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Letter to the Editor: Clinically Significant Hyperthyroidism and Hypothyroidism Following Exposure to Compounded Thyroid Products

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Dear Editor,

Compounded thyroid products (CTPs) may be considered to treat hypothyroidism if an alternative to Food and Drug Administration (FDA)-approved product formulations (liquid, tablet, capsule) is deemed necessary (e.g., excipient allergy). However, CTPs have limited safety data. No standard conversion guideline exists for switching from FDA-approved thyroid products to CTPs, so dosing errors may occur. Thyroid products have a narrow therapeutic index (NTI), and even slight variations in the potency of the active pharmaceutical ingredient (API) may potentiate major clinical sequelae (e.g., myxedema coma, thyrotoxic crisis) (1). Furthermore, a recent study found wide variations in percent labeled strength among compounded levothyroxine products (2).

We report a case series of clinically significant hyperthyroidism and hypothyroidism following exposure to CTPs, identified from the FDA Adverse Event Reporting System (FAERS) database and medical literature via Embase and PubMed through January 31, 2020.

The FDA identified 12 U.S. cases, including 4 literature cases (3–5), that we categorized as having a probable or possible association between CTPs and clinically significant hyperthyroidism and hypothyroidism based on the World Health Organization–Uppsala Monitoring Centre’s system for causality assessment. The median age was 53 years (range 20–75 years). The most common CTP was levothyroxine combined with liothyronine, followed by liothyronine alone. Table 1 summarizes these cases.

The eight probable cases contained specific thyroid function test (TFT) results (e.g., thyroid stimulating hormone [TSH], thyroxine [T4], triiodothyronine [T3]) that confirmed either

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clinically significant hyperthyroidism or hypothyroidism, lacked confounding factors, were reported by a health care professional, and described adverse events that improved or resolved following cessation of the suspected product. Clinical outcomes included thyrotoxic crisis requiring hospitalization and plasmapheresis, and pituitary enlargement secondary to marked hypothyroidism. The latter case described incorrect dose conversion from levothyroxine to a CTP, resulting in undertreatment and significant elevation in TSH to 150 μ U/mL (reference range 0.4–4.5 μ U/mL) (3).

Of the four possible cases, three reported approximate TFT results. The remaining case reported an elevated T3 value; however, it was confounded by concomitant Armour Thyroid use. Clinical outcomes included tachycardia, delirium, and hospitalization.

Clinically significant symptoms associated with extremes in thyroid hormone levels may result from even small deviations in the potency of NTI products (1). Compounding errors are one way in which these deviations may occur. Inconsistent potency in the APIs may also contribute to these issues. Recently, the FDA alerted drug makers of a recall of porcine thyroid API due to inconsistent levels of levothyroxine and liothyronine and cited the potential clinical risks (1).

We believe that the cases described are representative of many that likely exist because traditional pharmacies compounding under Section 503A (6) of the Federal Food, Drug and Cosmetic Act generally do not report adverse events of CTPs to the FDA. Despite this limitation, the data presented provide evidence of significant harm associated with CTPs.

Although compounded drugs can serve an important medical need for some patients (e.g., those with excipient allergy), they can pose safety risks. Therefore, FDA-approved products should be used to treat hypothyroidism unless a compounded alternative is clinically necessary and permitted by law.

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Table 1.

Summary of Cases Following Exposure to a Compounded Thyroid Product (N= 12)

Case no. (case event year)	Age (years)/sex	Compounded thyroid product/ dosing	Objective findings	Intervention	Outcome ^a
Probable cases based on the WHO-UMC causality assessment					
1 (2018)	70/F	“Compounded Nature Throid 81.5 mg” (equivalent to levothyroxine 47.5 µg and liothyronine 11.25 µg) ^b	Hypothyroidism TSH 15 units NR (RR 0.5–4.7 µU/L ^c)	Initiated Armour Thyroid 75 mg and discontinued CTP	Improved “blood TSH numbers as well as T3 and T4 have returned to almost normal range”
2 (2017)	75/F	Levothyroxine 42.5 µg and liothyronine 0.5 µg daily ^d	Hypothyroidism TSH 47.9 units NR (RR 0.358–3.8)	Discontinued CTP	Improved TSH 35.7 units NR
3 (2017) ⁴	53/F	Levothyroxine 75 µg and liothyronine 25 µg daily ^e	Hyperthyroidism Undetectable TSH; Total T3 525 ng/dL (RR 80–200 ng/dL); Free T3 28 pg/mL (RR 2–2.5 pg/mL); AST 230 U/L (RR 8–43 U/L); ALT 190 U/L (RR 7–45 U/L); Echocardiogram showed EF 25% (normal 45–55%); Temperature 38.5°C; BP 162/94 mmHg; HR 130 BPM	Plasmapheresis, propranolol, cholestyramine, glucocorticoids, and discontinued CTP	Improved Total T3 181 ng/dL; Free T3 4.8 pg/mL; AST 60 U/L; ALT 104 U/L
4 (2016) ³	63/F	Sustained release levothyroxine 57 µg and liothyronine 13.5 µg daily ^f	Hypothyroidism TSH 150 µU/L (RR 0.4–4.5 µU/L); CK 400 IU/L (RR 21–215 IU/L); Free T3 0.5 pg/mL (RR 2–4.4 pg/mL) MRI showed pituitary enlargement and a 5 mm hypodense lesion, believed to represent pituitary hyperplasia as a consequence of marked hypothyroidism and excessive hypothalamic stimulation with TRH	Initially increased dose of CTP to T4 63.3 µg and T3 15 µg followed by T4 76 µg and T3 18 µg; however, TSH did not improve; discontinued CTP and initiated levothyroxine 137 µg (1.6 µg/kg weight-based dose)	Resolved TSH 2.63 µU/L; CK 143 IU/L
5 (2016)	60/F	Levothyroxine 110 µg and liothyronine 16 µg daily	Hyperthyroidism TSH <0.015 units NR (RR 0.5–4.7 µU/L ^c); Free T3 > 32.6 units and RR NR; Free T4 > 6.99 units and RR NR	Plasmapheresis and discontinued CTP	Improved Free T3 1.6 units NR; Free T4 1.21 units NR
6 (2014) ⁵	44/F	Levothyroxine and liothyronine/NR ^g	Hyperthyroidism TSH 0.025 µU/L (RR 0.27–4.2 µU/L); Free T4 > 7.77 ng/dL (RR 0.93–1.7 ng/dL); Total T3 > 651 (RR 71–180 ng/dL)	Cholestyramine and discontinued CTP	Resolved TSH 2.62 µU/L; FreeT4 1.09 ng/dL; Total T3 90 ng/dL
7 (2011) ⁵	20/M	Liothyronine 10 µg twice daily ^g	Hyperthyroidism TSH 0.065 µU/L (RR 0.27–4.2 µU/L); Total T3 14982.6 ng/dL (RR 80–200 ng/dL)	Unspecified beta-blocker and discontinued CTP	Resolved TSH 2.76 µU/L; Total T3 88 ng/dL
8 (2008)	20/M	Levothyroxine 75 µg and liothyronine 10 µg twice daily ^g	Hyperthyroidism TSH 0.02 µU/L (RR 0.5–4.7 µU/L ^c); Total T3 2604 ng/dL (RR 60–181 ng/dL); Total T4 88.8 µg/dL (RR 4.5–10.9 µg/dL)	Metoprolol, cholestyramine, initiated levothyroxine 150 µg daily and discontinued CTP	Resolved TSH 0.82 µU/L; Total T3 123 ng/dL; Total T4 12 µg/dL
Possible cases based on the WHO-UMC causality assessment					

Case no. (case event year)	Age (years)/sex	Compounded thyroid product/ dosing	Objective findings	Intervention	Outcome ^a
9 (2018)	NR/F	Levothyroxine and liothyronine/NR ^h	Hypothyroidism TSH “over 100” units NR (RR 0.5–4.7 $\mu\text{U/L}$ ^c)	Initiated Armour Thyroid and discontinued CTP	Improved
10 (2013)	38/F	Liothyronine 12.5 μg daily ⁱ	Hyperthyroidism Free T3 7.6 (RR reported as “approx. 1 6”); HR 130+ BPM	NR	Improved
11 (2003)	50/F	Liothyronine 9.25 μg twice daily ^j	Hyperthyroidism “Toxic levels of thyroid; lumbar puncture, CT scan, blood, feces, and urine analysis done, all showing the toxicosis [sic], but nothing indicated origin”—actual results NR	Discontinued CTP	Improved
12 (2002)	55/F	Sustained release T3 52.5 μg twice daily ^k	Hyperthyroidism “BP 140s–170s/86 $\times$ last few months; T3 level 3 $\times$ the norm at 600 units; liver enzymes were also off”	Initiated Synthroid 75 μg daily (prescribed by another endocrinologist), furosemide and discontinued CTP	Improved gradually

^aOutcome of adverse event (e.g., improved, resolved) following cessation of the suspected product.

^bCase 1 was further investigated by the FDA, and the compounded product containing liothyronine and levothyroxine was tested. The result of liothyronine and levothyroxine was within label claim. However, this case was assessed as a probable causal association due to the positive dechallenge.

^cThe units for TSH may be expressed as mU/L, mU/mL, $\mu\text{U/L}$, or $\mu\text{U/mL}$ depending on the reference utilized; however, we use $\mu\text{U/L}$ throughout to be consistent with the units and reference range described by Kratz et al. (7).

^dCase 2 reported the reason for use of a CTP was that the patient wanted to take a “natural product.” The FDA investigated this case further and tested the compounded product containing liothyronine and levothyroxine. The result of liothyronine was within label claim; however, levothyroxine was subpotent. A for-cause inspection of the compounding pharmacy resulted in the issuance of a Warning Letter to the compounder.

^eCase 3 reported “the pharmacy was contacted and noted they recently released compounded thyroid replacement medications with ‘increased amounts of thyroid hormone’.”

^fCase 4 reported the reason for use of a CTP was to improve T3 levels.

^gCases 6, 7, and 8 reported that analysis of the CTP confirmed superpotent product: 10-fold the labeled amount of LT3 and LT4, more than 1000-fold the labeled amount of LT3, and 15-fold the labeled amount of T3 and T4, respectively.

^hCase 9 reported the reason for use of a CTP was because “Nature Throid” (an all-natural unapproved product) was unavailable at retail pharmacies; however, a compounding pharmacy offered to compound the product for the patient.

ⁱCase 10 reported concomitant use of Armour Thyroid and compounded liothyronine for 15 months.

^jCase 11 reported taking compounded liothyronine for “several years”; however, developed “thyroid toxicosis” 5 days following most recent refill.

^kCase 12 reported the reason for use of a CTP was to improve T3 levels because the patient’s body was unable to convert T4 to T3.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BPM, beats per minute; CK, creatine kinase; CT, computed tomography; CTP, compounded thyroid product; EF, ejection fraction; F, female; FDA, Food and Drug Administration; HR, heart rate; LT3, L-triiodothyronine; LT4, levothyroxine; M, male; MRI, magnetic resonance imaging; NR, not reported; RR, reference range; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone; WHO-UMC, World Health Organization–Uppsala Monitoring Centre.