Endocrine (2019) 66:79–86
https://doi.org/10.1007/s12020-019-02045-1

REVIEW

Check for updates

Thyroid hormone misuse and abuse

Victor J. Bernet[1,2]

Received: 11 June 2019 / Accepted: 2 August 2019

Abstract
Thyroid hormone (TH) plays an essential role in human physiology and maintenance of appropriate levels is important for good health. Unfortunately, there are instances in which TH is misused or abused. Such misuse may be intentional such as when individuals take thyroid hormone for unapproved indications like stimulation of weight loss or improved energy. There are instances where healthcare providers prescribe thyroid hormone for controversial or out of date uses and sometimes in supraphysiologic doses. Othertimes, unintentional exposure may occur through supplements or food that unknowingly contain TH. No matter the reason, exposure to exogenous forms of TH places the public at risk for potential adverse side effects.

Keywords Thyrotoxicosis · Thyroid hormone abuse · Thyroid hormone misuse · Factitious thyrotoxicosis · Supplements · Analogs Overdose

Thyroid hormone misuse and abuse

Almost any substance that impacts body physiology and function is at risk for misuse or frank abuse, usually in the misgiven belief that the particular agent whether it be a herb, supplement, medication, or hormone has healing properties beyond that of which it actually possesses. The definition for drug misuse consists of the use of substance for a purpose for which it either was not intended, at a dose beyond that recommended or one that was not prescribed for that individual. In regards to thyroid hormone (TH), misuse may stem from misunderstanding of the drug's actual therapeutic properties and/or unrealistic expectations for what ailments the hormone might improve. Medication abuse is felt to be a continuum of misuse, which is more chronic or severe in nature and associated with the development of either medical complications, physical dependence, or inability to carry out daily responsibilities. Thyrotoxicosis factitia represents cases of thyrotoxicosis secondary to exogenous TH ingestion that may be unintentional or purposeful such as in some cases of Munchausen syndrome. Instances of TH misuse can be associated with the development of significant side effects. There are other instances of chronic, low-grade over treatment with TH, which occur for various misreasoning such as weight maintenance or improved energy but which places the individual at risk for the development of long-term complications like increased bone turnover or cardiac-related problems. In this chapter, we will review the potential forms of TH misuse/abuse (Table 1).

The potential misuse of TH has been possible since the year 650 when Sun Ssu-Mo from China first reported using a combination of ground mollusk shells and chopped up thyroid glands for the treatment of goiter [1]. Animal-derived TH extract was the first TH available for clinical use. Initial limitations of TH therapy included lack of a reliable means to produce the product and the inability to accurately monitor TH levels. The isolation of thyroxine by Kendall at Mayo Clinic in December 1914 and its later production in 1927 were definite advances in the treatment of hypothyroidism as were the later isolation and production of purified T3 [2, 3]. However, once T4 and T3 could be mass-produced by the 1950s, its ready availability broadened the potential for its misuse [4].

Of course, initial misuse of TH was partially related to a still growing understanding of thyroid physiology and thyroid economy as well as the lack of a reliable means with

✉ Victor J. Bernet
bernet.victor@mayo.edu

[1] Division of Endocrinology, Mayo Clinic, Mayo Clinic School of Medicine, Jacksonville, FL 32224, USA

[2] F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MA, USA

Table 1 Forms of thyroid hormone (thyroid analog) misuse

Intentional
Weight loss
Improved energy
Overdose/suicide attempt
Physician prescribed
Excess dosing
Inappropriate indications
Supplement suspected to contain TH
Other: purported "Wilson's Temperature Syndrome"
Unintentional
Accidental pediatric overdose
TH in OTC product unknown to the patient or prescriber
Exposure to TH tainted food—(gullet trimming)
Compounding pharmacy errors
Out-of-date
Premenstrual syndrome
Lipid control (D-T4)
Nonthyroidal illness (euthyroid sick syndrome)
Controversial
Depression–augmentation therapy with TH

which to measure TH levels in blood. Also, in the late 1800's as various hormones were being discovered and their clinical effects were becoming evident, the potential positive properties of hormones became exaggerated to the point of erroneous claims of hormones being the "fountain of youth" or "elixir of life." Hormones started to be promulgated as potential cures for a wide assortment of ailments even though they were unproven to be related to a hormone deficiency. The famous physiologist and neurologist, Dr Charles-Édouard Brown-Séquard, who early in his career made notable contributions to the field of endocrinology, became somewhat infamous in later life for claims of rejuvenation of physical stamina and prolongation of life from animal-derived hormone preparations [5]. The phrase "snake oil salesmen" refers to a period starting in late 1800's when profiteers marketed quack remedies to a totally gullible and unsuspecting public [6]. While pure snake oil rich in omega-3 acids does possess anti-inflammatory properties that may alleviate symptoms of arthritis, Clark Stanley became notorious for selling his own concoction of snake oil claiming it held numerous medicinal uses well beyond arthritis. After the Pure Food and Drug Act of 1906 was passed a shipment of Clark's "Stanley's Snake Oil" was found to contain none of the claimed active ingredient and it became evident that the product was a sham [6]. Despite the well known history of "snake oil" salesmen, it appears that the general public continues to have an intact appetite for simple cures for whatever "ails them." Most physician's in practice today can relate numerous stories of a patient's consumption of misleading literature, which contained unsubstantiated health claims for some drug, supplement, or herb and resulted in the patient seeking that therapy while holding the belief that the unproven or downright false claims are indeed true.

Misuse of TH typically leads to a thyrotoxic state albeit cases of hypothyroidism are possible in special circumstances such as use of certain TH analogs with TH receptor anatogonist properties. The symptoms from exogenous and endogenous forms of thyrotoxicosis are basically indistinguishable and include but are not limited to: tachycardia, heat intolerance, anxiety, tremor, increased frequency of bowel movements, impaired mental acuity, and insomnia. Thyrotoxicosis related to exogenous TH intake leads to varying levels of TSH suppression. In cases of T4 exposure both T4 and T3 levels are expected to rise whereas pure T3 exposure results in T3 elevations with T4 being low within or below the reference range (Fig. 1). With exogenous exposure, the ratio of T4:T3 is much lower than the lowest ratio seen with endogenous hyperthyroidism (usually not <25) [7]. Thyrotoxicosis from exogenous T3 tends to produce severe symptoms more quickly but also tends to resolve more promptly with T3 having a much shorter half-life (24–36 h) in comparison with T4 (7 days). While elevated in the face of endogenous forms of thyrotoxicosis such as Graves' disease, toxic multinodular goiter, or nodule as well as various forms of thyroiditis, thyroglobulin levels are expected to be relatively low in the face of exogenous TH exposure. In contradistinction to endogenous forms of hyperthyroidism, thyroid radioiodine uptake is suppressed with exogenous TH exposure and also forms of thyroiditis during the thyrotoxic phase (Fig. 2). With thyrotoxicosis factitia, discontinuation of the exogenous source of TH leads to gradual normalization of TH levels.

In the modern era, there has been a growing market for herbs, nutrients, and supplements sometimes referred to as "Nutraceuticals" (a combination of the words: nutrient and pharmaceutical) to alleviate or "cure" various symptoms and medical concerns. As we will discuss, TH has become an innocent player in this arena. In 1994, passage of the Dietary Supplement Health and Education Act turned Food and Drug Administration (FDA) monitoring into a reactionary, rather than preventive, process for over-the-counter substances such as herbs and supplements [8]. The end result being the possibility for adulterated and/or mislabeled nutraceutical products being readily available for purchase, which only undergo review and investigation after apparent adverse effects related to the product are reported [9].

One survey found that 73% of responding adults had used a dietary supplement as had 29.1% of surveyed adolescents in another study [10, 11] In 2014, it was estimated that the market for dietary supplements had grown to a $32 billion a year industry [12]. The global dietary supplements

TH Exposure	TSH	FT4/TT4	FT3/TT3	Thyroglobulin	ESR	RAIU
T4	↓γ	↑ or Nl*	↑ or Nl*	↓ς	nl	↓δ
T3 only	↓γ	↓ or Nl*	↑ or Nl*	↓ς	nl	↓δ

Fig. 1 Test result patterns thyrotoxicosis factitia. TH thyroid hormone, FT4 free T4, TT4 total T4, FT3 free T3, TT3 total T3, ESR erythrosedimentation rate, RAIU radioactive iodine uptake; γ—level of TSH suppression may vary in severity depending on the level of exogenous TH exposure. An asterisk indicates T4 and T3 levels may remain in the reference range in cases of subclinical thyrotoxicosis. ς—thyroglobulin level may be unmeasurable or low normal. δ—RAIU will be reduced manytimes to <5%

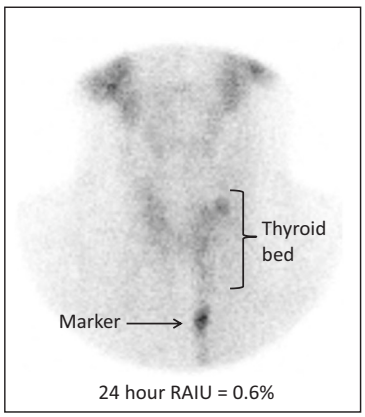

Fig. 2 Thyroid scan and uptake with thyrotoxicosis factitia. Note that the technetium−99 m uptake by thyroid is barely notable and 24 h RAIU is low with (reference range, 15–30%). This pattern can be seen in both cases of subacute thyroiditis and thyrotoxicosis factitia. In addition, testing such as thyroglobulin level and ESR can help differentiate between the two

market is predicted to reach 278.02 billion USD by 2024 with an expected compound annual growth rate (CAGR) of 9.6% between 2016 and 2024 [13]. Furthermore, there is a general belief that supplements are safe and effective as born out in a study of US Army soldiers 67% of which believed supplement claims are valid and 71% who understood all supplements to be safe [14].

Desire for weight loss is a common reason for use of supplements or misuse of TH. A survey performed in the US found that 20.6% of women and 9.7% of men had taken supplements for the intent of weight loss [15]. TH has pervasive effects throughout the body including an impact on metabolism and with increasing dose can precipitate weight loss as well. Patients with hypothyroidism who have insufficient thyroid levels can note an improved ability to lose weight once they achieve an euthyroid state. Increasing T3 levels seen are associated with rising maximal oxygen uptake (VO2) and energy expenditure with weight loss despite an increasing caloric intake. However, to precipitate weight loss in euthyroid individuals, TH levels need to be brought to elevated levels, which stimulate a catabolic state with an associated loss of lean body mass while also inducing thyrotoxic symptoms.

Irrespective of the fact that the majority of obesity is unrelated to TH deficiency, the use of TH for the intent of weight loss has been a recurrent theme over decades. A report in 1950, bemoans the "indiscriminate use of thyroid extract" with the author describing cases of obese patients requesting TH for weight loss or hypothyroid patients pursuing excess TH replacement dosing in the pursuit of weight control [16]. Actually, requests for TH therapy in apparently euthyroid individuals or supraphysiologic replacement doses in hypothyroid patients for weight loss, appear to remain common in current practice as of 2019 as estimated by this author's experience.

Requests for TH as a weight loss therapy appear to be promulgated by multiple websites on the world wide web. In 2009, there was a report of a 56-year-old female patient with "hypothyroid symptoms" who developed iatrogenic thyrotoxicosis from consumption of six grains of desiccated thyroid extract (DTE) daily with an expected TH content of: LT4 = 228 mcg and LT3 = 54 mcg [17]. The patient related that she had gotten the idea from a website called "Stop the Thyroid Madness", which reportedly encouraged individuals with hypothyroid symptoms to consume three to five grains of DTE daily. Apparently, the individual obtained the TH without prescription from Canada and Mexico by illegal means. She presented to the ED with atrial fibrillation as well as pulmonary and peripheral edema. With discontinuation of the supraphysiologic TH dosing, the patient appears to have recovered from the event without any serious complication. While weight loss can be achieved with significant excess in TH dosing, it is done at risk of inducing a thyroxic state with associated increased protein catabolism and muscle breakdown [18]. As such, excess dosing of TH is not recommended as a safe means to achieve weight loss.

A review of published medical literature is notable for multiple instances of supplement related thyrotoxicosis. In the majority of examples, TH content was not clearly listed as a ingredient and so individuals were unaware that TH

might be within the purchased product. A few examples of such unintentional incidents follow. In 1986, "Enzo-caps" an over-the-counter product purportedly only containing kelp, garlic, and papaya was found to contain variable amounts of LT4 and LT3 after patients presented with thyrotoxicosis and elevated serum T4 and T3 levels. Taken as recommended, pill analysis found that the daily intake would be T3-44.4 mcg and T4-450 mcg [19]. Another case involved an individual diagnosed with hypothyroidism who discontinued all FDA-approved TH formulations and instead took "natural" supplements. On these products, she experienced significant variations in TH levels, finally developing thyrotoxicosis secondary to exogenous TH with the last such product she consumed [19]. Furthermore, the same authors noted at least three similar supplements available in the Boston area that were associated with elevated TH levels with one labeled as containing "preserved natural constitutes" [20]. An additional example, is a patient initially suspected of having recurrent silent thyroiditis who was finally noted to have a low thyroglobulin level in the face of an elevated serum T3, which arose the suspicion of an exogenous TH source. Upon questioning the patient admitted to consuming "Talla Baja" vitamins that later were found to contain LT3 100 mcg/pill [21]. TH levels normalized with discontinuation of the product.

Having encountered several patients with abnormal TH levels related to OTC products, our group at Walter Reed decided to analyze the TH content of ten supplements marketed on the internet for the purpose of "thyroid support" [22]. Five of the sampled products contained measurable T4 between 5.77 and 22.9 mcg per tablet, whereas nine out of ten products contained T3 ranging between 1.3 and 25.4 mcg per tablet. The per daily dosing extended between 1.27–32.13 mcg for T3 and <1.0–91.6 mcg for T4 in the pills. The fact that 90% of these sampled products, which were readily available for purchase, contained clinically relevant amounts of TH is disconcerting. That four contained T3 alone implies intentional addition of T3 to the product as incidental TH contamination that might occur through inclusion of animal thyroid tissue would contain both T4 and T3. This fact is sobering and underscores a significant public health hazard. Of interest, additional studies assessing various OTC products for TH content have yielded variable results with 12 supplements marketed for "adrenal support" all containing T3 (and no T4) at lower levels 63 to 394.4 ng/tablet, while another study of 29 nonprescription weight loss products found negligible TH content by tandem mass spectrometry analysis [23, 24]. Based on these findings and as OTC supplements and herbal products remain readily available without premarketing FDA assessment, it is prudent to caution patients of these findings and to screen for use of such products in individuals with abnormal thyroid blood test results.

Advances in the understanding of TH action and thyroid receptor isoform variations allow for the design of TH analogs with selective agonistic or antagonistic properties [25]. A goal for the development of TH analogs includes retention of desireable effects like weight loss and cholesterol reduction, while avoiding adverse side effects such as tachycardia. Some of these agents have also fallen prey to misuse. TRIAC (3,5,3′-triiodothyroacetic acid; also referred to as tiratricol) is a metabolite of TH in humans. It is estimated that ~1% of an individual's thyroxine (T4) is converted to TRIAC. TRIAC has a short ½ life of ~6 h but possesses a high binding affinity for the nuclear T3 receptor, TH receptor β_1 (TRβ_1) of thyrotroph cells as well as transthyretin [26]. Studies in humans with postsurgical hypothyroidism revealed that oral TRIAC can produce biologic effects similar to that of thyroxine at about 5% of T4's potency [27]. For example, 1000 mcg of TRIAC is equivalent to ~50 mcg of LT4. Tissue responsiveness to TRIAC varies with liver and bone appearing to be more sensitive. Increasing doses of TRIAC can lead to development of symptoms of thyrotoxicosis with thyroid function analysis revealing a suppressed TSH with concomitantly low T4 while T3 levels may be elevated depending on the presence of assay cross-reactivity [28]. If taken as recommended, two to four 1000 mg capsules daily, individuals may experience similar thyrotoxic type adverse effects as if they had consumed 100–200 mg of thyroxine. Based on its pharmacologic properties, TRIAC related weight loss is associated with the same risk of thyrotoxic symptoms experienced with weight loss secondary to excess T4 and/or T3 levels. In 1999, the FDA issued a warning about the risks of tiratricol use [29].

A supplement labeled as Triax Metabolic Accelerator (Triax), marketed as a weight loss supplement, was found to contain TRIAC as its main ingredient. Use of Triax in one patient was associated with an episode of thyrotoxic periodic paralysis after the individual took it for 4 weeks at a dose of 2–3 capsules per day (each pill contained ~1 mg of TRIAC per capsule) [30, 31]. A case of TRIAC induced hypothyroidism has also been reported [32]. In addition to the previously mentioned FDA warning, the American Thyroid Association also posted a advisory in February 2000 and this statement remains posted on the ATA website (https://www.thyroid.org/ata-supports-fda-warning-on-triax/) at the time of publication of this article [27, 33].

TH has been reported as a drug used by individuals attempting suicide. In 2012, the American Association of Poison Control Centers reported that levothyroxine was one of the drugs consumed in nine cases of fatal polydrug overdoses. One case report notes an overdose with 15,800 mcg of levothyroxine and 2460 mg of citalopram in a

55-year-old female who presented with seizures and tachycardia [34]. Laboratory testing revealed a suppressed TSH with markedly elevated FT4 and undetectable thyroglobulin. Patient is described as being successfully treated with a combination of dexamethasone and cholestyramine, the former to decrease T4 to T3 conversion and the later to reduce GI absorption of TH by blocking reabsorption of the enterohepatic recirculation of TH excreted in bile. Additional data indicate that there appears to be no direct association between ingested dose of TH and the occurrence or severity of adverse symptoms [35]. However, a case report from 1981 describes sudden death suspected from ventricular arrhythmia induced by TH abuse [36]. The patient's total T4 level measured 26.9 mcg/dl (5.4–13) and calculated free thyroxine index 11.8 (1.2–4.6). During the postmortem investigation, it was uncovered that the patient had been taking 600–800 mcg of levothyroxine daily for purposes of weight loss. With regard to episodes of TH dosage, data indicate that accidental pediatric cases are much more common than intentional adult over dosage [37]. Fortunately, most children exhibit limited symptoms of thyrotoxicosis from such exposures. It is recommended that family members taking TH therapy carefully store their TH prescriptions safely out of the reach of children. Of note, supraphysiologic levels of TH are more worrsiome in the elderly and patients with underlying conditions that might be exacerbated by thyrotoxicosis such as coronary artery disease [38].

Thyrotoxicosis secondary to TH exposure through consumption of tainted food products has also been described. Henry Plummer reported an epidemic of thyrotoxicosis in Olmstead County, Minnesota in 1930 [39]. The episode was suspected to be related to a food source although ultimately unproven. In subsequent years, there was report of several Polish meat workers developing thyrotoxic symptoms. It was found that the group had regularly consumed a special sausage that was known to include animal thyroid tissue [40]. Subsequently, in 1983 an outbreak of thyrotoxicosis in 121 subjects was traced to consumption of ground beef contaminated with TH when "gullet" trimmings were harvested and included in the meat [41]. In response to this outbreak, the US Department of Agriculture (USDA) issued a nationwide advisory prohibiting the practice of gullet trimming so as to avoid the health risk of exposure to thyroid tissue contamination in meat [42].

In the 1980s, data were published that appeared to indicate low thyroid levels were associated with premenstrual syndrome (PMS) in women. In response, supraphysiologic doses of TH were recommended by some as an effective method for alleviating PMS symptoms. Later, follow up studies revealed no evidence of PMS associated TH deficiency nor any benefit on PMS symptoms from TH therapy in euthyroid women [43, 44]. TH is therefore not recommended for the treatment of PMS related symptoms.

D-T4, an isomer of L-T4, has been found to have cholesterol lowering effects. For a time, D-T4 was used for the treatment of hypercholesterolemia and hypertriglyceridemia. It was noted that 2 mg of D-T4 was the lowest effective dose, being estimated to have a similar lipid lowering effect as 50 mcg of L-T4. D-T4 was shown to be able to suppress the TSH response to TRH stimulation. Also, most formulations were found to contain between 0.5–2.3% of L-T4 [45]. However, as subjects taking D-T4 experienced a higher cardiac mortality, D-T4 therapy fell out of favor and is not recommended as a therapeutic option.

Over the years, TH has been proposed as an adjunct therapy for the treatment of depression. The use of TH treatment for the various forms of depression remains somewhat controversial as available studies have not yielded reproducible findings, many consisted of only a small number of subjects and the majority were limited by their design [46–48]. The topic of this chapter being the misuse or abuse of TH, we will focus comments on instances where the use of TH augmentation is not recommended in the treatment of depression. Depressed patients responding to traditional therapy need not be offered TH augmentation. Also, there are no data that supports the utilization of T3 alone as monotherapy sans concomitant antidepressant treatment. All patients being considered for TH augmentation therapy should undergo thyroid function testing first. TH should not be offered to patients with underlying thyrotoxicosis and standard L-T4 therapy for hypothyroidism should first be considered in those found to have untreated hypothyroidism. Of note, the monitoring of thyroid function tests during treatment with lithium, which can be associated with development of hypo- or hyperthyroidism, is warranted.

Depression treatment guidelines recommend that when T3 augmentation is used, dosing should start at 12.5–25 mcg daily and should not exceed 50 mcg daily [49]. If TSH suppression occurs or thyrotoxic symptoms develop, then the T3 dose should be reduced until symptoms resolve and/or the TSH normalizes. It should be clear that while TH appears to quicken the response to antidepressants, it has not been associated with a higher final response rate. Available recommendations state that TH augmentation therapy should not be offered to depressed patients with adrenal insufficiency, diabetes mellitus, unstable angina, recent myocardial infarction, underlying cardiac arrhythmias nor those who are frail or elderly.

In episodes of severe systemic illness, thyroid function changes related to nonthyroidal illness (previously known as euthyroid sick syndrome) can occur. In nonthyroidal illness, T3 levels are reduced while reverse T3 rises and in more severe or prolonged cases T4 levels start to drop as well [50]. An inverse correlation between T4 concentrations and survival has been reported. To address the TH changes, trials of LT4 and LT3 have been administered to severely ill

burn patients [51]. Such interventions with TH were not found to improve survival. No benefit was found with T4 therapy in ill ICU patients and low T4 levels from nonthyroidal illness. While one study noted some improvement in cardiac stroke volume in CABG patients receiving T3 therapy, the data as a whole do not support use of TH in this population as well [52, 53]. However, it is postulated that the TSH and TH changes seen with nonthyroidal illness represent a transient, acquired central hypothyroidism that acts as an adaptive response to reduce catabolic activity in the face of severe illness [54]. The overall findings in this area of study do not support the use of T4 or T3 for patients with TH alterations related to euthyroid sick syndrome.

On the internet and within some self-help books, TH has been proposed as a solution for a myriad of nonspecific symptoms to include fatigue. One relatively popular website propagates a condition named "Wilson's Temperature Syndrome" of which the proposed diagnostic criteria consist of low body temperature in conjunction with nonspecific signs and symptoms, such as fatigue, irritability, hair loss, insomnia, headaches, and weight gain [55]. While this syndrome has at times been a popular theory with patients and some select providers, no substantive scientific evidence supports the existence of Wilson's syndrome nor the premise that T3 therapy leads to resolution of an acquired reduced ability to convert T4 to T3 as proposed. This issue became so prominent that the ATA posted a statement on its website (https://www.thyroid.org/american-thyroid-association-statement-on-wilsons-syndrome/), which states that the ATA has found "no scientific evidence supporting the existence of "Wilson's syndrome [56]." Furthermore, it was felt that the proposed theory for Wilson's syndrome was not supported by well understood TH physiology.

The use of compounding pharmacies is popular with some groups. Medication compounding involves a process of geometric dilution where one starts with a drug at about ten times the final dose in weight and then is diluted by means of addition of inert agents and weighing of the capsules. If performed incorrectly, the capsules can contain 10–1000 times the intended dose. A report in 2015 noted two patients presenting with TH compound related thyrotoxicosis. The first patient presented with confusion, hallucinations, hypotension (BP 100/70 mm Hg), and evidence of a myocardial infarction [57]. The patient had known hypothyroidism and was thought to be taking a compounded formulation of liothyronine at 25 mcg daily. Admission laboratory testing revealed a Free T3 of 50 pmol/L (ref range: 3–6.8 pmol/L) and free T4 of 15 pmol/L (ref range: 10–23). The patient had been compliant with her TH dosing. A second similar case was presented 2 days later at the same hospital and the second patients's compounded TH preparation was traced to the same pharmacy as the prior patient. As the clinical parameters for both cases pointed to an exogenous source of TH and neither patient had any exposure to TH other than through the compounded product, it became readily apparent that a compounding error was responsible. Luckily, both patients recovered. In another incident a fatality occurred secondary to complications when a compounded diet pills contained 30 mg instead of 25 mcg of T3 [58].

To conclude, TH can be misused or abused in numerous ways. At times TH or an analog can be unexpectedly present in supplements, while some patients purposely take excess TH in an attempt to improve energy or stimulate weight loss. Some individuals include TH as one of the pills that they take during a suicide attempt. Thyrotoxicosis related to meat tainted with thyroid tissue has been reported and TH may also be prescribed for outdated reasons such as PMS or nonthyroidal illness. When a patient presents with an atypical course of thyrotoxicosis or unusual TFT patterns, there is need to investigate for the possibility of exogenous TH use.

Funding No funding was received for this activity.

Compliance with ethical standards

Conflict of interest The author does not have any conflicts of interest to report, including no: research grants, speaker honorarium, or relevant stock holdings. Dr Bernet is the presently Secretary/ Chief Operating Officer for the American Thyroid Association but this position is not expected to pose any conflict in interest with regard to the submitted manuscript.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. E.H. Hume, The contributions of China to the science and art of medicine. Science. **59**, 345–350 (1924)
2. E.C. Kendall, The isolation in crystalline form of the compound containing iodin, which occurs in the thyroid. Its chemical nature and physiologic activity. JAMA **21**(15), 2045–2046 (1983)
3. C.R. Harington, Chemistry of thyroxine: constitution and synthesis of desiodo-thyroxine. Biochem. J. **20**(2), 300–313 (1926)
4. J. Gross, R. Pitt-Rivers, 3:5:3'-triiodothyronine. 2. Physiological activity. Biochem. J. **53**(4), 652–657 (1953)
5. D. Schultheiss, J. Denil, U. Jonas, Rejuvenation in the early 20th century. Andrologia. **29**(6), 351–355 (1997)
6. L. Gandhi, A History of 'Snake Oil Salesmen. (National Public Radio, 2013) https://www.npr.org/sections/codeswitch/2013/08/26/215761377/a-history-of-snake-oil-salesmen (2013). Accessed 15 May 2019
7. K. Sterling, S. Refetoff, H.A. Selenkow, T3 thyrotoxicosis. Thyrotoxicosis due to elevated serum triiodothyronine levels. JAMA **27**(4), 571–575 (1970)
8. Dietary Supplement Health and Education Act of 1994. Pub L N0. 103-417, 21 USC § 3419

9. A.M. Abe, D.J. Hein, P.J. Gregory, Regulatory alerts for dietary supplements in Canada and the United States, 2005–13. Am. J. Health Syst. Pharm. **1**(11), 966–971 (2015)
10. B.B. Timbo, M.P. Ross, P.V. McCarthy, C.T. Lin, Dietary supplements in a national survey: prevalence of use and reports of adverse events. J. Am. Diet. Assoc. **106**(12), 1966–1974 (2006)
11. K.M. Wilson, J.D. Klein, T.S. Sesselberg, S.M. Yussman, D.B. Markow, A.E. Green, J.C. West, N.J. Gray, Use of complementary medicine and dietary supplements among U.S. adolescents. J. Adolesc. Health **38**(4), 385–394 (2006)
12. P.A. Cohen, Hazards of hindsight-monitoring the safety of nutritional supplements. N. Engl. J. Med. **370**(14), 1277–1280 (2014)
13. Dietary Supplements Market Worth $194.63 Billion By 2025 | CAGR 7.8%. (Grand View Research, Inc., 2019), https://www.grandviewresearch.com/press-release/global-dietary-supplements-market. Accessed 29 May 2019
14. C.E. Carvey, E.K. Farina, H.R. Lieberman, Confidence in the efficacy and safety of dietary supplements among United States active duty army personnel. BMC Complement. Alter. Med. **10** (1), 182–194 (2012)
15. A. Dickinson, J. Blatman, N. El-Dash, J.C. Franco, Consumer usage and reasons for using dietary supplements: report of a series of surveys. J. Am. Coll. Nutr. **33**(2), 176–82 (2014)
16. Abuse of Thyroid Medication. JAMA. **142**(4), 261–262 (1950) https://doi.org/10.1001/jama.1950.02910220041014
17. G.W. Neuberg, K.E. Stephenson, D.A. Sears, R.J. McConnell, Internet-enabled thyroid hormone abuse. Ann. Intern Med. **6**(1), 60–61 (2009)
18. G.A. Bray, K.E. Melvin, I. Chopra, Effect of triiodothyronine on some metabolic responses of obese patients. Am. J. Clin. Nutr. **26** (7), 715–721 (1973)
19. G.D. Braunstein, R. Koblin, M. Sugawara, A.E. Pekary, J.M. Hershman, Unintentional thyrotoxicosis factitia due to a diet pill. West J. Med. **145**(3), 388–391 (1986)
20. C.T. Sawin, M.H. London, 'Natural' desiccated thyroid. A 'health-food' thyroid preparation. Arch. Intern. Med. **149**(9), 2117–2118 (1989)
21. G.H. Daniels, P. Sluss, Pure T3-thyrotoxicosis from a Mexican weight losssupplement. Endocr. Pract. **19**(3), 559–560 (2013)
22. G.Y. Kang, J.R. Parks, B. Fileta, A. Chang, M.M. Abdel-Rahim, H.B. Burch, V.J. Bernet, Thyroxine and triiodothyronine content in commercially available thyroid health supplements. Thyroid **23** (10), 1233–1237 (2013)
23. H.K. Akturk, A.M. Chindris, J.M. Hines, R.J. Singh, V.J. Bernet, Over-the-counter "adrenal support" supplements contain thyroid and steroid-based adrenal hormones. Mayo Clin. Proc. **933**, 284–290 (2018)
24. C.D. Seger, X. He, L.E. Braverman, M.W. Yeh, V.J. Bernet, R.J. Singh, C.M. Rhee, A.M. Leung, Negligible thyroid hormone content present in nonprescription U.S. Weight Loss Products. Thyroid **27**(2), 300–301 (2017)
25. G. Brenta, S. Danzi, I. Klein, Potential therapeutic applications of thyroid hormone analogs. Nat. Clin. Pr. Endocrinol. Metab. **3**(9), 632–640 (2007)
26. G. Radetti, L. Persani, G. Molinaro, D. Mannavola, D. Cortelazzi, V.K. Chatterjee, P. Beck-Peccoz, Clinical and hormonal outcome after two years of triiodothyroacetic acid treatment in a child with thyroid hormone resistance. Thyroid. **7**(5), 775–778 (1997)
27. M. Moreno, P. de Lange, A. Lombardi, E. Silvestri, A. Lanni, F. Goglia, Metabolic effects of thyroid hormone derivatives. Thyroid. **18**(2), 239–253 (2008)
28. B.A. Bauer, P.L. Elkin, D. Erickson, G.G. Klee, M.D. Brennan, Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. Mayo Clin. Proc. **77**(6), 587–590 (2002)
29. Food and Drug Administration. *FDA warns against consuming dietary supplements containing tiratricol* (National Press Office: Talk Paper, Rockville, MD, 1999)
30. J. Cohen-Lehman, M.M. Charitou, I. Klein, Tiratricol-induced periodic paralysis: a review of nutraceuticals affecting thyroid function. Endocr. Pract. **17**(4), 610–615 (2011)
31. Y.C. Chen, J.T. Fang, C.T. Chang, H.H. Chou, Thyrotoxic periodic paralysis in a patient abusing thyroxine for weight reduction. Ren. Fail. **23**(1), 139–142 (2001)
32. M.C. Scally, A. Hodge, A report of hypothyroidism induced by an over-the-counter fat loss supplement (Tiratricol). Int J. Sport Nutr. Exerc Metab. **13**(1), 112–116 (2003)
33. American Thyroid Association Public Health Statemnt: ATA Supports FDA Warning on Triax. (American Thyroid Association, 2000), https://www.thyroid.org/ata-supports-fda-warning-on-triax/. Accessed 6 June 2019
34. K.M. Allen, V.B. Crawford, J.V. Conaglen, M.S. Elston, Case report: clues to the diagnosis of an unsuspected massive levothyroxine overdose. CJEM **17**(6), 692–698 (2015)
35. B. Nygaard, E.A. Saedder, K. Dalhoff, M. Wikkelsoe, G. Jürgens, Levothyroxine poisoning—symptoms and clinical outcome. Basic Clin. Pharm. Toxicol. **117**(4), 280–285 (2015)
36. S. Bhasin, W. Wallace, J.B. Lawrence, M. Lesch, Sudden death associated with thyroid hormone abuse. Am. J. Med. **71**(5), 887–890 (1981)
37. J.B. Mowry, D.A. Spyker, L.R. Cantilena Jr, J.E. Bailey, M. Ford, 2012 annual report of the American association of poison control centers' national poison data system (NPDS): 30th annual report. Clin. Toxicol. (Philos.). **51**(10), 949–1229 (2013)
38. J.H. Cohen 3rd, S.H. Ingbar, L.E. Braverman, Thyrotoxicosis due to ingestion of excess thyroid hormone. Endocr. Rev. **10**(2), 113–124 (1989)
39. Plummer H. Tr. Assn. Am. Phys. **46**, 171 (1931)
40. J.F. Dymling, D.V. Becker, Occurrence of hyperthyroidism in patients receiving thyroid hormone. J. Clin. Endocrinol. Metab. **27**, 1487–1491 (1967)
41. C.W. Hedberg, D.B. Fishbein, R.S. Janssen, B. Meyers, J.M. McMillen, K.L. MacDonald, K.E. White, L.J. Huss, E.S. Hurwitz, J.R. Farhie, J.L. Simmons, L.E. Braverman, An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. N. Engl. J. Med. **16**(316), 993–998 (1987)
42. M.S. Parmar, C. Sturge, Recurrent hamburger thyrotoxicosis. CMAJ **2**(5), 415–417 (2003)
43. N.D. Brayshaw, D.D. Brayshaw, Thyroid hypofunction in premenstrual syndrome. N. Engl. J. Med. **4**(23), 1486–1487 (1986)
44. T.F. Nikolai, G.M. Mulligan, R.K. Gribble, P.G. Harkins, P.R. Meier, R.C. Roberts, Thyroid function and treatment in premenstrual syndrome. J. Clin. Endocrinol. Metab. **70**(4), 1108–1113 (1990)
45. W.F. Young Jr, C.A. Gorman, N.S. Jiang, D. Machacek, I.D. Hay, L-thyroxine contamination of pharmaceutical D-thyroxine: probable cause of therapeutic effect. Clin. Pharm. Ther. **36**(6), 781–787 (1984)
46. X. Zhou, A.V. Ravindran, B. Qin, C. Del Giovane, Q. Li, M. Bauer, Y. Liu, Y. Fang, T. da Silva, Y. Zhang, L. Fang, X. Wang, P. Xie, Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J. Clin. Psychiatry **76**(4), e487–e498 (2015)
47. R. Aronson, H.J. Offman, R.T. Joffe, C.D. Naylor, Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch. Gen. Psychiatry **53**(9), 842–848 (1996)
48. T. Parmentier, P. Sienaert, The use of triiodothyronine (T3) in the treatment of bipolar depression: a review of the literature. J. Affect Disord. **15**(229), 410–414 (2018)
49. A.J. Gelenberg, M.P. Freeman, J.C. Markowitz, J.F. Rosenbaum, M.E. Thase, M.H. Trivedi, R.S. Van Rhoads, *Practice Guideline*

for the Treatment of Patients with Major Depressive Disorder, 2nd edn. (2010) https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed 4 June 2019
50. L. Wartofsky, K.D. Burman, Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr. Rev. **3**(2), 164–217 (1982)
51. R.A. Becker, G.M. Vaughan, M.G. Ziegler, L.G. Seraile, I.W. Goldfarb, E.H. Mansour, W.F. McManus, B.A. Pruitt Jr, A.D. Mason Jr., Hypermetabolic low triiodothyronine syndrome of burn injury. Crit. Care Med. **10**(12), 870–875 (1982)
52. D. Novitzky, D.K. Cooper, C.I. Barton, A. Greer, J. Chaffin, J. Grim, N. Zuhdi, Triiodothyronine as an inotropic agent after open heart surgery. J. Thorac. Cardiovasc Surg. **98**(5 Pt 2), 972–977 (1989)
53. G.A. Brent, J.M. Hershman, Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J. Clin. Endocrinol. Metab. **63**(1), 1–8 (1986)
54. S. Lee, A.P. Farwell, Euthyroid sick syndrome. Compr. Physiol. **15**(2), 1071–1080 (2016)
55. T.B. Nippoldt, Wilson's syndrome: An accepted medical diagnosis? (2017), https://www.mayoclinic.org/diseases-conditions/hypothyroidism/expert-answers/wilsons-syndrome/faq-20058414. Accessed 29 May 2019
56. American Thyroid Association Public Health Statement: American Thyroid Association Statement on "Wilson's Syndrome." American Thyroid Association. (2005) https://www.thyroid.org/american-thyroid-association-statement-on-wilsons-syndrome/. Accessed 7 June 2019
57. A. Bains, A.J. Brosseau, D. Harrison, Iatrogenic thyrotoxicosis secondary to compounded liothyronine. Can. J. Hosp. Pharm. **68**(1), 57–59 (2015)
58. V. Ioos, V. Das, E. Maury, J.L. Baudel, J. Guéchot, B. Guidet, G. Offenstadt, A thyrotoxicosis outbreak due to dietary pills in Paris. Ther. Clin. Risk Manag. **4**(6), 1375–1379 (2008)