Healthcare Costs Associated with Switching from Brand to Generic Levothyroxine

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Background: Controversy exists over the true therapeutic equivalence of branded and generic levothyroxine—the drug of choice for treating hypothyroidism—so professional societies recommend against switching between different formulations of the drug and suggest that patients who do switch be monitored. Payers typically encourage switching to generic drugs because of lower drug acquisition costs.

Objective: To evaluate the impact of switching levothyroxine formulations on actual healthcare costs.

Methods: Patients with hypothyroidism and at least 6 months of branded levothyroxine therapy were identified from a large healthcare claims database. Patients who subsequently switched to another levothyroxine formulation and could be followed for 6 months postswitch were matched to demographically similar patients who were continuous users of branded levothyroxine. Pre- and postswitch healthcare costs for each group were compared.

Results: The savings in prescription drug costs after switching from branded to generic levothyroxine are offset by increases in costs for other healthcare services, such that switching is actually associated with an increase, not a decrease, in total healthcare costs.

Conclusion: In the absence of cost-savings, there is no clear rationale for switching patients from brand to generic levothyroxine. [*AHDB*. 2010;3(2):127-134.]

The prevalence of hypothyroidism in the United States is estimated at 4% to 10%, including undiagnosed cases.[1,2] Higher rates have been found in women and the elderly.[1,2] The most common causes of hypothyroidism are autoimmune thyroid disease and surgical or radioiodine ablation; only a small percentage of cases result from secondary causes.[3,4]

Levothyroxine is the drug of choice for treating hypothyroidism.[3-6] It is available in branded and in generic forms. The US Food and Drug Administration (FDA) considers generic formulations meeting bioequivalence standards to be therapeutically equivalent to the specific brand-name drug used as a reference comparator. Such drugs, designated by the FDA as "AB-rated," meet the FDA's standards for bioequivalence and can be substituted for a brand-name levothyroxine with the same rating. Controversy exists, however, over the ability of the FDA's standard bioequivalence testing methodology to identify small differences in bioequivalence that may have clinical significance. This methodology, using single-dose pharmacokinetic data in healthy volunteers, may be relatively insensitive when comparing drugs with a narrow therapeutic index, or drugs that are endogenous substances.[7-10]

The American Association of Clinical Endocrinologists, The Endocrine Society, and the American Thyroid Association issued a joint position statement summarizing concerns about the sensitivity of the FDA's methodology for determining levothyroxine bioequivalence, pointing out the potential clinical importance of bioequivalence differences in levothyroxine agents, given the drug's narrow therapeutic index.[7] They recommend that for any given patient, levothyroxine formulation should not be switched, regardless of whether the change is to a branded drug or a generic. If a switch occurs, thyroid-stimulating hormone laboratory values should be monitored postswitch to ensure that levels remain consistent with appropriate treatment.[3,4,7]

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KEY POINTS

- The true therapeutic equivalence of branded and generic levothyroxine is still being debated.
- Payers typically encourage switching to generic drugs, as a cost-saving mechanism.
- Using a large healthcare claims database, this study investigated whether switching from brand to generic levothyroxine does indeed save costs to patients and payers.
- Results show that the savings in drug costs from switching to generic levothyroxine are often offset by increased costs for related healthcare services.
- Switching from brand to generic levothyroxine appears to be associated with an increase in total healthcare costs.
- These results raise a question regarding the economic and clinical benefits of switching patients to generic levothyroxine.

In general, payers encourage switching patients from brand-name to generic drugs because of the lower drug acquisition costs of generics.[11] However, the cost impact of a levothyroxine brand-to-generic switch has not been quantified. If reductions in levothyroxine drug acquisition costs are offset by increased costs for additional monitoring or by adverse clinical outcomes, the net effect may be zero cost-savings or even a cost increase.[12] The present study was undertaken to evaluate the impact of levothyroxine brand-to-generic switching on healthcare costs. Although of primary importance to payers, healthcare costs are increasingly important to patients, who typically bear a portion of the costs,[13] as well as to providers, who may be under pressure to minimize costs.[14]

Methods

Sample Selection

The study sample was selected from the Integrated Healthcare Information Services National Managed Care Benchmark Database (IHCIS; Waltham, MA). This database includes the medical claims history for approximately 25 million lives covered under more than 30 different managed care health plans throughout the United States. Claims are de-identified, so the use of the database for research purposes complies with HIPAA requirements and does not require institutional review board oversight. The data extract provided by IHCIS for use in conducting this study contained the complete claims history of all patients in the database with at least 1 pharmacy claim for levothyroxine (brand or generic) with a date of service between January 1, 2001, and June 30, 2005.

Patients with at least 6 months of branded levothyroxine (Levoxyl, Levothroid, Synthroid, or Unithroid) therapy at a constant daily dose were considered for study inclusion. Patients were stratified into continuous users and switchers. Patients who remained using the same brand of levothyroxine during their entire claims history were termed "continuous users." Those with claims for another brand of levothyroxine or for a generic levothyroxine preparation after at least 6 months of branded therapy were called "switchers." Switchers were further divided into those who switched to another branded levothyroxine drug, those who switched to a generic, and those with multiple switches (brand or generic).

Study inclusion required at least 1 claim carrying a hypothyroidism diagnosis (congenital hypothyroidism, *International Statistical Classification of Diseases, Ninth Revision* [ICD-9] code 243.XX, or acquired hypothyroidism, ICD-9 code 244.XX) sometime during the available claims history. Diagnosis was not restricted to a particular service setting, allowing both inpatient and outpatient claims to be used to select patients.

Several exclusion criteria were applied to help ensure a homogeneous sample. Patients with claims indicative of thyroid cancer (ICD-9 code 193.XX) were excluded, as were patients with drug claims for liothyronine (LT_3) or an LT_3-levothyroxine combination drug, because they did not represent the typical patient with hypothyroidism. The multiple-switch group was screened to exclude patients who were quick switchers, defined as having a second switch within 14 days of the first switch. Finally, patients without mental health benefits were excluded, because their available claims may not represent their complete utilization.

Index dates were assigned to both continuous users and switchers. For switchers, the index date was the date of the first prescription claim for a levothyroxine drug other than the branded drug used during the 6 months of continuous therapy required for patient selection. Switchers without at least 6 months of stable-dose levothyroxine therapy postindex were dropped. For continuous users, index dates were assigned during the matching process, such that the distribution of index dates by quarter and year would be similar for each matched group. Any date on which the patient had a levothyroxine drug claim was eligible for assignment as the index date, provided there were at least 6 months of stable-dose continuous use of the drug before and after the index date. The study period for all patients included a 6-month preperiod and a 6-month postperiod.

Matched groups of continuous users and switchers were created using propensity score analysis, a match-

ing technique commonly used in retrospective claims data analyses to approximate random assignment.[15] Using logistic regression, the probability (propensity score) that an individual patient would be included in the continuous-user group or a switch subgroup, given patient sex, age, census division, health plan type, levothyroxine dose, and index drug (Levoxyl, Levothroid, Synthroid, or Unithroid) was calculated. Switchers were then matched 1 to 1 to continuous users based on their propensity score. Switchers who could not be closely matched to a continuous user were dropped from the sample.

Data Analysis

A patient-level analytic file was created for the matched patients, consisting of all variables necessary to support the analyses. Variables were tabulated and compared using chi-square and *t*-tests to assess for differences between cohorts.

Demographic variables created as of the index date included age in years, age-group, and sex. The database also included patient geographic area at the level of census division (eg, the Northeast census region is comprised of the New England and Middle Atlantic divisions). Insurance plan type (eg, HMO, PPO) and payer type (commercial, Medicare, or Medicaid) also were available.

The mean daily dose of levothyroxine was calculated from the tablet strength, quantity dispensed, and days supply information on drug claims. For multiple switchers, the number of switches in the postperiod was determined. The Charlson Comorbidity Index (CCI)[16] was used as a global measure of comorbidity. This measure assigns a weight to each of 19 conditions identified from diagnoses on healthcare claims in the preperiod, based on their relative burden. Higher scores indicate a greater burden of comorbid illness. The presence of 8 comorbidities—depression, hyperlipidemia, atherosclerosis, angina, hypertension, myocardial infarction, stroke, and arrhythmia—was also assessed, based on the relevant diagnosis codes in the pre-index claims data.

Utilization and expenditure variables were created separately for the pre- and postperiods. The percentage of continuous users and switchers with utilization of specific service types was calculated. Service types included inpatient admissions, emergency department visits, outpatient visits, outpatient laboratories, and outpatient prescriptions. Expenditures associated with each type of service were tallied from the actual amount reimbursed by the insurer after subtraction of any patient cost-sharing. Mean expenditures were calculated using all patients in the cohort as the denominator. All dollar figures were adjusted to 2005 dollars using the medical component of the Consumer Price Index.

Utilization and expenditures specific to hypothyroidism also were tallied separately to determine if hypothyroidism was a driver of total costs. Inpatient and outpatient services with a primary (first) diagnosis of hypothyroidism (ICD-9 code 243.XX or 244.XX) and prescription drug claims for levothyroxine were considered hypothyroidism-specific services.

The primary outcome of interest was postswitch expenditures. Since postindex healthcare expenditures could be affected by patient-specific factors other than a levothyroxine switch, some of which were not controlled for in the matching (eg, comorbidities), the difference between pre- and postexpenditures was calculated. The significance of the difference in mean pre/post change was then assessed using *t*-tests. A value of $P < .05$ was considered evidence of a significant difference.

Results

A total of 97,670 continuous users, 10,367 brand-to-brand switchers, 21,901 brand-to-generic switchers, and 6193 multiple switchers met all study inclusion and exclusion criteria. Subsequent to matching drug users, 7195 brand-to-brand switchers, 6824 brand-to-generic switchers, 5344 multiple switchers, and an equal number of corresponding continuous users for each switch subgroup remained. These matched switcher-continuous user pairs comprised the final study population included in this analysis (see the **Appendix** online at www.AHDBonline.com/Appendix_Katz).

The branded levothyroxine drug used in the preperiod was either Levoxyl or Synthroid for about 90% of the sample across all cohorts. The mean daily dose of levothyroxine was approximately 0.1 mg (100 µg), regardless of the cohort. Although levothyroxine dosing is individualized and can vary between patients, this dose is consistent with the recommended dosing range of the drug.[3-6] Multiple switchers had 2.1 switches in the 6-month postperiod on average (range, 2-12).

The distribution of index dates within each matched group was similar since index dates were assigned to continuous users as part of the matching process. One half of the patients in the brand-to-brand switch group had an index date between mid-2001 and mid-2002. In the brand-to-generic switch group, however, most index dates were in 2003 and 2004. This was expected, considering that the release of the first generic drug occurred in mid-2002. In the multiple-switch group, where nearly three fourths of all first switches were to a generic drug, the index dates also fell primarily in 2003 and 2004.

Across all cohorts, the most common hypothyroidism diagnosis was ICD-9 code 244.9 or hypothyroidism not otherwise specified. Depending on the cohort, between 92% and 93% of patients in the sample had that diag-

Table 1 Characteristics of Study Population

	Matched group		Matched group		Matched group	
	Continuous users (n = 7195)	Brand-brand switchers (n = 7195)	Continuous users (n = 6824)	Brand-generic switchers (n = 6824)	Continuous users (n = 5344)	Multiple switchers (n = 5344)
Mean age (SD)	52.9 (13.3)	52.5 (12.8)	53.7 (13.4)	51.5 (13.3)	52.4 (13.3)	52.6 (13.7)
	Patients in each group, %					
Age-group, y						
0-17	1.1	0.7	1.2	1.2	1.1	1.1
18-34	7.8	7.7	6.1	8.6	7.7	8.0
35-44	16.9	17.9	15.6	18.3	17.5	17.0
45-54	26.6	28.9	27.7	29.6	28.7	29.2
55-64	31.4	29.9	31.1	29.5	29.6	28.1
≥65	16.3	14.9	18.3	13.3	15.3	16.6
Sex						
Male	16.7	17.3	18.7	18.1	15.1	15.4
Female	83.3	82.7	81.3	81.9	84.9	84.6
Census region[a]						
Northeast	66.3	66.4	66.3	62.9	66.3	65.1
South	10.6	10.8	6.1	10.5	7.7	8.0
Midwest	8.5	7.9	9.0	10.7	9.7	9.1
West	6.6	6.4	11.6	8.5	9.1	10.2
Other/missing	8.0	8.5	7.1	7.4	7.2	7.7
Insurance plan						
HMO	46.8	47.7	32.8	27.2	40.8	40.3
Indemnity	5.2	4.8	4.1	2.2	4.3	4.9
POS	10.2	9.8	10.4	5.3	10.4	11.0
PPO	34.3	34.3	45.6	63.1	39.0	37.5
Other/missing	3.4	3.5	7.1	2.2	5.5	6.4
Payer						
Commercial	89.7	90.6	89.3	94.3	89.7	88.7
Medicare	7.3	6.2	4.7	3.9	5.4	5.9
Medicaid	2.9	3.2	5.9	1.8	4.8	5.4
Comorbidities[b]						
Depression	7.4	8.0	7.2	7.4	7.5	7.7
Hyperlipidemia	23.5	24.7	26.6	27.1	24.4	23.1
Arteriosclerosis	4.3	4.7	4.7	4.6	3.4	4.4
Angina	0.9	1.0	0.9	1.1	0.7	1.0
Hypertension	22.8	25.3	25.0	25.4	23.2	24.9
Heart attack	0.4	0.5	0.4	0.2	0.3	0.6
Stroke	1.7	1.7	2.1	1.4	1.7	1.7
Arrhythmia	4.0	3.7	4.4	3.8	3.9	4.1

SD indicates standard deviation.
[a]Each census region contains 2 to 3 census divisions, which was the unit used in matching.
[b]Measured in the 6 months preindex.

Table 2 Overall and Hypothyroidism-Related Healthcare Utilization

	Matched group: Continuous users (n = 7195)		Matched group: Brand-brand switchers (n = 7195)		Matched group: Continuous users (n = 6824)		Matched group: Brand-generic switchers (n = 6824)		Matched group: Continuous users (n = 5344)		Matched group: Multiple switchers (n = 5344)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
PROPORTION OF PATIENTS WITH ANY UTILIZATION[a]												
Overall												
Outpatient visits	93.9	93.7	95.4	93.0	95.4	94.0	93.8	93.5	94.8	94.2	93.9	95.9
Prescription claims	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Inpatient admissions	4.4	5.4	5.4	5.0	4.0	4.2	4.4	4.8	3.7	4.8	5.7	5.6
Emergency department visits	10.8	10.3	10.4	10.2	11.0	10.1	9.4	9.6	10.7	10.7	11.5	11.7
Hypothyroidism[b]												
Outpatient visits	55.5	50.2	53.4	45.8	58.1	51.6	48.7	46.9	58.5	51.3	49.1	58.9
Inpatient admissions	—	<0.1	—	<0.1	—	<0.1	—	—	—	<0.1	—	<0.1
Emergency department visits	<0.1	—	—	—	—	<0.1	<0.1	—	—	<0.1	—	<0.1
MEAN NUMBER OF SERVICES AMONG PATIENTS WITH ANY UTILIZATION												
Overall												
Outpatient visits	8.0	8.1	8.0	8.2	8.5	8.2	7.6	7.7	8.3	8.2	8.4	9.3
Prescription claims	16.9	16.3	15.1	16.8	17.2	16.6	14.0	15.5	16.8	16.2	15.2	17.6
Hypothyroidism[b]												
Outpatient visits	1.5	1.3	1.4	1.5	1.5	1.3	1.3	1.4	1.5	1.4	1.4	1.5

[a]Numbers represent the percentage of patients in each cohort with ≥1 claim for each service listed.
[b]Primary diagnosis on claim is hypothyroidism (*International Statistical Classification of Diseases, Ninth Revision*, code 243 or 244.X).

nosis. Except for less than 1% of the sample with congenital hypothyroidism (ICD-9 code 243), the rest of the sample was coded as having postsurgical, postablative, or some other form of acquired hypothyroidism (ICD-9 code 244.0-244.8).

The demographic characteristics of the study population, by matched cohort, are presented in **Table 1**. Because switchers were propensity score matched to continuous users on these characteristics, few differences were seen within each matched group. Patients were predominantly female. Approximately 75% were aged ≥45 years.

These sample characteristics conform to findings from other research showing that more women than men have hypothyroidism, and that the prevalence of the condition increases with age.[1,2] The majority of the sample resided in the Northeast census region and had health insurance coverage from HMO or PPO commercial payers, factors consistent with the overall distribution of patients in the IHCIS database.

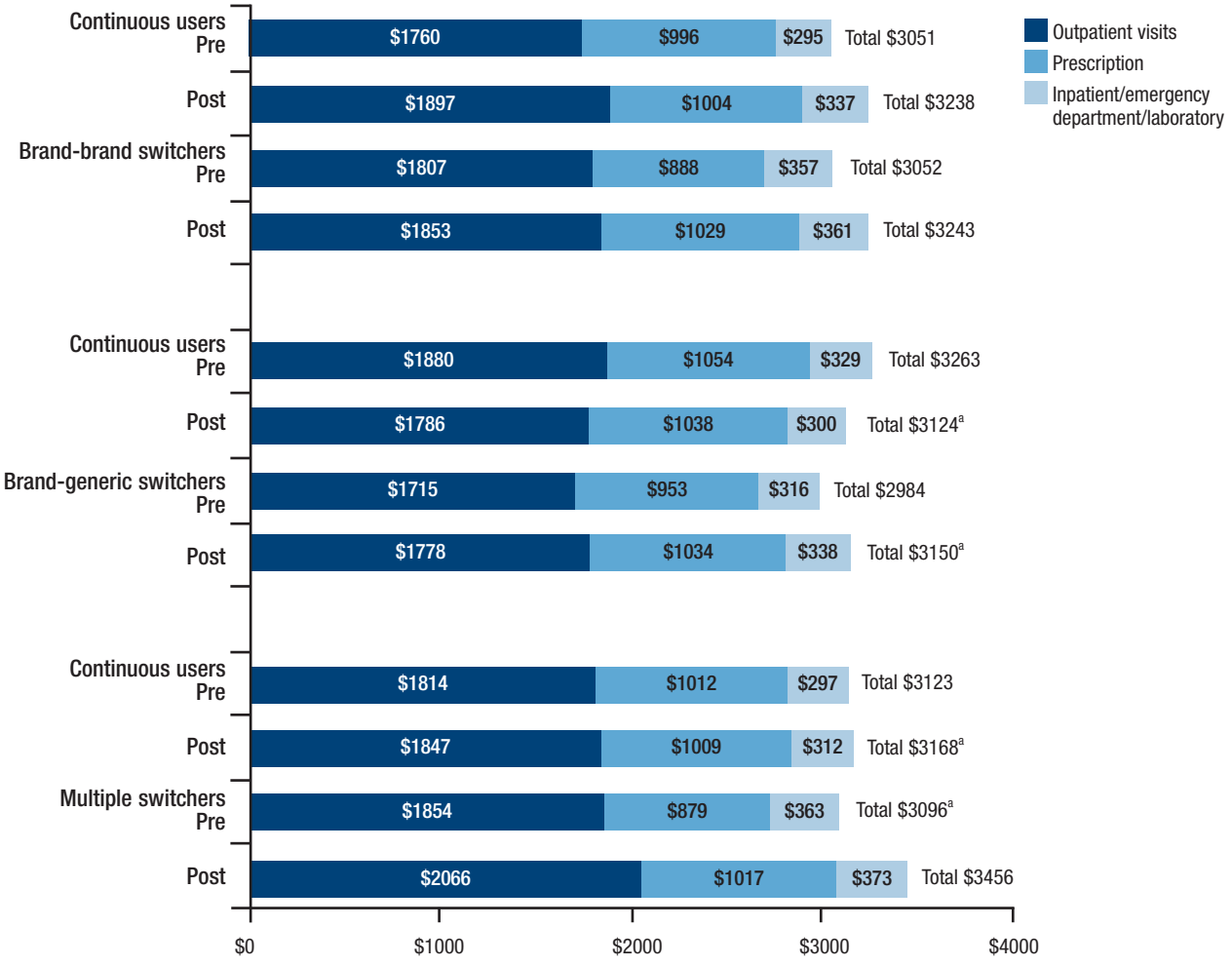
A low level of comorbidity was evident in all cohorts, as measured by preindex CCI scores in the 0.5 to 0.6 range. Although patients were not matched on preindex date comorbidities, the proportion of patients with each specific comorbidity assessed in the preperiod was similar. The most common comorbidities across all cohorts were hyperlipidemia and hypertension, each occurring in approximately 25% of the patients. Claims indicative of depression were present for 7% to 10% of patients, depending on the cohort. Atherosclerosis, angina, myocardial infarction, stroke, and arrhythmia were seen in ≤5% of patients.

Drug Utilization

All patients in the sample had prescription drug utilization as a result of the study inclusion requirement for levothyroxine therapy. The mean number of prescription drug claims (any medication) in the 6-month preperiod was between 14 and 17, depending on the cohort. The mean number of drug claims per patient increased postindex among switchers and declined slightly among continuous users (**Table 2**).

The majority of continuous users and switchers had claims for outpatient office visits (>90% all patients, all

Figure Total Healthcare Expenditures, by Service Type



[a]Pre/post increases in expenditures significantly greater for switchers compared with continuous users.

time periods). Approximately 50% of all patients had a hypothyroidism-specific outpatient visit. The proportion of patients with such a visit increased postindex for multiple switchers but decreased for other cohorts. The mean number of outpatient visits per 6-month period was around 8, although only 1 to 2 of those visits, on average, carried a primary diagnosis of hypothyroidism. More visits were with endocrinologists or other specialists than with primary care providers.

The percentage of patients with emergency department visits (about 10%) was much smaller than the percentage of outpatient office visits and was similar across all patient groups for all time periods. This was also the case with inpatient admissions; approximately 4% to 6% of patients were hospitalized. Few patients received hypothyroidism-specific inpatient or emergency department care. Not surprising, the primary driver of expenditures across all cohorts was outpatient visits, followed by prescription drugs. Inpatient and emergency department services added comparatively little to total expenditures. The **Figure** describes overall expenditures by treatment setting.

Overall Expenditures

Among the brand-brand switchers and their matched continuous users, the mean increases in total overall expenditures from the pre- to postperiods were $190 and $187, respectively. This pre/post increase in expenditures did not differ significantly by cohort (P = .969). Comparing the pre/post difference in expenditures for the other matched groups, however, revealed that switchers had a significant increase in expenditures postindex compared with continuous users. The pre/post increase in expenditures for the brand-generic switchers

was $165, whereas matched continuous users' expenditures decreased $138 on average ($P$ = .001). The increases for multiple switchers and matched continuous users were $360 and $44, respectively ($P$ = .004).

Although hypothyroidism-specific expenditures comprised less than 5% of total expenditures, the focus of this study on patients being treated with levothyroxine for hypothyroidism warranted examination of pre/post changes in these expenditures. Each of the continuous-user groups had slightly lower hypothyroidism-specific expenditures in the postperiod compared with the preperiod, with decreases of $20, $24, and $24 for the continuous users matched to the brand-brand, brand-generic, and multiple switchers, respectively.

Expenditures increased in the postperiod for 2 of the 3 switch subgroups—$14 in the brand-brand switchers, and $42 in the multiple switchers. Hypothyroidism-specific expenditures in the brand-generic switch subgroup decreased by $5. This difference was almost entirely attributable to lower prescription expenditures. All pre-post period hypothyroidism-specific cost differences for switchers compared with the differences for their respective continuous users were significant (P <.001).

Discussion

The results of this study do not demonstrate a cost-savings for patients who switch among levothyroxine drugs, raising the question whether substitution of generic for branded formulations is an effective cost-management approach for these patients. Most notably, although mean hypothyroidism-specific expenditures in the brand-generic switchers did decrease a small amount ($5) subsequent to the switch, overall total costs actually increased by $165. In contrast, matched continuous users had an overall cost decrease during their pre-post period of stable-dose branded treatment.

Of the 3 switch subgroups, multiple switchers demonstrated the greatest increase in postperiod versus preperiod hypothyroidism-specific and overall total expenditures. These switchers may be at the highest risk for adverse outcomes and increased expenditures, given the narrow therapeutic index of levothyroxine and the recommendations for monitoring after a switch.

The increase in patients with hypothyroidism-specific outpatient visits postindex among multiple switchers was notable, although it was not possible to ascertain from the claims if the increase was a result of monitoring, difficult-to-control hypothyroidism, or switch-related adverse clinical consequences.

Limitations

These results should be interpreted in light of the usual caveats surrounding the use of claims data. Although it is assumed that diagnosis codes listed on claims are correct, it is possible that some patients or services were misclassified as a result of coding errors.

In addition, hypothyroidism-specific services may have been undercounted, because classification was based on the primary diagnosis listed on each claim, and hypothyroidism diagnoses that occur on inpatient and emergency department claims may be in a secondary diagnosis field.

The results of this study are based on claims from a specific database and may not be generalizable to other populations. The study sample, however, did conform to expectations in terms of age,[1,2] sex,[1,2] and hypothyroidism diagnosis.[3,4]

Furthermore, this study did not adjust for all potential confounding variables. Although specific characteristics were used in the propensity score matching, these characteristics were not all-inclusive, and the distribution of other variables that may have had an impact on study outcomes may be dissimilar between the switch and continuous-user matched groups.

It was not possible to measure hypothyroidism severity from the claims, therefore cohorts were not matched on this characteristic. If difficult-to-manage hypothyroidism patients are more likely to switch levothyroxine preparations, this subgroup may be overrepresented in the switcher groups.

The claims of switchers were not assessed to determine if their switch was to a levothyroxine drug that has AB-rated bioequivalence to their index-branded drug. Although it is assumed that the majority of brand-generic switches involved the substitution of an AB-rated drug for a branded drug as an attempted cost-saving measure, it is possible that some switches were the result of an intentional therapy change in a difficult-to-manage patient.

Finally, some levothyroxine preparations were undergoing changes in the first half of 2001. Because the study period of some patients in the brand-brand and matched continuous-user groups included data from early 2001, a small number of patients who appeared to be receiving stable therapy might have experienced a change in their levothyroxine.

Conclusion

In the absence of cost-savings, and given the concerns regarding therapeutic equivalence that have been documented, there is no clear rationale for switching patients from brand to generic levothyroxine drugs. Further research is needed to better understand the factors driving increases in utilization postswitch and the clinical implications of changing levothyroxine formulations. ■

Continued

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Disclosure Statement

Drs Conard, Katz, and Scherger are Consultants to Abbott Laboratories, and Dr Scherger also serves on the Speaker's Bureau of Merck. Ms Chang and Ms Montejano have nothing to disclose.

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STAKEHOLDER PERSPECTIVE

Payers' Approaches to Generic versus Brand-Name Medications

PAYERS: Employers, plan sponsors, and other healthcare payers generally consider the therapeutic efficacy of brand and generic medications to be very similar. This has been demonstrated throughout the years in a variety of ways and is supported by the very fact that generic medications receive approval from the US Food and Drug Administration for marketing those products in the United States.

It is also generally accepted by payers that in some rare cases, the brand and generic versions of specific medications may not be interchangeable for some patients, for different reasons. In such cases, including the case of generic levothyroxin, as suggested in the article by Katz and colleagues, it is expected that healthcare payers will behave as they have done historically and choose one of the following common approaches:

- Current utilizers can be "grandfathered" to continue to receive the current brand drug if this is medically necessary (a common benefit provision)
- All new patients using this therapy could be required to begin therapy with the generic agent, and if therapy fails because of the use of the generic medication, the patient will then be allowed to use the brand medication (normally at a higher cost-sharing)
- All patients will have to at least try to use the generic; if a treatment failure occurs, the patient can then receive the brand-name medication at the higher cost-sharing level.

PATIENTS: Plan sponsors encourage the use of generic medications for patients as a cost-savings strategy for all involved stakeholders, including patients and payers, as well as the facilitation of a consistent message to their covered populations. To alter this benefit parameter and the message of cost-savings with generics because of 1 therapeutic class would be counterproductive and potentially confusing to patients.

No healthcare payer wants patients to be denied needed medication or therapy, which is the reason why override provisions are included in a prescription drug plan benefit design. This is but one example where the system can and should work to provide the therapy that patients need at a reasonable cost.

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