Impact of Cost Sharing on Specialty Drug Utilization and Outcomes: A Review of the Evidence and Future Directions

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ABSTRACT

Objectives: Specialty drugs often represent major medical advances for patients with few other effective options available, but high costs have attracted the attention of both payers and policy makers. We reviewed the evidence regarding the impact of cost sharing on utilization of specialty drugs indicated for rheumatoid arthritis (RA), multiple sclerosis (MS), and cancer, and on the use of nondrug medical services, health outcomes, and spending.

Study Design: Systematic review of Medline-indexed studies identified via an OVID search for articles published in English from 1995 to 2014, using combinations of terms for cost sharing and specialty drugs, and/or our 3 conditions of interest. We identified additional studies from reference lists.

Results: We identified 19 articles focusing on specialty drugs indicated for MS (n = 9), cancer (n = 8), and RA (n = 8). Studies examined prescription abandonment (n = 3), initiation or any utilization (n = 8), adherence (n = 9), persistence/discontinuation (n = 7), number of claims (n = 1), and drug spending (n = 1). Findings varied by disease, but generally indicated stronger effects for noninitiation or abandonment of a prescription at the pharmacy and somewhat smaller effects for refill behavior and drug spending once patients initiated therapy. Studies have not examined specialty tier cost sharing seen under Medicare Part D or health insurance exchanges, nor effects on medical utilization, spending, or health outcomes.

Conclusions: Evidence to date generally indicates reductions in specialty drug utilization associated with higher cost sharing; effects have varied by type of disease and specialty drug use outcome. We draw upon our findings and the gaps in evidence to summarize future directions for research and policy.

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Specialty drugs typically represent significant medical advances, either in the form of novel approaches for the treatment of complex chronic conditions (eg, rheumatoid arthritis [RA], multiple sclerosis [MS]) or because they target diseases with few prior treatment options (eg, rare diseases or advanced cancers). Although the definition of specialty drug varies by payer, these medications share certain key characteristics.[1] Typically, they are complex molecules and may be derived from biologic sources; require highly involved manufacturing processes; require special distribution and handling, such as refrigeration; involve intensive patient education and/or follow-up monitoring to ensure appropriate use; and are high cost. Many specialty medications require injection or infusion in clinical settings and are usually covered under the medical benefit. The remainder are administered at home by self-injection, or oral or inhaled administration, and are almost always covered under the pharmacy benefit.

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Despite the therapeutic advances offered by many of these agents, specialty drugs have attracted payer attention because they are often accompanied by higher costs than traditional medications. Although the percentage of patients using specialty drugs is quite small—ranging from 1% to 5%[2,3]—a recent report estimated specialty drug spending in the United States at $95 billion in 2013, or about 29% of total prescription drug spending.[4] Although published estimates vary depending on which agents are included, about two-thirds of specialty drug spending growth in 2013 was accounted for by agents to treat cancers, autoimmune conditions like RA, and MS.[4]

Since about half of specialty drug spending is on self-administered agents covered by pharmacy benefits, these have been the focus of payer efforts to control spending.[5] Insurers and pharmacy benefit managers seeking to manage costs have been unable to use the traditional 3-tiered cost-sharing design to encourage utilization of lower-cost drugs, however, given the fact that specialty drugs often have few close, less-

expensive substitutes. As a result, utilization management (UM) tools, such as prior authorization and quantity limits, have been applied instead.[6] Nevertheless, growing pressure to control spending has led insurers to increasingly place self-administered specialty drugs on new, separate "specialty tiers." Whereas tiered cost-sharing designs typically have fixed co-payments of increasing amounts for generics, preferred brands, and nonpreferred brands, respectively, newer specialty tiers usually impose a coinsurance requirement which can be as high as 30% to 50% of the cost of the drug. Although specialty tiers were first broadly implemented with Medicare Part D, use of this strategy (and associated high cost sharing) has grown significantly in other markets, including the employer-sponsored insurance market and the new health insurance exchange plans created under the Affordable Care Act.[7,8] Further, many plans—particularly those under Medicare Part D—place medications meeting a designated cost threshold (eg, $600 a month or more) on the specialty tier, regardless of whether those medications meet other common criteria for the specialty drug designation.

Take-Away Points

Current evidence indicates that higher specialty drug cost sharing is associated with reduced specialty drug utilization. Research examining broader health outcomes and spending is unavailable.

- Cost-sharing effects varied by type of disease and specialty drug utilization outcome examined.
- There is a critical need for methodologically rigorous research to further evaluate whether the aggressive cost-sharing arrangements found in the current marketplace may cause patients to forego, delay, or decrease adherence to specialty drugs, and whether that results in poor health outcomes and higher total spending.

Despite the market trends in increasing patient out-of-pocket (OOP) costs for specialty drugs, the impact of patient cost sharing on specialty drug utilization and outcomes is unclear. Numerous reviews have summarized the relationship between cost sharing and utilization of traditional oral drugs, but none have evaluated the evidence as it relates to specialty pharmaceuticals.[9-11] Such a review is needed for several reasons. First, patients may have strong demand for specialty drugs if they do not have other treatment options or if they perceive alternative, less expensive treatments to be ineffective or undesirable. In this context, they may be willing to pay a much higher cost share compared with traditional pharmaceuticals. On the other hand, the magnitude of OOP costs may exceed patients' ability to pay, particularly in the context of overall medical expenses and other basic needs. More information is needed to determine the degree to which patient cost sharing is associated with changes in specialty drug utilization, as well as with health outcomes, use of nondrug medical services, and overall healthcare spending.

We sought to address this gap with a systematic review of the published evidence. In light of the highly variable definitions of specialty drugs across insurers, we focused our review on cost-sharing studies of specialty drug classes with indications for 3 key disease areas: RA, MS, and cancer. These represented the top 3 drivers of specialty drug spending in the United States at the time of our review.[4] We examined associations between cost sharing and specialty drug utilization for these indications and draw upon our findings, including the gaps in evidence in light of current market trends, to highlight future directions for specialty drug research and policy.

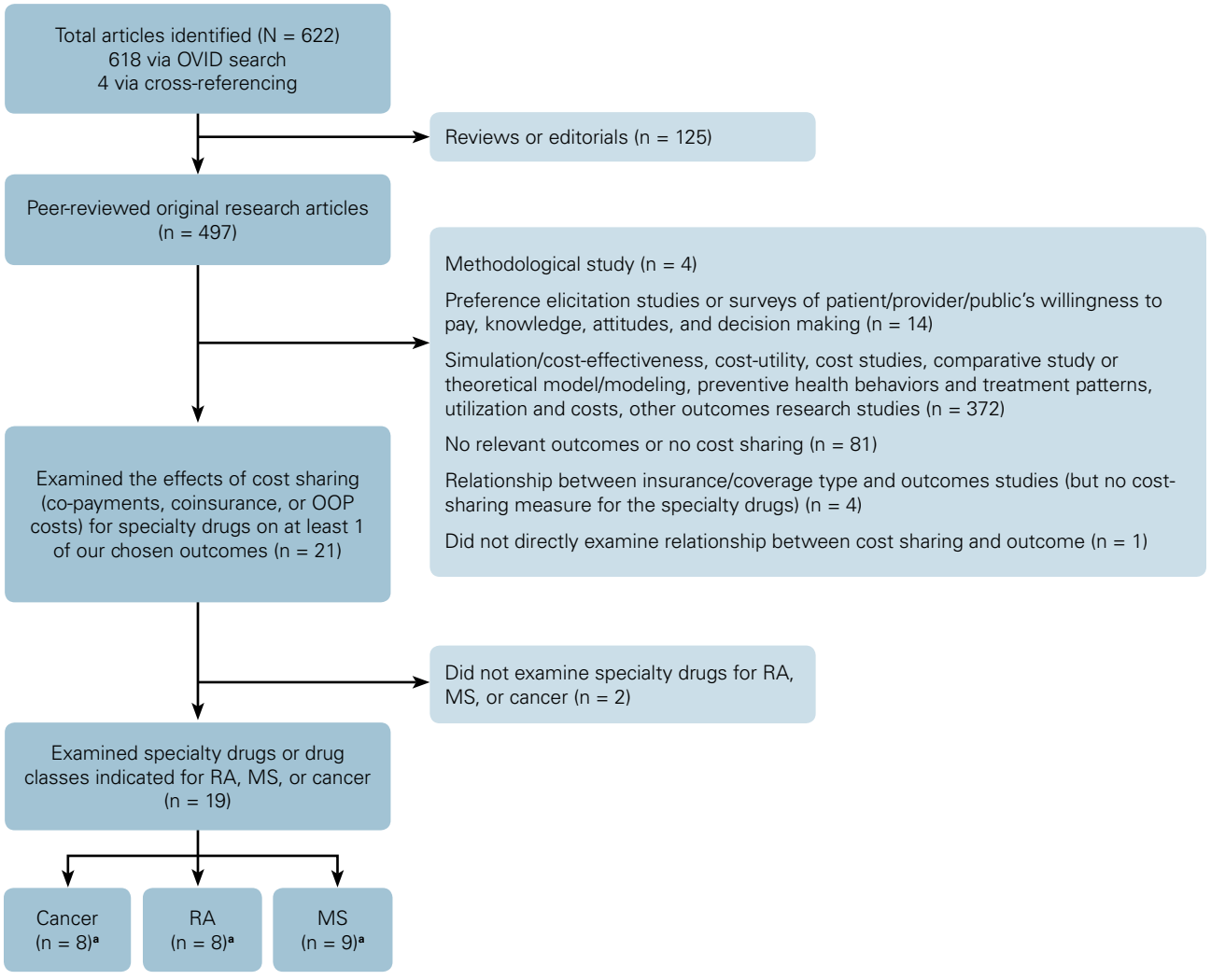
METHODS

Evidence Review

We conducted an OVID search for all Medline-indexed articles published in English between 1995 and 2014. The primary search was based on various combinations of 2 sets of search terms. The first set included cost sharing and related terms: co-pay, coinsurance, benefit design, tiered benefit, specialty tier, and out-of-pocket cost. The second set included terms for specialty medications and our indications of interest: specialty drug, specialty pharmaceutical, biologic, rheumatoid arthritis, multiple sclerosis, cancer, oncology, carcinoma, leukemia, oncolytics, myeloma, and tumor. Additional studies were obtained from reference lists of identified studies. Identified articles were then independently screened and reviewed by 2 members of the research team to determine whether they met our criteria for inclusion (**Figure**).

These inclusion criteria, applied in the following order, were: 1) published as a peer-reviewed original research article (ie, review articles, editorials, and letters were not eligible), 2) examined the effects of cost sharing (co-payments, coinsurance, or OOP costs) for specialty drugs on at least 1 of our chosen outcomes (specialty drug utilization or spending, medical utilization or spending, or health outcomes), and 3) examined drugs or drug classes that were indicated for RA, MS, or cancer and met the aforementioned high cost criterion for specialty drugs, along with at least 1 additional specialty drug criterion (eg, complex molecule or dispensed through specialty pharmacy). Because anti-inflammatory biologics used to treat RA are also approved for other indications (eg,

Figure. Literature Search and Study Selection Flow Chart



MS indicates multiple sclerosis; OOP, out-of-pocket; RA, rheumatoid arthritis.
[a]Some studies examined drugs for more than 1 indication, so groups are not mutually exclusive.

psoriatic arthritis, ankylosing spondylitis), we did not exclude studies that sampled patients based on use of such drugs rather than diagnosis, even though they may have included patents with conditions other than RA. In light of the limited number of studies available, we also did not impose additional restrictions based on study quality. Nineteen articles met our criteria.[12-30]

We extracted relevant information from each eligible study, including whether they reported cost sharing to have evidence of effects (ie, statistically significant nonzero effect) or no evidence of effects (ie, no statistically significant effect). When price elasticity of demand estimates were reported or could be derived, we captured this information as the expected relative change in the studied outcome if cost sharing were to double (ie, increase by 100%). Given the heterogeneity present in the cost-sharing measures, reported outcomes, study designs, and analytic approaches employed across the identified studies, our summary of the findings and conclusions are largely qualitative in nature.

RESULTS

Detailed characteristics of the 19 studies included in this review are available in the **eAppendix** (available at **www.ajmc.com**). Several studies examined 1 or more of our indications of interest, resulting in 8 studies for RA,

9 studies for MS, and 8 studies for cancer.[12-30] More than half of the studies (n = 10) examined the effect of cost sharing on specialty drugs covered under the pharmacy benefit only, whereas the remainder examined agents covered under either the pharmacy or medical benefit. The specific specialty drugs examined in each study varied, particularly for cancer. All studies were observational, and a majority (n = 13) used cross-sectional study designs to examine specialty drug use among patients in plans with lower cost sharing compared with patients in plans with higher cost sharing for the specialty drug(s) being studied.

Two studies examined data from individuals enrolled in Medicare Part D,[14,21] whereas all other studies used administrative claims data on privately insured patients in commercial plans or employer-sponsored health plans for current or retired employees. No study directly examined the effect of specialty tier–related cost sharing. In fact, databases used in the vast majority (84%) of these studies were from 2009 or earlier, during which time few private insurers were employing the use of specialty tiers and aggressive cost sharing for specialty drugs.

Studies used heterogeneous methods to measure specialty drug cost sharing; some used continuous measures of either co-payments or coinsurance, or an overall plan cost-sharing generosity index, whereas others created categories of cost-sharing groups based on either arbitrary cutoffs, medians, or quartiles for OOP payments observed in the data. A majority of patients were facing relatively low cost sharing, in keeping with the time frame of the data sources. For instance, 7 (64%) of 11 studies with information on mean OOP costs per month had mean co-payments less than $110 per month, and all 7 studies with median OOP information had median co-payments less than $50 per month. The OOP costs were substantially higher in the 2 studies examining Medicare Part D patients, yet these data are difficult to interpret due to a lack of detail. Medicare beneficiaries faced different levels of cost sharing during the calendar year (eg, 25%-33% coinsurance during an initial coverage phase vs 100% cost sharing during the "donut hole" coverage gap), but the studies did not examine changes during or between specific coverage phases.

Outcomes

A wide variety of specialty drug use outcomes were reported across the studies, including prescription abandonment (n = 3), initiation or any utilization (n = 8), adherence (n = 9), persistence/discontinuation (n = 7), number of claims (n = 1), and drug spending (n = 1). We found no studies examining the impact of specialty drug cost sharing on medical utilization, spending, or health outcomes. The Table summarizes key study findings by the type of outcome and indication(s) examined.

Prescription abandonment. In the 3 eligible studies, prescription abandonment was defined as a reversal of an adjudicated claim for a newly prescribed specialty drug (ie, the prescription was submitted and approved by the insurer but not obtained by the patient, so the pharmacy withdrew [reversed] the claim), with no subsequent paid claim within 90 days of the reversed claim.[15,21,26] Prescription abandonment may be thought of as a subcategory of primary nonadherence, which is when a physician prescribes a medication but the patient does not submit, or does not pick up, the prescription from the pharmacy.

All studies reported a strong association of higher cost sharing with abandonment (vs initiation) of specialty drug prescriptions, for all indications examined. In one study among privately insured patients, approximately 25% abandoned their specialty medication when the OOP cost on the claim was greater than $200 for MS specialty drugs and greater than $500 for anti-inflammatory biologics, compared with less than 5% to 6% abandonment rates when OOP costs on the claim were less than $100.[26] A follow-up study using similar, but more recent, data reported that 50% to 60% of privately insured patients abandoned anti-inflammatory biologics and MS specialty drugs when faced with $2000 or more in monthly OOP costs (ie, due to high deductibles) compared with 5% to 6% abandonment rates among patients facing less than $50 in monthly costs; however, it should be noted that only a small percentage (2%-4%) of patients were subject to such high cost-sharing levels.[15] Even for oral cancer agents, approximately one-fourth of privately insured and Medicare patients abandoned their specialty medication when OOP cost on the claim was greater than $500 compared with less than 5% to 6% abandonment rates with less than $100 in OOP costs.[21] Notably, the cost-sharing burden in this study was higher for Medicare patients relative to privately insured patients (46% vs 11% facing greater than $500 OOP costs), but subgroup analyses were not conducted.

Initiation. Initiation was typically defined as the first-time use of a specialty drug within a study period, among patients with a given disease. We grouped studies that examined any utilization (first time or repeated use) during the study period into this category as well. All studies examining initiation in patients with RA and MS reported a negative association with higher cost sharing. The magnitude of the effect varied across studies, with demand elasticities ranging from –0.03 to –0.33. For example, a 100% increase (ie, doubling) in cost sharing for MS drugs was

Table. Summary of Evidence Reported in the Literature by Type of Outcome and Disease

Outcome (number of studies)	Indication	Evidence of Effects	No Evidence of Effects
Prescription abandonment (n = 3)			
	RA	Starner (2014)[15,a] Gleason (2009)[26,a]	
	MS	Starner (2014)[15] Gleason (2009)[26]	
	Cancer	Streeter (2011)[21]	
Initiation (n = 8)			
	RA	Desai (2014) (for monotherapy non-biologic DMARD users at baseline)[12] Karaca-Mandic (2010)[24] Goldman (2006)[29]	Desai (2014) (for combination therapy nonbiologic DMARD users at baseline)[12]
	MS	Palmer (2012)[18] Romley (2012)[19] Goldman (2006)[29] Ozminkowski (2004)[30]	
	Cancer	Goldman (2010) (for rituximab)[23]	Goldman (2010) (for other cancer agents)[23] Darkow (2012)[16] Goldman (2006)[29]
Adherence (n = 9)			
	RA	Curkendall (2008)[27] Liu (2010)[25,a]	Kim (2011)[20,a]
	MS	Palmer (2012)[18] Dor (2010) (for coinsurance cohort)[22] Lafata (2008)[28]	Kim (2011)[20] Dor (2010) (for co-payment cohort)[22]
	Cancer	Dusetzina (2014) (for adherent vs nonadherent)[13] Engel-Nitz (2012) (for $30-$45 and ≥$65 vs $0-$30)[17]	Dusetzina (2014) (for continuous adherence)[13] Darkow (2012)[16] Engel-Nitz (2012) (for $45-$65 vs $0-$30)[17] Kim (2011)[20]
Persistence/discontinuation (n = 7)			
	RA	Kim (2011)[20,a] Karaca-Mandic (2010)[24] Curkendall (2008)[27]	
	MS	Palmer (2012)[18]	Kim (2011)[20]
	Cancer	Dusetzina (2014)[13] Kaisaeng (2014)[14]	Engel-Nitz (2012)[17] Kim (2011)[20]
Number of claims (n = 1)			
	Cancer	Goldman (2010)[23]	
Drug spending (n = 1)			
	RA	Goldman (2006)[29]	
	MS	Goldman (2006)[29]	
	Cancer		Goldman (2006)[29]

DMARD indicates disease-modifying antirheumatic drug; MS, multiple sclerosis; RA, rheumatoid arthritis.
[a]The study sample was not limited to RA patients; it also included patients with prescriptions for or existing users of anti-inflammatory biologic drugs that are indicated for RA and other autoimmune conditions (eg, psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn's disease).

associated with a 3% to 4% reduction in the probability of initiating these agents in 2 studies,[19,29] but was associated with a 33% reduction in initiation in another study.[30] Similarly, doubling of cost sharing for RA biologics was reported to reduce initiation by 5%[29] to 9%.[24] A recent study reported that drug benefit generosity was associated with initiation of RA biologics among the subgroup of patients deemed to have mild-to-moderate disease activity,

but not among the subgroup defined as having moderate-or-high disease activity with features of poor prognosis,[12] suggesting that disease severity may have been influencing initiation decisions.

Initiation of specialty drugs for cancer, on the other hand, was largely reported to be insensitive to cost sharing in the 3 studies examining this outcome.[16,23,29] One study found that cancer patients were 26% less likely to initiate the drug rituximab if cost sharing was doubled (ie, elasticity estimate of –0.26); yet, the same study did not find significant effects for the other cancer drugs it examined.[23]

Adherence. Treatment adherence was commonly measured by proportion of days covered (PDC), or the proportion of total days in a period that the patient had a supply of medication available. Some studies used a continuous measure of adherence, whereas others classified patients as being adherent (or nonadherent) based on whether ≥80% of the observation days were covered with a specialty drug supply (or not).

The evidence on the relationship between cost sharing and adherence was mixed across all 3 indications. As shown in the Table and eAppendix, findings varied based on the disease condition/drug class, the measure of adherence, and the level and type of cost sharing.[13,17,20,22] One study of cancer drugs, for example, measured adherence as both a dichotomous variable (PDC ≥0.80) and a continuous variable (PDC), and found effects for the former but not the latter.[13] A longitudinal study examining the effects of co-payment increases in an integrated HMO setting reported no relationship between cost sharing and adherence to MS, biologic anti-inflammatory, and cancer drugs.[20] This may have been related to the fact that 84% of the sample faced increases of only $25 to $50. Another study found that higher cost sharing was associated with significantly lower adherence to MS drugs in a subgroup of patients facing coinsurance, but not in a subgroup of patients facing co-payments.[22]

Discontinuation/persistence. Discontinuation was generally defined as having a continuous gap of time between prescription fills, during which the individual's specialty drug supply has run out. The number of days used to define a continuous gap varied across studies (30, 45, 60, 90, and 135 days). Persistence was generally characterized as the duration of time between treatment initiation and treatment discontinuation.

Six of the 7 studies reported a statistically significant increase in discontinuation (or decrease in persistence) associated with increased cost sharing for at least 1 of the indications examined. Although the evidence was mixed for MS and cancer drugs, with 2 studies reporting absence of effects, all 3 studies examining biologics indicated for RA showed associations with cost sharing. However, the magnitude of the effects appeared small even among RA biologic users. For example, one study of employer-sponsored plans reported demand elasticity of –0.04 on the probability of continuation of newly initiated RA biologics (doubling the cost sharing was associated with a 3.8% relative reduction in the probability of continuation of the RA biologics, from 0.80 to 0.77), with continuation defined as use in the subsequent year.[24]

Number of specialty drug claims. Only 1 study examined the association between higher cost sharing and the number of specialty drug claims,[23] which is an additional proxy for utilization. Among those patients who initiated therapy, demand elasticity on the number of claims was –0.04 for rituximab (a doubling in cost sharing was associated with approximately a 4% reduction in the number of claims) and –0.11 for other cancer drugs (bevacizumab, trastuzumab, imatinib mesylate, erlotinib).

Drug spending. One study captured spending on specialty drugs via both medical and pharmacy claims and reported varying effects of cost sharing based on the condition examined.[29] The demand elasticities ranged from –0.07 to –0.21 (doubling of cost sharing for MS and RA specialty drugs was associated with 7% and 21% reductions in total spending on specialty drugs for those conditions, respectively). However, a similar change in cost sharing was not associated with spending on specialty drugs for cancer. At the same time, the study found that once patients initiated the specialty drugs, cost sharing had no impact on total drug spending among patients with any of the 3 conditions.

DISCUSSION

Although numerous studies have examined the effects of cost sharing on traditional pharmaceuticals,[9,31] comparatively few have examined this issue for specialty drugs. Nevertheless, the literature on this topic is growing, with over half of the 19 studies included in this review published in the last 5 years. In general, findings from these studies revealed that higher cost sharing is associated with reductions in utilization of specialty drugs indicated for RA, MS, and cancer. Yet, the evidence is not consistent; the magnitude and/or statistical significance of the associations varied by type of specialty drug use outcome and by disease.

Higher cost sharing appears to have a stronger association with noninitiation or abandonment of a prescription at the pharmacy, and a somewhat smaller association—or

no association—with refill behavior (eg, adherence, number of claims) and with specialty drug spending once patients have initiated therapy. Patients who have already chosen to fill specialty drug prescriptions may be less sensitive to costs because they have a more established understanding of the potential benefits of treatment and/or have already committed to treatment.

Overall, associations between cost sharing and specialty drug utilization outcomes were not as strong as those found for traditional pharmaceuticals.[9,31] Based on the few studies in our review where price elasticity of demand estimates were available, price sensitivity for specialty drugs was lower than the –0.20 to –0.60 range reported in a 2007 review of cost sharing for traditional pharmaceuticals.[9] By comparison, the studies we reviewed reported elasticities of –0.03 to –0.33 for initiation, –0.04 for discontinuation, –0.04 to –0.11 for number of claims, and –0.07 to –0.21 for drug spending. On the one hand, higher prices for specialty drugs, combined with higher patient cost-sharing levels, may substantially reduce utilization for these medications. On the other hand, the lack of availability of close substitutes at lower OOP costs and the fact that these drugs are often used to treat complex chronic and life-threatening conditions means that patients have few alternatives; therefore, they may decide to pay the cost-sharing amount regardless of its magnitude.

In our review, cost sharing was more likely to show mixed or no associations with many specialty drug utilization outcomes for a life-threatening condition like cancer, as opposed to the relatively more consistent associations for RA. Costs may play a different role in patients' treatment decisions when a medication is perceived to be a life-saving option. Nevertheless, no matter how high the demand, some patients may be unable to pay in the context of competing obligations and others may purchase medications but subsequently have problems paying for other necessities, face depletion of their financial savings, or even face bankruptcy.[32] Such information is not captured in administrative claims, the data source typically used for examining the effects of cost sharing.

As with any review, our conclusions should be interpreted in the context of our methodological choices. We opted to focus on only 3 disease areas—RA, MS, and cancer—because of their relevance to specialty drug spending and also because they have been the focus of most available studies. A handful of singleton studies have examined specialty drugs indicated for serious infections, HIV, osteoporosis, kidney disease, and transplants, but it is difficult to draw conclusions about such conditions from such a limited research base.[20,29,33-35]

Limitations of the Evidence Base and Future Directions

In addition to summarizing the evidence, our review identified a number of important limitations in the existing literature that have implications for future research and policy:

Cross-sectional versus longitudinal study designs. The majority of available studies were cross-sectional, meaning they could not account for unmeasured differences between patients across plans. Thus, differences in characteristics that may be correlated with specialty drug use may have biased estimates of the effects of cost sharing. Although randomized designs are rarely feasible, there is a critical need for more quasi-experimental research studies using longitudinal data to evaluate outcomes before and after a specialty drug cost-sharing change, relative to a contemporaneous control group.

UM policies and other specialty drug management approaches. None of the cost-sharing studies in our review considered the confounding, interactive, and/or individual effect of UM policies on specialty drug use. Specialty drugs covered under the pharmacy benefit are increasingly subject to more stringent UM tools, such as prior authorization, quantity limits, and, more recently, step therapy.[5] If plans that required lower cost sharing were more likely to use UM tools as a substitute to help manage specialty drug costs, then the results from cross-sectional studies would underestimate the true effect of specialty drug cost sharing. Alternatively, if the plans that require higher cost sharing also use UM tools to further control costs, then the results from cross-sectional studies would potentially overestimate the true effect of cost sharing. Similar issues are pervasive if cost-sharing studies do not account for the presence or absence of other specialty drug management approaches, such as clinical care management, use of specialty pharmacies, and clinical pathway programs.[5] Understanding the individual and interactive effect of all these approaches on specialty drug use and outcomes is crucial for payers who are using them, or considering them, as a substitute or complement to higher cost sharing.

Specialty tier level or extremely high cost sharing. All but 2 studies in our review focused exclusively on private or employer-sponsored insurance data from 2009 or earlier, when lower cost sharing was more typical[21]; no studies examined the impact of a specialty tier benefit design.[15] As a result, the generalizability of findings is limited. Over 90% of Medicare Part D plans now have a specialty tier wherein cost sharing ranges from 25% to 33%.[36] Similarly, a recent analysis of exchange formularies found that approximately 60% of the Silver- and Bronze-level health insurance exchange plans offered in 19 states also contain

specialty tiers with coinsurance.[8] By 2013, almost one-fourth of workers with employer-sponsored coverage also faced a specialty tier.[7] This highlights the need for future research to examine the effects of the higher cost-sharing levels common in today's marketplace. In the meantime, it may be appropriate to establish policies that provide additional protection for patients against extremely high cost sharing for specialty drugs. This is of particular concern under Medicare Part D, where beneficiaries who do not qualify for low-income subsidies will need to spend up to $4850 out of pocket in 2016 before catastrophic coverage kicks in.[37] Similarly, the widespread use of high deductibles coupled with high OOP maximums under exchange plans also raises concern for the health and/or financial well-being of patients with serious chronic conditions.[38]

Coinsurance vs co-payments. Evidence is limited as to how the nature of cost sharing (ie, fixed co-payments vs coinsurance) may influence the impact it has on patient decision making and behavior. In addition to the Part D and exchange plans discussed above, almost half of the 1 in 4 employees facing the fourth (specialty) tier in 2013 were subject to coinsurance, and the average rate was reported to be 32%, whereas average co-payments in the same tier were $80 for employees facing fixed OOP cost arrangements.[7] Such coinsurance arrangements mean that patients not only pay a larger percentage of the cost of specialty medications, but they also face additional uncertainty in their OOP spending, which could change in conjunction with fluctuations in the price of the specialty drug and/or changes in drug treatment. Indeed, the one study in our review that explicitly examined the effect of requiring coinsurance versus co-payments for specialty drugs[22] did find a differential impact of fixed co-payments and coinsurance; there was no relationship between monthly average co-payment levels and adherence to specialty drugs indicated for MS, whereas patients facing coinsurance showed decreased adherence as coinsurance levels increased. Furthermore, patients with coinsurance arrangements showed lower adherence independent of the coinsurance amount paid by the patient.

Additional research is critically needed to better understand the ramifications of the increasing use of coinsurance arrangements on specialty medication initiation, adherence, and outcomes. In the meantime, it may be worthwhile for insurers requiring coinsurance to consider coupling coinsurance rates with other approaches, such as reasonable OOP maximums per specialty prescription fill, to protect patients from uncertain and very high OOP costs. Employers may also be able to consider income-based cost sharing or other OOP maximums for specialty medications.

Specialty drug substitution across benefit types. Some conditions, including RA, have multiple agents within the same specialty drug class that are covered by different benefit types (medical vs pharmacy) based on their mode of administration. High specialty tier cost sharing under the pharmacy benefit may result in patients substituting with specialty drugs under the medical benefit if OOP costs are lower (as is often the case with Medicare, where supplemental insurance held by the beneficiary may cover the medical benefit coinsurance). None of the reviewed studies examined such substitution, and this remains an area for further research. There is also an emerging trend among payers to consolidate specialty drugs under one benefit (by either covering all drugs under the pharmacy benefit regardless of mode of administration or moving all specialty drugs into a single specialty drug benefit with consistent levels of cost sharing, UM tools, and care management policies).[5] As this trend continues, it will be even more important to monitor the impact of cost sharing on access to specialty drugs.

Additional utilization, spending, and health outcomes. Studies that reported lower specialty drug initiation rates for patients facing higher cost sharing did not examine treatment history in a way that would reveal whether patients may have delayed specialty drug initiation by perhaps first substituting less expensive, less optimal treatments; attempting to enroll in patient assistance programs; or otherwise opting to defer treatment. Hence, it is essential for future studies to examine such delays and also any associated disease progression, particularly for conditions such as cancer, wherein negative consequences of delayed treatment can be substantial.

Furthermore, it is surprising that only 1 study examined specialty drug spending in addition to drug utilization outcomes, despite the fact that controlling spending is a goal of cost sharing.[29] No studies in our review reported the effect of specialty drug cost sharing on health outcomes or nondrug medical service use and expenditures. Studies that examine drug utilization outcomes in isolation are unable to detect any broader impact of cost-sharing policies on health outcomes and total spending. Because many specialty drugs are indicated for serious, chronic, complex, or life-threatening conditions, lower utilization of these agents in the face of higher cost sharing could have adverse short- and/or long-term health consequences and may lead to increases in the use of other medical services and spending. From a policy perspective, consideration should be given to whether value-based insurance design approaches may offer more optimal strategies for facilitating drug access to high-value specialty medications.[39] Such an approach may be particularly sensible

for employers who are also invested in broader outcomes, such as reducing the absenteeism and lost productivity that are associated with poor medication adherence.[40]

CONCLUSIONS

Evidence to date generally indicates reductions in specialty drug utilization associated with higher cost sharing, with effects varying by type of disease and specialty drug use outcome. We have identified several gaps in the evidence base that, if addressed, would help inform future specialty drug cost-sharing policies. It may be appropriate in the interim to establish policies that provide additional protection for patients against aggressive cost-sharing policies for specialty drugs. As payers continue to experiment and implement dramatic changes in specialty drug benefit design in the coming years, there is an urgent need for methodologically rigorous research to comprehensively evaluate whether and how such specialty drug cost-sharing arrangements cause patients to forego, delay, or decrease adherence to specialty drugs, and whether that results in poor health outcomes and total higher costs associated with treatment failure, progression of disease, and the need for more aggressive treatment down the road.

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eAppendix

Table. Summary of Characteristics of Studies Included in the Literature Review

First Author (year)	Indication	Specialty Drug(s)	Examined Drugs Covered Under	Study Design[a]	Data Source	Data Years	Cost Sharing For Specialty Drug(s)	Specialty Drug Use Outcome(s)
Desai (2014)[12]	RA	Adalimumab, certolizumab, etanercept, golimumab, infliximab	Pharmacy and medical benefit	Cross-sectional	Employer-sponsored health insurance claims	2007-2010	Proportion of annual total drug costs paid OOP (ie, drug benefit generosity index): <10% (1st quartile) 10%-20% (2nd quartile) 20%-33% (3rd quartile) >33% (4th quartile)	Initiation
Dusetzina (2014)[13]	Cancer	Imatinib	Pharmacy benefit	Repeated cross-sectional	Employer-sponsored health insurance claims	2002-2011	Mean monthly co-payment: $108 (median = $30; IQR = $17 to $53)	Adherence; discontinuation
Kaisaeng (2014)[14]	Cancer	Imatinib, erlotinib, thalidomide	Pharmacy benefit	Cross-sectional	Medicare Part D claims	2008	Mean monthly OOP: imatinib: $687 erlotinib: $850 thalidomide: $1,124	Discontinuation and delay (gap)[b]
Starner (2014)[15]	RA,[c] MS	Biologic anti-inflammatory drugs: abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, ustekinumab	Pharmacy and medical benefit	Cross-sectional	Commercial insurance claims	2010-2012	Mean monthly OOP: Anti-inflammatory agents: $0 to <$50 (45%) $50 to <$250 (29%) $250 to <$500 (7%) $500 to <$750 (3%) $750 to <$1000 (5%) $1000 to <$2000 (7%) $2000 or more (2%) MS drugs: $0 to <$50 (49%) $50 to <$250 (29%) $250 to <$500 (4%) $500 to <$750 (4%)	Prescription abandonment

		MS drugs: fingolimod, glatiramer, interferons, natalizumab					$750 to <$1000 (3%) $1000 to <$2000 (7%) $2000 or more (4%)	
Darkow (2012)[16]	Cancer	Imatinib, dastanib, nilotinib	Pharmacy benefit	Longitudinal	Employer-sponsored health insurance claims	1997-2009	Mean monthly co-payment = $56 (median = $25)	Initiation; adherence
Engel-Nitz (2012)[17]	Cancer	Erlotinib	Pharmacy benefit	Before-after (no control group)	Commercial insurance claims	2004-2009	Mean monthly co-payments for users pre-tier change = $77 (median = $40) Mean monthly co-payments for users post-tier change = $68 (median = $30)	Adherence; persistence/ discontinuation
Palmer (2012)[18]	MS	Interferons, glatiramer	Pharmacy benefit	Retrospective case control	Employer-sponsored health insurance claims	2004-2009	Distribution of monthly OOP: ≤$100 (91%) >$100 (9%)	Initiation; adherence; persistence/ discontinuation
Romley (2012)[19]	MS	Interferons, glatiramer, natalizumab, nitoxantrone	Pharmacy and medical benefit	Repeated cross-sectional	Employer-sponsored health insurance claims	2004-2008	Annual OOP: Mean = $691 Median = $251; 95th percentile = $2625. Coinsurance: Mean = 4.3%; Median = 1.6%; 95th percentile = 17.8%	Initiation
Kim (2011)[20]	RA,[c] MS, cancer	Biologic anti-inflammatory drugs: etanercept, adalimumab, anakinra, infliximab MS drugs: interferons, glatiramer	Pharmacy and medical benefit	Before-after (with control group)	Employer-sponsored health insurance claims and medical records from integrated HMO	2005-2007	Co-payments for monthly prescription supply: $0 (64%) and $1-50 (36%) at baseline; increased by $25-$50 (84%) $51-$100 (12%) $101-$250 (4%) for treatment group; no co-payment change in control group	Adherence; persistence

		Cancer drugs: anastrozole, exemestane, letrozole, imitinib, sunitinib, erlotinib, thalidomide, lapatinib, capecitabine						
Streeter (2011)[21]	Cancer	Capecitabine, imatinib, sorafenib, lenalidomide, sunitinib, erlotinib, temozolomide, lapatinib	Pharmacy benefit	Repeated cross-sectional	Commercial insurance and Medicare Part D claims	2007-2009	OOP per claim: Overall $0-$100 (73%) $101-$500 (11%) >$500 (16%) Commercial $0-$100 (80%) $101-$500 (9%) >$500 (11%) Medicare $0-$100 (35%) $101-$500 (19%) >$500 (46%)	Prescription abandonment
Dor (2010)[22]	MS	Interferons, glatiramer	Pharmacy and medical benefit	Repeated cross-sectional	Employer-sponsored health insurance claims	2005-2008	Mean monthly OOP: Co-payment cohort: $32 (SD = $51) Coinsurance cohort: $284 (SD = $1148)	Adherence
Goldman (2010)[23]	Cancer	Bevacizumab, trastuzumab, rituximab, erlotinib, imatinib	Pharmacy and medical benefit	Longitudinal	Employer-sponsored health insurance claims	1997-2005	Annual OOP: Mean = $3445; Median = $319; 75th percentile = $1470; 90th percentile = $9642	Initiation; number of drug claims
Karaca-Mandic (2010)[24]	RA	Etanercept, adalimumab, infliximab	Pharmacy and Medical benefit	Longitudinal	Employer-sponsored health insurance claims	2000-2005	Annual OOP cost: Pharmacy benefit: Mean = $426 Medical benefit: Mean = $1518	Initiation; continuation

Liu (2010)[25]	RA[c]	Adalimumab	Pharmacy benefit	Repeated cross-sectional	Commercial insurance claims	2003-2009	OOP per claim: Retail pharmacy: Mean = $83 (SD = $239); Median = $22 Specialty pharmacy: Mean = $115 (SD = $391); Median = $30	Adherence
Gleason (2009)[26]	RA,[c] MS	Biologic anti-inflammatory drugs: etanercept, adalimumab, infliximab MS drugs: interferons, glatiramer	Pharmacy and medical benefit	Repeated cross-sectional	Commercial insurance claims	2006-2008	Mean OOP per claim: MS: $128 (median = $40) RA: $126 (median = $40)	Prescription abandonment
Curkendall (2008)[27]	RA	adalimumab, etanercept	Pharmacy benefit	Repeated cross-sectional	Employer-sponsored health insurance claims	2002-2004	Mean co-payments per week: $7 (SD = $14) ≤$10 (85%) >$10-$30 (10%)	Adherence; persistence
Lafata (2008)[28]	MS	interferons, glatiramer	Pharmacy benefit	Cross-sectional	Insurance claims and medical records for patients in a multi-specialty salaried group practice	2004-2006	Mean co-payment = $14.27 Range = $2-$40	Adherence
Goldman (2006)[29]	RA, MS, cancer	Specialty drugs for RA, MS, cancer[d]	Pharmacy and medical benefit	Repeated cross-sectional	Employer-sponsored health insurance claims	2003-2004	Mean (median) annual OOP: Cancer: $1170 ($336) MS: $893 ($436) RA: $892 ($446)	Initiation; drug spending
Ozminkowski (2004)[30]	MS	interferons,[d] glatiramer	Pharmacy benefit	Repeated cross-sectional	Employer-sponsored health insurance claims	1996-2000	Mean annual OOP: Co-payments: $419 Coinsurance: 11.19% (SD = 9.78%)	Initiation

HMO indicates health maintenance organization; interferons, interferon 1-a and interferon 1-b; IQR, interquartile range; MS, multiple sclerosis; OOP, out-of-pocket cost; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumor necrosis factor.

[a]Study designs include: cross-sectional (patient-level data were compared across multiple health plans over a single time period); repeated cross-sectional (cross-sectional data from multiple time periods); longitudinal (patient-level data with repeated observations over time for the same patient); before-and-after without control (patient-level data were used to compare outcomes at 2 points in time, before and after a benefit change, with no comparison group); before-and-after with control (patient-level data were used to compare outcomes at 2 points in time, before and after a benefit change, among patients who faced a benefit change relative to patients who did not face a benefit change); retrospective case control (patients in treatment group [eg, receiving specialty drugs] were compared with patients in control group [eg, not receiving specialty drugs] to examine factors [eg, cost sharing and other control variables] associated with receiving treatment). Definitions adapted from Goldman (2007).[31]

[b]Medication delay was defined as at least a 30-day gap between the date that the patient's supply of the medication should have expired and the date that the patient obtained the next refill. This is typically referred to as a "gap" in treatment and was treated as such in our review.

[c]The study sample was not limited to RA patients but rather also included patients with prescriptions for or existing users of anti-inflammatory biologic drugs that are indicated for RA and other autoimmune conditions (eg, psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn's disease).

[d]The specific specialty drugs examined in Goldman (2006)[29] were not available. For patients with cancer, they included spending on renal-related agents as well as chemotherapeutic agents to account for the relatively large fraction of patients taking specialty products for anemia.

eAPPENDIX REFERENCES *(Beginning at 12 to correspond with the main manuscript)*

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