill). As mentioned earlier, higher days supply and lower OOP costs may increase adherence, and mail and retail pharmacies frequently differ on these variables. PAB, measured as adherence in the prestudy period,

TABLE 2 Summary of Articles Comparing Adherence at Mail and Retail Pharmacies

Part 1: Description of Study Samples

First Author and Reference	Ages in Sample (Years)	How Mail-Order Users Were Identified	New or Established Users in Sample	Sample Size	Source of Sample	Adherence Measure	Drug Classes	Major Baseline Differences in Mail and Retail Samples
Visaria ²⁰	12-63	The index medication claim was dispensed at a mail pharmacy or the days supply was >84 days	New	6,000	MSCCE	MPR	Antiasthmatics	No major differences
Khandelwal ¹⁵	Mean = 65.2 for retail, 61.4 for mail	Patients who used mail (retail) for all prescriptions in the therapeutic class were classified as mail (retail) patients. Patients using both channels were excluded	Established	54,000	PBM database	MPR	Antiasthmatics/bronchodilator agents, antidepressants, antidiabetics, antihypertensives, beta blockers, diuretics, and thyroid agents	No major differences
Pittman ²¹	18-63	Use of mail-order for >80% of antihypertensive medications	Both	625,000	Commercial insurance	MPR	Antihypertensives	Baseline characteristics for mail vs. retail patients were not reported
Adams ²²	18+	"voluntary enrollment in a mail-order program." This included having at least the first fill of the prescription from a mail-order pharmacy	New	44,000	KPNC	CMG	Antihypertensives	Baseline characteristics for mail vs. retail patients were not reported
Iyengar ²³	18-64	At least 66.7% of prescriptions from mail-order pharmacy; also had a mixed-channel group for patients with <66.7% of prescriptions through mail and <66.7% of prescriptions through retail	Both	4,000	Commercial insurance members from a PBM	MPR	Antidiabetics, antihypertensives, antihyperlipidemics	18-21 percentage points more mail patients were adherent in the baseline period
Iyengar ²⁴	65+	At least 66.7% of prescriptions from mail-order pharmacy; also had a mixed-channel group for patients with <66.7% of prescriptions through mail and <66.7% of prescriptions through retail	Both	800,000	Medicare Part D claims from a PBM database	PDC	Antidiabetics, antihypertensives, antihyperlipidemics	14-16 percentage points more mail patients were adherent in the baseline period; 17-25 percentage points more retail patients received LIS; mean OOP payments were \$3-\$5 higher for retail patients
White ²⁵	18-75	Mail-order patients were those who used mail pharmacies exclusively, and retail patients were those who used retail pharmacies exclusively. Patients using both types were excluded	New	15,000	Commercial and Medicare members of a large HMO	MPR, persistence	HMG reductase inhibitors	87% of mail patients were covered by Medicare vs. 56% of retail patients
Schmitt ²⁶	18-80+	Patients who used mail order "at least once"	New	100,000	KPNC	LDL-C levels	Statins	67.2% of mail patients vs. 45.3% of retail patients were non-Latino Caucasians; 30.4% of mail patients vs. 18.3% of retail patients had financial incentives to use mail order
Duru ²⁷	>17 years	Patients with >66% of refills by mail were classified as mail patients, and those with 100% of refills at retail were classified as retail patients. Patients with 1%-66% of refills at mail were excluded	Both	14,000	KPNC	CMG	Antilipids, antihypertensives, antihyperlipidemics	61% of mail patients vs. 37.1% of retail patients were non-Latino whites, 27.5% of mail patients vs. 17.8% of retail patients were in the least deprived SES quartile, and 49.6% of mail users vs. 23.0% of retail users had a financial incentive to use mail

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TABLE 2 Summary of Articles Comparing Adherence at Mail and Retail Pharmacies (*continued*)

First Author and Reference	Ages in Sample (Years)	How Mail-Order Users Were Identified	New or Established Users in Sample	Sample Size	Source of Sample	Adherence Measure	Drug Classes	Major Baseline Differences in Mail and Retail Samples
Gibson ²⁸	18+	Patients with “any mail-order use in the past year” were classified as mail patients	Both	97,000	Commercial insurance	PDC	Oral antidiabetics and insulin	Baseline characteristics for mail vs. retail patients were not reported
Devine ²⁹	18-64	Mail-order users were those who switched to mail after an initial retail fill of the medication; patients could have 2 retail fills after the switch to mail and still be considered mail patients	Both	58,000	MSCCE	MPR	Oral antidiabetics	No major differences
Zhang ³⁰	Mean = 72.3	Patients who used mail (retail) for all prescriptions in the therapeutic class were classified as mail (retail) patients. Patients using both channels were excluded	New	23,000	Medicare Part D claims from PBM database	PDC	Oral antidiabetics	30.7% of mail patients vs. 21.7% of retail patients were in MAPD plans; 95.3% of mail patients vs. 87.8% of retail patients were over 64 years of age; mail patients were on a mean of 3 distinct medications vs. 2.5 for retail patients
Sharma ³¹	18-64	Individuals were assigned to the pharmacy where they had a majority of their prescriptions filled. The database did not identify pharmacies as mail or retail; researchers classified pharmacies filling >50% of prescriptions in the sample through mail as mail pharmacies and those filling >50% at retail as retail pharmacies	Both	408,000	Employer-sponsored private health plans	PDC	Antidiabetics, including injectable insulin	Baseline characteristics for mail vs. retail patients were not reported
Curkendall ³²	≥ 18 years	“The index drug was characterized as to whether it was a mail-order prescription”	Established	53,000	MSCCE	PDC, persistence	Noninsulin antidiabetics	Baseline characteristics for mail vs. retail patients were not reported
Kirkman ³³	20-75+	Patients who filled any of their diabetes medications by mail were considered mail patients	Both	218,000	PBM covering predominantly commercial members	MPR	Noninsulin antidiabetics	Baseline characteristics for mail vs. retail patients were not reported

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was included to control for selection bias that would occur if patients who were more adherent were also more likely to use one of the channels. Both retail and mail-order pharmacies may offer patients the choice of having their prescriptions auto-refilled. Auto-refill prescriptions are automatically refilled and shipped to the patient so that there should never be gaps in the patient's drug therapy. Auto-refill prescriptions may artificially inflate adherence measures that are based on claims data. Other factors that were extracted included patient demographics, source of sample, and sponsor information.

Results

In this section, the relevant methods and results are briefly presented for each study. Studies are grouped by chronic disease, and a number of the studies examined more than 1 disease. Relevant information from each study is summarized in Table 2.

Asthma

Two studies examined medication adherence and the use of mail-order or retail pharmacies for patients with asthma. In a retrospective analysis, Visaria et al. (2012) measured

TABLE 2 Summary of Articles Comparing Adherence at Mail and Retail Pharmacies (continued)

Part 2: Statistical Controls, Results, and Sponsors

First Author and Reference	Controlled for OOP Costs	Controlled for PAB	Controlled for Days Supply	Controlled for Disease Severity	Numeric Results	Length of Follow-Up Period (Months)	Sponsor/Author Affiliation
Visaria ²⁰	Total OOP medical and pharmacy costs in the study year	No	No	CCI; comorbidities known to affect asthma severity or asthma-related resource use; ED, inpatient, and outpatient visits; and SABA claims in the baseline period	Adjusted MPR was 62.4% for mail vs. 39.7% for retail; 23.1% of mail vs. 11.1% of retail patients had an MPR >80%	12	Express Scripts
Khandelwal ¹⁵	Included only mail and retail patients with equal copays for 90-day prescriptions	No	Only included prescriptions with 90-day supply	Risk scores were developed based on NDCs from pharmacy claims	MPRs were 77.0% for mail vs. 76.0% for retail; no differences within therapeutic classes except in diabetes, which favored mail (83.1% vs. 80.2%)	12	Walgreens
Pittman ²¹	Copayment	No	No	CDS and presence of CAD, DM, dyslipidemia, stroke, CHF, depression, and ESRD	Adjusted OR of 2.24 for mail	12	Authors employed by Medco
Adams ²²	Medication copayment category	No	Not reported	HT medication used to initiate therapy; most recent SBP before initiating HT treatment; diagnosis of CVD, CKD, DM, schizophrenia, bipolar disorder, anxiety, and depression; number of medical office visits during the 12 months before starting antihypertensive therapy	Adjusted OR of 0.57 for nonadherence at mail	12	Federally funded; authors employed by KPNC
Iyengar ²³	OOP costs per 30-day adjusted prescription	Patient adherence ($\geq 80\%$ MPR) in the baseline period	Yes, also did SA using only patients receiving 90-day supplies	Number of therapy classes in which the patient had a prescription in baseline year	Adjusted OR for mail was 1.15 for DM, 1.11 for HT, and 1.19 for high cholesterol	12	Express Scripts
Iyengar ²⁴	OOP costs per 30-day adjusted prescription	PDC in baseline year	Yes, also did SA using only patients receiving 90-day supplies	Number of therapy classes in which the patient had a prescription in baseline year	Adjusted OR for mail was 1.25 for DM, 1.29 for HT, and 1.26 for high cholesterol	12	Express Scripts
White ²⁵	No	No	No	CDS during the study period	Adjusted MPR was 92.6% for mail vs. 82.5% for retail; persistence was 278 days for mail vs. 214 for retail	12	Prescription Solutions
Schmitt ²⁶	IV was financial incentive to use mail order; SA using only patients receiving no financial incentives to use mail order	IV and DID analyses	Most patients in both mail and retail samples received 100-day supplies; results indicated only minor differences in days supply between mail and retail patients	Number of comorbidities, presence of cardio-equivalent conditions, use of antidepressant medications, number of primary care visits in baseline period	85% of mail vs. 74.2% of retail achieved target LDL levels	3-15	KPNC
Duru ²⁷	Financial incentive to use mail order	IV analysis	Most patients in both mail and retail samples received 100-day supplies; results indicated only minor differences in days supply between mail and retail patients	Number of comorbidities, use of antidepressant medications, use of insulin	84.7% of mail vs. 76.9% of retail had good adherence (defined as CMG <20%); mail vs. retail percentages of good adherence were 81.8% vs. 75.2% for anti-glycemics, 88.1% vs. 80.4% for HT drugs, and 81.7% vs. 72.4% for lipid-lowering drugs	12-15	KPNC

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TABLE 2 Summary of Articles Comparing Adherence at Mail and Retail Pharmacies (continued)

First Author and Reference	Controlled for OOP Costs	Controlled for PAB	Controlled for Days Supply	Controlled for Disease Severity	Numeric Results	Length of Follow-Up Period (Months)	Sponsor/ Author Affiliation
Gibson ²⁸	"A cost-sharing index created for each employer/plan combination"	No	No	CCI, visits to cardiologist or endocrinologist in baseline year	Adjusted OR for mail was 2.2 for patients on oral drugs only and 2.3 for patients on oral drugs and/or insulin	18	Thomson Reuters
Devine ²⁹	OOP cost for the index antidiabetic claim	MPR in the baseline period	No	Depression diagnosis, CCI score, antihypertensive use, antidepressant use, modified DCSI score	Adjusted MPR was 84.8% for mail vs. 63.4% for retail	12-18	Express Scripts
Zhang ³⁰	No	No	No	CDS in baseline period, number of distinct medications	Adjusted PDC was 68% for mail vs. 61% for retail; 49.7% of mail vs. 42.8% of retail were adherent (PDC ≥80%)	12	Prescription Solutions
Sharma ³¹	Copay category	No	No	No	PDC was 8.6 percentage points higher for mail	12	Wayne State University School of Pharmacy
Curkendall ³²	Average cost-sharing amount per 30-day supply	No	No	3-digit ICD-9-CM diagnosis codes and DCI in the pre-period, visits to endocrinologists and cardiologists, presence of renal impairment, macrovascular disease or microvascular disease in pre-period	Adjusted OR for mail was 1.60	12	Bristol-Myers Squibb
Kirkman ³³	OOP costs per 30-day adjusted prescription	No	No	Pill burden for both diabetic and nondiabetic medications; whether patient was treated for GI problems, high cholesterol, HT, obesity, PVD, renal disease, or depression	Adjusted OR for mail was 2.09	12	"Support for the study was provided to the American Diabetes Association by Amylin Pharmaceuticals, Novo Nordisk, and Sanofi"

CAD=coronary artery disease; CCI=Charlson Comorbidity Index; CDS=chronic disease score; CHF=congestive heart failure; CMG=continuous measure of medication gaps; DCI=Deyo-Charlson Comorbidity Index; DCSI=Diabetes Complications and Severity Index; DID=difference in differences analysis; DM=diabetes mellitus; ED=emergency department; ESRD=end-stage renal disease; GI=gastrointestinal; HMO=health maintenance organization; HT=hypertension; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; IV=instrumental variable; KPNC=Kaiser Permanente Northern California; LDL-C=low-density lipoprotein cholesterol; LIS=low-income subsidy; MAPD=Medicare Advantage Prescription Drug; MSCCE=MarketScan Commercial Claims and Encounters; MPR=medication possession ratio; NDC=National Drug Code; OOP=out-of-pocket; OR=odds ratio; PAB=prior adherence behavior; PBM=pharmacy benefit manager; PDC=proportion of days covered; PVD=peripheral vascular disease; SA=sensitivity analysis; SABA=short-acting beta antagonist; SBP=systolic blood pressure; SES=socioeconomic status.

medication possession ratio (MPR) in commercially insured patients from 12 to 63 years old. This study concluded that adherence to medications to treat asthma was 22.73 percentage points higher in patients who utilized mail-order pharmacies (Table 3). The authors adjusted for various confounding factors, including patient age, gender, distance from a pharmacy, and total patient OOP drug expenditures by linear regression but did not account for days supply or PAB.²⁰

In 2011, Khandelwal et al. examined the adherence of patients within a PBM taking medications for various conditions including asthma.¹⁵ MPR was determined for patients with prescriptions for 90-day supplies. Patients were propensity score-matched based on age, gender, and an average risk score calculated from a model developed by the University of California, San Diego, Chronic Illness and Disability Payment System, which predicts overall medical costs. The authors found no statistically significant differences in MPR pre- or

TABLE 3 Comparison of MPRs and PDCs in Studies Comparing Mail and Retail Pharmacies.

Disease State	Group	Differences		
		Mail-Order Group (%)	Retail Group (%)	Difference (% points)
Asthma	Visaria et al. ^{20,a}	62.4	39.7	22.7 ^b
	Khandelwal et al. ^{15,a}	68.1	67.2	0.9
Hypertension	Khandelwal et al. ^{15,a}	79.0	79.0	0.0
	Duru et al. ^{27,c}	88.1	80.4	7.7 ^b
Cholesterol	White et al. ^{25,a}	92.6	82.5	10.1 ^b
	Khandelwal et al. ^{15,a}	77.6	76.7	0.9
	Duru et al. ^{27,c}	81.7	72.4	9.3 ^b
Diabetes	Duru et al. ^{27,c}	81.8	75.2	6.6 ^b
	Devine et al. ^{29,a,d}	84.8	63.4	21.4 ^b
	Zhang et al. ^{30,a}	68.0	61.0	7.0 ^b
	Khandelwal et al. ^{15,a}	83.1	80.2	2.9
	Sharma et al. ^{31,e}	Not reported	Not reported	8.6
Depression	Khandelwal et al. ^{15,a}	72.3	71.5	0.8
CHF, CAD	Khandelwal et al. ^{15,a}	77.3	78.9	1.6
Thyroid	Khandelwal et al. ^{15,a}	80.2	80.8	0.6
Other diseases				
Diuretics	Khandelwal et al. ^{15,a}	75.4	73.9	1.5
Calcium channel blockers	Khandelwal et al. ^{15,a}	78.9	79.3	0.4

^aMedication possession ratio.^bStatistically significant.^cContinuous measure of medication gaps (percentages of patients who were adherent, CMG ≤ 20%).^dPatients switched groups.^eProportion of days covered.

CAD = coronary artery disease; CHF = congestive heart failure; CMG = continuous measure of medication gaps; MPR = medication possession ratio; PDC = proportion of days covered.

postpropensity-matching between retail or mail-order use for 90-day prescriptions (Table 3).¹⁵ This study accounted for patient characteristics, patient OOP costs, and disease severity, but not for PAB or distance from a pharmacy.

Hypertension

In a 2010 study, Pittman et al. examined the relationship of adherence (MPR ≥ 80%) to antihypertensive medication and health care use and costs in commercially insured patients.²¹ The authors included percentage of prescriptions filled through mail-order pharmacies as a control variable in a multivariable regression analysis. The results indicated that patients who received more than 80% of their prescriptions through mail had 2.24 times higher odds of being adherent (Table 4). The analysis controlled for patient OOP costs but not for days supply, PAB, or distance from a pharmacy.

Adams et al. (2013) analyzed the relationship between race/ethnicity, specific health system factors, early nonpersistence (failure to obtain the prescribed medication) and nonadherence (proportion of days covered [PDC] < 80%) to antihypertensive medications for new users enrolled in a large integrated health system.²² Mail-order usage was measured as “voluntary enrollment in a mail-order program” and appeared to indicate that the patient received at least the first fill of the antihypertensive

prescription from a mail pharmacy. A multivariable logistic regression indicated that patients who used mail-order pharmacy had an odds ratio (OR) of 0.57 for nonadherence compared with nonusers of mail pharmacies (the OR of 0.57 for nonadherence is comparable to an OR of 1.75 for adherence) (Table 4). The analysis controlled for patient OOP costs but not for PAB or distance from a pharmacy. The article did not report whether days supply was controlled.

Iyengar et al. (2013) focused on various chronic conditions within a commercially insured population covered by a large PBM. In this study, where adherence was measured by MPR, hypertensive patients using mail-order pharmacies were more adherent than patients who used retail pharmacies after controlling, by multivariate logistic regression, for differences in age, gender, OOP cost, disease burden and severity, days supply and PAB.²³ The authors calculated an adherence OR of 1.11 in mail versus retail pharmacies (Table 4).

A year later, in 2014, Iyengar et al. examined adherence among Medicare Part D beneficiaries. Within the hypertensive therapy class, patients receiving home delivery of medications (Iyengar's term for mail-order pharmacy) had higher PDCs (OR of 1.29) compared with those utilizing retail pharmacies, after controlling for days supply, OOP cost, various patient demographics, and PAB by multivariate logistic regression (Table 4).²⁴

TABLE 4 Odds of Patients Using Mail-Order Pharmacies Being Adherent Compared with Patients Using Retail Pharmacies

Disease State	Group	Odds Ratio
Hypertension	Iyengar et al. 2013 ^{23,a}	1.11 ^b
	Iyengar et al. 2014 ^{24,c}	1.29 ^b
	Adams et al. ^{22,c}	1.75 ^b
	Pittman et al. ^{21,a}	2.24 ^b
Cholesterol	Iyengar et al. 2013 ^{23,a}	1.19 ^b
	Iyengar et al. 2014 ^{24,c}	1.26 ^b
Diabetes	Curkendall et al. ^{32,c}	1.60 ^b
	Kirkman et al. ^{33,a}	2.09 ^b
	Iyengar et al. 2013 ^{23,a}	1.15 ^b
	Iyengar et al. 2014 ^{24,c}	1.25 ^b
	Gibson et al. ^{28,c}	
	Oral medications only	2.2 ^b
	With or without insulin	2.3 ^b

^aMedication possession ratio.^bStatistically significant.^cProportion of days covered.

Conversely, the 2011 Khandelwal et al. study reported no statistically significant difference in medication adherence for patients using mail or retail pharmacies to fill 90-day prescriptions for antihypertensive agents.¹⁵

Cholesterol/Hyperlipidemia

In one of the first studies to describe differences in adherence between mail-order and retail pharmacies, White et al. (2002) calculated MPR for patients recently prescribed an HMG-CoA reductase inhibitor within a large managed care organization (MCO). After controlling for age, gender, and comorbidity by analysis of covariance, the authors found that patients receiving medications from mail-order pharmacies had 10.1 percentage points higher adherence than those using retail pharmacies (Table 3).²⁵ White did not control for PAB, days supply, or patients' OOP costs.

Schmittiel et al. (2011) reported that patients who used mail-order pharmacy in a large integrated health system versus the health system's local pharmacies had better low-density lipoprotein cholesterol (LDL-C) control. This study was completed in new users and controlled for differences between mail and retail patients using a difference-in-differences approach.²⁶ In addition, Schmittiel et al. used instrumental variable analysis, which, theoretically, controls for both observed differences (such as age and days supply) and unobserved differences (such as PAB) between retail and mail-order users. In this study, 10.8% more patients reached their target LDL-C levels in the mail-order group (Table 3).

Both Iyengar studies, which utilized MPR and PDC and reported ORs, reported better medication adherence in patients on hyperlipidemia medications utilizing mail-order rather than

retail pharmacies (Table 3).^{23,24} In contrast, Khandelwal et al. reported no statistically significant difference in medication adherence for patients taking antihyperlipidemics across dispensing channels (Table 3).¹⁵

Diabetes

In 2010, Duru et al. examined patients with diabetes in a large integrated health system who were prescribed antiglycemic, antihypertensive, or lipid-lowering medications. The authors reported that those filling prescriptions through mail-order pharmacies, based on continuous measure of medication gaps (CMG) and accounting for days supply and patient OOP costs by multivariate logistic regression, were 7.8% more adherent than those utilizing local pharmacies within the health system (Table 3).²⁷ An instrumental variable analysis yielded similar results. This should have controlled for confounding variables, such as PAB, that were not measured in the study.

Gibson et al. (2010) examined the relationship between cost-sharing and adherence, as measured by PDC, to antidiabetic medications in commercially insured patients with type 2 diabetes.²⁸ Mail-order usage was included as a control variable. The results indicated that any usage of mail-order pharmacies in the past year increased the odds of being adherent. The ORs were 2.2 for patients on oral antidiabetic medications and 2.3 for those on oral diabetic medications and/or insulin (Table 4). The analysis controlled for patient OOP costs but not for PAB or days supply.

Devine et al. (2010) found that patients aged under 65 years who switched from retail to mail-order pharmacy had 21.4 percentage point greater MPRs than patients who stayed with retail pharmacies (Table 3).²⁹ The authors calculated MPR for patients matched by propensity score to account for confounding factors such as disease severity. They controlled for PAB by comparing pre- to postchanges in adherence. However, they did not account for patients' OOP costs or days supply, the latter of which they acknowledged may lead to higher adherence.²⁹

Zhang et al. (2011) used claims data for Medicare Part D beneficiaries with diabetes to measure PDC. After propensity score matching on age, gender, disease severity, type of health plan, number of distinct medications, and duration of oral antidiabetic treatment in the prestudy period, they found that although antidiabetic medication adherence was low in both mail-order and retail pharmacies, patients who filled prescriptions at mail-order pharmacies had 7% higher adherence than those who filled at retail pharmacies (Table 3).³⁰ Zhang et al. did not control for days supply, patients' OOP costs, or PAB.

Khandelwal et al. (2011) reported a statistically significant difference in medication adherence for patients taking antidiabetics, where patients using the mail-order channel had higher adherence by 2.9 percentage points (Table 3).¹⁵ Of note, this study examined a number of therapeutic drug classes, and the antidiabetic drug class was the only one to have higher adherence in the mail-order group.

Sharma et al. (2012) measured PDC in a population of privately insured patients taking antidiabetic medications, including insulin. The authors used linear regression to control for patient demographics including age, gender, and race, as well as copays, education, and median household income. The analysis did not control for days supply or PAB. The authors reported that patients using mail-order had higher adherence by 8.6 percentage points (Table 3).³¹

Curkendall et al. (2013) measured PDC in commercially insured or Medicare patients taking noninsulin antidiabetics while accounting for patient factors including age, OOP costs, and region using a multivariate logistic regression. They did not control for days supply or PAB. Patients were assigned to adherent versus nonadherent cohorts based on $PDC \geq 0.8$. Results indicated that “patients [who] fill their prescriptions by mail-order were 60 percent more likely to be adherent than those who did not” (Table 4).³²

Kirkman et al. (2015) similarly assigned patients to adherent or nonadherent cohorts in a 2015 study. Adherence was determined by MPR for patients taking antidiabetics and enrolled in an MCO. The analysis controlled for age, gender, geographic region, OOP costs, disease burden, income, and education but not days supply or PAB using multivariate regression analysis. This study determined that patients who used mail-order pharmacies had higher adherence ($OR = 2.09$; Table 4).³³ Both Iyengar studies also examined patients with diabetes and found that patients using mail-order had higher adherence (Table 4).^{23,24}

Other Diseases

In addition to the disease states described above, Khandelwal et al. found no statistically significant differences in adherence between mail-order and retail pharmacies in patients using antidepressants, beta blockers, or thyroid agents.¹⁵ Khandelwal et al. also combined data for all disease states and determined that, overall, patients who use mail-order pharmacies have a statistically significant 1% higher MPR value of 77.0% as opposed to 76% for retail pharmacies with 90-day supplies.

Discussion

The existing research indicates that patients who use mail-order pharmacies have higher adherence than those using retail pharmacies. Of the 15 studies we examined, 14 found higher adherence at mail pharmacies, while the remaining study found equal adherence between channels. Further, most studies found substantial adherence differences between mail and retail pharmacies. The smallest statistically significant differences were an OR of 1.11,^{11,23} a 3 percentage point difference in number of adherent patients (MPR or $PDC > 0.80$),²³ and an MPR difference of 7.0 percentage points.³⁰ The largest differences were an OR of 2.3,^{3,28} a 12.0 percentage point difference in number of adherent patients,²⁰ and an MPR difference of 22.7 percentage points.²⁰

The research does not provide as conclusive an explanation for why mail-order patients have higher adherence. The difference may be due to some inherent advantage of mail-order pharmacies such as greater convenience or privacy or it may be due to confounding factors that are related to both use of mail-order and adherence. It is as important to know why mail-order has an adherence advantage as to know that it does. If usage of mail-order pharmacies leads to better adherence because of some factor unique to this channel, then health plans and Medicare policy should support efforts to encourage patients to use mail-order. However, if mail-order pharmacies are associated with higher adherence because of confounding factors, such as days supply, then efforts should be directed at equalizing these factors between the channels.

Three factors have been frequently suggested as confounders: days supply, PAB, and lower mail-order copays. Patients who get 90-day supplies rather than 30-day supplies, those who were more adherent in the prestudy period, and those who have lower copays have been shown to be more adherent.^{23,24,28,33,34} Iyengar's 2 studies document the importance of PAB.^{23,24} In these studies, the ORs associated with PAB and adherence ranged from 4.5 to 9.5 across 3 drug classes. These ORs were much higher than those of any other factor in the model. By comparison, the ORs for mail versus retail dispensing channel ranged from 1.11 to 1.29. Most of the studies we reviewed did not control for these confounders. In fact, many attributed mail-order's adherence advantage to greater days supply or lower patient cost-sharing.

Four studies controlled for all 3 confounders.^{23,24,26,27} All 4 found higher adherence in mail-order pharmacy users. However, the magnitude of the differences between mail and retail pharmacy users was smaller. ORs in these studies ranged from 1.11²³ to 1.29²⁴ versus 1.60³² to 2.09³³ in the studies not controlling for PAB, OOP, and days supply. Differences in percentages of adherent patients ranged from 3.2²³ to 10.8³⁴ in the studies that controlled for these confounders compared with 6.9³⁰ to 12.0²⁰ in the studies that did not. This indicates that part of the difference in adherence between channels may be due to mail-order pharmacies attracting patients who are more likely to be adherent, providing greater days supply, and having lower copays.

There are other reasons to question the conclusion that mail-order pharmacies have an inherent adherence advantage over retail pharmacies. Studies varied considerably in how they defined use of a mail-order pharmacy. At one extreme, Khandelwal and White studies required that patients get all study medications from a mail-order pharmacy to be considered mail-order users.^{15,25} At the other extreme, Schmittiel required only that patients use mail-order at least once during the study period.³⁴ The article does not indicate how many patients used mail-order pharmacies exclusively and how many used mail-order only once or twice.

If there were an inherent characteristic of mail-order pharmacies that led to greater adherence, we would expect that greater use of mail-order pharmacies would be associated with higher adherence. Iyengar's studies provide the best test of this hypothesis. These studies divided patients into 3 groups: those using mail for 66.7% or more of their study prescriptions were classified as mail-order users, those using retail for 66.7% or more of their medications were classified as retail users, and those not in either of those categories were classified as mixed-channel users.^{23,24} If mail had an inherent advantage, then mail users should have greater adherence than mixed-channel users who, in turn, should have greater adherence than retail users. In fact, Iyengar's studies indicated that mail-order users had greater adherence than retail users but that retail users had greater adherence than mixed-channel users.

In most studies, there were large differences in baseline characteristics between the mail and retail populations. As shown in Table 2, patients in the mail-order samples had substantially higher PAB and lower numbers with Medicare low-income subsidy, were more likely to receive financial incentives to use mail-order pharmacies, and had lower disease burden. All of these are confounding factors that would result in higher adherence in the mail-order group.

While most studies attempted to statistically control for differences between their retail and mail samples, it is useful to consider Schmittiel's comment that "observational studies... cannot entirely control for differences between patients who utilize mail-order pharmacy services and those that do not."²⁶

Two of the 4 studies that controlled for PAB, OOP, and days supply were conducted in the Kaiser Permanente integrated health care system.^{27,34} Patients in this system must use either Kaiser mail-order pharmacies or Kaiser outpatient pharmacies. The latter are located in Kaiser clinics. It seems likely that there are fewer Kaiser outpatient pharmacies than retail pharmacies that are located conveniently to Kaiser members. This may provide Kaiser members with an incentive to use mail-order pharmacies that would not exist for patients with access to traditional retail pharmacies.

The sponsorship and authors' employment for most of the studies raises the question of potential bias. Of the 15 articles reviewed, 1 was sponsored by a retail pharmacy chain; 9 were sponsored by or authored by employees of PBMs with a mail-order pharmacy; 3 were conducted in an integrated delivery system that owned a mail-order pharmacy; and 1 each was funded by the American Diabetes Association, a pharmaceutical company, and the Centers for Disease Control and Prevention. In reviewing the studies, however, the authors found no instances of bias.

Limitations

The vast majority of studies we reviewed used claims data to measure adherence and measured adherence as PDC, MPR, or CMG. These measures account for the days in which the patient had a "pill in hand" but do not necessarily reflect a "pill taken." As a result, they may overestimate adherence. However, this may have had minimal impact on the results of this review because the overestimation would have applied to both mail and retail pharmacies in the reviewed studies.

Of the 15 studies in this review, 2 specifically stated that they excluded auto-refill prescriptions,^{24,34} and 1 stated in a response to a letter to the editor that auto-refill prescriptions were not available at the time of the study.^{11,27} Of the remaining studies, 2 stated that they did not know how many of the prescriptions in their sample were auto-refills^{14,35} and the rest made no mention of auto-refill. As discussed earlier, auto-refill prescriptions may artificially inflate adherence estimates based on claims data. The effect of this limitation on the results of the review and on the individual studies depends on the extent to which one channel has a higher proportion of auto-refill prescriptions than the other. Because both mail and retail pharmacies offer auto-refill programs, and because the proportion of patients who select these programs probably varies from plan to plan, it is not possible to predict which channel would have more auto-refill prescriptions.

The definition of mail-order usage varied widely across studies, there were major differences in the baseline attributes of mail and retail users, and most studies did not control for potential confounders. This made comparing results across studies difficult.

All but 1 of the studies measured adherence as either PDC, MPR, or CMG. The descriptions of how these measures were calculated in the published articles do not make it clear how the measures differ. Articles basically described both PDC and MPR as number of days for which medication was available in a time period divided by the number of days in the period. CMG differed only in that it was the proportion of days medication was not available. That is, CMG was essentially defined as 100%–PDC%.

Two studies measured adherence to asthma medications that did or may have included inhalers.^{14,35} Claims data-based measures of adherence to inhalers may be less accurate than measures of adherence to tablets and capsules because many patients do not use inhalers correctly. This can cause patients to stop using their inhalers because they feel they are not working or to overuse inhalers to make up for the fact that they are not getting symptom relief.

This review may be subject to publication bias. The studies that were sponsored by organizations that could be perceived to have an obvious bias (e.g., retail chains, PBMs and integrated health delivery systems that owned mail-order pharmacies) reported results that supported the sponsors' interests. This

suggests that studies that did not support the sponsors' interests may not have been published. Further, this review only considered peer-reviewed journal articles. It did not include posters, published abstracts, or commercial reports. This probably increased the quality of the literature reviewed, but decreased the scope of the research evaluated.

Conclusions

The existing research provides strong evidence that patients who use mail-order pharmacies are more adherent than those who use retail pharmacies. At least part of the reason for the difference appears to be selection bias. Study patients who used mail-order pharmacies tended to have higher socioeconomic status and days supply of medicines received. In addition, in most cases, patients were offered financial incentives to use mail-order pharmacies, and, in the 2 studies that measured it, patients in the mail-order group had substantially higher PAB.^{23,24} Several studies attributed the mail-order adherence advantage to one or more of these factors. However, not all of the mail-order advantage appeared to be due to these factors: the few studies that statistically controlled for differences in these factors also found that patients using mail-order pharmacies were more adherent, although the differences between mail and retail users were smaller.^{23,24,26,27}

The extent to which these results indicate an inherent adherence advantage of mail-order pharmacies (as distinct from adherence benefits due to greater days supply, lower copays, or more adherent patients selecting mail-order pharmacies) depends on how well the statistical controls adjusted for the differences between the mail and retail samples. These differences, differing definitions of mail-order usage, and the fact that patients with substantial use of both retail and mail-order settings had lower adherence than those using primarily retail pharmacies provide some reasons to doubt that mail-order pharmacy offers an inherent adherence advantage. While the current research indicates that use of mail-order pharmacies is associated with higher adherence, more research is needed before it can be conclusively determined that use of mail pharmacies causes higher adherence.

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DISCLOSURES

No outside funding supported this study. Fernandez was partially funded by a Virginia Commonwealth University School of Pharmacy PharmD/PhD Summer Fellowship for work on this project. The authors declare no other potential conflicts of interest.

Study concept and design were contributed by Carroll and Fernandez. Fernandez took the lead in data collection, along with Carroll and McDaniel, and data interpretation was performed by Carroll and Fernandez. The manuscript was written and revised by Carroll and Fernandez, with assistance from McDaniel.

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