

# Medication Use Patterns and Predictors of Nonpersistence and Nonadherence with Oral 5-Aminosalicylic Acid Therapy in Patients with Ulcerative Colitis

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## ABSTRACT

**BACKGROUND:** 5-aminosalicylic acid (5-ASA) is the recommended first-line treatment for active mild-to-moderate ulcerative colitis (UC) and for maintenance of UC remission. However, persistence and adherence to prescribed 5-ASAs are often suboptimal.

**OBJECTIVE:** To evaluate 5-ASA medication use patterns and assess risk factors associated with nonpersistence and nonadherence to oral 5-ASA medications in UC patients.

**METHODS:** IMS LifeLink Health Plan claims data (January 2007 to June 2011) were analyzed. We identified adult patients (18 years or older) with at least 1 diagnosis of UC (ICD-9-CM code = 556.x [ulcerative colitis]) and at least 1 pharmacy claim for an oral 5-ASA (balsalazide disodium, sulfasalazine, mesalamine delayed-release, and Multi-Matrix System mesalamine) during the study period. Patients were required to have continuous eligibility on both health and pharmacy plans for 6 months pre- and 12 months post-initial pharmacy claim (index date). Medication use patterns (discontinuation, time to discontinuation [days], switch, and nonadherence) in the 12 months following the index date were evaluated. Nonpersistence or discontinuation with the index medication was defined as a treatment gap  $\geq 60$  days. Switch was identified as patients changing to another 5-ASA product after discontinuing the index medication. Nonadherence to index medication was determined by medication possession ratio (MPR)  $< 0.8$  for the index medication. Nonadherence to any 5-ASA treatment was determined by a proportion of days covered (PDC)  $< 0.8$  for any 5-ASA. A Cox model was used to assess the relative hazards associated with discontinuation. Multiple logistic regression models were used to assess risk factors associated with nonadherence to either the index or any 5-ASA medications.

**RESULTS:** A total of 5,664 patients met selection criteria. The median time to discontinuation of index drug differed significantly across index medications (range, 98.5 days [sulfasalazine] to 177.5 days [Multi-Matrix System mesalamine],  $P < 0.0001$ ). Patients on Multi-Matrix System mesalamine were less likely to discontinue (63.3% vs.  $\geq 68.6\%$ ,  $P = 0.001$ ) and more likely to adhere to their medication (MPR  $\geq 0.8$ ; 23.1% vs.  $\leq 17.4\%$ ,  $P < 0.0001$ ) than patients on other medications. Patients on mesalamine delayed-release (13.8%) or Multi-Matrix System mesalamine (14.3%) had lower switch rates than the patients on balsalazide (17.2%) or sulfasalazine (17.8%),  $P = 0.01$ . Significant predictors of nonpersistence included index medication versus Multi-Matrix System mesalamine (balsalazide disodium: HR = 1.21, 95% CI = 1.07-1.36; mesalamine delayed-release: HR = 1.21, CI = 1.11-1.32; sulfasalazine: HR = 1.40, CI = 1.25-1.57), female gender (HR = 1.16, CI = 1.09-1.23), never receiving specialist care (HR = 1.14, CI = 1.07-1.21), preferred provider organization (PPO) versus health maintenance organization (HR = 1.14, CI = 1.04-1.24), and Medicare fee for service or self-insured health plan versus commercial plan (HR = 1.29, CI = 1.10-1.52). Significant variables associated with nonadherence with 5-ASA treatment (PDC  $< 0.8$ ) included not switching medication (OR = 1.90, CI = 1.58-2.29), age  $< 65$  (OR = 1.90, CI = 1.56-2.31), index medication as

compared with Multi-Matrix System mesalamine (balsalazide disodium: OR = 1.43, CI = 1.10-1.85; mesalamine delayed-release: OR = 1.41, CI = 1.19-1.68; sulfasalazine: OR = 1.66, CI = 1.30, 2.12), female gender (OR = 1.33, CI = 1.17-1.52), residing in different regions as compared with the Midwest region (the South [OR = 1.40, CI = 1.20-1.64] and Northeast [OR = 1.29, CI = 1.05-1.58]), no use of rectal forms during the post-index period (OR = 1.28, CI = 1.08-1.50), no use of immunosuppressive/biologic agents during the post-index period (OR = 1.70, CI = 1.35-2.14), never receiving specialist care (OR = 1.25, CI = 1.08-1.44), and Medicaid/Medicare versus commercial plan (OR = 1.48, CI = 1.03-2.13).

**CONCLUSIONS:** Patients on once-daily dosed Multi-Matrix System mesalamine had the lowest risk of discontinuation and the highest adherence rate. Multiple factors were associated with either nonpersistence or nonadherence, including multiple-daily dosed index medication, younger age, female gender, residing in the South region, PPO plan, noncommercial payer, not using immunosuppressive/biologic agents, not using rectal 5-ASA, and never receiving specialist care.

*J Manag Care Pharm.* 2012;18(9):701-12

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## What is already known about this subject

- According to clinical practice guidelines from 2 organizations (the British Society of Gastroenterology and American College of Gastroenterology Practice Parameters Committee), 5-aminosalicylic acid (5-ASA) is a recommended first-line treatment for patients with mild-to-moderate ulcerative colitis (UC). However, adherence to medication is suboptimal. Literature reports show that 40% to 72% of patients are nonadherent to their treatment regimen.
- Most studies of adherence in UC patients have been based on either clinical trials or observational studies with small samples. Only 2 published studies have used administrative claims data to investigate 5-ASA medication persistence. All of them had significant limitations related to study design and adherence measurement.
- Multiple factors including age, gender, newly diagnosed patient status, disease duration, copayment amount, rectal 5-ASA and glucocorticoid use, and drug type and multiple daily dosed regimens have been associated with nonadherence to 5-ASA medications.

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### What this study adds

- The present study investigated various medication use patterns including discontinuation, restart, switch, and adherence using “real-world” pharmacy and medical claims data.
- Oral 5-ASA use patterns varied among patients initiated on different 5-ASA medications. The patients on Multi-Matrix System mesalamine had the lowest discontinuation/nonpersistence rate (63.3% vs.  $\geq$  68.6%), longest median time remaining on index drug (177.5 days vs.  $\leq$  148 days), lowest hazard to discontinuation (HR = 1.21 [balsalazide, mesalamine delayed-release], and 1.4 [sulfasalazine]) as compared with patients on other 5-ASA medications.
- Significant nonadherence with oral 5-ASA treatment in UC patients was shown with rates ranging from 74.2% to 82.0% for those initiated on Multi-Matrix System mesalamine and sulfasalazine, respectively.
- Several factors (multiple daily dosed index medication, younger age, female gender, residing in the South, preferred provider plan, noncommercial payer, not using immunosuppressive/biologic agents, not using rectal 5-ASA, and never receiving specialist care) were associated with nonpersistence or nonadherence with 5-ASAs.
- Analyses based on descriptive medication use patterns and different multivariable models confirmed that multiple daily dosed index medication (including balsalazide, mesalamine delayed-release, or sulfasalazine) was one of the significant factors associated with 5-ASA nonpersistence or nonadherence as compared with once-daily Multi-Matrix System mesalamine. Therefore, Multi-Matrix System mesalamine with once-daily dosing formulation may improve adherence in patients with UC.

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by chronic or recurring immune-mediated injury to the large intestine (i.e., colon and rectum). The inflammation in UC is typically limited to the mucosal lining, starting in the rectum and extending proximally to affect part or all of the colon. The inflammation is typically circumferential and continuous, with “skip areas” of normal mucosa. The estimated prevalence of UC ranges from 37.5 to 248.6 per 100,000 persons in North America.<sup>1</sup> UC is a costly disease and poses a significant economic burden, in which the estimated cost is in the range of \$8.1-\$14.9 billion in the United States.<sup>2</sup>

The nature of UC typically requires lifelong pharmacological therapy to induce and maintain remission. First-line treatment with 5-aminosalicylic acid (5-ASA) is recommended for mild-to-moderate disease.<sup>3-5</sup> However, clinical studies have reported medication nonadherence rates from 40% to 72%.<sup>6,7</sup> Current systematic reviews reveal that nonadherence with 5-ASA has substantial clinical implications, including a greater

risk of relapse of UC, impaired quality of life, increased health care costs, and the potential for increased lifetime risk of developing colorectal cancer.<sup>7-13</sup>

Multiple factors associated with nonadherence with UC medications have been identified.<sup>6,7,13-15</sup> These factors include age, gender, newly diagnosed patient status, disease duration, copayment costs, rectal 5-ASA and glucocorticoid use, and drug type and dosing regimens. Some of these studies have reported that adherence is related to dosing regimens, while other studies have not found a correlation between these concepts. For example, a few studies in UC patients showed that daily dose, regimen, and formulation do not significantly impact adherence.<sup>7,13</sup> In addition, adherence in UC patients appears to be independent of medication formulation.<sup>13</sup> However, the study conducted by Loftus (2006) from a survey of 1,595 patients with UC showed the most common reasons for nonadherence were “too many pills,” “dosing required too many times each day,” “medication too inconvenient,” and “forgetting to take medication.”<sup>16</sup>

Shale and Riley (2003) also identified that a 3-times-a-day regimen was associated with nonadherence.<sup>17</sup> Recent studies have demonstrated that once-daily mesalamine is effective for induction or maintenance of remission in quiescent patients.<sup>18-20</sup> Moreover, a recent patient survey reported significantly higher self-reported compliance and acceptability in the once-daily group than in the twice-daily group.<sup>18</sup> These studies supported the use of once-daily treatment for improving medication adherence in UC patients.

Most of the medication adherence studies in UC patients were either clinical trials or observational studies with small samples. The findings and conclusions from these types of studies may not be easily generalized to real-world clinical practice, since the study patients are monitored more closely than in conventional practice. Few studies have investigated 5-ASA utilization patterns and persistency using administrative claims data that may approximate real-world clinical practice.<sup>15,21</sup> However, the few published studies using claims data analysis have significant flaws in identifying appropriate UC patients (e.g., without using diagnosis codes to confirm UC patients<sup>21</sup>) and measurement of persistency (e.g., persistency was measured by refill rate at the third and the twelfth month.<sup>15</sup>). Moreover, these studies only investigated medication persistency but did not assess medication adherence. Identifying oral 5-ASA medication use patterns and risk factors associated with nonpersistence and nonadherence may help determine formulary decisions, as well as design and intervention programs to improve medication adherence and patients' health outcomes. The objective of this study was to evaluate oral 5-ASA medication use patterns and assess risk factors associated with nonpersistence and nonadherence for both index and subsequent oral 5-ASA medications in UC patients.

## ■ Methods

### Data Source and Patients Selection

The IMS LifeLink Health Plan Claims Database includes longitudinal, integrated, and patient-level medical and pharmaceutical claims from across the United States. The data include records of more than 70 million patients from over 75 health plans and incorporates the data for medical services and prescription drug information across the entire continuum of care.<sup>22</sup> The records in the database are generally representative of the national commercially insured population in terms of age and gender.<sup>22</sup> Multi-Matrix System mesalamine was approved by the U.S. Food and Drug Administration (FDA) on January 16, 2007, while other 5-ASA medications reported in the current study were approved by the FDA before this date; therefore, data from January 2007 to July 2011 were analyzed.

Patients were selected if they met the following criteria: (a) aged 18 years or older; (b) presence of at least 1 initial oral 5-ASA pharmacy claim (index date) based on the National Drug Codes (NDCs) during July 2007 to July 2010; (c) at least 1 UC diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code = 556.x [ulcerative colitis]) from the medical claims for the first 4 diagnosis codes for the 6 months prior to and the 12 months after the index date; (d) continuously enrolled in both health and pharmacy plans for the 6 months prior to and the 12 months after the index date; and (e) no pharmacy claim for any 5-ASA, corticosteroids, or immunosuppressive/biologic agents in the 6 months prior to the index date. Patients were excluded if they had a diagnosis in the medical claims data for the first 4 diagnosis codes for Crohn's disease (ICD-9-CM code = 555.x [regional enteritis]), or irritable bowel syndrome (ICD-9-CM code = 564.1 [irritable bowel syndrome, irritable colon, spastic colon, functional disorder of the colon that is generally psychosomatic]) during the 18-month study period.

5-ASA medications based on NDC codes used to identify patients included the products that are currently available in the United States: Multi-Matrix System mesalamine (Lialda); mesalamine delayed-release (Asacol); mesalamine controlled-release (Pentasa, Apriso); balsalazide (Colazal, generic balsalazide disodium); olsalazine (Dipentum); and sulfasalazine (Azulfidine, Azulfidine EN, Sulfazine, Sulfazine EC, and generic sulfasalazine). The initial 5-ASA was defined as index medication. The cohorts with small sample sizes (multiple index drugs, in which patients had pharmacy claims for more than 1 5-ASA on the index date [N=18], index olsalazine [N=43], and index mesalamine controlled-release (Apriso [N=68], Pentasa [N=171]) were excluded from the analysis (Figure 1).

### Medication Use Patterns

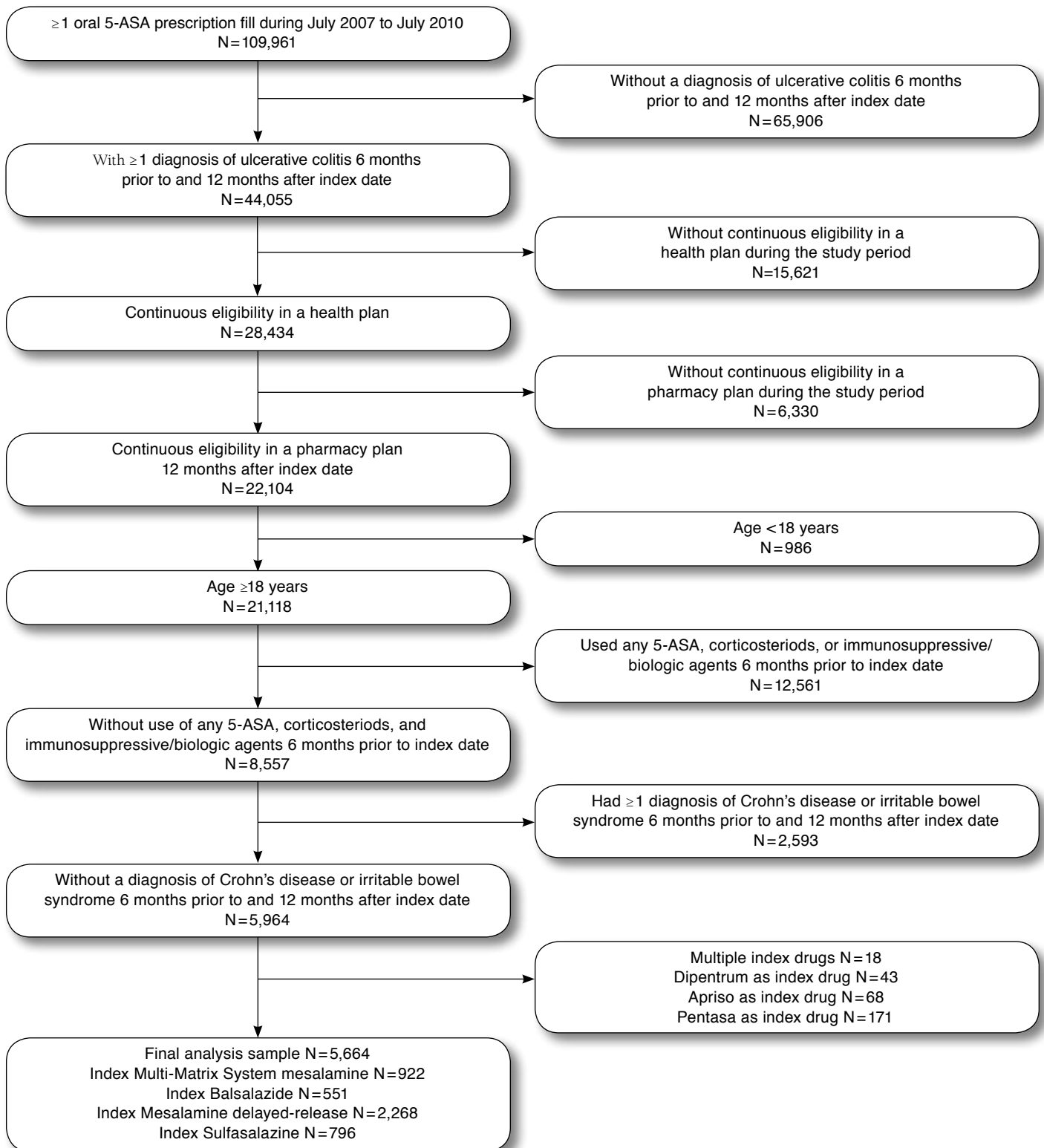
In order to provide a consistent study sample and to require that all patients had the same follow-up period for a valid

comparison, medication use patterns (discontinuation, restart of treatment after discontinuation, switch, and nonadherence) in the 12 months post-index date were evaluated. Patients with *discontinuation or nonpersistence* to index medication experienced a gap of at least 60 days for the index medication or at least 60 days without medication before the last day of the study period for that patient. A gap of 60 days (twice the duration of a monthly prescription) was consistent with a published 5-ASA persistent study.<sup>21</sup> Although patients may need to switch medications due to side effects, lack of treatment efficacy, or other reasons, investigating discontinuation or nonpersistence to index medication provided important information on how patients behaved on their index medications and how long they stayed on the index medication. *Restart* was defined as the patients who refilled the index medication following discontinuation. *Switch* was defined as the patients who changed to a second 5-ASA drug after discontinuing the index medication. Two types of switches were defined. The first, "switch without gap" categorized patients that overlapped or initiated the new 5-ASA medication within 60 days of the last index drug filled. The second type, "switch with gap," categorized patients that initiated the new 5-ASA medication at least 60 days after the discontinuation of the index 5-ASA. Therefore, patients were further stratified to 4 categories after discontinuing the index medication: (a) no further treatment (neither switch to other 5-ASA nor restart of the index 5-ASA medication); (b) switch to another 5-ASA medication, including switch with and without a gap; (c) restart the index medication; and (d) switch and restart, in which the patients may switch to another 5-ASA drug, then discontinue, and then restart the index 5-ASA drug, or they could restart the index 5-ASA drug during the rest of follow-up period, then switch to a different 5-ASA drug. The duration from initiation to the first discontinuation of the index medication represented *persistence*. Time to discontinuation, restart, and switch were evaluated.

Medication adherence was summarized using medication possession ratio (MPR) or proportion of days covered (PDC), in which we followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Outcomes Research Practices guidelines for the medication adherence methods.<sup>23,24</sup> In order to understand patients' medication taken behavior on their index medications and subsequent oral 5-ASA medications, we assessed adherence to index medication and adherence to any 5-ASA medication. The MPR was calculated as the total number of days of index medication supplied divided by the number of days in the specified time interval (360 days). The PDC was calculated as the number of days with any oral 5-ASA drug on hand divided by the number of days in the specified time interval (360 days). A uniform period of 1 year (360 days) was used in our calculation to ensure equal and accurate long-term adherence behavior profiles. Overlapping pharmacy claims (e.g., an early refill) for the

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**FIGURE 1** Sample Selection Flowchart



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index medication were assessed for MPR based on the assumption that the prior supply was taken fully before the new supply was initiated, so the start date for a refill was delayed until the prior supply had been exhausted. However, if switching therapy occurred, or a new prescription for a different medication was filled before a previous prescription was expected to expire, it was assumed that the leftover supply from the previous medication was discarded to begin the new drug. Because there may have been more than a total 360 days of prescription fills within one year, MPR was commonly truncated at 1.0. Nonadherence to index medication was determined by  $MPR < 0.8$ , while nonadherence to any 5-ASA medications was defined by  $PDC < 0.8$ .<sup>23</sup>

### Independent Variables

Sociodemographic risk indicators included age, gender, and region (Northeast, South, Midwest, and West). Health insurance information included payer type (commercial plan, self-insured, Medicare fee for service [FFS], Medicaid, Medicare Risk, and unknown) and plan product type (consumer-directed health care [CDHC], indemnity plan [IP], point of service [POS], health maintenance organization [HMO], preferred provider organization [PPO], and unknown).

Existing comorbid conditions were assessed by Elixhauser comorbidity scores measured during the 6 months prior to the index date.<sup>25</sup> This measure includes 31 conditions and was calculated as the sum of number of comorbidities present in the medical claims data.

Four clinical variables (specialist visits, currently used corticosteroids, immunosuppressive/biologics agents, and the rectal form of 5-ASA) were measured during the 12 months post-index date. A specialist visit was determined by a medical claim associated with a specialty of colorectal surgery or gastroenterology. Corticosteroid use was defined as having at least one pharmacy claim for the drug class of glucocorticosteroids based on the NDC codes. Immunosuppressive use was defined as having at least one pharmacy claim of either azathioprine, 6-mercaptopurine, cyclosporine, or tacrolimus. Biologic agent use was defined as having at least one pharmacy claim of either infliximab, adalimumab, or certolizumab based on the NDC codes. Patients who used immunosuppressive or biologic agents were identified and were treated as a covariate variable. Patients with the rectally applied 5-ASAs (Rowasa enemas or suppositories; Canasa suppositories) were identified from the pharmacy claims associated with the NDC codes.

### Statistical Analyses

Descriptive statistics summarize patient demographic and clinical characteristics, as well as medication use patterns across index medications. Differences among index medication cohorts were tested using chi-square tests for categorical variables, and one-way analyses of variance (ANOVAs) for continu-

ous variables. Due to skewed data distribution for the variables of time to events for medication use patterns, median and range were also calculated. Nonparametric Wilcoxon tests were performed to test the event differences among index medications. One-way ANOVA Kruskal-Wallis test statistics were reported. Analysis of covariance was used to compare MPR and PDC among index medications. Covariate adjusted mean MPR or PDC were estimated from the predicted population marginal mean. If significant differences were found, Tukey multiple comparison tests for adjusting the overall significance level were used to identify significant pairwise differences. A Cox proportional hazards model was used to assess relative hazards associated with discontinuation of index drugs. Multiple logistic regressions with stepwise selection were used to assess risk factors associated with nonadherence.

A survival curve describing the crude discontinuous behavior of oral index 5-ASA treatment was generated using the Kaplan-Meier method. Patients who remained on their index medication until the end of the 360 days follow-up period were considered as censored data, and the length of remaining therapy during follow-up was assigned as their survival time. All analyses were conducted using SAS software (Version 9.2, SAS Institute, Inc., Cary, NC).

## Results

### Patient Characteristics

A total of 5,644 patients were included in the analysis (Figure 1). Table 1 describes patient demographic and clinical characteristics stratified by index medication. Mean age was  $48.3 \pm 15.4$  years. Patients on Multi-Matrix System mesalamine were more likely to have a PPO plan (76.6%) than those on other index medication (range: 71.9% [sulfasalazine] to 73.0% [balsalazide],  $P < 0.0001$ ). Patients from the South were more likely to have a pharmacy claim for balsalazide (43.4%) than for the other 5-ASA drugs (range: 28.5% [sulfasalazine] to 39.7% [Multi-Matrix System mesalamine],  $P < 0.0001$ ). Mean Elixhauser comorbidity scores were significantly different across index medication samples ( $P < 0.0001$ ). Overall, 34.7% of patients had at least one pharmacy claim for corticosteroids, 6.8% for immunosuppressive/biologic agents and 18.3% for a rectal 5-ASA during the 12 months post-index date. There were a greater number of specialist visits in patients on Multi-Matrix System mesalamine ( $2.0 \pm 2.3$ ), balsalazide ( $1.9 \pm 2.2$ ), or mesalamine delayed-release ( $1.9 \pm 2.4$ ) than those on sulfasalazine ( $1.4 \pm 2.0$ ,  $P < 0.0001$ ).

### Medication Use Patterns

Sixty-nine percent of patients discontinued their index medication during the 12 months post-index date (Table 2). Approximately 57% of discontinued patients did not have further 5-ASA treatment (neither restart the index drug nor switch to another drug), while 23.4% restarted the index drug;

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**TABLE 1** Patient Characteristics Stratified by Index Drug

Variable	Total	MMS	Balsalazide	MDR	Sulfasalazine	P Value <sup>a</sup>
Number of patients (%)	5,664 (100.0)	922 (16.3)	551 (9.7)	3,395 (59.9)	796 (14.1)	NA
Age in years, mean (SD)	48.3 (15.4)	45.3 (14.5)	46.2 (14.7)	48.5 (15.5)	52.2 (15.4)	<0.0001
Age category (%)						<0.0001
<65 Years	4,921 (86.9)	851 (92.3)	489 (88.7)	2,938 (86.5)	643 (80.8)	
≥65 Years	743 (13.1)	71 (7.7)	62 (11.3)	457 (13.5)	153 (19.2)	
Gender (%)						<0.0001
Female	2,989 (52.8)	472 (51.2)	281 (51.0)	1,873 (55.2)	363 (45.6)	
Male	2,675 (47.2)	450 (48.8)	270 (49.0)	1,522 (44.8)	433 (54.4)	
Index year (%)						<0.0001
2007	1,553 (27.4)	139 (15.1)	200 (36.3)	971 (28.6)	243 (30.5)	
2008	2,243 (39.6)	396 (43.0)	211 (38.3)	1,337 (39.4)	299 (37.6)	
2009	1,422 (25.1)	303 (32.9)	95 (17.2)	823 (24.2)	201 (25.3)	
2010	446 (7.9)	84 (9.1)	45 (8.2)	264 (7.8)	53 (6.7)	
Payer type (%)						<0.0001
Commercial plan	4,379 (77.3)	722 (78.3)	451 (81.9)	2,610 (76.9)	596 (74.9)	
Medicare FFS/self-insured/unknown	1,023 (18.1)	181 (19.6)	83 (15.1)	632 (18.6)	127 (16.0)	
SCHIP/Medicaid/Medicare risk	262 (4.6)	19 (2.1)	17 (3.1)	153 (4.5)	73 (9.2)	
Plan product type (%)						<0.0001
CDHC/IP/POS	773 (13.6)	93 (10.1)	74 (13.4)	503 (14.8)	103 (12.9)	
HMO	854 (15.1)	100 (10.8)	72 (13.1)	569 (16.8)	113 (14.2)	
PPO	3,948 (69.7)	706 (76.6)	402 (73.0)	2,268 (66.8)	572 (71.9)	
Unknown	89 (1.6)	23 (2.5)	3 (0.5)	55 (1.6)	8 (1.0)	
Region (%)						<0.0001
Midwest	2,358 (41.6)	306 (33.2)	194 (35.2)	1,529 (45.0)	329 (41.3)	
Northeast	791 (14.0)	174 (18.9)	81 (14.7)	474 (14.0)	62 (7.8)	
South	1,823 (32.2)	366 (39.7)	239 (43.4)	991 (29.2)	227 (28.5)	
West	692 (12.2)	76 (8.2)	37 (6.7)	401 (11.8)	178 (22.4)	
Elixhauser comorbidity, mean (SD)	0.9 (1.4)	0.8 (1.2)	0.7 (1.2)	1.0 (1.4)	1.0 (1.4)	<0.0001
Used corticosteroids (%)	1,967 (34.7)	331 (35.9)	189 (34.3)	1,191 (35.1)	256 (32.2)	0.38
Used immunosuppressive/biologic agents (%)	386 (6.8)	70 (7.6)	56 (10.2)	224 (6.6)	36 (4.5)	0.001
Used rectal form of 5-ASA (%)	1,039 (18.3)	221 (24.0)	132 (24.0)	601 (17.7)	85 (10.7)	<0.0001
Number of specialist visits, mean (SD)	1.8 (2.3)	2.0 (2.3)	1.9 (2.2)	1.9 (2.4)	1.4 (2.0)	<0.0001

Note: Data were presented as mean (SD) for continuous variables, number (column percentage) for categorical variables.

<sup>a</sup>P values were calculated from one-way ANOVA for continuous variables, and chi-square tests for categorical variables.

5-ASA = 5-aminosalicylic acid; ANOVA = analysis of variance; CDHC = consumer-directed health care; FFS = fee for service; HMO = health maintenance organization; IP = indemnity plan; MMS = Multi-Matrix System mesalamine; MDR = mesalamine delayed-release; NA = not applicable; POS = point of service; PPO = preferred provider organization; SD = standard deviation.

18% switched to another 5-ASA drug, and approximately 2% of the patients had both restart and switch behaviors. The overall median time to discontinuation was 137 days (ranging from 2 to 300 days). The median times to discontinuation were significantly different among index medications, ranging from 98.5 days for the patients on sulfasalazine to 177.5 days for those on Multi-Matrix System mesalamine ( $P < 0.0001$ ). The probability that patients remained on the 5-ASA therapy substantially decreased after the 30th day (Figure 2), and further decreased on the 90th day, especially for those on sulfasalazine, mesalamine delayed-release, and balsalazide. The substantial decrease in persistence on the 30th and 90th days may relate to an initial fill with 30 or 90 days supply. The patients on sulfasalazine (23%) had higher proportion with 90 days supply than those

on other index drugs, e.g., 10% for Multi-Matrix System mesalamine. Patients on Multi-Matrix System mesalamine were significantly less likely to discontinue the index medication than those on other medications ( $P < 0.0001$ , Figure 2).

The median time to restart index medication after discontinuation was 98 days (ranging from 59 to 331 days) and was similar among the index drug groups ( $P = 0.31$ ). Within the whole sample, 14.8% of patients switched medications. Patients were less likely to switch if the index medication was mesalamine delayed-release ( $N = 468$ , 13.8%) or Multi-Matrix System mesalamine ( $N = 132$ , 14.3%) than if it were balsalazide ( $N = 95$ , 17.2%), or sulfasalazine ( $N = 142$ , 17.8%;  $P = 0.01$ ). Of the 837 patients who switched, 92% switched with at least a 60-day gap; median time to switch was similar among index



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**TABLE 2** Medication Use Patterns Stratified by Index Medication

Variable	Total	MMS	Balsalazide	MDR	Sulfasalazine	P Value <sup>a</sup>
N (%)	5,664 (100.0)	922 (16.3)	551 (9.7)	3,395 (59.9)	796 (14.1)	NA
Discontinuation of index medication (%)	3,891 (68.7)	584 (63.3)	378 (68.6)	2,356 (69.4)	573 (72.0)	0.001
Medication used after discontinuation (%) <sup>b</sup>						0.04
No further 5-ASA treatment	2,212 (56.9)	341 (58.4)	194 (51.3)	1,361 (57.8)	316 (55.2)	
Restart index drug	909 (23.4)	123 (21.1)	95 (25.1)	568 (24.1)	123 (21.5)	
Switch to another 5-ASA	699 (18.0)	107 (18.3)	80 (21.2)	392 (16.6)	120 (20.9)	
Restart and switch	71 (1.8)	13 (2.2)	9 (2.4)	35 (1.5)	14 (2.4)	
Time to discontinuation of index drug (days) <sup>b</sup>						
Mean (SD)	177.5 (135.9)	193.7 (138.2)	179.8 (135.1)	175.7 (135.5)	164.9 (133.9)	0.0001
Median	137.0	177.5	148.0	135.0	98.5	<0.0001
Range	2 to 300	2 to 300	2 to 300	2 to 300	4 to 300	
Time to restart index drug after discontinuation (days) <sup>b</sup>						
Mean (SD)	119.8 (61.5)	113.1 (57.4)	121.8 (62.8)	120.1 (62.9)	123.3 (58.5)	0.53
Median	98.0	94.0	98.5	98.0	104.0	0.31
Range	59 to 331	59 to 299	59 to 313	59 to 331	59 to 324	
Switch index drug (%)	837 (14.8)	132 (14.3)	95 (17.2)	468 (13.8)	142 (17.8)	0.01
Without gap (%)	67 (8.0)	12 (9.1)	6 (6.3)	41 (8.8)	8 (5.6)	
With gap (%)	770 (92.0)	120 (90.9)	89 (93.7)	427 (91.2)	134 (94.4)	
Time to switch index drug <sup>c</sup>						0.55
Mean (SD)	136.3 (106.2)	139.4 (109.1)	152.8 (116.5)	134.3 (101.5)	128.6 (110.9)	
Median	107.0	103.0	117.0	114.0	90.5	0.29
Range	2 to 360	2 to 357	2 to 352	2 to 358	5 to 360	

<sup>a</sup>P values were calculated from one-way ANOVAs (presented in the corresponding row for mean [SD]) and nonparametric Kruskal-Wallis tests (presented in the corresponding row for median) for the continuous variables and chi-square tests for the categorical variables.

<sup>b</sup>Data only included patients who discontinued index medication.

<sup>c</sup>Data only included patients who switched index drug.

5-ASA = 5-aminosalicylic acid; ANOVA = analysis of variance; MMS = Multi-Matrix System mesalamine; MDR = mesalamine delayed-release; NA = not applicable; SD = standard deviation.

medications—107 days (ranging from 2 to 360 days;  $P=0.29$ ).

The analysis of covariance reported in Table 3 shows that covariate-adjusted oral 5-ASA medication adherence was significantly greater in patients on Multi-Matrix System mesalamine (MPR/PDC:  $0.51 \pm 0.02/0.58 \pm 0.02$ ) than those on balsalazide ( $0.47 \pm 0.02/0.54 \pm 0.02$ ) or mesalamine delayed-release ( $0.46 \pm 0.01/0.54 \pm 0.01$ ) or sulfasalazine ( $0.42 \pm 0.02/0.52 \pm 0.02$ ), for MPR ( $P<0.01$ ) and PDC ( $P<0.02$ ), respectively. Nonadherence rates for each index drug ranged from a low of 76.9% for those on Multi-Matrix System mesalamine to 85.2% for those on sulfasalazine and were significantly different among index medications ( $P<0.0001$ ). Overall nonadherence rate for any 5-ASA medication was 79%, ranging from 74.2% for patients on Multi-Matrix System mesalamine to 82% for those on sulfasalazine.

### Risk Factors Associated with Discontinuation of Index Medication

Analysis from the multivariable Cox model indicated that factors associated with discontinuation of index medication included younger patients (hazard ratio [HR]=0.991, 95%

confidence interval [CI]=0.989-0.993), patients on index balsalazide (HR=1.21, CI=1.07-1.36), mesalamine delayed-release (HR=1.21, CI=1.11-1.32), or sulfasalazine (HR=1.40, CI=1.25-1.57), as compared with those on Multi-Matrix System mesalamine, female gender (HR=1.16, CI=1.09-1.23), never receiving specialist care (HR=1.14, CI=1.07-1.21), and a greater number of comorbidities (HR=1.05, CI=1.02-1.07). Patients with a PPO plan (HR=1.14, CI=1.04-1.24) versus HMO, or with a plan payer for Medicare FFS or self-insured (HR=1.29, CI=1.10-1.52) versus commercial plan were more likely to discontinue the index medication (Table 4).

### Predictors of Nonadherence with Index or Any 5-ASA Medication

Table 5 presents the results for stepwise multivariable logistic regression models. Significant predictors for index drug nonadherence (MPR<0.8) included the following: age younger than 65 years (odds ratio [OR]=1.84, CI=1.53-2.23); index medication versus Multi-Matrix System mesalamine (balsalazide: OR=1.49, CI=1.13-1.95, mesalamine delayed-release: OR=1.60, CI=1.33-1.92, sulfasalazine: OR=1.89, CI=1.47-2.45);

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**TABLE 3** Medication Adherence Measure Stratified by Index Drug

Variable	Total	MMS	Balsalazide	MDR	Sulfasalazine	P Value <sup>a</sup>
Number of patients (%)	5,664 (100.0)	922 (16.3)	551 (9.7)	3,395 (59.9)	796 (14.1)	NA
<b>Adherence to index drug</b>						
Unadjusted MPR, mean (SD)	0.43 (0.31)	0.47 (0.32)*	0.43 (0.30) <sup>†</sup>	0.43 (0.31) <sup>†</sup>	0.39 (0.30) <sup>†</sup>	<0.0001
Adjusted MPR, mean (SE)	NA	0.51 (0.02)*	0.47 (0.02) <sup>†</sup>	0.46 (0.01) <sup>†</sup>	0.42 (0.02) <sup>†</sup>	<0.01
Adherence of index drug (%)						<0.0001
MPR: <0.50	3,241 (57.2)	475 (51.5)	315 (57.2)	1,949 (57.4)	502 (63.1)	
MPR: 0.50-0.79	1,429 (25.2)	234 (25.4)	140 (25.4)	879 (25.9)	176 (22.1)	
MPR: ≥0.80	994 (17.6)	213 (23.1)	96 (17.4)	567 (16.7)	118 (14.8)	
<b>Adherence to any 5-ASA drug</b>						
Unadjusted PDC, mean (SD)	0.48 (0.31)	0.51 (0.31)*	0.48 (0.30)* <sup>†</sup>	0.48 (0.31) <sup>†</sup>	0.45 (0.30) <sup>†</sup>	<0.0001
Adjusted PDC, mean (SE)	NA	0.58 (0.02)*	0.54 (0.02) <sup>†</sup> <sup>‡</sup>	0.54 (0.01) <sup>†</sup>	0.52 (0.02) <sup>†</sup>	<0.02
Adherence of any 5-ASA drug (%)						0.002
PDC: <0.50	2,906 (51.3)	434 (47.1)	281 (51.0)	1,748 (51.5)	443 (55.6)	
PDC: 0.50-0.79	1,568 (27.7)	250 (27.1)	157 (28.5)	951 (28.0)	210 (26.4)	
PDC: ≥0.8	1,190 (21.0)	238 (25.8)	113 (20.5)	696 (20.5)	143 (18.0)	

<sup>a</sup>P values were calculated from chi-square tests for categorical adherence variables, one-way ANOVAs for unadjusted MPR and PDC. Analysis of covariance was used to compare adjusted mean of MPR or PDC across the different index medications. Covariates were the variables listed in Table 1. For each row, adjusted means with different symbols (\*,†,‡) across the index medication are statistically significantly different from one another using the Tukey multiple comparison procedure (P<0.05). The P value in the corresponding column for the row of adjusted MPR or PDC is the maximum across all significant Tukey pairwise comparisons of adjusted mean values, or the minimum across all nonsignificant Tukey pairwise comparisons.

5-ASA = 5-aminosalicylic acid; ANOVA = analysis of variance; MMS = Multi-Matrix System mesalamine; MDR = mesalamine delayed-release; MPR = medication possession ratio for index drug; NA = not applicable; PDC = proportion days covered for any oral 5-ASA drug; SD = standard deviation; SE = standard error.

**TABLE 4** Risk Factors Associated with Discontinuation of Index Drug from Cox Model

Variable	HR	95% CI		P Value
Age	0.991	0.989	0.993	<0.0001
Index drug				<0.0001
Multi-Matrix System mesalamine	1.00			
Balsalazide	1.21	1.07	1.36	0.002
Mesalamine delayed-release	1.21	1.11	1.32	<0.0001
Sulfasalazine	1.40	1.25	1.57	<0.0001
Female gender	1.16	1.09	1.23	<0.0001
Never receiving specialist care	1.14	1.07	1.21	<0.0001
Elixhauser comorbidities	1.05	1.02	1.07	0.0002
Plan product type				0.01
HMO	1.0			
CDHC/IP/POS	0.99	0.88	1.13	0.95
PPO	1.14	1.04	1.24	0.005
Plan payer type				0.008
Commercial plan	1.0			
Medicaid/Medicare risk	0.99	0.92	1.09	0.98
Medicare FFS/self-insured	1.29	1.10	1.52	0.002

Note: Cox proportional hazards model with stepwise selection was performed to assess the factors associated with discontinuing index drug. The variables presented in Table 1 with P values <0.2 from the univariate analyses were included in the model. Only the significant variables in the order of the steps entered to the model were presented in the table (variables with P values >0.05 are not reported).

CI = confidence interval, CDHC = consumer-directed health care; FFS = fee for service; HMO = health maintenance organization; HR = hazard ratio; IP = indemnity plan; POS = point of service; PPO = preferred provider organization.

female gender (OR = 1.34, CI = 1.16-1.54); residing in the different geographic regions as compared with the Midwest (West [OR = 1.38, CI = 1.10-1.75], South [OR = 1.46, CI = 1.23-1.72], and Northeast [OR = 1.28, CI = 1.03-1.58]); no use of immunosuppressive/biologic agents during 12 months post-index date (OR = 1.39, CI = 1.08-1.79), and never receiving specialist care (OR = 1.20, CI = 1.04-1.39).

Significant predictors for nonadherence with any 5-ASA drug (PDC < 0.8) were similar with those for nonadherence with the index drug (Table 5). In addition, no history of switching the index drug was the most important factor associated with nonadherence with any 5-ASA drug (OR = 1.90, CI = 1.58-2.29). Other factors included no use of the rectal form of 5-ASA (OR = 1.28, CI = 1.08-1.50) in the post-index study period. Those with a Medicaid/Medicare risk payer were significantly associated with nonadherence with any 5-ASA medication (OR = 1.48, CI = 1.03-2.13).

**Discussion**

The medication nonadherence rate in our study (79%) was higher than those previously reported from epidemiological or clinical studies based on nonstandardized self-report questionnaires, nonstandardized patient/parent interviews, pill counts, or pharmacy records, which ranged from 40% to 72%.<sup>6,7</sup> This finding confirms the problem of medication nonadherence in UC patients in the United States. Oral 5-ASA medication use



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**TABLE 5** Logistic Regression Models Predicting Nonadherence with Index or Any Oral 5-ASA Medication

Variable	Nonadherence with Index Drug (MPR < 0.8)					Nonadherence with Any 5-ASA Drug (PDC < 0.8)				
	OR	95% CI		P Value	Step Order <sup>a</sup>	OR	95% CI		P Value	Step Order <sup>a</sup>
No switch from index drug	NA					1.90	1.58	2.29	<0.0001	1
Age <65 years vs. ≥65 years	1.84	1.53	2.23	<0.0001	1	1.90	1.56	2.31	<0.0001	2
Index drug				<0.0001	2				0.0001	5
Multi-Matrix System mesalamine	1.0					1.0				
Balsalazide	1.49	1.13	1.95	0.004		1.43	1.10	1.85	0.007	
Mesalamine delayed-release	1.60	1.33	1.92	<0.0001		1.41	1.19	1.68	0.0001	
Sulfasalazine	1.89	1.47	2.45	<0.0001		1.66	1.30	2.12	<0.0001	
Female gender vs. male	1.34	1.16	1.54	<0.0001	3	1.33	1.17	1.52	<0.0001	4
Region				0.0003	4				0.0003	6
Midwest	1.0					1.0				
West	1.38	1.10	1.75	0.007		1.35	1.08	1.69	0.008	
South	1.46	1.23	1.72	<0.0001		1.40	1.20	1.64	<0.0001	
Northeast	1.28	1.03	1.58	0.02		1.29	1.05	1.58	0.02	
Rectal form of 5-ASA not used						1.28	1.08	1.50	0.004	7
Immunosuppressive/biologic agents not used	1.39	1.08	1.79	0.01	5	1.70	1.35	2.14	<0.0001	3
Never receiving specialist care	1.20	1.04	1.39	0.02	6	1.25	1.08	1.44	0.002	8
Plan payer type										9
Commercial plan						1.0				
Medicaid/Medicare risk						1.48	1.03	2.13	0.03	
Medicare FFS/self-insured						0.89	0.75	1.06	0.18	
C statistic	C = 0.61					C = 0.63				
Hosmer and Lemeshow Goodness of Fit Test	Chi-square = 13.21, P = 0.10					Chi-square = 4.04, P = 0.85				

Note: Logistic regression models with stepwise selection were performed to assess the factors associated with nonadherence with index drug (MPR < 0.8) and nonadherence with any oral 5-ASA medications (PDC < 0.8). Variables entered in the models for the analysis were those presented in Table 1. Only the statistically significant variables in the final step were presented in Table 5 (variables with P values > 0.05 are not reported).

<sup>a</sup>Step order is the order of the significant variables entered into the logistic regression model, which indicates the importance of the variables.

5-ASA = 5-aminosalicylic acid; CI = confidence interval; FFS = fee for service; MPR = medication possession ratio; NA = not applicable; OR = odd ratio; PDC = proportion of days covered.

patterns varied among patients initiated on different 5-ASA medications. Patients on Multi-Matrix System mesalamine were at the lowest risk to discontinue the index medication, as they had the lowest discontinuation/nonpersistence rate, the longest median days remaining on their index drug, the lowest probability to discontinue from the survival analysis, and were less likely to discontinue in a Cox proportional hazards model as compared with the patients on any of the other 5-ASA index drugs. Patients on Multi-Matrix System mesalamine were also less likely to switch drugs as compared with those on balsalazide or sulfasalazine. Patients on Multi-Matrix System mesalamine had the lowest oral index 5-ASA nonadherence rate (76.9%) among the index drug samples. Based on the survival curves, the probabilities of remaining on therapy (persistence to the index drug) at 360 days was 24% for patients on Multi-Matrix System mesalamine, 19% for mesalamine delayed-release, 18% for balsalazide, and 16% for sulfasalazine ( $P < 0.0001$ , Figure 2). Our results indicated that patients on Multi-Matrix System mesalamine had a significantly higher

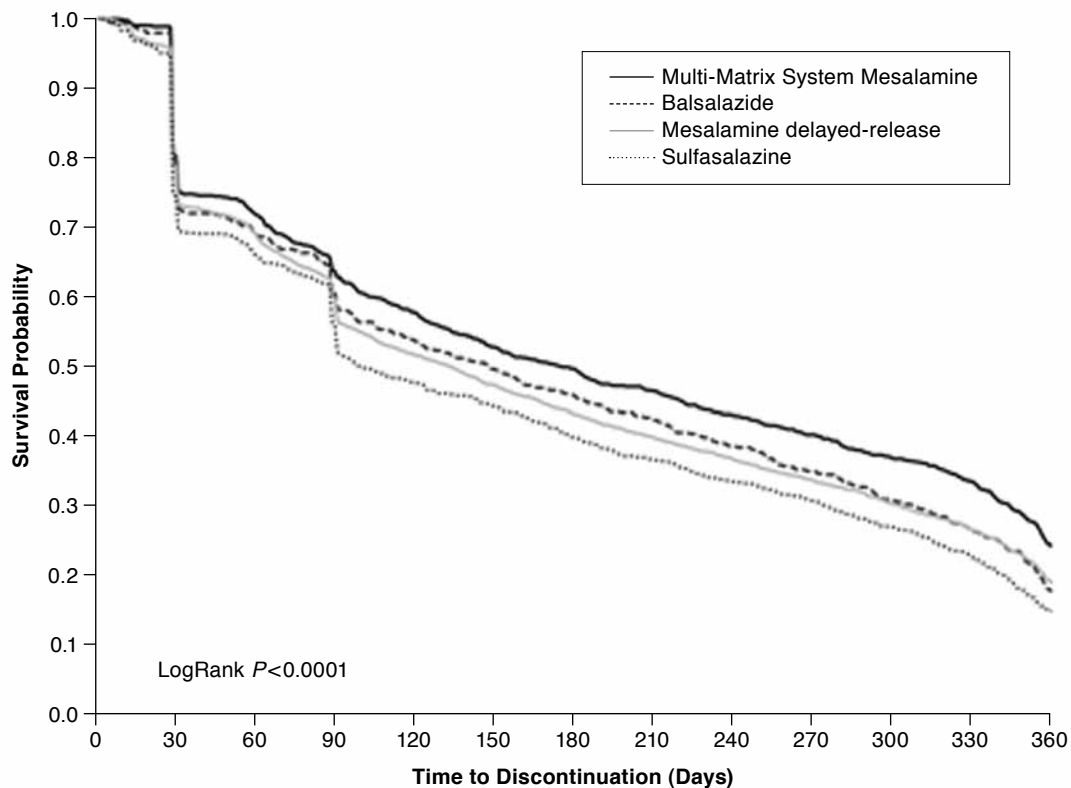
probability to be persistent to their medication than those on other 5-ASA medications.

A recent study conducted by Kane et al. (2011)<sup>21</sup> analyzed a large U.S. pharmacy data file to examine persistency with oral 5-ASA therapy in UC patients. They found that patients receiving once-daily Multi-Matrix System mesalamine had a significantly higher persistence rate after 1 year of treatment than those receiving other oral 5-ASA therapies. Our findings on discontinuation/nonpersistence to the index medication are consistent with these results, although our study used different patient selection criteria and different treatment pattern definitions.

The present study also addresses an important issue in the literature: the conflicting reports on the relationship between formulation and nonadherence.<sup>7,13,16-18,21,26,27</sup> Although a few studies reported that daily dose regimen and formulation do not significantly impact adherence,<sup>7,13</sup> 2 current studies using patient surveys revealed that frequent dosing and pill burden were important factors for nonadherence.<sup>16,26</sup> Similarly, 2

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**FIGURE 2** Time to Discontinuation by Index Medications in a 360-Day Study Period



clinical observational studies have indicated that multiple-daily dosing is associated with medication nonadherence in UC patients.<sup>8,17</sup> The results from our study indicated that patients on once-daily dosing Multi-Matrix System mesalamine had the lowest nonadherence as measured by either the mean MPR or by the proportion of patients with an MPR lower than 0.8. Moreover, the mean MPRs were significantly different across the index drug samples, even with demographic and clinical characteristics adjustments. When medication adherence measurement accounted for drug switching, adherence to any 5-ASA drug as measured by PDC was greater than MPR; patients on once-daily Multi-Matrix System mesalamine had the highest PDC. Moreover, the results from the logistic regression analyses indicated that the choice of index medication was a significant factor associated with nonadherence. Patients on balsalazide, mesalamine delayed-release, and sulfasalazine were more likely to be nonadherent as compared with those on Multi-Matrix System mesalamine. These results further demonstrated that the once-daily dosing 5-ASAs may have a significant impact on medication adherence.

From the logistic regression analyses, our study showed that the factors associated with nonadherence with index 5-ASA

or with any 5-ASA medication were similar. In addition, the results revealed that a history of switching was one of the most important factors associated with patient adherence with the oral 5-ASA medication therapy. Since the patients on mesalamine delayed-release or Multi-Matrix System mesalamine were less likely to switch, they were adherent with their index drug to remain on the therapy, while those on balsalazide or sulfasalazine switched from the index 5-ASA to nonindex 5-ASA more frequently.

A recent systematic review concluded that demographic, clinical, and treatment variables were not consistently associated with nonadherence to oral medication in IBD.<sup>27</sup> Specifically, reports of the impact of age and gender on nonadherence were inconsistent.<sup>26-32</sup> We found that being younger than 65 years and being female were independently associated with nonadherence. Although age and gender are not mutable factors, these factors may have different impacts on responses to drug therapy. Therefore, personalized therapy should be considered when treating patients with UC.

Clinical variables such as disease duration, clinical activity, and extent/location have been reported to be significantly associated with nonadherence.<sup>26</sup> As one of the limitations using

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claims data for adherence research, we do not have detailed clinical information. However, we found that patients who did not use immunosuppressive/biologic agents, or who did not use the rectal form of 5-ASA, were significantly associated with nonadherence to oral 5-ASA treatment. Immunosuppressive/biologic agents are usually given to patients who do not respond to 5-ASAs or corticosteroids or who are dependent on corticosteroids.<sup>3-5</sup> The rectal form of 5-ASA is effective in inducing and maintaining remission in patients with UC limited to the distal colon and rectum. Therefore, these variables served as a proxy measurement of disease severity or location. Patients with less severe conditions tended to be nonadherent. Also, patients taking the rectal form tended to be more adherent with oral 5-ASA medication.

Findings related to residential region may indicate that physician practices varied by region. In addition, we found that patients with a public insurance payer (Medicaid or Medicare risk) were significantly associated with nonadherence with any oral 5-ASA as compared with a commercial plan. Insurance coverage is known to increase access to care and to improve health outcomes.<sup>33,34</sup> Appropriate public insurance redesign for UC patients may adequately provide for health care that UC patients need to improve medication adherence.

### Limitations

Claims data analyses have some common limitations. We were not able to determine whether and to what extent patients actually used the prescribed medication because information in the data refers to filled prescriptions. Additionally, the reasons for the medication use patterns, such as discontinuation and switch cannot be determined. Administrative claims data lack socioeconomic (e.g., income and educational levels) and clinical information (e.g., disease severity, activity, and duration) and may also contain coding errors. Despite these limitations, results from previous studies support the use of pharmacy claims data to measure adherence<sup>35,36</sup> and have been widely applied in many chronic diseases.<sup>37-39</sup>

### Conclusion

Oral 5-ASA medication use patterns varied among index drugs. Once-daily Multi-Matrix System mesalamine had the lowest risk of discontinuation and highest adherence rate. Multiple factors were significantly associated with nonpersistence or nonadherence with 5-ASA, including multiple-daily dosed index medication, younger age, female gender, residing in the South region, PPO plan, noncommercial payer, not using immunosuppressive/biologic agents, not using rectal form of 5-ASA, and never receiving specialist care. This research provides clinicians with insights into patient variables associated with 5-ASA medication nonpersistence/nonadherence and may help make informed decisions on future programs designed to target specified risk factors to improve medication persistency and adherence in patients with UC.

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### DISCLOSURES

Sponsored by Shire Development LLC, Linnette Yen and Paul Hodgkins are employees of Shire Development LLC; Joanne Wu and Michael Nichol were financially supported by an unrestricted research agreement between Shire Development LLC and the University of Southern California. Russell Cohen reports consulting work for Shire, Salix, and Warner Chilcott and has received honoraria for lectures from Shire.

Concept and design were developed by Yen, Wu, Nichol, and Hodgkins. Data were collected by Wu and Yen, and interpreted by Wu, Yen, Nichol, Hodgkins, and Cohen. The manuscript was written by Wu with the assistance of Nichol and Yen. Revisions were made by all coauthors.

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