OFF-LABEL USE AND MISUSE OF TESTOSTERONE, GROWTH HORMONE, THYROID HORMONE, AND ADRENAL SUPPLEMENTS: RISKS AND COSTS OF A GROWING PROBLEM

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ABSTRACT

Over the past few decades, there has been an unprecedented rise in off-label use and misuse of testosterone, growth hormone, thyroid hormone, and adrenal supplements. Testosterone therapy is often promoted to men for the treatment of low energy, lower libido, erectile dysfunction, and other symptoms. Growth hormone is used in attempts to improve athletic performance in athletes and to attenuate aging in older adults. Thyroid hormone and/or thyroid supplements or boosters are taken to treat fatigue, obesity, depression, cognitive impairment, impaired physical performance, and infertility. Adrenal supplements are used to treat common nonspecific symptoms due to "adrenal fatigue," an entity that has not been recognized as a legitimate medical diagnosis. Several factors have contributed to the surge in off-label use and misuse of these hormones and supplements: direct-to-consumer advertising, websites claiming to provide legitimate medical information, and for-profit facilities promoting therapies for men's health and anti-aging. The off-label use and misuse of hormones and supplements in individuals without an established endocrine diagnosis carries known and unknown risks. For example, the risks of growth hormone abuse in athletes and older adults are unknown due to a paucity of studies and because those who abuse this hormone often take supraphysiologic doses in sporadic intervals. In addition to the health risks, off-label use of these hormones and supplements generates billions of dollars of unnecessary costs to patients and to the overall health-care system. It is important that patients honestly disclose to their providers off-label hormone use, as it may affect their health and treatment plan. General medical practitioners and adult endocrinologists should be able to begin a discussion with their patients regarding the unfavorable balance between the risks and benefits associated with off-label use of testosterone, growth hormone, thyroid hormone, and adrenal supplements. **(Endocr Pract. 2020;26:340-353)**

Abbreviations:
DHEA = dehydroepiandrosterone; **FDA** = U.S. Food and Drug Administration; **GH** = growth hormone; **IGF-1** = insulin-like growth factor 1; **LT3** = L-triiodothyronine; **LT4** = levothyroxine; **T3** = total triiodothyronine; **T4** = thyroxine; **TSH** = thyroid-stimulating hormone

EXECUTIVE SUMMARY

1. Over the past few decades, there has been an unprecedented rise in off-label use and misuse of testosterone, growth hormone (GH), thyroid hormone, and adrenal supplements.
2. Testosterone therapy is indicated for the treatment of primary and secondary male hypogonadism. GH is approved by the U.S. Food and Drug Administration (FDA) for use in children and adults with GH deficiency. Thyroid hormone is indicated for the treatment of primary and secondary hypothyroidism. Glucocorticoids are indicated for the treatment of adrenal insufficiency and a wide array of inflammatory diseases.
3. "Adrenal fatigue" is an unrecognized entity that supposedly is due to the overuse of the adrenal glands, which may lead to a general sense of unwellness, fatigue, body aches, nervousness, sleep disturbances, digestive problems, weight gain, and a multitude of other nonspecific symptoms.
4. Many patients seek treatment for common nonspecific symptoms such as fatigue, low energy, poor sleep, weight gain, and lower libido. Unfortunately, some clinics and websites lead people to believe that their symptoms are attributable to a deficiency of a hormone and that treatment with this hormone will improve or eliminate their symptoms.
5. The off-label use and misuse of hormones and supplements in individuals without an established endocrine diagnosis carries known and unknown risks.
6. Dietary supplements do not undergo rigorous premarket safety and effectiveness testing and may contain undeclared pharmaceuticals.
7. Practitioners should undergo appropriate training to interpret laboratory test results in a more comprehensive way than simply checking whether a value falls within the reference range. There are many causes of abnormal laboratory results that are not due to hormonal deficiency or excess.
8. Patients should disclose to their providers off-label hormone use as it may affect their overall health, diagnostic testing, and treatment plan.
9. General medical practitioners and adult endocrinologists should be able to begin a discussion with their patients regarding the unfavorable balance between the risks and benefits associated with off-label use of testosterone, GH, thyroid hormone, and adrenal supplements.

INTRODUCTION

Over the past few decades, there has been an unprecedented rise in the inappropriate and off-label use of testosterone, GH, thyroid hormone, and adrenal supplements (1). Much of this increase is linked to abundant and misleading information on the internet, which has become a very common source of medical information for the general public (2). This rapid upsurge of specious information has largely been driven by individuals with little to no medical training, as well as a subset of medical practitioners who promote hormones and supplements for common nonspecific symptoms such as fatigue or inability to lose weight—many of whom work at clinics that aggressively market their treatments for anti-aging and men's health, which

typically cost large amounts of out-of-pocket money (3). For example, the website of one such facility states "You have settled for a state of well-being that is less than ideal. At Nava, we strongly believe that you don't have to settle. Ever" (4). A substantial number of these facilities lack providers with the appropriate qualifications and expertise in the endocrine conditions that they purport to be able to diagnose and treat.

The following typical patient scenario illustrates the problem. A 53-year-old man has experienced fatigue, decreased libido, and increase in weight and abdominal fat over the past few years. Based on material that he read on the internet, he is convinced that most of his symptoms are attributable to a decline in several hormones associated with aging. He schedules an appointment at an anti-aging clinic. The practitioner employed by the clinic follows a standard protocol which includes ordering a multitude of tests that cost several hundred dollars. Many of these tests are endocrine-related and include commonly ordered tests such as total and free testosterone, thyroid-stimulating hormone (TSH), free thyroxine (free T4), total triiodothyronine (T3), dehydroepiandrosterone (DHEA)-sulfate, and cortisol. Other tests measure levels of more esoteric steroids and substances, such as pregnenolone and reverse T3 (3,3',5'-triiodothyronine, rT3). Although the testosterone results are within the reference range, the practitioner prescribes testosterone for the patient, as the clinic determined that his level was not optimal for a man of his age. Based upon anecdotal evidence, the clinic protocol recommends that men should have serum total testosterone levels over 700 ng/dL. Despite normal thyroid test results, the clinic practitioner prescribes liothyronine (thyroid hormone) to help the patient with fatigue and weight loss and also encourages him to take over-the-counter pregnenolone, as his pregnenolone level was lower than the reference range. Finally, the clinic practitioner recommends that the patient purchase a special package of vitamins and supplements sold by this clinic for $199/month.

Testosterone therapy is often promoted to men for the treatment of low energy, lower libido, erectile dysfunction, and other symptoms (2). GH is increasingly used off-label among athletes and older adults in attempts to improve athletic performance and attenuate aging, respectively (5-8). Besides GH, insulin-like growth factor 1 (IGF-1), and GH secretagogues ("ghrelin mimetics") are also taken surreptitiously for the same purported benefits (8,9). Despite its off-label abuse, there is no solid evidence that GH can reverse aging. In individuals with normal thyroid function tests, thyroid hormone and/or thyroid supplements or boosters are sometimes taken for fatigue, obesity, depression, cognitive impairment, impaired physical performance, and infertility (10). Finally, over-the-counter supplements are commonly used by individuals who believe that they suffer from a constellation of common nonspecific symptoms related to "adrenal fatigue," an entity that has not been recognized as a legitimate medical diagnosis (11). "Adrenal fatigue" describes a condition resulting from the supposed "overuse" of the adrenal glands. A Google search conducted in December 2019 for "adrenal fatigue" yielded 3,090,000 results, an increase from 640,000 results in 2016 (11). Many of the websites found in the search provide information on the self-diagnosis of "adrenal fatigue," commercialize informational products, and sell supplements to treat this condition (12,13). Despite the lack of efficacy or safety data to support the use of adrenal supplements, billions of dollars are spent on these supplements annually (14). In addition to the financial cost, many of the "adrenal support" supplements are deceptively advertised as hormone-free when they actually often do contain potentially harmful substances such as thyroid hormone and steroid hormones with glucocorticoid and/or androgenic effects (15).

In addition to the off-label use of hormones, the use of general dietary supplements in the United States is widespread, with 44% of adult men reporting use in 2003-2006 (16). Many men's health and anti-aging clinics promote or sell cocktails of dietary supplements that supposedly improve energy and sexual function. One major concern regarding dietary supplements is that they do not undergo rigorous premarket safety and effectiveness testing or have the same level of quality control in manufacturing that is required for medications. A second major concern is that dietary supplements may contain undeclared pharmaceuticals. Many of the adulterated products are marketed toward the same demographic of men who seek testosterone for sexual enhancement, weight loss, or muscle building. The most commonly reported adulterants are sildenafil in sexual-enhancement supplements and synthetic steroids or steroid-like ingredients in muscle-building supplements (17). Anabolic steroids carry many of the same risks of testosterone and have been reported to cause elevations in liver enzymes, depression and mood disorders, aggression, metabolic changes, and cardiovascular events (18). 17α-Alkylated anabolic steroids, including certain formulations of testosterone, have been associated with peliosis hepatis and hepatocellular carcinoma (19).

This position statement seeks to raise awareness in the medical community concerning the risks of off-label use and misuse of testosterone, GH, thyroid hormone, and adrenal supplements. The primary intended audience of this statement are general medical practitioners (family physicians, internists, nurse practitioners, physician assistants, and naturopathic providers) and adult endocrinologists. This statement may also be informative for individual patients and patient groups considering off-label use of hormone supplementation and will distinguish off-label hormone use from legitimate use for diagnoses such as male hypogonadism, GH deficiency, hypothyroidism, and adrenal insufficiency.

TESTOSTERONE THERAPY FOR MALE HYPOGONADISM

Testosterone therapy is indicated for the treatment of primary and secondary male hypogonadism. Other medications also have an important role in the treatment of certain types of male hypogonadism. For example, human chorionic gonadotropin and clomiphene citrate are used in men seeking to preserve or stimulate fertility (20,21). Human chorionic gonadotropin, clomiphene citrate, and aromatase inhibitors are also used to raise endogenous testosterone levels (20). Although this position statement does not focus on anabolic steroid use, it should be noted that testosterone is the most commonly used anabolic steroid by bodybuilders and athletes (22).

According to several guidelines, the diagnosis of male hypogonadism requires the presence of symptoms combined with several confirmed levels of low testosterone (23,24). Multiple testosterone levels are needed for diagnosis due to fluctuations of the hormone on any given day. Testing should be performed in the morning after fasting, as mean testosterone levels are higher in the morning. Four cohort studies suggest a harmonized reference range of 264 to 916 ng/dL for total testosterone (25). Discrepancies between total, free, and bioavailable testosterone are possible with less accurate assays and/or alterations in sex hormone–binding globulin due to conditions such as obesity or HIV. Clinicians should be familiar with the performance characteristics of their local laboratory assays. For example, measurements of total testosterone by liquid chromatography–mass spectrometry are more accurate than many immunoassays (26). Several medical societies have collaboratively worked together to promote testosterone assays that are accurate and reliable (27).

In actuality, only a minority of men who are prescribed testosterone are being properly evaluated for hypogonadism. In a study of men in the United States and United Kingdom, only 14% of men in the United Kingdom and 10% of the men in the United States had more than one testosterone test within 180 days of receiving a prescription for testosterone (28). Another study from the United States showed a similar result, with only 18% of men receiving at least two testosterone tests in the 12 months prior to initiating treatment (29).

Some guidelines do not distinguish adequately between well-established pathologic causes of hypogonadism (i.e., Klinefelter syndrome) and the controversial "late-onset" hypogonadism (30). Some physicians have argued that these guidelines have tacitly promoted off-label prescriptions for testosterone without sufficient evidence from large randomized controlled trials (1). Many men with borderline low testosterone levels can be managed with lifestyle measures such as weight loss, increased exercise, and improved sleep as opposed to testosterone therapy.

OFF-LABEL USE OF TESTOSTERONE & ADVERTISING

An increased number of men taking testosterone has been fueled by its off-label use for low energy, sexual symptoms, and the controversial "late-onset" hypogonadism in which testosterone levels often decline in the setting of obesity and other comorbidities such as hypertension, hyperlipidemia, type-2 diabetes, and obstructive sleep apnea (31,32). Several factors have contributed to the surge of prescriptions for testosterone: ambiguity among guidelines for treating androgen deficiency, direct-to-consumer advertising, establishment of men's health clinics, and local prescribing patterns. In 2014, the FDA convened a Bone, Reproductive, and Urologic Drugs Advisory Committee meeting to discuss age-related hypogonadism and potential cardiovascular risk based on adverse event data. The committee concluded that the efficacy and safety of testosterone treatment have not been established for age-related hypogonadism (33).

In the United States, several pharmaceutical companies launched a highly successful disease awareness campaign for "low T" (28). The goal of this campaign was to increase the rates of testosterone testing and initiation, particularly among middle- and older-aged men, by leading men to believe that androgen deficiency could be a cause of their nonspecific symptoms. Before 2012, Abbott Laboratories (now AbbVie) funded unbranded "low T" advertisements that were not FDA regulated. After 2012, competition for market share led AbbVie and Eli Lilly to promote brand-specific testosterone advertisements which were regulated by the FDA (28). According to Nielsen television ratings from the largest 75 designated market areas in the United States, the mean exposure to household advertisements for testosterone peaked in December 2012 at 13.6 advertisements/month (28). Increased awareness of "low T" resulted in increased internet traffic on the topic, as well as testing and prescriptions for testosterone. In 2012, internet searches on Google for "low testosterone" were four times more common among searches in the United States compared with the United Kingdom, which lacked the "low T" television advertisements (31).

Across the United States, several business ventures have been established to make a profit by administering testosterone to men with "low T." Ageless Men's Health is one such business, with over 40 centers. According to its website, "Who can have low testosterone? Anyone" (34). This company claims to "boost your energy with proven, long-term solutions to low testosterone" (34). Long-term randomized controlled trials of testosterone therapy, however, do not exist. Another business is the Low T Center, with over 47 locations across 11 states. According to its website, this company claims to be "reinventing men's healthcare" and states that "the good news is you don't have to feel sluggish" (35). It should be noted that

Ageless Men's Health agreed to pay a $1.6 million (U.S. dollar) fine to resolve allegations that it billed Medicare and TriCare for medically unnecessary office visits while administering testosterone injections.

TESTING OF AND PRESCRIPTIONS FOR TESTOSTERONE

Lab testing of testosterone dramatically increased from 2000-2011 in both the United States and the United Kingdom (31). Over this time period, testing of testosterone increased from 39.6 to 170/10,000 person-years in the United States and from 13.0 to 46.4/10,000 person-years in the United Kingdom. A dramatic increase in testing of testosterone from 2009-2013 took place in the United States that paralleled a direct-to-consumer television advertising campaign (28). Mean rates of testing testosterone per 10,000 men increased from 18.6 to 29.4 from 2009-2011 to 2012-2013 (28). It is important to recognize that wide variability occurred in testing of and prescriptions for testosterone based upon local practices. For example, from 2009-2013, rates for testing testosterone varied from 2.7 to 30.5 per 10,000 men across 75 designated market areas in the United States (28).

Although testing is required for the diagnosis of male hypogonadism, several studies show that men are commonly prescribed testosterone without any laboratory testing at all (29,31). Or, testosterone is prescribed to men with baseline testosterone levels that are normal or even high, with rates of such prescriptions ranging from 4 to 9% up to 20% (29,31). Primary-care providers, perhaps without training and expertise in the diagnosis of male hypogonadism, write the majority of prescriptions for testosterone in the United States; one study reported that, prior to starting testosterone, only 7% of users were seen by endocrinologists and 20% were seen by urologists (29).

For testosterone, global sales increased 12-fold (from $150 million to $1.8 billion) from 2000 to 2011 across 41 countries (1). In the United States, testing and initiation of testosterone quadrupled from 2000 to 2011 (31).

RISKS OF TESTOSTERONE AND SUPPLEMENTS

Supplementation of testosterone is associated with several well-established risks and potential unknown risks (36). Exogenous testosterone frequently reduces fertility due to decreased spermatogenesis (37). Many younger men of reproductive age may be unaware that off-label use of testosterone and other anabolic steroids could adversely affect their potential fertility. Use of exogenous testosterone has been associated with acne and erythrocytosis (23). Testosterone therapy also can worsen the clinical course and progression of metastatic prostate cancer (23). Transference of a topical testosterone gel from a man to a woman or child could result in unwanted hyperandrogenism and virilization (38).

There have been no large, long-term randomized controlled trials to evaluate the safety of testosterone therapy. Many unanswered questions remain. One major question is whether testosterone therapy increases the rates of cardiovascular events. Studies have yielded inconsistent and conflicting results (39-41). A review of seven systematic reviews found that testosterone treatment was not associated with an increased rate of cardiac events in six out of the seven reviews (42). In 2018, AbbVie launched an ongoing large randomized controlled trial called the TRAVERSE Study to investigate the incidence of major adverse cardiovascular events and efficacy measures in hypogonadal men.

Studies of human chorionic gonadotropin, clomiphene citrate, and aromatase inhibitors have been limited by their small sizes and short durations, and randomized controlled trials are lacking to establish their efficacy and safety (43,44). In one trial of 85 men treated with clomiphene citrate, adverse events among four participants included depression, erythrocytosis, ischemic stroke, and psoriatic arthropathy (43). In case reports, use of clomiphene citrate has been associated with acute mania, central retinal vein occlusion, pulmonary embolism, and suicidal behavior (45-48). Aromatase inhibitors decrease bone density and have been associated with breast tenderness, depression, joint pain, limb swelling, and tendon pain (44).

GH DEFICIENCY

GH is approved by the FDA for use in children and adults with GH deficiency (49-51). In addition, GH is an FDA-approved therapy for several nondeficient states in children and adults, which include HIV-associated wasting and cachexia, idiopathic short stature, Noonan syndrome, Prader-Willi syndrome, short bowel syndrome, short stature associated with chronic renal failure, short stature associated with *SHOX* gene (short stature homeobox-containing gene) haploinsufficiency, small for gestational age without catch-up growth and Turner syndrome (49,50). In other countries, the indications for GH may be fewer and not include idiopathic short stature, short bowel syndrome, *SHOX* deficiency, or Noonan syndrome. Careful patient evaluation, often including GH-stimulation testing, is required to establish the diagnosis of adult GH deficiency (49-51). Besides its well-established effects promoting growth in children and adolescents, GH replacement also has anabolic and lipolytic effects in GH-deficient adults (52). In that adult population, GH replacement has been shown to induce beneficial effects on body composition, bone mineral density, serum lipids, exercise capacity, and quality of life (49,52).

OFF-LABEL AND SURREPTITIOUS USE OF GH

Anecdotal and limited published evidence suggests that GH abuse is common among recreational and profes-

sional athletes. In a study conducted among 224 male high school students, 11 adolescents (5%) reported GH use to enhance athletic performance (53). A study from Germany found that 10 (0.4%) of 2,319 adolescents reported use of GH in the previous year, administered for its putative performance-enhancing properties (54). In another study of 231 male weightlifters (18 to 40 years old), 27 individuals (12%) reported nonprescription use of GH and/or IGF-1, often in association with anabolic steroids or opioids (55). In a study of 180 men who attended an outpatient clinic for users of anabolic steroids in the Netherlands, 36% reported GH use (22). This trend of GH abuse among high school students and young adults who administer GH either alone or in combination with anabolic steroids is worrisome. Using online search engines, a survey identified 277,000 websites on "GH bodybuilding" and 184,000 sites advertising to "buy GH online" (56).

Surreptitious use of GH is illegal in the United States (Crime Control Act, 1990), and GH and IGF-1 are on the prohibited list of substances promulgated by the World Anti-Doping Agency. Despite the introduction of validated methods to detect the presence of exogenous GH in athletes, including the biomarker method and the GH isoform method, the problem of GH doping has persisted (57-59). Several elite athletes have been found in possession of GH preparations or have admitted to using GH for its purported performance-enhancing effects (60).

EFFECTS OF GH

There is a paucity of data on the effects of GH on athletic performance in healthy individuals. A systematic review and meta-analysis of 11 placebo-controlled trials of GH administration in 254 young healthy adults reported that GH modestly increased lean body mass and decreased fat mass (61). However, there was no increase in muscle strength or maximum oxygen uptake during exercise (61). One randomized placebo-controlled trial of GH administration (2 mg/day) in 96 recreational athletes for 8 weeks reported a 3.9% increase in sprint (anaerobic) capacity, which was more marked (by 8.3%) when GH was co-administered with testosterone, and was reversible 6 weeks after drug discontinuation (62). In a randomized placebo-controlled trial, 56 recreational athletes were randomized to either IGF-1, co-administered with IGF-binding protein 3, or placebo for 4 weeks (63). In this study, there was a 7% increase in maximal oxygen consumption on IGF-1 treatment but no effect on body composition (63). It is not known whether elite athletes would experience similar effects. Furthermore, athletes have reported use of GH in a wide range of doses and regimens, alone or co-administered with other anabolic agents (64). Thus, the significance of the findings presented in these studies remains unclear.

Although endogenous GH and IGF-1 secretion decrease with aging, there is no evidence that GH administration in older adults improves body function. A study of 21 healthy older men reported on the effects of a 6-month treatment with GH versus no treatment (65). There was an increase in lean body mass (by 8.8%) and skin thickness (by 7.1%) as well as a decrease in fat mass (by 14.4%) in GH-treated adults (65). A systematic review of 31 studies on the effects of GH administration in 220 healthy older adults found small improvements in body composition but no evidence of improvement in functional capacity or mitigation of the aging process (66). In addition, a meta-analysis found that GH therapy in women with age-related osteoporosis does not appear to increase bone mineral density (67).

RISKS AND COSTS OF GH ABUSE

There are limited safety data from studies of healthy younger recreational athletes and older healthy adults who received GH in clinical trials (61,62,65,66). Similar to studies of GH replacement, 15 to 44% of healthy adults who received GH in clinical trials developed edema, carpal tunnel syndrome, arthralgias, myalgias, or sweating (49,50). These adverse events were generally dose related and more common in older adults. Glucose intolerance or diabetes mellitus may occur as a consequence of the anti-insulin effects of GH. In contrast, hypoglycemia can occur among those receiving IGF-1 (63). Other adverse events associated with GH administration include idiopathic intracranial hypertension and gynecomastia. Case reports have documented iatrogenic acromegaly as a complication of GH therapy (68,69). In general, available data suggest that GH replacement does not increase the risk of de novo neoplasia (70,71). In several animal models, however, GH may be linked to neoplasia (72,73). Uncertainties exist regarding the risk of secondary tumor formation in patients who received GH replacement (49,50,74). Commercially available GH preparations currently are produced using recombinant DNA methodology. However, human cadaveric GH may still be available on the black market and carries the risk of Creutzfeldt-Jakob disease (75).

There are no published data regarding adverse events among individuals who abuse GH or related agents, since they use GH surreptitiously. Safety information from trials of GH replacement in deficient adults or even studies of GH administration in healthy younger or older adults cannot be extrapolated to individuals who abuse GH or IGF-1 in supraphysiologic doses and regimens, which can result in much higher drug exposures than those studied in clinical trials (7). Indeed, prolonged administration of GH in large doses may recapitulate acromegaly, a condition associated with increased risk of mortality in association with cardiovascular and neoplastic disorders, if inadequately treated (68,69,76-79).

The cost of GH treatment is substantial and was estimated as $52 per milligram per day (in 2004 U.S. dollars) (80), which translates to approximately $4,700 per month

for someone taking a supraphysiologic dose of 3 mg of GH daily; however, many patients are likely taking higher GH doses. Indirect health-care costs associated with excess morbidity that might result from administration of GH in large doses over prolonged periods can be difficult to estimate but are likely to be substantial if these individuals develop type-2 diabetes mellitus or cardiovascular or neoplastic disorders as a consequence of excess GH exposure.

OFF-LABEL OR UNAUTHORIZED USE OF THYROID HORMONE

Thyroid hormone is indicated for the treatment of primary and secondary hypothyroidism. Thyroid hormones have been used off-label in euthyroid individuals for a myriad of different conditions, including fatigue, obesity, depression, cognitive impairment, impaired physical performance, and infertility (10). Despite the pervasive and characteristic symptoms and signs that are seen with biochemical hypothyroidism, many of the manifestations are common and can overlap with the manifestations of other conditions. Although patients with hypothyroidism generally have more symptoms and more progressive symptoms than euthyroid individuals, symptoms are also present in euthyroid controls (81). There is increased recognition that the upper limit of the reference range for TSH should be increased for elderly individuals due to a lack of benefit with treatment with thyroid hormone (82,83).

Treating euthyroid individuals with symptoms suggestive of hypothyroidism with levothyroxine (LT4) does not reverse the nonspecific symptoms. This was demonstrated in a randomized, placebo-controlled, crossover trial in which euthyroid individuals were treated with either LT4 or placebo, and LT4 was found to have no benefit in improving cognitive or psychological function compared with placebo (84). Another trial examined the effects on body composition, heart rate, energy metabolism, and muscular function of LT4 versus placebo given to euthyroid patients with thyroid nodules. With the achievement of a mean serum TSH in the low-normal range (TSH 0.59 mIU/L) in the treatment group, compared with 1.22 mIU/L in the placebo group, there was no effect on any of the parameters assessed (85). In addition to data suggesting that the TSH threshold at which LT4 therapy is being initiated is falling, it also appears that there may be a proportion of individuals in whom a diagnosis of hypothyroidism was never established prior to LT4 initiation. This was demonstrated in a study in which 61% of those discontinued from LT4 therapy were euthyroid after 6 to 8 weeks off therapy (86).

EFFECTS AND RISKS OF THYROID HORMONE

Any off-label use of thyroid hormones in a euthyroid individual carries risks of iatrogenic thyrotoxicosis. Adverse effects of excessive thyroid hormones, both in individuals with and without underlying hypothyroidism, have been documented, primarily in older studies (87,88), including studies of students (89) and prisoners (90). In an open-label study of healthy men treated with 50 to 62.5 μg of liothyronine (LT3) daily for 9 weeks to determine whether T3 thyrotoxicosis would serve as a model to study space flight–induced lean body mass loss, participants lost both fat mass and lean body mass (91). Negative effects on nitrogen balance and increased energy expenditure were documented. In a randomized study of obese individuals treated with either 225 μg LT3 (L-triiodothyronine) daily or placebo for up to 6 months, LT3-treated patients achieved more weight loss in a hospital setting at 8 weeks, but this was no longer significantly different in the hospitalized setting at 12 weeks, or after discharge (92). All patients experienced an increase in pulse rate. Other side effects included tremors, nervousness, and weakness, and one patient developed atrial fibrillation (92). The effect of large doses of desiccated thyroid extract has been studied in hospitalized patients, with progressive increases in basal metabolic rate paralleling incremental increases in dosage (93). Anticipated signs and symptoms of thyrotoxicosis such as tachycardia were also documented (93). Individuals without hypothyroidism should not be exposed to the risks of iatrogenic hyperthyroidism that are likely to accompany thyroid hormone use, because beneficial effects on cognitive, psychologic, or muscular function have not been shown, and weight loss cannot be achieved without concomitant loss of lean body mass.

USE OF THYROID SUPPLEMENTS, THYROID BOOSTERS, AND WEIGHT-LOSS MEDICATIONS

Over-the-counter and dietary supplements frequently are used for many diverse reasons in the United States; older individuals who take prescribed medications frequently participate in such usage (94). Specific interest in therapy to augment thyroid function is considerable, prompted no doubt in part by the similarity between symptoms of hypothyroidism and those of medical and psychological conditions, and the potential appeal of a single therapy that may impact many symptoms. This "therapy" may take the form of various thyroid supplements or boosters or may even involve use of thyroid hormones (LT4 or LT3) themselves or desiccated thyroid extract. Dietary supplements or nutraceuticals that may be utilized for their purported benefit in improving thyroid function include, but are not limited to, those containing iodine, tyrosine, and thyroid hormone analogues (95). There is little evidence for benefit of these supplements, with the possible exception of selenium as an agent to reduce thyroiditis in pregnant women (96). Although iodine in the appropriate amount is required for normal thyroid function, excessive amounts of iodine can cause dangerous degrees of hypothyroidism or thyrotoxicosis, and individuals with underlying thyroid autoim-

munity are most susceptible (97). Thyroid supplements are readily available and marketed for "thyroid support." A 2013 study which analyzed the content of 10 such supplements found that 9 out of 10 contained T4 and 5 out of 10 contained T3 (98). If thyroid supplements were taken at the recommended dosages, some of those products would deliver up to 92 μg of T4 daily and 10 μg of T3 daily. Computer modeling has demonstrated the potential thyrotoxic effects of over-the-counter supplements containing LT4 and LT3 (99). Tiratricol is a metabolite of T4, which has thyromimetic effects, with augmented effects on the liver and skeletal muscle (100). Although banned by the FDA, its use and subsequent side effects have been documented in case reports (101-103).

Drugs marketed for weight loss and subsequently found to contain substantial quantities of thyroid hormones have been associated with palpitations, diarrhea, heat intolerance, and amenorrhea, in addition to weight loss. Examples of such drugs that have been sold in Japan include "Basset Super" (104), "Dream Shape," and "Ever Youth" (105). With respect to the latter preparations and case reports on their effects, authors documented elevation in T4 and T3 that occurred after the authors themselves ingested the products. Case reports of thyrotoxic periodic paralysis have been described in individuals taking weight-loss supplements containing, or believed to contain, T3 (106-108). Death attributed to ventricular fibrillation also has been reported following ingestion of large amounts of LT4 by individuals using higher than prescribed doses of LT4 for weight loss (88).

"ADRENAL FATIGUE" & GLUCOCORTICOIDS

Glucocorticoids are indicated for the treatment of adrenal insufficiency and a wide array of inflammatory diseases. Glucocorticoids are also used off-label for the dubious diagnosis of "adrenal fatigue," a medical condition that supposedly results from the overuse of the adrenal glands. Proponents of "adrenal fatigue" postulate that chronic or extreme stress leads to a decrease in adrenal function with subsequent development of a general sense of unwellness, fatigue, body aches, nervousness, sleep disturbances, digestive problems, weight gain, and a multitude of other nonspecific symptoms. Purported symptoms and signs of "adrenal fatigue" can be divided into physical and mental domains (12,13,109). Symptoms commonly described online follow specific circadian patterns and are ineffectively counteracted by lifestyle changes such as taking a nap or drinking caffeinated drinks; for example, fatigue is described to be worse in the morning or mid-afternoon but possibly better in the evening. Various sleep problems frequently are indicated as part of the syndrome and include waking up unrefreshed after a full night of sleep or suffering from insomnia or hypersomnia. Depression, anxiety, inability to handle stress, and emotional lability are also listed as critical symptoms of "adrenal fatigue." Multiple other nonspecific symptoms listed in several online questionnaires that raise suspicion of "adrenal fatigue" include "brain fog," lightheadedness, weight gain or weight loss, decrease in sex drive, craving for salty or sweet snacks, and unexplained aches and pains. A strong association with previous or current stress of any kind is usually described.

DIAGNOSIS OF "ADRENAL FATIGUE"

The endocrine community, including the Endocrine Society and the Hormone Health Network, does not recognize "adrenal fatigue" as a legitimate medical condition (11). According to some online content not authorized by medical professionals, the diagnosis of "adrenal fatigue" is based upon questionnaires and biochemical hormonal testing. Commonly used questionnaires listed on several websites have not followed scientific methods for the development and validation of questionnaires in any population (110). These questionnaires usually cover a multitude of nonspecific symptoms, vary in length, scoring, and interpretation, and are often biased in the direction of adrenal fatigue. A systematic review of 58 studies found 19 different types of questionnaires and scores reported, including the Maslach Burnout Inventory, SF-36, Chalder Fatigue Scale, the Multidimensional Fatigue Inventory, General Fatigue Scale, and others (11).

Proponents of "adrenal fatigue" recommend several hormonal assessments for diagnosis. The most popular tests include the direct awakening cortisol, cortisol awakening response, salivary cortisol rhythm (3 to 5 times a day), and morning and night salivary cortisol measurements (11). Current evidence on the accuracy of these tests is extremely limited by the heterogeneity of populations and methods used in the studies, differences in assays, limited considerations of normal interindividual variability in the circadian cortisol rhythm of participants, exposure to exogenous glucocorticoids, or concomitant use of opioids or other medications affecting the hypothalamic-pituitary-adrenal axis. Moreover, subgroup classifications of patients and controls relied on subjective assessments with no optimal reference standard in any of the studies. As reported in a systematic review, patients with "adrenal fatigue" have inconsistent and sometimes opposite-from-expected results on hormonal assessments (11). Suggested hormonal panels also frequently include salivary measurements of DHEA and pregnenolone, in addition to sex steroids (11,111,112). Such testing and interpretation of the results can be purchased via the internet without any clinical evaluation. The accuracy and reproducibility of these tests have not been established and would need to consider factors such as diurnal variation, medical comorbidities, and concomitant medication use. Most of the available salivary hormonal panels are not FDA approved and have not undergone adequate validation needed for translation into clinical practice.

ADRENAL SUPPLEMENTS

Over-the-counter supplements marketed for "adrenal fatigue" are widely used, with limited or no data on efficacy or safety. These supplements are frequently advertised on websites that also offer a survey-based self-diagnosis of "adrenal fatigue," as well as costly treatment programs (12,13). While some "adrenal support" supplements are advertised as hormone free, many actually contain undisclosed amounts of thyroid and steroid hormones (15). A study of 12 dietary adrenal support supplements found that 8 to 42% contained adrenal steroids (pregnenolone, 17-hydroxyprogesterone, androstenedione, cortisol, and cortisone) and/or budesonide, while detectable amounts of T3 were detected in all examined supplements (15).

Pregnenolone is a precursor hormone that has been promoted as an anti-aging treatment to boost the production of downstream steroid hormones such as androgens, estrogens, and glucocorticoids. A small number of studies suggest that pregnenolone may have a role in the treatment of certain brain-related disorders such as schizophrenia and depression (113-115). A pilot trial reported that supplementation with pregnenolone 500 mg/day for 8 weeks led to significant increases in serum concentrations of DHEA-sulfate and progesterone and side effects of mild restlessness and mild muscle pain/stiffness, which raises concern about long-term use (116). There is no scientific evidence to support the use of pregnenolone in the treatment of adrenal insufficiency or androgen deficiency.

Supplements containing DHEA are also marketed to support adrenal health and increase energy. A systematic review of DHEA supplementation in postmenopausal women with normal adrenal function found that short-term supplementation with DHEA 50 mg/day was not associated with an improvement in well-being. However, dermatologic and androgenic symptoms were reported in as many as 25% of patients (117). Both hydrocortisone and fludrocortisone therapies have been studied in patients with chronic fatigue syndrome. While several short-term studies have reported mild improvement in fatigue with hydrocortisone therapy (118,119), a combination of low-dose hydrocortisone and fludrocortisone was not found to be effective in a 6-month, randomized, placebo-controlled, double-blind, crossover study of 100 patients who received this treatment (120).

RISK OF DIAGNOSIS AND THERAPY FOR "ADRENAL FATIGUE"

Unknown exposure to thyroid and steroid hormones, as well as other compounds, may lead to serious negative consequences, such as iatrogenic hyperthyroidism, Cushing syndrome, and adrenal insufficiency if supplements are discontinued abruptly after chronic use. Fatalities have been documented with unregulated use, including the case of a woman who died after taking seven supplements which subsequently were found to contain 14 active compounds (121).

It is likely that taking supplements for adrenal fatigue may delay the diagnosis and treatment of a legitimate medical condition for months to years and possibly adversely affect the severity of the condition. The diagnosis of adrenal insufficiency needs to be considered in patients presenting for evaluation of "adrenal fatigue," especially in patients with a history of glucocorticoid exposure, opioid usage, traumatic brain injury, or other endocrine disorders (122). Hypothyroidism, GH deficiency, hypogonadism, and undiagnosed diabetes mellitus can also present with fatigue and other nonspecific symptoms. Finally, several nonendocrine disorders, such as obstructive sleep apnea, chronic fatigue syndrome, post-viral fatigue, and fibromyalgia, are frequently misdiagnosed as "adrenal fatigue."

CONCLUSION

Off-label use and misuse of testosterone, GH, thyroid hormone, and adrenal supplements have become increasingly prevalent. Many patients seek treatment for common nonspecific symptoms such as fatigue, low energy, poor sleep, weight gain, and lower libido. Unfortunately, some clinics and websites lead people to believe that their symptoms are attributable to a deficiency of a hormone and that treatment with this hormone will eliminate their symptoms. While it is true that aging and chronic diseases are associated with a decline in serum concentrations of testosterone and GH, there is no scientific evidence to support prescribing these hormones for anti-aging purposes. Physicians and other health-care professionals should therefore only prescribe testosterone, GH, thyroid hormone, and glucocorticoids to patients with clearly established diagnoses of male hypogonadism, GH deficiency, hypothyroidism, adrenal insufficiency, and other conditions where these medications are an accepted standard treatment.

The American Association of Clinical Endocrinologists (AACE) strongly recommends that board-certified endocrinologists diagnose GH deficiency and adrenal insufficiency, as these conditions are uncommon diagnoses that require a high level of expertise in endocrinology. Testing protocols for these conditions can be complex. While the diagnoses of male hypogonadism and hypothyroidism do not necessarily need to be confirmed by endocrinologists, practitioners who prescribe testosterone and thyroid hormone need to have adequate knowledge about these conditions and understand the potential risks of related therapies. Practitioners should have training to interpret lab results in a more comprehensive way than simply checking whether a testosterone or TSH value falls within the reference range. There are many causes of abnormal laboratory results that are not due to hormonal deficiency.

When evaluating patients who have been prescribed testosterone, GH, thyroid hormone, and/or adrenal supplements by other providers, it is important to confirm that

Table 1
Indications, Unproven Claims, and Risks of Testosterone, Growth Hormone, Thyroid Hormone and Glucocorticoids in Adults

	Approved indications	Unproven claims that the hormone will improve the symptoms or entities below in individuals without the approved indications	Risks & adverse effects
Testosterone	• Male hypogonadism	• Low energy • Sexual symptoms • Weight gain	Acne, benign prostatic hypertrophy, decreased HDL cholesterol, erythrocytosis, depression, gynecomastia, hypertension, increased serum bilirubin, increased serum creatinine, infertility, nervousness, peripheral edema, progression of metastatic prostate cancer, rash, sleep apnea, testicular atrophy
Growth hormone	• Growth hormone deficiency • HIV-associated wasting and cachexia • Short bowel syndrome	• Aging • Athletic performance	Abdominal pain, arthralgias, carpal tunnel syndrome, facial edema, flatulence, glucose intolerance/diabetes, headache, hypoesthesia, infection, myalgias, nausea, ostealgia, pain, paresthesia, peripheral edema, sweating, upper respiratory tract infection, vomiting
Thyroid hormone	• Hypothyroidism	• Cognitive impairment • Depression • Fatigue • Impaired physical performance • Infertility • Obesity	Abdominal cramps, alopecia, amenorrhea, angina pectoris, anxiety, atrial fibrillation, cardiac failure, decreased bone mineral density, diaphoresis, diarrhea, dyspnea, emotional lability, fatigue, fever, flushing, headache, heat intolerance, hyperactivity, hyperdefecation, increased appetite, increased blood pressure, increased liver enzymes, increased pulse, insomnia, irritability, menstrual disease, muscle spasm, myasthenia, myocardial infarction, nervousness, palpitations, rash, reduced fertility, tachycardia, tremor, vomiting, weakness, weight loss
Glucocorticoids	• Adrenal insufficiency • Allergies • Dermatologic diseases • Hematologic diseases • Inflammatory diseases • Rheumatologic diseases • Pulmonary diseases	• Anxiety • “Brain fog” • Craving for salty or sweet snacks • Decrease in sex drive • Depression • Digestive problems • Emotional lability • Inability to handle stress • Lightheadedness • Sleep disturbances • Unexplained aches and pains • Weight gain or weight loss	Amenorrhea, amyotrophy, aseptic necrosis of bones, decrease in bone mineral density, decreased serum potassium, depression, diaphoresis, easy bruising, emotional lability, facial erythema, fluid retention, glaucoma, glucose intolerance/diabetes, headache, hirsutism, hypertension, hypokalemic alkalosis, iatrogenic Cushing syndrome, increased intracranial pressure, increased intraocular pressure, increased serum alkaline phosphatase, increased serum ALT, increased serum AST, insomnia, irregular menses, menstrual disease, myasthenia, negative nitrogen balance, osteoporosis, pathological fracture, personality changes, proximal muscle weakness, seizure, sodium retention, steroid myopathy, subcapsular posterior cataract, tendon rupture, thin skin, urticaria, vertigo, weight gain

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; HDL = high-density lipoprotein; HIV = human immunodeficiency virus.
Adverse effects were derived from Lexicomp®.

the diagnosis was firmly established. This may involve reviewing the patients' outside test results prior to starting hormone therapy and/or discontinuing treatment in order to reassess the endocrine axis. For patients in whom repeat testing does not confirm their initial suspected diagnoses, clinicians should collaborate with other members of the patients' health-care team to consider other potential explanations and etiologies for their unexplained symptoms. For example, many obese men have fatigue secondary to undiagnosed obstructive sleep apnea.

General medical practitioners and adult endocrinologists should be able to begin a discussion with their patients regarding the unfavorable balance between the risks and benefits associated with off-label use of testosterone, GH, thyroid hormone, and adrenal supplements. Table 1 summarizes the approved indications, unproven claims, and potential risks and adverse effects of the hormones described and glucocorticoids. Patients can be directed to reputable online educational resources, including the Endocrine Society's Hormone Health Network and AACE's Disease State Resources (123,124). Many leading health systems, such as the Mayo Clinic and Cleveland Clinic, also have online resources for patients (125,126). Clinical practice guidelines are also available for clinicians on the diagnosis and treatment of androgen deficiency, GH deficiency, hypothyroidism, and adrenal insufficiency (10,23,49,50,122).

Given the increase in off-label use and misuse of testosterone, GH, thyroid hormone, and adrenal supplements, it is important that reputable medical organizations and journals work together to increase awareness of this topic among the general public, as well as among the medical community. Given the rise of health-care costs associated with tests and medications, practitioners should strive to be good stewards of the health-care system by minimizing the ordering of unnecessary tests and medications. Treatment recommendations should be based upon well-designed scientific studies. Finally, we should always keep in mind one of the most important principles of medicine, which is to do no harm.

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