REPORT 5 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-09)
The Use of Hormones for "Antiaging": A Review of Efficacy and Safety
(Reference Committee E)

EXECUTIVE SUMMARY

Objective: This report reviews the scientific evidence on the benefits and risks of human growth hormone (hGH), dehydroepiandrosterone (DHEA), testosterone, and estrogens with or without progestins as supplements to prevent, slow, or reverse age-related changes in otherwise healthy adults.

Methods**:** Four MEDLINE searches were conducted using the MESH terms "human growth hormone" AND "aging," "dehydroepiandrosterone" AND "aging," "testosterone" AND "aging," and "estrogens" AND "aging." Searches were limited to reviews, meta-analyses, and controlled clinical trials in humans aged 45 years and older that were published in core clinical journals. A total of 26, 21, 230, and 139 articles were identified. Additional articles were identified by a review of references cited in these publications. In addition, searches of government web sites (National Institute on Aging [NIA], Agency for Healthcare Research and Quality [AHRQ], and Food and Drug Administration [FDA]), the Institute of Medicine (IOM) web site, and selected medical specialty society web sites (American Association of Clinical Endocrinologists [AACE], Endocrine Society, American Geriatrics Society, and American College of Obstetricians and Gynecologists [ACOG]) were conducted to identify clinical guidelines and position statements.

Results: Based on an AHRQ-funded systematic review and a more recent randomized, controlled clinical trial, current evidence fails to support the efficacy of hGH as an antiaging therapy and adverse events are significant. A review of 11 randomized, placebo-controlled clinical trials indicates that the use of DHEA as an antiaging supplement shows neither meaningful benefit nor serious adverse events. Based on systematic reviews conducted by the IOM and the Endocrine Society, as well as the Council's evaluation of seven more recent randomized, placebo-controlled clinical trials, definitive evidence of the value of testosterone as an antiaging therapy in older men does not exist, and further research is indicated. Estrogens with or without progestins are highly effective in treating the vasomotor symptoms associated with menopause. However, primarily based on the Women's Health Initiative (WHI), a large, randomized, placebo-controlled, primary (chronic condition) prevention clinical trial in postmenopausal women, the long-term use of estrogens with or without progestins causes more risks than benefits in this population. No credible scientific evidence exists on the value of so-called "bioidentical hormones," and there are concerns about their purity, potency and quality because they are not approved by the FDA.

Conclusion**:** Despite the widespread promotion of hormones as antiaging agents by for-profit web sites, antiaging clinics, and compounding pharmacies, the scientific evidence to support these claims is lacking. The use of hGH and DHEA as antiaging agents is not recommended. Similarly, the long-term use of estrogens with or without progestins for the prevention of chronic conditions in postmenopausal women is not recommended. Considerable research has been conducted on testosterone in older men, but current evidence does not support its use in all older men with low testosterone levels. Physicians should consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency, after explicit discussion of the uncertainty about the risks and benefits of testosterone therapy. The IOM has defined a research agenda for the study of testosterone therapy in older men and this agenda should be followed.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 5-A-09

Subject: The Use of Hormones for "Antiaging": A Review of Efficacy and Safety

Presented by: Carolyn B. Robinowitz, MD, Chair

Referred to: Reference Committee E
(Martin G. Guerrero, MD, Chair)

A Google search of the term, "antiaging," resulted in more than 34 million hits on January 12, 2009. Many of the highest ranked listings were for-profit web sites, antiaging clinics, and compounding pharmacies that promoted a plethora of products, including hormones, antioxidants, vitamins, herbal supplements, and other substances, as proven treatments to prevent, slow, or reverse age-related changes in otherwise healthy adults. It is estimated that the United States market for antiaging products is around $50 billion annually.[1,2]

Our American Medical Association's (AMA) House of Delegates has raised questions and concerns about the benefits and risks of medications and other substances touted to be "antiaging," and adopted Resolution 501 at the 2008 Annual Meeting (Directive D-100.979, AMA Policy Database). This resolution asks:

> That our AMA Council on Science and Public Health (CSAPH) undertake a review of "anti-aging" medications, their efficacy, benefits, and risks, and report back to the House of Delegates.

The number of medications and other substances being promoted as "antiaging" is vast, and the Council believes it is impossible to consider them all in a single report. Therefore, this report will focus on the use of hormones that have been promoted for antiaging. The report will review the scientific evidence on the benefits and risks of human growth hormone (hGH), dehydroepiandrosterone (DHEA), testosterone, and estrogens with or without progestins as supplements to prevent, slow, or reverse age-related changes in otherwise healthy adults.

AMA POLICY

Currently, the AMA has no policy on antiaging. Directive D-120.969 (AMA Policy Database) calls for Food and Drug Administration (FDA) oversight of "bioidentical hormone" (BH) preparations.

METHODS

Four MEDLINE searches were conducted using the MESH terms "human growth hormone" AND "aging," "dehydroepiandrosterone" AND "aging," "testosterone" AND "aging," and "estrogens" AND "aging." Searches were limited to reviews, meta-analyses, and controlled clinical trials in humans aged 45 years and older that were published in core clinical journals. A total of 26, 21, 230, and 139 articles were identified, respectively. Additional articles were

identified by a review of references cited in these publications. In addition, searches of government web sites (National Institute on Aging [NIA], Agency for Healthcare Research and Quality [AHRQ], and FDA), the Institute of Medicine (IOM) web site, and selected medical specialty society web sites (American Association of Clinical Endocrinologists [AACE], Endocrine Society, American Geriatrics Society, and American College of Obstetricians and Gynecologists [ACOG]) were conducted to identify clinical guidelines and position statements.

RESULTS

Human Growth Hormone (hGH)

Growth hormone, a protein hormone produced by the anterior pituitary gland, reaches maximal secretion in adolescence and then decreases in an age-related manner in adulthood.[3] Replacement therapy in adults with FDA-approved recombinant human growth hormone is indicated for adults with adult-onset growth hormone deficiency (GHD) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or for adults who had childhood-onset GHD as a result of congenital, genetic, acquired, or idiopathic causes. In both instances, confirmation of the diagnosis of adult GHD requires an appropriate growth hormone stimulation test to justify hGH therapy except in cases of congenital/genetic GHD or multiple pituitary hormone deficiencies. Adult GHD is very rare (approximately three cases per 10,000 adults).[4] However, despite the limited approved indications, hGH is widely used as an antiaging therapy in otherwise healthy individuals.[4,5]

Under a grant from the AHRQ, Liu and colleagues performed a systematic review of the published literature through November 2005 to evaluate the safety and efficacy of hGH, injected subcutaneously, in the healthy elderly. The authors only included randomized, controlled trials that compared hGH therapy (with or without lifestyle interventions) with no hGH therapy for two weeks or longer in community-dwelling men and women with a mean age of 50 years or more and a body mass index (BMI) of 35 kg/m^2 or less. Thirty-one articles describing 18 unique study populations were included, but only 220 total participants completed the studies. Initial hGH dose (mean, 14 ug/kg/day; range, 1.7 to 43 ug/kg/day), final hGH dose (mean, 11.2 ug/kg/day; range, 1.7 to 25 ug/kg/day), and study duration (mean 26.6 weeks; range, 2 to 52 weeks) varied widely across studies. No study was longer than one year in duration. Therapy with hGH produced small changes in body composition, i.e., increased lean body mass and decreased fat body mass, but selection bias could not be ruled out. However, hGH therapy failed to improve other clinically important outcomes, such as maximal oxygen consumption, bone mineral density, lipid levels, and fasting glucose and insulin levels. Of particular importance, persons receiving hGH experienced significantly higher rates of adverse events, including soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia, and were somewhat more likely to experience the onset of diabetes mellitus and impaired fasting glucose. The authors concluded that the published literature, albeit limited, failed to support the use of hGH as an antiaging therapy and recommended against such use.[5]

The CSAPH's literature review identified only one additional randomized, controlled trial that was conducted after the systematic review described above. Giannoulis et al compared hGH (initial dose, 0.1 mg/day by subcutaneous injection) to placebo (and also to testosterone with or without hGH) in 80 healthy, community-dwelling men aged 65 to 80 years over a period of six months. Twenty patients were in the placebo arm and 18 patients were in the hGH arm of the study. While hGH modestly increased lean body mass, it had no effect on fat body mass, muscle strength, or maximal oxygen consumption. Forty-one percent of individuals receiving hGH had

adverse events, but most were mild.[6] This study failed to add any new information that would support the use of hGH as an antiaging therapy.

Based on the available scientific evidence, the FDA, Endocrine Society, and AACE have taken positions that there is no justifiable reason to use hGH for antiaging.[7-9] Furthermore, the Food, Drug and Cosmetic Act (FDCA) prohibits the distribution of hGH for any use in humans other than for the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 505 [of the FDCA] and pursuant to an order of a physician. Violation of this provision of the FDCA can result in up to five years in prison and substantial fines.[10]

Dehydroepiandrosterone (DHEA)

DHEA is produced by the adrenal gland and is released into the circulation as a water-soluble, sulfate conjugated form (DHEAS). DHEA is a metabolic intermediate in the pathway for the synthesis of testosterone, estrone, and estradiol. With age, levels of DHEA and DHEAS in both sexes decrease at a relatively constant rate of 2% per year; hence at age 80 years, levels are only about 20% of those at age 20 years. The administration of exogenous DHEA has been widely promoted to prevent, slow, or reverse age-related changes in otherwise healthy adults.[11]

Eleven randomized, placebo-controlled clinical trials assessing the efficacy and safety of DHEA as an antiaging supplement were identified and summaries of these clinical trials are presented in the Table. Studies were conducted in both men and women, primarily those over 55 years of age (age range, 40-80 years). The most common daily dose of DHEA, administered orally, was 50 mg (range 50 mg-1,600 mg); most studies were from 6 months to 1 year in duration (range, 28 days to 2 years). The two most common outcomes measured were changes in bone mineral density (BMD) and changes in body composition. Some studies also assessed muscle strength, physical performance, quality of life, and effect on libido.

In some studies, DHEA resulted in increases, albeit small increases, in BMD in specific bones and this occurred more frequently in elderly women.[12-14,19] However, these inconsistent increases in BMD were considerably less than what has been observed with current osteoporosis therapies, such as the bisphosphonates, and there is no evidence that DHEA has any effect on reducing fractures.[23] Almost all studies observed no effect of DHEA on body composition, i.e., reduced BMI or fat mass or increased fat-free mass.[12-15,17,20-22] DHEA also failed to increase muscle strength,[13,17] physical performance,[13] quality of life,[13,20] or to reduce the negative effects of physical frailty.[15] Effects on libido were inconsistent.[19-21] Significant differences in adverse events (e.g., increases in prostate specific antigen [PSA]) associated with DHEA therapy versus placebo were not observed in these studies. However, because only one study was carried out beyond one year, the safety of prolonged therapy with DHEA remains unknown.

Based on the available scientific evidence, the use of DHEA demonstrates neither meaningful benefit nor adverse events, and its use as an antiaging supplement should be discouraged. Unfortunately, DHEA currently is regulated as a dietary supplement in the United States and it is widely available for over-the-counter sale with no restrictions on its use.[23] The NIA does not recommend taking any dietary supplement touted as an “antiaging” remedy because there is no proof of benefit and risks are unknown.[24]

Testosterone

Endogenous testosterone, produced by the Leydig cells of the testes in males, is the principal circulating androgen in males. Testosterone produces physiologic effects that are related to male

sexual differentiation, including urogenital development, increased libido, increased muscle mass and strength, and increased bone mass. Endogenous serum testosterone levels peak in early adulthood and then decline with aging. Exogenous testosterone therapy is clearly indicated for men with hypogonadism. However, there is concern over the widespread promotion and use of exogenous testosterone by middle-aged and older men with borderline – or even normal – testosterone levels as an antiaging therapy.[24,25]

In response to a request from the NIA and the National Cancer Institute in 2002, the IOM systematically reviewed and assessed the current state of knowledge on the benefits and potential risks of testosterone therapy in older men who did not meet the clinical diagnostic criteria for hypogonadism. In addition, the IOM made recommendations regarding future clinical trials of testosterone therapy in this population.[25]

In its review, the IOM identified 31 randomized placebo-controlled clinical trials of testosterone therapy in older men. Most of these clinical trials were of short duration (with only three studies lasting 12 months or longer) and involved a small number of participants (only six studies included 50 or more participants and only one clinical trial had more than 100 participants). Types of testosterone and routes of administration (e.g., intramuscular, transdermal) varied across studies. Most of the placebo-controlled clinical trials used doses of testosterone that raised serum testosterone levels to the normal physiologic range for young adult males.[25]

Based on its systematic review of the literature, the IOM found no clear evidence of benefit for any of the health outcomes examined. For several health outcomes, results of these clinical trials suggested a potential benefit from testosterone therapy. These areas – including beneficial effects on body composition, strength, bone density, frailty, cognitive function, mood, sexual function, and quality of life – require further study. Testosterone treatment consistently increased hematocrit, but definitive evidence of other risks, such as increased prostate hyperplasia or prostate cancer, were not observed. However, the size and length of the studies were inadequate to really assess such risks.[25]

The IOM concluded that the available clinical research on testosterone therapy in older men in 2003 produced only suggestions of benefit and potential risks, but little definitive evidence. Therefore, the IOM recommended a research agenda to study testosterone in older men who would be most likely to benefit. The IOM emphasized that testosterone, because of its potential risks, should be studied as a therapeutic intervention and not be considered as a preventive measure. Initially, the focus should be on conducting additional well-designed, randomized, placebo-controlled trials to determine whether testosterone therapy provided any clear benefit in any of the areas noted in the preceding paragraph. The IOM cautioned that large, long-term studies to better assess risk should not be pursued until efficacy had clearly been shown.[25]

In 2006, the Endocrine Society conducted a systematic review of the scientific evidence to develop a clinical practice guideline on testosterone therapy in adult men with androgen deficiency syndromes. A section of this clinical practice guideline focused on testosterone therapy in older men with low serum testosterone concentrations. The clinical trials that were identified and reviewed primarily included healthy older men with low or low-normal testosterone levels and who were asymptomatic. Similar to what was found by the IOM, these clinical trials were characterized by small sample size and the use of surrogate outcomes. The studies lacked sufficient power to detect either meaningful gains in patient-important outcomes or changes in prostate or cardiovascular event rates.[26]

The Endocrine Society's review of the literature resulted in the following findings: 1) the effect of testosterone on BMD yielded inconsistent and imprecise results and none of the studies assessed the effect of testosterone on bone fractures; 2) testosterone therapy was significantly associated with increased lean body mass and reduced fat mass; 3) testosterone was associated with greater improvement of grip strength, but changes in lower-extremity muscle strength and measures of physical function were inconsistent; 4) two placebo-controlled clinical trials on the effect of testosterone on sexual function yielded imprecise results; 5) results of testosterone therapy on quality-of-life were inconsistent; 6) testosterone had no effect on depression in older men; and 7) results of clinical trials on cognition reported imprecise effects with no finding achieving statistical significance after the studies were pooled. Based on a review of 19 randomized clinical trials for adverse events associated with testosterone therapy in older men, the combined rate of prostate events (e.g., prostate cancer, PSA > 4 ng/ml, prostate biopsies) was significantly greater in the testosterone group, but differences between testosterone and placebo for any individual event failed to achieve statistical significance. Testosterone-treated men were nearly four times more likely than placebo-treated men to experience hematocrits greater than 50%. No statistical differences were found for cardiovascular events, sleep apnea, or death between groups.[26]

The Endocrine Society recommended against offering testosterone therapy to all older men with low testosterone levels. This was a strong recommendation, but one based on very low quality evidence. The clinical practice guideline also suggested that physicians should consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency, after explicit discussion of the uncertainty about the risks and benefits of testosterone therapy. This was considered a weak recommendation, also based on very low quality evidence.[26]

The CSAPH identified five additional randomized, placebo controlled trials, published from 2006 to 2008, that evaluated the effects of testosterone in healthy, community-dwelling elderly men (age range, 55-85 years) with low serum testosterone levels.[6,13,27-29] Between 43 and 70 older men were included in four studies,[6,13,28-29] and one study included more than 200 subjects.[27] The testosterone dose was 5 mg/day, administered by transdermal patch, in four studies[6,13,28-29]; testosterone undecenoate, administered orally in a dosage of 80 mg twice daily, was used in the fifth study.[27] The durations of the studies were 2 years,[13] 1 year, [28] 6 months,[6,27] and 12 weeks.[29] Study outcomes varied, but included body composition,[6,13,27-29] muscle strength,[6,13,27] aerobic capacity,[6,13] BMD,[13] cognition,[27] and quality of life.[6,13,26] Testosterone was associated with increased lean body mass and decreased fat mass in three studies,[13,27,28] but there was no effect on body composition in the other two clinical trials.[6,29] In one study, an increase in BMD only in the femoral neck (but not in any other bones) was noted in the testosterone group.[13] There was no effect of testosterone observed on muscle strength,[6,13,27] aerobic capacity,[6,13] cognition,[27] or quality of life.[6,13,27] In one study, quality of life, based on answers to the short form (SF)-36 questionnaire, improved only if testosterone was combined with an exercise program.[29] Serious adverse events associated with testosterone generally were not observed in these studies. None of these more recent clinical trials would alter the conclusions drawn by the IOM or the Endocrine Society.

Bhasin and colleagues conducted a randomized, double-blind, placebo-controlled trial to examine the anabolic effects of graded doses of testosterone (25-600 mg, administered intramuscularly, weekly for 20 weeks) on skeletal muscle in healthy, older men (n = 60) aged 60 to 75 years. Subjects also received a monthly injection of a long-acting GnRH agonist (Lupron depot, 7.5 mg) to suppress endogenous testosterone production. Testosterone was associated with significant dose-dependent increases in skeletal muscle mass and maximal strength, but the frequency of

serious adverse events (hematocrit > 54%, leg edema, prostate events) also increased with dose.[30] Interestingly, despite the increased skeletal muscle mass and strength, testosterone had no effect on muscle fatigability or on various tests of physical function (stair climb, timed up-and-go, walking speed) in this population. The authors believed that physical function did not improve because these high-functioning older men were already in the asymptotic region of the curve describing the relationship between physical function and strength. Thus, the authors suggested that future clinical trials of testosterone should be conducted in older individuals who have more functional limitations. However, the authors also cautioned that the potential for serious adverse events in older men at higher doses of testosterone could temper its potential application as a function-promoting therapy.[31]

Information on the use of testosterone as an antiaging therapy in women is extremely limited. The North American Menopause Society (NAMS) conducted an evidence-based review of testosterone therapy in postmenopausal women and identified a few randomized, controlled clinical trials that indicated exogenous testosterone, both in oral and nonoral formulations, has a positive effect on sexual function, primarily desire, arousal, and orgasmic response, in women after spontaneous or surgically induced menopause. In all of the clinical trials, estrogen (with or without progestin) was administered concomitantly and all of the studies were of short duration ($\leq$ 6 months). Data were insufficient to determine whether testosterone had an effect on increasing BMD, reducing hot flashes, increasing lean body mass, or improving well-being in women who participated in these studies. Side effects included hirsutism and acne. NAMS concluded that postmenopausal women with decreased sexual desire associated with personal distress and with no other identifiable cause may be candidates for a short course of low dose testosterone therapy with concomitant estrogen, but only after a comprehensive clinical evaluation.[32]

A more recent long-term, randomized, placebo-controlled, multicenter clinical trial assessed the efficacy and safety of a testosterone patch at a dose of either 300 ug per day or 150 ug per day in 814 women with low sexual desire and who were either naturally or surgically menopausal and not taking estrogen or progesterone. Efficacy was measured to week 24; safety was evaluated over a period of 52 weeks, with a subgroup of participants followed for an additional year. The primary endpoint was the change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes. At 24 weeks, the increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 ug of testosterone per day versus the placebo group, but not in the group receiving 150 ug of testosterone per day. Both doses of testosterone, however, were associated with significant increases in sexual desire and decreases in distress. The rate of androgenic adverse events – primarily unwanted hair growth – was higher in the group receiving 300 ug of testosterone versus placebo. Breast cancer was diagnosed in four women who received testosterone, but in no women receiving placebo.[33] While this study confirms the potential value of testosterone – given without estrogen and/or progestin – as a treatment for hypoactive sexual desire, the breast cancer findings suggest the need for caution in the use of testosterone until the potential relationship to breast cancer is better understood.[34]

Testosterone (and other anabolic steroids) are regulated by the Drug Enforcement Administration (DEA) as Schedule III controlled substances, and can only be prescribed or dispensed for a legitimate medical purpose in the usual course of professional practice.[35]

Estrogens With or Without Progestins

The Women's Health Initiative (WHI) was a large, randomized, placebo-controlled, primary prevention clinical trial whose goal was to define the risks and benefits of estrogen plus progestin,

or estrogen alone (in women with hysterectomy), in postmenopausal women. Postmenopausal women, aged 50 to 79 years, with an intact uterus received either conjugated equine estrogens (CEE) (0.625 mg/day) plus medroxyprogesterone acetate (MPA) (2.5 mg/day) [n = 8506] or placebo [n = 8102]. Postmenopausal women, aged 50 to 79 years, with prior hysterectomy received either CEE (0.625 mg/day) [n = 5310] or placebo [n = 5429]. The WHI estrogen plus progestin trial was terminated early at an average of 5.2 years of follow-up because health risks exceeded benefits.[36] The WHI estrogen-only trial also was terminated early after an average of 6.8 years of follow-up.[37]

The WHI study found some benefits of CEE plus MPA in reducing the risk for fracture and colorectal cancer.[36] However, combined therapy increased the risk of breast cancer,[36] venous thromboembolism,[36] stroke,[36] dementia,[38] and lower global cognitive function.[39] Initial results of the WHI study for the entire population suggested that CEE plus MPA also increased the risk of coronary heart disease (CHD),[36] but further analysis of the data suggested women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with an increase in CHD risk among women more distant to menopause.[40]

Estrogen, used alone in postmenopausal women with hysterectomy, also reduced the risk of fractures,[37] but increased the risk of stroke,[37] venous thromboembolism,[37] dementia,[38] and lower global cognitive function.[39] No effect on the incidences of CHD,[37] breast cancer,[41] or colorectal cancer[37] were observed. Further analysis of the data suggested women who received CEE therapy closer to menopause tended to have a reduced CHD risk,[40] and an ancillary substudy of the WHI showed that CEE reduced the calcified-plaque burden in the coronary arteries of women aged 50 to 59 years when compared to placebo.[42] The AACE and NAMS have taken positions that additional, randomized clinical trials are necessary in younger women who are closer to menopause to more clearly determine the effects of estrogen with or without progestin on CHD risk in this population.[43,44]

Based primarily on the results of the WHI clinical trial, as well as other studies,[45,46] the U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of combined estrogen plus progestin for the prevention of chronic conditions in postmenopausal women.[47] The USPSTF also recommends against the routine use of estrogen alone for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.[47] The FDA also requires estrogen/progestin or estrogen-only products to contain a black box warning regarding potential serious adverse events with long-term administration.[48,49]

Estrogens alone or estrogens plus progestins are highly effective for alleviating the vasomotor symptoms (hot flashes, night sweats) associated with menopause,[44,50-52] and have FDA-approved labeling for this indication.[48,49] Currently, the FDA and ACOG's Committee on Gynecologic Practice recommend that estrogen or estrogen plus progestin therapy be limited to the treatment of menopausal symptoms at the lowest effective dosage over the shortest duration possible, and continued use should be reevaluated on a periodic basis.[48,49,53] The AACE also has a position statement supporting the use of estrogen (or estrogen plus progestin) for the relief of menopausal symptoms, and recommends that each patient be evaluated for severity of symptoms, age, and specific risk factors and receive appropriate counseling from her physician.[43] Estrogens alone or estrogens plus progestins also are effective for treating the symptoms of vulvar and vaginal atrophy associated with menopause, but topical administration is preferred.[48,49]

In light of the WHI findings, numerous web sites, books, and antiaging clinics that promote the use of hormones for antiaging are touting the use of so-called "bioidentical hormones" (also called natural hormones) as superior in efficacy and safety to estrogen or estrogen-progestin drug

products that are approved by the FDA. The term "bioidentical hormones" is quite vague, and is used in various contexts. Most commonly, this term denotes hormones that are derived from plants (e.g., soy or yams) and custom compounded for patients by pharmacists. These steroids may include estrone, estradiol, estriol, and progesterone. However, reliable clinical trial data on the benefits and adverse effects of compounded bioidentical hormones are essentially nonexistent.[24,51] The FDA, ACOG, AACE and the Endocrine Society have all taken the position that, absent evidence to the contrary, all estrogen-containing hormone therapies, whether bioidentical or traditional FDA-approved, carry essentially the same risks and benefits.[48,49,54-56] Thus, claims of superior efficacy and safety for bioidentical hormones are unfounded, and the FDA has issued warning letters to compounding pharmacies that have made such claims.[57] Compounded bioidentical hormones carry additional concerns about efficacy, safety, purity, potency, and quality because they have not undergone the rigorous FDA approval process.[44,54-56] As discussed above, current AMA Directive D-120.969 calls for FDA oversight of bioidentical hormone preparations.

CONCLUSION

Despite the widespread promotion of hormones as antiaging agents by for-profit web sites, antiaging clinics, and compounding pharmacies, the scientific evidence to support these claims is lacking. In some cases, the evidence suggests long-term use of a particular hormone can present more risks than benefits. Based on current evidence, this clearly is the case for hGH.

A number of randomized, placebo-controlled clinical trials have evaluated DHEA as an antiaging agent and essentially all were negative. While adverse events associated with DHEA in these clinical trials were minimal, the long-term safety of this dietary supplement could not be determined. The regulatory status of this hormone as a dietary supplement allows it to be available over-the-counter and this raises additional concerns. The NIA does not recommend taking any dietary supplement touted as an "antiaging" remedy because there is no proof of benefit and risks are unknown.[24]

Considerable research has been conducted on testosterone in older men, but current evidence does not support its use in all older men with low testosterone levels. The Endocrine Society suggests that physicians should consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency, after explicit discussion of the uncertainty about the risks and benefits of testosterone therapy. This was considered a weak recommendation, and one based on very low quality evidence.[26] The IOM has defined a research agenda for the study of testosterone therapy in older men and this agenda should be followed.

While estrogens with or without progestins are indicated for women with menopausal symptoms, the long-term use of estrogens with or without progestins for the prevention of chronic conditions in postmenopausal women is not recommended. There is no credible evidence to support claims of for-profit web sites, anti-aging clinics, and compounding pharmacies that so-called bioidentical hormones have superior efficacy and safety over traditional FDA-approved estrogen or estrogen/progestin drug products. Because compounded bioidentical hormones are not subject to the FDA approval process, additional concerns exist about their purity, potency, and quality.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted and that the remainder of this report be filed:

1. That our American Medical Association widely disseminate this report to inform physicians, policy makers, and the public of the current scientific evidence on the use of hormones as antiaging agents. (Directive to Take Action)

2. That our AMA take the position that proponents of any hormone or other substance as an antiaging agent have the responsibility to prove that any claims of positive benefit/risk be supported by well-designed, randomized, placebo-controlled clinical trials. (New HOD Policy)

3. That Directive D-100.979 be rescinded because it has been effected.

Fiscal Note: $1,000

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TABLE: DEHYDROEPIANDROSTERONE AND ANTIAGING: SUMMARY OF RANDOMIZED, PLACEBO-CONTROLLED TRIALS

Study	*Patient population*	*Daily dose (mg)*	*Duration of therapy*	*Effect on BMD*[a]	*Effect on body composition*[b]	*Other effects*
von Muhlen et al (2008)[12]	225 healthy men and women; aged 55-85 years	50 po	1 year	Slight increase in spine BMD in women; all other measures negative	No effect	No serious AEs[c]
Nair et al (2006)[13]	144 elderly men and women; aged ≥ 60 years	75 po	2 years	Slight increase in ultradistal radius BMD in women and femoral BMD in men; all other measures negative	No effect	No effect on physical performance[e] or quality of life[f]; no serious AEs
Jankowski et al (2006)[14]	140 men and women with low DHEA; aged 60-88 years	50 po	1 year	Increase in hip BMD and slight increase in spine BMD in women	No effect	Three serious AEs reported
Muller et al (2006)[15]	100 men; aged ≥ 70 years	50 po	36 weeks	No effect	Increased BMI	No effect on physical frailty[g]
Villareal and Holloszy (2004)[16]	56 elderly men and women; aged 65-78 years	50 po	6 months	Not studied	Decreases in abdominal visceral and subcutaneous fat	No serious AEs
Percheron et al (2003)[17]	280 healthy men and women; aged 60-79 years[d]	50 po	1 year	Not studied	No effect	No effect on muscle strength[h]
Kahn and Halloran (2002)[18]	43 healthy men; aged 56-80 years	90 po	6 months	No effect on bone turnover[i]	Not studied	

Table (continued)

Study	*Patient population*	*Daily dose (mg)*	*Duration of therapy*	*Effect on BMD*[1]	*Effect on body composition*[2]	*Other effects*
Baullieu et al (2000)[19]	280 healthy men and women; aged 60-79 years[d]	50 po	1 year	Bone turnover slightly improved only in women > 70[j]	Not studied	Increase in libido in women >70[k] and some improvement in skin[l]; no serious AEs
Flynn et al (1999)[20]	39 healthy men; aged 60-84 years	100 po (50 mg bid)	3 months	Not studied	No effect	No effect on sense of well being or on libido[m]
Morales et al (1994)[21]	30 men and women; aged 40-70 years	50 po	3 months	Not studied	No effect	Increased sense of well being but no effect on libido[n]; no serious AEs
Mortola and Yen (1990)[22]	6 postmenopausal women	1600 po (400 mg qid)	28 days	Not studied	No effect	No serious AEs

[a]BMD is bone mineral density.
[b]Measures of body composition varied across studies, and included lean body mass, abdominal fat mass, lean/fat index, total fat mass, BMI and waist to hip ratio.
[c]AEs are adverse events associated with dehydroepiandrosterone.
[d]The populations studied in these two publications were the same.
[e]Peak VO_2 and changes in muscle strength were measures of physical performance.
[f]Changes in scores on the Physical Component Scale and Mental Component Scale of the Health Status Questionnaire were measures of quality of life.
[g]Tests to measure physical frailty included isometric grip strength, leg extensor power, standing balance, walking speed, and ability to rise from chair.
[h]Measures of muscle strength included handgrip strength and knee muscle strength.
[i]Measures of bone turnover included serum measurements of procollagen peptide, bone-specific alkaline phosphatase, and deoxypyridinoline.
[j]Measures of bone turnover included dual energy x-ray absorptiometry (DEXA) technique and decrease of osteoclastic activity.
[k]Based on a questionnaire.
[l]Measurements included sebum production, skin hydration, and skin pigmentation.
[m]Based on a questionnaire.
[n]Sense of well being was assessed by an open-ended questionnaire, and libido was assessed by a visual analog scale.