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REVIEW

# Levothyroxine Formulations: Pharmacological and Clinical Implications of Generic Substitution

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## ABSTRACT

Oral levothyroxine (LT4) is the standard therapy for patients with hypothyroidism. Oral LT4 is available in several formulations, including tablets, soft gel capsules and oral solution. Multiple brand-name and generic LT4 tablets are available. In the US, the Food and Drug Administration (FDA) has developed a protocol for establishing bioequivalence of LT4 formulations based on serum thyroxine (T4) levels after a single oral dose administered to healthy

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volunteers. This protocol has been criticized by professional endocrinology associations for using healthy individuals and ignoring serum thyroid-stimulating hormone (TSH) levels. In addition, the protocol did not initially correct for baseline T4 levels, although this was changed in a later version. There are concerns that the FDA's protocol could allow products with clinically significant differences in bioavailability to be declared therapeutically equivalent and interchangeable. Once a generic LT4 has been shown to be bioequivalent to a brand-name LT4, it may be substituted for that brand-name LT4 with no need for dose adjustment or follow-up therapeutic monitoring. Often, the substitution is made by the pharmacy without the physician's knowledge. Even small differences between LT4 formulations can cause significant changes in TSH levels. This may be a particular concern in vulnerable populations, including elderly, pregnant, and pediatric patients. Problems that can be encountered when switching between formulations or when original products are reformulated are discussed in this review. These problems include altered efficacy and adverse events, some of which can be caused by excipients. Patients should be maintained on the same LT4 preparation if possible. If the LT4 preparation is changed, TSH levels should be evaluated and, if necessary, the dose of LT4 adjusted.

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## PLAIN LANGUAGE SUMMARY

Orally administered levothyroxine (LT4) is the standard treatment for hypothyroid patients. Several different LT4 products are available. Sometimes, pharmacists may substitute a patient's usual LT4 product for a less expensive one, especially if this is the policy of the organisation that is paying for the medicine (e.g., health insurer or public health provider). Because even small differences between LT4 products can have significant effects on how well the drug works, or the types of side effects it may cause, most clinical practice guidelines recommend that patients stay on the same LT4 preparation if possible. If the patient needs to switch to a new LT4 product, physicians should ensure that the dose is adjusted to suit the patient.

## INTRODUCTION

Thyroid hormone replacement therapy with oral levothyroxine (LT4) is the standard treatment for patients with hypothyroidism [1–3]. The goals of treatment include resolution of symptoms and signs of hypothyroidism and normalization of circulating thyroid-stimulating hormone (TSH) levels [3]. Orally administered LT4 is available in several formulations (including tablet, soft gel capsule and liquid formulations) [2, 4], and LT4 tablets are available in multiple branded and generic forms [2]. The traditional tablet formulation contains LT4 sodium, a stable salt, and a variety of inactive excipients, the composition of which may affect tablet stability and pharmacokinetics [4–8].

The US Food and Drug Administration (FDA) defines a 'generic drug' as a medication that has

the same dosage form, safety, strength, route of administration, quality, performance characteristics and intended use as an already marketed brand-name medication [9]. The European Medicines Agency (EMA) defines generic drugs as those that have the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference drug and whose bioequivalence with the reference drug has been demonstrated by appropriate bioavailability studies [10]. With regard to generic and branded LT4 preparations, endocrinologists around the world differ in their preferences. According to a survey of 880 members of The Endocrine Society (TES), the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE), 49.9% of respondents preferred brand-name LT4, while 49.3% preferred generic LT4. However, among European members, who represented 9.2% of respondents, the proportion of those who preferred a brand-name drug was 58.8% [11].

At present, the FDA uses serum thyroxine (T4) levels to establish the bioequivalence of LT4 products [12]. Based on the FDA criteria for bioequivalence (described in detail in the section "[Bioequivalence and interchangeability](#)"), substitution between bioequivalent generic and brand-name LT4 can be automatically performed with no need for dose adjustment. There is ongoing debate around concerns that the currently used pharmacokinetic approach for assessing the bioequivalence of LT4 products could allow products with clinically significant differences in bioavailability to be declared therapeutically equivalent and interchangeable [3, 12–19]. Therefore, the ATA, the ES and the AACE have issued a joint statement encouraging consistent use of the same branded or generic LT4 formulation in individual patients (i.e., patients should not be regularly switched from one brand to another, from a branded to a generic product or from a generic product to another generic product) [13]. These recommendations have since been reinforced by guidelines from the Endocrine Society of Australia, the European Thyroid Association and Thyroid Federation International [3, 20, 21], and are summarized in Table 1. If a switch to

**Table 1** Summary of practices for physicians and patients, with regard to switching levothyroxine formulations, that were proposed in international/national guidelines/statements [3, 13, 20, 21]

For physicians

Patients should be maintained on the same brand name of levothyroxine product

If the brand of levothyroxine medication is changed from one brand to another brand, from a brand to a generic product or from a generic product to another generic product:

Patients should be re-evaluated and retested by measuring serum TSH in 6 weeks;

The drug should be retitrated as needed

For patients

Use the same brand of thyroid medication throughout your treatment

Thyroid disease often requires lifelong therapy and is best managed with consistent and precise treatment with the same brand of thyroid hormone

Your doctor may change your dose of thyroid hormone, but the brand of your thyroid hormone medication should always stay the same

When you go to the pharmacy, do not change the brand of your thyroid medication without checking with your doctor

You should not change your dose from one brand of thyroid medication to another, from your brand of thyroid medication to a generic product, or from one generic product to another without first checking with your doctor

If your doctor changes the type of thyroid medication you are taking, you will need to have repeat blood tests and visits to your doctor to make sure that you are on the correct dose. Your dose may need to be readjusted if your thyroid medication is changed

another LT4 formulation is made (for instance, because the waiting time between LT4 ingestion and breakfast is an issue for the patient or because the patient is co-ingesting drugs known to impair the intestinal absorption of LT4), repeat thyroid function testing is recommended (i.e., serum TSH testing within 4 weeks to determine whether dose adjustment is required) [3, 13, 19, 21].

Switching was considered to be a particular concern in vulnerable populations, including elderly, pregnant and pediatric patients [3, 13], especially since these patients are often excluded from the studies undertaken to establish bioequivalence [10]. This review describes problems that can be encountered when switching between formulations or when original products are reformulated.

## METHODS

In December 2018, the PubMed database was searched for articles of potential interest using “levothyroxine” in combination with each of the following search terms: “interchangeability”, “bioequivalence”, “formulations” and “generic”. These combinations returned 10, 120, 128 and 79 entries, respectively. The titles and abstracts of English-language articles identified through the search were then reviewed to determine relevance. Furthermore, the reference lists of the relevant articles were used to identify additional literature. This article is based on previously conducted studies and does not contain any studies with animals performed by any of the authors. Some of studies cited include analyses, or studies with human

participants, performed by the authors and completed prior to the initiation of this manuscript.

## BIOEQUIVALENCE AND INTERCHANGEABILITY

Bioequivalence of LT4 formulations is defined as the absence of a significant difference in bioavailability, expressed in terms of the maximum concentration ( $C_{\max}$ ) or area under the curve (AUC), of the active ingredient of a drug product when administered at the same molar dose in healthy volunteers [14, 18, 22]. A specific LT4 pharmacokinetic protocol for bioequivalence has been developed by the FDA [2, 23]. In this protocol, a single oral dose of 600  $\mu\text{g}$  of LT4 is administered to healthy volunteers [12]. The 90% confidence interval (CI) for test/reference product geometric mean AUC and  $C_{\max}$  ratios of serum T4 must be in the 80–125% range [14]. Note that the 90% CI for narrow therapeutic index drugs is 90–111.1%, and LT4 is often considered a narrow therapeutic index drug [13, 14, 24]. The FDA assigns an AB + number TE code to LT4 tablets (Table 2) [25–33]. Products with the same TE code are considered therapeutically equivalent [32].

The LT4 bioequivalence protocol produced by the FDA has been criticized by professional endocrinology associations. In their joint letter, the ATA, the ES and the AACE pointed out that pharmacokinetic assessments are not suitable for biologics and that the protocol does not include TSH assessment [13]. Omitting TSH is illogical, considering that it is the most sensitive and easily measurable biochemical target of thyroid hormone action and because of its importance for monitoring the adequacy of LT4 treatment [14, 24]. Yet, we think that with a half-life of approximately 1 h, a minimum of four measurements (two baseline, one intermediate and one final) could be added to the FDA protocol with little extra cost incurred. In addition, the FDA protocol did not initially include correction for baseline T4 levels [12]. According to the 2014 ATA guidelines, a more appropriate measure of bioequivalence would

be based on T4, triiodothyronine (T3) and TSH levels after daily administration for at least 4–6 weeks conducted in athyreotic individuals [3]. These guidelines refer to research conducted by Mayor and colleagues [34], who re-analyzed data previously published by Dong and colleagues [35], showing that LT4 products considered to be both pharmacokinetically and therapeutically bioequivalent were not in fact therapeutically bioequivalent when correction for baseline T4 was applied [34]. The FDA later included correction for baseline T4 in its protocol [12]. Another drawback of FDA's protocol is the use of healthy volunteers. In a study that included 4 patients with goiter, 12 euthyroid controls and 10 primary hypothyroid controls who were administered LT4 1000- $\mu\text{g}$  tablets, serum T4 curves in the two control groups were shown to be not entirely superimposable [36].

There are no equivalent European guidelines for the demonstration of LT4 formulation bioequivalence, but the FDA bioequivalence guidelines for LT4 are referred to in European countries [37, 38]. Instead, the relevant European guideline is the 2010 European Medicines Agency Guideline on the Investigation of Bioequivalence [10]. This guideline is focused on immediate-release formulations of chemical entities with systemic action, while modified-release, transdermal and orally inhaled formulations, as well as biologicals, are not covered. According to this Guideline, medicinal products containing the same active substance are considered to be bioequivalent “if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e., similarity in terms of safety and efficacy” [10]. Medicinal products are considered to be pharmaceutically equivalent if they “contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards” [10]. Of note, pharmaceutical equivalence does not always imply bioequivalence because differences in excipients and the manufacturing process can affect pharmacokinetics [10].

**Table 2** FDA therapeutic equivalence ratings for currently available levothyroxine tablet products [25–33]

Levothyroxine tablet product	Reference listed drug <sup>a</sup>	Therapeutic equivalence code <sup>b</sup>	Inactive ingredients <sup>c</sup>
Brand name			
Unithroid	Yes	AB1, AB2, AB3	Acacia, colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate
Synthroid	Yes	AB1, AB2	Acacia, confectioner's sugar (contains corn starch), lactose monohydrate, magnesium stearate, povidone, talc
Levoxyl	Yes	AB1, AB3	Calcium sulfate dehydrate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium bicarbonate
Levo-T	No	AB1, AB2, AB3	Magnesium stearate, microcrystalline cellulose, colloidal silicone dioxide, sodium starch glycolate
Euthyrox	No	AB2	Citric acid anhydrous, corn starch, gelatin, magnesium stearate, mannitol, sodium croscarmellose
Generic			
Levothyroxine sodium (Mylan)	No	AB1, AB2, AB3, AB4	Butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, ethyl alcohol, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, sucrose

<sup>a</sup> A drug identified by the FDA as a product on which an applicant relies in seeking approval of an abbreviated new drug application for a generic product

<sup>b</sup> If bioequivalence to a reference listed drug product is demonstrated, the product will be given the same code as the reference listed drug it was compared against: AB1 vs. Unithroid, AB2 vs. Synthroid, AB3 vs. Levoxyl; AB4 vs. Levotheroid/Thyro-Tabs (now discontinued). One common code indicates therapeutic equivalence between products

<sup>c</sup> All formulations except Euthyrox also contain colorants that differ according to tablet dose

According to this Guideline, bioequivalence studies should be conducted in healthy volunteers unless the drug is associated with safety concerns that would make this unethical. In most cases, it should be possible to extrapolate the results of such studies to other populations such as the elderly, children and patients with renal or liver impairment [10].

In order to assess bioequivalence after a single dose, the Guideline recommends analyzing  $AUC_{(0-t)}$  or, when relevant,  $AUC_{(0-72h)}$ , and  $C_{max}$ . In order to assess bioequivalence of immediate release formulations at a steady state, analysis of  $AUC_{(0-\tau)}$  and  $C_{max,SS}$  is recommended. Bioequivalence is established when the 90% CI for the ratio of the test and reference products is  $\geq 80.00\%$  and  $\leq 125.00\%$  when

rounded to two decimal places. The acceptance interval may need to be narrowed to 90.00–111.11% for products with narrow therapeutic range [10].

In Europe, medicinal products are considered to be therapeutically equivalent if they contain the same active substance or therapeutic moiety and have the same clinical efficacy and safety. Therapeutic equivalence can be established by demonstrating bioequivalence if the excipients contained within the products are generally recognized as not affecting their safety and efficacy. Bioequivalence can be established using pharmacokinetic instead of therapeutic data if, in the same individual, similar plasma concentrations over a similar

time course will result in similar concentrations at the site of action [39].

### Tablet Formulations

In the US, physicians currently have a choice of several LT4 sodium tablet preparations, five branded products and one generic formulation (Table 2) [31]. According to the US FDA system of evaluation for therapeutic equivalence, preparations with the same TE code are considered to be interchangeable (Table 2) [31, 32]. Although several LT4 products do have similar pharmacokinetic performance, this is not assured for each of the AB-rated pairs because not all have been directly compared in pharmacokinetic studies [2]. A range of LT4 tablet brand-name and generic formulations are also available in Europe and used interchangeably (brand-name products include Eltroxin, Euthyrox/Levothyrox, Thyrax, Tirosint, Eutirox, Letrox and Levaxin) [21, 38, 40, 41].

According to an analysis of US medical insurance claims data between 2007 and 2016, 73.6% of thyroid hormone prescription fills were for generic LT4 and 23.4% were for brand-name LT4 (the remainder comprised other thyroid hormone drugs) [42]. The proportion of generic LT4 fills increased from 59.8% in 2007 to 84.9% in 2016. Prescription of brand-name LT4 was more common for women and by endocrinologists, while it was less common for elderly patients [42].

Interestingly, generic LT4 preparations are no longer used in France, partly because doctors are reluctant to prescribe them [43]. Based on the authors' experience, generic LT4 tablets are rarely used in Italy or Denmark. In addition, Danish pharmacies produce small amounts of lactose-free LT4 tablets with microcrystalline cellulose and potato starch as the only excipients present.

### Soft Gel and Liquid Formulations

Soft gel and liquid LT4 formulations are alternative dosage forms of LT4 [2, 22, 37]. Lower doses of LT4 are generally required with these formulations compared with traditional tablets,

because dissolution of tablet excipients does not need to occur before LT4 is available for bowel absorption [2, 44]. Soft gel and liquid formulations are preferable in patients who have reduced intestinal absorption of LT4 due to gastrointestinal disorders or concomitant drugs [41]. Any change between various LT4 formulations in such patients should be performed with special care.

Tirosint/Tiche/Syntroxine is a unique LT4 product available in the USA and Europe as a soft-gel capsule, and in Europe as a liquid formulation [2, 31, 37]. Lactose-free soft gel (LT4 dissolved in glycerin surrounded by a layer of gelatin) and liquid formulations (LT4 dissolved in glycerol and ethanol) are bioequivalent to traditional LT4 tablets in healthy volunteers, but may perform better in patients with gastrointestinal malabsorption conditions and when taken with foods and certain interacting drugs, and in patients with TSH values close to the limits of the desired therapeutic range [6, 37, 41, 44–53]. However, most studies showing better absorption with soft gel or liquid LT4 formulations compared with tablets were published after the ATA guidelines were released. As a result, there are no specific recommendations for the use of such formulations in these circumstances, but it has been suggested that they may be useful in patients with allergies or side effects to the excipients found in some LT4 tablets (e.g., lactose in Synthroid) [3, 54–56].

Caution is advised when prescribing ethanol-containing products to certain patients, including pregnant and lactating women and patients with liver disease or epilepsy [41]. However, no adverse events were reported in a study that included 14 pregnant women treated with liquid LT4 [57]. A new oral solution free from ethanol, propylene glycol and preservatives that has been shown to be bioequivalent to Tirosint capsules has also been developed [58]. An ethanol-free liquid formulation of Eltroxin is also available in Europe, as are several generic versions [41]. However, this formulation contains sodium methyl parahydroxybenzoate as a preservative, which may cause allergic reactions, including delayed reactions [59].

## REFORMULATION

To minimize the variability of LT4 products, the FDA now requires LT4 products to retain 95–105% of labeled LT4 content over the expected shelf life of the product instead of the previously accepted range of 90–110% [60]. The US Pharmacopeia revised their monograph for levothyroxine sodium tablets to support this change. These revisions went into effect in October 2009 [61]. The French Agence Nationale de Sécurité des Médicaments (ANSM) also requires that LT4 products retain 95–105% of LT4 content, whereas 90–105% is acceptable in the UK [24, 38].

Several branded products have been reformulated to meet the new standards, including Euthyrox/Levothyrox and Levoxyl tablets and Tirosint soft-gel capsules [2, 62–64]. Using the FDA criteria, the new formulations have been shown to be bioequivalent to the old formulations (Table 3) [62–64]. Geometric mean  $AUC_{(0-72h)}$  and  $C_{max}$  ratio 90% CIs for Euthyrox were both within the 90–111% acceptance range for narrow therapeutic index drugs [62, 63]. The Euthyrox tablet formulation available since March 2017 no longer contains a lactose excipient, which may be beneficial for patients who are lactose-intolerant [24, 43].

## TSH LEVELS AFTER GENERIC SUBSTITUTION

The TSH reference range for the general population is 0.4–4.5 mIU/L [1, 3], but may increase with age (depending on dietary iodine intake),

so that the upper limit is ~ 5–6 mIU/L in patients aged > 70–90 years [65]. For example, in Denmark, where the populations in most regions are at least mildly iodine-deficient, TSH levels do not increase with age and may actually decrease in areas with moderate iodine deficiency [66, 67]. Considering the limitations in methodology for establishing bioequivalence for LT4 products, some variation in response (biochemical and possibly symptomatic) can be expected if patients are freely substituted from refill to refill [2, 68].

Between 2005 and 2007, a pharmacovigilance study was conducted by the major American endocrine societies to evaluate their members' experience with LT4 substitution [68]. At the time, four brand-name and four generic LT4 tablet preparations were available in the US. A total of 199 adverse events associated with changes in TSH values were reported. Of these, 177 (88.9%) were reported after LT4 tablets had been switched [68]. The switch was made by the pharmacy in 99.4% of cases, and 91.6% of these were carried out without the physician's knowledge. There was a switch from a brand-name LT4 preparation to a generic preparation in 156 (88.1%) cases, from one brand to another in 12 (6.8%) and from one generic to another in 9 (5.1%) [68]. In 11.1% of cases, adverse events were reported after refills with the same LT4 preparation, while in most cases, adverse events were reported after generic substitution for brand-name LT4. Overall, TSH values were within the expected reference range in 78.9% of patients before the reported event, whereas, at the time of the event, 47.7% exceeded the expected reference range and

**Table 3** Geometric mean ratios of pharmacokinetic parameters for baseline-adjusted total plasma thyroxine after administration of new versus old formulations of levothyroxine (600 µg) in healthy volunteers [70–72]

Parameter	Euthyrox	Levoxyl	Tirosint
$C_{max}$	101.7 (98.8–104.6)	92.5 (87.1–98.2)	103.1 (93.5–113.6)
$AUC_{(0-48h)}$	NA	96.9 (90.5–103.8)	NA
$AUC_{(0-72h)}$	99.3 (95.6–103.2)	NA	109.8 (100.3–120.3)

$AUC_{(0-48h)}$  area under the concentration–time curve from 0 to 48 h,  $AUC_{(0-72h)}$  area under the concentration–time curve from 0 to 72 h,  $C_{max}$  maximum concentration, NA not assessed

35.2% had suppressed TSH values [68]. Symptoms suggestive of hyper- or hypothyroidism were reported [68]. Some potentially serious consequences of suboptimal LT4 therapy were identified in vulnerable populations (e.g., elderly or very young patients), most of which occurred after switching (96.3%) [68]. However, several of the events described as serious by the reporting clinicians may not have reached the “serious” threshold in clinical trials [68]. Of note, in the US, only 9% of thyroid hormone prescriptions were made by endocrinologists according to the IMS National Prescription Audit 2009. Although not specifically assessed in this pharmacovigilance study, the cost of additional clinical activity associated with adverse clinical events after switching appear to outweigh the lower prescription costs for generic drugs [69, 70]. Similar pharmacovigilance data are lacking in European countries, such as the UK [38].

A retrospective study of children with congenital hypothyroidism treated with either Synthroid or generic LT4 noted no difference in TSH levels or clinical outcomes, and the authors suggested that this implied interchangeability [71]. However, in an editorial published in the *Journal of Clinical Endocrinology and Metabolism*, Hennessey criticized this study for not directly assessing interchangeability [19]. Moreover, the generic preparation used could not be identified in 44% of patients and only 11% used an interchangeable generic preparation (the Mylan LT4 product) [19].

A prospective, randomized, cross-over trial conducted in pediatric patients with severe congenital hypothyroidism showed that TSH levels with Synthroid were significantly lower than with another AB2-rated product (Levo-T distributed as a generic and considered by the FDA to be interchangeable with Synthroid) [72]. These results were unexpected because the generic was reported to be 12.5% more bioavailable than Synthroid. These results suggest that these AB-rated products are not clinically interchangeable in patients with severe congenital hypothyroidism, and may have implications for other vulnerable populations [19, 72]. Hennessey, in the aforementioned editorial, notes that these results highlight the

limitations of the FDA protocol for establishing the bioequivalence of LT4 preparations, and suggests that further consideration should be given to the TSH-based protocol for establishing the therapeutic equivalence that was proposed by the AACE/ATA/TES [19, 73].

## PROBLEMS ENCOUNTERED AFTER FORCED SWITCHING ON A NATIONAL LEVEL

Problems have been encountered in several countries when patients have been forced to switch LT4 products because of supply problems or mandated transition to a reformulated product that contained different excipients [21, 43, 74].

### Generic or Brand Substitution

In the Netherlands, there was a recent shortage of the most commonly used LT4 brand (Thyrax), resulting in a forced brand switch (mainly to LT4 Teva or Euthyrox) and an increase in the reported number of adverse events [21]. Although Thyrax and Euthyrox share some excipients in common (corn starch, gelatin, lactose monohydrate), most excipients are different. Thyrax Duotab 0.025-, 0.100- and 0.150-mg tablets contain talc, sodium citrate dihydrate (E 331), gelatin, glycerol (E 422), colloidal anhydrous silica (E 551), magnesium stearate (E572), as well as colorants (E132 in the 0.025-mg tablet and E127 in the 0.150-mg tablet) [75]. Teva levothyroxine tablets contain maize starch, mannitol (E421), microcrystalline cellulose, sodium citrate, acacia and magnesium stearate [76]. Euthyrox tablets contain magnesium stearate (E 572) and croscarmellose sodium (E 468) [77]. Overall, 53% of patients using > 100 µg/day showed biochemical signs of over-supplementation [21]. In response, general advice was issued to check serum TSH 6 weeks after any brand change, and to consider dose reduction for patients receiving > 100 µg/day [21].

In February 2012, the UK Medicines and Healthcare products Regulatory Agency suspended the license for Teva levothyroxine 100-µg tablets following reports from

prescribers and patients describing reduced efficacy when switching from other levothyroxine products [78]. In October 2016, the suspension was lifted after Teva reformulated the tablets by making them lactose-free and changing the manufacturing process [79].

## Reformulation

In 2017, a switch was made to the new formulation of Levothyrox (Euthyrox in other EU countries) in France to comply with the requirement for 95–105% potency specification, and, by 2018, there had been > 17,000 reports of adverse events [21, 43]. As previously mentioned, the new formulation (lactose removed and mannitol and citric acid added) had been shown to be bioequivalent to the previous formulation, and complied with the relatively stringent bioequivalence criteria for narrow therapeutic index drugs [21, 43, 63]. For adverse events with reported TSH levels, approximately 60% occurred in patients with normal TSH levels (suggesting that patients were receiving the right dose), and 15–20% in patients with TSH levels indicative of hypothyroidism or hyperthyroidism [21]. These numbers are not unusual by themselves. In a cross-sectional study conducted in the US, 60.1% of patients who were taking thyroid drugs had normal TSH, while 18.3% were hypothyroid and 21.6% were hyperthyroid [80]. There was therefore no scientific explanation for the scale of the surge in adverse events in France after the reformulation, which may have been largely fueled by poor communication (many patients were not initially informed about the change or the need to check TSH levels if they noticed any change in their overall health), social media and the nocebo effect [21, 43].

Similar problems occurred in New Zealand and Denmark a decade ago in relation to reformulated Eltroxin [21, 43, 74, 81]. A major review of the New Zealand situation also found no clear reason for the level of reported adverse events with reformulated Eltroxin [82]. Again, suggested contributing factors included poor communication and intense media interest [74, 81, 82]. Misinterpretation of the new

formulation, which looked different to the old formulation may also have been a factor, i.e., a belief that the new formulation was generic leading to negative perceptions (nocebo effect) [82]. Alternative brands were made available in both countries, and the level of adverse event reporting returned to baseline, with many patients still receiving the new Eltroxin formulation [21, 74].

## CONCLUSIONS

Physicians should alert patients that their LT4 prescription may be switched at the pharmacy, encourage patients to ask to remain on the same preparation at every refill, and make sure that patients understand that they need to have their TSH retested every time their LT4 product is switched [13, 19]. In some countries, such as the USA and Denmark, physicians can state on the prescription that switching is not allowed [2].

Great care must be taken to keep clinicians and patients fully informed when a reformulated branded product is introduced, and pharmacovigilance plans should be in place to monitor adverse events [21, 24, 81].

Patients need to understand that the recommendation to stay on the same LT4 formulation is based on the concern that switching products could lead to changes in TSH that require TSH testing and dose adjustment [3].

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