Patient Adherence with HMG Reductase Inhibitor Therapy among Users of Two Types of Prescription Services

by T. Jeffrey White, Pharm.D., M.S., Eunice Chang, Ph.D., Scott Leslie, M.P.H., Alex Gilderman, Pharm.D., David M. Berenbeim, M.D., M.B.A., F.A.C.P., Christopher M. Dezii, R.N., M.B.A., and Caron Melikian, R.N., M.S.N.

OBJECTIVE: The primary objective of this study was to compare patient adherence with HMG reductase inhibitor drug therapy (HMG) between two types of prescription service: mail-service pharmacy and community pharmacies.

METHODS: This study was a retrospective database analysis of pharmacy and medical claims for 14,826 commercial (40.9%) and Medicare+Choice (59.1%) members of a large HMO in California who were newly started on HMG therapy during the identification period, continuously enrolled during the review period (defined as each member's 6-month pre-index period through 360 days of follow-up), and between 18 and 75 years of age. Members who exclusively used only the mail-service pharmacy for HMG prescriptions were compared to members who used only community pharmacies for HMG prescriptions. The main outcome measures were adherence, medication possession ratio (MPR), persistence, prescription count, and duration of therapy.

RESULTS: All outcome measures were significantly greater for the mail-service cohort than for the community pharmacy cohort ($p<0.0001$).

CONCLUSION: This analysis suggests that patients who use mail-service systems to fill prescriptions exhibit a higher degree of adherence with HMG therapy compared to those who use community pharmacies.

KEYWORDS: Dyslipidemia, HMG therapy, compliance, adherence, managed care, prescription mail service, mail-service pharmacy, community pharmacies.

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Authors

T. JEFFREY WHITE, Pharm.D., M.S. is Principal Investigator Manager, Pharmacoeconomics & Health Outcomes Research, Prescription Solutions, Costa Mesa, California. EUNICE CHANG, Ph.D., is Associate Manager, Biostatistics, Prescription Solutions. SCOTT LESLIE, M.P.H., is Senior Health Data Analyst, Prescription Solutions. ALEX GILDERMAN, Pharm.D., is Director of Clinical Services, Prescription Solutions. DAVID M. BERENBEIM, M.D., M.B.A., F.A.C.P., is Vice President and Medical Director, Prescription Solutions. CHRISTOPHER M. DEZII, R.N., M.B.A., is Associate Director, Clinical Analysis and Adherence, Bristol-Myers Squibb, Plainsboro, New Jersey. CARON MELIKIAN, R.N., M.S.N., is Senior Principal Research Analyst, Prescription Solutions.

AUTHOR CORRESPONDENCE: Sheri Hopson, M.P.A., Project Manager, Prescription Solutions, 3515 Harbor Boulevard, Costa Mesa, California 92626 Tel: (714) 825-6820; Fax: (714) 825-3898; E-mail: Sheri.Hopson@rxsol.com

Medication noncompliance is recognized as a complex problem that is a significant cause of preventable relapse, disease progression, and morbidity. Failure to adhere to medication instructions has been associated with increased hospital and nursing home admissions, loss of productivity, premature deaths, and increased treatment costs.[1] In chronic disease conditions such as dyslipidemia, long-term adherence to lipid-lowering medication therapy is of particular importance. Several published studies have reported the frequency of discontinuation and/or percentage of adherence with lipid-lowering drug therapy. Schectman[2] et al. report that among patients attending a Veterans Administration medical clinic during the period 1988 to 1991, the frequency of lipid-lowering drug discontinuation and percentage of nonadherence with lovastatin was 2% compared to 37% with the bile acid sequestrants. In this same medical center, patients attending clinic during the period 1988 to 1994 reported the frequency of discontinuation was 4% with statins, 52% with niacin, 61% with gemfibrozil, and 65% with the bile acid sequestrants.[3]

Patients attending a military medical-center cardiology clinic reported discontinuation or non-adherence rates of between 13% to 37% for lipid-lowering drugs. The same investigators reported percentages of patients discontinuing therapy as high as 50% for lovastatin in a civilian population.[4,5] Andrade[6] and associates, using computerized HMO pharmacy files and medical charts of 2,369 new users of lipid-lowering agents, estimated the one-year probability of discontinuation of lipid-lowering drugs at two HMOs to be 38% for all drugs combined.

Evidence indicates that treatment with lipid-lowering drugs to decrease low-density lipoprotein cholesterol reduces the incidence of coronary heart disease, estimated to cost $111 billion dollars annually in the United States.[7,8] Based on guidelines from the Adult Panel of the National Cholesterol Education Program (NCEP), an estimated 36 million of U.S. adults require drug therapy to reach the proposed low-density lipoprotein level goals.[9] Due to the prevalence of dyslipidemia, difficulty in achieving NCEP proposed lipoprotein goals and documented poor adherence to lipid lowering ther-

apy, there is a need to explore methods which may improve medication adherence. A recent study found greater adherence to HMG therapy among patients that utilized mail service to fill prescriptions.[10] More research is needed to determine if mail-service pharmacy utilization is associated with improved medication adherence. This study utilized various techniques to examine medication adherence and persistence. Medication adherence was measured by the total number of days for which a patient possessed medication as prescribed during the study timeframe. Persistence was measured by the duration, in days, of continuous therapy during the study timeframe.

Objectives

The primary objective of this study was to examine the relationship between patient adherence with HMG reductase inhibitor therapy and type of prescription service used—mail service compared to community pharmacies. The researchers hypothesized that patients receiving their prescriptions through mail service have a greater adherence rate and medication possession ratio than those receiving prescriptions through community pharmacies.

Methods

This was a retrospective database analysis using pharmacy and medical claims from a pharmacy benefit and medical management company serving a large managed care organization in California that provides health care coverage for approximately 1.9 million members. Members were included in the analysis if they were newly started on HMG therapy during the Identification Period between January 1, 1998, and December 31, 1998, continuously enrolled in the health plan during the entire study period (defined as each member's 6-month pre-index period through 360 days of follow-up) and between 18 and 75 years of age. All patients on all HMG therapies were included in this study. A washout period of 6 months prior to the Identification Period was used to identify newly started patients. The date of first HMG prescription was marked as the index date from which each patient was followed for up to 360 days during the Follow-up Period.

Two types of prescription services used to obtain HMG prescriptions were compared in this study. Members who exclusively filled all of their prescriptions during the Follow-up Period through the mail service were assigned to the mail service cohort. Members who utilized only community pharmacies during the Follow-up Period to fill all their HMG prescriptions were assigned to the community pharmacy cohort. Members were excluded from the study if they utilized a combination of mail service and community pharmacies for their HMG therapy. We also determined if patients had met their drug benefit maximum. In this health plan, a maximum drug benefit existed for some within the Medicare+Choice population. The maximum drug benefit varied by county, and not all counties had a maximum limit for prescription drugs. Of the counties with a maximum drug benefit, the dollar amount of the maximum ranged from $500 to $1,600 per year. Approximately 37.7% of the Medicare+Choice beneficiaries had an unlimited annual maximum, 3.2% had an annual maximum benefit of $500, 21.8% had $1,000, 10.9% had $1,500, and 26.4% had a $1,600 annual maximum benefit. An example of the impact of a maximum benefit follows. If a patient has a maximum benefit of $1,500 and is taking a Proton Pump Inhibitor (PPI), an HMG, and a Metered Dose Inhaler (MDI), he may reach his maximum benefit 6 months after treatment. This patient may elect to: (1) ration medications or selectively refill prescriptions; (2) pay out-of-pocket for medications; or (3) stop taking medications. Therefore, if a patient was taking a more expensive HMG, he may have reached his maximum benefit early during the year compared to a patient prescribed a less expensive HMG. Of the community pharmacy cohort, 0.18% (n=26) reached their maximum drug benefit and 0.01% (n=2) of the mail-service cohort did. It was determined that these patients would not have significant impact on study outcomes and therefore they were not excluded from the final study cohorts.

Outcome measures evaluated in this study include adherence, medication possession ratio (MPR), persistence, prescription count, and duration of therapy.

Adherence: For each study participant the adherence rate for drug therapy was defined as the total number of covered days (days for which the patient possessed medication) during the study period divided by the total days in the study period (360 days).

Medication possession ratio (MPR): MPR was a proxy measure of patient adherence and was defined as the sum of the days supply for all prescription fills divided by the number of days of therapy between the first prescription fill and last fill, plus the days supply for the last prescription fill. In the event that this calculation resulted in an MPR that was greater than 1.0, the MPR value was reduced to 1.0.

Persistence of therapy[11]: A patient was deemed persistent if they refilled a prescription within 60 days from the end of days supply of the previous prescription. However, each patient was credited only for the actual days of supply from the last prescription when determining the end of persistent therapy. For example, if a patient had a 30-day supply prescription at index date and refilled it 89 days from the index date with another 30-day supply, this patient would be persistent for 119 days. However, if the same patient had a 30-day supply prescription at index and refilled it 91 days post index, she would be counted as persistent for 30 days only. Survival analysis was performed to compare persistence between the two cohorts, where persistence was measured as time to HMG discontinuation.

Prescription count: In order to calculate the total number of prescriptions filled, a weighted category was created using the days supply. A days supply of less than or equal to 30 represented one prescription, 31 to 60 represented two prescriptions, and greater than or equal to 61 represented three prescriptions.

Duration of therapy: Determined as the length of time between

TABLE 1 Study Population Characteristics

		Cohort			
		Community (n=13,254)	Mail service (n=1,572)	Total (n=14,826)	P-value
Age	Mean	61.4	68.0	62.1	<0.0001
	s.d.	11.4	6.6	11.2	
Gender					
Male	%	51.8	46.8	51.2	0.0002
Female	%	48.2	53.2	48.8	
Chronic Disease Score	Mean	4.57	5.34	4.65	<0.0001
	s.d.	3.07	2.87	3.06	
Type of Insurance					
Medicare+Choice	%	55.8	87.0	59.1	<0.0001
Commercial	%	44.2	13.0	40.9	

TABLE 2 Outcome Measures (Unadjusted Means)

		Cohort			
		Community (n=13,254)	Mail service (n=1,572)	Total (n=14,826)	P-value
Adherence	Mean	0.57	0.81	0.60	<0.0001
	s.d.	0.34	0.26	0.34	
Medication Possession Ratio	Mean	0.82	0.93	0.84	<0.0001
	s.d.	0.21	0.12	0.20	
Duration of Therapy (days)	Mean	260	316	266	<0.0001
	s.d.	131	89	129	
Persistence (days)	Mean	214	280	221	<0.0001
	s.d.	143	113	141	
Number of Transactions	Mean	6.46	3.72	6.17	<0.0001
	s.d.	4.08	1.35	3.98	

the date of the first fill and the date of the last fill plus the days supplied in the last fill (maximum duration of therapy was 360 days).

Data conversion and statistical analyses were performed using the SAS System, Version 8.1. Cohorts were compared by using F-tests, two sample t-tests, or chi-square tests, as appropriate. For the prescription level analysis, prescriptions were standardized by days of medication supplied. For the patient level analysis, HMG prescriptions were used to calculate adherence, MPR, duration of therapy, persistence, and number of transactions. Comorbidities and disease severity were estimated by using the Chronic Disease Score (CDS) method of Von Koreff[12] et al., and the CDS was based on all prescriptions received in the Follow-up Period. Adherence and MPR were measured for an abbreviated treatment interval, rather than the entire Follow-up Period, where the first 90 days supply were deleted for each patient. Excluding the *first three* fills with the traditional community system and the *first* fill of HMG medications with the mail system (both equivalent to a 90-day supply) was believed to yield a better comparison of the two cohorts. Truncating the treatment interval may minimize a potential adherence bias whereby patients that are generally more compliant may be inclined to utilize mail service to obtain their prescription medications. These HMG prescriptions were therefore not counted toward assessment of patients' adherence. Adherence and MPR were calculated using this truncated treatment interval and compared to the initial adherence and MPR measures. To control for the possible confounding factors of age, gender, and patient comorbidity, analysis of covariance (ANCOVA) was conducted to compare adherence, MPR, duration of therapy, and persistence between the mail-service and community pharmacy cohorts. Adjusted means (least squares means) and 95% confidence intervals were calculated under the assumption that the distribution of each covariate was similar to the overall distribution across the two groups.

Results

Study Population Characteristics

The demographic characteristics of all patients who met the inclusion criteria are shown in Table 1. There were 14,826 patients included in the study. Among the identified patients, 13,254 (89.4%) utilized community pharmacies to receive their HMG therapy and 1,572 (10.6%) utilized the mail-service pharmacy. Overall, the majority of patients were male (51.2%), with a mean age of 62.1 years and mean CDS of 4.65. While 40.9% of the patients had commercial insurance, 59.1% of patients had Medicare+Choice coverage.

As noted in Table 1, patients in the mail-service cohort were older than patients in the community pharmacy cohort by more than six years (68.0 +/- 6.6 vs. 61.4 +/- 11.4, p<0.0001). There was also a significantly higher proportion of females in the mail-service cohort than in the community pharmacy cohort (53.2% vs. 48.2%, p=0.0002) and the majority of patients in the mail-service cohort were Medicare+Choice members (87.0% vs. 55.8%, p<0.0001). In addition, patients in the mail-service cohort showed a significantly higher CDS when compared to patients in the community pharmacy cohort (5.34 +/- 2.87 vs. 4.57 +/- 3.07, p<0.0001).

Outcome Measures (Unadjusted Means)

All outcome measures were significantly greater for the mail-service cohort than the community pharmacy cohort (p<0.0001) (see Table 2). Survival analysis showed a statistically significant differ-

ence in persistence between the two cohorts (p<0.0001)(see Figure 1). The survival curves appear parallel after approximately 150 days showing that the mail-service cohort continues to maintain higher persistence throughout the remaining study time period. The number of transactions was significantly less for patients in the mail-service group, as would be expected since they received 90-day supplies, when compared to the community pharmacy cohort (3.72 +/- 1.35 vs. 6.46 +/- 4.08, p<0.0001) (see Table 2). The truncated adherence and medication possession ratio, which excluded the first supply, were higher in the mail-service cohort when compared to the community pharmacy cohort (p<0.0001) (see Table 3).

Analysis of Covariance to Adjust for Baseline Differences

To compare outcome measures, analysis of covariance (ANCOVA) was conducted to control for significant baseline characteristic differences between the mail-service and community pharmacy cohorts (see Table 4, next page). The covariates included in the model were age group, gender, and CDS. Results of the adjusted analysis showed that patients in the mail-service cohort continued to show higher adherence, MPR, duration of therapy, and persistence when compared to patients in the community pharmacy cohort (see Table 5, next page).

Discussion

Adjusted outcome measures revealed that patients from the mail-service group had higher adherence, MPR, duration of therapy, and persistence when compared to patients in the community pharmacy cohort although patients were older and had more illnesses (per Chronic Disease Score). This finding was somewhat surprising since older patients and those taking multiple therapies for different conditions may tend to be less compliant with their medications. Adherence in elderly patients may be of particular concern because of increased susceptibility to adverse drug reactions; differential response to side effects; deficits in physical dexterity, cognitive skills, and memory; and the larger number of medications prescribed.[13-15] The higher adherence observed in the mail-service cohort in this study may be attributable to the greater convenience of mail service for filling prescriptions. This convenient process of refilling HMG drug therapy may remove barriers to reordering and may contribute to and enhance patient adherence with their chronic medications, especially if they have multiple therapies for different conditions. Mail service allows patients to refill prescriptions without relying on transportation or physically being at a community pharmacy to pick up the medications. An argument could be made that elderly patients or those on multiple medications would particularly benefit from the convenience of mail service.

After truncating the treatment interval, the differences between the two cohorts decreased, but the mail-service cohort continued to demonstrate greater adherence and MPR rates. Further investigation may be required to determine if patients who are generally more compliant are those who would utilize a mail service to refill prescriptions, thus resulting in greater adherence patterns.

Since the standard number of days supply is 90 days with the mail service compared to 30 days with the traditional community service, it was also not surprising that the duration of therapy and persistence were higher in patients with the mail-service group versus the traditional service group. Again, for a chronic medication such as HMG therapy, providing a 90-day supply was appropriate and minimized patients' effort to have to refill their medication every 30 days. Further research is needed to investigate the

FIGURE 1 Survival Curves Persistence for Mail Service and Community Pharmacy Cohorts

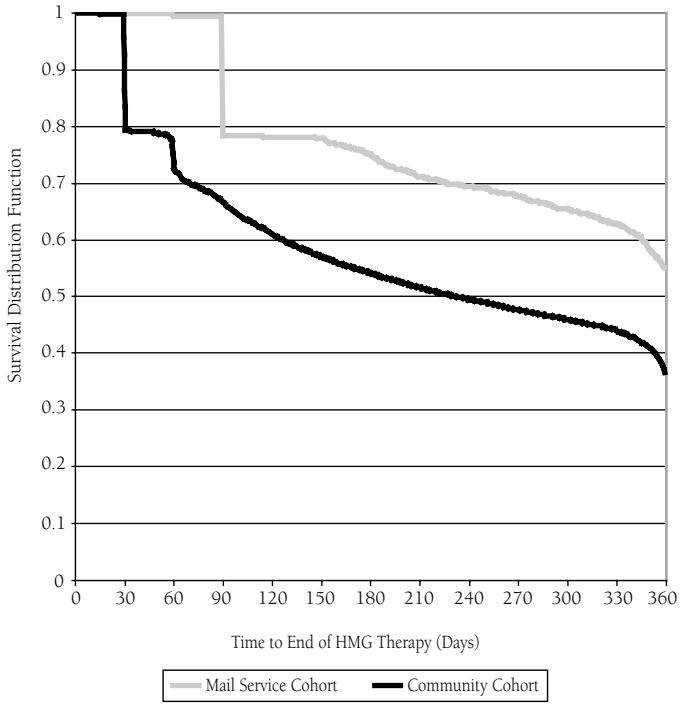

TABLE 3 Adherence and MPR within Truncated Treatment Interval[a]

		Cohort			
		Community (n=8,973)	Mail service (n=1,398)	Total (n=10,371)	P-value
Adherence	Mean	0.81	0.92	0.82	<0.0001
	s.d.	0.25	0.17	0.25	
Medication Possession Ratio	Mean	0.88	0.95	0.89	<0.0001
	s.d.	0.15	0.08	0.14	

[a]*Treatment interval truncated by removing the first prescription for the mail-service cohort and the first three prescriptions for the community cohort.*

TABLE 4 Parameter Estimates from ANCOVA

	OUTCOME VARIABLE							
	ADHERENCE		MPR		DURATION		PERSISTENCE	
	Estimate	Pr > |t|	Estimate	Pr > |t|	Estimate	Pr > |t|	Estimate	Pr > |t|
Parameter								
Intercept	0.520	<0.0001	0.820	<0.0001	243.620	<0.0001	193.727	<0.0001
age 18-64	-0.011	0.4191	-0.003	0.6768	-4.634	0.3649	2.241	0.6899
age 65-69	0.011	0.5028	0.006	0.5317	1.241	0.8410	8.171	0.2293
gender F	-0.018	0.0585	-0.009	0.1223	-4.336	0.2364	-6.869	0.0877
CDS[1]	0.013	<0.0001	0.002	0.0142	4.178	<0.0001	4.696	<0.0001
Age*gender 18-64 F	-0.027	0.0309	0.004	0.6105	-10.125	0.0386	-12.343	0.0217
Age*gender 65-69 F	-0.011	0.4453	0.008	0.3723	-6.281	0.2616	-6.617	0.2817
CDS*age 18-64	0.004	0.0302	-0.001	0.4665	2.023	0.0111	1.467	0.0937
CDS*age 65-69	-0.001	0.5882	-0.001	0.3450	0.124	0.8927	-0.882	0.3835
cohort: mail service	0.227	<0.0001	0.100	<0.0001	52.334	<0.0001	64.048	<0.0001

Referent Groups: Age group = 70-75; Gender = Male; Cohort = Community; [1]CDS = Chronic disease score

TABLE 5 Outcome Measures (Adjusted Means)

		Lower 95% CI	MEAN	Upper 95% CI
OUTCOME VARIABLE	COHORT			
Adherence	**Mail service**	0.784	0.800	0.816
	Community	0.568	0.574	0.579
MPR	**Mail service**	0.915	0.926	0.936
	Community	0.822	0.825	0.829
Duration (days)	**Mail service**	307	313	320
	Community	259	261	263
Persistence (days)	**Mail service**	271	278	285
	Community	212	214	217

CI = Confidence Interval

impact of a 90-day supply of HMG therapy dispensed in the community pharmacy setting.

While the methodology utilized for this study differs from the methodology utilized in a previous study examining mail-service use among various medication classes, certain results corroborate our findings.[10] Mail service was utilized more frequently by females and those of more advanced age. Medications used to treat chronic conditions, for example HMGs, were more likely to be filled through mail service and showed greater adherence.

As with all studies, limitations exist that may have influenced the findings. While most prescription claims are available within 45 days of submission, we could not be certain all claims were captured. Additionally, patients may have paid for prescription drugs out of pocket, and therefore no claim would have been generated and captured in the database. We also cannot assume that although patients' prescription claims were submitted, and therefore represent apparent use of HMG therapy, the patient actually consumed the medication at all or consumed the medication as prescribed. Additionally, the association between adherence, medication possession ratio, persistence and duration of therapy as process measures may not necessarily result in improved clinical outcomes.

This pharmacy benefit management company offered a financial incentive that may have drawn patients to mail service. There were 14 specific drug copay plans among the patients of this study. The most common copay plan at the time of this study for both the commercial population and the Medicare+Choice population was a $5 generic copay and $10 brand copay for a 30-day supply at a community pharmacy and a $10 generic and $20 brand copay for brand for 90-day supply from mail service. We did not measure the extent to which financial incentives in copay differences affected utilization. Moreover, it is possible that patients who elect to fill prescriptions through mail service possess different characteristics than patients who elect to fill prescriptions at community pharmacies.

Patients were eligible for this study if they were newly treated with HMG therapy; however, this may have influenced the study findings. It was not determined if patients who were newly treated with HMG therapy were previously using mail service to obtain their other medications or if patients started using mail service at the point when HMG therapy was initiated. Finally, we did not determine if patients experienced negative side effects or adverse

events leading to their discontinuation of HMG therapy, since medical record review was not performed.

Conclusion

In this managed care population, through retrospective database analysis, patients who used mail service to fill HMG prescriptions exhibited a higher degree of adherence compared to those who used community pharmacies. Even after adjusting for potential confounding factors such as age, gender, and chronic disease score (CDS), patients utilizing mail service to receive their HMG therapy continued to show greater adherence, MPR, duration of therapy, and persistence when compared to patients utilizing community pharmacies. More research must be conducted to further explore the relative impact of mail service on medication adherence versus the relative contribution of a 90-day supply compared to a 30-day supply limit for medications for chronic conditions.

DISCLOSURES

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