Prescription Drug Cost Sharing

Associations With Medication and Medical Utilization and Spending and Health

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Context Prescription drugs are instrumental to managing and preventing chronic disease. Recent changes in US prescription drug cost sharing could affect access to them.

Objective To synthesize published evidence on the associations among cost-sharing features of prescription drug benefits and use of prescription drugs, use of nonpharmaceutical services, and health outcomes.

Data Sources We searched PubMed for studies published in English between 1985 and 2006.

Study Selection and Data Extraction Among 923 articles found in the search, we identified 132 articles examining the associations between prescription drug plan cost-containment measures, including co-payments, tiering, or coinsurance (n=65), pharmacy benefit caps or monthly prescription limits (n=11), formulary restrictions (n=41), and reference pricing (n=16), and salient outcomes, including pharmacy utilization and spending, medical care utilization and spending, and health outcomes.

Results Increased cost sharing is associated with lower rates of drug treatment, worse adherence among existing users, and more frequent discontinuation of therapy. For each 10% increase in cost sharing, prescription drug spending decreases by 2% to 6%, depending on class of drug and condition of the patient. The reduction in use associated with a benefit cap, which limits either the coverage amount or the number of covered prescriptions, is consistent with other cost-sharing features. For some chronic conditions, higher cost sharing is associated with increased use of medical services, at least for patients with congestive heart failure, lipid disorders, diabetes, and schizophrenia. While low-income groups may be more sensitive to increased cost sharing, there is little evidence to support this contention.

Conclusions Pharmacy benefit design represents an important public health tool for improving patient treatment and adherence. While increased cost sharing is highly correlated with reductions in pharmacy use, the long-term consequences of benefit changes on health are still uncertain.

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MEDICAL PRACTICE IN THE United States has changed dramatically in the last several decades, including an increase in use of prescription drugs. More and better-quality drugs are available to prevent and manage chronic illness, and these drugs reduce mortality, forestall complications, and make patients more productive.[1] Thus, access to outpatient drugs is now a cornerstone of an efficient health care system.

But with recent increases in pharmacy spending, pharmacy benefit managers and health plans have adopted benefit changes designed to reduce pharmaceutical use or steer patients to less-expensive alternatives. The rapid proliferation of mail-order pharmacies, mandatory generic substitution, coinsurance plans, and multitiered formularies has transformed the benefit landscape. In this review, we analyze how the salient cost-sharing features of prescription drug benefits may affect access to prescription drugs and synthesize what is known about how these features may affect medical spending and health outcomes.

Most beneficiaries are now covered by incentive-based formularies in which drugs are assigned to one of several tiers based on their cost to the health plan, the number of close substitutes, and other factors.[2] For example, generics, preferred brands, and nonpreferred brands might have co-payments of $5, $15, and $35, respectively. In contrast, plans may require beneficiaries to pay coinsurance—ie, a percentage of the total cost of the dispensed prescription. The purpose of tiered co-payments and coinsurance is to give beneficiaries an incentive to use generic or low-cost brand-name medications and to encourage manufacturers to offer price discounts in exchange for inclusion of their brand-name products in a preferred tier. By 2005, most workers with employer-sponsored coverage (74%) were enrolled in plans with 3 or more tiers, nearly 3 times the rate in 2000 (27%).[3]

Some plans also impose benefit caps that limit either the coverage amount or the number of covered prescriptions. For example, the standard Medicare Part D benefit offers beneficiaries coverage of up to $2400 in spending in 2007, at which point coverage stops until beneficiaries reach a catastrophic cap

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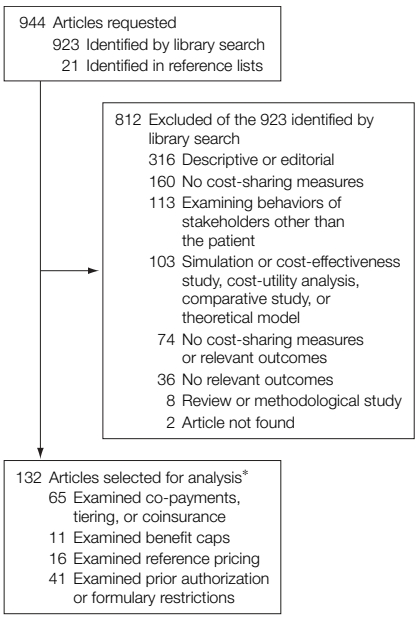
Figure. Study Design



*One article examines the effects of both co-payments and benefit caps.

($5451). Once the catastrophic cap is reached, coverage resumes with minimal cost sharing. Prior to the introduction of Part D, benefit caps—without this catastrophic limit—were a standard feature of Medicare + Choice plans (now known as Medicare Advantage) and some retiree plans. As of 2002, 94% of Medicare + Choice plans that covered branded drugs had an annual dollar cap ranging from $750 to $2000 per year.[4] Analogous policies used by state Medicaid programs place limits on the number of prescriptions dispensed per patient per month. Because benefit caps represent an extreme version of cost sharing—patients who reach them must pay all additional pharmacy costs out of pocket—and their central role in Part D, we include them in our review.

Additional cost-saving measures include prior authorization (requiring permission before certain drugs can be dispensed), step therapy (requiring use of lower-cost medications before providing coverage for more expensive alternatives), closed formularies, mandatory generic substitution, and reference pricing (a cap on the amount a plan will pay for a prescription within a specific therapeutic class). There is a growing literature on each of these cost-containment measures.

METHODS

We conducted electronic searches of PubMed for studies published in English between 1985 and 2006. The primary search was based on combinations of 2 sets of key words. The first set included various terms for drug cost sharing: *cost-sharing*, *incentive-based*, *copay*, *coinsurance*, *tiered benefit*, *benefit cap*, *patient charge/fee*, *user charge/fee*, *prescription charge/fee*, *step therapy*, *reference pricing*, *prior authorization*, *formulary*, *formulary restriction*, *formulary limit*, *closed formulary*, *open formulary*, and *generic only*. The second set included *drug spending*, *drug cost*, *prescription drug*, *medication*, and *pharmacy benefit*. Articles that contained at least 1 term were included. We performed another search specifically for Medicaid-related drug cost sharing measures by combining one of the terms *access restriction*, *drug/prescription/reimbursement limit*, or *preferred drug list* with *Medicaid* and with one of the terms *spending*, *use*, or *cost*. We excluded issue briefs, comments, letters, editorials, essays, articles without author names, and reviews. This process yielded 923 studies. We then screened these studies based on titles, abstracts, and, in a few cases, the full text, as described in the FIGURE.

A study was included in this review if (1) the article was published in a peer-reviewed journal; (2) it examined the effects of cost sharing (co-payments, tiers, coinsurance, reference pricing, formulary restrictions, or benefit caps) on at least 1 of the relevant outcomes (prescription drug utilization or spending, medical utilization or spending, or health outcomes); and (3) it analyzed primary or secondary data (to exclude simulations).

Among the 923 studies, 111 met these criteria. An additional 21 studies were added based on reference lists, resulting in 132 studies for final analysis. Sixty-five studies examined co-payments, tiers, or coinsurance[5-69]; 11 examined benefit caps[4,43,70-78]; 41 examined formulary restrictions[79-119]; and 16 examined reference pricing.[120-135] (One study examined both co-payments and benefit caps.[43])

Because the majority of these studies analyzed observational data, understanding how the associations between cost sharing and the outcomes of interest were measured is important. We classified study designs as follows:

- (Aggregated) time series: analyzed changes over time in data aggregated at the geographic or plan level, with the data spanning a period when benefits changed
- Cross-sectional: analyzed individual-level data at a single time point for multiple benefit designs—for example, across health plans
- Repeated cross-sectional: analyzed cross-sectional data from multiple time periods
- Longitudinal: analyzed individual-level data with repeated observations for the same beneficiaries over time
- Before-and-after: compared outcomes at 2 points in time, before and after a benefit change
- Randomized trial

The literature on cost sharing is much more diffuse than many medical interventions, which benefit from clear delineation of primary and secondary clinical end points. For example, some articles examine pharmaceutical spending, while others observe utilization. And, among the latter, utilization is measured in at least 5 different ways: medication possession ratio, proportion of days covered, cumulative multiple-refill gap, number of prescriptions, and aggregate days supplied. This problem is further exacerbated by the wide range of "treatments"—eg, adding a second or third tier, raising co-payments, requiring coinsurance—and treated populations with very different diseases. The result is tremendous heterogeneity in benefit changes, the way results are re-

ported, and for which affected populations. Thus, many of the conclusions of this review are necessarily qualitative.

RESULTS

Details from the 132 studies in this review, including study sample, study design, drug benefit variation, outcomes, and key findings, are available online (http://www.jama.com).

Co-payments, Coinsurance, and Pharmacy Spending

The evidence from the 65[5-69] studies that examined the relationship between 3 of the most important features of drug benefits—co-payments, tiering, and coinsurance—and pharmacy utilization and costs is summarized in eTable 1.

Most of the evidence comes from observational studies, with the exception of 2 studies of the RAND Health Insurance Experiment (HIE). The HIE randomized 2750 families to different levels of cost sharing ranging from free care to 95% coinsurance. The HIE demonstrated that individuals subject to higher coinsurance rates reduced their demand for care and that the cost-sharing response for prescription drugs was similar to the response for all ambulatory care.[66,68] However, data from the HIE are nearly 3 decades old. In addition, the health insurance packages in the HIE varied the prescription drug benefit at the same time as other benefits. Thus, it is unclear whether the higher drug expenditures among patients with more generous coverage were due to lower out-of-pocket costs for drugs or lower cost sharing for office visits and other medical services that are the usual pathways for receiving prescriptions.

All of the remaining studies are observational. Key features of the best studies include large sample sizes, variation in benefit design both across plans and over time, and attempts to control for other factors known to affect pharmaceutical use.[19,20,22-24,27,36,38,42] Of particular value are studies that used data from multiple plans and controlled for medical benefits, especially when they may have been changing in concert with the pharmacy benefit.[8,9,26,34,40,49,50,52] For example, changing office visit co-payments affects how frequently patients see a physician and, hence, the number of prescriptions they receive. Poor features include analyses that do not control for other factors that might be changing, including observations before and after a benefit change with no control group. These designs include (but are not limited to) many international studies in which co-payments changed for the entire population.*

Some of the studies found relatively small changes in utilization in response to higher cost sharing,[17,51,55,60,62,69] but these focused on small changes in co-payments. In some studies, the control groups had very different characteristics,[28,32,39,45,46,53,67] patients may have self-selected into treatment groups on the basis of medication choice,[13] or the source of co-payment variation was not clear.[25] Given the evidence that there is differential response by condition or class of medication, studies that restrict attention to a specific patient population or conduct subgroup analysis can yield additional insight.

The effects of cost sharing can be summarized using the price elasticity of demand. This measure represents the percentage change in drug spending that would be associated with a 1% increase in cost sharing. When we excluded the studies that involved very small cost-sharing changes or did not have an adequate control group, we found elasticities ranging from –0.2 to –0.6, indicating that cost sharing increases of 10% (through either higher co-payments or coinsurance) would be associated with a 2% to 6% decline in prescription drug use or expenditures.

Eleven of the 65 studies in our review explicitly looked at changes in coinsurance rates,† with 2 of these coming from the HIE and 4 from a benefit change in Quebec in 1996. Overall, increasing coinsurance is at the low end of our range of –0.2 to –0.6, but these associations are attenuated by the simultaneous imposition of out-of-pocket maximums in most of these studies.

*References 5, 7, 12, 15, 16, 29, 30, 35, 37, 41, 44, 57, 59, 61, 64, 65, 67.
†References 28, 32, 35, 41, 42, 44, 48, 54, 55, 66, 68.

Differential Responses by Therapeutic Class

Several studies suggest that consumer sensitivity to cost sharing depends on a drug's therapeutic class and that increased cost sharing may decrease "nonessential" drug use (eg, antihistamines) more than "essential" drug use such as antihypertensives and oral hypoglycemics. However, the empirical evidence in this area is mixed. Harris et al[62] found substantially larger reductions in the use of discretionary medications than essential medications in response to a modest increase in co-payments. More recently, Goldman et al[26] found that doubling co-payments was associated with reduced use of 8 classes of medication by 25% (antidiabetics) to 45% (anti-inflammatories). Patients were less likely to reduce use of these drugs if they were receiving ongoing care from a physician for the disorder, ranging from 8% (antidepressants) to 31% (antihistamines). Landsman et al[20] found similar price responses across 9 therapeutic classes. Several other studies found modest but inconsistent effects of higher co-payments on use of essential and nonessential drug classes.[33,47,50,55,69]

Benefit Caps, Prescription Drug Use, and Costs

Information from the 11 studies [4, 43, 79-78] that examined the association between benefit caps, including caps that limit the number of prescriptions and caps on an annual pharmacy benefit, and drug use and drug costs is summarized in eTable 2.

Soumerai et al[77] compared Medicaid patients in New Hampshire—for whom the program had imposed a 3-drug limit per patient per month—with those of New Jersey, where no such cap was introduced. They found a 35% reduction in drug use relative to the control group. For patients taking psychotropic medications, they found that the cap was associated with a 15%

to 49% reduction in the use of these drugs.[76]

The most salient evidence on the impact of benefit caps comes from an analysis of medical and pharmacy claims from a single closed-network health maintenance organization.[70] Members whose benefits were capped at $1000 had 31% lower pharmacy costs than comparable enrollees not subject to a cap. One survey of Medicare beneficiaries suggested that elderly individuals who experience gaps in coverage report using fewer medications, are more likely to switch to generics or lower-cost medications, and rely more on drug samples from their physicians.[71] Two other studies found that patients exceeding the cap were 2 to 3 times more likely to discontinue a medication[73] and unenroll from the plan.[136]

Reference Pricing

Information from the 16 studies[121-135] examining reference pricing, wherein insurers cap the amount they will pay for a prescription within a specific therapeutic class, is summarized in eTable 3.

Few health plans in the United States have adopted reference pricing so far. However, it is widely used in parts of Canada and Europe. In general, almost all of the studies found large increases in use of drugs priced at or below the reference price and sharp declines in use of higher-cost drugs that require some patient cost sharing. In a series of studies of reference pricing in British Columbia, Schneeweiss et al[123,128,129] found that an increase in co-payments for the most expensive angiotensin-converting enzyme inhibitors (drugs priced above the reference price) was not associated with stopping treatment for hypertension or higher health care utilization. They found similar associations with use of calcium channel blockers[125] and proton pump inhibitors.[121] The only potential concern raised by these studies was that low-income patients were more likely than high-income patients to stop hypertensive therapy (odds ratio, 1.65; 95% confidence interval, 1.43-1.89).[128] Grootendorst and colleagues[122,131] examined similar policies for nonsteroidal anti-inflammatory drugs (NSAIDs) and nitrates. They found that most of the savings to British Columbia's Pharmacare program could be explained by the substitution of low-cost drugs and higher patient cost sharing for restricted medications. The remaining studies listed in eTable 3 found that reference pricing was only weakly associated with overall use within the restricted drug class and uncorrelated with medical service use.

Prior Authorization and Formulary Restrictions

Evidence from the 41 studies [79-119] examining the association between prior authorization or formulary restriction and drug and medical utilization and spending is summarized in eTable 4.

Increasingly, public and private health plans are imposing prior authorization and/or fail-first requirements on nonpreferred prescription drugs. These programs require use of older or less expensive medications before covering newer therapies. For example, a plan may require a patient to try at least 1 generic NSAID before paying for a cyclooxygenase 2 inhibitor. The main concern about these cost-containment policies is that patients may switch to less-effective medications or become nonadherent and, as a result, experience adverse health effects. Several studies support such concerns. Two studies found that Medicaid beneficiaries taking a restricted statin medication filled fewer prescriptions and were more likely to be nonadherent than unrestricted patients.[79,84] Similar associations were found for antihypertensive medications.[95] Another study found that a preferred drug list for cardiovascular medications was associated with an increase in outpatient visits in the first 6 months of implementation, but these differences did not persist over time.[93]

Most other studies, in contrast, suggest that the outcomes associated with prior authorization and step therapy requirements are modest, although these policies can have strong associations with use of restricted medications. For example, Tennessee Medicaid's expenditures for NSAIDs declined by 53% following implementation of prior authorization and fail-first requirements for brand-name NSAIDs.[113] The reduction in spending was associated with higher use of generic NSAIDs and a 19% decline in overall NSAID use. The findings of Kotzan et al[114,115] were similar. More generally, prior authorization programs are associated with lower drug spending within the restricted class but are uncorrelated with medical care utilization and spending.[90,91,99] Two studies on step therapy[82,111] also reported decreased drug spending without adverse effects on drug utilization or physician concerns.

The outcomes associated with closed formularies or generic-only drug coverage may differ substantially from those of prior authorization requirements. One study found that a closed formulary was associated with lower rates of medication continuation among patients with chronic conditions.[106] Two other studies found that limiting coverage to generic drugs was associated with decreased medication use[87] and increased hospitalizations.[96] Another study[108] found that the degree of formulary restrictions was positively correlated with higher drug costs, more office visits, and high likelihood of hospitalization among patients with certain diseases.

Drug Cost Sharing, Medical Costs, and Health Outcomes

The evidence clearly demonstrates that increased cost sharing is associated with lower pharmaceutical use. These effects can be quite large—even for long-term medications—suggesting that there are long-term health consequences. In fact, the direct evidence on the link between cost sharing and health is rather limited. Most studies examine important proxies for health (and medical spending), such as emergency department use and hospitalizations. The findings from studies focusing solely on chronically ill patients are unambiguous: for patients with congestive heart failure,[6] lipid disorders,[8,10] diabetes,[21] and schizophre-

nia,[76] greater use of inpatient and emergency medical services are associated with higher co-payments or cost sharing for prescription drugs or benefit caps. These findings are corroborated by the only article that studied clinical outcomes in a population with benefit caps.[70]

In contrast, studies that observed the outcomes associated with cost sharing more broadly (on all drugs or a wide range of classes) were ambiguous in their findings. Some found that higher cost sharing is associated with adverse outcomes,[137] particularly among vulnerable populations such as elderly and poor patients.[48,77] But most found that when the population is not limited to those with certain chronic illnesses, the outcomes associated with prescription drug cost-containment policies are mostly benign. For example, studies by Fairman et al,[33] Motheral and Fairman,[47] Johnson et al,[54] and Smith and Kirking[138] found that increased co-payments were not associated with more outpatient visits, hospitalizations, or emergency department visits.

Socioeconomic Differences and Cost Sharing

Although there is ample evidence that the demand for pharmaceuticals declines with higher co-payments, there is concern that low-income beneficiaries will be more responsive to cost sharing. Most evidence on this point comes from nonexperimental studies of state Medicaid programs that introduced very modest co-payments. Medicaid enrollees in South Carolina used significantly fewer drugs after the imposition of a $0.50 co-payment.[69] A more recent study found that elderly Medicaid recipients residing in states with co-payment provisions consumed fewer drugs and were less likely to fill any prescriptions during the year than those in states without co-payments.[51] Survey data indicate that 1 in 4 Medicaid patients aged 18 to 64 years could not afford to fill at least 1 prescription in the past year compared with less than 1 in 10 among privately insured individuals.[139] A study of Medicare beneficiaries in Pennsylvania found that elderly individuals with annual incomes of more than $18 000 were 18% more likely to treat medical problems with prescription drugs than those with incomes of less than $6000.[140]

COMMENT

We reviewed studies examining the association of co-payments and other salient benefit features with pharmaceutical utilization and spending, as well as their association with nonpharmaceutical services and health outcomes. The evidence summarized here suggests that for each 10% increase in cost sharing, overall prescription drug spending decreases by 2% to 6%, depending on class of drugs and patient condition. Benefit changes are not without consequences: for some chronic conditions, we found that higher cost sharing for prescription drugs was associated with greater use of expensive medical services.

It is interesting to compare these effects with other interventions designed to improve use of chronic medications. A 2002 review, for example, identified 33 interventions designed to improve patient adherence to prescribed medications.[141] Even the most successful interventions did not result in large improvements in adherence and generally relied on complicated, labor-intensive regimens of uncertain effectiveness. Thus, pharmacy benefit design represents one of the most important public health tools for improving patient treatment and adherence.

Several key research issues remain unresolved. First, while greater cost sharing is clearly associated with reduced access, the precise mechanisms are not clear. Less pharmaceutical use could come about through 3 different behavioral pathways: reduced initiation of prescription drug treatment, worse adherence among existing users, or more frequent discontinuation of therapy (although the latter could be interpreted as an extreme example of poor adherence among users). Distinguishing among these hypotheses is important because it affects the advice and monitoring that physicians and plans should use to counteract any adverse consequences of plan design changes. We found evidence that all 3 pathways may be complicit when cost sharing rises, although adherence among existing users seems to be the primary mechanism. On the other hand, if one accepts the criteria in current national guidelines, then even small effects of cost sharing on the likelihood of initiating therapy could have dramatic health consequences. For example, Topol[142] notes that 36 million people in the United States should be taking a statin but only 11 million are currently being treated.

Second, increased cost sharing is associated with adverse medical events such as hospitalizations and worsening clinical outcomes over 1 to 2 years for patients with congestive heart failure, lipid disorders, diabetes, and schizophrenia. Additional evidence suggests that there may be adverse consequences for asthma as well. Because patients leave employers and plans with relative frequency, and plan benefit designs change rapidly, it is difficult to isolate the long-term health consequences of changes in cost sharing using existing study designs.

A key challenge in this type of analysis is that disease severity cannot be measured directly and that patients who are more severely ill tend to use more drugs and more of other services. If this tendency is not properly accounted for in the data analysis, estimates of the effects of prescription drug use on other costs will demonstrate little or no cost savings. This spurious correlation probably has limited past efforts in this area. This is especially problematic when patients have a choice of drug plans—a feature that introduces bias in the same way that patients self-select into treatment regimens. Some of this bias is mitigated because while many employers offer employees a choice of medical plans, the majority standardize 1 drug benefit regardless of medical plan

choice. Ultimately, the long-term consequences of benefit changes remain elusive.

Third, if cost containment policies have adverse effects, those effects are likely to be magnified among low-income groups, whose high rate of chronic health problems and low incomes may result in more price-sensitive behavior. Survey data indicate that nearly 40% of chronically ill low-income persons with public insurance and 35% with private coverage report that they have been unable to fill at least 1 prescription because of cost concerns.[143] One of the severe limitations of analyses of claims data is that they do not include information on race, ethnicity, income, education, and wealth, and, when economic status is included using national survey data, there is substantial bias in its measurement.[144] Thus, while it is often claimed that low-income groups are most sensitive to cost sharing changes, there is little reliable evidence to support this contention.

Fourth, the introduction of Medicare Part D has initiated a bold experiment with benefit caps. While the effects of benefit caps clearly are consistent with those of other cost-sharing features, little is known about the dynamics of these changes. For example, if patients do discontinue therapy or take their medicine less frequently once they reach their benefit cap, how quickly—if ever—do they reinitiate drug therapy once coverage resumes in the next benefit year? Benefit caps also provide a counterpoint to consumer-directed health plans that encompass high-deductible catastrophic coverage. With these plans, patients must pay all the costs until a cap is reached, beyond which they pay nothing. Benefit caps, in contrast, provide coverage up to a specified limit. A comparison of these financing alternatives is needed, especially with regard to how they might affect those with chronic illness.

Fifth, there has been a dramatic increase in the use of specialty drugs (ie, agents targeting a gene or protein, which are typically injected or infused). They are often used to treat complex, chronic conditions such as anemia, cancer, growth hormone deficiency, and multiple sclerosis, but at prices that can be substantially higher than traditional medications. Historically, only a small percentage of plan members had these conditions, so the total population of specialty drug users was quite small. However, spending on specialty drugs is expected to increase substantially in the near future as new drugs enter the market for treatment of diabetes, osteoporosis, and rheumatoid arthritis—diseases that affect much larger populations. Many insurers are contemplating a variety of cost-sharing strategies to control their use and costs. There is some evidence that patients are less price-responsive for these products than for traditional oral agents,[11] perhaps because of relatively few alternative therapeutic options. Whatever the reason, this area may be the next frontier on which we observe dramatic changes in benefit design, and it will be important to assess the consequences for spending and health.

The majority of articles that we examined in this review were outcomes studies conducted using administrative data. The researchers typically isolated a plan or plans that changed their benefit design and analyzed the resulting patterns of prescription drug use and (less frequently) medical utilization, with the best designs including a control plan that did not change benefits during the same period. Such data are rich in sample size and measures of utilization, but they have limitations beyond the lack of important clinical detail. There is no information on socioeconomic status and one cannot control for key health-related behaviors such as diet, exercise, and smoking. Physician prescribing practices—especially whether a prescription was written but not filled—are unobserved. Furthermore, long-term follow-up is difficult because plan enrollment often changes over the course of the study.

In sum, the evidence suggests that patients are responsive to cost-sharing arrangements in prescription drug plans—even among chronically ill patients. For certain conditions, the evidence clearly indicates that more cost sharing is associated with increased use of other medical services, such as hospitalizations and emergency department visits. These findings make benefit design an important public health tool for improving population health. The challenge for public and private plans is to make patients more sensitive to the cost of treatment without encouraging them to forego cost-effective care. This requires knowing how patients respond to different incentives and cataloging the net benefits of alternative therapies, not only for health, but also for current and future health care costs, productivity, and patient utility.

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Study concept and design: Goldman, Joyce.
Acquisition of data: Goldman, Zheng.
Analysis and interpretation of data: Goldman, Joyce, Zheng.
Drafting of the manuscript: Goldman, Joyce, Zheng.
Critical revision of the manuscript for important intellectual content: Goldman, Joyce.
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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Studies That Examined Prescription Drug Utilization Only					
Andersson et al,[5] 2006	Delivery of pharmaceuticals to the Swedish population from Jan 1986 to Dec 2002, at the chemical subgroups level (aggregated data from National Corporation of Swedish Pharmacies)	Time series	Three national policies (Jan 1, 1991; Jan 1, 1995; and Jan 1, 1999) in Sweden increasing patient drug co-payment	Total DDDs; total drug costs	Co-payment increases were not associated with changed level or slope of drug cost or volume
Dormuth,[7] 2006	173 076 Elderly patients with chronic obstructive pulmonary disease or asthma in BC (pharmacy claims and administrative medical records, 1997-2004)	Before-after (no control group)	Drug policies in 3 periods for BC elderly on patients' prescription payment: (1) 100% dispensing fee up to an annual ceiling of Can$200 (before 2002); (2) $10 or $25 drug co-payment with annual ceilings of $200 or $275, depending on income (Jan 2002–Apr 2003); and (3) 25% coinsurance plus income based deductible plus revised income-based annual ceilings (May 2003–present)	DDDs per 10 000 patient-mo; drug initiation and cessation	Drug policy changes in 2002-2003 for BC elderly were associated with significant reductions in use of inhaled medications (–12.3% to –5.8%); patients with new diagnoses were 25% less likely to initiate treatment in period 2 or 3 compared with period 1; long-term users were 47% and 22% more likely to cease treatment during periods 2 and 3
Gibson et al,[9] 2006	234 685 Statin users continuously enrolled in a health plan (enrollment and pharmacy and medical claims data, 2000-2003)	Longitudinal	Variation in statin co-payments across health plans and over time	MPR	100% Co-payment increase lowered monthly adherence rates for statin medications by 2.6% and 1.1% among new and continuing users, respectively; those who recently initiated statins therapy were more price-sensitive
Goldman et al,[10] 2006	62 774 Adults continuously enrolled in a health plan for at least 1 y before and after initiating cholesterol therapy (pharmacy and medical claims data, 1997-2002)	Repeated cross-sectional	Variation in statin co-payments across health plans	MPR	100% Co-payment increase lowered fraction of fully adherent patients for cholesterol therapies by 6% to 10%, depending on patient risk; eliminating co-payments for high- and medium-risk patients, while raising them (from $10 to $22) for low-risk patients predicted to avert 79 837 hospitalizations and 31 411 ED visits annually among national sample of 6.3 million adults taking cholesterol-lowering therapy
Goldman et al,[11] 2006	Patients with ≥ 2 primary diagnoses for cancer, kidney disease, rheumatoid arthritis, or multiple sclerosis among 1.5 million private insurance enrollees (pharmacy and medical claims data, 2003-2004)	Repeated cross-sectional	Variation in drug coverage generosity (ratio of total OOP payments to total payments for specific drug category) across health plans and over time (2003-2004)	Drug spending	A 100% increase in effective coinsurance rate was associated with 7% decrease in multiple sclerosis total drug spending and 21% decrease in rheumatoid arthritis drug spending; spending reductions for cancer drugs and kidney disease drugs were smaller at 1% and 11%, respectively, and were not statistically significant
Taira et al,[13] 2006	114 232 Hypertension patients who filled prescriptions for hypertension medications Jan 1999–June 2004 (administrative data and pharmacy claims data from a managed care organization, 1999-2004)	Repeated cross-sectional	Three co-payment levels in a tiered formulary: $5, $20, and $20-$165	Adherence (MPR ≥ 0.8)	Relative to medications with a $5 co-payment, the odds ratio for adherence to drugs having a $20 co-payment was 0.76; for drugs requiring a $20-$165 co-payment, the odds ratio was 0.48
Wang et al,[14] 2006	47 115 Adult prescription users in Medical Expenditure Panel Survey, 1996-2001	Repeated cross-sectional	Cross-sectional variation in generosity of drug benefit (share of annual drug cost paid by insurance)	No. of filled prescriptions	Non-Hispanic blacks were less likely than non-Hispanic whites to receive essential new drugs; the number of essential new drugs acquired was negatively correlated with co-payments

(continued)

eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Contoyannis et al,[16] 2005	173 426 Elderly patients randomly selected from population of Quebec Pharmacare beneficiaries (administrative data, Aug 1993–June 1997)	Before-after (no control group)	Two drug policy changes in program: before Aug 1996, low-income elderly had free drug coverage while other elderly paid Can$2 per prescription; since Aug 1996 all paid 25% coinsurance with income-based annual ceilings; beginning Jan 1997, quarterly deductible added and annual ceiling applied per quarter and still varied by income	Drug spending	100% Increase in effective drug price (price an individual would face under new cost-sharing policy if their consumption remained at the pre-policy level) was associated with 16% to 12% reduction in total drug spending in a given period
Gibson et al,[17] 2005	18 767 Employees in 2 firms (pharmacy claims and medical claims data, 1995-1998)	Before-after with control group	Co-payment level in one firm changed from $2 to $2 for generics and $7 for brand-name drugs; co-payment level in the other firm remained unchanged	No. of filled prescriptions; drug spending	100% Co-payment increase in brand drugs was associated with 4% decrease in total drug use, 27% decrease in use of multisource brand drugs, and 3.2% decrease in use of single-source brands; total drug expenditures decreased by about 10%; enrollees with newly diagnosed chronic condition were less price-sensitive
Hansen et al,[18] 2005	9819 Privately insured PPI users in 1998 (pharmacy and medical claims data, 1997-1998; direct-to-consumer advertising expenditure data)	Cross-sectional	Whether a plan had > $5 co-payment for a brand-name PPI prescription across multiple drug benefit plans	Drug switching	Patients with > $5 co-payment for brand-name PPI prescription were 12% less likely to switch from lansoprazole to omeprazole than patients with lower co-payments
Huskamp et al,[19] 2005	36 102 Children continuously enrolled for 33 mo as dependents in 2 employer-sponsored managed care plans (eligibility file and pharmacy claims data, 1999-2001)	Before-after with control group	One employer changed formulary from 1-tier to 3-tier and increased co-payments in all tiers; the other employer had a stable 2-tier formulary	Initiation of drug therapy; discontinuation rate; drug spending; OOP and plan drug spending	Adding a third tier with a $30 co-payment decreased probability that children received a drug for attention-deficit/hyperactivity disorder by 17%, decreased total medication spending by 20%, and shifted more medication costs to patients
Landsman et al,[20] 2005	Users of 9 drug classes continuously enrolled for 2 y in 1 of 4 managed care plans with 1 630 000 total members (enrollment and pharmacy claims data, 1999-2001)	Before-after with control group	Three plans changed from 2-tier formulary to 3-tier formulary and 1 plan had a stable 2-tier formulary	MPR; discontinuation rate; drug switching; No. of filled prescriptions	Patients had statistically significant decreases in MPRs in 7 of 9 drug classes; a 100% co-payment increase lowered the number of monthly filled prescriptions in each of the 9 drug classes; reductions ranged from 10%-60%
Roblin et al,[22] 2005	26 220 12-mo Episodes of oral hypoglycemic drug use in 5 managed care organizations (enrollment and pharmacy claims data, 1997-1999)	Time series	Variations over time in co-payment increase ($0 to ≥ $10) across 5 MCOs	Standard oral hypoglycemic drug average daily dose per mo	≥ $10 Co-payment increase decreased use of oral hypoglycemic drugs by 18.5%; smaller co-payment increases had no significant effect on oral hypoglycemic drug spending
Briesacher et al,[23] 2004	20 868 Patients with arthritis enrolled in 32 employer-sponsored drug plans and using NSAIDs during 2000 (pharmacy claims, medical claims, and encounter data, 2000)	Cross-sectional	Variation in drug tiers and co-payments for COX-2 selective inhibitors across drug plans	Probability of using COX-2 selective inhibitors	Odds of using COX-2 selective inhibitors were significantly lower (odds ratio, 0.36) if drug formulary designated COX-2 as only nonpreferred products compared with patients with 1-tier drug coverage; co-payments exceeding $15 were also associated with lower odds ratio (0.49) of drug initiation relative to co-payments of $5 or less; such relationship persisted even for patients with gastrointestinal comorbidities
Crown et al,[24] 2004	63 231 Asthma patients with employer-sponsored drug plans (pharmacy claims, medical claims, and encounter data, 1995-2000)	Repeated cross-sectional	Cross-sectional variations of drug co-payments	Initiation of drug therapy; days of supply; controller-to-reliever ratio of asthma drugs	Level of patient cost sharing did not affect use of asthma medications; however, physician/practice prescribing patterns strongly influenced patient-level treatment patterns

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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Ellis et al,[25] 2004	4802 Non-Medicaid enrollees with statin prescriptions in 1 managed care organization (pharmacy and medical claims, Jan 1998–Nov 2001)	Repeated cross-sectional	Cross-sectional variations of drug co-payments	Cumulative multiple refill-interval gap; discontinuation rate	Median duration for statin therapy was 3.9 y, 2.2 y, and 1.0 y for patients whose average monthly statin co-payments were < $10, $10-20, and > $20, respectively
Goldman et al,[26] 2004	528 969 Privately insured beneficiaries aged 18-64 y enrolled from 1 y to 4 y in 1 of 52 health plans (pharmacy and medical claims data, 1997-2000)	Repeated cross-sectional	Cross-sectional variations of indexes of drug plan generosity	Days of supply	100% Co-payment increase in a 2-tier plan lowered use in each of 8 therapeutic classes; reductions ranged from 25%-45%; largest reductions were for drugs with close over-the-counter substitutes
Kamal-Bahl et al,[27] 2004	149 243 Hypertension patients who had prescriptions for ≥ 1 of 5 drug classes (pharmacy claims, medical claims, and encounter data, 1999)	Cross-sectional	Cross-sectional variations in co-payments within 1-, 2-, or 3-tiered formularies	Initiation of drug therapy; drug spending; OOP and plan drug spending	Lower likelihood of using ACE inhibitors and angiotensin II receptor blockers with co-payment differences of ≥ $10 between generic and brand drugs; a 100% increase in drug-co-payment was associated with a predicted decrease of 8.9% in total drug spending in a 1-tier plan
Liu et al,[28] 2004	> 3 Million prescriptions for a sample of elderly patients randomly drawn from 21 hospitals in Taipei, Taiwan (administrative data, 1998-2000)	Before-after with control group	Since Aug 1999, prescription drug policy in Taiwan changed from full coverage to 20% coinsurance with a maximum of US $15.63 per prescription for prescriptions costing more than $3.13; selected groups were exempt	Average prescription cost	Compared with non–cost-sharing group, cost-sharing group experienced lower growth of average prescription cost since drug policy change; elderly patients with nonchronic diseases were more price-sensitive
Lurk et al,[29] 2004	Aggregated monthly data, Nov 1999–Dec 2002, in 1 safety-net provider	Before-after (no control group)	Change over time in drug co-payments	No. of filled prescriptions; OOP and plan drug spending	An average $5 increase in co-payment was associated with reduced drug utilization and a $26.07 decrease in prescription drug cost to the clinic per visit per mo in an ambulatory care safety-net provider setting
Meissner et al,[30] 2004	8643 Beneficiaries continuously enrolled in a public employer health plan (pharmacy claims data, 1998-1999)	Before-after (no control group)	Change over time in drug co-payments	Days of supply; No. of filled prescriptions; plan drug spending	An average $10 co-payment increase for 2 classes of allergy medications was not associated with significant change in combined lower-sedating antihistamines and nasal steroids; instead, it was associated with 13% reduction in plan drug cost for allergic rhinitis patients; unadjusted elasticity, 0.39 for lower-sedating antihistamines and –0.22 for nasal steroids
Blais et al,[32] 2003	34 627 Quebec residents receiving social assistance, aged ≤64 y, with any prescription for medications studied (Quebec Administrative claims data, 1992-1997)	Time series	Drug policy changed for Quebec elderly in 1996-1997 from 0 or Can$2 drug co-payment to 25% coinsurance with income-based annual ceiling of $200-$925; control group included privately insured individuals	No. of prescriptions dispensed per mo	Drug policy change did not reduce total monthly consumption of neuroleptics and anticonvulsants but reduced total monthly consumption of inhaled corticosteroids by 37%
Huskamp et al,[34] 2003	151 222 Enrollees covered by 2 employers and were users of 1 of 3 classes of drugs: ACE inhibitors, PPIs, or statins (eligibility file and pharmacy claims data, 1999-2001)	Before-after with control group	1 Employer changed drug co-payment from $7/$15 to $8/$15/$30; the other changed from $6/$12 to $6/$12/$24; enrollees from other employers with stable 2-tier benefits were chosen as control groups	Initiation of drug therapy; adherence/MPR; drug switching; discontinuation rate; drug spending; OOP and plan drug spending	Dramatic increases in drug co-payments were associated with higher rate of discontinuation of drug therapy (21% vs 11%) and higher switching to lower-cost medications (49% vs 17%) in all 3 drug classes; a more moderate increase in drug co-payments was associated with higher drug switching but not higher discontinuation rates; there were no consistent effects of co-payment increase on total drug spending in the 3 drug classes

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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Liu et al,[35] 2003	> 1.6 Million prescriptions for sample of elderly patients randomly drawn from 21 hospitals in Taipei, Taiwan (administrative data, 1998-2000)	Before-after (no control group)	Since Aug 1999, prescription drug policy in Taiwan changed from full coverage to 20% coinsurance with a maximum of $15.63 per prescription for prescriptions costing more than $3.13; selected groups were exempt	Drug spending	Imposing cost sharing was associated with a 12.9% increase in total prescription drug costs in the cost-sharing group, mainly due to an increase in average drug costs per prescription (explaining 69.2% of the variance)
Nair et al,[36] 2003	8312 Patients with chronic conditions in a managed care plan (membership data and pharmacy claims data, 2000-2001)	Before-after with control group	Intervention group's drug benefit changed from 2 tiers to 3 tiers; 2 control groups had stable 2- or 3-tier drug benefits	Drug switching; formulary adherence rate; discontinuation rate	Moving from a 2-tier to a 3-tier drug benefit was associated with an increased use of generic drugs (6%-8%) and formulary adherence
Ong et al,[37] 2003	Monthly drug-use data for 3 therapeutic classes (antidepressants, anxiolytics, and sedatives) from July 1990–Dec 1999 in Sweden	Time series	Drug co-payment increases in 1995 and 1997	DDD per 1000 inhabitants	Permanent increases in men's antidepressant and sedative use occurred before 1995 reform; only women's antidepressant use was permanently reduced by the 1997 reform
Rector et al,[38] 2003	Pharmacy claims for 3 therapeutic classes (ACE inhibitors, PPIs, and statins) in 4 independent physician practice association health plans (1998-1999)	Before-after with control group	Four plans changed drug benefits from 2-tier plans to 3-tier plans in different quarters during 1998-1999	Use of preferred brands	Moving from a 2-tier to a 3-tier drug benefit led to increases in % use of preferred brands for ACE inhibitors, PPIs, and statins by 13.3%, 8.9%, and 6.0%, respectively, over 21-mo period
Artz et al,[39] 2002	6237 Elderly patients covered by Medicare (Medicare Current Beneficiary Survey, 1995)	Cross-sectional	Variation in drug coverage generosity	No. of filled prescriptions; drug spending	Prescription drug spending increased with drug plan generosity across a range of insurance types
Joyce et al,[40] 2002	420 786 Primary beneficiaries aged 18-64 y with employer-provided drug benefits (pharmacy and medical claims data, 1997-1999)	Repeated cross-sectional	Cross-sectional variations of drug benefits (number of tiers, co-payments, and coinsurance rates)	Drug spending; OOP and plan drug spending	Doubling co-payments decreased annual drug spending by 22%-33% and increased fraction of beneficiaries paying OOP from 17.6% to 25.6% in a 2-tier plan
Pilote et al,[41] 2002	22 066 Quebec elderly patients who experienced acute myocardial infarction (Quebec administrative claims data, 1994-1998)	Before-after (no control group)	Drug policy changed for Quebec elderly in 1996-1997 from 0 or Can$2 drug co-payment to 25% coinsurance with income-based annual OOP maximum of $200-$925	Initiation of drug therapy; "medication persistence" (proportion of days covered by drug therapy); drug switching; hospital admissions; ED and physician visits; mortality	Drug policy change did not reduce use of essential cardiac medications among Quebec elderly who experienced acute myocardial infarction nor medical utilizations; the findings did not vary by sex or socioeconomic status
Thomas et al,[42] 2002	29 435 Elderly with employer-based drug benefit plans for retirees (pharmacy claims data, 2001)	Cross-sectional	Variation in drug formulary tiers, co-payments, and coinsurance rates across 96 health plans	No. of filled prescriptions; drug switching; prescription size (mail/retail); drug spending; OOP drug spending	Increased patient cost sharing and formulary restrictions were associated with lower drug spending, higher OOP costs, and a shift to lower-cost medications (generics and mail order)
Blais et al,[44] 2001	259 616 Quebec elderly residents who had any prescription for study drugs during the study period (Quebec administrative claims data, Aug 1992–Aug 1997)	Time series	Drug policy changed for Quebec elderly in 1996-1997 from 0 or Can$2 drug co-payment to 25% coinsurance with maximum OOP payment ceiling with income-based annual OOP maximum of $200-$925	No. of prescriptions dispensed per mo	Drug policy change did not reduce total number of prescriptions dispensed per mo for nitrates, antihypertensive agents, benzodiazepines, or anticoagulants
Kozyrskyj et al,[45] 2001	10 703 School-aged children in Manitoba who had asthma (administrative data, Apr 1995–Apr 1998)	Before-after with control group	Before Apr 1996, Manitoba's drug benefit program required a fixed deductible payment of $237 per family plus 40% co-payment on prescription costs above $237; since April 1996 this policy was replaced by income-based deductibles with low-income family paying up to 2% of their income as deductible and high-income family paying up to 3%	Initiation of drug therapy; No. of prescriptions filled	Implementation of income-based deductible in was associated with decrease in use of inhaled corticosteroids by high-income children with severe asthma and did not improve use of these drugs by low-income children

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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Kozyrskyj et al,[46] 2001	12 481 School-aged children in Manitoba who had asthma (administrative data, July 1995–March 1998)	Repeated cross-sectional	Before Apr 1996, Manitoba's drug benefit program required a fixed deductible payment of $237 per family plus 40% co-payment on prescription costs above $237; since April 1996 this policy was replaced by income-based deductibles with low-income family paying up to 2% of their income as deductible and high-income family paying up to 3%	Initiation of drug therapy	Compared with higher-income children with asthma, odds ratio of receiving inhaled corticosteroid prescriptions was 0.82-0.88 for low-income children with asthma, controlling for asthma severity, type of drug insurance, or health care utilization patterns
Hillman et al,[49] 1999	134 937 Nonelderly enrollees of 9 managed care plans (pharmacy claims data, 1990-1992)	Repeated cross-sectional	Variation of drug co-payments both across and within health plans	Initiation of drug therapy; days of supply; drug spending	Higher co-payments for prescription drugs were associated with lower drug spending in independent practice associations but not in networks where physicians bore financial risk for prescription drug costs
Motheral et al,[50] 1999	3184 Individuals continuously enrolled in commercial plans (pharmacy claims data, 1996-1997)	Before-after with control group	Enrollees in 2 different employer plans experienced brand-name co-payment increase from $10 to $15, while those in the control group had brand-name co-payment of $10 during the study period	Initiation of drug therapy; No. of filled prescriptions; drug switching; discontinuation rate; drug spending; OOP and plan drug spending	Increasing co-payment from $10 to $15 was associated with lower use of brand drugs, lower plan drug spending, and lower total ingredient costs but no statistically significant difference in overall use or discontinuation rates for long-term medications
Stuart et al,[51] 1999	1302 Elderly and disabled Medicaid recipients (Medicare Current Beneficiary Survey, 1992)	Cross-sectional	Variation of drug co-payments across state Medicaid programs	Initiation of drug therapy; No. of prescriptions filled OOP; drug spending	Imposing $0.50-$3 drug co-payments in state Medicaid programs reduced drug use among study group by 15.5% in 1992; primary effect of co-payments was to reduce likelihood of any prescription filling (by 7.7%); those reporting poor health status were most adversely affected by co-payments
Grootendorst et al,[53] 1997	5743 Ontario residents aged 55-75 y (survey data, 1990)	Cross-sectional	Discontinuity in drug benefit availability: the provision of first-dollar prescription drug insurance coverage for Ontario residents at age 65 y	Initiation of drug therapy; No. of prescriptions filled	Provision of first-dollar prescription drug insurance coverage at age 65 y increased drug use, primarily among individuals with lower health status; most of the increased use was among drug users rather than an increase in the probability of use
Hong et al,[56] 1996	3144 Children enrolled in 5 drug benefit plans (pharmacy claims and enrollment database, Dec 1992–Dec 1993)	Cross-sectional	Variations in drug co-payment and cost-sharing differentials between generic and brand name drugs across plans	Drug initiation; No. of filled prescriptions; OOP drug spending; drug spending	Higher levels of cost sharing per prescription were associated with higher drug utilization; larger cost-sharing differentials between generic and brand drugs were associated with higher rates of generic drug use but were not always associated with lower expenditure rates
McManus et al,[57] 1996	Summary statistics on total number of prescriptions (Australia Pharmaceutical Benefits Scheme administrative data, 1987-1994)	Time series	In Nov 1990, patient contributions increased from $A11 to $A15 for the general population; in Jan 1992, a $A2.50 co-payment was required for returned servicemen and -women	Total monthly No. of prescriptions	Increased drug co-payment was associated with decreased level of drug consumption but not associated with a changing trend among both the general population and returned servicemen and -women; the effect was larger for "discretionary drugs" relative to "essential drugs"
Coulson et al,[58] 1995	4508 Elderly Medicare beneficiaries in Pennsylvania (survey data linked with administrative claims data, 1989)	Cross-sectional	Variation in drug coverage generosity by different insurance types	No. of prescriptions filled	Low-income elderly (< $12 000 single or < $15 000 married) were covered by the program of Pharmaceutical Assistance Contract for the Elderly and only paid $4 per 30-d dosage; Enrollees in the program had 0.29 more prescriptions per 2-wk period than did elderly patients who had no prescription drug coverage

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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Hughes et al,[59] 1995	Published monthly government statistics in England in 1969-1992	Time series	Variation over time of drug co-payments in UK National Health Service	No. of nonexempt prescriptions dispensed per y per capita	10% Increase in prescription charge was associated with 3.2% decrease in per capita utilization of drugs in the nonexempt category
Smith et al,[60] 1993	Aggregated data on use and costs of prescription drugs for 212 employer groups covered by 1 managed care organization in 1989	Cross-sectional	Variation of drug co-payments ($1-$8) across employer groups	No. of filled prescriptions; drug spending; OOP and plan drug spending	Increasing co-payments from $3 to $5 was associated with a 5% decrease in the number of filled prescriptions and a 10% decrease in employer drug spending
Ryan et al,[61] 1991	Published monthly government statistics in England in 1979-1985	Time series	Variation over time of drug co-payments in UK National Health Service	No. of nonexempt prescriptions dispensed per mo per capita; drug spending	10% Increase in prescription drug charge was associated with 1% reduction in per capita drug utilization in study period; approximately two-thirds of government expenditure savings were due to reduction in utilization vs increased charges per item of drugs
Harris et al,[62] 1990	43 146 Beneficiaries continuously enrolled in a HMO for a 4-y period (administrative pharmacy data, 1982-1986)	Before-after with control group	Intervention group experienced co-payment rates of $1.50, $1.30, $3 plus other benefit changes during a 3-y period while the control group in the same plan had no drug co-payment during the period	No. of filled prescriptions; drug spending	Graduated increases in drug co-payments (from $0 to $1.50 to $3) plus other formulary restrictions were associated with 10% to 12% reductions in the number of prescriptions and 6.7% reduction in per capita drug costs
Lavers,[64] 1989	Published monthly government statistics in England and Wales in 1971-1982	Time series	Variation over time of drug co-payments in UK National Health Service	No. of nonexempt dispensed prescriptions per mo	10% Increase in prescription drug charge was associated with 2.0% to 1.5% decrease in monthly volume of nonexempt items
O'Brien,[65] 1989	Published monthly government statistics in England in 1969-1986	Time series	Variation over time of drug co-payments in UK National Health Service	No. of nonexempt dispensed prescriptions per mo	10% Increase in prescription drug charge was associated with 3.3% decrease in volume of nonexempt items during the study period; reduction was 2.3% in 1969-1977 and 6.4% in 1978-1986
Foxman,[66] 1987	5765 Nonelderly enrollees who were in their second year of participation in RAND HIE in the fee-for-service plans at 6 sites, 1974-1982	Randomized trial	Participants were randomly assigned to health plans with 0, 25%, 50%, or 95% coinsurance rates or an individual deductible plan	No. of filled prescriptions	People with free medical care used 85% more antibiotics than those required to pay some portion of their medical bills
Birch,[67] 1986	Published annual government statistics in UK National Health Service, 1979-1983	Time series	Patient charges for pharmaceuticals increased from 1979 to 1983; part of the population was required to pay the charges while others were exempt from charges	No. of items dispensed per capita per y	Per capita consumption of prescriptions in nonexempt group decreased by 7.5% while per capita consumption in exempt group increased by 1%
Leibowitz et al,[68] 1985	3860 Nonelderly enrollees who were in their first year of participation in RAND HIE in the fee-for-service plans at 3 sites, 1974-1982	Randomized trial	Participants were randomly assigned to health plans with 0, 25%, 50%, or 95% coinsurance rates or an individual deductible plan	No. of filled prescriptions; drug switching; samples from physicians; drug spending	Consumers with a 95% coinsurance rate for prescription drugs (up to a maximum dollar expenditure) spent 57% as much as those in a free-care plan
Reeder et al,[69] 1985	62 176 Medicaid recipients in South Carolina (claims data, 1976-1979)	Time series	Change in Medicaid outpatient drug co-payments since Jan 1977: from 0 to $0.50 per prescription	Drug spending	Imposing a $0.50 co-payment for outpatient prescriptions covered by South Carolina Medicaid programs had differential effects on use of drugs in 10 therapeutic classes; drug utilizations decreased immediately after co-payment increase in 8 out classes (not in analgesics or sedatives/hypnotics); the long-term utilization trends in 4 classes were significantly changed after co-payment increase

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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Studies That Also Examined Medical Utilization and Spending					
Cole et al,[6] 2006	12 776 Congestive heart failure patients taking ACE inhibitors, β-blockers, or both in 2002 (claims data, 2002- 2003)	Cross-sectional	Variation in drug co-payments across health plans	MPR; total medical costs; congestive heart failure–related hospitalizations	A $10 increase in drug co-payment is associated with 2.6% and 1.8% decreases in MPRs for patients taking ACE inhibitors and β-blockers, respectively; such decreases were associated with predicted increases of congestive heart failure–related hospitalizations by 6.1% and 8.7%; predicted total medical costs were not affected
Gibson et al,[8] 2006	117 366 Statin users continuously enrolled in a health plan during 2000-2003 (pharmacy and medical claims data, 2000-2003)	Repeated cross-sectional	Variation in statin co-payments across health plans	MPR; hospital admissions; ED visits; physician visits	$10 Increase in co-payment resulted in 1.8% and 3.0% reduction in adherence among new and continuing statin users, respectively; among continuing users, higher statin adherence was associated with lower negative events (hospital admissions and ED visits) but not with total costs
Li et al,[12] 2006	8017 Elderly BC residents with rheumatoid arthritis (administrative data, 1996-2002)	Before-after (no control group)	Drug policy changes for BC elderly on patients' prescription payment: (1) 100% dispensing fee up to annual ceilings of Can$200 (before 2002); (2) $10 or $25 drug co-payment with annual ceilings of $200 or $275, depending on income (Jan 2002–Apr 2003)	No. of prescriptions filled; physician visits	100% Increase in effective drug price (price an individual would face under new cost-sharing policy if their consumption remained at prepolicy level) was associated with 20% to 11% reduction in drug use and 6% to 4% increase in physician visits for low-income seniors and other seniors, respectively
Anis et al,[15] 2005	2968 Elderly BC residents with rheumatoid arthritis (pharmacy claims data and administrative medical records, 1996-2000)	Before-after (no control group)	Periods before and after annual drug co-payments reached the maximum within a calendar year	No. of filled prescriptions; hospital admissions	Among elderly patients with rheumatoid arthritis who exceeded the maximum annual co-payment of Can$200 at least once during 1997-2000, there were 0.38 more physician visits per mo, 0.50 fewer prescriptions filled per mo, and 0.52 fewer prescriptions filled per physician visit during the "cost-sharing" period vs the "free" period; frequency of hospital admissions did not differ
Mahoney et al,[21] 2005	Diabetes-related claims and drug use and cost statistics in 1 company, 2001-2003	Before-after (no control group)	Coinsurance rates on diabetes drugs reduced to 10% (before policy change, ranged from 25%-50%) in Jan 2002	Adherence; drug spending; drug and medical spending; ED visits	From 2001 to 2003, adherence and use of fixed-combination therapy increased among diabetes patients; average total pharmacy costs decreased by 7% and overall medical costs decreased by 6%; ED visits decreased by 26%
Winkelmann,[31] 2004	37 319 Individuals in Germany (survey data, 1995-1999)	Before-after with control group	Co-payment for prescriptions increased by DM6 in 1997; certain groups were exempted from such an increase and served as the control group	Physician visits	Additional DM6 prescription fee reduced the number of physician visits by 10% on average
Fairman et al,[33] 2003	7709 Enrollees in a preferred provider organization (pharmacy and medical claims data, 1997-2000)	Before-after with control group	Enrollees in the intervention group experienced a formulary change from 2-tier to 3-tier; enrollees in the control group had stable 2-tier formulary	No. of filled prescriptions; drug continuation rate; drug spending; OOP and plan drug spending; hospitalizations, ED visits, and ambulatory visits	Moving from a 2-tier to a 3-tier drug benefit was associated with reduced growth in plan cost and lowered use of nonformulary medications but not with lower growth of total prescription claims or total drug spending; associations between adding tiers and drug continuation rates were mixed for 4 classes of long-term medications; such drug benefit change was not associated with number of hospitalizations, ED visits, or office visits

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eTable 1. Studies Examining the Associations of Co-payment, Tiering, and Coinsurance With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Balkrishnan et al,[43] 2001	2411 Medicare HMO enrollees in 1998 and 1999 (data source unknown)	Before-after (no control group)	In 1998, co-payments were $7/$15 for generics and brand names, respectively, with per-quarter OOP maximum of $200; in 1999, there was unlimited coverage for generics and limited coverage for brand drugs	Plan drug spending; plan drug and medical spending; physician visits	Changing to a drug policy with unlimited coverage for generics and limited coverage for brand drugs was associated with 27% decrease in plan drug costs, 4% decrease in physician visits, and 5% decrease in plan total costs
Motheral et al,[47] 2001	20 160 Individuals continuously enrolled in a preferred provider organization (pharmacy and medical claims data, Jan 1997–Dec 1999)	Before-after with control group	Intervention group had drug benefit changed from 2-tier to 3-tier; control group had stable 2-tier benefit	Initiation of drug therapy; No. of filled prescriptions; drug discontinuation rate; drug spending; OOP and plan drug spending; hospitalizations, ED visits, and ambulatory visits	Moving from a 2-tier benefit with co-payments of $7/$12 to a 3-tier benefit with co-payments of $8/$15/$25 was associated with slower growth in prescription drug use and drug spending (15% vs 22%); adding tiers was not consistently associated with medication discontinuation rates of 4 long-term therapy classes or with hospitalizations, ED visits, or office visits
Tamblyn et al,[48] 2001	149 283 Quebec residents aged ≥ 65 y or receiving welfare (administrative data, 1993-1997)	Time series	Drug policy changed for Quebec elderly in 1996-1997: from 0 or Can$2 drug co-payment to 25% coinsurance with income-based annual out-of-pocket maximum of $200-$925	Mean daily drug use; serious adverse events (acute care hospitalizations, long-term care admission, or death)	Drug policy change was associated with 9% and 14% reduction in use of essential drugs for elderly and welfare recipients, respectively; such reductions were associated with increased number of serious adverse events and ED visits; use of less essential drugs decreased by 15% and 22%
Berndt et al,[52] 1997	3470 Privately insured individuals from 26 plans treated for depression (medical and pharmacy claims data, 1993)	Cross-sectional	Variations of drug co-payment across 26 health benefit plans	Initiation of drug therapy; hospitalizations	Among patients with depression receiving outpatient treatment, higher prescription drug co-payment was associated with higher share of selective serotonin reuptake inhibitor use in all antidepressant medications; higher drug co-payment was not associated with higher probability of hospitalizations
Johnson et al,[54] 1997	Elderly HMO members during a 4-y period (administrative data, 1987-1991)	Before-after with control group	Two Medicare risk groups in an HMO setting had co-payments and coinsurance rates increased in different years over a 3-y period	Initiation of drug therapy; days of supply; drug spending; health status index	Graduated increases in co-payments from $1 to $5 and coinsurance (from 50% to 70%, with a $25 maximum) did not reduce prescription drug utilization and costs in a consistent manner among each of 22 drug classes; health status may have been adversely affected as measured by combined chronic disease score and diagnostic cost groups
Johnson et al,[55] 1997	Elderly HMO members during a 4-y period (administrative data, 1987-1991)	Before-after with control group	Two Medicare risk groups in an HMO setting had co-payments and coinsurance rates increased in different years over a 3-y period	No. of filled prescriptions; drug spending; OOP drug spending; hospitalizations, ED visits and ambulatory visits; drug and medical spending	Graduated increases in co-payments from $1 to $5 and coinsurance (from 50% to 70%, with a $25 maximum) resulted in lower prescription drug use and expenses and did not affect medical care utilization and expenses in a consistent manner
Lingle et al,[63] 1990	9966 Elderly Medicare beneficiaries and those not eligible for Medicaid benefits (Medicare claims data, 1975 and 1979)	Before-after with control group	Intervention group included Medicare beneficiaries covered by New Jersey's Pharmaceutical Assistance for the Aged; control group included beneficiaries in eastern Pennsylvania	Medical utilization; plan medical spending	Reimbursement for inpatient care for New Jersey recipients was, on average, $238.50 lower than that in eastern Pennsylvania; there was no significant increase in total medical costs reimbursed by Medicare among New Jersey recipients

Abbreviations: ACE, angiotensin-converting enzyme; BC, British Columbia; COX-2, cyclooxygenase 2; DDD, defined daily dose; ED, emergency department; HIE, Health Insurance Experiment; HMO, health maintenance organization; MPR, medication possession ratio; OOP, out-of-pocket; PPI, proton pump inhibitor.
[a]Unless otherwise specified, all study sites were in the United States.

eTable 2. Studies Examining the Association of Benefit Caps With Prescription Drug Utilization and Spending and With Medical Utilization and Spending

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Studies That Examined Prescription Drug Utilization Only					
Tseng et al,[71] 2004	1308 Medicare managed care enrollees in 2001 whose drug benefits were capped and annual spending exceeded annual caps of $750 or $1200 (survey data, 2002)	Cross-sectional	Variations in annual drug benefit caps across counties	Underuse due to cost; drug switching	Medicare + Choice beneficiaries exceeding annual drug benefit cap were more likely than those not exceeding cap to switch medications (15% vs 9%), use samples (34% vs 27%), and report difficulty paying for prescriptions (62% vs 37%)
Tseng et al,[4] 2003	438 802 Medicare managed care enrollees in 2001 whose drug benefits were capped at $750, $1000, or $2000 (pharmacy claims data, 2001)	Cross-sectional	Levels of annual drug benefit caps	% Exceeding benefit caps; OOP drug spending	22%, 14%, and 4% of Medicare patients exceeded annual drug benefit caps of $750, $1000, and $2000, respectively
Cox et al,[72] 2002	212 Medicare + Choice beneficiaries with capped annual prescription drug benefits of $500 or $1000 in 2000 (survey data)	Cross-sectional	Capped drug benefits	Adherence discontinuation	Those who exceeded cap prior to Oct 2000 were more likely to stop taking ≥ 1 medications or took less than prescribed amount after reaching the cap compared with precap period; these differences were not statistically significant
Balkrishnan et al,[43] 2001	259 Medicare HMO enrollees in 1997-1998 (data source unknown)	Before-after (no control group)	Benefit cap increased from $500 per y in 1997 to $200 per quarter in 1998; co-payments changed from $6/$12 to $7/$15, for generics and brand names, respectively	Plan drug spending; Plan drug and medical spending	Change in benefit cap and increased drug co-payments were associated with a 29% increase in plan drug costs and 38% increase in total plan costs
Cox et al,[73] 2001	378 Medicare HMO enrollees who had reached ≥ 60% of prescription drug cap in 1997 (survey data)	Cross-sectional	Capped drug benefits ($750 for rural counties, $1500 for urban counties)	Initiation of drug therapy; adherence/ medication possession ratio; drug switching	Those who reached prescription cap were more likely to reduce drug use (odds ratio, 2.83), to discontinue a medication (odds ratio, 3.36), and to obtain samples from physician (odds ratio, 2.02) vs those who had not reached cap
Fortess et al,[74] 2001	343 Chronically ill New Hampshire Medicaid enrollees (pharmacy claims data), 1980-1983	Before-after (no control group)	State program imposed a 3-prescription monthly reimbursement limit (12 mo before and 6 mo after policy change)	Standard monthly doses for essential medications	3-Prescription monthly reimbursement limit in Medicaid program was associated with 34.4% reduction in use of essential medications
Martin et al,[75] 1996	743 Georgia Medicaid enrollees (pharmacy claims data, 1991-1992)	Time series	State program reduced monthly reimbursement limit of prescriptions from 6 to 5 (6 mo before and 6 mo after policy change)	No. of filled prescriptions; drug spending; OOP and plan drug spending	Reducing maximum No. of monthly reimbursable prescriptions from 6 to 5 was associated with 6.6% reduction in total prescriptions among beneficiaries with high use of prescription drugs
Soumerai et al,[78] 1987	10 734 New Hampshire Medicaid enrollees (pharmacy claims data, 1980-1983)	Time series	State program imposed a 3-prescription monthly reimbursement limit in Sep 1981 but later discontinued the policy (20 mo before and 11 mo after policy change; 17 mo after limit was replaced by $1 co-payment)	No. of filled prescriptions	3-Prescription monthly reimbursement limit was associated with 30% reduction in the number of prescriptions filled; use approached precap levels after the cap was replaced with a $1 co-payment

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eTable 2. Studies Examining the Association of Benefit Caps With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Studies That Also Examined Medical Utilization and Spending					
Hsu et al,[70] 2006	199 179 Medicare managed care enrollees (administrative data, 2003)	Cross-sectional	In 2003, 157 275 Medicare + Choice enrollees had annual drug benefit capped at $1000; another 41 904 enrollees had unlimited drug coverage due to employee supplements	Adherence; drug and medical spending; hospitalizations, emergency department visits, and ambulatory visits; blood pressure, low-density lipoprotein, glycated hemoglobin, and mortality	Those with $1000 drug benefit cap had 31% lower pharmacy costs, higher rates of drug nonadherence (odd ratios, 1.27-1.33), emergency visits (relative risk, 1.09), nonelective hospitalizations (relative risk, 1.13), and death (relative risk, 1.22); their total medical costs were not significantly different from those without drug benefit cap
Soumerai et al,[76] 1994	2227 New Hampshire Medicaid enrollees with schizophrenia (pharmacy and medical claims data, 1980-1983)	Time series	State program imposed a 3-prescription monthly reimbursement limit in Sep 1981 but later discontinued the policy (14 mo before and 11 mo after policy change; 17 mo after limit was replaced by $1 co-payment)	Days of supply; plan drug spending; plan medical spending; ambulatory visits; hospitalizations	3-Prescription monthly reimbursement limit was associated with immediate reduction (range, 15%-49%) in use of psychotropic drugs and significant increase in use of emergency mental health services and partial hospitalization but not with hospital admissions; drug and medical utilizations approached precap levels after the cap was replaced with $1 co-payment
Soumerai et al,[77] 1991	1786 New Hampshire Medicaid enrollees who in a baseline year had taken ≥ 3 prescriptions per mo (pharmacy and medical claims data, 1980-1983)	Time series	State program imposed a 3-prescription monthly reimbursement limit in Sep 1981 but later discontinued the policy	Days of supply; nursing home admissions; hospitalizations	3-Prescription monthly reimbursement limit was associated with 35% reduction of drug utilization and increased risk of nursing home admissions but not with hospitalizations among older patients (≥ 60 y) and who were frequent drug users

Abbreviations: HMO, health maintenance organization; OOP, out-of-pocket.
[a]Unless otherwise specified, all study sites were in the United States.

eTable 3. Studies Examining the Association of Reference Pricing With Prescription Drug Utilization and Spending and With Medical Utilization and Spending

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Studies That Examined Prescription Drug Utilization Only					
Mabasa et al,[120] 2006	PPI prescriptions for Canadians with private employer-sponsored drug plans (claims data, June 2002–May 2005)	Before-after with control group	One employer group adopted reference pricing for PPIs beginning June 2003 while other employer groups did not have reference pricing for PPIs throughout study period	Days of supply; drug spending	Introduction of reference-based pricing for PPIs in 1 employer in Canada reduced plan spending on PPIs by approximately 26%; less than one-third of the reduction was attributed to average price of PPIs and more than two-thirds to a decline in use of PPIs
Grootendorst et al,[122] 2005	BC Pharmacare for the elderly (aggregated data, 1993-2001)	Time series	Pharmacare introduced 2 types of reference pricing for NSAIDs: type 1 in Apr 1994 and type 2 in Nov 1995; under type 1 reference pricing, generic and brand versions of the same NSAIDs were exchangeable; under type 2 reference pricing, different NSAIDs were considered interchangeable	Drug plan spending	Imposing reference pricing among all NSAIDs (type 2 reference pricing) achieved more savings vs reference pricing among each NSAID (type 1 reference pricing); after type 2 reference pricing, annual plan expenditures for NSAIDs were cut by $4 million (50%); most savings accrued from substitution of low-cost NSAIDs for most costly alternatives; about 20% of savings represented expenditures by seniors who paid for cost-sharing NSAIDs
Schneeweiss et al,[123] 2004	BC Pharmacare for the elderly (aggregated data, 1995-1998)	Before-after (no control group)	Introduction of reference pricing to ACE inhibitors in elderly BC residents in 1997	Drug plan spending	Reference pricing to ACE inhibitors in elderly BC residents was associated with savings of Can$6 million among continuing users and $0.2 million among new users during the first year of the implementation; approximately five-sixths were achieved by utilization changes and one-sixth by cost shifting to patients; there were no savings through drug price changes
Marshall et al,[127] 2002	BC Pharmacare beneficiaries (aggregated data, 1993-1999)	Time series	Introduction of reference pricing to H_2 RAs and special authority for PPIs in elderly BC residents in 1995	No. of DDDs per 10 000 beneficiaries; OOP and plan drug spending per 10 000 beneficiaries	Reference pricing reduced plan expenditures by $1.8 to $3.2 million per y for H_2 RAs and special authority by $5.5 million per y for PPIs; beneficiary contributions for H_2 RAs increased from negligible amount to approximately 16% of total drug expenditures
Schneeweiss et al,[128] 2002	119 074 BC Pharmacare beneficiaries who used ACE inhibitors (administrative data, 1995-1998)	Longitudinal	Introduction of reference pricing to ACE inhibitors in elderly BC residents in 1997	No. of prescriptions; plan drug spending; drug switching discontinuation rates	Reference pricing for ACE inhibitors was associated with 11% reduction in use of all ACE inhibitors but use of overall antihypertensives was unchanged; the policy saved $6.7 million in pharmaceutical expenditures for existing users during its first 12 mo; relative to high-income patients, patients with low incomes were more likely to stop all antihypertensive therapy (odds ratio, 1.65)
Aronsson et al,[130] 2001	Quarterly time-series data on prices and quantities for 12 brand-name drugs and their generic substitutes, 1972-1996	Time series	Introduction of reference pricing in 1993 that specified that any costs exceeding the price of the least expensive generic substitute by more than 10% must be borne by patients	Market share of brand-name drugs; relative price of brand-name vs generics	Introduction of reference pricing was negatively associated with market shares for 3 brand-name drugs while positively associated with market shares for other 2; reference pricing was also associated with decreased relative price of brand-name vs generics

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eTable 3. Studies Examining the Association of Reference Pricing With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Grootendorst et al,[131] 2001	BC Pharmacare for the elderly (aggregated data, 1994-1999)	Before-after (no control group)	Introduction of reference pricing to nitrates in elderly BC residents in 1995	Monthly total No. of prescriptions; plan and OOP drug spending	During the 3.5 y after introduction of reference pricing for nitrates, BC Pharmacare expenditures on nitrates for elderly declined by $14.9 million; most of these savings were due to lower prices that Pharmacare paid for restricted nitrates; prescribing of reference-standard nitrates increased immediately after the policy was introduced but later dropped after nitroglycerin patch was exempted from additional charges; $1.2 million of the savings represented expenditures by senior citizens who bought restricted nitrates; there were no compensatory increases in expenditures for other antiangina drugs
McManus et al,[132] 2001	Prescriptions in Australia under government subsidy (claims data, 1990, 1994, and 1999)	Before-after (no control group)	Introduction of minimum pricing policy in 1990 and generic substitution policy in 1994	Drug switching	After implementation of minimum pricing, share of generic drugs increased from 0 in 1990 to 17% in 1994; generic substitution policy further increased share to 45% in 1999
Narine et al,[133] 2001	BC Pharmacare for the elderly (aggregated data, 1994-1996)	Before-after (no control group)	In 1995, Pharmacare introduced a reference-based pricing system for H_2 RAs, nitrates, and NSAIDs	Plan drug spending; total No. of prescriptions; drug switching	Introduction of reference pricing was associated with a 44% decrease in Pharmacare drug costs; total number of prescriptions for H_2 RAs and nitrates decreased by 5.2% and 2.5%, respectively; a significant number of patients switched from one drug to the other after introduction of reference pricing
Narine et al,[134] 1999	BC Pharmacare (aggregated data, 1994-1996)	Before-after (no control group)	Introduction of reference pricing to H_2 RAs in elderly BC residents in 1995	Annual total No. of prescriptions; plan drug spending	In year following introduction of reference pricing for H_2 RAs, total number of prescriptions decreased by 5.2% and market share of reference drug increased by 410%; Pharmacare expenditures for H_2 RAs decreased by 38%; no substantial changes in drug prices
Jonsson,[135] 1994	Swedish reimbursement system for drugs (aggregated data, 1992-1993)	Before-after (no control group)	Introduction of a reference pricing system in Jan 1993	Plan drug spending; OOP drug spending	During first 3 mo of introduction of a reference system in Sweden, relative to same period in previous year, there was a slight decrease (1.6%) in total expenditure for reimbursement scheme but a 14% increase for patient co-payments
Studies That Also Examined Medical Utilization and Spending					
Schneeweiss et al,[121] 2006	5 Million BC elderly residents (administrative data, Jan 2002–June 2004)	Longitudinal	Beginning in 2003, BC Pharmacare program only covered 1 PPI, rabeprazole, and imposed access restrictions on 3 leading PPIs	DDDs per mo; drug discontinuation rates; drug spending; gastrointestinal hemorrhage rates	Within 6 mo of policy change, 45% of all PPI users switched to covered PPI and provincial health plan saved at least Can$2.9 million; there was no increased use of H_2 blockers, discontinuation of gastroprotective drugs, or hospitalizations for hemorrhage
Schneeweiss et al,[124] 2004	5463 Patients covered by BC Pharmacare with ≥ 1 prescription for nebulized respiratory drug in preceding 12 mo (administrative data, Sep 1997–Aug 1999)	Randomized controlled trial, observational time series	Beginning in March 1999, Pharmacare restricted reimbursement for nebulized respiratory medications to patients with physician's exemption; patients in intervention group in randomized control trial were not subject to this restriction for 6 mo	Drug utilization; drug spending; contacts with physicians and services; emergent admissions to hospitals	Both randomized trial and observational analysis found that restricting reimbursement for nebulized respiratory drugs was not associated with increase of unintended health outcomes

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eTable 3. Studies Examining the Association of Reference Pricing With Prescription Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Schneeweiss et al,[125] 2003	61 763 Elderly BC residents who were dihydropyridine CCB users and covered by Pharmacare (administrative data, 1995-1997)	Longitudinal	Introduction of reference pricing to dihydropyridine CCBs in 1997	Median monthly doses; drug switching; hospital admissions; ED visits; admissions to long-term care facilities	Reference pricing for dihydropyridine CCBs was associated with increased use of fully covered dihydropyridine CCBs and reduced total medical costs by Can$1.6 million in the first 12 mo of implementation; overall antihypertensive use did not decline and there were no increases in hospitalizations, ED visits, or long-term care admissions
Hazlet et al,[126] 2002	20 000 British Columbia Pharmacare beneficiaries exposed to H_2 RAs and other antisecretory drugs (administrative data, 1993-1996)	Longitudinal	Introduction of reference pricing to H_2 RAs in 1995	No. of prescriptions filled; hospital visits; ED visits; hospital admissions; length of hospital stay	Reference pricing for H_2 RAs in elderly BC residents was not associated with worsening health outcomes among antisecretory drug users
Schneeweiss et al,[129] 2002	37 362 BC Pharmacare beneficiaries who used selective ACE inhibitors before the reference pricing policy for ACE inhibitors (administrative data, 1995-1998)	Longitudinal	Introduction of reference pricing to ACE inhibitors in 1997	Hospital admissions; ED visits; admissions to long-term care facilities; drug plan spending	Reference pricing for ACE inhibitors was not associated with cessation of treatment or changes in the rates of visits to physicians, hospitalizations, admissions to long-term care facilities, or mortality; net savings were estimated to be $6 million during the first 12 mo of reference pricing

Abbreviations: ACE, angiotensin-converting enzyme; BC, British Columbia; CCB, calcium channel blocker; DDD, defined daily dose; ED, emergency department; HMO, health maintenance organization; H_2 RA; histamine 2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; OOP, out-of-pocket; PPI, proton pump inhibitor.
[a] Unless otherwise specified, all study sites were in the United States.

eTable 4. Studies Examining the Associations of Prior Authorization and Formulary Restrictions With Drug Utilization and Spending and With Medical Utilization and Spending

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Studies That Examined Prescription Drug Utilization Only					
Abdelgawad et al,[79] 2006	Aggregated measures (at county level) for filled statin prescriptions paid by Medicaid in 6 states (retail pharmacy transaction records, Apr 200–May 2005)	Before-after with control group	Three state Medicaid programs implemented PDLs for statins in Feb-Apr 2004 while the other 3 states did not	No. of prescriptions filled	Imposing PDLs for statins was associated with reduced Medicaid prescription fills for statins
Carroll et al,[81] 2006	104 568 fee-for-service patients enrolled in Medicaid programs in 2 states, 2002-2003	Before-after with control group	Missouri initiated a prior authorization program for COX-2 inhibitors while the Medicaid program of a controlled state did not	Drug spending; No. of prescriptions filled	Initiating a prior authorization program for COX-2 inhibitors resulted in reduced use and expenditures for COX-2 inhibitors and reduced net expenditures for all pain and gastrointestinal-protective medications; these effects were greatest for patients at low risk of gastrointestinal complications
Dunn et al,[82] 2006	191 002 HMO enrollees (administrative claims data, 2004-2005)	Before-after with control group	Step therapy for generic antidepressants implemented in Jan 2005	Days of supply; drug spending	Requiring HMO members to use generic antidepressant as first-line therapy reduced spending on antidepressants by 9%; decrease of use of antidepressants was 1.5%, smaller than the 5% decrease in a comparison group
Kahan et al,[83] 2006	Prescriptions for cefuroxime during three 3-mo periods in 2001-2005 in a managed care organization in Israel	Before-after (no control group)	The managed care organization initiated prior authorization program for cefuroxime and later revoked the program	No. of prescriptions filled	Implementation of a prior authorization requirement significantly reduced proportion of cefuroxime among antibiotic prescriptions (from 8% to 1.2%); after the revocation of the program, proportion rose to 4.3%
Ridley et al,[84] 2006	13 517 Statin users covered by Medicaid programs in North Carolina and Alabama (retail pharmacy transaction records, 2001-2005)	Before-after with control group	Alabama Medicaid program implemented PDL for statins in 2004 while North Carolina Medicaid program did not	Discontinuation rate; drug switching	Implementation of PDL for statins was associated with higher nonadherence in statin users (odds ratio, 1.82); in addition, patients taking restricted statins and elderly patients were more likely to be nonadherent (odds ratios, 1.42 and 1.33, respectively)
Roughead et al,[85] 2006	Use of COX-2 inhibitors and nonselective NSAIDs in 35 state Medicaid programs (quarterly aggregated data from Centers for Medicare & Medicaid Services, 1996-2003)	Before-after with control group	Some state Medicaid programs implemented prior authorization programs for COX-2 inhibitors at different times (market entry or 2 y after market entry), while others did not implement such a program	DDD per 1000 population per d	States implementing prior authorization policy for COX-2 inhibitors at market entry had lowest use of uptake (10.9 DDD/1000 per d); states implementing policy > 2 y after market entry experienced 40% drop in use (23.0 to 13.9 DDD/1000 per d); states that never restricted access had the highest use, averaging 29.0 DDD/1000 per d
Spence et al,[86] 2006	1624 Elderly Kaiser Permanente patients who had a diagnosis of COPD and received at least 1 prescription for COPD-related medication in 2003 (survey data)	Cross-sectional	Cross-sectional variations in types of pharmacy benefit: generic-only, single co-payment tier, and 2 co-payment tiers	Adherence discontinuation rate	COPD patients with generic-only benefits were significantly more likely to report taking less than prescribed amount of medication (odds ratio, 1.70) and that they stopped taking ≥ 1 regular medications (odds ratio, 1.77)
Tseng et al,[87] 2006	611 Elderly Medicare managed care enrollees (survey data, 2002)	Before-after (no control group)	Enrollees in 1 state had $2000 capped brand name benefits in 2001 and generic-only drug coverage in 2002	Drug switching; discontinuation rate	Generic-only drug coverage decreased medication use and increased switching rates
West et al,[88] 2006	127 495 State employees (claims data, Dec 2002–May 2005)	Before-after (no control group)	Coverage of over-the-counter omeprazole and an increase in pharmacy reimbursement for omeprazole were implemented in March 2004	Days of supply; plan drug spending	Coverage of over-the-counter omeprazole and increase in pharmacy reimbursement for omeprazole resulted in 38% savings to plan despite 6% increase in PPI use

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eTable 4. Studies Examining the Associations of Prior Authorization and Formulary Restrictions With Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Cunningham et al,[89] 2005	3200 Medicaid enrollees (community tracking survey, 2000, 2001, 2003)	Repeated cross-sectional	Variations of Medicaid cost-containment strategies across states and over time	Initiation of drug therapy	Medicaid cost-containment strategies, including prior authorization, step therapy, generic mandates, co-payments, and spending limits, reduced probability of receiving a drug
Lichtenberg,[92] 2005	Medicaid and non-Medicaid prescriptions (pharmacy claims data, 2001, 2003)	Time series	Variations of Medicaid drug access restrictions (PDLs) across states, with non-Medicaid prescriptions as control group	Use of innovative drugs	Medicaid restrictions such as a PDL increased average age or "vintage" of prescribed drugs in 6 classes
Virabhak et al,[94] 2005	Prescriber-level and payer/prescriber-level data on prescriptions for 4 states (2002 and 2003)	Time series	Illinois and Louisiana implemented PDL in 2002-2003 while New York and Mississippi did not	Share of off-PDL drugs	Introduction of PDL was associated with 67.7% to 40.5% decrease for off-PDL Medicaid prescriptions and 6.8% to 8.6% decreases for off-PDL prescriptions in third-party insurance market for Illinois and Louisiana, respectively; for physicians whose practices were more than 50% Medicaid, average third-party shares of off-PDL products decreased by 37.5%
Wilson et al,[95] 2005	5798 Medicaid enrollees in 1 state (pharmacy claims data, 2000-2003)	Before-after with control group	Program implemented a PDL in June 2002	Discontinue rate; drug switching; medications added on	PDL increased discontinuation rates of antihypertensive medications (odds ratio, 1.39) vs 1 y earlier
Fischer et al,[97] 2004	NSAID prescriptions covered by 50 state Medicaid programs (aggregated data, 1999-2003)	Time series	22 States implemented prior authorization programs for selective COX-2 inhibitors during study period	Drug spending; proportion of coxib uses among NSAIDs	Prior authorization for selective COX-2 inhibitors reduced proportion of coxib NSAID doses by 15% and decreased cost per NSAID prescription by $10.28
Harris et al,[98] 2004	28 162 Arkansas state employees (administrative claims data, Jan 2004–Apr 2004)	Before-after (no control group)	Drug benefit change beginning March 2004: inclusion of over-the-counter omeprazole in drug coverage and increase in pharmacy reimbursement for omeprazole	Plan and out-of-pocket drug spending; drug switching	Coverage of over-the-counter omeprazole and increase in pharmacy reimbursement for omeprazole lowered average co-payment for a PPI by $4.20; total costs of PPI drugs were reduced by as much as 50%; over-the-counter omeprazole represented 60% of all PPI claims within 2 mo of change
Motheral et al,[100] 2004	20 000 Enrollees in an employer-sponsored drug plan and a comparison group with 1.9 million members who were commercially insured (claims and mailed survey, 2001-2003)	Before-after with control group	Intervention group implemented 3 step-therapy programs for PPIs, SSRIs, and NSAIDs in Sep 2002 vs random sample of members from commercial plans without step-therapy programs	Per-member, per-mo net cost; experience with step therapy	Step-therapy program covering 3 drug classes was associated with reduction in plan drug spending by $0.93 per member per mo; under this program, 30% of patients eceived a generic drug, 23% were granted a medical exception for the brand, 17% received no medication, and 16% paid full retail price
Campbell et al,[101] 2003	Elderly enrollees in Nova Scotia Seniors' Pharmacare Program (administrative data, 1999-2001)	Time series	Beginning Apr 2000, all but 2 combination topical corticosteroid products were removed from the covered list	No. of prescriptions filled; plan drug spending	Prescribing of topical corticosteroid combination products decreased after formulary restriction while prescribing of preferred potent topical corticosteroid increased during same period
Huskamp et al,[102] 2003	Veterans Health Administration aggregated monthly market share data for 6 drug classes, monthly Veterans' Integrated Service Network–level price data and aggregated spending data for each drug product in these classes (1995-1999)	Time series	Change of formulary status over time (closed, preferred, or open) for a certain drug	Market share; drug spending	Imposing a closed formulary on certain drug classes was effective at shifting prescribing behaviors toward selected drugs, achieving lower drug prices from manufacturers, and greatly decreasing drug spending

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eTable 4. Studies Examining the Associations of Prior Authorization and Formulary Restrictions With Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Wang et al,[103] 2003	PPI prescriptions in 3 states (claims data, 2000-2001)	Time series	Maine Medicaid drug program implemented restricted formulary for PPIs, with pantoprazole as the only preferred drug; New Hampshire and Vermont both had open formulary for Medicaid programs and served as controls	Pantoprazole's market share of all PPI prescriptions by mo	Restricting coverage of PPIs to pantoprazole was associated with 72% increase in pantoprazole share among Medicaid prescriptions; for each 10% increase in Medicaid share, pantoprazole's market share increased 1.8% among cash prescriptions and 1.4% among third-party payer prescriptions
Mccombs et al,[104] 2002	6409 Treatment periods for California Medi-cal recipients with a diagnosis of major depressive disorder (pharmacy claims data, Sep 1994–Jan 1999)	Before-after (no control group)	Program removed prior authorization restrictions for 2 SSRIs in May 1996	Therapy completion rate; drug switching	Removing prior authorization restrictions for 2 SSRIs was associated with reduction in likelihood of completed therapy without increasing in switching
Motheral,[106] 1999	5890 Government employees (pharmacy claims data, 1996-1998)	Before-after with control group	An employer plan implemented a closed formulary in July 1997 while another employer plan had no drug benefit change during study period	Initiation of drug therapy; No. of filled prescriptions; discontinuation rate; drug spending	A closed formulary was associated with slower growth in drug utilization and spending and lower rates of medication continuation with chronic conditions in 9 mo following implementation
Streja et al,[107] 1999	187 Enrollees of 2 HMOs who were newly prescribed SSRIs (administrative pharmacy data and chart review in physician office, 1996-1997)	Cross-sectional	82 Patients were in HMO with single preferred SSRI while 105 were in another HMO with 2 preferred SSRIs	Discontinuation rate	Patients with a single preferred SSRI (paroxetine) were 80% less likely to complete therapy than were patients with 2 preferred SSRIs (fluoxetine and paroxetine)
Phillips et al,[109] 1997	Iowa Medicaid drug prior authorization program (monthly prescription claims summaries, 1990-1992, 1995; program operation records during 2-wk period in 1995)	Before-after (no control group)	Prior authorization program initiated in 1992-1993	Operational performance of prior authorization; drug spending	82.9% of new and extension prior authorization requests were approved for coverage; total net savings (savings in drug spending minus prior authorization administrative costs) for 4 classes of drugs ranged from $2.51 million to $3.83 million
Jones et al,[111] 1996	NSAID prescriptions at 2 military medical centers (1992-1994), questionnaire to 203 clinicians	Before-after 21-mo trial with 1 study site and 2 control sites	Study site implemented NSAID prescribing protocol requiring a trial of either ibuprofen or indomethacin before new prescription of more expensive NSAID	Proportion of expensive NSAIDs prescribed; total NSAID costs; clinician acceptance	Quarterly use of expensive NSAIDs decreased from 34% to 21%, decreasing total NSAID costs by 30%, while one control site experienced 5% decrease and the other had 2% increase; surveyed clinicians reported few protocol-reported patient problems
Kotzan et al,[112] 1996	Medicaid and cash prescriptions in Georgia (pharmacy claims data, Jan–Mar 1994)	Cross-sectional	Program initiated prior authorization before 1994; privately paid prescriptions considered the control group	Market share of prior authorization products	Controlling for age and sex, odds ratio of privately paid patients getting a prior authorization prescription was 2.26 relative to Medicaid patients
Kreling et al,[118] 1989	Prescriptions for internal analgesic products dispensed to Medicaid recipients during Apr-June 1984 and Apr-June 1985 (Pharmacy claims data, 1984-1985)	Before-after (no control group)	Beginning Feb 1985, Wisconsin Medicaid drug program no longer covered propoxyphene napsylate	Drug spending	Removing propoxyphene napsylate from covered drug list was not associated with decreased expenditures for internal analgesic drugs, measured either by overall expenditures or per recipient expenditures
Studies That Also Examined Medical Utilization and Spending					
Ackman et al,[80] 2006	112 Elderly patients who received a coronary stent between Sep 2001–Aug 2002 at 1 hospital and who were eligible for Alberta Blue Cross coverage in Canada	Before-after (no control group)	A prior authorization process for patients prescribed clopidogrel following stent insertion was changed to an authorized prescriber list process in Mar 2002	Initiation of drug therapy; medical utilization	Patients in the prior authorization period were less likely to have prescriptions filled on day of charge (31% vs 54%), and median time to fill was longer (4 vs 0 d); fill rate after 28 d postdischarge was not significantly different between 2 periods; 2 repeated revascularization procedures were necessary within 6 wk after stent placement, both in prior authorization patients who delayed or failed to fill prescription

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eTable 4. Studies Examining the Associations of Prior Authorization and Formulary Restrictions With Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Delate et al,[90] 2005	> 1.2 Million Medicaid enrollees (pharmacy and medical claims data, 2001-2003)	Time series	Medicaid program required prior authorization to be obtained for all PPI prescriptions beginning Feb 2002	Plan drug spending; drug switching; plan medical spending	In month immediately following implementation of prior authorization for PPIs, Medicaid spending for PPIs reduced by 91% while spending for histamine 2 receptor antagonists increased by 223%; enrollees who received histamine 2 receptor antagonists or no antisecretory drugs were no more likely to have incurred greater total medical care expenditures than those who received a PPI during year following the 6-mo postpolicy period
Gleason et al,[91] 2005	737 COX-2 inhibitor users continuously enrolled in employer-sponsored health insurance plan (pharmacy and medical claims data, 2002-2003)	Before-after (no control group)	Prior authorization program for COX-2 inhibitors implemented Jan 2003 (study period included 3 mo before and 12 mo after policy change)	Initiation of drug therapy; drug spending; medical spending	For patients denied coverage for COX-2 inhibitors after implementation of prior authorization program, pharmacy costs declined without increase in gastrointestinal-related medical costs
Murawski et al,[93] 2005	3250 Medicaid and 3788 non-Medicaid cardiovascular patients in 1 state (pharmacy and medical claims data, 2001-2003)	Before-after with control group	Program implemented PDL in June 2002	Hospital visits; physician visits	PDL program was associated with increased outpatient hospital visits and physician visits among cardiovascular patients during first 6 mo after implementation but such an increase became insignificant during second 6 mo after implementation
Christian-Herman et al,[96] 2004	957 500 Medicare HMO enrollees (administrative data, 2001-2002)	Before-after with control group	In 2002, some enrollees had drug benefit changed to generic-only coverage while other enrollees in same HMO continued to have same drug benefits as in 2001	No. of filled prescriptions; switching rate; adherence/ medication possession ratio; hospitalizations; drug spending; plan and out-of pocket drug spending	Generic-only drug coverage was associated with lower health plan pharmacy costs, increased hospitalizations, and lower quality measures for some conditions
Hartung et al,[99] 2004	Monthly aggregated claims data for a Medicaid managed care organization (pharmacy and medical claims data, 1999-2000)	Time series	Implementation of a prior authorization program for celecoxib during 22-mo study period	Days of supply; hospitalizations; ED visits; ambulatory visits	After implementation of prior authorization policy for celecoxib, use of celecoxib immediately reduced by 50% and monthly rate of increase was also reduced; no important changes in use of other related drug classes detected; no significant changes in medical service utilizations found
Cromwell et al,[105] 1999	Quarterly summary from Medicaid drug claims and eligibility data (1989-1993), acute care hospital discharge abstract data (1989-1993)	Before-after (no control group)	Beginning Aug 1991, Florida Medicaid program initiated a policy restricting reimbursement for antiulcer medicines	No. of prescriptions reimbursed; peptic-related hospitalizations	Restricting Medicaid reimbursement for antiulcer drugs was associated with 33% reduction in quarterly number of prescriptions reimbursed; no associated increase occurred in the rate of Medicaid peptic-related hospitalizations
Horn et al,[108] 1998	12 997 HMO enrollees (data collected in a clinical practice improvement study in 1992)	Cross-sectional	Variations of formulary restrictions across 6 HMOs	No. of filled prescriptions; hospitalizations, ED visits; ambulatory services	Formulary restrictions were associated with higher rates of ED visits and hospital admissions for most conditions
White et al,[110] 1997	Use of antimicrobials in urban county teaching hospital in July-December 1993 and 1994 (administrative data)	Before-after (no control group)	In Jan 1994, hospital implemented prior authorization program for selected parenteral antimicrobial agents	Drug spending; susceptibilities to antibiotics	Implementing prior authorization program for selected antimicrobials reduced total parenteral antimicrobial expenditures by 32% and improved susceptibilities to antibiotics without compromising patient outcomes or length of hospital stay

(continued)

eTable 4. Studies Examining the Associations of Prior Authorization and Formulary Restrictions With Drug Utilization and Spending and With Medical Utilization and Spending (cont)

Source	Study Sample[a]	Study Design	Drug Benefit Variation	Outcomes	Key Findings
Smalley et al,[113] 1995	495 821 Tennessee Medicaid recipients (pharmacy and medical claims data, 1988-1991)	Before-after (no control group)	Program required prior authorization for NSAIDs beginning Oct 1989	No. of prescriptions filled; drug switching; plan drug and medical spending	Prior authorization requirement for NSAIDs associated with 53% decrease in Medicaid expenditures for NSAIDs; reduction resulted from increased use of generic NSAIDs (generic rate increased from 43% to 79%), as well as from 19% decrease in overall NSAID use; no concomitant increase in Medicaid expenditure for other medical use
Kotzan et al,[114] 1993a	80 064 Georgia Medicaid NSAID patients from Jan 1989 to July 1990 (pharmacy and medical claims data, 1989-1990)	Time series	Prior authorization program initiated for single-source NSAIDs beginning Jan 1990	Drug spending; physician visits; medical spending	Total costs for NSAID therapy decreased by more than $3 million during first 7 mo of prior authorization for NSAIDs; no additional medical or physician costs observed in 7 mo of the program
Kotzan et al,[115] 1993b	39 604 Continuously eligible Georgia Medicaid H_2 receptor antagonist recipients (pharmacy and medical claims data, 1989-1990)	Time series	Program imposed maintenance dose program for 4 single-source H_2 receptor antagonist products beginning Jan 1990	Physician visits; inpatient and outpatient claims; gastrointestinal endoscopic procedure claims	Total costs for H_2 receptor antagonists reduced by $1.4 million during first 7 mo of program; no significant change in medical utilizations observed
Moore et al,[116] 1993	47 State Medicaid programs (summary statistics from National Pharmaceutical Council, 1985-1989)	Cross-sectional	20 State Medicaid programs initiated restricted formulary before 1985 while the others had open formulary	Plan drug spending; plan medical and drug spending	Restricted formulary associated with lower per capita drug spending but not associated with lower total Medicaid spending
Kozma et al,[117] 1990	12 139 Prescription drug users continuously enrolled in South Carolina Medicaid program for 2 y (data source unknown, 1983-1986)	Longitudinal	On Oct 1984, drug program changed from restrictive to nonrestrictive drug formulary	No. of drug claims; physician visits; outpatient visits; hospitalizations	Changing a restrictive drug formulary to an open formulary associated with increased number of drug claims, physician visits, and outpatient visits and reduced number of hospitalizations
Bloom et al,[119] 1985	Patients with peptic ulcer disease in West Virginia Medicaid program (pharmacy and medical claims data, 1981-1983)	Before-after (no control group)	Beginning March 1982, closed drug formulary imposed	Plan drug spending; physician payments; hospital inpatient costs	Introduction of a closed formulary was associated with 79% decrease in drug costs, 3.1% increase in physician payments, and 23% increase in hospital costs

Abbreviations: COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase 2; DDD, defined daily doses; ED, emergency department; HMO, health maintenance organization; NSAID, nonsteroidal anti-inflammatory drug; PDL, preferred drug list; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Unless otherwise specified, all study sites were in the United States.