Impact of Cost-Sharing Increases on Continuity of Specialty Drug Use: A Quasi-Experimental Study

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Objective. To examine the impact of cost-sharing increases on continuity of specialty drug use in Medicare beneficiaries with multiple sclerosis (MS) or rheumatoid arthritis (RA).

Data Sources/Study Setting. Five percent Medicare claims data (2007–2010).

Study Design. Quasi-experimental study examining changes in specialty drug use among a group of Medicare Part D beneficiaries without low-income subsidies (non-LIS) as they transitioned from a 5 percent cost-sharing preperiod to a ≥ 25 percent cost-sharing postperiod, as compared to changes among a disease-matched contemporaneous control group of patients eligible for full low-income subsidies (LIS), who faced minor cost sharing ($\leq \$6.30$ copayment) in both the pre- and postperiods.

Data Collection/Extraction Methods. Key variables were extracted from Medicare data.

Principal Findings. Relative to the LIS group, the non-LIS group had a greater increase in incidence of 30-day continuous gaps in any Part D treatment from the lower cost-sharing period to the higher cost-sharing period (MS, absolute increase = 10.1 percent, OR = 1.61, 95% CI 1.19–2.17; RA, absolute increase = 21.9 percent, OR = 2.75, 95% CI 2.15–3.51). The increase in Part D treatment gaps was not offset by increased Part B specialty drug use.

Conclusions. Cost-sharing increases due to specialty tier-level cost sharing were associated with interruptions in MS and RA specialty drug treatments.

Key Words. Medicare, pharmaceuticals: prescribing/use/costs, observational data/quasi-experiments, chronic illness

Specialty drugs often represent significant new treatment options for chronic and/or life-threatening diseases, but they are increasingly subject to high cost sharing that may interfere with patients' access to treatment (Doshi et al. 2016). Rising specialty drug spending has made these agents a particular focus

of payer cost management strategies, including the use of a “specialty tier” that typically requires patients to pay a percentage of the drug cost (coinsurance) rather than a flat copayment. This extra tier is added to the traditional tier structure that commonly charges copayments of increasing amounts for generics (sometimes divided into preferred generics and nonpreferred generics), preferred brands, and nonpreferred brands. Specialty tiers were first introduced with the implementation of the Medicare Part D benefit in 2006, wherein the Center for Medicare and Medicaid Services (CMS) explicitly allowed Part D plans to assign drugs with prices exceeding a CMS-established monthly cost threshold (\$600/month for the past 5 years) to specialty tiers with cost sharing ranging from 25 to 33 percent (Hoadley et al. 2009; Centers for Medicare and Medicaid Services 2014). Today, a substantial percentage of patients face such specialty tiers. Virtually all Medicare Part D plans that use a tiered benefit structure have a specialty tier (Centers for Medicare and Medicaid Services 2014), and they have also become commonplace across the insurance market, including employer-sponsored insurance plans and health insurance exchanges (Claxton et al. 2014; Pearson 2014).

The high out-of-pocket costs associated with specialty tiers are of particular concern for patients with chronic conditions where long-term specialty drug treatment is typically recommended. While several studies have examined the impact of cost sharing on specialty drug use, further research is needed on the impact of specialty tier-level cost sharing, particularly in the Medicare population (Doshi et al. 2016). Furthermore, given that Medicare Part D plans have a variable cost-sharing structure over the course of the coverage year, they provide a natural laboratory in which to study whether cost

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sharing is associated with treatment continuity. Starting at the beginning of each calendar year, patients are typically responsible for a deductible (usually \$250–\$360), followed by specialty tier coinsurance (25–33 percent) during an initial coverage phase. After reaching an initial coverage limit, they enter a coverage gap, followed by a catastrophic coverage phase (requiring 5 percent coinsurance) that continues for the remainder of the calendar year (Kaiser Family Foundation 2015a). Coverage resets on January 1 of the next calendar year, and patients again face a deductible and 25–33 percent coinsurance for specialty drugs under the new year's initial coverage phase. In contrast, patients eligible for full low-income subsidies under Medicare Part D face nominal cost sharing throughout the year and thus represent a natural control group.

In this study, we used nationally representative data from the 2007 to 2010 5 percent Medicare files to examine the impact of cost-sharing increases on continuity of treatment in Medicare Part D patients receiving specialty drug treatment for multiple sclerosis (MS) or rheumatoid arthritis (RA). Both MS and RA are highly relevant disease areas in which to examine the impact of cost sharing on specialty drug treatment continuity, for several reasons. First, both are chronic inflammatory conditions with major pharmacological treatments that fall under the specialty drug classification. For patients with relapsing forms of MS (Lublin et al. 2014), an often disabling demyelinating disease of the central nervous system, a class of specialty drugs known as disease-modifying therapies target inflammation and are proven to reduce relapses and disability (Freedman 2013; Costello et al. 2015). For RA, the most common idiopathic inflammatory arthritis (Helmick et al. 2008), current clinical management guidelines support aggressive treatment, including biologic specialty drugs, in patients with moderate to high disease activity in order to slow radiographic disease progression, reduce signs and symptoms of RA, and achieve higher rates of disease remission (Smolen et al. 2010; Singh et al. 2016).

Second, for both conditions, ongoing treatment is typically recommended even when disease activity is well controlled on the specialty drug, and interruptions in treatment with specialty drugs have been linked with worsening of disease and increased disability (Lagana et al. 2009; Contreras-Yanez et al. 2010; Smolen et al. 2010; Tanaka et al. 2010; O'Connor et al. 2011; Siger et al. 2011; Ghezzi et al. 2013; Menzin et al. 2013; Fox et al. 2014; Gueguen et al. 2014; Kremer et al. 2014; Bluett et al. 2015; Cohen et al. 2015; Markusse et al. 2015; Mjaavatten et al. 2015; Singh et al. 2016). Third, MS and RA are among the top drivers of specialty drug spending in the United

States (Aitken et al. 2016). Fourth, the two conditions differ somewhat in regard to availability of alternative treatment options at lower cost sharing. During our study period, a majority of the commonly used specialty drugs for MS were covered only under Part D and hence subject to high levels of specialty tier coinsurance. For RA, several biologics were available as infusibles and thereby available to most beneficiaries at low or no out-of-pocket costs under the Medicare Part B medical benefit (due to supplemental insurance coverage). Fifth, the implications of relapses and disease progression also differ somewhat between the two diseases. MS patients may be more cognizant of the potential severity of the consequences associated with treatment interruption, which may include risk of relapse and associated temporary or permanent disability such as weakness, vision loss, or cognitive dysfunction. Examining both conditions allowed us to assess whether MS patients would show relatively lower price sensitivity (the degree to which increases in out-of-pocket price would affect specialty drug utilization behavior) than RA patients.

METHODS

Data Source

Data were drawn from the most recent (2007–2010) Chronic Conditions Data Warehouse 5 percent Medicare files available at the time of our analyses. This included Medicare Part A (inpatient), Part B (outpatient hospital, physician services, other outpatient services, durable medical equipment), and Part D (prescription drug event) claims files for a 5 percent random sample of Medicare beneficiaries. These files were linked to personal summary files that contain patient demographic and eligibility information, Part D plan characteristics files, and Part D plan formulary characteristics files.

Study Design and Samples

We used a quasi-experimental study design. We examined the change in specialty drug use among patients without low-income subsidies (“non-LIS group/study group”) as they transitioned from a period of lower cost sharing (preperiod) to a period of higher cost sharing (postperiod). As shown in Figure 1, the preperiod was defined as the start of the Part D catastrophic coverage phase (i.e., following the coverage gap) through December 31 of the previous year, when cost sharing was at the 5 percent level. The postperiod was

defined as January 1 through the end of the Part D initial coverage phase in the current year (i.e., prior to the coverage gap), when cost sharing jumped back to 25 percent or more. Our claims data indicated that these specialty drugs had average costs of approximately \$2,000 (MS) and \$1,600 (RA) per 30-day supply. Thus, pre/post changes in cost sharing translated into our disease-specific non-LIS groups facing an increase in out-of-pocket costs from \$80-\$100 in the preperiod to more than \$400-\$500 in the postperiod. We then compared the study group's pre/post change in specialty drug use with the pre/post change in specialty drug use among disease-matched contemporaneous control groups of full LIS patients ("LIS group/control group"), who were not subject to a deductible or specialty tier cost sharing. Rather, they faced a \$0 copayment in the preperiod and nominal cost sharing (up to \$6.30) in the postperiod (Figure 1).

In defining the higher cost-sharing period (postperiod), we began on January 1 and combined the deductible phase and initial coverage phase for two reasons. First, about half of Medicare Part D plans did not require a deductible during our study period. Second, given the cost of the Part D specialty drugs we examined, non-LIS patients who were subject to a deductible would have met it with the first fill on or after January 1, since the standard Part D deductible has been set by CMS at \$250 to \$360 for the past 10 years (Kaiser Family Foundation 2015a).

The study samples consisted of beneficiaries with continuous fee-for-service Medicare coverage who were enrolled in a stand-alone Part D plan during both the previous year and the current year. We then identified patients with at least one inpatient or two outpatient claims with diagnoses for MS (ICD-9-

Figure 1: Study Design

	Low Cost-Sharing Period (Pre-Period)	High Cost-Sharing Period (Post-Period)
Non-LIS* (study group)	Catastrophic coverage phase in prior year Cost sharing: 5% of total drug cost	Initial coverage phase in current year Cost sharing: 25%-33% of total drug cost
LIS (control group)	Catastrophic coverage phase in prior year Cost sharing: \$0	Initial coverage phase in current year Cost sharing: ≤\$6.30

Notes. *LIS indicates low-income subsidy. In these analyses, initial coverage phase includes the initial deductible phase, typically ≤\$360 in a standard Part D plan.

CM code 340) or RA (ICD-9-CM code 714) in both years. As claims data lack the clinical details necessary to identify patients who are eligible for treatment with Part D specialty drugs for these conditions, we included only those patients who had used Part D–covered disease-modifying treatments for MS or biologics for RA during the lower cost-sharing period (i.e., preperiod). Because patients could theoretically have entered the catastrophic coverage phase very late in the calendar year, we further restricted the sample to patients who spent at least 30 days each in the pre- and postperiods. This ensured that sufficient time would have passed to allow for the possibility of a 30-day gap in treatment during each observation period (i.e., to observe the primary categorical outcome, described below, of presence or absence of one or more 30-day gaps in specialty drug treatment). Finally, a few patients whose LIS status changed across the pre- and postperiods were excluded. When patients met these eligibility criteria for more than one of the 2-year segments included in our study period (e.g., 2007–2008 and 2009–2010), multiple pairs of pre/post observations from individual patients were permitted.

Outcome Measures

Outcomes were measured in both the preperiod (lower cost sharing) and postperiod (higher cost sharing). In keeping with prior studies, the primary study outcome was presence or absence of a gap in specialty drug treatment (Curkendall et al. 2008; Lafata et al. 2008; Borah et al. 2009; Yazici et al. 2009; Reynolds et al. 2010; Kim et al. 2011; Evans et al. 2012). This was captured via a dichotomous measure of whether a patient's claims data indicated at least one continuous gap of ≥ 30 days with no supply of a disease-specific Part D specialty drug (Sikka, Xia, and Aubert 2005; Peterson et al. 2007). To check for these treatment gaps, we spread the reported days' supply from each Part D specialty drug prescription from the fill date to the date the supply would have been exhausted. We then calculated whether each day in the pre- and postperiod was covered (or not covered) by a specialty drug fill. This was calculated at the Part D specialty drug class level so that patients who switched from one Part D specialty drug to another would not be erroneously classified as having a gap in treatment. Any day a patient spent in the hospital or in a skilled nursing facility (SNF) was not counted as a gap day in the 30-day gap measurement because patients may have received their medication in the facility.

As some MS disease-modifying treatments (e.g., natalizumab) and RA biologics (e.g., infliximab) fall under Medicare's Part B medical benefit

because they are infusions received under medical supervision (Tu and Samuel 2012), we also examined Part B claims to account for cases where patients may have switched to Part B specialty drugs during an observed Part D gap. This was important both to avoid mischaracterizing a switch in treatment as a gap and because cost sharing is lower for specialty drugs accessed under Part B. While Part B requires a flat 20 percent coinsurance for all services, the vast majority of Medicare beneficiaries have supplemental insurance plans that pick up this cost sharing, meaning that Part B specialty drugs are available at no or low out-of-pocket costs to most patients (Kaiser Family Foundation 2015b). Thus, we also captured a dichotomous measure of a ≥ 30 day continuous gap in *any* (Part D or Part B) specialty drug use during the pre- and postperiods. As there is no “days’ supply” data field associated with Part B disease-modifying therapies or biologics in medical claims, we assigned days’ supply following each drug administration using its recommended dosage regimen (Li et al. 2010) and applied our gap measure based on the prescription fill (or administration) date and days’ supply (or assigned days’ supply) for each Part D or Part B specialty drug. Table S1 in Appendix SA2 contains a full list of the Part D and Part B specialty drugs that were approved for use during our study period.

Statistical Models

Descriptive statistics were generated to characterize the MS and RA samples. For the main analysis, risk-adjusted outcomes of the proportion of patients with a treatment gap were estimated using a two-period difference-in-difference approach. Specifically, logistic regression models with the generalized estimating equation method were used to estimate changes in the odds of having a continuous gap during the high cost-sharing period versus the low cost-sharing period, for the non-LIS study group relative to the LIS control group. Models were run separately in MS and RA samples and included indicators for group (non-LIS vs. LIS), study period (high cost sharing vs. low cost sharing), and interaction terms between group and study period (difference-in-difference). The difference-in-difference measured the effect of the increased cost sharing faced by the non-LIS group on the odds of having a continuous gap relative to the LIS group. Models also included covariates for beneficiary age, gender, race/ethnicity, census region of residence, per capita income in the beneficiary’s county of residence, use of assistive devices for mobility (as a marker of disability), and prescription drug hierarchical condition category (RxHCC) risk score (Robst, Levy, and Ingber 2007), which has been used to

adjust for potential selection biases in drug use studies among Medicare patients (Doshi, Li, and Puig 2010; Donohue et al. 2012; Li et al. 2012). Models also included measures that captured the proportion of disease-specific Part D specialty drugs covered by the beneficiary's Part D plan formulary as well as the proportion of the covered Part D specialty drugs that were subject to prior authorization, step therapy, or quantity limits. Finally, models included year indicators to control for any underlying time trends. Standard errors and 95% confidence intervals for risk-adjusted outcomes were estimated based on the delta method.

For both the MS and RA samples, we repeated all analyses in the subgroup of LIS and non-LIS patients aged <65 years (i.e., those who were Medicare-eligible due to disability). We also performed several sensitivity analyses to test the robustness of study findings. First, we included control variables for the number of days spent in the preperiod and in the postperiod. Second, we adjusted our criterion regarding days spent in the period of lower cost sharing and higher cost sharing, to include patients who spent at least 60 days each in the pre- and postperiods (instead of ≥ 30 days, as in the main sample). Third, we repeated our analyses using only one pair of pre/post observations per patient (i.e., the first pair that met our inclusion criteria during the study period). Finally, we repeated all analyses using within-person fixed-effects models, which account for time-stable unobserved differences between comparison groups. All analyses were conducted in *SAS* version 9.4 (SAS Institute Inc., Cary, NC, USA) and *STATA* version 13.1 (StataCorp LP., College Station, TX, USA).

The University of Pennsylvania Institutional Review Board deemed the study exempt from informed consent procedures, as no data were collected directly from human subjects.

RESULTS

Table 1 shows baseline characteristics of the non-LIS study group and the LIS control group for the MS ($N = 1,887$) and RA ($N = 2,296$) samples, respectively. In both disease samples, the non-LIS group was older, more likely to be white, and had lower RxHCC risk scores than the LIS group. A larger proportion of the LIS group was <65 years of age (i.e., Medicare-eligible because of disability), with 92.6 percent of the MS LIS group falling into this category. Most Part D plans covered a majority of the FDA-approved Part D specialty drugs for MS and RA, with the mean proportion covered ranging from 0.86 to

Table 1: Baseline Characteristics of Multiple Sclerosis and Rheumatoid Arthritis Samples

	<i>MS Sample (N = 1,887)</i>		<i>RA Sample (N = 2,296)</i>	
	<i>Non-LIS</i>	<i>LIS</i>	<i>Non-LIS</i>	<i>LIS</i>
<i>N</i>	364	1,523	677	1,619
Female	289 (79.4%)	1,191 (78.2%)	550 (81.2%)	1,345 (83.1%)
Mean age (SD), years	60.13 (9.22)	48.44 (10.61)	71.97 (8.13)	61.65 (12.72)
Medicare disabled (age <65 years)	223 (61.3%)	1,410 (92.6%)	92 (13.6%)	932 (57.6%)
Race				
White	345 (94.8%)	1,123 (73.7%)	628 (92.8%)	1,136 (70.2%)
Black	15 (4.1%)	305 (20.0%)	25 (3.7%)	247 (15.3%)
Hispanic	0 (0.0%)	54 (3.5%)	8 (1.2%)	156 (9.6%)
Other	4 (1.1%)	41 (2.7%)	16 (2.4%)	80 (4.9%)
Region				
Northeast	74 (20.3%)	358 (23.5%)	118 (17.4%)	254 (17.7%)
Midwest	109 (29.9%)	437 (28.7%)	163 (24.1%)	294 (18.2%)
South	120 (33.0%)	480 (31.5%)	265 (39.1%)	698 (43.1%)
West	61 (16.8%)	248 (16.3%)	131 (19.4%)	340 (21.0%)
Mean county-level per capita income (SD), \$10,000s	3.97 (1.19)	3.81 (1.02)	4.08 (1.29)	3.73 (1.30)
Use of assistive device(s) for mobility				
Unilateral	6 (1.6%)	24 (1.6%)	6 (0.9%)	22 (1.4%)
Bilateral	16 (4.4%)	70 (4.6%)	20 (3.0%)	87 (5.4%)
Wheelchair	29 (8.0%)	193 (12.7%)	24 (3.5%)	125 (7.7%)
Mean RxHCC risk score (SD)	1.05 (0.33)	1.86 (0.56)	0.78 (0.40)	1.07 (0.49)
Part D plan formulary characteristics for disease-specific				
Part D specialty drugs				
Mean proportion of all approved specialty drugs covered by the plan (SD)	0.98 (0.07)	0.97 (0.08)	0.90 (0.15)	0.86 (0.16)
Mean proportion of covered specialty drugs subject to prior authorization (SD)	0.66 (0.47)	0.70 (0.46)	0.88 (0.28)	0.94 (0.19)
Mean proportion of covered specialty drugs subject to step therapy (SD)	0.03 (0.12)	0.05 (0.16)	0.07 (0.25)	0.03 (0.14)
Mean proportion of covered specialty drugs subject to quantity limits (SD)	0.45 (0.50)	0.32 (0.47)	0.33 (0.36)	0.27 (0.32)
Mean time in coverage phases, months (SD)				
Lower cost-sharing period*	8.33 (1.67)	8.50 (1.93)	6.20 (3.34)	7.02 (2.98)
Higher cost-sharing period*	3.17 (3.37)	2.90 (2.90)	3.26 (2.94)	2.80 (2.58)

*Lower cost-sharing period indicates the catastrophic coverage phase in the prior year. Higher cost-sharing period indicates the deductible plus initial coverage phase in the current year.

LIS, low-income subsidy; MS, multiple sclerosis; RA, rheumatoid arthritis; RxHCC, prescription drug hierarchical condition category risk score.

0.98. On average, the non-LIS and LIS groups with MS spent approximately 8 months in the lower cost-sharing period (preperiod) and 3 months in the higher cost-sharing period (postperiod). Similarly, the non-LIS and LIS groups with RA spent an average of 6–7 months in the lower cost-sharing period and approximately 3 months in the higher cost-sharing period. Approximately 90 percent of the non-LIS RA group and 91 percent of the non-LIS MS group faced specialty tiers in the higher cost-sharing period; the remainder still faced specialty drug cost-sharing levels similar to those of patients facing specialty tiers (data not shown).

Table 2 presents risk-adjusted outcomes and odds ratios for the impact of cost sharing on gaps in specialty drug use in the MS and RA samples (Table S2 in Appendix SA2 presents unadjusted descriptive outcomes). In both the MS and RA samples, the non-LIS group had larger absolute increases in the proportion of patients with a 30-day gap in Part D specialty drug use upon transitioning from the lower cost sharing to higher cost-sharing period, as compared to the control group of LIS patients. For instance, in the MS sample, the proportion of non-LIS patients with a 30-day gap in Part D DMT use increased by 11 percentage points (i.e., 27.2 percent to 38.2 percent, compared to a 0.9 percentage point increase in the control group of LIS patients. The magnitude of this effect was even larger in the RA sample, where the increase in the proportion of patients with a 30-day gap in Part D biologic use was 21.9 percentage points higher in the non-LIS group compared to the LIS group. The odds of having a 30-day gap in Part D specialty drug use in the higher cost-sharing period relative to the lower cost-sharing period were also significantly higher in both non-LIS groups, compared to the LIS groups (MS sample, OR 1.61; 95% CI, 1.19–2.17, $p = .002$; RA sample, OR 2.75; 95% CI, 2.15–3.51, $p < .001$).

Gaps in Part D specialty drug treatment were not offset by increased Part B specialty drug use. Across groups, only 3 percent of the MS sample and 2–5 percent of the RA sample filled disease-specific Part B specialty drugs during the observation periods (data not shown). Therefore, the overall specialty drug use outcomes (including both Part B and Part D specialty drugs) were very close to measures based solely on Part D specialty drugs. Even when Part B use was taken into account, the non-LIS group transitioning from lower cost sharing to higher cost sharing had greater odds of having a gap in specialty drug use compared to the LIS group (Table 2). Subgroup analyses in beneficiaries qualifying for Medicare due to disability showed consistent findings (Table 2). Sensitivity analyses based on generalized estimating equation models adjusting for number of days spent in each period, among the sample of

Table 2: Impact of Cost Sharing on Gaps in Specialty Drug Treatment for MS or RA: Risk-Adjusted Outcomes and Odds Ratios*

	Non-LIS (Study Group)			LIS (Control Group)			p-Value
	Lower Cost-Sharing Period	Higher Cost-Sharing Period	Difference	Lower Cost-Sharing Period	Higher Cost-Sharing Period	Difference	
Overall							
MS sample (N = 1,887)							
Gap in any Part D DMT use	27.2%	38.2%	11.0%	32.6%	33.5%	0.9%	1.61 (1.19–2.17)
Gap in any Part D or Part B DMT use	25.5%	35.9%	10.5%	31.0%	31.3%	0.4%	1.63 (1.2–2.22)
RA sample (N = 2,296)							
Gap in any Part D biologic use	25.0%	42.7%	17.7%	37.1%	32.8%	–4.2%	2.75 (2.15–3.51)
Gap in any Part D or Part B biologic use	23.1%	40.4%	17.3%	36.3%	31.9%	–4.4%	2.81 (2.18–3.61)
Subgroup of patients aged <65 years							
MS sample (N = 1,633)							
Gap in any Part D DMT use	27.7%	41.2%	13.5%	33.6%	35.0%	1.4%	1.74 (1.22–2.49)
Gap in any Part D or Part B DMT use	26.1%	39.6%	13.5%	31.9%	32.7%	0.8%	1.81 (1.25–2.6)
RA sample (N = 1,075)							
Gap in any Part D biologic use	32.8%	54.2%	21.4%	38.7%	36.5%	–2.2%	2.74 (1.61–4.64)
Gap in any Part D or Part B biologic use	30.4%	51.8%	21.4%	37.8%	35.6%	–2.3%	2.79 (1.63–4.77)

*Lower cost-sharing period indicates the catastrophic coverage phase in the prior year (cost sharing at 5% level for non-LIS and \$0 for LIS). Higher cost-sharing period indicates the deductible phase plus initial coverage phase in the current year (cost sharing ≥25% for non-LIS, up to \$6.30 for LIS). Gap indicates a continuous gap of ≥30 days in availability of disease-specific specialty drug, at the class level. Adjusted outcomes were estimated using generalized estimating equations logit models controlling for repeated measures at the patient level with compound symmetry correlation structure including variables for study group (non-LIS vs. LIS); study period (high- vs. low- cost sharing); interaction terms between study group and study period; age; gender; race/ethnicity; census region of residence; area-level characteristics (per capita income) in beneficiary's county of residence; prescription drug hierarchical condition category (RxHCC) risk score; use of assistive devices for mobility; Part D plan formulary characteristics (percentage of available disease-specific Part D specialty drugs covered by the plan and percentage of covered Part D specialty drugs facing prior authorization, quantity limits, and step therapy); and year indicators. 95% confidence intervals for risk-adjusted outcomes were estimated based on the delta method.

†Represent absolute differences. All difference-in-difference estimates were statistically significant at $p < .05$.

‡Odds ratios presented here were based on the coefficient of the interaction term of the indicators for non-LIS (study group) and higher cost-sharing period (study period) and represent the difference-in-difference estimate.

CI, confidence interval; DID, difference-in-difference; DMT, disease-modifying therapy; LIS, low-income subsidies; MS, multiple sclerosis; RA, rheumatoid arthritis.

patients who spent at least 60 days each in the pre- and postperiods, including only one pair of pre/post observations per patient, and using fixed-effects logistic regressions (Table 3) also showed findings consistent with our main analyses.

DISCUSSION

To our knowledge, this is the first quasi-experimental study in the Medicare population to examine the relationship between increases in cost sharing and treatment continuity among patients on established specialty drug regimens for MS or RA. Examining Medicare claims data from 2007 to 2010, we found that entry into Part D coverage periods with specialty tier-level cost sharing was associated with an increase in ≥ 30 day gaps in disease-specific specialty drug treatment among beneficiaries in both disease groups who were not receiving low-income subsidies. In contrast, disease-matched comparison groups of beneficiaries with full low-income subsidies, who continued to face nominal cost sharing ($\leq \$6.30$ copay), did not show parallel changes in specialty drug utilization over the same timeframe. Finally, we did not observe increases in substitution with Medicare Part B specialty drugs that were available at relatively low or no out-of-pocket costs during periods of higher specialty tier-level cost sharing, suggesting that patients were completely foregoing any disease-specific specialty drugs during the observed gaps in treatment. Indeed, non-LIS beneficiaries with gaps in any disease-specific specialty drugs during the period of high cost sharing were lacking specialty drug coverage for substantially longer than our minimum threshold of 30 days (i.e., a mean of 169 days [SD = 135] without any specialty drugs in the high cost-sharing period for the MS sample and a mean of 128 days [SD = 103] for the RA sample; data not shown.)

Although claims data do not provide sufficient clinical details or patient-reported details to allow us to determine whether gaps in treatment were due to deliberate decisions (unrelated to cost) on the part of patients or providers, we would not expect to see systematic differences in clinical decision making regarding continuous versus intermittent use of specialty drugs between the non-LIS and LIS groups. Thus, out-of-pocket costs do appear to be influencing the utilization patterns we observed, and these treatment gaps could have clinical impact. For MS patients with relapsing–remitting disease (prior to progression), there is overwhelming evidence that gaps in disease-modifying therapy lead to higher rates of relapses, disability, and worse disease outcomes

Table 3: Impact of Cost Sharing on Gaps in Specialty Drug Treatment for MS or RA: Odds Ratios from Sensitivity Analyses

	GEE Models*: Adjusting for Number of Days Spent in Pre- and Post-Periods†		GEE Models*: ≥ 60 days in the Pre- and Post-Periods‡		GEE Models*: One Pair of Pre/Post Observations per Patient*		Patient-Level Fixed-Effects Models	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Overall								
MS sample								
Gap in any Part D DMT use	1.45	(1.06–1.99)	1.71	(1.05–2.80)	1.86	(1.31–2.64)	2.12	(1.32–3.41)
Gap in any Part D or Part B DMT use	1.48	(1.07–2.04)	1.71	(1.06–2.79)	1.93	(1.33–2.79)	2.11	(1.32–3.40)
RA sample								
Gap in any Part D biologic use	2.43	(1.87–3.15)	2.63	(1.89–3.65)	2.94	(2.17–3.98)	4.39	(3.07–6.29)
Gap in any Part D or Part B biologic use	2.45	(1.88–3.19)	2.64	(1.89–3.68)	2.93	(2.15–4.00)	4.36	(3.05–6.25)
Subgroup of patients aged <65 years								
MS sample								
Gap in any Part D DMT use	1.56	(1.07–2.28)	1.87	(1.04–3.36)	2.06	(1.36–3.11)	2.15	(1.23–3.73)
Gap in any Part D or Part B DMT use	1.63	(1.11–2.39)	1.97	(1.10–3.53)	2.08	(1.35–3.19)	2.20	(1.26–3.84)
RA sample								
Gap in any Part D biologic use	2.40	(1.37–4.21)	2.59	(1.27–5.26)	2.92	(1.52–5.63)	3.91	(1.78–8.61)
Gap in any Part D or Part B biologic use	2.38	(1.35–4.20)	2.56	(1.26–5.20)	2.95	(1.51–5.76)	3.65	(1.71–7.80)

*Indicates GEE logit regressions with compound symmetry correlation structure.

†Preperiod (lower cost-sharing period) indicates the catastrophic coverage phase in the prior year (cost sharing at 5% level for non-LIS and \$0 for LIS). Postperiod (higher cost-sharing period) indicates the deductible phase plus initial coverage phase in the current year (cost sharing ≥25% for non-LIS, up to \$6.30 for LIS).

‡Among observations from individual patients when they first met our inclusion criteria, to allow one pair of observations per individual.

All models include variables for study group (non-LIS vs. LIS); study period (post- vs. pre-); interaction terms between study group and study period; number of days spent in each study period; age; gender; race/ethnicity; census region of residence; area-level characteristics (per capita income) in beneficiary's county of residence; prescription drug hierarchical condition category (RxHCC) risk score; use of assistive devices for mobility; Part D plan formulary characteristics (percentage of available disease-specific Part D specialty drugs covered by the plan and percentage of covered Part D specialty drugs facing prior authorization, quantity limits, and step therapy); and year indicators. Odds ratios presented here were based on the coefficient of the interaction term of the indicators for non-LIS (study group) and postperiod (study period) and represent the difference-in-difference estimate. CI, confidence interval; DMT, disease-modifying therapy; GEE, generalized estimating equations; MS, multiple sclerosis; RA, rheumatoid arthritis; SNF, skilled nursing facility.

(O'Connor et al. 2011; Siger et al. 2011; Ghezzi et al. 2013; Menzin et al. 2013; Fox et al. 2014; Gueguen et al. 2014; Cohen et al. 2015; Costello et al. 2015), and consensus guidelines recommend continuous treatment (Costello et al. 2015). Although the evidence regarding the impact of tapering or discontinuing biologic treatment in RA patients has been mixed, treatment gaps or nonpersistence has been shown to lead to a higher risk of disease flare and persistent disability in some patients (Contreras-Yanez et al. 2010; Kremer et al. 2014; Markusse et al. 2015; Singh et al. 2016). Further, some studies have found that many patients experience higher disease activity in the year following carefully planned discontinuation (Lagana et al. 2009; Tanaka et al. 2010; Bluett et al. 2015; Fautrel and Den Broeder 2015; Mjaavatten et al. 2015).

It is notable that a substantive proportion (23–37 percent) of both MS and RA patients in our sample had gaps in treatment in the baseline period even before the increase in cost sharing, which is in keeping with prior studies documenting poor adherence to both MS and RA medications (Blum, Koo, and Doshi 2011; Menzin et al. 2013). Thus, increases in cost sharing appeared to represent an additional adherence barrier and exacerbate existing issues. We captured gaps in treatment, yet high costs can also put patients at risk of altering their treatment regimens in more minor ways that would not have been captured in our analysis (e.g., skipping doses), a phenomenon that has been observed in seniors with higher out-of-pocket medication costs (Steinman, Sands, and Covinsky 2001; Shenolikar et al. 2011). Further, anxiety related to the affordability of continuous access to treatment may be clinically relevant in light of the link between stress and symptom exacerbations in MS and other chronic diseases (Mohr et al. 2004; Cohen, Janicki-Deverts, and Miller 2007; Fogarty et al. 2015). Additionally, patients who opted to discontinue their medication due to financial burden during the coverage gap phase of the prior year would not have been included in our sample but constitute another group affected by high out-of-pocket costs for treatment.

While our results indicated that patients in both disease groups were affected, the magnitude of the observed increase in the percentage of patients with treatment gaps during periods of specialty tier-level cost sharing was greater in the RA group (~22 percent) relative to the MS group (~10 percent). As hypothesized earlier, this may be because MS patients perceive the potential risks associated with breaks in treatment to be more severe. Surprisingly, our findings also suggest that few RA patients with interruptions in Part D biologic use were switching to one of the several infusible Part B biologics that are typically available at low or no out-of-pocket costs due to supplemental insurance coverage. Hence, it is possible that patients with RA who

experienced gaps in biologic treatment in our study were restricting their treatment to use of less expensive oral systemic agents such as methotrexate and over-the-counter medications for pain management during periods of high cost sharing. While these medications may help to continue to manage symptoms of RA, there remains the possibility of disease progression, both clinically and radiographically. Thus, our findings raise the question of whether patients are aware that some biologics carry lower out-of-pocket costs and highlight that clinicians discussing treatment options with Medicare patients may need to consider not only a patient's preferences and disease activity but also cost sharing and a patient's ability to pay, in order to facilitate consistent access to treatment.

At first glance, the level of price sensitivity we observed in our study may seem relatively low considering that out-of-pocket costs increased approximately fivefold as patients moved from the lower cost-sharing period to the higher cost-sharing period. However, it is important to note that our study sample included patients with a high need for the specialty drug who would be expected to be less sensitive to out-of-pocket costs. That is, they had (1) already made the decision to initiate the indicated Part D specialty drugs at some point in the past, and (2) continued to use the Part D specialty drugs long enough to have cycled through the high cost sharing of the deductible, initial coverage phase, and coverage gap of the previous year, in order to have reached the catastrophic coverage phase. Yet we still found significant disruptions in treatment during the initial coverage phase of the following year, when cost sharing increased again. Furthermore, the magnitude of our findings was greater than those found in prior studies, which have primarily captured the experience of privately insured patients from a time period when very few patients were subject to aggressive cost-sharing strategies for specialty drugs (Ozminkowski et al. 2004; Goldman et al. 2006; Curkendall et al. 2008; Lafata et al. 2008; Gleason et al. 2009; Karaca-Mandic et al. 2010; Kim et al. 2011; Palmer et al. 2012; Romley et al. 2012; Desai et al. 2014; Starner et al. 2014). Those studies documented that higher cost sharing appeared to have a stronger impact on noninitiation or abandonment of prescriptions at the pharmacy but minimal impact (as measured by refill behavior, adherence, and discontinuation) once patients decided to initiate therapy (Ozminkowski et al. 2004; Goldman et al. 2006; Curkendall et al. 2008; Lafata et al. 2008; Gleason et al. 2009; Karaca-Mandic et al. 2010; Kim et al. 2011; Palmer et al. 2012; Romley et al. 2012; Desai et al. 2014; Starner et al. 2014). Thus, future examinations of specialty tier-level cost sharing among new users of MS and RA specialty drugs might be expected to show even greater effects.

Several caveats deserve mention. Although the LIS control groups differed from the study groups in several respects, the pre/post study design with a contemporaneous control group and difference-in-difference estimates are validated methods that control for confounding related to both observed and unobserved time-invariant differences between groups. In addition, patient-level fixed-effects models confirmed that our findings are robust, and we also included several covariates in our regressions to adjust for observed confounders such as RxHCC score. Subgroup analyses in the subsample of beneficiaries eligible for Medicare due to disability were also consistent. Our estimates might still be biased by time-varying unobserved variables such as treatment response, yet these would not be expected to systematically vary across the non-LIS and LIS groups during the transition from the preperiod to the postperiod.

Additional factors could have led to an under- or overestimation in our findings. First, although the LIS group was subject to relatively small cost-sharing increases in the transition from lower cost sharing to higher cost sharing (\$0 to $\leq$ \$6.30), this increase could still be a burden for such low-income patients. If our comparison groups were also experiencing financial barriers to continuous use of their disease-specific specialty drugs, then our difference-in-difference results may be conservative estimates of the true impact of specialty tier cost sharing. (Nevertheless, our study results did not indicate any increases in the proportion of LIS patients with a 30-day gap in treatment when moving from the lower to higher cost-sharing period.) Similarly, as Medicare data do not allow for accurate identification of patients receiving other forms of medication assistance, non-LIS patients who would not have been able to afford their medication without copayment assistance from charities and nonprofit foundations would be correctly coded as refilling their prescription, but the effects of high cost sharing would be underestimated. On the other hand, any patient who was receiving a specialty drug for free via a manufacturer assistance program would not have a corresponding Medicare prescription claim and might be incorrectly coded as experiencing a gap in treatment. In addition, we also were unable to isolate the influence of cost sharing at a given refill decision point from the influence of anticipated cost sharing during the next Part D coverage phase, which may have led patients to reduce utilization during the initial coverage phase in order to delay or avoid the coverage gap. Although such anticipation is inherent in the design of the Part D benefit, recent evidence suggests that Medicare patients' decision making is influenced more by actual out-of-pocket costs at the point in time than by anticipation of future out-of-pocket costs (Kaplan and Zhang 2014).

Finally, as our study focused on the Medicare fee-for-service population, it is possible that specialty tier-level cost sharing may show different associations with treatment utilization among younger patients or patients without qualifying disabilities, or among those with alternate insurance arrangements, including Medicare managed care plans or commercial plans. As noted earlier, individuals considering whether to initiate specialty drug treatment are likely to be more sensitive to cost sharing as compared to our sample of established users.

Current Medicare Part D policy focuses solely on a medication's cost by allowing plans to place all expensive agents on a specialty tier and subjecting them to 25–33 percent coinsurance, disregarding the value of individual specialty drug treatments. In doing so, it seems to place patients at risk of foregoing treatments that can decrease or delay disease progression and progressive disability (Chambers et al. 2014; Zalesak et al. 2014). More clinically nuanced classifications, such as those promoted under value-based insurance design (Fendrick, Buxbaum, and Westrich 2015), may be more appropriate. Additional research is needed to further examine specialty drug treatment access, utilization, and outcomes in the context of the specialty drug cost-sharing structures being observed in the current marketplace.

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REFERENCES

- Aitken, M., M. Kleinrock, J. Lyle, and L. Caskey. 2016. "Medicines Use and Spending in the U.S.: A Review of 2015 and Outlook to 2020" [accessed on October 27, 2016]. Available at <http://www.imshealth.com/en/thought-leadership/quintile-sims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020>
- Bluett, J., C. Morgan, L. Thurston, D. Plant, K. L. Hyrich, A. W. Morgan, A. G. Wilson, J. D. Isaacs, L. Cordingley, A. Barton, and BRAGGSS. 2015. "Impact of Inadequate Adherence on Response to Subcutaneously Administered Anti-Tumour Necrosis Factor Drugs: Results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate Cohort." *Rheumatology (Oxford, England)* 54 (3): 494–9.
- Blum, M. A., D. Koo, and J. A. Doshi. 2011. "Measurement and Rates of Persistence with and Adherence to Biologics for Rheumatoid Arthritis." *Clinical Therapeutics* 33 (7): 901–13.
- Borah, B., X. Huang, V. Zarotsky, and D. Globe. 2009. "Trends in RA Patients' Adherence to Subcutaneous Anti-TNF Therapies and Costs." *Current Medical Research and Opinion* 25 (6): 1365–77.
- Centers for Medicare and Medicaid Services. 2014. "Medicare Part D Specialty Tier" [accessed on October 27, 2016]. Available at <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/Downloads/SpecialtyTierMethodology.pdf>
- Chambers, J. D., T. Thorat, J. Pyo, M. Chenoweth, and P. J. Neumann. 2014. "Despite High Costs, Specialty Drugs May Offer Value for Money Comparable to That of Traditional Drugs." *Health Affairs (Project Hope)* 33 (10): 1751–60.
- Claxton, G., M. Rae, N. Panchal, A. Damico, N. Bostick, K. Kenward, and H. Whitmore. 2014. "Employer Health Benefits: 2014 Annual Survey" [accessed on October 27, 2016]. Available at <http://files.kff.org/attachment/2014-employer-health-benefits-survey-full-report>

- Cohen, S., D. Janicki-Deverts, and G. E. Miller. 2007. "Psychological Stress and Disease." *Journal of the American Medical Association* 298 (14): 1685–7.
- Cohen, B. A., P. K. Coyle, T. Leist, M. A. Oleen-Burkey, M. Schwartz, and H. Zwibel. 2015. "Therapy Optimization in Multiple Sclerosis: A Cohort Study of Therapy Adherence and Risk of Relapse." *Multiple Sclerosis and Related Disorders* 4 (1): 75–82.
- Contreras-Yanez, I., S. Ponce De Leon, J. Cabiedes, M. Rull-Gabayet, and V. Pascual-Ramos. 2010. "Inadequate Therapy Behavior Is Associated to Disease Flares in Patients with Rheumatoid Arthritis Who Have Achieved Remission with Disease-Modifying Antirheumatic Drugs." *American Journal of the Medical Sciences* 340 (4): 282–90.
- Costello, K., J. Halper, R. Kalb, L. Skutnik, and R. Rapp. 2015. "The Use of Disease Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence" [accessed on October 27, 2016]. Available at http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color
- Curkendall, S., V. Patel, M. Gleeson, R. S. Campbell, M. Zagari, and R. Dubois. 2008. "Compliance with Biologic Therapies for Rheumatoid Arthritis: Do Patient Out-of-Pocket Payments Matter?" *Arthritis & Rheumatism* 59 (10): 1519–26.
- Desai, R. J., J. K. Rao, R. A. Hansen, G. Fang, M. L. Maciejewski, and J. F. Farley. 2014. "Predictors of Treatment Initiation with Tumor Necrosis Factor-Alpha Inhibitors in Patients with Rheumatoid Arthritis." *Journal of Managed Care Pharmacy: JMCP* 20 (11): 1110–20.
- Donohue, J. M., N. E. Morden, W. F. Gellad, J. P. Bynum, W. Zhou, J. T. Hanlon, and J. Skinner. 2012. "Sources of Regional Variation in Medicare Part D Drug Spending." *New England Journal of Medicine* 366 (6): 530–8.
- Doshi, J. A., P. Li, and A. Puig. 2010. "Impact of the Medicare Modernization Act of 2003 on Utilization and Spending for Medicare Part B-Covered Biologics in Rheumatoid Arthritis." *Arthritis Care & Research* 62 (3): 354–61.
- Doshi, J. A., P. Li, V. P. Ladage, A. R. Pettit, and E. A. Taylor. 2016. "Impact of Cost Sharing on Specialty Drug Utilization and Outcomes: A Review of the Evidence and Future Directions." *American Journal of Managed Care* 22 (3): 188–97.
- Evans, C., J. Tam, E. Kingwell, J. Oger, University of British Columbia MS Clinic Neurologists, and H. Tremlett. 2012. "Long-Term Persistence with the Immunomodulatory Drugs for Multiple Sclerosis: A Retrospective Database Study." *Clinical Therapeutics* 34 (2): 341–50.
- Fautrel, B., and A. A. Den Broeder. 2015. "De-Intensifying Treatment in Established Rheumatoid Arthritis (RA): Why, How, When and in Whom Can DMARDs be Tapered?" *Best Practice & Research: Clinical Rheumatology* 29 (4–5): 550–65.
- Fendrick, M., J. Buxbaum, and K. Westrich. 2015. "Supporting Consumer Access to Specialty Medications Through Value-Based Insurance Design" [accessed on October 27, 2016]. Available at <http://www.npcnow.org/system/files/research/download/2014-vbid-specialty-medications-npc-final-web.pdf>
- Fogarty, F. A., R. J. Booth, G. D. Gamble, N. Dalbeth, and N. S. Consedine. 2015. "The Effect of Mindfulness-Based Stress Reduction on Disease Activity in People with

- Rheumatoid Arthritis: A Randomised Controlled Trial." *Annals of the Rheumatic Diseases* 74 (2): 472–4.
- Fox, R. J., B. A. Cree, J. De Seze, R. Gold, H. P. Hartung, D. Jeffery, L. Kappos, M. Kaufman, X. Montalban, B. Weinstock-Guttman, B. Anderson, A. Natarajan, B. Ticho, P. Duda, and RESTORE. 2014. "MS Disease Activity in RESTORE: A Randomized 24-Week Natalizumab Treatment Interruption Study." *Neurology* 82 (17): 1491–8.
- Freedman, M. S.. 2013. "Present and Emerging Therapies for Multiple Sclerosis." *Continuum (Minneapolis, Minn.)* 19 (4 Multiple Sclerosis): 968–91.
- Ghezzi, A., M. A. Rocca, D. Baroncini, P. Annovazzi, M. Zaffaroni, G. Minonzio, G. Comi, and M. Filippi. 2013. "Disease Reactivation after Fingolimod Discontinuation in Two Multiple Sclerosis Patients." *Journal of Neurology* 260 (1): 327–9.
- Gleason, P. P., C. I. Starner, B. W. Gunderson, J. A. Schafer, and H. S. Sarra. 2009. "Association of Prescription Abandonment with Cost Share for High-Cost Specialty Pharmacy Medications." *Journal of Managed Care Pharmacy* 15 (8): 648–58.
- Goldman, D. P., G. F. Joyce, G. Lawless, W. H. Crown, and V. Willey. 2006. "Benefit Design and Specialty Drug Use." *Health Affairs (Project Hope)* 25 (5): 1319–31.
- Gueguen, A., P. Roux, R. Deschamps, A. Moulignier, C. Bensa, J. Savatovsky, F. Heran, and O. Gout. 2014. "Abnormal Inflammatory Activity Returns after Natalizumab Cessation in Multiple Sclerosis." *Journal of Neurology, Neurosurgery, and Psychiatry* 85 (9): 1038–40.
- Helmick, C. G., D. T. Felson, R. C. Lawrence, S. Gabriel, R. Hirsch, C. K. Kwok, M. H. Liang, H. M. Kremers, M. D. Mayes, P. A. Merkel, S. R. Pillemer, J. D. Reveille, J. H. Stone, and National Arthritis Data Workgroup. 2008. "Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States. Part I." *Arthritis and Rheumatism* 58 (1): 15–25.
- Hoadley, J., E. Hargrave, J. Cubanski, and T. Neuman. 2009. "Medicare Part D 2009 Data Spotlight: Specialty Tiers" [accessed on October 27, 2016]. Available at <http://www.kff.org/medicare/upload/8008.pdf>
- Kaiser Family Foundation. 2015a. "The Medicare Part D Prescription Drug Benefit" [accessed on October 27, 2016]. Available at <http://files.kff.org/attachment/fact-sheet-the-medicare-part-d-prescription-drug-benefit>
- Kaiser Family Foundation. 2015b. "A Primer on Medicare: Key Facts about the Medicare Program and the People It Covers" [accessed on October 27, 2016]. Available at <http://files.kff.org/attachment/report-a-primer-on-medicare-key-facts-about-the-medicare-program-and-the-people-it-covers>
- Kaplan, C., and Y. Zhang. 2014. "The January Effect: Medication Reinitiation among Medicare Part D Beneficiaries." *Health Economics* 23 (11): 1287–300.
- Karaca-Mandic, P., G. F. Joyce, D. P. Goldman, and M. Laouri. 2010. "Cost Sharing, Family Health Care Burden, and the Use of Specialty Drugs for Rheumatoid Arthritis." *Health Services Research* 45 (5 Pt 1): 1227–50.
- Kim, Y. A., K. L. Rascati, K. Prasla, P. Godley, N. Goel, and D. Dunlop. 2011. "Retrospective Evaluation of the Impact of Copayment Increases for Specialty Medications on Adherence and Persistence in an Integrated Health Maintenance Organization System." *Clinical Therapeutics* 33 (5): 598–607.

- Kremer, J. M., C. Peterfy, A. S. Russell, P. Emery, C. Abud-Mendoza, J. Sibilia, J. C. Becker, R. Westhovens, and H. K. Genant. 2014. "Longterm Safety, Efficacy, and Inhibition of Structural Damage Progression over 5 Years of Treatment with Abatacept in Patients with Rheumatoid Arthritis in the Abatacept in Inadequate Responders to Methotrexate Trial." *Journal of Rheumatology* 41 (6): 1077–87.
- Lafata, J. E., M. Cergnet, E. Dobie, L. Schultz, K. Tunceli, J. Reuther, and S. Elias. 2008. "Measuring Adherence and Persistence to Disease-Modifying Agents Among Patients with Relapsing Remitting Multiple Sclerosis." *Journal of the American Pharmacists Association* 48 (6): 752–7.
- Lagana, B., A. Picchianti Diamanti, C. Ferlito, V. Germano, A. Migliore, A. Cremona, G. Argento, V. David, S. Salemi, and R. D'Amelio. 2009. "Imaging Progression Despite Clinical Remission in Early Rheumatoid Arthritis Patients after Etanercept Interruption." *International Journal of Immunopathology and Pharmacology* 22 (2): 447–54.
- Li, P., M. A. Blum, J. Von Feldt, S. Hennessy, and J. A. Doshi. 2010. "Adherence, Discontinuation, and Switching of Biologic Therapies in Medicaid Enrollees with Rheumatoid Arthritis." *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 13 (6): 805–12.
- Li, P., S. McElligott, H. Bergquist, J. S. Schwartz, and J. A. Doshi. 2012. "Effect of the Medicare Part D Coverage Gap on Medication Use among Patients with Hypertension and Hyperlipidemia." *Annals of Internal Medicine* 156 (11): 776, 84, W-263, W-264, W-265, W-266, W-267, W-268, W-269.
- Lublin, F. D., S. C. Reingold, J. A. Cohen, G. R. Cutter, P. S. Sorensen, A. J. Thompson, J. S. Wolinsky, L. J. Balcer, B. Banwell, F. Barkhof, B. Bebo Jr, P. A. Calabresi, M. Clanet, G. Comi, R. J. Fox, M. S. Freedman, A. D. Goodman, M. Inglese, L. Kappos, B. C. Kieseier, J. A. Lincoln, C. Lubetzki, A. E. Miller, X. Montalban, P. W. O'Connor, J. Petkau, C. Pozzilli, R. A. Rudick, M. P. Sormani, O. Stuve, E. Waubant, and C. H. Polman. 2014. "Defining the Clinical Course of Multiple Sclerosis: The 2013 Revisions." *Neurology* 83 (3): 278–86.
- Markuse, I. M., L. Dirven, A. H. Gerards, J. H. van Groenendaal, H. K. Ronday, P. J. Kerstens, W. F. Lems, T. W. Huizinga, and C. F. Allaart. 2015. "Disease Flares in Rheumatoid Arthritis are Associated with Joint Damage Progression and Disability: 10-Year Results from the Best Study." *Arthritis Research & Therapy* 17: 232.
- Menzin, J., C. Caon, C. Nichols, L. A. White, M. Friedman, and M. W. Pill. 2013. "Narrative Review of the Literature on Adherence to Disease-Modifying Therapies among Patients with Multiple Sclerosis." *Journal of Managed Care Pharmacy* 19 (1 Suppl A): S24–40.
- Mjaavatten, M. D., H. Radner, K. Yoshida, N. A. Shadick, M. L. Frits, C. K. Iannaccone, T. K. Kvien, M. E. Weinblatt, and D. H. Solomon. 2015. "Do Rheumatologists Know Best? An Outcomes Study of Inconsistent Users of Disease-Modifying Anti-Rheumatic Drugs." *Seminars in Arthritis and Rheumatism* 44 (4): 399–404.
- Mohr, D. C., S. L. Hart, L. Julian, D. Cox, and D. Pelletier. 2004. "Association Between Stressful Life Events and Exacerbation in Multiple Sclerosis: A Meta-Analysis." *British Medical Journal (Clinical Research Edition)* 328 (7442): 731.

- O'Connor, P. W., A. Goodman, L. Kappos, F. D. Lublin, D. H. Miller, C. Polman, R. A. Rudick, W. Aschenbach, and N. Lucas. 2011. "Disease Activity Return During Natalizumab Treatment Interruption in Patients with Multiple Sclerosis." *Neurology* 76 (22): 1858–65.
- Ozminkowski, R. J., W. D. Marder, K. Hawkins, S. Wang, S. C. Stallings, S. N. Finkelstein, A. J. Sinskey, and D. Wierz. 2004. "The Use of Disease-Modifying New Drugs for Multiple Sclerosis Treatment in Private-Sector Health Plans." *Clinical Therapeutics* 26 (8): 1341–54.
- Palmer, L., S. Abouzaid, N. Shi, R. Fowler, G. Lenhart, H. Dastani, and E. Kim. 2012. "Impact of Patient Cost Sharing on Multiple Sclerosis Treatment." *American Journal of Managed Care* 4 (Special Issue): SP28–36.
- Pearson, C. 2014. "Consumers Likely Face High Out-of-Pocket Costs for Specialty Drugs in Exchange Plans" [accessed on October 27, 2016]. Available at <http://avalere.com/expertise/managed-care/insights/consumers-likely-face-high-out-of-pocket-costs-for-specialty-drugs-in-excha>
- Peterson, A., D. Nau, J. Cramer, J. Benner, F. Gwadry-Sridhar, and M. Nichol. 2007. "A Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases." *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 10 (1): 3–12.
- Reynolds, M. W., R. Stephen, C. Seaman, and K. Rajagopalan. 2010. "Persistence and Adherence to Disease Modifying Drugs among Patients with Multiple Sclerosis." *Current Medical Research and Opinion* 26 (3): 663–74.
- Robst, J., J. M. Levy, and M. J. Ingber. 2007. "Diagnosis-Based Risk Adjustment for Medicare Prescription Drug Plan Payments." *Health Care Financing Review* 28 (4): 15–30.
- Romley, J., D. Goldman, M. Eber, H. Dastani, E. Kim, and S. Raparla. 2012. "Cost-Sharing and Initiation of Disease-Modifying Therapy for Multiple Sclerosis." *American Journal of Managed Care* 18 (8): 460–4.
- Shenolikar, R., A. S. Bruno, M. Eaddy, and C. Cantrell. 2011. "Sensitivity of Medication Use to Formulary Controls in Medicare Beneficiaries: A Review of the Literature." *American Health & Drug Benefits* 4 (7): 465–74.
- Siger, M., A. Durko, A. Nicpan, M. Konarska, M. Grudziecka, and K. Selmaj. 2011. "Discontinuation of Interferon Beta Therapy in Multiple Sclerosis Patients with High Pre-Treatment Disease Activity Leads to Prompt Return to Previous Disease Activity." *Journal of the Neurological Sciences* 303 (1–2): 50–2.
- Sikka, R., F. Xia, and R. E. Aubert. 2005. "Estimating Medication Persistency Using Administrative Claims Data." *American Journal of Managed Care* 11 (7): 449–57.
- Singh, J. A., K. G. Saag, S. L. Bridges Jr, E. A. Akl, R. R. Bannuru, M. C. Sullivan, E. Vaysbrot, C. McNaughton, M. Osani, R. H. Shmerling, J. R. Curtis, D. E. Furst, D. Parks, A. Kavanaugh, J. O'Dell, C. King, A. Leong, E. L. Matteson, J. T. Schousboe, B. Drevlow, S. Ginsberg, J. Grober, E. W. St Clair, E. Tindall, A. S. Miller, and T. McAlindon. 2016. "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis." *Arthritis Care & Research* 68 (1): 1–25.
- Smolen, J. S., R. Landewe, F. C. Breedveld, M. Dougados, P. Emery, C. Gaujoux-Viala, S. Gorter, R. Knevel, J. Nam, M. Schoels, D. Aletaha, M. Buch, L. Gossec, T. Huizinga, J. W. Bijlsma, G. Burmester, B. Combe, M. Cutolo, C. Gabay, J.

- Gomez-Reino, M. Kouloumas, T. K. Kvien, E. Martin-Mola, I. McInnes, K. Pavelka, P. van Riel, M. Scholte, D. L. Scott, T. Sokka, G. Valesini, R. van Vollenhoven, K. L. Winthrop, J. Wong, A. Zink, and D. van der Heijde. 2010. "Eular Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs." *Annals of the Rheumatic Diseases* 69 (6): 964–75.
- Starner, C. I., G. C. Alexander, K. Bowen, Y. Qiu, P. J. Wickersham, and P. P. Gleason. 2014. "Specialty Drug Coupons Lower Out-of-Pocket Costs and May Improve Adherence at the Risk of Increasing Premiums." *Health Affairs (Project Hope)* 33 (10): 1761–9.
- Steinman, M. A., L. P. Sands, and K. E. Covinsky. 2001. "Self-Restriction of Medications Due to Cost in Seniors without Prescription Coverage." *Journal of General Internal Medicine* 16 (12): 793–9.
- Tanaka, Y., T. Takeuchi, T. Mimori, K. Saito, M. Nawata, H. Kameda, T. Nojima, N. Miyasaka, T. Koike, and RRR study investigators. 2010. "Discontinuation of Infliximab after Attaining Low Disease Activity in Patients with Rheumatoid Arthritis: RRR (Remission Induction by Remicade in RA) Study." *Annals of the Rheumatic Diseases* 69 (7): 1286–91.
- Tu, H. T., and D. Samuel. 2012. "Limited Options to Manage Specialty Drug Spending" [accessed on October 27, 2016]. Available at <http://www.hschange.org/CONTENT/1286/1286.pdf>
- Yazici, Y., S. Krasnokutsky, J. Barnes, P. Hines, J. Wang, and L. Rosenblatt. 2009. "Changing Patterns of Tumor Necrosis Factor Inhibitor Use in 9074 Patients with Rheumatoid Arthritis." *Journal of Rheumatology* 36 (5): 907–13.
- Zalesak, M., J. S. Greenbaum, J. T. Cohen, F. Kokkotos, A. Lustig, P. J. Neumann, D. Pritchard, J. Stewart, and R. W. Dubois. 2014. "The Value of Specialty Pharmaceuticals—A Systematic Review." *American Journal of Managed Care* 20 (6): 461–72.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article:

Appendix SA1: Author Matrix.

Appendix SA2:

Table S1. Specialty Drugs Approved to Treat Multiple Sclerosis or Rheumatoid Arthritis During the Study Period (2007–2011).

Table S2. Descriptive Outcomes.