Association of Out-of-Pocket Pharmacy Costs with Adherence to Varenicline

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ABSTRACT

BACKGROUND: Varenicline, a nicotinic acetylcholine receptor partial agonist, is a pharmacotherapy indicated for smoking cessation treatment. To date, no research has examined the relationship between out-of-pocket (OOP) expense and varenicline adherence among Medicare beneficiaries.

OBJECTIVES: To (a) characterize medication utilization patterns of varenicline among Medicare members newly initiated on varenicline and (b) examine the relationship between member OOP expense and varenicline medication adherence.

METHODS: In this retrospective cohort study, pharmacy claims data were used to identify Medicare Advantage Prescription Drug Plan (MAPD) members newly initiated on varenicline. Demographic and clinical characteristics, varenicline medication utilization patterns, and pharmacy costs (total and varenicline-specific) were determined for members included in the study. Varenicline adherence was measured by calculating the proportion of days covered (PDC) over a period of 84 days (12 weeks) after initiation. Multiple regression analysis was used to examine the relationship between varenicline OOP cost and varenicline medication utilization, while controlling for sociodemographic characteristics, clinical factors, and nonvarenicline pharmacy costs.

RESULTS: A total of 15,452 MAPD members were included in the analysis. Mean (SD) subject age was 62.6 (10.0) years; 21.1% (n = 3,256) were dual eligible; and 33.0% (n = 5,106) received a low-income subsidy. Mean (SD) initial varenicline treatment episode duration was 50.8 (37.8) days, with a mean (SD) varenicline days' supply of 47.8 (32.6) obtained by members during the initial treatment episode. Mean (SD) PDC was 0.51 (0.24), and 14.9% (n = 2,302) of members were classified as adherent to treatment (PDC ≥ 0.80). Greater varenicline OOP expense was significantly associated with lower PDC (regression coefficient = -0.058, $P < 0.001$) and significantly associated with lower odds of receiving a refill for varenicline (odds ratio 0.594, 95% CI: 0.540-0.655, $P < 0.001$).

CONCLUSIONS: Among Medicare beneficiaries newly initiated on varenicline, medication adherence was suboptimal, and greater OOP cost was associated with lower adherence and lower odds of refilling varenicline.

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What is already known about this subject

- Quitting smoking has immediate health benefits, and long-term abstinence is known to reduce the risk of heart disease, stroke, lung disease, and cancer, as well as other cancers.
- Clinical trial data demonstrate that varenicline is an effective smoking cessation treatment; however, research also indicates that treatment success is strongly associated with treatment adherence.
- Among Medicare beneficiaries, cost-related nonadherence to medication treatment is common.

What this study adds

- The results from this retrospective, claims-based study indicate adherence to the minimum recommended 12-week varenicline treatment course in a "real-world" setting was generally low among Medicare Advantage Prescription Drug Plan members.
- Approximately 20% of members initiated on varenicline had 2 or more treatment episodes during the 12-month post-index observation period, with a mean time between treatment episodes of approximately 4 months.
- The findings of this analysis indicate greater out-of-pocket expense for varenicline is associated with lower adherence to varenicline treatment and with lower odds of receiving a refill for varenicline.

Quitting smoking has immediate health benefits, and long-term abstinence is known to reduce the risk of lung disease and cancer, heart disease, stroke, and other cancers.[1] According to the Center for Disease Control, 70% of U.S. smokers desire to stop smoking, and close to 45% attempt to quit yearly[2]; however, fewer than 10% actually succeed.[3]

Smoking cessation treatments include counseling and behavioral treatments, psychosocial interventions, and pharmacological treatment.[3] Pharmacological treatment options include first-line treatment interventions such as nicotine replacement therapy (NRT), bupropion, and varenicline.[3] Clinical trial data suggest that varenicline, a nicotinic receptor partial agonist, may be associated with higher rates of smoking abstinence than other first-line pharmacological interventions[4-7]; however, findings from clinical trials of varenicline also indicate that treatment success is strongly associated with treatment adherence thus amplifying the need to identify barriers to adherence.[8,9]

Among Medicare beneficiaries, cost-related nonadherence is a significant issue with over one-quarter reporting nonadherence to treatment due to costs.[10] To date, there is a dearth of research examining the relationship between out-of-pocket (OOP) expense and varenicline adherence among Medicare beneficiaries. To address this lack of information, the current study investigated the relationship between OOP expense and varenicline utilization among Medicare Advantage Prescription Drug Plan (MAPD) members.

Methods

Data Sources

Data were collected from a large national MAPD plan for the time period covering January 1, 2007, through December 31, 2010. The dataset included approximately 1.9 million active MAPD members with heavy South and Midwest geographic representation. Study data included enrollment information, medical claims, and pharmacy claims. Enrollment data were used to determine date of benefit enrollment and termination and sociodemographic characteristics including age, gender, race/ethnicity, dual eligible (DE) status, and low-income subsidy (LIS) status. Pharmacy claims data included prescription fill dates, National Drug Code numbers, quantity dispensed, days' supply, member OOP expense, and plan paid expense. Medical claims data included *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes associated with medical encounters, which were used to identify comorbid medical conditions.

Design and Study Population

This was a retrospective, noninterventional, claims-based, observational cohort study. MAPD members newly initiated on varenicline between July 1, 2007, and December 31, 2009, were identified based on prescription claims records. Members were selected from plans with a variety of pharmacy cost-sharing designs. The date of first prescription claim for varenicline was treated as the index date, and all members were required to have 6 months of pre-index continuous health plan enrollment and 12 months of post-index continuous enrollment. In order to ensure that all members represented those newly initiated on varenicline treatment, a 6-month varenicline-free pre-index period was required. Members were excluded if they were aged < 18 or > 90 years at index, or if they utilized mail order prescription services for varenicline. The study protocol was reviewed and approved by an independent institutional review board prior to execution of the study.

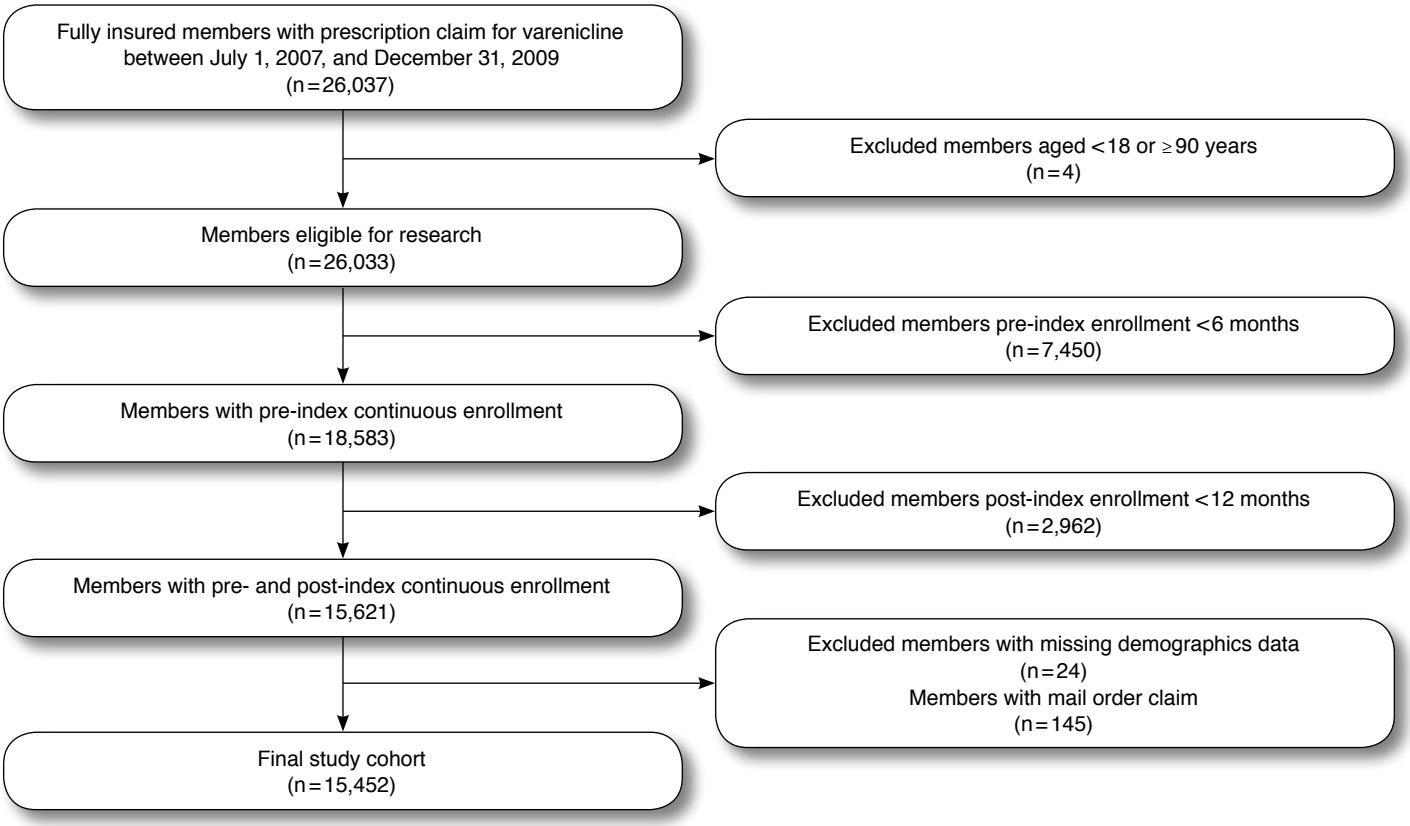
Measures

Varenicline Treatment Episode. A varenicline treatment episode was defined as the period of time between initiation and termination of varenicline use. Based on the 12-week recommended treatment period of varenicline, it is possible for a member to undergo multiple, discrete episodes of treatment during an extended period of observation. Varenicline treatment episodes were therefore classified as either an index (initial) treatment episode or a subsequent (retrial) treatment episode. The index treatment episode was identified based on the initial varenicline prescription claim observed in the pharmacy claims data for a member. All index treatment episodes were required to be preceded by a minimum of 6 months continuous enrollment during which no prescription claim for varenicline was observed. The index treatment episode was considered to be terminated once a period of 28 consecutive days with no varenicline medication available to the member had elapsed. If a member had a subsequent prescription claim for varenicline after the termination of the index treatment episode, this was considered the initiation of a subsequent treatment episode. The total duration of the index varenicline treatment episode was calculated as the number of days between the index date and the date of the last varenicline prescription obtained during the index treatment episode plus the number of days' covered by the last varenicline prescription. Number of varenicline prescription claims and refill status (whether a member had a prescription refill for varenicline or not) was measured for the index varenicline treatment episode. Based on this approach to defining treatment episodes, a member might have had multiple treatment episodes over the course of the study observation period. For descriptive purposes, the total number of treatment episodes during the overall 12-month post-index observation period was determined, and the number of days between the end of 1 treatment episode and the beginning of the next was calculated for members with 2 or more treatment episodes. Subsequent treatment episodes were not included in the analysis of medication adherence, as will be described. Use of NRT or bupropion during the pre-index period was determined based on pharmacy claims.

Proportion of Days Covered. Varenicline medication coverage during the index treatment episode was measured using the proportion of days covered (PDC),[11] which represents the proportion of the total days during a given time period that the member has medication available to consume. The observation period (denominator) for PDC was fixed at 84 days (i.e., 12 weeks) beginning at the index date; thus, the PDC is a hybrid measure that captures both adherence and persistence during the defined time frame. The observation period of 84 days was chosen to capture medication coverage over the minimum recommended varenicline treatment duration of 12 weeks.[12] Number of days covered with varenicline (numerator) was calculated based on days' supply data with adjustment for overlapping medication coverage. Medication coverage extending beyond the 84-day observation period was truncated and not included in the determination of coverage days. PDC values were dichotomized to classify individual members as adherent (≥ 0.80) or nonadherent (< 0.80) with varenicline treatment. While there is lack of consensus in the literature regarding threshold levels for adherence, 0.80 is commonly used in medication adherence research, and previous research involving varenicline has used similar adherence thresholds.[13] Furthermore, existing research has shown that taking varenicline for ≥ 80% of days during the treatment period is associated with tobacco abstinence.[8,9]

Cumulative Varenicline Gap Days. Gap days were defined as days without varenicline medication coverage during the index varenlicline treatment episode. The cumulative number of gap

FIGURE 1 Study Attrition Flowchart



days was calculated as the total number of days in the index varenicline treatment episode minus the cumulative number of days covered during the index treatment episode.

Comorbidities. Medical comorbidities were identified based on the presence of ICD-9-CM diagnostic codes during the pre-index period (see Appendix, available in online article, for code list). A RxRisk-V score, which is a prescription claims-based comorbidity index score, was also calculated for each member.[14,15] The RxRisk-V score is determined based on the identification of 45 distinct comorbid conditions via their associated treatments. Unweighted RxRisk summary scores were measured; therefore, the RxRisk-V score reflects the summary count of unique medical conditions identified via medication proxy. Three RxRisk-V categories that are defined based on claims for durable medical equipment or incontinence supplies (neurogenic bladder, ostomy, and urinary incontinence) were not included, since claims for these products are not captured in pharmacy claims (Rx-Risk-V score potential range = 0-42).

Pharmacy Expenses. Health plan members included in the current analysis were enrolled in plans with a variety of pharmacy cost-sharing designs. Cost-sharing levels may vary by the design of the plan in which they enroll. For these reasons, we analyzed the relationship between direct member OOP expense and varenicline adherence and refill status rather than the relationship between specific characteristics of cost-sharing structure (e.g., copay vs. coinsurance). This allowed us to examine the relationship between OOP expense and varenicline adherence and refill status across a variety of cost-sharing arrangments. Pharmacy expenses were determined for the first 12 weeks of the post-index treatment period in order to coincide with the period of observation used to determine PDC. Total pharmacy expenses were defined as the cumulative total expenses associated with adjudicated pharmacy claims. Pharmacy expenses were decomposed into varenicline and nonvarenicline expenses, which were further decomposed into plan-paid and member-paid components based on the cost data captured with the pharmacy claims. Varenicline OOP expense per fill quantity was defined as the cumulative member share of the total pharmacy expenses associated with varenicline claims divided by the total quantity of varenicline dispensed during the first 12 weeks post-index. All pharmacy cost calculations were adjusted to 2010 U.S. dollars using the annual medical care component of the Consumer Price Index.

TABLE 1 Demographic Characteristics for MAPD Plan Members Newly Initiated on Varenicline

Variable	Overall Cohort (N = 15,452)	
Age, mean [SD]	62.6	[10.0]
Gender, n (%)		
Male	7,092	(45.9)
Female	8,360	(54.1)
Race/ethnicity, n (%)		
White	14,158	(91.6)
Black	1,010	(6.5)
Hispanic	179	(1.2)
Other	105	(0.7)
Geographic region, n (%)		
Northeast	353	(2.3)
Midwest	3,986	(25.8)
South	9,901	(64.1)
West	1,212	(7.8)
Dual eligible, n (%)	3,256	(21.1)
Low-income subsidy, n (%)	5,106	(33.0)
RxRisk-V score, mean [SD]	4.7	[2.9]

MAPD = Medicare Advantage Prescription Drug Plan; SD = standard deviation.

Statistical Analysis

A series of multiple regression analyses were conducted to examine the relationship between varenicline OOP expense per-fill-quantity and varenicline medication utilization. A linear regression model was fitted with varenicline PDC as the dependent variable, and a logistic regression model was fitted using varenicline refill status as the dependent variable. The independent variable of interest in both models was varenicline OOP expense per fill quantity. Covariates included in both models were total nonvarenicline OOP pharmacy expenses, sociodemographic characteristics (age, gender, race/ethnicity, geographic region of residence), RxRisk-V comorbidity score, and LIS/DE status. LIS/DE status was coded as a binary variable, indicating whether members were DE or receiving LIS versus otherwise. Total nonvarenicline OOP pharmacy expenses were converted to ranks for inclusion in the regression model. Gender, race/ethnicity, and geographic region were dummy coded (gender reference group, male; race/ethnicity reference group, white; geographic region reference group, South). Using the results of the linear regression model, a PDC estimate based on OOP varenicline prescription cost was calculated for 3 hypothetical prescription price points ($25, $50, and $75). For these calculations, estimated PDC was calculated by solving the regression equation with covariates set at the values observed for the study sample (i.e., mean age, percentage female, percentage within each race/ethnicity and geographic region category, percentage LIS or DE, and mean Rx-Risk-V score).

TABLE 2 Summary of Key Study Outcome Variables

Variable	Overall Cohort (N = 15,452)	
Index treatment episode duration days, mean [SD]	50.8	[37.8]
Cumulative varenicline days' supply, mean [SD]	47.8	[32.6]
Cumulative gap days, mean [SD]	2.9	[7.8]
Proportion of days covered, mean [SD]	0.51	[0.24]
Adherence status (PDC ≥ 0.80), n (%)	2,302	(14.9)
Count of varenicline Rx claims, n (%)		
1	7,940	(51.4)
2	4,259	(27.6)
3	2,104	(13.6)
≥ 4	1,149	(7.4)

PDC = proportion of days covered; Rx = prescription; SD = standard deviation.

Sensitivity analysis was performed to examine the impact of including a status variable for pre-index bupropion use in the regression models. Sensitivity analysis was also conducted to determine the impact of including members < 65 years of age and DE/LIS members on the study findings. This analysis was conducted by excluding members aged < 65 years and by segmenting the linear regression analysis using the DE/LIS status. Statistical significance was reached when two-sided $P < 0.05$.

Results

A total of 15,452 MAPD members met the study inclusion/exclusion criteria and were included in the analytic cohort (Figure 1). Table 1 shows that among these MAPD members, 21.1% (n = 3,256) were dual eligible; 33.0% (n = 5,106) were receiving LIS; and mean (SD) RxRisk-V score was 4.7 (2.9). Common medical comorbidities included hypertension (52.6%, n = 8,123), hyperlipidemia (49.3%, n = 7,622), obstructive lung disease (40.8%, n = 6,299), diabetes mellitus (21.6%, n = 3,342), and ischemic heart disease (21.3%, n = 3,290). Common psychiatric comorbidities included mood disorder (18.2%, n = 2,817) and anxiety disorder (9.8%, n = 1,508). A pre-index prescription claim for bupropion or NRT was observed among 5.4% (n = 841) and 0.8% (n = 117) of members, respectively.

Key outcomes, including treatment episode duration, mean (standard deviation [SD]) cumulative days' supply of varenicline, mean (SD) cumulative gap days, mean (SD) PDC, and count of varenicline prescription claims during the index treatment episode, are summarized in Table 2. A total of 3,259 members (21.1%) were observed to have 2 or more discrete varenicline treatment episodes (including the index treatment episode) during the 12-month post-index observation period. Among these, 78.4% (n = 2,556) had 2 treatment,episodes, and 21.6% (n = 703) had 3 or more treatment episodes. For members with 2 or more treatment episodes, mean (SD) number of days between treatment episodes was 121.1 (77.6) days.

TABLE 3 Pharmacy Expenses for MAPD Plan Members During the 12-Week Post-index Period

	Overall Cohort (N = 15,452)		Non-LIS/DE (N = 10,310)		LIS/DE (N = 5,142)	
Cost Component, US$[a]	**Mean**	**[SD]**	**Mean**	**[SD]**	**Mean**	**[SD]**
Total pharmacy expenses	1,006	[1,424]	767	[931]	1,485	[2,002]
Total varenicline expenses	193	[96]	184	[92]	211	[102]
Total nonvarenicline expenses	813	[1,410]	583	[920]	1,274	[1,991]
OOP pharmacy expenses	201	[265]	269	[295]	64	[97]
Varenicline OOP expenses	72	[66]	101	[61]	15	[22]
Nonvarenicline OOP expenses	129	[239]	168	[277]	50	[88]
Varenicline OOP cost per fill quantity[b]	0.83	[0.60]	1.17	[0.40]	0.16	[0.24]

[a]*All costs are adjusted to 2010 US$ via the medical care component of the Consumer Price Index.*
[b]*Varenicline OOP cost per fill quantity was defined as the cumulative member share of the total pharmacy expenses associated with varenicline claims divided by the total quantity of varenicline dispensed during the first 12 weeks post-index.*
DE = dual eligible; LIS = low-income subsidy; OOP = out of pocket; SD = standard deviation; US$ = U.S. dollars.

Pharmacy expenses for members initiated on varenicline are reported for the overall cohort and for DE/LIS and non-DE/LIS members in Table 3. Mean (SD) varenicline OOP prescription cost per prescription dispensed was $44.42 ($31.86) for the overall MAPD cohort (non-LIS/DE members: $62.45 [$21.66]; LIS/DE members: $8.28 [$12.31]). The mean (SD) observed quantity dispensed was 54 (8), with a range of 1-180 tablets, with associated days' supply ranging from 1-90 days (greater than 90% of observed days' supply was 28 or 30 days). Mean (SD) varenicline OOP expense per tablet was $0.83 ($0.60) for the overall MAPD cohort, $1.17 ($0.40) for non-LIS/DE MAPD members, and $0.16 ($0.24) for LIS/DE MAPD members. The mean member varenicline cost share was 37.3% for the overall MAPD cohort, 54.9% for non-LIS/DE members, and 7.1% for LIS/DE members.

After controlling for covariates, greater varenicline OOP expense was associated with lower varenicline PDC (regression coefficient [B] = -0.058, standard error [SE] = 0.006, $P < 0.001$; Table 4). The regression coefficient associated with varenicline OOP expense indicates that, after controlling for potentially confounding variables included in the regression model, for every unit increase in dollar per fill quantity (i.e., dollar unit per tablet), the PDC by varenicline medication would decrease by 5.8 percentage points. Based on the results of the regression model, estimated PDC associated with OOP prescription costs of $25, $50, and $75 are 0.529, 0.503, and 0.477, respectively. In the multiple regression model, greater age and black race/ethnicity were also associated with lower varenicline adherence. All geographic region groups (compared with the South geographic region), greater comorbidity score, and greater nonvarenicline OOP pharmacy expenses were associated with greater varenicline adherence.

Results of the logistic regression of refill status on varenicline OOP cost and included covariates are presented in Table 5. In the multivariable logistic regression model, greater varenicline OOP cost was associated with reduced odds ratio (OR) for a prescription refill for varenicline (OR = 0.594, 95% confidence interval [CI] 0.540-0.655, $P < 0.001$). The OR associated with varenicline OOP expense indicates that, after controlling for potentially confounding variables included in the regression model, for each unit increase in dollar per fill quantity (i.e., dollar unit per tablet) the odds of observing a prescription refill for varenicline was reduced 41%. Given the quantity of a continuing pack unit (56 tablets), this can be interpreted as the ratio of the odds of observing a prescription refill associated with a $56 increase in the member prescription cost share.

Inclusion of pre-index bupropion use as a covariate in the linear and logistic regression models did not impact the direction, magnitude, or statistical significance of the relationship between OOP costs and PDC or refill status, respectively; however, pre-index bupropion use was found to have a statistically significant relationship with the outcome measure in both models (PDC, linear regression model: B = 0.032, $P < 0.001$; refill status, logistic regression model: OR = 1.357, 95% CI 1.174-1.569, $P < 0.001$). A total of 6,776 non-DE/LIS members aged ≥ 65 years were included in the subgroup analysis, and the relationship between varenicline OOP cost and PDC was similar (B = -0.049, $P < 0.001$). Likewise, among DE/LIS members aged ≥ 65 years, findings were similar in terms of statistical significance and magnitude (B = -0.060, $P = 0.007$).

Discussion

Treatment adherence is necessary to achieve desired outcomes associated with tobacco cessation and persistent smoking abstinence. The results from this retrospective, claims-based study indicate that adherence to the minimum recommended 12-week varenicline treatment course in a real-world setting was generally low. Approximately 15% of members included in the current study were adherent (PDC ≥ 0.80) to the 12-week varenicline treatment course. Furthermore, mean initial treatment episode duration was approximately 7 weeks with a mean cumulative days' supply of 47.8 days obtained during the index

TABLE 4 Regression of Varenicline PDC on Member OOP Varenicline Expense Per Fill Quantity and Included Covariates[a]

Independent Variables[b]	Estimate (SE)	*P* Value
Varenicline OOP expense per fill quantity	-0.058 (0.006)	<0.001
Total nonvarenicline OOP pharmacy expenses (ranks)	<0.001 (<0.001)	0.030
Age	-0.001 (<0.001)	<0.001
Female gender	-0.001 (0.004)	0.702
Race/ethnicity		
Black	-0.063 (0.008)	<0.001
Hispanic	-0.011 (0.018)	0.537
Other	-0.002 (0.023)	0.945
Geographic region		
Midwest	0.010 (0.005)	0.024
Northeast	0.029 (0.013)	0.026
West	0.048 (0.007)	<0.001
LIS/DE status	-0.001 (0.007)	0.871
RxRisk-V score	0.003 (0.001)	<0.001

[a]*n = 15,452; Model F = 40.82, df = 12, P < 0.001; R square = 0.031.*

[b]*Reference groups for categorical variables: reference group for gender is male; reference group for race/ethnicity is white; reference group for geographic region is South.*

LIS/DE = low-income subsidy or dual eligible; OOP = out of pocket; SE = standard error.

TABLE 5 Logistic Regression of Varenicline Refill Status on Member OOP Varenicline Expense Per Fill Quantity and Included Covariates[a]

Independent Variables[b]	Estimate (SE)	*P* Value	OR	95% CI
Varenicline OOP expense per fill quantity	-0.520 (0.049)	<0.001	0.594	0.540-0.655
Total nonvarenicline OOP pharmacy expenses (ranks)	<0.001 (<0.001)	0.384	1.000	1.00-1.00
Age	-0.011 (0.002)	<0.001	0.989	0.986-0.993
Female gender	0.039 (0.017)	0.019	1.081	1.013-1.153
Race/ethnicity				
Black	-0.238 (0.080)	0.028	0.706	0.619-0.806
Hispanic	-0.148 (0.126)	0.240	0.772	0.571-1.045
Other	0.285 (0.156)	0.075	1.180	0.798-1.743
Geographic region				
Midwest	-0.051 (0.040)	0.198	1.123	1.041-1.212
Northeast	-0.034 (0.083)	0.679	1.142	0.920-1.417
West	0.252 (0.053)	<0.001	1.521	1.345-1.719
LIS/DE status	-0.135 (0.060)	0.026	0.874	0.777-0.984
RxRisk-V score	0.026 (0.006)	<0.001	1.023	1.013-1.039

[a]*n = 15,452; LR = 445.64, df = 12, P < 0.001; c = 0.593.*

[b]*Reference groups for categorical variables: reference group for gender is male; reference group for race/ethnicity is white; reference group for geographic region is South.*

CI = confidence interval; LIS/DE = low-income subsidy or dual eligible; OOP = out of pocket; OR = odds ratio; SE = standard error.

treatment episode. In the COMPASS trial, Catz et al. (2011) found that over half of the patients (52.2%) who took ≥80% of the prescribed varenicline regimen were abstinent at the 6-month follow-up, compared with 25.4% who took less than 80% of the days prescribed.[9] Other trials have reported similar relationships between varenicline adherence and abstinence rates.[8] Days of treatment supplied was lower in the current study compared with the prospective COMPASS trial, where medication was provided to patients at no charge and coupled with a behavioral health intervention (mean days supplied: 69.4, SD = 32.2 days).[9]

These findings are concerning given that the durability of abstinence with varenicline is related to completion of the full course of treatment[16] and demonstrate the importance of minimizing potential barriers to medication adherence. Notably, in the COMPASS trial varenicline treatment was coupled with a behavioral intervention that provided subjects with smoking cessation support, and modality of behavioral intervention (telephone vs. web) was associated with differing levels of medication utilization.[9] Research examining real-world treatment adherence with varenicline is necessary in order to confirm our findings in MAPD and other populations (e.g., commercial health plan members), as well as to examine the potential benefit of behavioral health counseling and other interventions to enhance medication adherence among individuals receiving treatment with varenicline in nonclinical trial settings.

An interesting finding regarding varenicline utilization patterns was that 20% of members initiated on varenicline had a subsequent discrete treatment episode during the 12-month post-index observation period, with a mean time between treatment episodes of approximately 4 months. These cases may represent members on a variety of clinical paths that result in discontinuation and subsequent retreatment with varenicline. Within the context of a retrospective claims-based analysis, there is limited ability to determine the reason for discontinuation and subsequent retreatment with varenicline. A variety of potential explanations may explain the observed retreatment rate including early response followed by medication discontinuation and subsequent relapse, discontinuation related to adverse events and subsequent retreatment attempt, or temporary barriers to treatment persistence (e.g., financial hardship). Further investigation is warranted to better understand member characteristics and clinical factors associated with varenicline retreatment.

To our knowledge, this is the first analysis to address this relationship between OOP expenses and adherence among Medicare beneficiaries treated with varenicline. Cost-related nonadherence is a significant issue among Medicare beneficiaries. In response to cost-related concerns, individuals may skip doses, take smaller doses to prolong medication coverage, shift spending from other basic needs to cover prescription costs, or simply not fill necessary prescriptions.[10,17] Our results show that greater varenicline OOP expense is associated with lower

adherence to varenicline treatment and with lower odds of refilling varenicline after the initial prescription fill, which is in line with previous research that has examined the relationship between medication expenses and adherence across a variety of disease states and populations.[18-24]

Limitations

Administrative claims data utilized for this study included paid claims only and cannot identify the provision of medications or therapies by providers for which members did not use their pharmacy benefit. This limitation may specifically impact the pre-index smoking cessation treatment patterns that were observed, since NRT is available OOP and may not be covered by a member's pharmacy benefit. Bupropion use during the pre-index period is reported; however, bupropion has other indications (e.g., depression), and a prescription claim may not indicate treatment for smoking cessation. For these reasons, the rates of NRT and bupriopion use pre-index should be interpreted with caution; however, the use of NRT and bupropion in the current study is similar to findings from another claims-based analysis examining rates of NRT and bupropion use among individuals initiated on varenicline.[25] Also for these reasons, we did not include measures of NRT and/or bupropion use at index or during the post-index period as study measures. Inclusion of pre-index bupropion use in sensitivity models did not have a meaningful impact on the study findings in terms of the relationship between OOP cost and varenicline medication utilization; however, pre-index bupropion use was significantly associated with greater PDC and greater odds of receiving a refill of varenicline. Although the current study did not examine smoking cessation as an outcome, previous studies have shown that adjunctive treatment of bupropion with varenicline may result in improved rates of smoking cessation.[26,27] Based only on speculation, individuals on combination therapy for smoking cessation may have higher self-efficacy and motivation to quit, which in turn may be reflected in improved adherence.[28]

Finally, a substantial limitation is that administrative claims data do not allow for valid and reliable assessment of clinical outcomes associated with smoking cessation treatment (i.e., tobacco abstinence). The relationship between varenicline OOP costs and medication adherence measured by PDC was modest, and the relationship between days' coverage with medication and tobacco cessation in the real-world setting has not been established. On the other hand, the findings from the analysis of refill status indicates that increased OOP expense is associated with lower odds of refilling a varenicline prescription and may be more useful for health plan administrators.

In order for members to be included in this study, a paid prescription claim for varenicline was required. Previous research indicates that 1 in 5 adults prescribed a tobacco cessation treatment do not fill the prescription, and among patients over the age of 65, nearly 1 in 3 do not fill a tobacco cessation treatment prescription obtained from their physicians.[29] Members who may have received a prescription for varenicline from their providers but did not attempt to fill the prescription at a pharmacy could not be identified in the claims database and were not included in this study. Similarly, members with first-fill prescription abandonment (i.e., a varenicline prescription claim was adjudicated but later reversed) were not included in the study cohort. In addition, a number of psychosocial and clinical factors that may be particularly relevant to varenicline adherence and/or tobacco cessation were not available to be included in the regression models (e.g., health beliefs and attitudes, motivation to quit, previous quit attempts). While we observed a statistically significant relationship between black race/ethnicity and PDC in the multivariable regression model, the validity and generalizability of that finding may be limited in that blacks comprised only 6.5% of the members in the sample.

Finally, our analysis was designed to examine the relationship between direct varenicline OOP expenses and varenicline adherence independent of pharmacy benefit design. This study did not examine factors affecting the OOP expenses of the members included, which may include variation in MAPD pharmacy benefit designs. Plans may have different cost-sharing levels and/or formularies, and members may be exposed to the prescription drug coverage gap based on coverage type, medication utilization, and medication costs. Variability in MAPD benefit design may bias the study findings and is thus acknowledged as a limitation.

Conclusions

Treatment adherence to varenicline was generally low, and greater OOP varenicline cost was associated with lower varenicline medication adherence among MAPD members. This suggests that development of effective strategies and interventions to improve medication adherence to varenicline, including ways to reduce member OOP expense, is warranted. Furthermore, the identification of clinical and demographic factors associated with varenicline retreatment may aid in the identification of individuals at risk for treatment failure, as well as development of programs to support smoking cessation. Future research is necessary to confirm these findings in other populations (other MAPD health plans as well as non-Medicare populations). The finding related to the relationship between bupropion use and varenicline medication utilization is noteworthy, and additional research is necessary to understand the impact of concomitant medication therapies on smoking cessation and abstinence. Further research should also incorporate patient-reported outcomes, direct assessment of tobacco use, and other appropriate measures to examine the relationship between varenicline treatment adherence and smoking cessation in real-world settings.

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DISCLOSURES

This research was conceived, funded, and carried out collaboratively by Humana Inc., Pfizer Inc., and Comprehensive Health Insights, Inc. The research concept was approved by the Joint Research Governance Committee, consisting of Humana Inc. and Pfizer Inc. employees, and plans to publish results were made known prior to commencing the study. Suehs, Davis, and Patel are employees of Comprehensive Health Insights, a wholly owned subsidiary of Humana Inc., who were paid consultants to Pfizer in connection with conducting this study and the development of this manuscript. Galaznik and Zou are employees of Pfizer Inc. Joshi was a Pfizer employee at the time this study was conducted.

Study concept and design were contributed equally by all authors. Data collection was primarily the responsibility of Davis, with assistance from Suehs and Patel. Suehs, Davis, and Galaznik were primarily responsible for data interpretation, with assistance from Patel and Zou. The manuscript was written by Suehs, Davis, and Patel and revised primarily by Galaznik, Joshi, and Zou, with assistance from Suehs and Constantino.

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APPENDIX Comorbidities and Associated ICD-9-CM Diagnostic Codes

Comorbidity	ICD-9-CM Diagnosis Codes
Cancer	140.xx - 208.xx
Lung cancer	162.xx
Diabetes	250.xx
Hyperlipidemia	272.0x - 272.4x
Mood disorder	296.xx, 300.4, 311
Anxiety disorder	300.0x
Cataract	366.xx
Hypertension	401.xx - 405.xx
Ischemic heart disease	410.xx - 414.xx
Diseases of pulmonary circulation	415.xx - 417.xx
Other forms of heart disease	420.xx-427.xx; 429.xx
Heart failure	428.xx
Cerebrovascular disease	430.xx - 438.xx
Atherosclerosis	440.xx
Peripheral vascular disease	443.8x, 443.9x
Acute respiratory infection	460.xx-466.xx
Chronic pharyngitis	472.xx
Chronic sinusitis	473.xx
Chronic laryngitis	476.xx
Allergic rhinitis	477.xx
Pneumonia	480.xx - 487.xx
Any chronic obstructive pulmonary disease	490.xx - 496.xx
Chronic bronchitis	491.xx
Emphysema	492.xx
Asthma	493.xx
Ulcer	531.xx - 534.xx
Osteoporosis	733.xx

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.