RESEARCH

Association of Prescription Abandonment with Cost Share for High-Cost Specialty Pharmacy Medications

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ABSTRACT

BACKGROUND: In 2008, specialty medications accounted for 15.1% of total pharmacy benefit medication spending, and per member expenditures have increased by 11.1% annually from 2004 to 2008 within a commercially insured population of 8 million members. Insurers face increasing pressure to control specialty medication expenditures and to rely on increasing member cost share through creation of a fourth copayment tier within the incentive-based formulary pharmacy benefit system. Data are needed on the influence that member out-of-pocket (OOP) expense may have on prescription abandonment (defined as the patient never actually taking possession of the medication despite evidence of a written prescription generated by a prescriber).

OBJECTIVE: To explore the relationship between prescription abandonment and OOP expense among individuals newly initiating high-cost medication therapy with a tumor necrosis factor (TNF) blocker or multiple sclerosis (MS) biologic agent.

METHODS: This observational cross-sectional study queried a midwestern and southern U.S. database of 13,172,480 commercially insured individuals to find members with a pharmacy benefit-adjudicated claim for a TNF blocker or MS specialty medication during the period from July 2006 through June 2008. Prescription abandonment was assessed among continuously enrolled members newly initiating TNF blocker or MS therapy. Prescription abandonment was defined as reversal of the adjudicated claim with no evidence of a subsequent additional adjudicated paid claim in the ensuing 90 days. Separate analyses for MS and TNF blocker therapy were performed to assess the association between member OOP expense and abandonment rate using the Cochran-Armitage test for trend and multivariate logistic regression. Members were placed into 1 of the 7 following OOP expense groups per claim: $0-$100, $101-$150, $151-$200, $201-$250, $251-$350, $351-$500, or more than $500. The association of MS or TNF blocker abandonment rate with OOP expense was tested with logistic regression models using the $0-$100 OOP as the reference group and adjusting for age, gender, formulary status, ZIP code-level income and education, earliest specialty medication claim, and methotrexate use for the TNF blocker analysis.

RESULTS: Of 2,791 members presenting a prescription to newly initiate high-cost MS therapy, 1,985 (71.1%) of the claims were for a 1-month supply with most of the remainder for a 3-month supply; 2,303 (82.5%) had an OOP expense of $0-$100, and 5.4% had an OOP expense greater than $500. The abandonment rate increased as OOP increased (test for trend, $P<0.001$). Members with an OOP expense of $100 or less had an abandonment rate of 5.7%. Among members in all OOP expense groups greater than $200, the abandonment rate was significantly higher, with more than 1 in 4 members abandoning their MS claims ($P<0.001$). In the multivariate logistic regression analysis, the abandonment rate became significantly higher at OOP expenses of $201 to $250 compared with an OOP expense of $100 or less (odds ratio [OR] = 7.3, 95% confidence interval [CI] = 3.3-16.2). The odds ratios ranged between 6.1 and 7.3 for OOP expense groups greater than $200. Of 7,313 members presenting a prescription to newly initiate TNF blocker therapy, 5,809 (79.4%) of claims were for a 1-month supply with most of the remainder for a 3-month supply; 6,123 (83.7%) had an OOP expense of $0-$100 and 5.7% had an OOP expense greater than $500. The abandonment rate increased as OOP expense increased (test for trend, $P<0.001$). In the multivariate logistic regression analysis, the TNF blocker medication abandonment rate was significantly higher for all OOP expense groups greater than $100, with abandonment odds ratios of 2.3 to 4.4 for OOP expense between $101 and $500 compared with OOP expense of $0-$100. The odds of abandonment at OOP expense of greater than $500 were 7-fold higher (OR = 7.0, 95% CI = 5.4-9.1).

CONCLUSIONS: This is the first study to perform a focused assessment of an association between specialty medication OOP expense and new therapy prescription abandonment. The study found that per claim OOP expenses greater than $100 for TNF blocker medication and greater than $200 for MS medication were associated with increased prescription abandonment. These findings coupled with previous research identifying a negative relationship between OOP expense above $100 per month and adherence, and the commercial insurance market response to fourth-tier OOP expenses, suggests that insurers should consider the impact that specialty OOP expense may have on adherence and member satisfaction. Further prospective research should be performed to confirm these findings and assess the clinical outcomes associated with prescription abandonment.

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What is already known about this subject

- It is estimated that 10% of commercial plans, corresponding to more than 20 million Americans, include a pharmacy benefit specialty (or fourth) copayment tier, with cost share ranging from 5% to 50% per 30-day supply.
- In the Federal Employees Health Benefits Program from November 2008 to April 2009, representing almost 8 million enrollees, specialty medication out-of-pocket (OOP) maximums per prescription ranged from $50 to $400 per 30-day supply, and from $1,500 to $7,000 annually, or $4,264 annual average. For the median household income in 2007 of $50,233, a single specialty medication OOP expense could represent up to 9% of a household's total gross income.
- An analysis of MEDSTAT administrative claims data from 2002-2004 for 45 large self-insured employer health plans found that weekly OOP expense of $0-$40, accounting for approximately 95% of individuals treated with adalimumab or etanercept (tumor necrosis factor [TNF] blockers), was associated with a weighted medication possession ratio of 0.53 compared with 0.35 among approximately 5% of individuals with a weekly OOP expense greater than $40. Multivariate modeling found individuals were 8% more likely to stop therapy for every $10 increase in weekly OOP expense.

What is already known about this subject

- Among patients currently treated with a specialty drug for multiple sclerosis (MS, n = 7,985) or hepatitis C (n = 1,245), or with a TNF blocker (n = 10,734), multivariate modeling found an increased risk of nonadherence with OOP expense greater than $150 for patients with MS (hazard ratio [HR] = 1.19, 95% CI = 1.03-1.37), hepatitis C (HR = 1.14, 95% CI = 1.00-1.28), and TNF blockers (HR = 1.46, 95% CI = 1.15-1.85), compared with patients paying less than $20 per month.

What this study adds

- This is the first study to assess whether there is an association between OOP expense and new therapy prescription abandonment for TNF blocker medication and MS specialty medication.
- In a managed care organization with more than 13 million commercially insured enrollees, during 2006 through 2008, we identified 2,791 members newly initiating MS self-injectable therapy, of whom 2,303 (82.5%) had a per claim OOP expense of $0-$100, and 5.4% had a per claim OOP expense greater than $500. Members with an OOP of $100 or less had an abandonment rate of 5.7%, compared with more than 25% for members with an OOP expense greater than $200 ($P < 0.001$). In multivariate logistic regression analysis, MS medication OOP expense greater than $200 per claim was associated with at least 6-fold higher odds of abandonment compared with OOP expense of $100 or less.
- For members presenting a prescription to newly initiate TNF blocker therapy, 6,123 (83.7%) of 7,313 had a per claim OOP expense of $0-$100, and 5.7% had a per claim OOP expense greater than $500. The unadjusted abandonment rate was significantly higher for all OOP expense groups above $100 ($P < 0.05$). In multivariate logistic regression analysis, the TNF blocker medication abandonment rate was significantly higher for all OOP expense groups greater than $100 per claim with abandonment odds ratios (OR) of 2.3 to 4.4 for OOP expense between $101 and $500. The odds of abandonment at OOP expense greater than $500 were 7-fold higher (OR = 7.0, 95% CI = 5.4-9.1) compared with OOP expense of $100 or less.

Approximately 400,000 people in the United States have been diagnosed with multiple sclerosis (MS), with an additional 10,000 new cases annually.[1] Rheumatoid arthritis (RA) affects approximately 1.3 million Americans.[2] Combined, MS and RA affect approximately 1% of the population and are often treated with specialty medications. Specialty medications, in general, are injected or infused but may also include high-cost medications taken by mouth, may have unique storage or shipment requirements, are expensive, and are used to treat complex medical conditions such as MS, RA, hemophilia, and hepatitis.[3] The most common self-administered specialty medications used to treat MS and RA are the interferon beta-1a intramuscular (Avonex), interferon beta-1a subcutaneous (Rebif), interferon beta-1b (Betaseron), glatiramer acetate (Copaxone), and the tumor necrosis factor (TNF) blocking agents etanercept (Enbrel) and adalimumab (Humira). In a commercially insured population of 8 million members in 2008, the self-injectable TNF blockers and MS medications represented 0.2% of pharmacy benefit utilization, but 5.6% of total costs, which translates into 36.9% of pharmacy benefit specialty medication expenditures.[4] Despite the small condition prevalence and utilization, considerable attention has been focused on specialty medications because of the increasing financial burden they are placing on the health care system.[3]

In the next 5 years, it is anticipated that specialty medications will account for approximately 25% of total pharmacy benefit costs, up from their current 15% of costs.[5] Most specialty products are expensive at a unit cost level, and significant price inflation has driven specialty drug trends.[6] In 2007, the average wholesale price of specialty drugs increased at 3 times the rate of inflation.[7] With the annual individual specialty medication treatment costs ranging from $18,000 to at least $350,000, pharmacy benefit sponsors have been exploring methods to address expenditures by influencing specialty product price and utilization.[3,5,8-10]

One recommended method to help control expenditures is to build upon the current incentive-based formulary pharmacy benefit system by adding a fourth copayment tier for specialty medications, thereby increasing member cost share.[10] Currently, it is estimated that 10% of commercial plans, accounting for more than 20 million Americans and almost 90% of Medicare plans, include a specialty (or fourth) tier, with cost shares ranging from 5% to 50% per 30-day supply.[7,11] Results from a survey of 28 large employers found they were interested in the fourth tier to help encourage employees to consider lower-cost alternatives whenever possible.[11] The employers from the survey also commented that if the cost of the specialty medications continues to increase, the industry will likely see a corresponding increase in fourth-tier use. Unfortunately, most specialty medications lack lower-cost therapeutic alternatives, leaving individuals with no option but to incur the out-of-pocket (OOP) expense, and some have suggested that higher OOP expenses may lead to decreases in utilization.[10,11]

To help protect members from extremely large OOP expenses, the pharmacy benefit may have a maximum per-prescription OOP expense and/or an annual OOP maximum (sometimes called member stop-loss). For example, the use of a 20% coinsurance benefit design applied to a fourth tier comprising specialty MS medications will result in a member OOP expense of greater than $400 per prescription at standard dosing.[6] Nationally, per prescription OOP expense maximums have been reported to range from $75 to $375.[5,12,13] In the Federal Employees Health Benefits Program from November 2008 to April 2009, representing almost 8 million enrollees, specialty medication OOP maximums per prescription ranged from $50 to $400 and from $1,500 to $7,000 annually, or $4,264 annual average.[8] For the median household income in 2007 of $50,233, a single specialty medication OOP expense could represent up to 9% of a

household's total gross income.[14]

The literature contains conflicting information on the impact that rising specialty medication OOP expense has had on utilization and is limited to current utilizers, defined as individuals with at least 1 paid adjudicated claim. Goldman et al. (2006) found that increasing OOP expense among individuals currently utilizing a specialty medication had a minimal impact on utilization, suggesting price inelasticity.[9] Another study found that MS or TNF blocker current utilizers who had to pay more than $150 per prescription were at 14% to 19% greater odds of not having a medication supply at 1 year of follow-up compared with those paying less than $20.[15] In a subset of individuals who had newly initiated therapy, the new initiators were significantly more likely to discontinue at 1 year than were those with prior use. Little is known of the impact that specialty medication OOP expense may have on prescription abandonment. The primary objective of this study was to explore the relationship between OOP expense among individuals newly initiating MS or TNF blocker therapy and prescription abandonment, defined as a sequence of a successfully adjudicated claim, followed by a reversal of that claim, with no evidence of subsequent additional adjudicated claims—suggesting the patient never actually took possession of the medication despite evidence of a written prescription generated by a prescriber.

Methods

This observational cross-sectional study queried a database of 13,172,480 eligible members from 8 commercial BlueCross BlueShield plans in the Midwest and South to find members with an adjudicated pharmacy claim for a TNF blocker or MS medication during July 2006 through June 2008. MS medications were defined using the Medi-Span Generic Product Identifiers (GPI; Wolters Kluwer Health, Indianapolis, IN), as interferon beta 1-a using GPI starting with 624030604564 and 624030604520, interferon beta-1b using GPI 624030605021, and glatiramer acetate using GPI starting with 6240003010. TNF blockers were defined as etanercept (GPI starting with 6629003000) or adalimumab (GPI starting with 6627001500). For the TNF blocker analysis, we also identified members who had a final paid claim during the 180 days prior to their initial TNF blocker or during the 180 days after their initial TNF blocker for methotrexate (GPI starting with 21300050 or 6625005010) or infliximab (Remicade, GPI starting with 5250504000).

Members were required to be continuously enrolled in the 90 days prior to their initial adjudicated specialty medication claim and for 90 days thereafter. Each member's earliest MS (interferon beta-1a, interferon beta-1b, or glatiramer acetate) or TNF blocker (etanercept or adalimumab) claim during July 2006 through June 2008 was found. To ensure that members were attempting to newly initiate a specialty medication, members with a paid MS (interferon beta-1a, interferon beta-1b, or glatiramer acetate) or TNF blocker (etanercept, adalimumab, or infliximab) claim in the prior 90 days were excluded. A sensitivity analysis excluding members with an MS or TNF blocker paid claim in the prior 180 days was also performed.

Members with an adjudicated claim were then classified as either initiating therapy, defined as a paid claim, or as abandoning therapy (i.e., not initiating therapy). Abandoning therapy was defined as reversal of the adjudicated claim with no subsequent evidence of additional adjudicated paid claim(s) for MS (interferon beta-1a, interferon beta-1b, or glatiramer acetate) or TNF blocker (etanercept, adalimumab, or infliximab) in the ensuing 90 days. A sensitivity analysis was performed defining abandonment as no subsequent evidence of an adjudicated claim in the ensuing 180 days.

For 4 of the 8 plans representing 11,470,092 lives, medical claims for injectable specialty medications were available for analysis and were queried from January 2005 through December 2008 for the presence of a TNF blocker or MS medication claim. Among the 87.1% of members for whom medical claims were available, the pharmacy and medical claims were combined to identify new initiators and a combined pharmacy and medical claims abandonment rate.

Healthcare Common Procedure Coding System (HCPCS) codes were used to identify paid medical claims for MS medications including J1595 and Q2010 for glatiramer acetate, J1825 and Q3025 for interferon beta-1a intramuscular, J1830 for interferon beta-1b, and Q3026 for interferon beta-1a subcutaneous. The HCPCS codes used to identify paid medical claims for the TNF blockers were J0135 for adalimumab, J1438 for etanercept, and J1745 for infliximab. Additional HCPCS codes (J3490, J3590) were used in combination with the medical diagnosis on the claim, as well as a total paid amount on the drug claim of more than $500, to further identify MS or TNF blocker medical claims. HCPCS codes J3490 and J3590 are codes for "unclassified drugs" or "unclassified biologics" and combined with a higher dollar amount on the claim, these codes help increase the capture rate of the specialty medications. For MS medication medical claims the presence of an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of 340.xx was required. For the TNF blocker medical claims, a diagnosis of other inflammatory conditions of skin and subcutaneous tissue (ICD-9-CM 690.xx through 696.xx), RA and other inflammatory polyarthropathies (ICD-9-CM 714.xx), ankylosing spondylitis and other inflammatory spondylopathies (ICD-9-CM 720.xx), spondylosis and allied disorders (ICD-9-CM 721.xx), regional enteritis (ICD-9-CM 555.xx), or ulcerative enterocolitis (ICD-9-CM 556.xx) was required.

Separate analyses for MS and TNF blocker therapy were performed to assess the association between member OOP expense and abandonment rate. The member OOP expense for the first specialty medication claim, either paid or abandoned (reversed), was captured. Members were then placed into 1 of the 7 following OOP expense groups: $0-$100, $101-$150, $151-$200, $201-$250, $251-$350, $351-$500, or more than $500. The proportions of members abandoning therapy in each OOP expense

group were calculated along with 95% confidence intervals. The Cochran-Armitage Trend Test was performed to evaluate the trend in abandonment rates as the OOP expense increased (SAS Institute Inc., version 9.1.3, Cary, NC). The Cochran-Armitage Trend Test was selected a priori. Univariate abandonment rates were compared for each of the OOP expense groups with the $0 to $100 reference group using the Pearson chi-square statistic with 95% confidence intervals reported.

The association of MS or TNF blocker abandonment rate and OOP expense was tested with logistic regression models using $0-$100 OOP as the reference group and adjusting for age (dichotomous variable: aged 0 to 44 years vs. aged 45 years or older), gender, formulary status (an indicator of preferred formulary placement), income using ZIP code-level census data, education using ZIP code-level census data, earliest specialty medication, and methotrexate use for the TNF blocker analysis.[16] ZIP code-level census data represent the distribution of income (median) and proportion of individuals' educational attainment within the ZIP code. The income variable in the model used the ZIP code median income for the individual, and a dichotomous variable was created, $0 to $50,000 and greater than $50,000. Similarly, the education variable in the model used the percent of persons with a college degree within the ZIP code of the individual. College degree was defined as a bachelor's degree, master's degree, professional degree, or doctoral degree. Income and education assignment at the ZIP code level was done because actual income and education data were unavailable for subscribers or members. The specialty medication variable was the specific medication recorded in the member's earliest specialty medication claim, with the most common specialty medications for MS (i.e., glatiramer acetate) and TNF blocker (i.e., etanercept) used as the reference group. The overall fit of the logistic regression models was assessed using the Hosmer-Lemeshow test and c-statistic (SAS Institute Inc., version 9.1.3, Cary, NC). For all statistical tests, the significance level was set a priori at $P<0.05$.

Results

From January 2006 through December 2008, there were 13,172,480 members with at least 1 month of eligibility for whom claims were queried. There were 33,702 members identified with a claim for either a TNF blocker (n = 22,270) or MS medication (n = 11,432; Figure 1). During the 2-year period of July 2006 through June 2008, 12,660 TNF blocker and 5,561 MS medication utilizing members were defined as newly initiating therapy. After continuous enrollment criteria were applied, the final cohort consisted of 7,313 and 2,791 members who presented a prescription to newly initiate TNF blocker or MS therapy, respectively.

Tables 1 and 2 provide member characteristics for the MS and TNF blocker populations, respectively. Among those presenting a prescription for an MS agent, the distribution of members was as follows: 995 (35.7%) glatiramer acetate, 739 (26.5%) interferon beta-1a intramuscular, 633 (22.7%) interferon beta-1a subcutaneous, and 424 (15.2%) interferon beta-1b. The overall mean (standard deviation [SD]) cost share for members attempting to initiate MS therapy was $128 ($314) with a median of $40. The majority of members were in the $0-$100 cost-share group, in which the mean cost share was $38 (median $35). MS medication member characteristics were mean (SD) age 42.0 (10.4) years, ZIP code-level income $51,253 (SD $18,184), 27.0% within ZIP code with a college degree, and 24.1% male. MS claims for a 1-month supply were adjudicated for 1,985 (71.1%) patients, with a mean cost share of $136 (median $30). MS claims for more than a 1-month supply, typically 84-90 days, were adjudicated for 806 (28.9%) patients, with a mean cost share of $109 (median $50).

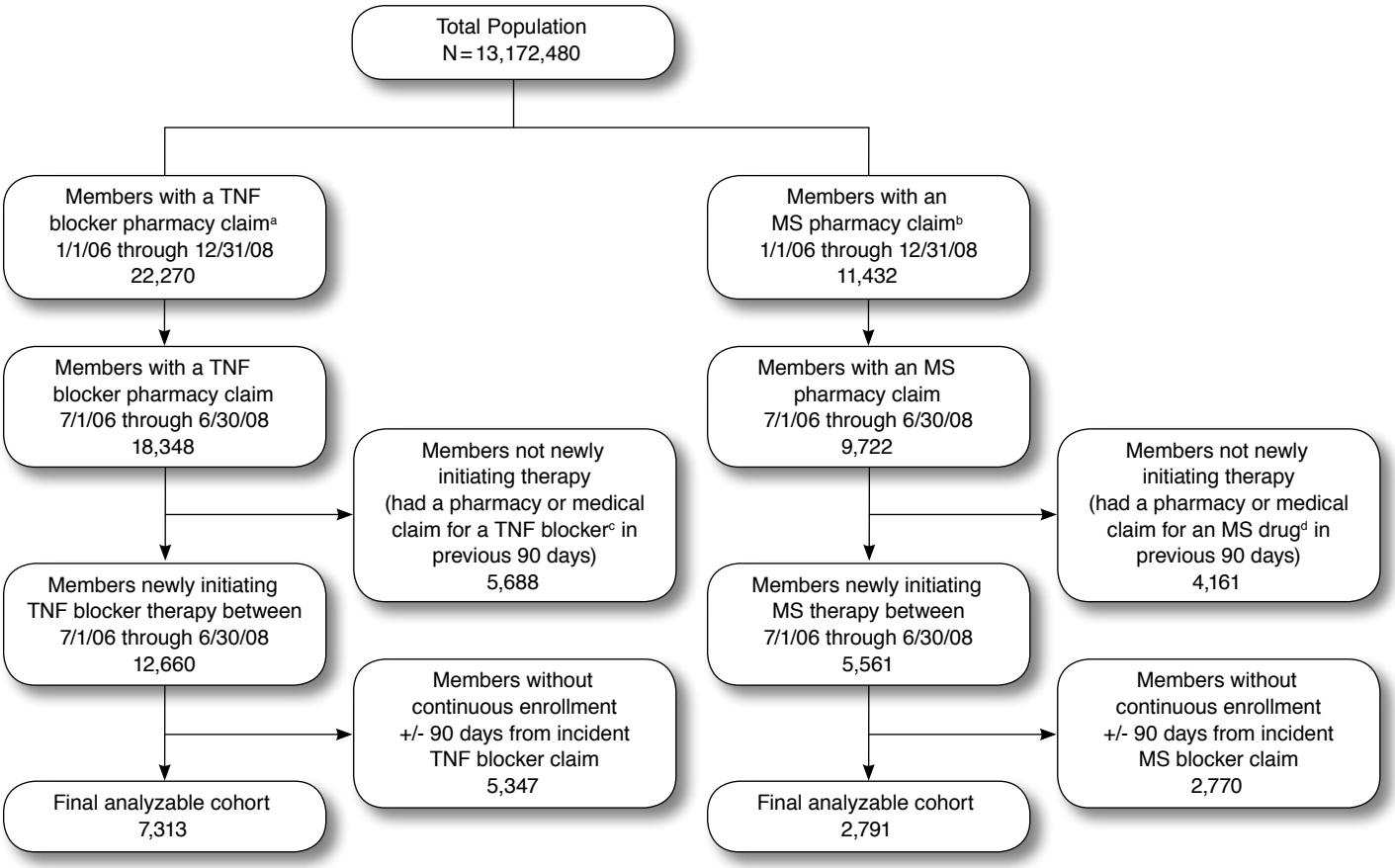
The most frequent TNF blocker was etanercept (4,679 members, 64.0%). TNF blocker member characteristics were mean (SD) age 44.5 (12.9) years, ZIP code-level income $50,305 (SD $18,649), 26.3% with a ZIP code-level college degree, and 40.2% male. The overall mean (SD) cost share for members attempting to initiate TNF blocker therapy was $126 ($309) with a median of $40. The majority of members were in the $0-$100 cost-share group, in which the mean cost share was $37 (median $35). TNF blocker claims for a 1-month supply were adjudicated for 5,809 (79.4%) patients, with a mean cost share of $128 (median $35). TNF blocker claims for more than a 1-month supply, typically 84-90 days, were adjudicated for 1,504 (20.6%) patients, with a mean cost share of $119 (median $50).

Of 2,791 members presenting a prescription to newly initiate MS therapy, 2,303 (82.5%) had an OOP expense for the initial claim of $0-$100, and 5.4% had an OOP expense greater than $500. As shown in Table 3 and Figure 2, the abandonment rate increased as OOP increased (test for trend, $P<0.001$). Members with an OOP of $100 or less had an abandonment rate of 5.7%. The abandonment rate was significantly higher among members with an OOP expense greater than $200 compared with $0-$100; of members who paid more than $200 per prescription, more than 1 in 4 abandoned their MS claims (Pearson chi-square $P<0.001$ for each cost group more than $200 compared with the $0 to $100 cost group). In the multivariate logistic regression analysis, the odds of abandonment for each MS medication OOP expense group greater than $200 were at least 6-fold higher than for groups with OOP expense of $100 or less.

In the MS multivariate logistic regression model, age, ZIP code-level income and education, and gender were not significantly associated with likelihood of abandoning therapy. Formulary status and the specialty medication interferon beta-1a (subcutaneous) were not associated with abandonment. Members utilizing interferon beta-1a (intramuscular) or interferon beta-1b were significantly less likely to abandon therapy compared with glatiramer acetate (odds ratio [OR] = 0.6, 95% confidence interval [CI] = 0.4 to 0.8, and OR = 0.5, 95% CI = 0.3-0.9, respectively). The MS logistic regression model had a Hosmer-Lemeshow goodness-of-fit test P value of 0.125, suggesting that the model fits the data ($\chi 2[8] = 12.65$) and a c-statistic of 0.698, suggesting weak to fair concordance between OOP expense and abandonment.

Sensitivity analyses excluding an additional 641 (23.0%) of

FIGURE 1 Derivation of Study Sample



[a]*Etanercept or adalimumab.*
[b]*Interferon beta-1a (intramuscular or subcutaneous), interferon beta-1b, or glatiramer acetate.*
[c]*Etanercept, adalimumab, or infliximab.*
[d]*Interferon beta-1a (intramuscular or subcutaneous), interferon beta-1b, or glatiramer acetate.*
MS = multiple sclerosis, TNF = tumor necrosis factor.

2,791 members with a paid MS claim in the prior 180 days produced similar results. Sensitivity analysis defining abandonment rate as no subsequent evidence of a paid MS claim in the ensuing 180 days resulted in the group with an OOP expense $151 to $200 becoming significantly different than those with an OOP expense $0 to $100 (OR = 3.6, 95% CI = 1.3 to 9.7).

Of 7,313 members presenting a prescription to newly initiate TNF blocker therapy, 6,123 (83.7%) had an OOP expense of $0-$100, and 5.7% had an OOP expense greater than $500. As shown in Table 4 and Figure 3, the abandonment rate increased as OOP expense increased (test for trend, $P < 0.001$). The unadjusted abandonment rate was significantly higher for all OOP expense groups above $100 compared with $0-$100 (Pearson chi-square $P < 0.05$). In the multivariate logistic regression analysis, the TNF blocker medication abandonment rate was significantly higher for all OOP expense groups greater than $100, with abandonment odds ratios of 2.3 to 4.4 for OOP expense between $101 and $500. The odds of abandonment rate at OOP expense of greater than $500 were 7-fold higher (OR = 7.0, 95% CI = 5.4-9.1) compared with OOP expense of $100 or less.

In the TNF multivariate logistic regression model, age, ZIP code-level income and education, and gender were not significantly associated with likelihood of abandoning therapy. Members with a paid methotrexate claim in the 180 days prior to their initial TNF blocker prescription were significantly more likely to abandon therapy (OR = 1.8, 95% CI = 1.3-2.5). A methotrexate paid claim within 180 days after the initial TNF blocker prescription was not significantly associated with abandonment. Formulary status and the specialty medication adalimumab were not associated with abandonment. The TNF blocker

TABLE 1 Characteristics of Members with Claims for Biologic Agents for Multiple Sclerosis

Cost Groups[a]	Members N (%)	Mean Age [SD]	Males N (%)	ZIP Code Level Median Household Income 1999 [SD]	ZIP Code Level % with College Degree[b]	Cost Share Mean [SD]	Cost Share Median (25th, 75th Quartiles)	Glatiramer Acetate (Copaxone)	Interferon Beta-1a (Avonex)	Interferon Beta-1a (Rebif)	Interferon Beta-1b (Betaseron)
$0-$100	2,303 (82.5%)	42.0 [10.5]	547 (23.8%)	$52,066 [$18,185]	27.1%	$38 [$21]	$35 ($25, $50)	805 (35.0%)	620 (26.9%)	525 (22.8%)	353 (15.3%)
$101-$150	57 (2.0%)	44.4 [9.6]	17 (29.8%)	$46,952 [$16,605]	26.5%	$131 [$18]	$130 ($120, $150)	23 (40.4%)	15 (26.3%)	9 (15.8%)	10 (17.5%)
$151-$200	47 (1.7%)	43.0 [9.8]	9 (19.1%)	$55,683 [$26,377]	29.4%	$187 [$18]	$200 ($167, $200)	18 (38.3%)	18 (38.3%)	5 (10.6%)	6 (12.8%)
$201-$250	41 (1.5%)	42.1 [10.2]	8 (19.5%)	$46,419 [$16,637]	28.3%	$242 [$12]	$250 ($237, $250)	21 (51.2%)	6 (14.6%)	8 (19.5%)	6 (14.6%)
$251-$350	89 (3.2%)	40.9 [10.6]	19 (21.3%)	$45,149 [$13,950]	24.5%	$317 [$20]	$318 ($300, $335)	39 (43.8%)	23 (25.8%)	22 (24.7%)	5 (5.6%)
$351-$500	103 (3.7%)	42.0 [9.3]	30 (29.1%)	$44,263 [$16,019]	23.9%	$408 [$44]	$402 ($368, $446)	44 (42.7%)	25 (24.3%)	21 (20.4%)	13 (12.6%)
> $500	151 (5.4%)	42.2 [10.2]	43 (28.5%)	$48,834 [$17,518]	27.0%	$1,154 [$747]	$960 ($640, $1,509)	45 (29.8%)	32 (21.2%)	43 (28.5%)	31 (20.5%)
Overall	2,791 (100%)	42.0 [10.4]	673 (24.1%)	$51,253 [$18,184]	27.0%	$128 [$314]	$40 ($25, $65)	995 (35.7%)	739 (26.5%)	633 (22.7%)	424 (15.2%)

[a]*Cost-sharing amounts shown are for a 1-month (up to 34-day) supply for 2,791 (71.1%) patients and for greater than a 34-day supply (typically 84-90 days) for 806 (28.9%) patients.*

[b]*Percent of members with a bachelor's degree, master's degree, professional degree, or doctoral degree (college degree) based on the ZIP code population college degree mean.*

SD = standard deviation.

TABLE 2 Characteristics of Members with Claims for Tumor Necrosis Factor Blockers

Cost Groups[a]	Members	Mean Age [SD]	Males N (%)	ZIP Code Level Median Household Income 1999 [SD]	ZIP Code Level % with College Degree[b]	Cost Share Mean [SD]	Cost Share Median (25th, 75th Quartiles)	Etanercept (Enbrel)	Adalimumab (Humira)
$0-$100	6,123 (83.7%)	44.3 [12.9]	2,460 (40.2%)	$50,892 [$18,665]	26.5%	$37 [$20]	$35 ($25, $50)	3,950 (64.5%)	2,173 (35.5%)
$101-$150	162 (2.2%)	46.9 [11.9]	75 (46.3%)	$51,284 [$20,673]	26.3%	$133 [$17]	$136 ($120, $150)	93 (57.4%)	69 (42.6%)
$151-$200	82 (1.1%)	45.2 [14.9]	31 (37.8%)	$48,646 [$17,175]	27.4%	$186 [$16]	$196 ($175, $200)	55 (67.1%)	27 (32.9%)
$201-$250	94 (1.3%)	43.4 [14.8]	31 (33.0%)	$41,366 [$14,203]	26.0%	$232 [$18]	$236 ($214, $250)	53 (56.4%)	41 (43.6%)
$251-$350	307 (4.2%)	46.0 [13.3]	110 (35.8%)	$45,104 [$16,956]	24.4%	$291 [$20]	$287 ($278, $300)	189 (61.6%)	118 (38.4%)
$351-$500	129 (1.8%)	47.0 [13.2]	53 (41.1%)	$45,581 [$16,018]	23.8%	$420 [$42]	$421 ($384, $453)	81 (62.8%)	48 (37.2%)
> $500	416 (5.7%)	44.0 [13.0]	177 (42.5%)	$48,822 [$19,373]	26.4%	$1,186 [$618]	$1,103 ($694, $1,432)	258 (62.0%)	158 (38.0%)
Overall	7,313 (100%)	44.5 [12.9]	2,937 (40.2%)	$50,305 [$18,649]	26.3%	$126 [$309]	$40 ($25, $60)	4,679 (64.0%)	2,634 (36.0%)

[a]*Cost-sharing amounts shown are for a 1-month (up to 34-day) supply for 5,809 (79.4%) patients and for greater than a 34-day supply (typically 84-90 days) for 1,504 (20.6%) patients.*

[b]*Percent of members with a bachelor's degree, master's degree, professional degree, or doctoral degree (college degree) based on the ZIP code population college degree mean.*

SD = standard deviation.

TABLE 3 Unadjusted and Adjusted Association Between Multiple Sclerosis Medication Out-of-Pocket Member Expense and Abandonment Rate at 90 Days Post-Index

Out-of-Pocket Member Expense	Members (N = 2,791)[a]	Unadjusted Abandonment Rate N (%) at 90 Days Post-Index[b]	Multivariate Logistic Regression Model[c] Odds Ratio (95% CI)
$0-$100	2,303 (82.5%)	131 (5.7%)	Reference Group
$101-$150	57 (2.0%)	3 (5.3%)	0.9 (0.3-3.0)
$151-$200	47 (1.7%)	5 (10.6%)	2.0 (0.8-5.2)
$201-$250	41 (1.5%)	11 (26.8%)	7.3 (3.3-16.2)
$251-$350	89 (3.2%)	23 (25.8%)	6.5 (3.8-10.9)
$351-$500	103 (3.7%)	27 (26.2%)	6.1 (3.7-9.9)
> $500	151 (5.4%)	43 (28.5%)	6.7 (4.4-10.1)

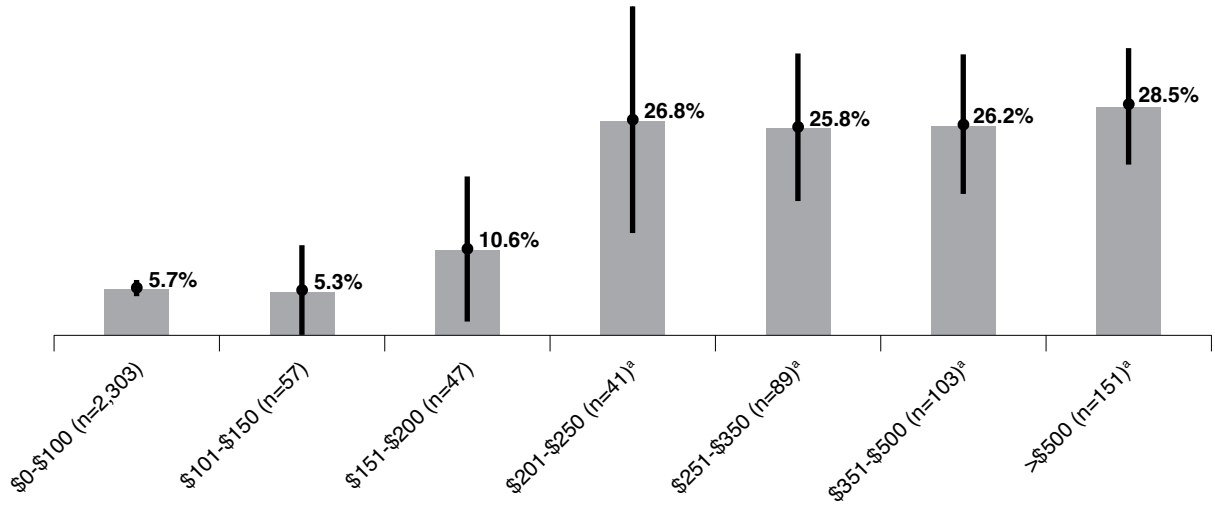
[a]*Members newly initiating MS medication, defined as no MS claim(s) in prior 90 days.*

[b]*The index date for a member is the earliest date of an adjudicated claim for an MS medication for that member. Abandonment was defined as an adjudicated claim that was reversed with no subsequent evidence of additional adjudicated paid claim(s) for MS medication (interferon beta-1a, interferon beta-1b, or glatiramer acetate) in the ensuing 90 days. Cochran-Armitage test for trend, P < 0.001.*

[c]*Model adjusts for age, gender, formulary status of the earliest MS claim, income ($0-$50,000 and > $50,000 of the median income for residents in the individual's ZIP code), education (mean percent of residents in a member's ZIP code with a college degree), and earliest MS medication (glatiramer acetate is the reference group). C-statistic = 0.698. Hosmer-Lemeshow goodness of fit $\chi 2$ [8] = 12.65, P = 0.125.*

CI = confidence interval; MS = multiple sclerosis.

FIGURE 2 Unadjusted Multiple Sclerosis Prescription Abandonment Rate by Out-of-Pocket Member Expense



Source: Pearson chi-square test.

[a]*P < 0.001 compared with $0-$100 group.*

Bars represent 95% confidence intervals.

Hosmer-Lemeshow goodness-of-fit test *P* value was 0.465, suggesting that the model fits the data ($\chi 2[11] = 7.69$), and the c-statistic was 0.676, suggesting weak to fair concordance between OOP expense and abandonment.

For the TNF blocker sensitivity analysis, when new initiators were defined as no paid TNF blocker claim in the prior 180 days, an additional 1,063 (14.5%) of 7,313 members were excluded, and the OOP expense group of $201 to $250 became nonsignificant (OR = 1.8, 95% CI = 0.8-3.7). Results for all other OOP expense groups were similar. The sensitivity analysis for TNF blockers with an increased post-abandonment period window for identifying paid claims produced similar results.

Medical data were unavailable for 12.9% of the membership; however, for members with medical claims history, prior medical claims for a TNF blocker or MS medication resulted in exclusion of 211 of the 16,222 TNF members and 10 of the 8,205 MS members. In addition, among the analyzed members with medical claims available, a paid medical claim for an MS medication

TABLE 4 Unadjusted and Adjusted Association Between Tumor Necrosis Factor Blocker Medication Out-of-Pocket Expense and Abandonment Rate at 90 Days Post-Index

Out-of-Pocket Member Expense	Members (N = 7,313)[a]	Unadjusted Abandonment Rate N (%) at 90 Days Post-Index[b]	Multivariate Logistic Regression Model[c] Odds Ratio (95% CI)
$0-$100	6,123 (83.7%)	288 (4.7%)	Reference Group
$101-$150	162 (2.2%)	17 (10.5%)	2.3 (1.3-3.9)
$151-$200	82 (1.1%)	12 (14.6%)	3.7 (2.0-7.0)
$201-$250	94 (1.3%)	10 (10.6%)	2.1 (1.0-4.2)
$251-$350	307 (4.2%)	41 (13.4%)	3.3 (2.3-4.7)
$351-$500	129 (1.8%)	21 (16.3%)	4.4 (2.7-7.2)
> $500	416 (5.7%)	110 (26.4%)	7.0 (5.4-9.1)

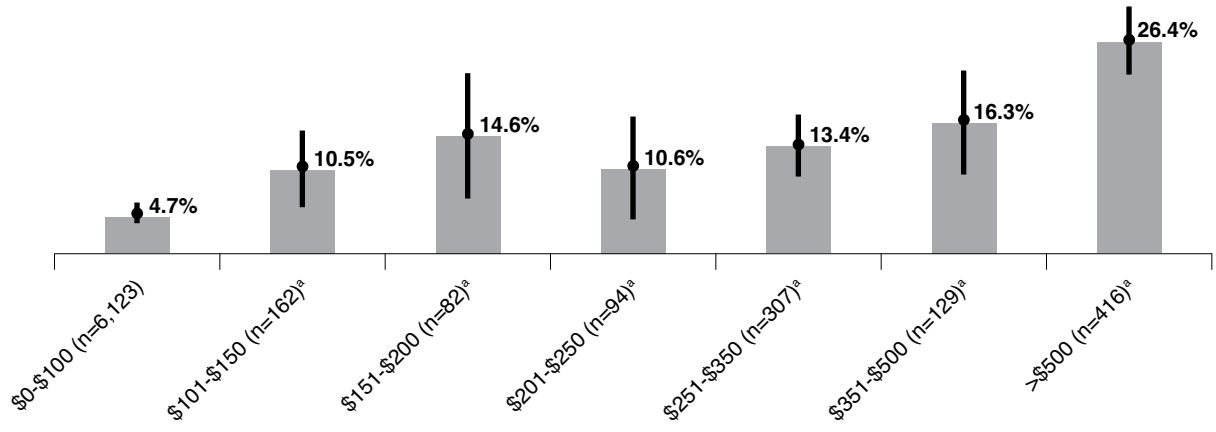
[a]*Members newly initiating TNF blocker medication, defined as no TNF blocker claim(s) in prior 90 days.*

[b]*The index date for a member is the earliest date of an adjudicated claim for a TNF medication for that member. Abandonment was defined as an adjudicated claim that was reversed with no subsequent evidence of additional adjudicated paid claim(s) for a TNF blocker (etanercept, adalimumab, or infliximab) in the ensuing 90 days. Cochran-Armitage test for trend, P < 0.001.*

[c]*Model adjusts for age, gender, formulary status of the earliest TNF blocker claim, income ($0-$50,000 and > $50,000 of the median income for residents in the individual's ZIP code), education (mean percent of residents in a members' ZIP code with a college degree), pre-index and post-index methotrexate use, and earliest TNF blocker medication (etanercept is the reference group). C-statistic = 0.676. Hosmer-Lemeshow goodness of fit $\chi 2$ [8]M = 7.69, P = 0.465.*

CI = confidence interval; TNF = tumor necrosis factor.

FIGURE 3 Unadjusted Tumor Necrosis Factor Blocker Prescription Abandonment Rate by Out-of-Pocket Member Expense



Source: Pearson chi-square test.

[a]*P < 0.001 compared with $0-$100 group.*

Bars represent 95% confidence intervals.

without any post-abandonment paid pharmacy claim was found in 7 of 2,415 members (0.3%), and for TNF blocker members the rate was 39 of 6,516 (0.6%). Using data for the 2,415 MS members and 6,516 TNF blocker members with medical claims data, multivariate model sensitivity analyses were performed, and the results were similar to those of complete data set models.

Discussion

Specialty medications accounted for 15.1% of total pharmacy benefit medication spending, and per member per month (PMPM) expenditures have increased from $6.04 to $9.18 for an 11.1% annual increase from 2004 to 2008 within a commercially insured population of 8 million members.[4] Insurers face increasing pressure to control specialty medication expenditures and may choose to increase member cost share to accomplish this within their fully insured populations and offer this to their self-insured populations; however, few studies have examined the impact of such policies. This study is the first to examine the impact of OOP expense on prescription abandonment among members newly initiating MS or TNF blocker therapy.

Among new initiators to MS therapy, the abandonment rate became significantly higher at OOP expenses of $201 to $250

TABLE 5 Previous Reports on Fourth-Tier Specialty Medication Benefit, Impact, and Change

Organization (Reporting Source)	Previous Specialty Medication Benefit	New Specialty Medication Benefit	Duration of New Benefit	Impact and Changes
HMO insurer[13] *(New York Times)*	$20 cost share	Tier 4; 25% coinsurance; $325 per month OOP maximum	Less than 1 year	Member and provider complaints to insurer and employer. Suspension of fourth tier, reimbursement to affected members.
Self-insured employer[19] (personal communication with authors)	Open 3-tier benefit with specialty medication cost share of $20 formulary or $40 nonformulary	Tier 4; 20% coinsurance; $200 per month OOP maximum	3 months	Member complaints to insurer and employer. Changed OOP maximum to $100.
Commercial insurer, fully insured population[12] (anonymous report, *Kansas City infoZine News*)	Open 3-tier benefit	Tier 4; 20%-40% coinsurance with no OOP maximum	Less than 1 year	Member and provider complaints. Changed benefit to 10% coinsurance with a $200 per claim OOP maximum.

OOP = out-of-pocket.

compared with OOP expense of $100 or less. Among new initiators to TNF blockers, the abandonment rate became significantly higher at OOP expenses of $101 to $150 compared with OOP expense of $100 or less. The risk of abandonment was even greater among those paying more than $500 in OOP expense. These results establish potential break points, at which OOP expenses may negatively influence medication utilization, of greater than $100 for TNF blockers and greater than $200 for MS medications.

Our findings are consistent with the findings of Curkendall et al. (2008), who studied the effect of increasing OOP expense on individuals currently treated with adalimumab or etanercept (TNF blockers).[17] Their analysis of MEDSTAT administrative claims data from 2002-2004 for 45 large self-insured employer health plans found that weekly OOP expense of $0-$40, accounting for 95% of individuals currently treated with adalimumab or etanercept, was associated with a weighted medication possession ratio of 0.53, compared with 0.35 among approximately 5% of individuals with a weekly OOP expense greater than $40. Individuals with an OOP expense of greater than $50 per week (approximately $200 per month) were 58% more likely to discontinue therapy (hazard ratio [HR] = 1.579, $P < 0.001$).[17] The authors concluded that individuals were 8% more likely to stop therapy for every $10 increase in weekly OOP expense. Another study analyzed adherence in relation to cost-share amount for patients currently treated with a specialty MS (n = 7,985), hepatitis C (n = 1,245), or TNF blocker (n = 10,734) medication.[15] Members paying less than $20 per month were the reference group. Risk of nonadherence increased with OOP expense greater than $150 for patients with MS (HR = 1.19, 95% CI = 1.03-1.37), hepatitis C (HR = 1.14, 95% CI = 1.00-1.28), and TNF blockers (HR = 1.46, 95% CI = 1.15-1.85).[15] Together with our findings, which suggest increased abandonment at cost-sharing levels as low as $100 for TNF blocker medications, these data indicate that adherence to specialty medications may be sensitive to monthly OOP expense above $100 when initiating or continuing therapy.

The influence of cost sharing on specialty medication utilization is important. As the current incentive-based formulary pharmacy benefit evolves, specialty medications are being placed in a high cost share fourth tier.[3] Incentive-based pharmacy benefits are predicated on influencing the individual to reduce overutilization of expensive branded products through the selection of the most cost-effective alternative to treat their disease. Incentive-based pharmacy benefits often utilize a tiered benefit design, in which the member OOP expense varies according to the cost of the medication and/or formulary status.[18] Placing specialty medications in a fourth tier implies that there are alternative equally safe, efficacious, and less expensive agents. For the TNF blocker medication class, methotrexate may be a reasonable generic therapeutic alternative. Our finding of an independent association between prior methotrexate use and abandonment suggests that individuals may be evaluating the need for a TNF blocker in context of their methotrexate experience. However, with the exception of methotrexate, equally safe and efficacious nonspecialty medications do not exist for individuals with moderate to severe autoimmune disorders such as RA. MS pharmacotherapy currently has no nonspecialty medication alternatives. The lack of alternatives to many specialty medications leaves patients either incurring the cost or abandoning the therapy and potentially disillusioned with their pharmacy benefit.

Member disillusionment and a negative response to OOP expense have resulted in some commercial insurers rescinding or lowering specialty medication fourth-tier OOP expenses. As shown in Table 5, a health maintenance organization, fully insured population, and a self-insured employer independently implemented a fourth-tier specialty benefit with coinsurances of 20% to 40% and per claim OOP expenses of $200 to $600.[12,13,19] Within a year, the fourth-tier OOP expenses were eliminated, or the OOP was lowered by at least one-half because of complaints from providers and members. For insurers and self-insured employers, consideration of the fourth-tier OOP expense impact on utilization and member disillusionment should be part of the pharmacy benefit design decision-making process.[20]

Insurers have options other than a fourth tier with increased

OOP expense. For example, insurers could encourage the use of the lowest-cost pharmacy channel such as a specialty pharmacy network, apply utilization management programs such as step-therapy, or initiate care management.[21] Typically a specialty pharmacy network will have care management clinicians trained in managing pharmacotherapy for the less common conditions treated with specialty medications. As an alternative to a fourth tier with increased OOP expense to address potential overutilization, insurers should consider utilization management programs. Utilization management programs are particularly viable because of the infrequent use of specialty medications. If a specialty medication fourth tier is created, deference to the associated negative influence on utilization and unfavorable public response suggests that an OOP expense maximum per 30-day supply should be considered.

Limitations

First, the observational cross-sectional study design employed here is intended to explore potential associations between MS or TNF blocker claim OOP expense and member abandonment rates; hence, a direct cause-and-effect link cannot be made. Second, the biologic agents for MS and the TNF blockers examined in this study represent a subset of high-cost specialty medications; therefore, the associated OOP expense to abandonment relationships may not translate to other specialty medication classes, particularly for lower-cost specialty drugs. Third, this study used pharmacy claims and medical claims data that are intended for administrative and payment purposes, and as such, they may be an incomplete record of an individual's therapy. For example, an individual may have received medication samples from his or her physician, or he or she may have opted to abandon therapy prior to presenting a prescription to the pharmacy.

Fourth, the time from the index prescription, pre-index to identify new initiators and post-index to define abandonment, was arbitrarily set at 90 days. Individuals may have had prior therapy earlier than 90 days or initiated therapy after 90 days. Therefore, we performed a secondary sensitivity analysis using 180 days prior to and following the index claim, which did not change our findings appreciably. Expanding the definition of a new initiator to 180 days resulted in excluding 1,063 (14.5%) of 7,313 TNF blocker utilizers and 641 (23.0%) of 2,791 MS utilizers. Longer pre-index and post-index periods could potentially result in different findings. Fifth, our analysis assumes that the member is presented with the amount of OOP expense at the time of intended purchase, and the reversed claim without a subsequent paid claim indicates the member chose to abandon therapy. Other reasons why individuals may have chosen to abandon therapy include concerns about self-administered injections or side effects that are mentioned when the pharmacist provides medication counseling.

Sixth, our pharmacy data are limited to the Midwest and South; therefore, our findings may not be generalized to Medicare or Medicaid populations or other geographic regions. Seventh, some of the OOP expense categories had a small number of members, potentially limiting our power to find differences in abandonment rates. Eighth, the concordance c-statistics of 0.698 and 0.676 in our logistic regression models suggests weak to fair concordance between OOP expense and abandonment. However, this is a common problem in cross-sectional studies examining the relationship between cost share and utilization. Finally, it is unknown whether a correlation between prescription abandonment and negative clinical outcomes exists.

Conclusion

Specialty medications have been experiencing the largest expenditure growth within the pharmacy benefit, and this growth is expected to continue into the foreseeable future. Insurers and employers face pressure to control specialty medication expenditures, and increasing member OOP expense through the creation of a fourth copayment tier may influence utilization as well as spread costs between members and health plans. In 2009, fourth-tier member OOP expense of more than $100 has been reported; however, few studies have examined the impact of increased OOP expenses. This study found an association between OOP expense and new therapy prescription abandonment at OOP expenses greater than $100 for TNF blocker medication and greater than $200 for MS medication. A negative relationship between OOP expense of more than $100 per month and adherence has been identified, and the commercial insurance market has had to respond to fourth-tier OOP expenses. These findings suggest that insurers should consider the impact that specialty OOP expense may have on adherence and member satisfaction. Further prospective research should be performed to confirm these findings and assess the clinical outcomes associated with prescription abandonment.

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DISCLOSURES

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Gleason, Starner, and Gunderson were responsible for the concept and study design. Gunderson was primarily responsible for data collection, with the assistance of Gleason and Starner. The data were interpreted by Gleason, Starner, Gunderson, and Schafer. All authors contributed to writing the manuscript, and the revision was primarily the work of Gleason and Saran, with assistance of the other authors.

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