REPORT 4 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-16)
Hormone Therapies: Off-Label Uses and Unapproved Formulations
(Resolution 512-A-15)
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. To develop a report, update recommendations, and inform physicians about the use of off-label and unapproved uses of hormones, especially compounded hormone therapies (bioidentical hormones).

Methods. English-language articles were selected from a search of the PubMed database through August 2016 using the search terms “off-label hormone therapy,” “bioidentical hormone,” and “off-label” with the terms “estrogen,” “progesterone,” “thyroid hormone,” “dehydroepiandrosterone,” “testosterone,” “growth hormone,” and “hCG.” Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society websites were conducted to identify clinical guidelines and position statements. Additionally, Internet searches were conducted for “wellness clinics.”

Results. Females, males, children, transgender individuals, and athletes are all recipients of hormone therapies. The use of the therapies can be categorized as FDA-approved, off-label use supported by scientific evidence; off-label use in the absence of scientific evidence, and use of non-FDA-approved products. A number of FDA-approved hormone products exist and are being used for labeled indications as well as for off-label uses, both with and without support of scientific evidence. In addition, many hormones being prescribed for both medical and non-medical indications are not FDA-approved products, including dietary supplements and compounded products. Even though compounded hormone therapies are not FDA-approved, they do require a prescription. Little scientific evidence exists to support specific claims of efficacy of compounded hormone therapy preparations; a literature review produced no adequate randomized placebo-controlled trials to support their use.

Conclusion. Current AMA policy supports the clinical decision-making authority of a physician to use an FDA-approved product off-label when such use is based upon sound scientific evidence or sound medical opinion; however, to date the use of compounded hormone therapies is not supported by such evidence. Additionally, traditional compounding is recognized as a legal and important therapeutic approach when an FDA-approved drug product is not available or does not meet the clinical needs of individual patients. However, in the case of many of the uses for compounded hormones, comparable FDA-approved therapies are available. Further concern is prompted by the fact that compounding pharmacies are exempt from including specific and important safety information on labeled instructions. That lack of information may put some patients at risk.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 4-I-16

Subject: Hormone Therapies: Off-Label Uses and Unapproved Formulations (Resolution 512-A-15)

Presented by: Bobby Mukkamala, MD, Chair

Referred to: Reference Committee K (, MD, Chair)

INTRODUCTION

Resolution 512-A-15, "Off-Label Use of Hormone Therapy," introduced by the Women Physicians Section and referred by the House of Delegates asked:

> That our American Medical Association work with national health care organizations to advocate on behalf of the public and our patients on the appropriate evaluation and treatment of hormone deficiencies, as well as the side effects from use of hormone therapy without objective evidence to guide treatment, especially when given to promote weight loss or a general feeling of well-being.

Hormone therapy is the treatment of diseases or conditions with hormones that are derived from endocrine glands or substances that simulate or modulate hormonal effects.[1] The most common uses of U.S. Food and Drug Administration (FDA) approved hormone therapies include replacement during menopause, oncology therapies, and for endocrine or genetic disorders. Although oral contraceptives are a common use of hormones, their primary use for the prevention of pregnancy is not considered a therapy. Over the past several years there has been a large expansion in the use of hormones for off-label uses such as "well-being," anti-aging, low libido and sexual dysfunction and other conditions in the absence of an evidence base to guide treatment (e.g., human chorionic gonadotropin (hCG) for weight loss).[2] Clinicians prescribing hormone therapies off-label are found in primary care clinics or practices, hospital settings, specialty practices, and "commercial wellness clinics." Products being prescribed include both FDA-approved pharmaceuticals and unapproved hormones, including compounded preparations.

Recently, the pursuit of individual health and well-being has been put in the spotlight and become an evolving trend. The global wellness industry is now a $3.4 trillion market, more than 3-fold larger than the worldwide pharmaceutical industry.[3] In the U.S., the sale of compounded hormone therapies is estimated at $1.5 billion, with continued growth projected over the next several years.[4]

Females, males, children, transgender individuals, and athletes are all recipients of hormone therapies. These therapies can be categorized as follows (see Figure 1):

- Use of approved drugs according to a labeled indication
- Off-label use of FDA-approved hormone therapies supported by scientific evidence

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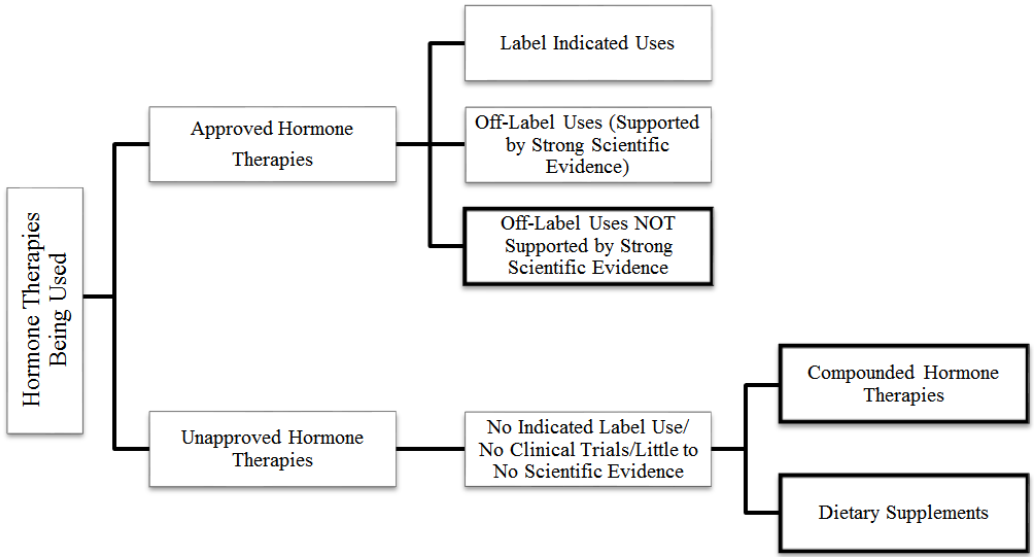
Action of the AMA House of Delegates 2016 Interim Meeting: Council on Science and Public Health Report 4 Recommendations Adopted as Amended and Remainder of Report Filed.

- Off-label use of FDA-approved hormone therapies in the absence of scientific evidence
- Widespread use of unapproved hormone therapies, including compounded hormone therapies. While subject to some FDA regulation, hormone-containing dietary supplements can also be considered in this category.

Figure 1. Flow chart of hormone therapy uses (bold boxes indicate the focus of this report).



CURRENT AMA POLICY

Current AMA Policy H-120.988, "Patient Access to Treatments Prescribed by Their Physicians," supports the decision-making authority of a physician and the lawful use of FDA-approved drug products for an off-label indication when such use is based upon sound scientific evidence or sound medical opinion. Policy D-120.969, "FDA Oversight of Bioidentical Hormone (BH) Preparations," is a set of directives urging stronger FDA oversight over bioidentical hormones; this report will update this policy. Policy H-100.962, "The Use of Hormones for Anti-Aging: A Review of Efficacy and Safety," based on a previous Council report, states that proponents of anti-aging therapies have the responsibility to prove claims of a positive risk/benefit profile through well-designed, randomized, placebo-controlled clinical trials. The goal of Policy H-460.907, "Encouraging Research Into the Impact of Long-Term Administration of Hormone Replacement Therapy in Transgender Patients," is reflected in the title of the policy. Finally, Policy D-140.957, "Ethical Physician Conduct in the Media," seeks to establish guidelines for physician endorsement and dissemination of medical information in the media.

METHODS

English-language articles were selected from a search of the PubMed database through August 2016 using the search terms "off-label hormone therapy," "bioidentical hormone," and "off-label" with the terms "estrogen," "progesterone," "thyroid hormone," "dehydroepiandrosterone," "testosterone," "growth hormone," and "hCG." Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society websites were conducted to identify clinical guidelines and position statements. Additionally, Internet searches were conducted for "wellness clinics."

BACKGROUND

Women's Health Initiative

The findings of the Women's Health Initiative (WHI) are an important backdrop to the marketing of off-label hormone therapies. The initial results of the WHI were summarized in CSAPH Report 5-A-09.[5] Briefly, following publication and analysis of the results of the WHI, the U.S. Preventive Services Task Force (USPSTF) recommended against the routine use of combined hormone therapy (estrogen plus progestin) for the prevention of chronic conditions in postmenopausal women and the routine use of estrogen alone for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. Subsequently, the FDA also required estrogen/progestin or estrogen-only products to contain a black box warning on the potential serious adverse events associated with long-term administration.[5] A reanalysis of the WHI data suggests that combined hormone therapy may be appropriate for younger, low-risk women who are seeking short-term relief from menopause symptoms, but the USPSTF continues to recommend against the use of combined hormone therapy for disease prevention or long-term health improvement.[6]

Off-Label Prescribing

When the FDA approves a drug or device and its product labeling, it does so for a specific use or indication. When a physician prescribes a drug for an indication that is not included in the product labeling, or at a dosage outside the recommended range, or uses a different route of administration, or for a patient from a population excluded from the label recommendation (e.g., pediatric), such uses are termed "unlabeled" or "off-label." Off-label prescribing is not illegal because the FDA does not regulate the practice of medicine (21 U.S.C. § 396). Once a drug product has been approved for marketing, physicians may prescribe it for uses or in treatment regimens or patient populations that are not included in the approved product labeling. AMA Policy H-120.988 strongly supports the option of off-label prescribing "when such use is based upon sound scientific evidence or sound medical opinion."

The prevalence and clinical importance of off-label prescribing in routine patient care are substantial. In general, off-label prescribing ranges from 10-20%, but is much higher in certain medical specialties (e.g., oncology) and patient populations (e.g., pediatrics, patients with rare diseases).[7-12] Accordingly, the spectrum of off-label uses is wide. They can be a source of innovation and new practices, represent primary therapy or the standard of care, or they may represent the only available therapy or be a therapy of last resort. Concerns include a lack of substantial evidence supporting safety and efficacy for many off-label uses and the potential for increased costs when newer branded drugs are used in this manner. Recently, the lack of strong scientific evidence to support many common off-label uses, and an increased frequency of adverse events leading to discontinuation of therapy, have led to calls for more scrutiny of such practices.[10,13,14]

In one study of hormone prescribing in primary care clinics, more than 20,000 new prescriptions were issued between 2005 and 2009; 5.2% of them were for off-label uses.[15] Additionally, a recent survey of the activity of compounding pharmacies estimated that 26 to 33 million hormone therapy prescriptions are compounded annually for 2 to 3 million individuals.[4,16] All compounded preparations are by definition not FDA-approved, even if they include FDA-approved drugs. Limited pathways exist for non-FDA-approved drugs to be compounded and supplied to patients.

APPROVED HORMONE THERAPIES

A number of FDA-approved hormone products exist. These include, but are not limited to, steroidal hormones, aromatase inhibitors, gonadotropin releasing hormones (GnRHs), GnRH analogs, GnRH antagonists, selective estrogen receptor modulators (SERMs), antiandrogens, somatostatin analogs, growth hormone (hGH), hGH secretagogues, human chorionic gonadotropin (hCG), and thyroid hormones. There are several labeled uses for these hormone therapies; Table 1 provides class examples of FDA-approved hormones and examples of indicated uses for the class. Table 1 also notes some off-label uses of hormone therapies, most of which lack supporting scientific evidence.

UNAPPROVED HORMONE THERAPIES

Beyond the pattern of FDA-approved medications being used off-label without support of scientific evidence, many hormones being prescribed for both medical and non-medical indications are not FDA-approved products. These include dietary supplements and compounded products.

Dietary Supplements

Dietary supplements are regulated by the Dietary Supplement Health and Education Act of 1994 (DSHEA).[17] Under DSHEA, dietary supplements are not regulated as drugs. Manufacturers, not the FDA, are responsible for evaluating the safety and labeling of products before marketing to ensure that they meet all legal requirements. Thyroid hormone and dehydroepiandrosterone (DHEA) are two common hormones found in commercially available dietary supplements. Recent studies have revealed that one in three older adults are using five or more prescription medications and approximately half regularly use over-the-counter dietary supplements and medications.[18] In addition to concerns with dietary supplement quality and contamination,[19] there is a high risk of adverse events associated with the use of multiple medications and dietary supplements. Half of all potential major drug-drug interactions identified in outpatients involved over-the-counter products.[18]

Compounded Hormone Therapies (Bioidentical Hormones)

Bioidentical hormones are semi-synthetic hormones that are chemically synthetized from a natural starting material, most commonly a plant sterol sourced from soybeans or the Mexican yam.[20] Bioidentical hormones are structurally identical to hormones produced in the body. Some are commercially available products approved by the FDA (e.g., micronized estradiol), and many are compounded preparations that are not FDA-approved. Compounded bioidentical hormones have become popular because of direct-to-consumer marketing by compounding pharmacies, commercial wellness clinics, and some individuals outside of the medical community along with media depiction as safer, natural, and more effective alternatives to prescription hormone therapies. Although compounded bioidentical hormones are not FDA-approved, they do require a prescription. The term bioidentical hormones does not include over-the-counter herbal preparations or plant-based products with estrogenic activity.

The term “bioidentical hormone” does not have a standardized definition, which adds to the confusion regarding the identity, use, and safety of the products. Depending on the context in which it is used, the term can imply natural (not synthetic), compounded, plant derived, or structurally identical to human hormones.[21] The term “bioidentical hormone therapy” has been recognized by the FDA and The Endocrine Society as a marketing term and not a description based on scientific evidence.[20,22-24] Therefore “compounded hormone therapy” (CHT) will be used to

describe these preparations throughout this report. Furthermore, CHT often not only refers to compounded hormone preparations, but may be inclusive of the initial diagnostic testing and monitoring that is repeated over time on a patient.

Regulation. CHTs are prepared in compounding pharmacies and are regulated under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Section 503A applies to traditional compounding pharmacies and §503B applies to compounding outsourcing facilities which produce bulk amounts of products (e.g., for hospitals or in the event of drug shortages). The vast majority of the products that are the focus of this report are compounded in traditional compounding pharmacies and are therefore regulated under §503A. Compounded drugs are not subject to the same rigorous evaluation and approval process as prescription drugs that are FDA-approved. Section 503A describes that compounded drug products are exempt from three sections of the FD&C Act including those concerning current good manufacturing practice (cGMP); the labeling of drugs with adequate directions for use, standardized labels, or product inserts (including any black box warnings); and the approval of the drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs).[25] Additionally, the statute puts restrictions on the compounding of products that are essentially copies of drugs that are commercially available.[26] Previously, §503A also included restrictions on advertising or promotion of the compounding of drugs or drug classes or the solicitation of prescriptions for compounded drugs, but these provisions were deemed unconstitutional by the U.S. Supreme Court in 2002.[27] Traditional compounding pharmacies are not required to register with the FDA, investigate or report adverse events, or report sales under §503A. Currently, individual state boards of pharmacy maintain oversight of traditional compounding pharmacies under §503A while the FDA maintains a risk-based enforcement approach with respect to violations of the FD&C Act.

Evidence Base. Little scientific evidence exists to support specific claims of efficacy of CHT preparations. A literature review produced no adequate randomized placebo-controlled trials. Authors of a literature review of randomized controlled trials of CHT progesterone cream for the relief of menopause-related vasomotor symptoms found three studies.[28] None of the trials applied FDA methodology for evaluating symptom relief and the search authors determined in their review that the data presented do not support the use of CHT progesterone cream for the relief of menopause-related vasomotor symptoms.

Two observational studies were found evaluating menopausal symptom relief for 3-6 months in patients receiving CHT preparations from a wellness clinic which offer low-level evidence that CHT improves menopausal symptoms. The first study involved 296 women receiving various CHT treatments, doses, and routes of administration and showed a statistically significant improvement in emotional symptoms such as irritability and anxiety.[29] The second study involved 200 women receiving estrogen, progesterone, testosterone, or some combination of the three hormones either via topical or sublingual administration. The results of this study showed that topical CHT was not as effective as sublingual CHT at reducing vasomotor, mood, and quality-of-life symptoms.[30]

CHT preparations can be inconsistent in dose and purity. After reports of quality control problems associated with CHT, the FDA conducted two surveys to evaluate compounded drugs. In 2001, the FDA evaluated 29 compounded drugs from 12 different compounding pharmacies and reported that while none of the samples failed identity testing, 10 (34%) of the samples failed standard quality testing, including potency testing.[31] In another survey in 2006, the FDA collected 198 samples from compounding pharmacies; 73 were finished compounded drug products; 33% of these products did not conform to information on the label.[32] Other reports of both subpotent products and products containing excessive amounts of active ingredient(s) exist.[22] One preliminary pharmacokinetic study in which plasma estradiol levels achieved with CHT doses

commonly thought to be bioequivalent to FDA-approved products were compared to the FDA-approved estradiol patch. The plasma levels achieved with all doses of the CHTs were significantly lower than with the estradiol patch.[33]

The Endocrine Society, The American Association of Clinical Endocrinologists, American Congress of Obstetricians and Gynecologists, American Society for Reproductive Medicine, The North American Menopause Society, and The Women's Health Practice and Research Network of the American College of Clinical Pharmacy have issued position statements outlining their concerns regarding CHT, specifically mentioning patient safety because of the lack of evidence-based research regarding clinical effectiveness and inherent risks associated with hormone compounding.[1,23,34-37] Policy D-120.969, "FDA Oversight of Bioidentical Hormone (BH) Preparations," urges the FDA to take several actions regarding bioidentical hormones.

CHT Marketing and Conflicts of Interest. There have been some ethical and conflict of interest issues associated with commercial wellness clinics and compounding pharmacies that prescribe and dispense CHT. Some compounding pharmacies that sell CHT also market the products to the public by providing listings of their offerings and offer referrals to providers who can prescribe the CHT. Some proprietors of commercial wellness clinics have published peer-reviewed journal articles that have been viewed as misleading[38] and questionable rhetorical approaches may be used to appeal to those lacking scientific literacy, for example, failing to distinguish between "cutting edge medicine" and "untested or unproven therapies."[39]

CHT proponents often use the WHI trial results as part of a marketing approach to promote CHT as safer than traditional hormone therapies, emphasizing that CHT is different from the hormones used in the WHI study, and either implying or directly claiming that CHT is safer than FDA-approved preparations, despite a lack of evidence to substantiate this claim.[39,40] In addition, the FDA requires that patient package inserts and class labeling black box warnings reflective of the findings of the WHI be included with all FDA-approved estrogen and progesterone products. Because CHTs are not FDA-approved products, they are exempt from FDA labeling and warning requirements, and patient package inserts and the black box warnings are not included.[22] The lack of warnings may lead some patients to conclude CHTs are safer.[1]

Additional claims often employed as marketing tactics by CHT prescribers and compounders also cannot be substantiated.[21,41] For example, the claim that CHT has improved delivery compared to FDA-approved hormone therapies has not been evaluated in clinical trials.[21] Some clinicians also advocate for saliva testing as a way to provide customized therapy for patients, an approach that lacks scientific validity (see below).[35]

Patient Perspective. Surveys indicate that approximately one in three individuals who use hormone therapy rely on CHT and believe it is "natural."[16] Using terms such as "bioidentical" and "natural," health care providers are able to market and prescribe CHT as distinctly different treatments from traditional hormone replacement therapies and as alternatives to prescription drugs. CHT appeals to consumers who seek more holistic healthcare approaches and tend to reject synthetic, manufactured pharmaceutical drugs.[42] Surveys indicate that patients who seek CHT do so because of a lack of satisfaction with their primary care physicians. Wellness practitioners are perceived as better listeners, and as validating their symptoms and willing to find solutions.[42] There is abundant promotion from celebrities who have published popular books and magazine articles discussing hormone therapies.[39,43-46]

Among patients receiving hormone replacement therapies, only 14% of respondents knew that CHT was not FDA-approved.[47] Additionally, those patients view the fact that compounding of

CHT is not under FDA purview as part of the appeal. Furthermore, they view the customization as less dangerous even though opponents view this as one of the biggest risks of CHT.[42] Even when it is pointed out that a lack of safety data and product information does not mean CHT is safe, patients continue to believe CHTs are safer than FDA-approved hormone therapies.[48]

Hormone Customization. A major appeal of CHT is that the treatment is marketed as customized to each individual patient, compared to mass-produced FDA-approved pharmaceuticals. Most compounding pharmacies have the capability to prepare hormone therapies for various routes of administration including oral, sublingual, percutaneous, implant, injectable, or suppository. The pharmacokinetic properties are unknown for the majority of these compounded hormone preparations.

To achieve "individualized" hormone therapy for each patient, many CHT clinicians recommend saliva (and occasionally blood, serum, or urine) hormone testing. The implication is that the results of the saliva hormone test will aid in the determination of the type, dosage, and route of administration of hormone therapy prescribed for the patient.[34] However, actual hormone customization is very difficult to achieve because of hormone pharmacokinetics and physiologic variation. There is no evidence that hormonal concentrations in saliva are biologically meaningful, can be used to customize hormone therapies, or predict therapeutic effect.[37] Furthermore, saliva hormone assays do not have independent quality control programs, lack an accepted reference range[36] and the FDA has stated that no scientific evidence supports the use of saliva testing to titrate hormone dosages or monitor hormone levels.[35]

Commonly Prescribed CHTs. Two of the most commonly prescribed CHTs in the United States are bi-est (two estrogens) and tri-est (three estrogens).[21] Bi-est is a formulation of 20% 17β-estradiol and 80% estriol and tri-est is a formulation of 10% estrone, 10% 17β-estradiol, and 80% estriol (see Table 2). These percentages are calculated on a milligram-per-milligram basis and not estrogenic potency or concentration. Because these formulations are not FDA-approved, the actual milligram amounts can vary depending on the specific prescription that is written for each patient. No placebo-controlled clinical trials evaluating the safety or effectiveness of bi-est or tri-est preparations have been conducted. Also of note is that there is no form of estriol that is an FDA-approved product; however, estriol can be legally compounded because a USP monograph on estriol exists.

The Wiley Protocol is a commonly prescribed, patented[49] CHT that uses high amounts of estradiol and progesterone in a "cyclical and rhythmic pattern" as opposed to "static dosing" to mimic the hormone levels of a 20 year-old female. Since the development of the first protocol, additional protocols have been developed utilizing testosterone (for women), testosterone and DHEA (for men), thyroid hormones, and cortisol (see Table 2).[50] One study examined the standardization of Wiley Protocol CHT preparation concentrations from a selection of the compounding pharmacies approved to distribute the product. Despite the use of standardized instructions and compounding materials distributed with the Wiley Protocol products, not all pharmacies passed quality control measures for the CHTs tested.[51] This study did not evaluate the clinical effectiveness of the Wiley Protocol but made the claim that clinical studies are currently underway evaluating its effectiveness in pre- and post-menopausal women and in patients with cancer, osteoporosis, and multiple sclerosis. No evidence of such trials could be located in PubMed, clinicaltrials.gov, or the Cochrane Register of Controlled Clinical Trials.[51]

TX-001HR is solubilized 17β-estradiol and natural progesterone combined in a single gelatin capsule for the treatment of vasomotor symptoms in postmenopausal women.[52] It is currently being evaluated in a phase 3 placebo-controlled clinical trial (REPLENISH) for the treatment of

menopause-related moderate to severe vasomotor symptoms. If it is approved, TX-001HR would become the first FDA-approved hormone therapy that combines 17β-estradiol and natural progesterone in a single treatment similar to CHT.[52]

SPECIFIC CONDITIONS

Below are some disorders and conditions for which CHT and off-label therapies are commonly prescribed.

Aging

Hormone therapy for anti-aging was reviewed in CSAPH Report 5-A-09.[5] The decline of endogenous hormones is common with aging and the off-label use of hormone therapies to reverse the effects of aging is wide-spread. Large scale, randomized, placebo-controlled studies are still lacking to support the use of any hormone therapies for anti-aging purposes. Studies evaluating their long-term effects and risks when used off-label are also lacking.[53]

Female Sexual Dysfunction, Low Libido, and Sexual Desire

The most common sexual dysfunction in women is known as female sexual interest/arousal disorder (FSAD) in *DSM-5* (previously hypoactive sexual desire disorder (HSDD) in *DSM-IV-TR*).[54] Treatment options include non-pharmacologic approaches such as education, counseling, and psychotherapy. There is currently one FDA-approved product, flibanserin, for FSAD.[55] It is a non-hormone, mixed function serotonin agonist/antagonist. In addition to flibanserin, several hormone therapies have been used off-label to treat FSAD. Randomized controlled trials using testosterone for sexual dysfunction in women had mixed results and efficacy is unclear. Testosterone may benefit secondary outcomes such as well-being and vitality, but these are difficult to distinguish from the combined effects of testosterone and estrogen.[36] The American Congress of Obstetricians and Gynecologists reaffirmed their Practice Bulletin in 2015 summarizing clinical management guidelines for female sexual dysfunction. These guidelines support the use of transdermal testosterone as an effective short-term treatment of FSAD (≤ 6 mos), with little evidence to support longer use.[56] Other possible off-label hormone therapies for this condition include conjugated estrogens, the SERM ospemifene, and DHEA, but evidence to support their use is limited or inconsistent.[1,57,58] CHT has become an option because the limited number of FDA-approved products containing testosterone does not meet the needs of all women and the ability to customize a hormone therapy is readily available.[1] However, the inconsistencies in CHT dose and purity remain a concern.

Perimenopause/Menopause

Currently, numerous FDA-approved hormone replacement therapies are available to treat menopausal symptoms and to prevent osteoporosis including estrogen-only therapies, progestin-only therapies, combination estrogen/progestin therapies, and combination estrogen/SERM therapy.[59] These formulations vary in dosage, route of administration, and source (i.e., some are considered bioidentical, others are synthetic, and some are derived from animals). Non-oral estrogen formulations may be associated with reduced risk of venous thromboembolism and stroke.[36] Women who still have a uterus and are taking estrogen therapy for the relief of menopausal symptoms are advised to also take progestin therapy; evidence shows that progestins inhibit estrogen-induced endometrial stimulation and reduce the risk of endometrial hyperplasia and cancer.[60] Topical progesterone is not adequate for endometrial protection, and there are case reports of endometrial cancer associated with its use.[61-64]

Many women have turned to CHTs as a treatment for menopausal symptoms despite the limited data to support improved safety or efficacy with these therapies.[1] In one comparative pharmacokinetic study, plasma estradiol levels achieved with CHTs (commonly thought to be bioequivalent to FDA-approved products) were significantly lower than with the estradiol patch. Even higher doses of the compounded product resulted in lower levels of estradiol than the patch. Also of note were the variable patterns of estrogen absorption observed with some of the compounded formulations.[33] There is no evidence to support the use of CHTs with unpredictable pharmacokinetics in place of several FDA-approved and tested choices for hormone replacement therapy.

Male Hypogonadism and Infertility

Although the term hypogonadism commonly refers to low testosterone levels, by definition, it describes impaired spermatogenesis and low hormonal production. Testosterone supplementation in hypogonadic men further decreases sperm production and many of these patients seek alternative treatments for increasing testosterone in order to maintain (or restore) spermatogenesis and fertility. The goal in these patients is typically to inhibit the negative feedback on the hypothalamic-pituitary axis, promote endogenous testosterone production, and increase the production of the gonadotropins LH and FSH. The hormone therapies used for male hypogonadism and fertility include hCG injections, hCG and human menopausal gonadotropin (hMG) injections, the SERM clomiphene citrate, hCG injections with testosterone, or aromatase inhibitors such as anastrozole. All of these therapies are off-label except for the hCG injections.[65,66] Evidence is lacking to support the routine use of aromatase inhibitors for this condition.[65,67,68]

Gender Re-affirming

Several hormone therapies are used in transition therapy for transgender individuals. All of the treatments for gender re-affirming therapy are off-label. No randomized clinical trials have been conducted to determine the optimal dosages and treatment paradigms for gender re-affirming hormone therapies, but specific treatment guidelines have been recommended.[69-71]

The treatment goal for transgender men (female to male patients) is to induce virilization, including the cessation of menses and the development of male-pattern hair growth and physique.[69] Hormone therapies recommended in The Endocrine Society's Clinical Practice Guideline include testosterone cypionate, enanthante, and undecanoate injections, transdermal testosterone gels, and testosterone patches.[70] Other therapies being used include implantable testosterone pellets, medroxyprogesterone or lynestrenol (for cessation of menses), and finasteride (for treatment of male pattern baldness that may occur with testosterone treatments).[69,72]

The treatment goals for transgender females (male to female patients) are to induce breast formation, obtain a more female distribution of fat, and reduce male-pattern hair growth. To accomplish these goals, endogenous action of androgens must be stopped.[69] Hormone therapies recommended in The Endocrine Society's Clinical Practice Guideline include estradiol valerate or cypionate injections, transdermal estradiol patches, oral estradiol tablets, the antiandrogens spironolactone and cyproterone acetate (which is not an approved drug in the U.S.), and GnRH agonists (such as goserelin). Other therapies, not considered first-line, that are used include the antiandrogens flutamide, nilutamide, or bicaluatmide, and 5α-reductase inhibitors finasteride, and dulasteride.[69,72] Some clinics that provide services for transgender individuals recommend CHT preparations made by compounding pharmacies such as topical testosterone and estradiol creams for cost saving purposes, since many of the necessary drug therapies are not covered by

insurance.[72] There is no evidence that custom CHTs are safer or more effective than FDA-approved therapies.

Adverse effects are a concern with the use of any hormone therapy. However, serious short-term complications appear to be uncommon, or at least have yet to be reported in literature, for transition therapy; long-term effects have not been characterized. Policy H-460.907 encourages research into the long-term administration of hormone replacement therapy in transgender patients.

SPECIFIC HORMONE THERAPIES

Some FDA-approved drugs and individual CHTs are used as stand-alone therapies for several medical (and non-medical) conditions, and are prescribed by clinicians in various settings.

Testosterone

Testosterone is FDA-approved only for men who have low testosterone levels (≤ 300 ng/dL) in conjunction with an associated medical condition such as cancer chemotherapy or a genetic or endocrine disorder.[73] Replacement therapy for idiopathic low levels or low testosterone due to aging are off-label uses for the drug.[74] A significant proportion of men receiving testosterone therapies lack adequate testosterone serum measurements prior to receiving prescriptions.[74,75] The most common diagnoses for testosterone therapy include hypogonadism, fatigue, erectile dysfunction, and psychosexual dysfunction.[76] The FDA warns about a potential link between exogenous testosterone and the risk of heart attacks and strokes[77] and is requiring manufacturers of testosterone products to conduct a clinical trial to determine the effects of testosterone replacement therapy on cardiovascular outcomes.[74,78] The American Association of Clinical Endocrinologists and the American College of Endocrinology conclude in a position statement, that there is no convincing evidence of an increase or decrease in cardiovascular risk related to testosterone therapy and randomized controlled trials are needed.[79] If physicians choose to prescribe testosterone off-label, they should be well-informed about any potential risks, especially the cardiovascular outcomes.[75]

Androgen deficiency syndrome in women is a controversial concept. For women, testosterone has been used for the treatment of diminished libido, decreased well-being, dysphoric mood, and unexplained fatigue. However, there are no FDA-approved testosterone therapies for women.[36] Patients are increasingly utilizing compounding pharmacies for these therapies, at times in combination with estrogen and progestin. The use of CHT can result in excessive doses and adverse effects.[75]

Dehydroepiandrosterone, Dehydroepiandrosterone Sulphate, and Androstenedione

DHEA and dehydroepiandrosterone sulphate (DHEAS), the sulphate ester of DHEA, are converted to androstenedione and then to estrone or testosterone and further to estradiol or estriol. Studies have associated low DHEA and DHEAS with a myriad of conditions affecting both sexes including depression and reduced cognition, as well as decreased bone mineral density, arthritis, systemic lupus erythematosus and decreased libido and sexual dysfunction in women, and congestive heart failure and increased mortality in men. High levels have been associated with postmenopausal breast cancer and decreased sense of well-being in women.[36,58] Currently, DHEA and DHEAS are not FDA-approved; no pharmaceutical grade DHEA or DHEAS is available in the U.S.; and there are no indications for their use. Nonpharmaceutical grade DHEA and DHEAS are available in over-the-counter dietary supplement products and from compounding pharmacies, but DHEA and

DHEAS content can vary significantly.[36,42] Evidence that DHEA or DHEAS is beneficial for any condition is lacking.

Androstenedione was previously available over-the-counter as a prohormone in dietary supplements. The Anabolic Steroid Control Act of 2004 amended the Controlled Substances Act, classified androstenedione as a Schedule III controlled substance, and it was removed from the market.[80]

Human Chorionic Gonadotropin (hCG)

Human chorionic gonadotropin (hCG) is a hormone produced by the human placenta. Injectable hCG is an FDA-approved prescription hormone therapy for treating some forms of female infertility and male hypogonadism. First described in 1954, the "hCG diet" has reemerged as a fad where injectable and/or oral forms of hCG have been prescribed by physicians or distributed by commercial wellness clinics, and a modified version of the diet has been promoted on television.[81,82] Homeopathic hCG-containing products also are sold via the Internet and over-the-counter for weight loss.[83]

Patients on this diet are typically restricted to approximately 500 calories per day and receive hCG doses of approximately 200 international units daily. The hCG diet has been repeatedly refuted in studies and meta-analyses. Experts agree that it is inappropriate and that any weight loss is due to the severe caloric restriction.[2,84-86]

FDA-approved hCG preparations are injections while many of the purported hCG products being sold on the Internet are oral and nasal formulations. There is no evidence to support absorption of hCG via oral or nasal routes of administration. The FDA has received reports of serious adverse events associated with hCG use for weight loss, and there have been recent reports of adverse events and risks associated with the hCG diet in the literature.[2,85] The FDA requires the following warning statement on approved hCG products:

> HCG has not been demonstrated to be effective adjunctive therapy in the treatment of obesity. There is no substantial evidence that it increases weight loss beyond that resulting from caloric restriction, that it causes a more attractive or 'normal' distribution of fat, or that it decreases the hunger and discomfort associated with calorie-restricted diets.

hCG is also used as a doping agent by athletes to stimulate endogenous production of testosterone or to prevent testicular atrophy during prolonged administration of other anabolic substances. It also stimulates the endogenous production of epitestosterone which means that the ratio of testosterone to epitestosterone (T/E ratio), a common parameter in antidoping testing, stays within a normal range and increases the chances of evading detection.[87] There have been, however, analytical tests developed to directly detect doping with hCG.[88]

Human Growth Hormone (hGH)

Human growth hormone (hGH) is an FDA-approved hormone therapy available since the late 1980s for short stature caused by specific diseases or syndromes. In 2003, it was approved despite controversy for the treatment of idiopathic short stature in children. The American Association of Clinical Endocrinologists and the Pediatric Endocrine Society, in position statements[89,90] concluded that information on the safety and effectiveness of hGH for idiopathic short stature was limited and its use should be individualized and carefully monitored.

hGH also is commonly used off-label for its purported anti-aging effects and ability to increase performance, endurance, lean muscle mass, and exercise capacity. Although studies have evaluated hGH for performance enhancement, none of them have produced evidence to support use by athletes for this purpose.[91] There also is insufficient evidence to support the use of hGH as an anti-aging medicine.[53]

Thyroid Hormone

Thyroid hormone has been used for weight loss and depression in euthyroid individuals despite a lack of evidence for these indications.[92,93] In some cases, thyroid hormone has been found in commercial dietary supplements in doses equal to or greater than those used as replacement therapy in patients with hypothyroidism.[94] These products can cause serious adverse events, including thyrotoxicosis.

FDA-approved formulations of the endogenous thyroid hormones, levothyroxine (LT4) and liothyronine (LT3), are highly effective and safe therapies for the treatment of hypothyroidism. LT4 monotherapy is the recommended first-line hormone therapy. LT4 and LT3 can be administered in a combination therapy with a LT4/LT3 ratio of approximately 14:1 to mimic the ratio secreted by the thyroid gland.[36,95]

"Natural" desiccated, non-synthetic thyroid products of porcine or bovine origin also are available. Compounding pharmacies can use any of the available thyroid medications to create preparations containing various ratios or concentrations according to the prescription request.

CONCLUSIONS

Off-label use of hormone therapies that is not supported by scientific evidence and the use of unapproved hormone therapies (Figure 1, bold) have been the focus of this report. Patients receiving off-label therapies not backed by scientific evidence are more likely to experience adverse drug events.[13,15] Patients are relying on media information to educate themselves about their medical conditions–whether accurate or not.[96] Marketing veiled as educational material and promotion by celebrities has made CHT appear as panacea for many ailments.

Policy H-120.988 supports the clinical decision-making authority of a physician to use an FDA-approved product off-label when such use is based upon sound scientific evidence or sound medical opinion; however, to date the use of compounded hormone therapies is not supported by such evidence. Additionally, traditional compounding is recognized as a legal and important therapeutic when an FDA-approved drug product is not available or does not meet the clinical needs of individual patients. However, in the case of many of the uses for compounded hormones, comparable FDA-approved therapies are available. Further concern is prompted by the fact that compounding pharmacies are exempt from including specific and important safety information on labeled instructions. That lack of information may put patients at risk.

RECOMMENDATIONS

The Council on Science and Public Health recommends the following recommendations be adopted in lieu of Resolution 512-A-15 and the remainder of the report be filed:

1. That Policy D-120.969 be amended by addition and deletion to read as follows:

    D-120.969 ~~FDA Oversight of Bioidentical~~ Compounded Hormone ~~(BH)~~ Therapy Preparations

Our AMA ~~will~~: (1) recognizes the term “bioidentical hormone” as a marketing term not grounded in science; use of the term “compounded hormone therapy” is preferred; (~~1~~2) will urge that renewed attention be devoted to the ~~of the Food and Drug Administration (FDA) to conduct surveys for~~ purity and potency ~~dosage accuracy~~ of ~~all~~ compounded hormone therapy ~~"bioidentical hormone"~~ formulations; (~~2~~3) will urge continued attention to the ~~FDA to require mandatory~~ reporting ~~by drug manufacturers, including compounding pharmacies,~~ of adverse events related to the use of compounded hormone therapies ~~"bioidentical hormones"~~; ~~(3) urge the FDA to create a registry of adverse events related to the use of compounded "bioidentical hormone" preparations~~; (4) recommends that physicians and other prescribers fully inform patients of the potential side effects and risks of the use of compounded hormone replacement therapy; and (5) will request that when drug ingredients with black box warnings are used in compounded products, patients should be informed about the ~~FDA require the inclusion of uniform patient information, such as~~ warnings and precautions associated with the use of such drug ingredients~~, in packaging of compounded "bioidentical hormone" products; and (5) urge the FDA to prohibit the use of the term "bioidentical hormones" unless the preparation has been approved by the FDA. (Res. 706, I-06)~~ (Modify HOD Policy)

2. Our AMA supports that patients be informed that compounded products are not FDA-approved (New HOD Policy)

3. That our AMA urge the United States Pharmacopeia to re-examine the validity of the current estriol monograph. (Directive to Take Action)

4. That our AMA establish a position that the use of human chorionic gonadotropin (HCG) for weight loss in inappropriate. (New HOD Policy)

Fiscal Note: Less than $500

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Table 1. Examples of FDA approved hormones.

Class	Class Examples	Examples of Indicated Uses (for Class)	Examples of Off-Label Use (for Class)
Steroidal Hormones	Estradiol Progesterone Testosterone	HRT Breast, endometrial, prostate cancer Male hypogonadism	Gender re-affirming therapy[a] FSAD Low Testosterone, ED, fatigue[a]
Aromatase Inhibitors	Letrozole Anastrozole	Breast cancer treatment; endocrine disorders	Sports doping[a]
GnRH Analogs	Leuprolide Goserelin	Prostate cancer	Gender re-affirming therapy[a]
SERMs	Raloxifene Fulvestrant	Chemoprevention of breast cancer; metastatic breast cancer	FSAD[a] Male hypogonadism
Antiandrogens	Flutamide Bicalutamide	Prostate cancer	Gender re-affirming therapy[a]
Somatostatin Analogues	Octreotide	Acromegaly, gigantism, thyrotropinoma, carcinoid syndrome, VIPomas	Sports doping[a]
Growth Hormone	hGH	hGH deficiency; cachexia from AIDS; SHOX deficiency; Turner syndrome; chronic renal failure; Prader-Willi syndrome; children of short stature because of intrauterine growth retardation; idiopathic short stature	Antiaging[a]; sports doping[a]
hGH secretagogues	Tesamorelin	HIV-associated lipodystrophy	Sports doping[a]; anti-aging[a]
GnRHs	LH FSH	Infertility therapy; reversal of anovulation	Sports doping[a]
GnRH antagonists	Ganirelix Abarelix	Infertility therapy; prostate cancer	
Human Chorionic Gonadotropin	hCG	Infertility therapy	Weight loss[a]
Thyroid Hormone	Levothyroxine Liothyronine	Hypothyroidism	Weight loss[a]; Sports doping[a]

HRT = hormone replacement therapy; ED = Erectile dysfunctin; FSAD = female sexual interest/arousal disorder; GnRH = gonadotropin releasing hormone; SERMs = selective estrogen receptor modulator; VIPomas = vasoactive intestinal peptide-secreting tumors; hGH = human growth hormone; SHOX = Short stature homeobox gene; LH = lutenizing hormone; FSH = Follicle stimulating hormone; HCG = Human chorionic gonadotropin

[a]Lacks scientific evidence

Table 2. Common Compounded Hormone Preparations[a]

Compounded Formulation	Ingredients	Dose	Route of Administration
Bi-est	20% estradiol 80% estriol[c]	1.25-2.5 mg/d[b]	Oral, transdermal, sublingual, or vaginal
Tri-est	10% estradiol 10% estrone 80% estriol[c]	1.25-2.5 mg/d[b]	Oral, transdermal, sublingual, or vaginal
Estriol	Estriol[c]	2.0-8.0 mg/d[b]	Oral, transdermal, sublingual, or vaginal
Progesterone	Progesterone	100-200 mg/d[b]	Oral, transdermal, sublingual, vaginal, or injectable
Wiley Protocol Original™[49]	Estradiol and Progesterone	Multi-phasic rhythmic dosing (amounts vary throughout a 28 day cycle)[49]	Topical
Wiley Protocol for Men™	DHEA and Testosterone	Multi-phasic rhythmic dosing	Topical
Wiley Protocol Thyroid™		Multi-phasic rhythmic dosing	Topical
Wiley Protocol Testosterone™ for Women	Testosterone	Multi-phasic rhythmic dosing	Topical
Wiley Protocol Sparc™ Therapy	Cortisol	Multi-phasic rhythmic dosing	Topical

[a]Data was compiled from several Internet sources and Files et al.[21]
[b]mg amounts can vary depending on the compounding pharmacy
[c]Not an FDA approved drug