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The Economic Impact of Changing Levothyroxine Formulations in Difficult-to-Treat Hypothyroid Patients: An Evidence-Based Model

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Abstract

Objective: To determine the budget impact of incorporating levothyroxine gel caps in the treatment plan of patients diagnosed with hypothyroidism who experience multiple levothyroxine dose or formulation changes annually due to inadequate efficacy or tolerability.

Methods: Cost estimates of levothyroxine formulations were obtained. Estimated utilization patterns and costs of physician services, laboratory tests, ancillary healthcare services, and lost productivity were quantified based on published literature and government/public sources. The patient population was based on epidemiology reports and estimates from the American Association of Clinical Endocrinology and the American Thyroid Association. All calculations of economic outcomes were determined using a budget impact model constructed in a MS Excel platform.

Results: The economic model demonstrated for a population of 500,000 persons, there are 23,000 (4.6%) people with hypothyroidism, of which 18,400 (80.0%) receive pharmacologic treatment, including 17,480 (95.0%) that receive levothyroxine. The proportion of patients requiring ≥ 1 dosage changes annually is 31.4%, producing 5,489 "hard-to-treat" patients. Similarly, the proportion of patients requiring ≥ 2 dosage changes annually is 8.0% or 1,398 "harder-to-treat" patients. Using evidence-based data of the tolerability and absorption characteristics of levothyroxine gel caps, changing 20.0% of the target cohort to the gel cap formulation produced annual net cost savings of $542,901 in direct medical costs and $564,650 in lost productivity for "hard-to-treat" patients and savings of $409,107 in direct medical costs and $441,926 in lost productivity for "harder-to-treat" patients.

Conclusions: Consideration of switching levothyroxine product from a tablet to a gel cap formulation is justified on an economic and therapeutic basis for hypothyroid patients at risk of subadequate drug efficacy or tolerability as measured by the need for one or more annual levothyroxine dosage or formulation adjustments.

Keywords: Budget impact; Dose changes; Economic model; Gel caps; Hypothyroidism; Levothyroxine

Background

Hypothyroidism is the most common thyroid disorder in the US. It occurs as a result of the inability of the thyroid gland to produce sufficient amounts of the thyroid hormone thyroxine (T4) [1]. Hypothyroidism may be categorized as either subclinical or overt. According to the American Thyroid Association (ATA) and the American Academy of Clinical Endocrinology (AACE), subclinical hypothyroidism is characterized by a level of thyroid activity that is determined by a thyroid stimulating hormone (TSH) test above the upper reference limit of normal in combination with a normal level of free thyroxine in the absence of ongoing severe illness. An elevated TSH in combination with subnormal T4 characterizes overt hypothyroidism [2]. Subclinical hypothyroidism has been reported to occur with a prevalence of 4.3%, while overt hypothyroidism has a prevalence of 0.3% in the United States (US) [3].

In general, hypothyroidism is adequately treated with a consistent daily dose of levothyroxine – the exogenous form of T4. Levothyroxine is classified as a narrow therapeutic index (NTI) medication, which indicates that small differences in absorption or bioavailability may lead to therapeutic failure or adverse drug reactions [4-9]. Currently, levothyroxine medications are available in various formulations, including compressed tablets (generic and branded) and soft gel caps.

Many patients require dose adjustments during the course of levothyroxine therapy [10-15]. McMillan et al. [16] reported that up to 31% of hypothyroid patients receiving levothyroxine therapy for >2 years require one or more levothyroxine dosage adjustments annually. Common factors that can lead to, or necessitate, levothyroxine dose adjustments include a lack of medication persistence, dosage errors, changes in medical conditions, use of concomitant medications, body mass changes, and dietary habits [10-16].

It has been reported that oral absorption of levothyroxine may be hindered by certain foods, coffee beverages, and drugs [1,5,9,17-22]. There is also evidence indicating that hypothyroid patients treated with

levothyroxine gel caps may experience less thyroid hormone fluctuation than with treatment using levothyroxine tablets [23-28].

Methods

The aim of this study was to determine the incremental and total costs associated with substituting levothyroxine tablet formulations with levothyroxine gel caps in patients at risk for multiple dosage adjustments or formulation changes. A secondary aim was to quantify the difference in direct costs, indirect costs, and resource units based on the number of levothyroxine dose changes experienced by patients. In order to accomplish these objectives, a budget impact model was constructed for the determination of incremental and total costs – both direct medical and indirect costs – associated with switching targeted patients from levothyroxine tablets to a gel cap formulation of levothyroxine. The model was based on the hypothesis that the gel cap formulation reduces overall healthcare costs among patients who cannot achieve adequate hypothyroid symptom control with, or tolerate, traditional levothyroxine tablet formulations [29]. Only patients who had been on levothyroxine therapy for >1 year and required ≥ 1 levothyroxine dose changes in the past 12 months were included in the analysis. The model incorporates data obtained from the AACE/ATA Clinical Practice Guidelines for Hypothyroidism in Adults [2] to estimate the number of patients diagnosed and treated for hypothyroidism.

The model was developed using a series of cross-linked spreadsheets in Microsoft Excel. For purposes of transparency and flexibility, the model was designed to allow users to view all calculations, observe all default values with referenced data sources, and to input customized data to analyze different hypothetical scenarios.

The costs of managing two types of difficult-to-treat hypothyroid patients were explored in this study:

"hard-to-treat" patients who experience ≥ 1 levothyroxine dose change(s) annually

"harder-to-treat" patients who experience ≥ 2 levothyroxine dose changes annually.

Both patient cohorts were static without attrition or new patients entering the model population.

Economic parameters included medical interventions (i.e., emergency department (ED) visits, hospitalizations), clinical investigations (i.e., pathology and imaging), monitoring (e.g., laboratory tests, electrocardiograms), primary care provider (PCP) visits, and specialist visits. Costs used in the model were derived from published literature [30] and government/public sources [31].

Direct Costs	Cost per Event (US $)	Source/Method
Physician office visit	$123.42	Average of physician fees calculated by Physician Fee Schedule; Centers for Medicare & Medicaid Services [31]. Includes using Current Procedural Terminology (CPT-4) office visit codes (99203-99205, 99213-99215).
Specialist office visit	Low: $150.15 High: $290.25	CPT-4 codes for follow-up physician visits only, with pricing taken from 2014 Kaiser Permanente Endocrinology service cost estimates. A low value of $150.15 and a high value of $290.25 were assigned for each visit, and calculations using low values and high values were performed separately in order to consider the sensitivity of the range on overall costs [34].
Hospitalization (inpatient)	Low: $19,011 High: $29,186	Considered principal diagnosis of hyperthyroidism (ICD-9-CM code 244.9) derived from weighted national estimates available from the US Healthcare Utilization Project (HCUP) National Inpatient Sample (NIS). A low value of $19,011.00 and a high value of $29,186.00 were assigned for each visit, and calculations using low values and high values were performed separately in order to consider the sensitivity of the range on overall costs [35].
Emergency Department (ED) visit	Low: $580 High: $700	Estimated using average Medicare costs. A low value of $580.00 and a high value of $700.00 were assigned for each ED visit, and calculations using low values and high values were performed separately in order to consider the sensitivity of the range on overall costs [36].
Laboratory tests and imaging	Variable amounts, by category	Medicare Clinical Laboratory Fee Schedule (MCLFS), and grouped by type of test whenever multiple options were available (e.g., TSH, T3, T4); general 'thyroid panel', and other similar tests were categorized as 'thyroid tests/levels'. A value was assigned for each category of lab test, using values available from the MCLFS, and calculations using low values and high values were performed separately in order to consider the sensitivity of the range on overall costs. Test categories included the following: thyroid tests/levels, drug levels, kidney/renal function, hormone levels, except thyroid, cholesterol/lipid tests, infection markers/microbiology, cardiac tests, electrolytes, except panels, diabetes laboratories, anemia/hematology/bleeding/clotting, ob/gyn tests, imaging, GI tests, metabolic panels, general, liver/hepatic function, prostate health, pancreatic function, autoimmune tests, pituitary function, and other [31].
Synthroid: Medication Cost	WAC prices $33.88/28 day supply	MediSpan, October 2016 [32].
Tirosint: Medication Cost	WAC prices $111.82/28 day supply	MediSpan, October 2016 [32].

Table 1: Methods used to calculate Direct Medical Costs. Adapted from Ernst et al. 2017 [30].

The wholesale acquisition costs (WAC) of levothyroxine medications (tablets and gel caps) were obtained from MediSpan® [32]. Synthroid was chosen to be the comparator in this model because it is the most frequently prescribed brand of levothyroxine, representing over 90% of all dispensed prescriptions for branded levothyroxine products in 2016 [33]. All costs used in the model and results produced are reported in US dollars ($) (Table 1).

For ED visits and hospitalization, clinical considerations were drawn from studies in the literature, and only patients with hyperthyroid symptoms (tachycardia, tremors, or anxiety) with a reduction in levothyroxine dose within 3 weeks of the documented ED visit or hospitalization were included in the analysis [30]. Patients treated with levothyroxine less than 12 months were excluded based upon the assumption that dosage adjustments were likely attributable to treatment initiation rather than inadequate therapeutic effect [29].

Increased frequency of levothyroxine dose adjustments has been associated with higher direct and indirect resource costs [30]. In the CONTROL Switch Study, a medical chart review of 99 patients switched from levothyroxine tablets to levothyroxine gel caps, a statistically significant (P <0.0001) reduction of dose adjustments was observed among patients initiated on levothyroxine tablet formulation [29]. Using these data, the present model aggregates resource costs for each patient cohort ("hard-to-treat" and "harder-to-treat" patients) after a specified percentage of patients experience a switch to the gel cap formulation. The model calculates the direct resource costs from reductions in physician office visits, laboratory testing, specialist referrals, ED visits and other care episodes associated with the change in levothyroxine dose and formulation. Indirect costs are calculated based on the lost work productivity, or lost work time, associated with these additional care episodes. Lost productivity was calculated at a rate of $31.52/hour based on government and published sources (Table 2).

Indirect Costs	Cost per Event (US $)	Source/Method
Economic value of 1 hour of work	$31.52	Includes lost time and productivity, based on $31.52/ hour in average employee wages. Primary source was Food and Drug Administration Office of Public Health Strategy and Analysis paper entitled: "The Public Health Evidence of FDA Oversight of Laboratory Tests: 20 Case Studies". Published November, 2015 [37].
Physician office visit	$43.00	Average cost per visit according to a secondary analysis of the 2003-2010 American Time Use Survey (ATUS). Each visit was estimated at 121 minutes in average duration [38].
Specialist office visit	$43.49	Average cost per visit according to a secondary analysis of the 2003-2010 ATUS [38]. Each specialist visit was estimated at 122 minutes in average duration, assuming a slightly longer time with the clinician (21 minutes) versus a non-specialist physician (20 minutes), as reported by Shaw et al. 2014 [39].
Hospitalization (inpatient)	Cardiac cases: $882.56	Based on the $252.16-per-day value calculated by the FDA [40] and the estimated length of stay (LOS) for cardiac-related hospital stays and non-cardiac stays from the 2014 study by Shaw et al. (3.5 days for cardiac cases; 2.2 days for non-cardiac cases) [39].
	Non-cardiac cases: $554.75	
ED visit	$141.84	Estimated based on 4.5 hours of duration and the average value of an hour's lost work time of $31.52 per hour [37].
Laboratory tests and imaging	$18.48	From an estimated 15 minutes required for a blood draw by a phlebotomist, [41] plus an assumed 37 minutes of travel to the laboratory site (similar to a physician's office), [38] an average laboratory visit would take 52 minutes. Borrowing from the estimated time and cost of a physician visit noted above (121 minutes), the cost of the laboratory visit was calculated at $18.48.

Table 2: Methods used to calculate Indirect Costs. Adapted from Ernst et al. 2017 [30].

Results

The economic model demonstrates that, for every 500,000 persons, there are 23,000 (4.6%) hypothyroid patients, of which 18,400 (80.0%) receive treatment, and 17,480 (95.0%) of those patients receive levothyroxine. The proportion of patients requiring ≥ 1 dosage changes annually is 31.4%, producing 5,489 "hard-to-treat" patients. Similarly, the proportion of patients requiring ≥ 2 dosage changes annually is 8.0%, or 1,398 "harder-to-treat" patients. Using evidence-based data demonstrating the tolerability/absorption of levothyroxine gel caps and converting 20.0% of "hard-to-treat" patients to this formulation produced an annual net cost savings of $542,901 in direct medical costs and $564,650 in lost productivity. Upon converting 20.0% of "harder-to-treat" patients, an annual potential net cost savings of $409,107 in direct medical costs and $441,926 in lost productivity was observed. The following are highlights from the analysis:

Summary results - Direct Medical Costs

The reduction in direct medical costs for "hard-to-treat" patients was 9.8% for hospitalizations, 9.5% for ED visits, 4.8% for laboratory tests, 3.4% for office visits, and 1.0% for specialist visits. Savings were higher for "harder-to-treat" patients, with savings of 16.1% for ED visits, 15.5% for hospitalizations, 6.9% for laboratory tests, 6.2% for office visits, and 2.7% for specialist visits.

The largest driver of savings for direct medical costs was hospitalizations, with absolute annual savings of $296,244 and $272,963 for the "hard-to-treat" and "harder-to-treat" patient groups, respectively. Laboratory tests were the second largest contributor to

savings, with annual savings of $64,326 and $27,334, followed by ED visits with savings of $9,346 and $10,892 for each cohort, respectively. A summary of savings for direct medical costs is shown in Table 3.

"Hard-to-Treat" Cohort (n=5,489)					
Resource	**Annual Cost Before Switch to Gel Caps (US $)**	**Annual Cost After 20% Cohort Switch to Gel Caps (US $)**	**Savings (US $)**	**Savings (%)**	**Savings (US $/ patient)**
Labs	$1,341,935.06	$1,277,609.05	$64,326.00	4.8	$11.72
Specialists	$473,969.85	$469,396.52	$4,573.33	1	$0.83
ED Visits	$97,967.18	$88,621.13	$9,346.06	9.5	$1.70
Hospitalizations	$3,029,211.63	$2,732,967.47	$296,244.16	9.8	$53.97
Office Visits	$5,000,344.36	$4,831,933.11	$168,411.24	3.4	$30.68
TOTAL	$9,943,428.08	$9,400,527.28	$542,900.79	5.5	-
Total Per patient	$1,811.52	$1,712.61	$98.91	5.5	-
"Harder-to-Treat" Cohort (n=1,398)					
Resource	**Annual Cost Before Switch to Gel Caps (US $)**	**Annual Cost After 20% Cohort Switch to Gel Caps (US $)**	**Savings (US $)**	**Savings (%)**	**Savings (US $/ patient)**
Labs	$396,621.20	$369,287.03	$27,334.17	6.9	$19.55
Specialists	$132,959.87	$129,354.05	$3,605.82	2.7	$2.58
ED Visits	$67,514.75	$56,622.60	$10,892.15	16.1	$7.79
Hospitalizations	$1,759,208.18	$1,486,245.05	$272,963.12	15.5	$195.20
Office Visits	$1,530,996.29	$1,436,684.32	$94,311.96	6.2	$67.44
TOTAL	$3,887,300.29	$3,478,193.05	$409,107.22	10.5	-
Total Per patient	$2,780.62	$2,487.98	$292.64	10.5	-

Table 3: Direct Medical Costs and savings by resource.

Summary results - Indirect Medical Costs

There is a reflexive increase in indirect costs as measured by lost work time and productivity as medical care is consumed. In our analysis, indirect cost estimates were generated by using projected wait and treatment times for PCP office visits, specialist office visits, ED visits, hospitalizations, and laboratory tests. When projecting the effect of switching 20% of patients in each cohort from tablet formulations to the gel cap formulation, the following were observed:

For the 5,489 "hard-to-treat" patients, annual indirect costs are reduced by $564,650 (-4.8%).

For the 1,398 "harder-to-treat" patients, annual indirect costs are reduced by $441,926 (-9.9%).

Summary results – Resource units

The consumption of individual resource events per annum was estimated using per unit resource costs from the literature [30] (Table 1). In cases where more than one direct cost was available, the higher cost was used, which allowed for a conservative estimate. After converting 20.0% of patients in each cohort to the levothyroxine gel cap formulation, the following were observed:

The largest reduction in resource events consumed was for office visits, with the "hard-to-treat" and "harder-to-treat" patient groups experiencing a net reduction of 1,365 and 764 office visits per annum, respectively.

Specialist visits, ED visits, and hospitalizations had considerably fewer individual resource units saved per annum, with a reduction of no more than 16 annual events saved per resource in each cohort (resource units saved for laboratory events could not be estimated due to the large variability in costs for lab tests in CONTROL HE). A summary of annual resource units consumed is provided in Table 4.

Discussion

For over 60 years, the "gold standard" for treating hypothyroidism has been thyroid hormone replacement therapy with oral levothyroxine. With over 115 million prescriptions dispensed in 2013, [42] levothyroxine is one of the most frequently used medications in the US. Numerous published studies have demonstrated the difficulty of maintaining patients in the guideline-recommended therapeutic range for TSH using levothyroxine, with as many as 32-48% of patients being categorized as having either a "subadequate" or "excessive" response to therapy [3,43-46]. Factors affecting levothyroxine efficacy include patient persistence and compliance, medication tolerability,

and the presence of GI diseases and their treatments that can affect gastric acidity that is required for drug absorption [1,5,9-22].

"Hard-to-Treat" Cohort (n=5,489)						
Resource	**Cost Per Unit[30] (US $)**	**Annual Cost Before Switch to Gel Caps (US $)**	**Estimated Annual Units Consumed Before Switch**	**Annual Cost After 20% Cohort Switch to Gel Caps (US $)**	**Estimated Annual Units Consumed After Switch**	**Savings in Annual Units Consumed**
Specialists	$290.25	$473,969.85	1,633	$469,396.52	1,617	16
ED Visits	$700.00	$97,967.18	140	$88,621.13	127	13
Hospitalizations	$29,186.00	$3,029,211.63	104	$2,732,967.47	94	10
Office Visits	$123.42	$5,000,344.36	40,515	$4,831,933.11	39,150	1,365
"Harder-to-Treat" Cohort (n=1,398)						
Resource	**Cost Per Unit[30] (US $)**	**Annual Cost Before Switch to Gel Caps (US $)**	**Estimated Annual Units Consumed Before Switch**	**Annual Cost After 20% Cohort Switch to Gel Caps (US $)**	**Estimated Annual Units Consumed After Switch**	**Savings in Annual Units Consumed**
Specialists	$290.25	$132,959.87	458	$129,354.05	446	12
ED Visits	$700.00	$67,514.75	96	$56,622.60	81	15
Hospitalizations	$29,186.00	$1,759,208.18	60	$1,486,245.05	51	9
Office Visits	$123.42	$1,530,996.29	12,405	$1,436,684.32	11,641	764

Table 4: Resource event per annum savings. Values adapted from Ernst et al. 2017 [30].

Since levothyroxine is an NTI drug, small differences in dose or blood concentration may lead to therapeutic failures or adverse drug reactions [4-9,47]. It is not surprising that patients, pharmacists, and physicians have been concerned regarding the use of generic NTI drugs with varying levels of potency [48], particularly in diseases such as hypothyroidism. Accordingly, guidelines from the ATA Task Force state that clinical evidence favors consistent use of the same identifiable formulation of levothyroxine to avoid altered absorption that could lead to changes in serum TSH levels [49]. Once the therapeutic target is reached, the Task Force recommends that patients remain on the same dose and same preparation of levothyroxine [49]. In spite of these recommendations, changes in levothyroxine dosing and formulations are common.

The frequencies of levothyroxine dose and formulation changes have been documented in the published clinical literature. In the CONTROL Surveillance Study [16], a survey of 925 levothyroxine-treated patients, more than 23.4% of respondents claimed to have experienced one levothyroxine dose or formulation change in the prior 12 months. An additional 8% reported having experienced two or more such changes during the same period of time. Almost half of the patients receiving levothyroxine (435, 47.0%) had at least one comorbid condition that may adversely affect its absorption: gastroesophageal reflux disease (33.8% of patients), irritable bowel syndrome (9.7%), lactose intolerance (7.8%) or a history of gastric bypass surgery or bowel resection (3.0%). In our model, estimates for the mean number levothyroxine dose or formulation changes for the "hard-to-treat" and "harder-to-treat" patient populations correspond with these data.

The results of CONTROL Surveillance confirm those observed in other large-scale studies. In 2014, the AACE, ATA, and The Endocrine Society (TES) conducted a survey of 18,000 of their society members who are frequent prescribers of levothyroxine [48]. Respondents reported that switches from a branded levothyroxine product to a generic, or the interchange of generic formulations, occurred frequently. These changes were often made without the knowledge of the prescribing physician. According to the study's authors, changes in dosage and formulation are the most prevalent factors contributing to sub-optimal TSH levels among levothyroxine-treated patients [48].

The economic impact of levothyroxine dose changes has been described in the literature as well. Results of the CONTROL HE Study, a review of the medical charts of 454 hypothyroid patients with a history of prolonged levothyroxine treatment, demonstrated that healthcare resource utilization was $2,658 (US) higher per annum in patients experiencing ≥ 1 levothyroxine dose changes versus those with no dose adjustments during a 24-month study period [30]. When the direct and indirect healthcare costs were combined, patients requiring ≥ 3 dose adjustments incurred approximately 2.5 times greater total costs per annum compared with patients requiring no dose adjustments ($8,220 vs. $3,166, $P<0.05$).

In CONTROL HE, the authors reported that levothyroxine dose changes led to increases in both direct medical costs and lost work productivity, an important metric for employers and health policy makers. For patients who experienced no levothyroxine dose adjustments, the authors estimated the total cost of care (direct and indirect costs) at $1,583 per annum. The greatest contributors to this were laboratory testing, office visits, hypothyroidism drugs and lost work productivity. When frequent levothyroxine dose changes are needed, the situation changes. The authors estimated that the cost of managing hypothyroidism in patients requiring multiple levothyroxine dose changes escalated to $4,110 per annum (≥ 3 dose changes) during

the study period. Although these costs estimated for levothyroxine therapy may seem high, they appear to be modest when compared to the costs of other common chronic conditions (Table 5).

Disease	Est Direct Costs (US$)	Est Lost Productivity (US$)	Est Total Costs (US$)
Hypothyroidism - No Dose Change[a]	$1,091	$492	$1,583
Hypothyroidism ≥ 3 Dose Changes[a]	$3,194	$916	$4,110
Rheumatoid Arthritis [50,51]	$5,720	$5,822	$11,542
Fibromyalgia [52]	$10,312	$4,950	$15,262
Hypertension [53]	$6,645	$4,230	$10,875

Table 5: Per patient cost comparison of selected chronic disease categories/drugs per year. Adapted from Hallert 2014; Owens 2014; Sun 2014; Rachana 2014; Ernst 2017 [30,50-53]. [a]Estimated levothyroxine annual costs are 50% of 24-month study period costs [30].

"Hard-to-Treat" Cohort (n=5,489)					
Percentage Switched to the Gel Cap Formulation					
Annual Net Change	**10%**	**20%**	**30%**	**40%**	**50%**
Direct Cost	-$271,450.40	-$542,900.79	-$814,351.19	-$1,085,801.59	-$1,357,251.99
Indirect Cost	-$282,325.10	-$564,650.20	-$846,975.30	-$1,129,300.41	-$1,411,625.51
Subtotal	-$553,775.50	-$1,107.550.99	-$1,661,326.49	-$2,215,102.00	-$2,768,877.50
Drug Cost	$557,655.91	$1,115,311.82	$1,672,967.74	$2,230,623.65	$2,788,279.56
Total Budget Impact (US$)	$3,880.41	$7,760.83	$11,641.24	$15,521.66	$19,402.07
"Harder-to-Treat" Cohort (n=1,398)					
Percentage Switched to the Gel Cap Formulation					
Annual Net Change	**10%**	**20%**	**30%**	**40%**	**50%**
Direct Cost	-$204,553.62	-$409,107.24	-$613,660.86	-$818,214.47	-$1,022,768.09
Indirect Cost	-$220,962.99	-$441,925.97	-$662,888.96	-$883,851.94	-$1,104,814.93
Subtotal	-$425,516.61	-$851,033.21	-$1,276,549.82	-$1,702,066.41	-$2,127,583.02
Drug Cost	$142,077.94	$284,155.88	$426,233.82	$568,311.76	$710,389.70
Total Budget Impact (US$)	-$283,438.66	-$566,877.33	-$850,315.99	-$1,133,754.66	-$1,417,193.32

Table 6: Net budget impact as a factor of increasing gel cap formulation use.

As previously mentioned, our model is based on the potential that the gel cap formulation may reduce healthcare costs in patients who do not achieve adequate hypothyroid symptom control with, or tolerate, traditional levothyroxine tablet formulations. Evidence for this beneficial feature of the gel cap formulation has been previously reported. In a study of 99 patients who had previously been treated with traditional levothyroxine tablet therapy for ≥ 1 year before being switched to the gel cap formulation, Ernest et al. reported a 55% reduction in the mean number of documented dose changes required post medication switch (P<0.0001) [29]. Among patients who were switched to the gel cap for efficacy reasons rather than tolerability, there was a statistically significant 72.5% reduction in the mean number of dose changes observed post switch (P<0.0001). Equally important, hypothyroid symptom control improved in 64.0% of patients switched for efficacy reasons (P=0.0024). Patients switched for tolerability reasons experienced similar improvements in hypothyroid symptom control. It should be noted that most patients (75%) were switched from branded formulations of levothyroxine to the gel cap. Branded formulations are generally considered to offer more consistent drug absorption than generic formulations that are available at lower cost. All patients were under the care of a specialist physician [29].

Our model allows the user to adjust the percentage of targeted "hard-to-treat" and "harder-to-treat" patients switched to the gel cap formulation. For the purposes of our results, the default selection was a conservative 20% of each study cohort. When increasing the percentage of patients switched from traditional levothyroxine tablets to levothyroxine gel caps, direct and indirect costs are reduced substantially for both the "hard-to-treat" and "harder-to-treat" patient

cohorts. When evaluating the annual budget impact, "hard-to-treat" patients have a modest increase in overall budget impact, while "harder-to-treat" patients continue to experience substantial savings. Table 6 provides the net budget impact of direct costs, indirect costs, and drug costs as target cohorts are switched in larger numbers to the gel cap formulation.

In the contemporary healthcare systems, calculating the per-member-per-month (PMPM) costs are important economic assessments. Our analyses demonstrate that on a PMPM basis, net cost savings are achieved when a conservative percentage of "harder-to-treat" levothyroxine patients (20%) are switched to the levothyroxine gel cap formulation. Among this population, which, as stated previously, may represent up to 8% of all levothyroxine-treated patients, our model demonstrates PMPM savings of $0.09 (Table 7).

"Hard-to-Treat" Cohort (n=5,489)					
Before Switch to Gel Caps (US$)			**After 20% Cohort Switch to Gel Caps (US$)**		
Resource	**Total Annual Cost**	**PMPM Cost**	**Total Annual Cost**	**PMPM Cost**	**PMPM Cost Difference (US$)**
Direct Cost	$9,943,428.08	$1.66	$9,400,527.29	$1.57	$-0.09
Indirect Cost	$11,678,214.60	$1.95	$11,113,564.40	$1.85	$-0.09
Drug Cost	$2,424,093.19	$0.40	$3,539,405.01	$0.59	$0.19
Total	$24,045,735.87	$4.01	$24,053,496.70	$4.01	$0.00
"Harder-to-Treat" Cohort (n=1,398)					
Before Switch to Gel Caps (US$)			**After 20% Cohort Switch to Gel Caps (US$)**		
Resource	**Total Annual Cost**	**PMPM Cost**	**Total Annual Cost**	**PMPM Cost**	**PMPM Cost Difference (US$)**
Direct Cost	$3,887,300.29	$0.65	$3,478,193.05	$0.58	$-0.07
Indirect Cost	$4,465,671.54	$0.74	$4,023,745.56	$0.67	$-0.07
Drug Cost	$617,603.36	$0.10	$901,759.24	$0.15	$0.05
Total	$8,970,575.19	$1.50	$8,403,697.85	$1.40	$-0.09

Table 7: Per-Member-Per-Month (PMPM) cost and savings.

While no savings were observed in the "hard-to-treat" patient cohort on a PMPM basis, the improvement in clinical symptoms experienced by many patients when switched from traditional levothyroxine tablets to the gel cap formulation may be viewed as coming without significant incremental cost to healthcare payers. These findings may contribute to building a value-based outcomes approach to the treatment of targeted levothyroxine patients by health plan providers, resulting in reduced direct and indirect costs that outweigh increased drug acquisition costs.

Study limitations

The studies used to support our analyses represent a cohort of patients treated for hypothyroidism in ambulatory settings in the US, from physicians who agreed to participate in a medical record review. This population may not be representative of the overall levothyroxine-taking population. Similarly, costs used in the model for various care episodes such as lab tests, physician office visits, ED visits, and hospitalizations were estimated average costs cited in published sources and may not represent differences that exist between various geographies and healthcare systems.

Another limitation of our analysis concerns the estimates used to calculate the number of dose adjustments that occur after patients are switched to the gel cap formulation. In the CONTROL Switch Study, patient records were reviewed for six months *prior to* switching from traditional levothyroxine tablets to the gel cap formulation and then for six months post medication switch. In total, medical records were available for 86% of patients for six months or more *after* switching to gel caps. These records documented all dose changes and subsequent episodes of care. However, records were not available for six months post switch for 14% of patients. Among those patients, the authors concluded that episodes of dose changes and incremental medical care were not statistically different from those of the overall population.

A point needs to be made about the costs of acute care episodes used in our model. The cost estimates relative to ED visits and hospitalization found in CONTROL HE are plausible based on prior published observations. Several studies have shown that excessive exposure to levothyroxine occurs frequently, ranging from 14 to 22% of all patients [3,43-46]. While many patients experiencing excessive doses of levothyroxine do not require hospitalization or ED visits, the financial impact of acute care episodes linked to levothyroxine overdosing is poorly understood. The lack of additional data to corroborate the findings of CONTROL HE represents an unavoidable limitation of our analysis. Measuring the costs associated with these episodes is an important health policy matter that deserves to be further investigated in well-controlled studies.

Our model does not take into consideration the addition of newly-treated patients or patient attrition. The static nature of our analysis may be viewed as a limitation. However, hypothyroidism is a long-

standing condition for which the incidence and prevalence of disease has not changed considerably [3].

The use of generic instead of branded levothyroxine as the main comparator would have yielded different net budget impact savings, as generic formulations tend to be less expensive. This can be viewed as a limitation of our analysis. It is important to consider the stated objectives of the CONTROL Switch and CONTROL HE studies [29,30]. The primary objective was to measure the prevalence and health economic costs associated with the therapeutic failure of levothyroxine tablets (branded or generic formulations) as measured by dose and formulation changes. An additional objective [29] was to measure the clinical and economic advantages of switching to the levothyroxine gel cap formulation in patients who had failed levothyroxine tablet therapy. Many healthcare plans in the US advocate the use of generic levothyroxine tablets for newly-diagnosed hypothyroid patients, with branded versions of levothyroxine (including the gel cap) reserved as second-line therapy. Our model therefore compares the costs of using the levothyroxine gel caps versus the leading branded formulation of levothyroxine tablets, rather than generic formulations, for second-line treatment of hypothyroidism. It is important to note that in the CONTROL Switch Study, 75% of the patients were on branded levothyroxine tablets prior to changing to gel caps; 25% of patients were on generic levothyroxine tablet therapy prior to switching [29]. The authors concluded that there was no statistically significant difference in reduced dose changes between patients initiated on either generic or branded levothyroxine therapy after switching to the gel cap formulation, with both cohorts receiving equal benefit from the medication change.

Finally, our cost calculations did not take into account product rebates, discounts, risk-sharing agreements, and other cost-reduction initiatives that may be available to payers. This information is proprietary and not widely available. We used the well-known wholesale acquisition cost (WAC) for comparisons between products. The ability to customize our model based on differing patient population characteristics and differing estimated costs of care recognizes these limitations and allows users to project the potential costs of various care scenarios.

Conclusion

Most hypothyroid patients are adequately managed with a consistent daily dose of levothyroxine. However, levothyroxine dose adjustments and formulation changes occur often in clinical practice. These can have profound implications for healthcare payers given the size of the levothyroxine-treated population as well as the magnitude of additional direct and indirect costs associated with each incremental change in levothyroxine dose or formulation.

The use of real-world data that reflects current clinical practice has become an accepted part of health outcomes research. The best budget impact models for individual drugs utilizing real-world data are those that reflect costs of specific therapies to individual healthcare payers (direct costs) as well as costs to society as a whole (indirect costs). Modeling this data provides an opportunity to more fully understand the various factors that contribute to the savings or cost that an individual therapy may produce in clinical practice.

Our model quantitatively expands the results and conclusions reported in prior studies. It demonstrates that the cost of the management of hypothyroidism is significantly higher for patients who are unable to achieve adequate TSH or hypothyroid symptom control with traditional tablet formulations of levothyroxine. The clinical and economic benefits of switching these patients to a gel cap formulation of levothyroxine, rather than adjusting the dose or changing tablet formulations, represents an opportunity to improve the quality of care and reduce the economic burden of hypothyroidism.

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Conflicts of Interest

Riad Elmor is a former employee of Indegene Inc., which received a fee for services related to the development of the analytical model described. Charles Carter has been a consultant for Akrimax, has contributed to research funded by Akrimax, and has received an honorarium for his contributions to the development of this research. Walter Sandulli is an employee of Akrimax Pharmaceuticals.

Ethical Standards

All studies whose results are used as supporting data for our analysis were reviewed and approved by licensed institutional review boards. To insure the research complied with HIPAA legislation, a waiver of authorization was obtained according to 45 CFR 164.512 (i)(1)(i) for each study which allowed the collection of protected health information without the authorization of the research participants for research purposes.

References

1. Ward LS (2010) The difficult patient: drug interaction and the influence of concomitant diseases on the treatment of hypothyroidism. Arq Brasil Endocrinol Metab 54: 435-442.
2. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, et al. (2012) Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 22: 1200-1233.
3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, et al. (2002) Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87: 489-499.
4. Khandelwal D, Tandon N (2012) Overt and subclinical hypothyroidism: who to treat and how. Drugs 72: 17-33.
5. Liwanpo L, Hershman JM (2009) Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab 23: 781-792.
6. Fasano A, Catassi C (2012) Clinical practice. Celiac disease. N Engl J Med 367: 2419-2426.
7. Gaitonde DY, Rowley KD, Sweeney LB (2012) Hypothyroidism: an update. Am Fam Physician 86: 244-251.
8. Cellini M, Santaguida MG, Gatto I, Virili C, Del Duca SC, et al. (2014) Systematic appraisal of lactose intolerance as cause of increased need for oral thyroxine. J Clin Endocrinol Metab 99: E1454-E1458.
9. Ianiro G, Mangiola F, Di Rienzo TA, Bibbò S, Franceschi F, et al. (2014) Levothyroxine absorption in health and disease, and new therapeutic perspectives. Eur Rev Med Pharmacol Sci 18: 451-456.
10. Dar RA, Chowdri NA, Parray FQ, Wani SH (2012) An unusual case of Hashimoto's thyroiditis with four lobed thyroid gland. N Am J Med Sci 4: 151-153.

11. Yaturu S, Fontinot J, Rowland T (2011) Mixed medullary thyroid cancer and follicular cancer. Am J Case Rep 12: 1-4.
12. Robertson HM, Narayanaswamy AK, Pereira O, Copland SA, Herriot R, et al. (2014) Factors contributing to high levothyroxine doses in primary hypothyroidism: an interventional audit of a large community database. Thyroid 24: 1765-1771.
13. Santini F, Pinchera A, Marsili A, Ceccarini G, Castagna MG, et al. (2005) Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J Clin Endocrinol Metab 90: 124-127.
14. Roos A, Linn-Rasker SP, Van Domburg RT, Tijssen JP, Berghout A (2005) The starting dose of levothyroxine in primary hypothyroidism treatment. A prospective, randomized, double-blind trial. Arch Intern Med 165: 1714-1720.
15. Mandel SJ, Brent GA, Larsen PR (1993) Levothyroxine therapy in patients with thyroid disease. Ann Intern Med 119: 492-502.
16. McMillan M, Rotenberg KS, Vora K, Sterman AB, Thevathasan L, et al. (2016) Comorbidities, concomitant medications, and diet as factors affecting levothyroxine therapy: results of the CONTROL Surveillance project. Drugs R D 16: 53-68.
17. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F (1995) Delayed intestinal absorption of levothyroxine. Thyroid 5: 249-253.
18. Ramadhan A, Tamilia M (2012) Treatment-refractory hypothyroidism. CMAJ 184: 205-209.
19. Sachmechi I (1997) Vitamin D reduces thyroxine efficacy in patients on L-thyroxine therapy. AACE 6th Annual Meeting 134: 4.
20. Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J (2009) Timing of levothyroxine administration affects serum thyrotropin concentration. J Clin Endocrinol Metab 94: 3905-3912.
21. Irving SA, Vadiveloo T, Leese GP (2015) Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS). Clin Endocrinol (Oxf) 82: 136-141.
22. Trifirò G, Parrino F, Sultana J, Giorgianni F, Ferrajolo C, et al (2015) Drug interactions with levothyroxine therapy in patients with hypothyroidism: observational study in general practice. Clin Drug Investig 35: 187-195.
23. Pabla D, Akhlaghi F, Zia H (2009) A comparative pH-dissolution profile study of selected commercial levothyroxine products using inductively coupled plasma mass spectrometry. Eur J Pharm Biopharm 72: 105-110.
24. Virili C, Santaguida MG, Cellini M, Del Duca SC, Gargano L, et al. (2013) Pilot study with softgel thyroxine preparation in the treatment of patients with T4 malabsorption due to gastric disorders. Endocrine Rev 34: 50-54.
25. Santaguida MG, Virili C, Del Duca SC, Cellini M, Gatto I, et al. (2015) Thyroxine softgel capsule in patients with gastric-related T4 malabsorption. Endocrine 49: 51-57.
26. Seng Yue C, Benvenga S, Scarsi C, Loprete L, Ducharme M (2015) When bioequivalence in healthy volunteers may not translate to bioequivalence in patients: differential effects of increased gastric pH on the pharmacokinetics of levothyroxine capsules and tablets. J Pharm Pharm Sci 18: 844-855.
27. Vita R, Benvenga S (2014) Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in gel cap capsule. Endocr Pract 20: e38-e41.
28. Vita R, Saraceno G, Trimarchi F, Benvenga S (2012) In patients with no interference on the intestinal absorption of L-T4 caused by gastro-intestinal disorders or drugs, a liquid formulation of L-T4 permits to reach target TSH levels that were missed by the conventional tablet formulation. Eur Thyroid 1: 125.
29. Ernst FR, Sandulli W, Elmor R, Welstead J, Sterman AB, et al. (2017) Retrospective Study of Patients Switched from Tablet Formulations to a Gel Cap Formulation of Levothyroxine: Results of the CONTROL Switch Study. Drugs RD 17: 103-115.
30. Ernst FR, Barr P, Elmor R, Sandulli W, Thevathasan L, et al. (2017) The economic impact of levothyroxine dose adjustments: the CONTROL HE study. Clin Drug Investig 37: 71-83.
31. Centers for Medicare & Medicaid Services (2015) Physician Fee Schedule Search. Available from: https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx
32. Medi-Span®. Indianapolis (IN): Medi-Span®. Master Drug Data Base v2.5 (MDDB®). Available from: http://www.medispan.com/master-drug-database.aspx
33. IMS Health, NPA Extended Insights Audit, August, 2017.
34. Endocrinology (2014) Deductible plan members or non-covered services. http://info.kaiserpermanente.org/info_assets/colorado-deductible-plans/pdfs/endocrinology_fee_list.pdf
35. HCUP-US NIS Overview - Agency for Healthcare Research. https://hcupnet.ahrq.gov/#setup
36. Blue Cross Blue Shield of Massachusetts. Typical Costs for Common Medical Services. http://www.bluecrossma.com/blue-iq/pdfs/TypicalCosts_89717_042709.pdf
37. Food and Drug Administration (2015) Office of Public Health Strategy and Analysis. The Public Health Evidence of FDA Oversight of Laboratory Tests: 20 Case Studies. https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM4727.pdf
38. Ray KN, Chari AV, Engberg J, Bertolet M, Mehrotra A (2015) Opportunity costs of ambulatory medical care in the United States. Am J Manag Care 21: 567-574.
39. Shaw MK, Davis SA, Fleischer AB, Feldman SR (2014) The duration of office visits in the United States, 1993 to 2010. Am J Manag Care 20: 820-826.
40. Red Book online (database online). Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com. Accessed 3 Aug 2015.
41. Mijailovic AS, Tanasijevic MJ, Goonan EM, Le RD, Baum JM, et al. (2014) Optimizing outpatient phlebotomy staffing: tools to assess staffing needs and monitor effectiveness. Arch Pathol Lab Med 138: 929-935.
42. IMS Institute for Healthcare Informatics (2014) Medicine use and shifting costs of healthcare. IMS Health 46.
43. Ross DS, Daniels GH, Gouveia D (1990) The use and limitations of a chemiluminescent thyrotropin assay as a single thyroid function test in an out-patient endocrine clinic. J Clin Endocrinol Metab 71: 764-769.
44. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC (1993) Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment. Br J Gen Pract 43: 107-109.
45. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160: 526-534.
46. Vaisman F, Coeli CM, Ward LS, Graf H, Carvalho, et al. (2013) How good is the levothyroxine replacement in primary hypothyroidism patients in Brazil? Data of a multicentre study. J Endocrinol Invest 36: 485-488.
47. Tamargo J, Le Heuzey JY, Mabo P (2015) Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. Eur J Clin Pharmacol 71: 549-567.
48. Hennessey JV, Malabanan AO, Haugen BR, Levy EG (2010) Adverse event reporting in patients treated with levothyroxine: results of the pharmacovigilance task force survey of the American Thyroid Association, American Association of Clinical Endocrinologists, and the Endocrine Society. Endocr Prac 16: 357-370.
49. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, et al. (2014) American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid 24: 1670-1751.
50. Hallert E, Husberg M, Kalkan A, Skogh T, Bernfort L (2014) Early rheumatoid arthritis 6 years after diagnosis is still associated with high direct costs and increasing loss of productivity: the Swedish TIRA project. Scand J Rheumatol 43: 177-183.
51. Owens GM (2014) Managed care implications in managing rheumatoid arthritis. Am J Manag Care 20: S145-S152.

52. Sun P, Peng X, Sun S, Novick D, Faries DE, et al. (2014) Direct medical costs and medication compliance among fibromyalgia patients: duloxetine initiators vs. pregabalin initiators. Pain Pract 14: 22-31.

53. Rachana PR, Anuradha HV, Shivamurthy MC (2014) Anti hypertensive prescribing patterns and cost analysis for primary hypertension: a retrospective study. J Clin Diagn Res 8: HC19-HC22.