The association between cost sharing, prior authorization, and specialty drug utilization: A systematic review

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Plain language summary

The cost of some specialty drugs is very high. Insurance companies try to control these costs by having patients pay more for the drugs and making it so that the patient needs approval before using the medicine. In this review, we looked at how much higher patient costs and requiring approval kept patients from using these specialty drugs that the physician ordered.

Implications for managed care pharmacy

Payers can manage and reduce the cost of highly expensive specialty drugs in the short term through strategies such as increasing cost sharing and requiring prior authorization. However, these strategies have some negative impacts on patients' utilization of specialty drugs, which may, in the long term, increase payer spending to manage complications that result from delayed initiation or increased abandonment of these drugs.

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ABSTRACT

BACKGROUND: Specialty drugs are identified by high monthly costs and complexity of administration. Payers use utilization management strategies, including prior authorization and separate tiers with higher cost sharing, to control spending. These strategies can negatively impact patients' health outcomes through treatment initiation delays, medication abandonment, and nonadherence.

OBJECTIVE: To examine the effect of patient cost sharing on specialty drug utilization and the effect of prior authorization on treatment delay and specialty drug utilization.

METHODS: We conducted a literature search in the period between February 2021 and April 2022 using PubMed for articles published in English without restriction on date of publication. We included research papers with prior authorization and cost sharing for specialty drugs as exposure variables and specialty drug utilization as the outcome variable. Studies were reviewed by 2 independent reviewers and relevant information from eligible studies was extracted using a standardized form and approved by 2 reviewers. Review papers, opinion pieces, and projects without data were excluded.

RESULTS: Forty-four studies were included in this review after screening and exclusions, 9 on prior authorization and 35 on cost sharing. Patients with lower cost sharing via patient support programs experienced higher adherence, fewer days to fill prescriptions, and lower discontinuation rates. Similar outcomes were noted for patients on low-income subsidy programs. Increasing cost sharing above $100 was associated with up to 75% abandonment rate for certain specialty drugs. This increased level of cost sharing was also associated with higher discontinuation rates and odds. At the same time, decreasing out-of-pocket costs increased initiation of specialty drugs. However, inconsistent results on impact of cost sharing on medication possession ratio (MPR) and proportion of days covered (PDC) were reported. Some studies reported a negative association between higher costs and MPR and PDC; however, MPR and PDC of cancer specialty drugs did not decrease with higher costs. Significant delays in prescription initiation were reported when prior authorization was needed.

CONCLUSIONS: Higher levels of patient cost sharing reduce specialty drug use by increasing medication abandonment while generally decreasing initiation and persistence. Similarly, programs that reduce patient cost sharing increase initiation and persistence. In contrast, cost sharing had an inconsistent and bidirectional effect on MPR and PDC. Prior authorization caused treatment delays, but its effects on

specialty drug use varied. More research is needed to examine the effect of cost sharing and prior authorization on long-term health outcomes.

Specialty drugs are medications distinguished by their high production costs, their requirements for special manufacturing, distribution, or handling, and their ability to treat and/or manage rare conditions such as cancer, multiple sclerosis (MS), or rheumatoid arthritis (RA).[1] Historically, most specialty drugs were derived from biologic sources and injected or infused in clinical settings, but oral dosage forms and self-injectables are becoming increasingly available in the market. The Centers for Medicare and Medicaid Services uses a cost threshold to define specialty drugs; for 2023, the threshold is $830 per month based on 30-day equivalent ingredient cost.[2]

Payers often target specialty drugs for additional management because of their high cost compared with traditional medications. The percentage of patients who use specialty drugs is small, ranging from 1% to 5%,[3,4] but the cost is high. It is estimated that $301 billion was spent on specialty drugs in 2021 in the United States, an increase of 43% since 2016.[5] By 2021, spending for specialty drugs represented approximately 40% of retail drug spending and nearly 70% of nonretail drug spending.[5]

To manage prescription drug spending, payers use many tactics that can be combined under the term "utilization management (UM)." One UM strategy is categorizing specialty drugs in a separate tier that requires patients to pay higher copayment or coinsurance, resulting in higher patient out-of-pocket (cost sharing) costs compared with nonspecialty drugs.[6,7] It is estimated that 49% of covered workers are in a plan with a separate tier for specialty drugs.[8] Plans without a separate tier for specialty drugs typically place them in the highest cost-sharing tier. Coinsurance can be particularly problematic because patients pay a percentage of the high specialty drug prices. Of the covered workers facing a separate specialty drug tier, 42% had coinsurance with an average coinsurance rate of 27%.[8] For plans without a separate tier for specialty drugs, 43% of covered workers had coinsurance for fourth-tier drugs and the average coinsurance percentage was 32%.[8] It is estimated that patients spend approximately $35.8 billion annually in drug cost sharing.[9]

Another UM technique is prior authorization (PA), in which insurers require patients to obtain approval before using a drug or medical service. The PA process requires providers to complete a form and wait for a response of approval (or denial) from the insurer. The PA request must be approved for the drug or service to be a covered benefit. According to 2020 Medication Access Report, 37% of prescriptions denied because of PA requirements were abandoned.[10]

Although these UM tactics can help payers to control expenditures, they potentially affect specialty drug use, particularly medication nonadherence. Measures of nonadherence include initiation, abandonment, persistence, continuity gaps, proportion of days covered (PDC), and medication possession ratio (MPR). Medication initiation is defined as the first fill or any fill of any drug prescription within a predefined period of time (ie, 90 days, 180 days, or 2 years as defined by Doshi et al and Romley et al).[11-13] Abandonment is failure to fill a prescription (ie, prescription is left at the pharmacy and never picked up), a reversed claim, or an unpaid claim within 90 days or 180 days of prescription date.[14,15] Persistence is defined as continuation of and time of medication use after the first refill. Continuity gaps measure whether patients are without their medication for a specified length of time. PDC and MPR are 2 quantitative methods that are used to measure nonadherence. MPR is the sum of days supply dispensed within a period of time divided by the number of days in the time period, which could exceed 100%. PDC is the proportion of time period in which medication supply was available. PDC is more conservative than MPR and never exceeds 100%. A cut point of 0.8 is commonly used to set the MPR or PDC threshold for an acceptable level of adherence.[16-18]

An earlier systematic review published by Doshi et al. reviewed evidence regarding the association between cost sharing and specialty drugs utilization for RA, MS, and cancer.[19] This review updates the review by Doshi et al and expands the scope to include any specialty drug indication and the impact of PA.

The objectives for this systematic review of the literature were to examine (1) the effect of patient cost sharing on specialty drug utilization and (2) the effect of PA on treatment delay and specialty drug utilization.

Methods

We conducted a literature search using PubMed for all articles published in English without restriction on date of publication, in the period between February 2021 and April 2022. The first primary search was based on combination of 2 key words; the first included "specialty drug," "specialty medication," "biologic," or "biopharmaceutical" and 1 of the following: PA, abandonment, patient cost, claims, out-of-pocket, adherence, utilization, initiation, copayment,

coinsurance, deductibles, drug spending, specialty tier, tiered benefit, or benefit design. The second search aimed to identify specific classes of medications that are classified as "specialty drug" and the diseases they are prescribed to manage. The search included a combination of the former words, in addition to autoimmune, rheumatoid, irritable bowel disease (IBD), Crohn's, ulcerative colitis, psoriasis, cancer, PCSK9i, or tumor necrosis factor. References of included papers were checked for eligible articles.

Studies from search results were reviewed independently by 2 members of the research team (Mr Ismail and Dr Urmie) to identify eligible studies through applying predefined inclusion criteria. Disagreements on inclusion were resolved through discussion and mutual agreement. An abstraction form was used to collect data from the studies. All abstracted information was reviewed and approved by 2 reviewers, independently (Mr Ismail and Dr Urmie).

We included research papers with PA and/or cost sharing (including out-of-pocket cost, copayment, and coinsurance) as the exposure variable of interest (independent variable) and specialty drug use as the outcome of interest. Specialty drug use encompassed multiple measures of medication nonadherence, including time to initiation, initiation, abandonment, persistence, discontinuation, PDC, and MPR. We excluded papers that were literature reviews, opinion pieces, analysis of trends, and projects without data. Studies were grouped by exposure variable (cost sharing and PA) for syntheses of evidence. The patient support program studies were only included if they had a reduced patient cost sharing component.

Institutional review board approval was not needed because this project is a systematic review of published literature.

Results

The first primary search identified 2,307 records. After screening, excluding duplicates and applying inclusion criteria, 44 studies were included in this review (Figure 1). According to exposure variable, 5 studies focused on patient support program (PSP) that reduced patient cost sharing,[20–24] 8 on Medicare Part D low-income subsidies (LIS),[25–32] 9 on PA,[33–41] and 22 on cost sharing other than via a PSP or Part D LIS.[11–15,42–58] Table 1 summarizes the included studies.

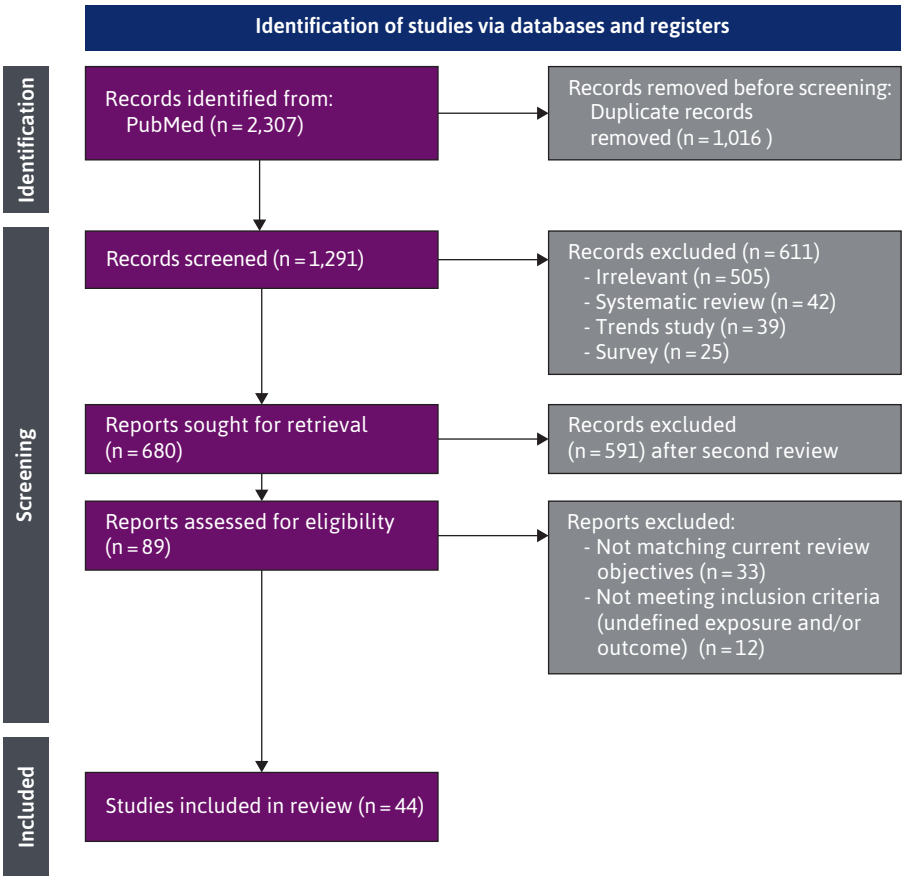
PATIENT COST SHARING

Patient cost sharing includes copayments, coinsurance, and deductibles. Studies on cost sharing were mostly cross-sectional studies comparing specialty drug use across different cost-sharing levels, but a few studies examined the effect of cost sharing changes.

Effects on Initiation, Abandonment, and Time to Use. Cost sharing is associated with changes in specialty drugs initiation and prescription abandonment. With low cost sharing (between $0 and $50), the abandonment rate for specialty drugs was 1.3%–10%.[13–15,42,43] Increasing patient cost sharing above $100 was associated with a 32%–75% abandonment rate for specialty drugs.[13–15] Compared with patients who paid less than $100, patients who paid $100 or more were 2–26 times more likely to abandon their prescriptions.[42,44] A similar pattern was noticed between cost sharing and medication initiation. Increasing the cost sharing was associated with delayed initiation of medications.[11–13,45–47] Included studies used different cutoff points to define delayed initiation. These points ranged between 90 days and 2 years. The delayed initiation of oral anticancer specialty drugs was approximately 18% for patients who paid more than $2,000,[13] but it reached 35% for some medications such as imatinib (annual out-of-pocket cost of $8,400) and even up to 70% for thalidomide (annual out-of-pocket cost of $13,700).[45] Romely et al[11] found that the impact of an 18% cost sharing increase delayed the initiation of MS disease-modifying agents by 13% within 2 years of initial diagnosis. Goldman[46] reported that decreasing cost sharing by 20% increased initiation by 5%. This effect was affirmed by the simulation by Ozmainkowski et al,[47] in which MS medication (namely, interferon and glatiramer) initiation increased by 55% when the copayment was reduced by 50%. However, initiation decreased by 33% when the copayment was increased by 50%. If the copayment was set at $0, the probability of initiation increased to 70%.

Effects on Persistence. Cost sharing was also associated with medication persistence. As cost sharing increased, the discontinuation rate of imatinib, adalimumab, etanercept and infliximab increased by 4%–26% when compared with groups with lower copayments.[12,45,48,49,52] The hazard ratio of discontinuation with a $25-$250 increase in copayments for the MS disease-modifying agents, etanercept and adalimumab, ranged between 1.57 and 3.01.[50,51] In terms of discontinuation odds, Hopson et al[15] showed that patients with RA who paid more than $250 had 0.27 odds of specialty drugs refilling when compared with patients who paid less than $250. Bonafede et al[53] also found that higher etanercept and RA biologics copayments were associated with a higher rate of discontinuation, but the association was not statistically significant. Kaisang et al[45] compared the risk of discontinuation for several kinds of cancer specialty drugs. They found that with each $10 extra copayment, the risk of discontinuation increased by 13% and 14% for imatinib and erlotinib, respectively. However, the risk of discontinuation decreased (ie, increased persistence) by 26% for anastrozole and letrozole with the

FIGURE 1 Flow Diagram of Search Results (PRISMA)



same extra $10 copayment.[45] It is worth mentioning that the anastrozole and letrozole sample, whose size was 10 times larger than the sample size of imatinib and erlotinib users, was restricted to female beneficiaries who used these medications to treat breast cancer. Additionally, there was a higher noncancer drug cost burden for imatinib and erlotinib users.[45]

Effects on Adherence as Measured by MPR and PDC. The impact of cost sharing on specialty drug MPR and PDC was inconsistent. Higher cost sharing has often been associated with lower PDC and MPR for biologic disease-modifying antirheumatic drugs (including etanercept and adalimumab), imatinib, and MS drugs.[49,51,52,54,55] Dusetzina et al[52] found that higher copayments were associated with decreased PDC (ie, 82% vs 87% PDC for higher and lower copayments, respectively). Dor et al[58] examined the association between different types of cost sharing and adherence to MS drugs. They found that a 10% increase in coinsurance decreased the MPR by 8.6%, but copayment increases did not affect MPR. Sherman et al[48] reported that implementation of a program that reduced patient cost sharing significantly decreased PDC.

Interestingly, insignificant or very weak associations between cost-sharing changes and MPR or PDC were reported by Darkow,[56] Kim,[50] and Liu.[57] Darkow et al[56] reported a 5% increase in the MPR for imatinib with a $38 increase in cost sharing, but the increase was statistically insignificant. Kim et al[50] studied several specialty drugs with multiple indications. They found that PDC for anticancer, anti-inflammatory, and MS drugs did not change following up to a $250 increase in cost sharing, but there was a very small decrease (approximately 0.04) in PDC for immunosuppressants with a similar cost change. Higher copayments weakly reduced adherence to adalimumab (approximately 0.01) as reported by Liu et al.[57]

COST SHARING REDUCTION VIA A PSP

Some pharmaceutical manufacturers and specialty pharmacies offer PSPs to assist patients with specialty drug use. These broader programs may offer multiple forms of support; this literature review focused on PSPs that included financial assistance with specialty drug cost sharing.

The impact of adalimumab-treated PSPs is well examined in the literature. Following patients in these programs for 12 months, PDC rates of adalimumab significantly increased, with increases between 14% and 29%.[20,21,23,24] Approximately 44% of patients in adalimumab PSP were able to maintain PDC above 80% threshold, significantly higher than the 26% of adherent patients who were not in a patient support program. Moreover, they were able to continue using adalimumab for 134 extra days when compared with patients not participating in such programs as reported by Brixner et al.[21]

Also, discontinuation rates were significantly reduced at 12 months. In general, the amount of reduction ranged between 12% and 30%,[21,24] with a reduction of 70% reported by Brixner et al.[20] This high rate differed across indications of adalimumab: 66% for RA,

TABLE 1 Summary of Reviewed Studies

Author (year)	Data source	Data years	Design	Disease (agents)	Exposure	Outcome	Main results
Abdelnabi (2016)	EHRs	2009-2014	Retrospective chart review	Psoriasis	Prior authorization	Use and time to initiate	The mean duration in days between PA submission and coverage decision from the insurance company increased from 3.7 days in 2009 to 6.7 days in 2014. PA denial rates increased from 0% in 2009 to 19% in 2014.
Agarwal (2017)	Medical and Pharmacy records	2015	Retrospective review and prospective tracking of PA process	Breast cancer	Prior authorization	Use and time to initiate	Requirements to fax PA requests were associated with greater delay in approval time (1.31 vs 0.17 days for phone/online requests; $P<0.001$).
Berger (2020)	EHRs and pharmacy claims	2016-2017	Retrospective cohort	RA	Cost sharing	Adherence	The odds of higher adherence are greatest for patients with $0 cost per fill, and decrease until roughly $6, around which the odds of higher adherence level off.
Bonafede (2019)	IBM Watson MarketScan Claims	2013-2015	Retrospective cohort	RA (etanercept and bDMARDs)	Cost sharing	Adherence and Persistence	Patients with a copayment change had 1.88 higher odds of switching biologic agents during the post-index period than patients without a copayment change ($P=0.009$). Patients with copayment change tended to show higher rates of discontinuation (10.5% vs 7.9%; $P=0.293$) and lower rates of persistence (54.1% vs 60.7%; $P=0.135$).
Boytsov (2020)	IBM MarketScan claims	2014-2015	Retrospective cohort	RA and psoriatic arthritis (bDMARDs)	Prior authorization	Adherence	The odds of adherence were 19% lower (OR=0.81, 95% CI=0.68-0.96; $P=0.014$) among RA patients and 29% lower (OR=0.71, 95% CI=0.54-0.94; $P=0.017$) among psoriatic arthritis patients in plans with vs without step therapy.
Brixner (2019)	AbbVie and Symphony Health Solutions Claims	2015-2017	Longitudinal retrospective cohort	ADA	Cost-sharing (PSP)	Use and initiation	The ADA overall abandonment rate across all indications was reduced by 70% for the PSP cohort compared with the non-PSP cohort (OR=0.30, 95% CI=0.27-0.33, $P<0.001$).
Brixner (2019)	Symphony Health Solutions Medical and Pharmacy Claims	2015-2017	Longitudinal retrospective cohort	ADA	Cost sharing (PSP)	Adherence	Participation in the PSP was associated with 29.3% higher ADA adherence and 22.0% lower ADA discontinuation rate ($P<0.0001$).
Constant (2022)	EHRs	2010-2020	Retrospective cohort	IBD (Biologics)	Prior authorization	Time to initiate	PA was associated with 10.2 days increase in biologics initiation time.
Curkendall (2008)	MEDSTAT MarketScan Medical and Prescriptions Claims	2002-2004	Retrospective cohort study	RA (etanercept, adalimumab)	Cost sharing	Adherence and persistence	Adherence significantly decreased with increased weekly cost sharing (coefficient=-0.0035) translating into approximately 1 week of therapy lost per $5.50 increase in weekly cost sharing. Patients whose weekly cost exceeded $50 were more likely to discontinue than patients with lower costs (hazard ratio 1.58, $P<0.001$).

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TABLE 1 Summary of Reviewed Studies *(continued)*

Author (year)	Data source	Data years	Design	Disease (agents)	Exposure	Outcome	Main results
Darkow (2012)	Private Administrative Medical and Pharmacy Claims	1997-2009	Retrospective longitudinal cohort study	CML (TKI)	Cost sharing	Adherence (MPR)	The median patient out-of-pocket payment was $25, which increased to $63 at the 75th percentile and to $122 at the 95th percentile. MPRs were 94.8 at the median cost sharing level and 100.0 at the 75th percentile and higher. There was no statistically significant association between cost sharing and MPR.
Dor (2010)	Truven Health MarketScan Claims	2005-2008		MS	Cost sharing	Adherence (MPR)	Coinsurance cohort increased cost sharing was significantly associated with decreased adherence to DMT medication; with a 10% increase in cost sharing leading to an 8.6% decline in adherence. (not significant in copayment cohort).
Doshi (2016)	Medicare Part A, B, and D	2009-2012	Retrospective claims analysis	Psoriasis (infliximab, etanercept, adalimumab, or ustekinumab)	Cost sharing (LIS)	Adherence (PDC=0.80)	Being ineligible for LIS were associated with increased odds of decreased adherence (OR=0.67 [95% CI=0.51-0.88]).
Doshi (2016)	Medicare Part A, B, and D	2007-2010	Retrospective cross-sectional study	RA	Cost sharing (LIS)	Use and initiation	The non-LIS group was less likely to fill Part D biologic agents (61.2% vs 72.7%, OR=0.58 [95% CI=0.46-0.72]), more than twice as likely to receive Part B biologic agents (9.9% vs 4.4%, OR=2.41 [95% CI=1.61-3.60]), and less likely to use any biologic agent (70.1% vs 76.9%, OR=0.69 [95% CI=0.55-0.88]).
Doshi (2016)	Medicare Part A, B, and D	2011-2013	Retrospective claims-based analysis	CML (TKI)	Cost sharing (LIS)	Use and time to initiate	Non-LIS patients were less likely than LIS patients to have a TKI claim within 6 months of diagnosis (45.3% vs 66.9%; $P<0.001$) and those initiating a TKI took twice as long to fill it (mean=50.9 vs 23.7 days; $P<0.001$) (lower proportions within 1 and 3 months as well).
Doshi (2017)	Medicare and Commercial Claims	2014-2015	Retrospective claims-based study	Oral anticancer drugs	Cost sharing	Use, initiation, and persistence	Risk-adjusted abandonment rates were higher in greater cost-sharing categories (10.0% for=$10 group vs 13.5% for $50.01 to $100 group, 31.7% for $100.01 to $500 group, 41.0% for $500.01 to $2,000 group, and 49.4% for>$2,000 group; $P<0.001$ compared with=$10 group). Delayed initiation was also more frequent for higher cost categories (3% in=$10 group v 18% in>$2,000 group; $P<0.001$).
Doshi (2020)	Medical and Prescriptions Claims from Medicare, Medicaid, and private payers	2015-2017	Retrospective review	PCSK9-i	Prior authorization	Use and initiation	PA-related rejections increased from 22% initially to 48% in the last quarter of the study period (90 days). Patients in plans with a higher number of PA criteria had lower odds of both index prescription approval and 90-day approval.

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TABLE 1 Summary of Reviewed Studies *(continued)*

Author (year)	Data source	Data years	Design	Disease (agents)	Exposure	Outcome	Main results
Dudiak (2021)	Private clinic / prescriptions	2014-2019	Retrospective prescriptions review	Asthma and urticaria (omalizumab, benralizumab, mepolizumab, dupilumab)	Prior authorization	Time to initiate therapy	The patients with asthma were at high risk of exacerbations and need for prednisone while awaiting initiation of the biologics; 28 of 59 patients (47%) required prednisone.
Dusetzina (2014)	Truven Health MarketScan Claims	2002-2011	Retrospective cohort analysis	CML (TKI: imatinib)	Cost sharing	Adherence	Approximately 17% of patients with higher copayments and 10% with lower copayments discontinued TKIs during the first 180 days following initiation (aRR = 1.70; 95% CI = 1.30-2.22). Similarly, patients with higher copayments were 42% more likely to be nonadherent (aRR = 1.42; 95% CI = 1.19-1.69).
Dusetzina (2022)	Medicare claims, Part D, and EHRs	2012-2018	Retrospective review of records	Cancers, hepatitis C, hypercholesterolemia, immune system disorders	Cost sharing (LIS)	Initiation of therapy	Noninitiation was 37% higher among people without a low-income subsidy than among those with a low-income subsidy (partial or full) for all 4 conditions.
Fendrick (2021)	Symphony Health Claims	2015-2016	Longitudinal, retrospective matched cohort	RA, CD, UC, psoriasis, Ankylosing spondylitis (ADA)	Cost sharing (PSP)	Adherence (PDC) and persistence	PSP cohort had higher adherence at 12, 24, and 26 months that non-PSP by 29%, 29%, and 12%, respectively. Also, they had 30% lower hazard of discontinuation.
Fischer (2008)	Medicaid	1999-2005	Interrupted time series analysis	RA (bDMARDs [abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab])	Prior authorization	Use and initiation	There were 18 states with PA requirements for adalimumab or etanercept. States that implemented PA for these agents initially had lower use of the targeted medications, but use increased over time to a level similar to that in states that did not have PA requirements.
Gleason (2009)	BlueCross BlueShield Pharmacy Claims	2006-2008	Cross-sectional study	MS (etanercept, adalimumab, interferon β, glatiramer)	Cost sharing	Use and initiation	The abandonment rate of biological agents increased as cost sharing increased (test for trend, $P < 0.001$). Members with an expense of $100 or less had an abandonment rate of 5.7%. Among members in all cost-sharing expense groups greater than $200, the abandonment rate was significantly higher, with more than 1 in 4 members abandoning their MS claims ($P < 0.001$). The TNF blocker medication abandonment rate was significantly higher for all cost-sharing expense groups greater than $100.
Guo (2021)	Academic site / prescriptions	2017	Cross-sectional analysis	Dermatology conditions	Prior authorization	Use and time to initiate therapy	Patients with submitted PAs had significantly lower treatment initiation than those without (52.8% vs 78.2%, $P < 0.001$).

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TABLE 1 Summary of Reviewed Studies *(continued)*

Author (year)	Data source	Data years	Design	Disease (agents)	Exposure	Outcome	Main results
Hawkes (2019)	Symphony Health Solutions Medical and Pharmacy Claims	2012-2015	Retrospective cohort	ADA	Cost sharing (PSP)	Use and time to initiate	PSP patients had a greater frequency of initiation at a specialty pharmacy (66% vs 56%; $P<0.001$), lower copay for ADA ($206 vs $265; $P=0.011$) as well as lower abandonment rate (6.4% vs 13.9%; $P<0.001$) and reduced days to prescription fill (7.0 vs 14.4; $P<0.001$).
Hopson (2016)	Medicare Advantage Prescription Plan	2007-2012	Retrospective cohort analysis	RA (bDMARDs)	Cost sharing	Use, initiation, and persistence	The overall initial abandonment rate was 18.2% for biologic DMARDs, ranging from 1.3% for the lowest cost group ($0-$250) to 32.7% for the highest cost group (>$550; $P<0.0001$ for Cochran-Armitage trend test). The negative association between cost sharing and likelihood of refilling a prescription was highly significant ($P<0.0001$).
Jung (2017)	Medicare (FFS beneficiaries)	2009-2013	Quasi-experiment	Six uncommon cancers (leukemia, kidney, pancreatic, skin, sarcoma, and non-Hodgkin lymphoma)	Cost sharing (LIS)	Use and initiation	The in-gap discount did not influence specialty cancer drug use but reduced annual cost-sharing spending for specialty cancer drugs among users without LIS by $1,108.
Karaca-Mandic (2010)	Private medical and dispensing claims	2000-2005	Retrospective analysis of records	RA (adalimumab, etanercept, infliximab)	Cost sharing	Initiation and persistence	Patients with RA in families with high cost-sharing costs are much less likely to initiate biologics (2% annually) compared with those in less constrained families (5.6%).
Kaisaeng (2014)	Medicare	2008	Cross-sectional	Imatinib, erlotinib, anastrozole, letrozole, or thalidomide	Cost sharing	Persistence and time to initiate	For each $10 increase in cost sharing spending per month, the likelihood of discontinuation or delay increased 13%, 14%, and 20% for imatinib, erlotinib, and thalidomide users, respectively, but decreased 26% for anastrozole and letrozole users.
Kim (2011)	Scott & White Health Plan Medical and Pharmacy Claims	NA	Retrospective longitudinal cohort study	Anti-inflammatory, cancer, immunosuppressant, and MS medications	Cost sharing	Adherence (PDC) and persistence	The growth models did not indicate any significant changes in PDC after copayment changes for anti-inflammatory, cancer, and MS drugs but showed significant changes for immunosuppressants. The persistence results varied by drug type. The Cox regression analysis showed a significant difference in discontinuation of therapy between groups after the copay change for anti-inflammatory and immunosuppressant drugs.
Lafata (2008)	Private Pharmacy Claims	2004-2006	Retrospective cohort study	MS	Cost sharing	Adherence and persistence	Among those with 2 or more dispensing, mean MPR between the first and last dispensing date was 83.8% (95% CI = 80.8-86.8), whereas mean MPR for the entire 24-month period was 68.0% (64.4-71.7).

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TABLE 1 **Summary of Reviewed Studies** *(continued)*

Author (year)	Data source	Data years	Design	Disease (agents)	Exposure	Outcome	Main results
Li (2018)	Medicare Part D claims	2007-2010	Quasi-Experimental	RA and MS	Cost sharing (LIS)	Persistence	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% compared with 0.9 percentage points increase in LIS, OR = 1.61, 95% CI = 1.19-2.17; RA, absolute increase = 21.9%, OR = 2.75, 95% CI = 2.15-3.51).
Li (2018)	Medicare Part D claims	2011-2013	Retrospective claims-based study	Metastatic renal cell carcinoma (injected/ infused and oral medications covered under Medicare Part B or D benefits)	Cost sharing (LIS)	Use and initiation	Compared with LIS patients, a lower percentage of non-LIS patients initiated oral therapies (risk-adjusted rates, 20.7% vs 33.9%; OR = 0.49, 95% CI = 0.36-0.67; $P < 0.001$) and any targeted therapies (26.7% vs 40.4%, OR = 0.52, 95% CI = 0.38-0.71, $P < 0.001$). Non-LIS patients were also slower to access therapy.
Liu (2010)	Private Dispensing records	2003-2009	Retrospective analysis of records	Adalimumab	Cost sharing	Adherence (MPR)	Copayment/payment amount per prescription has significant but very weak association.
Navar (2017)	Symphony Health Solutions Pharmacy Claims	2015-2016	Retrospective review	PCSK9-i	Cost sharing	Use and time to initiate	Prescription abandonment by patients was most associated with copay costs (C statistic, 0.86); with abandonment rates ranging from 7.5% for those with $0 copay to more than 75% for copays greater than $350. Of the patients given a prescription, 20.8% received approval on the first day, and 47.2% ever received approval.
Ozminkowski (2004)	Medstat's MarketScan Medical and Pharmacy Claims	1996-2000	Retrospective analysis of claims	MS (interferon, glatiramer)	Cost sharing	Use and time to initiate	Each 1% increase in the share of drug expenditures accounted for by drug copayments was associated with an approximately 14% drop in the rate at which newer drugs were used (hazard ratio, 0.865; $P < 0.001$).
Romley (2012)	Private Administrative Medical and Pharmacy Claims	2004-2008	Retrospective longitudinal cohort study	MS (DMT)	Cost sharing	Use and initiation	An increase in the cost sharing rate from zero to the 95th percentile (17.8%) was predicted to decrease initiation within 2 years of diagnosis by 2.9 percentage points, or 12.7% ($P = 0.019$).
Rubin (2017)	Symphony Health Solutions administrative claims data	2008-2014	Longitudinal Retrospective Cohort	Crohn's disease, UC, RA, psoriasis, ankylosing spondylitis (ADA)	Cost sharing (PSP)	Adherence	ADA adherence was 14% greater in the PSP cohort than for the non-PSP cohort (67.0% vs 58.8%; $P < 0.001$). The discontinuation rate for ADA was 14% lower in the PSP cohort compared with the non-PSP cohort (39.7% vs 46.2%; $P = 0.001$).

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TABLE 1 Summary of Reviewed Studies *(continued)*

Author (year)	Data source	Data years	Design	Disease (agents)	Exposure	Outcome	Main results
Streeter (2011)	Wolters Kluwer Dynamic Pharmacy Claims	2007-2009	Cross-sectional cohort study	Oncolytic agents (capecitabine, imatinib, sorafenib, lenalidomide, sunitinib, erlotinib, temozolomide, and lapatinib)	Cost sharing	Use and initiation	Claims with cost sharing greater than $500 were 4 times more likely to be abandoned than claims with cost sharing of $100 or less (OR = 4.46; $P < 0.001$).
Wallace (2020)	EHRs	2016-2018	Retrospective review	RA (infused biologics)	Prior authorization	Time to initiate	Compared with cases in which no PA was required, those requiring PAs were associated with a greater number of days to infusion (median 31 days vs 27 days, $P = 0.045$).
Winn (2016)	SEER-Medicare	2007-2011	Retrospective cohort	CML (TKIs)	Cost sharing (LIS)	Adherence (PDC) and initiation	No significant difference in adherence or initiation adjusted RR between those who received and did not receive cost subsidy.

ADA = adalimumab; aRR = adjusted risk ratio; bDMARDs = biologic disease-modifying antirheumatic drugs; CAAP = copay accumulator adjustment program; CD = Crohn's disease; CML = chronic myelogenous leukemia; DMARDs = disease-modifying antirheumatic drugs; DMT = disease-modifying therapy; EHR = electronic health record; HR = hazard ratio; HSA = health savings account; IBD = inflammatory bowel disease; LIS = low-income subsidy; MPR = medication possession ratio; MS = multiple sclerosis; OR = odds ratio; PA = prior authorization; PCSK9-i = proprotein convertase subtilisin/kexin type 9 inhibitor; PDC = proportion of days covered; PPO = preferred provider organization; PSP = patient support program; RA = rheumatoid arthritis; TKI = tyrosine kinase inhibitor; TNF = tumor necrosis factor; UC = ulcerative colitis.

72% for IBD, and 76% for ankylosing spondylitis.[20] Hawkes et al[22] showed that patient support programs reduced abandonment rate by 43%. Patients in these programs took approximately 50% fewer days (ie, 7 days) to fill their first prescription compared with nonparticipants (ie, 14 days),[22] and the rate of refills for adalimumab was increased by 36%.[20]

COST-SHARING REDUCTION VIA THE MEDICARE PART D LOW-INCOME SUBSIDY PROGRAM

One subcategory of cost-sharing studies was studies examining the effects of LIS in Medicare Part D. LIS programs are designed to help qualified patients with their out-of-pocket costs by lowering the medications coinsurance and copayments. Dusetzina et al[30] found that noninitiation of drugs among non-LIS patients was 21% for hepatitis C drugs, 28% for cancer drugs and 67% for hypercholesterolemia drugs. Non-LIS patients were 37% less likely to fill their prescriptions within 90 days.[30]

Compared with LIS-eligible patients, it was found that non-LIS patients have lower odds of initiating their specialty drugs prescriptions. These odds were 0.49 for oral therapies, 0.52 for renal carcinoma targeted therapies, and 0.69 for RA biologics.[25,29] Lower fill rates for specialty drugs used to treat RA, renal cell carcinoma, and chronic myelogenous leukemia (such as tyrosine kinase inhibitors) were also noted for non-LIS groups with odds ratios of filling between 0.55 and0.59.[25,26,29] Doshi et al[26] found that non-LIS groups consistently took longer periods of times (almost twice the time of LIS patients) to initiate tyrosine kinase inhibitors for chronic myelogenous leukemia within 1, 3, and 6 months of prescribing. LIS-receiving patients had higher tyrosine kinase inhibitor PDC (risk ratio [RR] = 1.12; $P > 0.05$), lower time to initiate (RR = 1.35; $P < 0.05$) and higher initiation within 180 days (RR = 1.08; $P > 0.05$) when compared with non-LIS patients, as reported by Winn et al.[31]

In a separate study, Doshi et al[27] found that non-LIS patients had 33% lower odds of adherence (ie, PDC > 0.8) to psoriasis biologics when compared with LIS patients. They also experienced almost double the odds of discontinuation.

Non-LIS patients diagnosed with MS also experienced 1.61 times the odds of LIS patients of 30-day continuity gaps in Part D medications on transitioning from the low cost sharing period into the high cost sharing period. And even larger effect was found for patients with RA, where non-LIS patients experienced 2.75 times the odds of a 30-day continuity gap compared with LIS patients.[28] Continuity gaps in this study were measured by whether the claims data indicated the presence of at least 1 continuous gap of 30 days or more with no supply of Part D MS or RA medications.[28]

PRIOR AUTHORIZATION

PA requirements created delays in treatment but had somewhat mixed effects on specialty drug utilization.

Prior authorization was needed for 47%-71% of RA and asthma biologics.[34,37] It took between 6.7 days and 21 days for insurance companies and payers to process PA requests.[34,35,40] Several studies reported that prior authorization increased time to treatment initiation. This increase ranged between 3.6 days for cancer drugs[39] and up to 31 days for RA and inflammatory bowel disease biologics.[33,37] Ultimately, the delay caused by prior authorization lowered initiation of dermatologic treatment by 26%,[35] and patients filled only 14% of non–PA-approved prescriptions, compared with 78% of approved prescriptions.[35]

In contrast, Boytsov[36] did not find any significant difference in adherence (defined as PDC>0.8) to RA biologic disease-modifying antirheumatic drugs or treatment effectiveness because of PA. Fischer et al[41] also showed that PA in state Medicaid programs initially decreased the use of RA biologics (eg. adalimumab, etanercept), but biologic use subsequently returned to levels similar to state Medicaid programs that did not have PA requirements.

Discussion

Higher levels of patient cost sharing consistently resulted in lower levels of medication initiation and mostly reduced persistence, but the effect of cost sharing on MPR and PDC was inconsistent. PA led to some treatment delays, but its effects on specialty drug utilization varied.

COST SHARING AND ADHERENCE

Patient cost sharing seems to have a particularly strong association with rates of medication initiation and abandonment. In the studies included in our literature review, cost sharing of $100 or more was associated with abandonment rates between 32% and 75%. A broader study on the effect of cost sharing on abandonment of both specialty and nonspecialty drugs found that abandonment rates increased steadily as patient cost sharing increased and reached 69% when cost sharing was $250 or more.[59] As a result of the Affordable Care Act, all employer plans have out-of-pocket maximums for covered health care expenses and some employers have implemented separate prescription drug out-of-pocket maximums.[8] These out-of-pocket maximums, although important in protecting patients from catastrophic costs, will not help reduce medication abandonment because the abandonment stems from high initial out-of-pocket costs. With increasing drug list prices, patients exposed to deductible and coinsurance benefit designs face increasingly higher out-of-pocket costs. Rome et al[60] reported that the average launch price for a new drug increased from $2,155 per year in 2008 to $180,007 per year in 2021.

Although patient cost sharing generally had negative effects on specialty drugs initiation and abandonment, the effects of cost sharing on MPR and PDC were more mixed. There are different possible explanations for these mixed effects. Specialty drugs are often used for medical conditions that are either life-threatening or have significant negative effects on quality of life, so patients who start a specialty drug may be reluctant to take less than prescribed because they do not want to lose its beneficial effects. However, an alternative explanation is that the reported patient cost-sharing amount is not the true patient cost sharing amount because of manufacturer copay offset programs that reduce patient cost sharing for some brand-name medications. These programs typically are open to privately insured patients of all income levels. They substantially reduce patient out-of-pocket costs and are widely used for some specialty drugs.[44,61] Cost-sharing reductions from copayment offset programs may not have been fully captured in claims data. Another possible explanation is that some of the MPR and PDC studies were from patient support programs that included patient adherence support beyond cost sharing assistance, making it difficult to disentangle effects of the cost sharing from effects of the broader support program.

PRIOR AUTHORIZATION

This review examined the impact of PAs on medication use. The prevalence of PA has increased substantially over time.[62] A benefit of PA is that it can potentially reduce the use of inappropriate or expensive medications, but it is costly in terms of provider time and potential delays in treatment initiation. Our review of the literature found that PA was associated with treatment delay of up to 31 days. Although not an a priori outcome of interest in our study, it was interesting to note that prior authorization approval rates varied from 19% to 97.5%.[38-40] For medications for which the approval rate is very high, the small reduction in drug use may not justify the cost of the PA process and the delay in initiating therapy, although it is possible that it deters providers from seeking approval for patients who they know do not meet the PA criteria. In situations in which the PA approval rate is very low, the PA requirement would result in substantial prescription cost-savings. It was beyond the scope of our review to determine the appropriateness of the medication denials, but inappropriately denying medications may have unintended long-term consequences for health and health care costs, which would be relevant to multiple stakeholders, including payers.

The UM strategies of PA and cost sharing generally have been shown to reduce use of and adherence to specialty drugs. From a cost-saving perspective, one could argue that because reducing the use of specialty drugs decreases costs, the UM strategies are achieving their purpose. The more difficult question to answer is whether the cost savings comes at the expense of patient health outcomes. It is possible patients prescribed a specialty drug could have been successfully treated with a less expensive nonspecialty drug. Although not specific to specialty drugs, one study found that more than 75% of patients who abandoned a prescription failed to start any therapy within 90 days.[63] There is also evidence from the literature that nonadherence negatively affects patient outcomes.[34,37,64-68] Given the environment of increasingly high drug prices, payers and policy makers need to carefully consider the impact of patient cost sharing on specialty drug adherence.

BIAS IN THE LITERATURE

Bias in published literature is always of concern. Many of the included studies were funded by pharmaceutical manufacturers. It was important to assess potential bias because pharmaceutical manufacturers theoretically would oppose drug benefit management strategies such as higher cost sharing and PA because these strategies may reduce use of their products. On one hand, more than half of the included studies related to adherence in this review were funded by pharmaceutical manufacturers. However, among the studies showed that patient cost sharing negatively impacted PDC, only 3 out of 6 studies disclosed funding by industry,[48,51,52] whereas all 3 studies showing insignificant or weak association between cost and PDC/MPR were funded by pharmaceutical manufacturers.[50,56,57] If pharmaceutical manufacturer bias was a problem, the expected direction is that studies showing an insignificant association between cost and PDC/MPR would have been less likely to be funded by pharmaceutical manufacturers. However, it is possible that traditional publication bias exists if studies reporting an insignificant effect of cost sharing on specialty drug utilization were less likely to be published.

LIMITATIONS

There are several limitations of our study and the reviewed literature. First, the included studies may not have accounted for manufacturer copayment offset programs, which reduce patient cost sharing. Also, outcomes from studies that examined patient support programs may have been affected by broader patient support and not solely because of cost-sharing reductions. Second, different authors sometimes defined and measured the same outcome in different ways. For example, initiation was measured as starting the medication within 90 or 180 days. This limited our ability to combine some results. Third, most studies measured adherence via claims data. Claims data capturing medication dispensing may not always reflect actual patient medication use. Fourth, although most studies controlled for confounding variables such as demographics, comorbidities, and socioeconomic status, these control variables differed somewhat across studies and there may have been unmeasured confounders. Finally, we only included intermediate outcomes of specialty drug use, rather than health outcomes such as disease progression. Future research is needed to study the long-term effects of specialty drugs UM strategies on health outcomes.

Conclusions

Higher levels of patient cost sharing reduced specialty drug use by increasing medication abandonment while generally decreasing medication initiation and persistence. Similarly, programs that reduced patient cost sharing increased medication initiation and persistence. In contrast, patient cost sharing had an inconsistent and bidirectional effect on MPR and PDC. PA effects on specialty drug utilization varied. More research is needed to better understand the role of manufacturer copay offset programs on specialty drug utilization and to examine the effect of UM strategies on long-term health outcomes.

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