A Systematic Review of Reference Pricing: Implications for US Prescription Drug Spending

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Rising expenditures for prescription drugs are a major problem for public and private payers in many countries. In the United States, prescription sales reached $300.3 billion in 2009, a 5.3% increase from the previous year.[1] Pharmaceutical cost-control measures frequently involve increasing patient cost-sharing, for example through tiered formularies.[2] While these approaches effectively reduce drug spending for payers, they can also cause patients to reduce their use of essential medications; this may have adverse clinical consequences which can increase rather than decrease total healthcare expenditure.[3-6]

In other countries, "reference pricing" has been used as a cost-containment instrument that appears not to have the undesirable effects of other pharmacy benefit designs.[7] This policy strategy sets a standard price or reimbursement level for a group of therapeutically interchangeable drugs, often based on the price of the lowest cost member in the class. Manufacturers of other products may price their products above or below this level and patients are responsible for any costs above the reference price. In the American context, the policy is sometimes described as a "maximum allowable cost (MAC) program."[8]

Reference drug pricing has been advocated as a policy solution in the United States.[9] For example, Pearson and Bach have proposed that reference pricing be used by Medicare, with coverage and reimbursement decisions informed by comparative effectiveness research.[10] Even though domestic experience with reference pricing has been extremely limited, its widespread international adoption, beginning in Germany in 1989, followed by the Netherlands in 1991 and New Zealand in 1993 and more than half a dozen countries since, provides an evidence base on which to estimate its potential role in the United States.[11,12] Accordingly, we systematically reviewed the scientific literature to understand the effects of reference pricing on medication use, payer and patient spending, and resource consumption.

Given rising pharmaceutical expenditures and the widespread use of reference pricing as a cost-containment instrument abroad, we systematically reviewed the evidence evaluating reference pricing policies. We performed a structured electronic search of peer-reviewed journals for studies published before that reported on the effects of reference pricing policies on medication use, payer and patient spending, and resource consumption. Our search yielded 16 studies describing 9 reference-pricing policies from 6 countries. Reference-pricing policies led to decreases in drug prices and increases in utilization of targeted medications, while also reducing payer and patient expenditures. In addition, these policies did not lead to increased use of medical services, such as physician office visits and hospitalization. These results suggest that reference pricing may be an attractive policy strategy for the US healthcare system.

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For author information and disclosures, see end of text.

METHODS

We performed a structured electronic search of peer-reviewed journals using PubMed, EconLit, Embase, Business Source Complete, and the National Bureau of Economic Research for studies published before May 2012 that reported on the effects of reference drug pricing policies on medication

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Take-Away Points

- Reference pricing has been widely used in other countries as a cost-containment instrument.
- Reference pricing policies lead to decreases in drug prices, as well as payer and patient expenditures.
- Reference pricing policies do not lead to increased use of medical services.
- Reference pricing may be an attractive policy strategy for the US healthcare system.

use, payer and patient spending, and resource consumption.

Our electronic search strategy included medical subject headings and keywords related to pharmaceuticals (eg, "economics, pharmaceutical," "drug utilization," or "fees, pharmaceutical"), healthcare policy (eg "health government policy regulation," "health policies"), and policy analysis (eg "health economics," "cost and cost analysis"), in addition to those specifically related to reference pricing by name ("reference pricing," "reference price," "reference drug pricing"). Search terms were adjusted for each database while maintaining a common overall architecture.

Using predefined inclusion and exclusion criteria, abstracts were evaluated to identify potentially relevant articles. We retrieved the published version of all candidate articles and reviewed their reference lists to identify additional relevant studies. The review was limited to papers that evaluated the introduction of reference price policies on either specific or all drug classes within a health system, leaving out studies that evaluated incremental policy changes on reference pricing. In addition, we excluded studies that (1) did not evaluate the effects of a reference pricing policy on drugs, (2) did not present original data, or (3) did not assess our outcomes of interest.

Data on study populations and characteristics, results, and study quality were extracted from each article using a standardized protocol and reporting form. Specific information collected included study and analysis design (ie, cohort, cross-sectional, randomized control trial), policy design (ie, targeted medications, how the price is set), patient sample (ie national, provincial, private), drug classes, implementation date, and outcomes. Outcomes and study results were categorized into 3 groups: (1) drug prices, (2) utilization, switching, and adherence, and (3) expenditures and resource consumption. When not explicitly presented, we calculated percent change in expenditure and/or per capita savings based on the published findings.

Study quality was assessed with the Agency for Healthcare Research and Quality (AHRQ)[13] tool for rating observational cohort studies. A study quality score from each study was calculated as a proportion of total points that each paper received. The studies were scored with a maximum of 9 points, 1 for each study domain evaluated, and judged on the presence of key study elements such as study question, comparability of subjects, and outcome measurement.

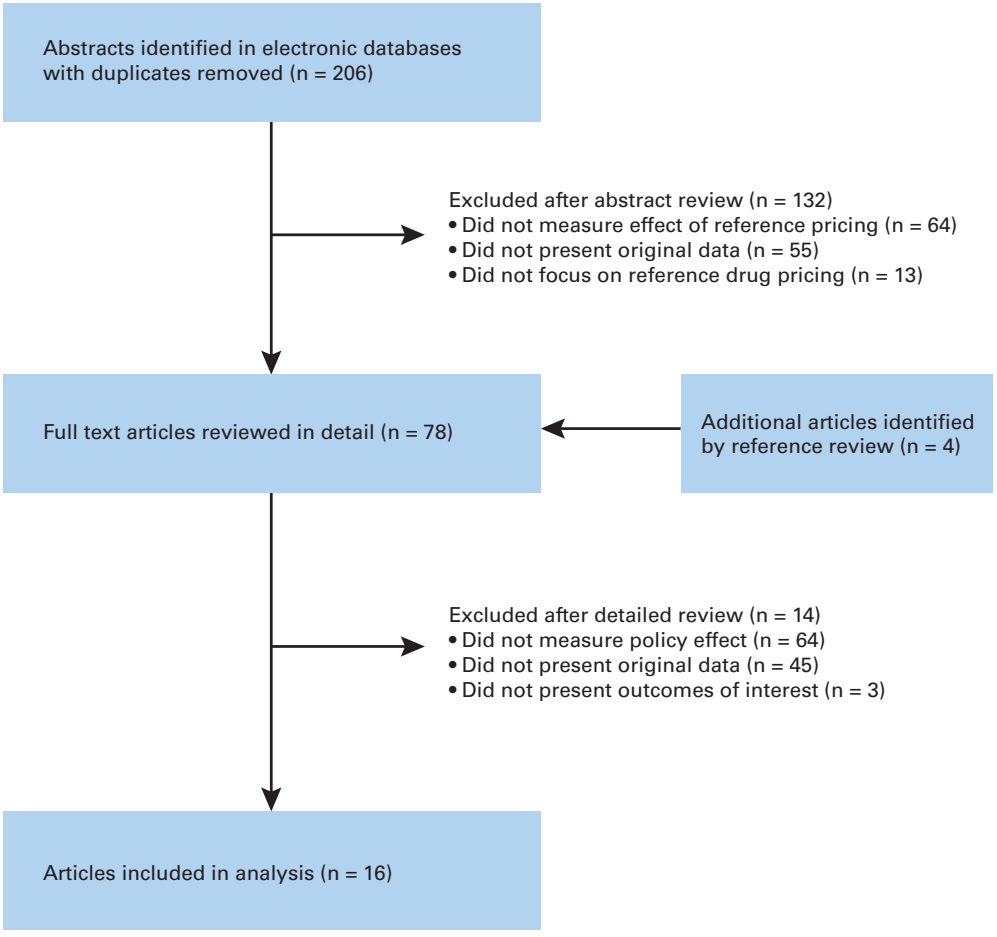
RESULTS

Our search yielded 16 studies describing 9 reference-pricing policies from 6 countries (**Figure 1**).[8,9,14-28] All the studies were published in the last decade. Of the policies examined, 1 was applied regionally in British Columbia, Canada, 2 were applied in private, employer-sponsored health plans (1 in Canada and 1 in the United States), and the remaining policies were implemented on a national level in Germany, Norway, and Spain (**Table 1**). The 9 policies encompassed 2 types of reference pricing, "generic reference pricing" and "therapeutic reference pricing." Four of the 9 policies (evaluated by 5 out of 16 studies) pertained to generic reference pricing and the other 5 (11 out of 16 studies) pertained to therapeutic reference pricing. Generic reference pricing (or "maximum allowable cost") involves only off-patent drugs within a certain therapeutic class while therapeutic reference pricing (or "therapeutic maximum allowable cost") pertains to all eligible products, on- and off-patent, within a therapeutic class.

In Germany, a committee of healthcare providers and sickness funds, with input from manufacturers, decides how drugs are to be grouped and sets the reference prices. The reference prices were always below the price of the highest cost product in the group and above the lowest third of the market price.[14] Norway and Spain follow similar practices and manufacturers may adjust their product prices in response. Norway's national referencing pricing policies have since been repealed because savings in expenditures were not as great as expected.[15] Regulators in British Columbia, Canada, select specific products to be reference drugs rather than set a reference price. An independent advisory committee decides which therapeutic group of products will be subject to the program as well as the products that will not face any cost sharing under reference pricing.[18] In Canada, the reference price program for nonsteroidal anti-inflammatory drugs (NSAIDs) was introduced 18 months after a generic substitution policy was put in place for the same class.[17] In Spain, several other cost-containment policies were implemented around the time of the introduction of the reference pricing system in 2000, including markup adjustments of the margins obtained by manufacturers, wholesalers, and pharmacies in 1999 and 2000 and the compulsory reduction of ex-factory prices in 1999 and 2000.[28] No other policies had these concurrent changes.

The studies were generally of good methodological quality, with scores ranging from 56% to 100% on the AHRQ scale

Figure 1. Study Selection Flow Diagram



(mean of 82%). While the majority of studies focused on 1 or 2 classes of drugs, others focused on a wider range of unrelated classes. Most of the studies on the British Columbia policy, for example, focused on individual classes of cardiovascular medication (eg, angiotensin-converting enzyme [ACE] inhibitors, nitrates, calcium channel blockers) while the study by Brekke et al on Norway's policy targeted antidepressants, antiulcerants, antihistamines, ACE inhibitors, and statins.[15] Target classes were not specified by Augurzky et al, while Puig-Junoy examined the effects of reference pricing on 4 top-selling representative products rather than specific drug classes.[14,21]

Drug Prices

Four of the 9 reference price policies were associated with significant reductions in the price of the targeted drug classes, with a mean reduction of 11.5% (range 7%-24%) (Figure 2). In Spain, prices fell for the highest priced products of 3 out of the 4 targeted classes, but there was no change in the price of omeprazole.[21] In British Columbia, Canada, the price of calcium channel blockers fell by $0.80 per median monthly dose (standard deviation: $0.60), but this change was not statistically significant, likely because drug prices are set at a national level in Canada and thus manufacturers cannot easily adjust the price of products in response to the introduction of a regionally applied reference pricing policy.[24]

Utilization and Switching

The reference pricing policies had varying effects on utilization of the targeted drug classes (Table 2). Grootendorst found a 101% increase in the use of unrestricted (referent) NSAIDs associated with the reference pricing policy introduced in British Columbia in 1997.[17] Pavnick also observed an increase in the use of anti-ulcerants after Germany began its policy in 1989, but the 6.4% (standard error 16.2%) change was not statistically significant.[19]

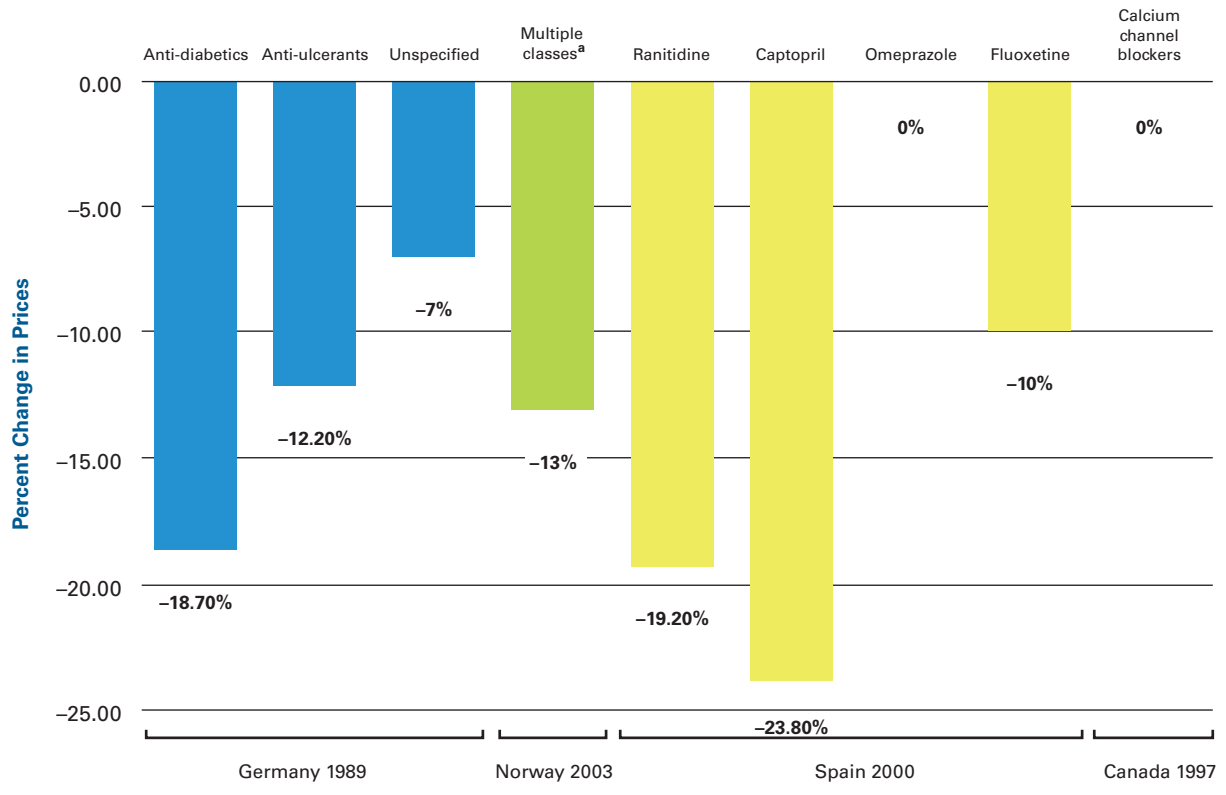
In several evaluations, results were presented separately for those agents for which prices fell in response to reference pricing. Mabasa and Ma observed a 12% decrease in the use of proton pump inhibitors as a class; the use of the referent drug, rabeprazole, increased by 21%.[8] Likewise, Schneeweiss

Table 1. Description of Reference Pricing Policies

Jurisdiction and Policy Year	Reference Pricing Mechanism	Reference Pricing Type	Patients	Drug Class	Author (Year)	Outcomes Evaluated	Quality Score
British Columbia, Canada 1995	Lowest priced brand-name agent in targeted drug class	Therapeutic	All residents 65 years and older	Nitrates	Grootendorst (2002)	Payer expenditures	100%
				H_2 receptor antagonists	Hazlet (2002)	Physician visits, hospitalizations	100%
British Columbia, Canada 1997	Lowest priced brand-name agent in targeted drug class	Therapeutic	All residents 65 years and older	ACE inhibitors and calcium channel blockers	Grootendorst (2002)	Payer expenditures	100%
				NSAIDs	Grootendorst (2004)[a]	Payer expenditures	67%
				NSAIDs	Grootendorst (2005)	Payer expenditures	78%
				ACE inhibitors	Schneeweiss (2002)	Utilization	89%
				ACE inhibitors	Schneeweiss (2002)	Physician visits, hospitalizations	100%
				Calcium channel blockers	Schneeweiss (2003)	Switching, patient expenditures, physician visits	100%
				ACE inhibitors	Schneeweiss (2004)	Prices, switching	89%
Employer-sponsored drug plan, Canada 2003	Price of rabeprazole	Therapeutic	Employees, spouses, independents	Proton pump inhibitors	Mabasa (2006)	Utilization, patient expenditures	89%
Germany 1989[b]	Fixed priced below the price of the most expensive brand product and above the price of generics	Generic	All residents	Antidiabetics	Pavcnik (2000)	Prices	67%
				All	Augurzky (2009)	Prices	67%
Germany 1992	Fixed priced below the price of the most expensive brand product and above the price of generics	Generic	All residents	Antiulcerants	Pavcnik (2000)	Prices	67%
Germany 2005	Fixed priced below the price of the most expensive brand product and above the price of generics	Therapeutic	All residents	Statins	Stargardt (2010)	Utilization, patient expenditures, payer expenditures	100%
Norway 2003	Price of select drugs representing high volume of sales	Generic	All residents	Antidepressants, antiulcerants, antihistamines, ACE inhibitor, statins	Brekke (2007)	Prices, payer expenditures	56%
Spain 2000	Average of the lowest priced products that account for at least 20% of sales[c]	Generic	All residents	Ranitidine, captopril, omeprazole, fluoxetine[d]	Puig-Junoy (2004)	Prices	67%
				Statins	Puig-Junoy (2007)	Utilization	67%
Employer-sponsored drug plan, US 2005	$0.90/unit (price of least expensive product)	Therapeutic	Employees, spouses, independents	Proton pump inhibitors	Johnson (2011)	Payer expenditures	78%

ACE indicates angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug.
[a]Generic substitution was implemented concurrent with reference pricing.
[b]The policy was introduced over several years as drug classes were added and the policies expanded from applying only to bioequivalent products with the same active ingredient to drugs within the same therapeutic class.
[c]Additionally, if the difference in price between the highest price in the group and the reference price was less than 15%, the reference price was the result of applying a 10% reduction to the highest price. If the difference was more than 50%, the reference price was recalculated as exactly 50% of the highest priced product.
[d]While the policy applied to 114 homogeneous groups, the analysis concentrated on 4 top-selling active ingredients under the reference price system.

Figure 2. Impact of Reference Pricing on Utilization



[a]Antidepressants, antiulcerants, antihistamines, angiotensin-converting enzyme inhibitors, statins.

et al observed a 60% increase in the use of calcium channel blockers whose prices were affected (P <.0001), but saw no changes in utilization of other antihypertensive medications.[24] Puig-Junoy found a decrease of 1% to 12% in the use of drugs whose prices fell after the change to reference pricing, perhaps because the Spanish reference pricing system evaluated was introduced in conjunction with a number of other policies aimed at decreasing overall drug utilization.[29]

The policies led to an increase in switching from more expensive drugs to those that fell in price because of reference pricing and a decrease in switching away from referent drugs to more expensive drugs. For example, Schneeweiss et al observed that 9% of patients switched from a cost-sharing calcium channel blocker to one with a price that fell below the reference price.[24] Stargardt et al observed that 49% of patients on atorvastatin, which was above the reference price, switched to another statin following policy implementation, while only 4% of patients on statins at or below the price switched to another statin. The policies were also associated with significant improvements in medication adherence.[24-26] Stargardt reported nonadherence to be significantly lower for patients treated with statins at the reference price compared with atorvastatin, which was above the reference price (31.1 vs 39.0%, P <.001).[26]

Expenditures and Resource Consumption

Reference price policies significantly decreased both patient and payer expenditures (Table 3). Three studies that evaluated changes in patient expenditures found out-of-pocket savings ranging from 12% to 18% per month. The 4 studies that reported the impact of reference pricing on payer expenditures found reductions of 14% to 52% on targeted drug classes. These correspond to per capita savings of $81 to $650.[26]

Although the policies reduced payer spending, the 3 studies that evaluated the effects of reference pricing on hospitalizations and physician visits found no significant changes in these outcomes. While Schneeweiss et al found a temporary 11% (95% confidence interval [CI] 1.07-1.15) increase in physician visits shortly after British Columbia's ACE inhibitor policy went into effect, perhaps as a result of patients visiting their physicians to switch to reference products, 3 to 10 months after the policy, there were no significant changes in physician visits compared with baseline, –3% (95% CI 0.86-0.91).[22] The analysis by Schneeweiss et al of a reference pricing program for calcium channel blockers also revealed non-significant changes in physician visits and hospitalizations shortly after the implementation of the policy (95% CI

Table 2. Impact of Reference Pricing on Utilization

Policy	Author (Year)	Drugs Class	Overall Affected Drug Class	Effect for Drugs That Fell in Price Because of Reference Pricing
British Columbia, Canada 1997	Grootendorst (2004)	NSAIDs	101%[a]	
	Schneeweiss (2002)			24%[a]
	Schneeweiss (2003)	Calcium channel blockers	0%	60%[a]
Canada 2003	Mabasa (2006)	Proton pump inhibitors	–12%[a]	21%[a]
Germany 1989	Pavcnik (2000)	Anti-ulcerants	Non-significant	
		Anti-diabetics	Non-significant	
Spain 2000	Puig-Junoy (2007)	Statins		–12% to –1%[a]
Spain 2004	Moreno-Torres (2011)	Unspecified		

NSAID indicates non-steroidal anti-inflammatory drug.
[a]Statistically significant.

1.00-1.03 and 0.89-1.06), followed by significant decreases (4% and 15% respectively, 95% CI 0.95-0.98 and 0.79-0.93) at 3 to 10 months after implementation. The evaluation by Hazlet and Blough of British Columbia's H2 antagonist policy found very similar results.[18,24,25]

Only 1 study directly evaluated the impact of reference pricing on clinical end points, and found non-significant differences in cardiovascular death rates between users exposed to reference pricing for ACE inhibitors, calcium channel blockers, and nitrates and those who were not ($P = .11$).[16]

DISCUSSION

Our meta-analysis of 16 studies evaluating the impact of 9 reference pricing policies suggests that this strategy reduced drug prices, increased utilization of and adherence to targeted drugs, and promoted switching behavior from expensive products to alternatives at or below the reference price. These outcomes were associated with significant reductions in both patient out-of-pocket and total payer expenditures. Although the rate of physician visits increased for a short period after policy implementation, reductions in visits and hospitalizations over a longer time period were not consistently observed. Thus, the policies appeared to achieve cost savings without negative effects on resource consumption. Furthermore, Moreno-Torres's study on the incremental effects of reference pricing in Spain suggests that while generic reference pricing reduced payer costs, by including brand name products of the same active ingredient in reference pricing policies, per capita pharmaceutical costs also decreased, benefiting insurers and consumers (4.06€ per capita savings, a 1.54% saving).[28]

Reference pricing appears to have effects different from many other strategies to contain prescription drug spending. While prescription cap limits protect payers from excessive cost, the limits cannot distinguish between medically necessary and unnecessary drug use and may prevent patients from purchasing drugs that they need. Among frail, low-income, elderly patients, these caps lead to increased risk of institutionalization.[30] Therapeutic interchange is a widely used procedure that allows pharmacists to substitute a brand name product for a generic product from the same therapeutic class of drugs. Savings in payer expenditures have been observed in settings in which therapeutic interchange has been implemented, especially within the Veterans Affairs population.[31-34] However, the success of therapeutic interchange depends on the active cooperation of physicians, consumers, and pharmacies. As such, some US plans have found that therapeutic interchange has not been as effective as hoped, especially in influencing physicians.[35] Virtually all publicly and privately insured individuals in the United States receive coverage through plans that include tiered formularies,[36] which create incentives for patients to use generic medications or lower-cost brand-name drugs for which discounts have been negotiated.[37] Their introduction has been shown to result in lower spending on drugs by payers but to increase spending for patients and to lead to gaps in use in some cases.[38,39]

Implementation of reference pricing in the United States could potentially occur in several different ways. For example, in line with current interest in comparative effectiveness, Pearson and Bach call for Medicare to use reference pricing to set coverage and reimbursement standards.[10] Under this paradigm, a reference price would be set for new products of comparable clinical effectiveness. Although the Affordable Care Act legislation prohibits the use of comparative effectiveness in coverage decisions, the law does appear to allow for research findings to be used for setting reimbursement rates as part of a larger, "iterative and transparent process which includes public comment and considers the effect on subpopu-

Table 3. Impact of Reference Pricing on Expenditures and Resource Consumption

Policy	Author (Year)	Drugs Class	Time Frame[a]	Percent Change	Absolute Change
Monthly Patient Expenditure					
Canada 1997	Schneeweiss (2003)	Calcium channel blockers		–12%	–$6
Canada 2003	Mabasa (2006)	Proton pump inhibitors		–12%	–$8
Germany 2005	Stargardt (2010)	Statins		–18%	–€49
US 2005	Johnson (2011)	Proton pump inhibitors		–7%	–$2
Changes in Annual Payer Expenditure					
Canada 1995	Grootendorst (2002)	Nitrates		–52%	–$3.8 million[b]
Canada 1997	Grootendorst (2002)	ACE inhibitors			–$84,000
		Calcium channel blockers			–$4.09 million[b]
	Grootendorst (2004)	NSAIDs		–44%	–$4 million[b]
Norway 2003	Brekke (2007)	Multiple classes[c]		–14%	–$75 million NOK
Germany 2005	Stargardt (2010)	Statins			–€94.4 –108.7 million
US 2005	Johnson (2011)	Proton pump inhibitors	at 1 year		–$2.5 million
			at 2 years		–$2 million
			at 3 years		–$1.6 million
Physician Visits					
Canada 1995	Hazlet (2002)	H_2 receptor antagonists	at 6 months	–2%[b]	
			at 1 year	1% (not significant)	
Canada 1997	Schneeweiss (2002)	ACE inhibitor	at 1 month before index date	1% (not significant)	
			at 1-2 months	11%[b]	
			at 3-10 months	3% (not significant)	
	Schneeweiss (2003)	Calcium channel blockers	at 1 month before index date	–1% (not significant)	
			at 1-2 months	2% (not significant)	
			at 3-10 months	–4%[b]	
Hospitalization					
Canada 1995	Hazlet (2002)	H_2 receptor antagonists	at 6 months	4% (not significant)	
			at 1 year	5% (not significant)	
	Schneeweiss (2002)	ACE inhibitor	at 1 month before index date	17% (not significant)	
			at 1-2 months	5% (not significant)	
			at 3-10 months	–10% (not significant)	
	Schneeweiss (2003)	Calcium channel blockers	at 1 month before index date	5% (not significant)	
			at 1-2 months	–3% (not significant)	
			at 3-10 months	–15%[b]	

ACE indicates angiotensin-converting enzyme; NOK, Norwegian Krone; NSAID, non-steroidal anti-inflammatory drug.
[a]At 1 year, unless otherwise specified.
[b]Statistically significant.
[c]Antidepressants, antiulcerants, antihistamines, ACE inhibitors, statins.

lations."[10] As the German and Spanish experiences suggest, this could be done through an incremental approach, first implementing reference pricing for only a few classes of drugs, such as statins and proton pump inhibitors, before scaling up to include more classes.[14,28]

Alternatively, reference pricing could be embedded in tiered formularies. For example, in contrast to placing all generic products in the lowest tier of incentive formularies as is currently practiced, 1 generic product in each therapeutic class could be set as the referent drug and the prices of other generics set according to this. For brand name products, reference pricing could be used to set the same price for multiple products in the same therapeutic class. Currently, preferred prices are set through negotiations between pharmacy benefit

management and manufacturers and only 1 brand name product in each class has preferred status. By setting a fixed level of reimbursement, more than 1 product may effectively obtain preferred status, making the prices more competitive and increasing the transparency of the price negotiation and setting process. On the other hand, this process may eliminate incentives for manufacturers to provide pharmacy benefit managers with discounts in exchange for preferred formulary status, and thus the application of reference pricing to brand-name products may have unclear implications for pricing.

Of course, these mechanisms of introducing reference pricing in the US healthcare system add complexity to patient benefit plans, which may also undermine the benefits that the policy strategy offers. It is reassuring that the introduction of reference drug pricing in other settings did not adversely affect patient health and utilization results.

Ultimately, implementation of reference pricing could be consistent with current efforts in the United States to increase healthcare value.[40] For example, while value-based insurance designs have generally lowered cost-sharing for high-value services, there is much interest from the payer community in developing methods for more cost-sharing for low-value services.[41] By setting a reference price for all therapeutically equivalent interventions, this strategy creates incentives for patients to reduce their use of those specific services that are the most costly, and therefore have the least value.

The scope of reference pricing may be much broader than prescription drugs and may, in fact, more easily apply to other healthcare services. For example, payers may set a reference price, or fixed level of reimbursement, for colonoscopy based on the assumption that when performed by different providers for the same indication this procedure should have equal diagnostic performance.

Our study is constrained by the short time frame of many of the studies and the relatively limited data on the clinical effects of the policies. Further, the studies differ in many important ways, including sample size, basic methodology, and the outcomes measured. Each country implemented its reference pricing policy on the baseline of a different healthcare system, and generalizability to any specific country is challenging. As a result, we were unable to pool data across studies in order to generate summary measures of the impact of reference pricing. Further, given the lack of comparative effectiveness data on different cost-containment policies, it was difficult to compare the policies and decide the incremental value of adding one cost-containment policy to another. Another limitation is that the outcomes of these reference drug policies may be specific to, and dependent on, the target drug class. Thus, good outcomes in one reference drug price class may not translate into good outcomes in another.

Nevertheless, our review identified a substantial peer-reviewed literature on this policy strategy that provides an empirical base from which to make policy decisions. Based on this, reference drug pricing appears to be an effective tool for controlling pharmaceutical expenditures for private and public payers. Unlike other cost-control mechanisms, reference pricing reduces expenditures without negatively affecting medication use or resource consumption. As such, reference pricing could be a useful policy for wider adoption in the United States.

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