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Estimation of Potential Savings Through Therapeutic Substitution

Michael E. Johansen, MD, MS; Caroline Richardson, MD

IMPORTANCE Therapeutic substitution offers potential to decrease pharmaceutical expenditures and potentially improve the efficiency of the health care system.

OBJECTIVE To estimate potential savings through therapeutic substitution in terms of both overall and out-of-pocket expenditures of branded drugs when a generic in the same class with the same indication was available.

DESIGN, SETTING, AND PARTICIPANTS Repeated cross-sectional study using the 107 132 individuals included in the nationally representative Medical Expenditure Panel Survey (2010-2012) along with their reported prescribed medicine use. The Orange Book, company financial statements, US Food and Drug Administration records, and published research were used for adjunctive information.

MAIN OUTCOMES AND MEASURES Estimated excess expenditure due to branded drug overuse when a lower-cost generic in the same class with the same indication was available.

RESULTS The study included 107 132 individuals between 2010 and 2012, of whom 62.1% (95% CI, 61.4%-62.8%) reported use of any prescribed medicine. A total of 31.5% (95% CI, 30.7%-32.2%) used a medication from an included drug class, whereas 16.6% (95% CI, 16.0%-17.1%) of the population used a branded drug from the included classes compared with 24.0% (95% CI, 23.4%-24.7%) who used a generic and 9.1% (95% CI, 8.7%-9.4%) who used both. In the included drug classes, the majority of the drugs were generics, with a total of 93.5 billion standardized doses compared with 47.4 billion standardized doses of branded drugs. Total expenditure of the branded drugs accounted for $147 (95% CI, $137-$156) billion compared with $62.7 (95% CI, $58.9-$66.5) billion for the generics. Between 2010 and 2012, an estimated $73.0 (95% CI, $67.6-$78.5) billion in total excess expenditure and $24.6 (95% CI, $22.6-$26.5) billion in out-of-pocket excess expenditure was attributable to branded drug overuse. The excess was present across numerous drug classes throughout many aspects of medicine and equates to 9.6% of total and 14.1% of out-of-pocket prescribed medicine expenses. The drug classes with the highest excess expenditure included statins ($10.9 [SE, $0.41] billion), atypical antipsychotics ($9.99 [SE, $1.03] billion), proton pump inhibitors ($6.12 [SE, $0.38] billion), selective serotonin reuptake inhibitors ($6.08 [SE, $0.49] billion), and angiotensin receptor blockers ($5.53 [SE, $0.35] billion).

CONCLUSIONS AND RELEVANCE Although therapeutic substitution is controversial, it offers a potential mechanism to significantly decrease drug costs if it can be implemented in a way that does not negatively affect quality of care.

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Author Affiliations: Department of Family Medicine, College of Medicine, Ohio State University, Columbus (Johansen); Department of Family Medicine, College of Medicine, University of Michigan, Ann Arbor (Richardson).

Corresponding Author: Michael E. Johansen, MD, MS, Department of Family Medicine, Ohio State University, 2231 N High St, Columbus, OH 43201 (mikejoha3@gmail.com).

The United States spends more per capita on health care and pharmaceutical agents than any other country.[1] Despite this, the country continues to lag behind the world in terms of health care outcomes.[2(pp25-90)] The prescription drug market became notably more efficient after numerous states passed laws that allowed for generic substitution.[3] A similar but more controversial way to improve the efficiency of the pharmaceutical market is therapeutic substitution, which consists of substituting chemically different compounds within the same class for one another.

Most physician organizations are opposed to therapeutic substitution and see it as an attack on physician autonomy.[4-7] In addition, there are concerns regarding efficacy, adverse effects, drug interactions, and different indications for drugs within a class.[8,9] A previous study showed substantial potential savings if therapeutic substitution were introduced to Medicare Part D.[10] In addition, a nationally representative study showed high levels of branded proton pump inhibitor (PPI) use and expenditure between 2007 and 2011 when a therapeutically equivalent generic medication was available.[11]

Given these findings, we set out to rigorously estimate potential savings on prescribed medicines through therapeutic substitution between 2010 and 2012. To accomplish this, methods similar to the analysis of PPIs were broadened to other drug classes to estimate total and out-of-pocket excess expenditure compared with available generic drugs within the class.

Key Points

Question What was the estimated excess expenditure due to branded drug overuse when a lower-cost generic in the same class with the same indication was available?

Findings In this cross-sectional study, a high level of excess expenditure was identified among 26 drug classes between 2010 and 2012 due to the use of branded drugs when a generic drug was available in the same class.

Meaning Therapeutic substitution offers a potential mechanism to decrease drug costs if it can be implemented in a way that does not negatively affect quality of care.

Methods

Study Design

The 2010 to 2012 Medical Expenditure Panel Survey (MEPS) was used for this repeated cross-sectional analysis.[12] This nationally representative survey of the noninstitutionalized civilian population of the United States is sponsored by the Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention. It annually comprises approximately 15 000 households and gathers information through 5 interviews over 2 years on 2 overlapping cohorts. The survey uses a complex survey design and includes demographic characteristics, expenditures by payer and type, self-reported medical conditions, and prescribed drug information. The primary study outcome was total estimated excess expenditure due to overuse of brand drugs when a generic drug was available within the same class with the same indication. This study was considered to be exempt by the Ohio State University institutional review board. Informed consent was obtained through MEPS procedures.

Drug Classes

Drug classes were identified for potential inclusion by isolating classes identified in the top 200 grossing drugs of 2010[13] or the top 100 grossing drugs of 2011[14] or 2012.[15] Drug classes were included in a given year if they contained both a generic or widely accessible over-the-counter (OTC) drug and a brand-name drug without an available chemically equivalent generic. A previous study was used to guide placement of pharmaceutical agents into drug classes.[16]

Some drug classes were excluded. Antibiotics (only fluoroquinolones) were excluded because of concerns about therapeutic substitution related to different bacterial susceptibility patterns. Insulin was not included because no generics were available. Respiratory anticholinergics (ie, tiotropium bromide) and testosterone were not included because of the difficulty in comparing equivalent dosing related to different formulations. For instance, testosterone could be given as a shot, topical gel, or patch, whereas ipratropium bromide and tiotropium have different dosing schedules and formulations.

Prescribed Medications

Within the MEPS, prescribed drug information, including medical reason for use, was collected during interviews with the head of the household. After gaining approval, pharmacies were contacted to collect additional data, such as the National Drug Code (NDC), medication name, strength, quantity, expenditures, and payment source. National Drug Codes were imputed if pharmacies reported an invalid NDC. The survey's drug data have been found to be valid, especially for medications for long-term use.[17] Combination pharmaceuticals were included only if the medication of interest was combined with a low-cost generic. When it was necessary to determine a formulation such as extended release, NDCs were used in combination with drug names.

Certain prescribed medications were excluded from the study if they were not clearly included in a drug class. Aripiprazole was also not included in the primary analysis because the study that was used to guide drug classes classified it as the first "atypical antipsychotic–dopamine system stabilizer."[16] Vilazodone hydrochloride was not included because its class affiliation was uncertain.

Medications were excluded if the branded medication was US Food and Drug Administration (FDA) approved for an indication for which no in-class generic was approved (only milnacipran hydrochloride). In additional, branded drugs were excluded if the drug was used for an FDA-approved indication for which no available generic medication was approved. Participant-reported indications, *International Classification of Diseases, Ninth Revision (ICD-9)* coded, were used for this purpose. Specifically, duloxetine hydrochloride was excluded if it was associated with diabetes mellitus or musculoskeletal complaints that could be associated with fibromyalgia. Raloxifene hydrochloride was excluded if it

was associated with bone health. Quetiapine fumarate and olanzapine were excluded in 2010 through 2011 if they were associated with depression and there was no secondary diagnosis of psychosis, bipolar disorder, or neurotic disorders noted (see eText 1 in the Supplement for *ICD-9* codes). The only exception to exclusion on the basis of FDA-approved indication was pregabalin, which included all prescriptions given the widespread use of gabapentin for the same indications, as well as a lack of published comparative studies between the two.[18(pp17-31)19(pp21-28)20]

Brand vs Generic Determination

A data set available through the National Bureau of Economic Research was used to determine New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or an NDA Authorized Generic for individual drugs.[21] These distinctions were primarily used to determine brand or generic status. Authorized generics were categorized by whether the cost of the medication was more similar to the brand or generic cost. Of the included prescriptions, 13.4% (2010), 9.5% (2011), and 6.9% (2012) did not match via NDC.

In conjunction with the application status, the Orange Book was used to identify the initial ANDA for all included drugs to help classify prescriptions as brand or generic.[22] An Internet search (http://www.google.com) was also used to identify legal actions or agreements that prevented generic drug availability. Generic approval dates and delayed generic market entry dates are listed in eTable 1 in the Supplement. When no application status was matched, drugs that had predominant brand/generics were assumed to be associated with the predominant status. At times, an Internet search (http://www.google.com) was used for drugs with a large number of unmatched prescriptions (>10%) or drugs that had a fairly even split of brand and generic prescriptions.

Pharmaceutical Rebates

Pharmaceutical companies frequently provide rebates to payers, which are not accounted for in the MEPS. Because rebates are proprietary information, they were estimated in a similar fashion to previous estimates.[23] Company financial statements were used to identify revenues for individual drugs in the United States (see eTable 2 in the Supplement). This information was then compared with estimates from both MEPS and Veraspan[13]/IMS Health.[14,15] (see eTable 2 in the Supplement). The Veraspan/IMS Health data were included to allow a comparison to another estimate given the potential for overreporting or underreporting of individual drugs in the MEPS.

The rebate was assumed to be consistent among a class if 1 drug in the class had data available through financial reports. It was calculated by dividing the difference between the MEPS estimate and the financial statement data by the MEPS estimate. When financial statement data were available for multiple drugs in a class, rebate estimates were made by combining the drugs to create a class mean. When no data were available within a class, all available data from other drug classes were combined to estimate a mean rebate. The estimated rebate for drug classes was 32%.

Standardized Dosing

Total quantity was identified for each brand and generic drug. Quantity was standardized for each individual drug to a normal daily dose (see eTable 1 in the Supplement). For instance, total quantity of gabapentin was divided by 3 because the typical recommended dosage is 3 times per day whereas pregabalin was divided by 2 because the typical recommended dosage is 2 times per day. Atypical antipsychotics and stimulants had varied dosing patterns, so estimates of dosing had to be based on the number of doses that were dispensed in different prescriptions (30 vs 60 doses). Nonpill formulations such as eyedrops and nasal preparations were compared by weight or volume.

Expenditure Data

Within the MEPS, expenditures and payment source are determined through information obtained from the pharmacy. Total and out-of-pocket expenditures were identified for all branded and generic drugs. To more accurately represent actual cost to payers, the branded drug total expenditures were then reduced by the applicable estimated pharmaceutical rebate percentage for the class.

In addition, total prescribed drug expenditures (excluding diabetic testing supplies) were identified for all prescriptions drugs via the MEPS. To better estimate total prescribed drug expenditures, the cumulative estimated drug rebate of all classes was subtracted from the total prescription drug expenditure along with an estimated 5% pharmaceutical rebate. The 5% reduction was included because drug classes without multiple drugs or classes that are predominantly generic likely have a lower rebate than those investigated in this study. When a first-in-class generic was approved between 2010 and 2012, the total cost and quantity of the branded drug was prorated to include only the portion of the year during which the new generic was available.

Overuse Estimates

Given a lack of previous overuse estimates for branded drugs when there is an in-class generic, estimates were made for the frequency that the branded drug could be replaced by an alternative generic drug. Randomized clinical trials, systematic reviews, level of innovation,[16] and number of alternative generics were used to make estimates (see eText 2 in the Supplement). Statin overuse was estimated at 66% because 33% of atorvastatin and/or rosuvastatin users reported coronary artery disease.

Data Analysis

A mean cost per standardized dose of all generic medications within a class was calculated. Generics with much higher mean cost (mostly recently off patent) were excluded from this mean when there were numerous in-class generics available. Branded drugs were included as generics for ketotifen fumarate and zafirlukast because of unstable estimates related to high standard errors.

For branded drugs, cost per standardized dose was calculated by dividing the post–pharmaceutical rebate total or total out-of-pocket cost by the standardized dose. Each branded

drug's mean (total and out of pocket) cost was then subtracted by the mean (total and out of pocket) cost per dose of the in-class generic(s) on a yearly basis. The difference was then multiplied by total number of standardized doses and then multiplied by the overuse estimate.

Sensitivity Analysis

The estimated excess use was decreased by 10% for all drug classes, hence decreasing the estimated excess expenditure. Aripiprazole was included in the atypical antipsychotics and treated like olanzapine and quetiapine.

Statistical Analysis

The analysis was conducted using STATA, version 13 (STATA Corporation), and included the recoding of 1 omeprazole expense, 1 eszopiclone quantity, and 1 alendronate sodium quantity outlier. Complex survey weighting was used throughout the analysis. All expenditures were converted to 2012 dollars by using the Consumer Price Index.[23]

Results

The study included 107 132 individuals between 2010 and 2012, of whom 62.1% (95% CI, 61.4%-62.8%) reported use of any prescribed medicine. Demographic characteristics of the population are included in **Table 1**. A total of 31.5% (95% CI, 30.7%-32.2%) used a medication from an included drug class, whereas 16.6% (95% CI, 16.0%-17.1%) used a branded drug from an included class compared with 24.0% (95% CI, 23.4%-24.7%) who used a generic and 9.1% (95% CI, 8.7%-9.4%) who used both. In the included drug classes, excluding those standardized by weight or volume, the majority of the drug use was among generics, with a total of 93.5 billion standardized doses compared with 47.4 billion standardized doses among branded medications. The percentage of generic medications varied among drug classes, with some consisting of predominantly brand use such as leukotriene antagonists and stimulants, while others had low levels of brand use such as β-blockers, hypnotics, and antihistamines (**Table 2**).

Prerebate total expenditures are reported in eTable 2 in the Supplement, and postrebate class-level total expenditures are listed in Table 1. The included drug classes had a total expenditure of $213 (95% CI, $201-$225) billion. Of this, $147 (95% CI, $137-$156) billion was spent on branded drugs after estimated pharmaceutical rebates ($217 billion prior to rebate estimates), while $62.7 (95% CI, $58.9-$66.5) billion was spent on generics. The final estimated excess was $73.0 (95% CI, $67.6-$78.5) billion (Table 2), which was $97 (95% CI, $90-$104) billion prior to overuse estimates. Of the excess, $24.6 (95% CI, $22.6-$26.5) billion was paid directly by the consumer in out-of-pocket expenses after factoring in overuse estimates ($30.4 billion prior to overuse estimates).

In total, an estimated $760 (95% CI, $708-$813) billion was expended on prescribed medications between 2010 and 2012. The excess expenditure due to branded drug overuse accounted for 9.6% of total prescribed medication expenditure. Total out-of-pocket expenditures were $175 (95% CI, $167-$184) billion between 2010 and 2012, of which out-of-pocket excess expenditure due to brand drug overuse was 14.1%.

The excess was present in numerous drug classes throughout many aspects of medicine (Table 1). The 2 largest drug classes in terms of estimated excess expenditure were statins and atypical antipsychotics. Some drug classes with numerous branded and/or generic options had high levels of estimated rebates, including 59% for PPIs, 53% for β-blockers, 47% for statins, 38% for angiotension receptor blockers, 37% for selective serotonin reuptake inhibitors, and 36% for fibrates. Other drug classes did not have substantial rebates, including

Table 1. Sample Demographic Characteristics and Medication Use[a]

Characteristic	% (SE) (N = 107 132)
Age, mean (SE), y	37.2 (0.24)
Female sex	51.0 (0.2)
Race	
White (non-Hispanic)	63.7 (1.1)
Black (non-Hispanic)	12.1 (0.6)
Hispanic	16.8 (0.9)
Other	7.4 (0.5)
Insurance	
Private	64.9 (0.7)
Public only	22.3 (0.5)
Other	12.8 (0.3)
Region	
Northeast	17.9 (0.6)
South	21.5 (0.6)
Midwest	37.1 (0.8)
West	23.5 (0.7)
Poverty category	
Poor/near poor	19.9 (0.5)
Low/middle income	44.3 (0.5)
High income	35.7 (0.7)
Medication use	
Any	62.1 (0.4)
Medication from included drug class	31.5 (0.4)
Included drug class medication use	
Branded medication use	16.6 (0.3)
Generic medication use	24.0 (0.3)
Both brand and generic use	9.1 (0.2)
Drug Classes	
Branded, No.	
0	83.4 (0.3)
1	12.2 (0.2)
2	3.2 (0.1)
≥3	1.1 (0.1)
Generic, No.	
0	76.0 (0.3)
1	14.9 (0.2)
2	5.9 (0.1)
≥3	3.2 (0.1)

[a] Sample includes all individuals included in the Medical Expenditure Panel Survey between 2010 and 2012.

Table 2. Drug Classes and Potential Savings From Therapeutic Substitution Between 2010 and 2012[a]

Drug Class	Total Quantity (SE), $ Billions	Brand Use, %	Total Expenditure(SE), $ Billions	Brand Expenditure, %	Estimated Rebate, %	Total Excess Expenditure (SE), $ Billions	Total Out-of-Pocket Excess (SE), $ Billions	Excess That Is Out of Pocket, %
Statins	33.4 (0.93)	29.7	33.3 (1.02)	64.9	47	10.9 (0.41)	4.74 (0.24)	43.5
Atypical antipsychotics	2.05 (0.16)	58.0	17.9 (1.75)	88.8	0	9.99 (1.03)	0.86 (0.16)	8.6
Proton pump inhibitors	16.9 (0.62)	34.6	22.1 (0.92)	54.3	59	6.12 (0.38)	2.35 (0.18)	38.4
Selective serotonin reuptake inhibitors[b]	19.2 (0.67)	17.3	16.5 (0.90)	45.9	37	6.08 (0.49)	2.92 (0.34)	48.0
Angiotensin receptor blockers	10.1 (0.38)	66.2	16.1 (0.70)	82.0	38	5.53 (0.35)	3.79 (0.24)	68.5
Serotonin-norepinephrine reuptake inhibitors	4.11 (0.28)	61.1	15.7 (1.06)	77.7	0	4.77 (0.37)	0.75 (0.13)	15.7
Extended-release narcotics	1.82 (0.18)	36.0	6.77 (0.83)	80.2	32[c]	3.75 (0.52)	0.47 (0.08)	12.5
Hypnotics	2.72 (0.18)	22.8	4.34 (0.39)	71.0	14	2.59 (0.33)	1.26 (0.19)	48.6
Gabapentin/pregabalin	4.67 (0.26)	28.7	8.86 (0.63)	54.1	32[c]	2.36 (0.26)	0.60 (0.11)	25.4
Anticholinergics	2.20 (0.17)	55.5	4.83 (0.43)	81.8	32[c]	2.32 (0.25)	0.78 (0.13)	33.6
Fibrates	3.55 (0.22)	45.8	6.24 (0.44)	66.0	36	2.23 (0.21)	0.82 (0.09)	36.8
Omega-3 fatty acids	1.99 (0.24)	92.5	2.67 (0.34)	98.9	0	2.14 (0.27)	0.17 (0.04)	7.9
Niacin	1.36 (0.16)	94.1	2.83 (0.35)	98.9	27	2.02 (0.26)	0.31 (0.06)	15.3
Stimulants	4.09 (0.29)	76.8	18.2 (1.37)	89.6	0	2.01 (0.17)	0.14 (0.04)	7.0
Triptans	0.23 (0.03)	57.1	2.76 (0.34)	83.7	32[c]	1.60 (0.22)	0.40 (0.10)	25.0
Nasal steroids	1.42 (0.07)	47.9	4.51 (0.26)	68.3	32[c]	1.59 (0.12)	0.63 (0.07)	39.6
Bisphosphonates	3.34 (0.42)	29.0	3.32 (0.31)	64.2	32[c]	1.50 (0.20)	0.29 (0.06)	16.7
5-α Reductase inhibitors	1.65 (0.13)	38.8	2.74 (0.26)	36.5	13	1.13 (0.15)	0.60 (0.10)	53.1
Leukotriene antagonists	2.06 (0.16)	87.4	6.58 (0.52)	92.2	32[c]	1.06 (0.11)	0.98 (0.12)	92.5
β-Blockers	21.8 (0.72)	9.1	8.91 (0.32)	17.3	53	0.80 (0.08)	0.89 (0.09)	111.3
Prostaglandin analogues	0.09 (0.01)	56.4	1.54 (0.18)	78.6	32[c]	0.69 (0.10)	0.26 (0.04)	37.7
α-Blockers[b]	4.84 (0.30)	9.1	3.18 (0.22)	26.4	32[c]	0.43 (0.06)	0.22 (0.04)	51.2
Selective estrogen receptor modulators	0.48 (0.07)	22.9	0.69 (0.15)	68.1	0	0.40 (0.12)	0.08 (0.03)	20.0
Aromatase inhibitors	0.28 (0.05)	45.5	1.22 (0.29)	66.0	60	0.39 (0.15)	0.07 (0.03)	17.9
Ocular antihistamines	0.04 (0.01)	90.5	0.49 (0.07)	98.0	32[c]	0.30 (0.04)	0.11 (0.02)	36.7
Antihistamines[b]	1.57 (0.11)	6.9	1.55 (0.14)	23.2	0	0.30 (0.07)	0.06 (0.02)	20.0
Totals	144 (3.69)	32.9	213 (6.13)	69.0	...	73.0 (2.78)	24.6 (0.98)	33.4

[a] Total expenditure is the entire drug class after the estimated pharmaceutical rebate has been taken into account. Ocular antihistamines, nasal steroids, and prostaglandins excluded from calculation of total quantity due to difference in units in both total quantity and percent branded medications of quantity. Both excess total and out-of-pocket expenditure take into account the cost of generic(s) as well as estimates for overuse. Total quantity is standardized to be the mean daily use with the exception of those that were measured by weight or volume.

[b] More expensive generic medication not included in calculation of total or self excess expenditure.

[c] Estimated by taking the mean of all drugs with data available in financial statements.

0% for atypical antipsychotics, serotonin-norepinephrine reuptake inhibitors, omega-3 fatty acids, and stimulants.

In sensitivity analysis, a 10% decrease in the estimated overuse resulted in a total excess expenditure of $63.3 (95% CI, $58.3-$68.4) billion. The inclusion of aripiprazole increased the excess expenditure by $5.87 (95% CI, $4.38-$7.37) billion.

Discussion

Between 2010 and 2012, an estimated $73.0 billion in excess of generic cost was spent on brand drugs within the same class. Importantly, this estimate takes into consideration pharmaceutical rebates to payers, as well as unique indications for branded medications and overuse estimates. Much of the excess expenditure was concentrated in a few drug classes (statins, atypical antipsychotics, angiotension receptor blockers, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and PPIs) but was identified throughout different aspects of medicine. In total, this accounted for nearly 1 in 10 dollars spent on prescribed medications. In contrast to payers, patients do not get rebates on their purchases and were responsible for a considerable portion of the excess by expending 33% of the total excess, or $24.6 billion in out-of-pocket expenses.

The general acceptance of generic substitution has increased the efficiency of the prescription drug market. Use of generic drugs leads to higher levels of adherence[24] and has decreased health care costs while improving outcomes. Critical to the growth of the generic drug market was the idea of therapeutic equivalence and hence substitution of generic for branded drugs.[3]

There is limited support for therapeutic substitution[25,26]; however, it is opposed by many groups.[4-6] Similar to generic substitution in the past, physician opposition, in part, is related to the degradation of physician autonomy.[3] There is legitimate concern that therapeutic substitutions could lead to worse clinical outcomes, but this would likely be concentrated in high-risk drug classes. It is also possible that therapeutic substitution could lead to lower than anticipated returns if nonpharmaceutical costs increase (eg, hospitalizations).[27] If therapeutic substitution were to become commonplace, more efficient systems that allow for seamless communication among prescribers, pharmacies, and insurance companies should be in place. With the ever-increasing paperwork burden[28,29] and high burnout rates among physicians,[30] increasing the complexity of care could be counterproductive.

At present, drug prices are higher in the United States than in other countries partially as a result of "a mix of laws that force insurers to include all expensive drugs in their policies."[31] Recent efforts to price drugs on the basis of value are a step in the right direction.[32,33] In addition, the American Medical Association recently called for an end to direct-to-consumer advertising.[34] Direct-to-consumer advertising and physician promotion have been used as marketing techniques by industry[35-38] and have had a significant impact on the use of branded drugs.[39,40] Given the general lack of high-quality, randomized clinical trials to guide use within a drug class,[41] along with a recognized bias in pharmaceutical-funded trials,[42] these marketing strategies may be increasing costs without delivering improved outcomes. In addition, patients seem to perceive more expensive drugs as more effective,[43] whereas physicians can have negative perceptions of generic drugs.[44] Few pivotal trials include active comparators,[45] and trials that do compare active treatments are less likely to be published if the results support therapeutic equivalence as a result of the well-documented phenomenon of publication bias in favor of trials with positive results.[46-48] Unbiased information, such as independent high-quality, randomized clinical comparative effectiveness research, could substantially reduce health care costs and make interventions such as therapeutic substitution less lucrative.

This study has numerous important limitations. Pharmaceutical rebates to payers are proprietary information. Estimates were made on the basis of US-specific numbers in company annual reports. These numbers were not available for many drug classes, which necessitated estimates based on unrelated drug classes. Even when numbers were available within a class, the assumption that all drugs within a class have similar levels of rebates is also potentially problematic, as is the assumption that exclusively branded and nonexclusively branded drugs have the same rebate levels. It is also important to note that company financial statements do not necessarily align with the medication expenditure (even after rebate) because wholesalers could buy pharmaceuticals that would be counted on financial statements, but not within the actual expenditure during that period.[23]

Given a lack of literature to determine the overuse of branded drugs within each drug class, estimates were made using a variety of sources. Given the subjectivity of the estimates, a sensitivity analysis was conducted and individual estimates were listed to allow readers to alter the estimates. It is possible that estimates overestimated or underestimated branded drug overuse.

Whereas NDCs were used in instances in which ANDAs and/or NDAs did not match to the FDA data set, there is potential that incorrect allocation could have occurred. Use of OTC drugs in comparison with branded prescription counterparts limited the strength of total quantity comparisons as a result of the underreporting of OTC drugs within the MEPS, but the assumption that we used for the mean price per dose for OTC drugs is likely reasonable. In addition, drug classes that include both generic and OTC drugs (ie, PPIs and ocular/oral antihistamines) could overestimate mean generic cost if OTC drugs were underreported and were lower in cost.

There are numerous additional limitations. First, each standardized dose of medications within a class was assumed to be equal (eg, 20 mg of omeprazole vs 40 mg of esomeprazole magnesium), which is frequently not the case. It is unclear how clinically relevant these differences would be in terms of cost or effectiveness. In addition, the dosing schedules that were assumed for individual drugs are not necessarily how the drugs are actually used in clinical practice for all medication users. Only when there was a large amount of variance in use or an obvious discrepancy from recommended dosing were dosing patterns from individuals used to construct the standardized dosing. Finally, this analysis did not include inpatient medications, testosterone, respiratory anticholinergics, drug classes that included generic substitution for all drugs, or aripiprazole (sensitivity analysis only), which could lead to this analysis underestimating the overall excess expenditure.

Conclusions

There was a large amount of excess expenditure on branded drugs between 2010 and 2012 in classes that could have incorporated therapeutic substitution. Although therapeutic substitution is controversial, it offers a potential mechanism to decrease drug costs if it can be implemented in a way that does not negatively affect quality of care.

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Study concept and design: Johansen.
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