Corewell Health™

Managing Requests for Male and Female Hormone Replacement Therapy

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MICHIGAN OSTEOPATHIC ASSOCIATION SPRING 2024

Conflict

- My wife works for Bayer
- I’ve been a hired consultant with Insulet, Bayer, Boehringer Ingelheim, and Novo Nordisk Corporations

A 53-year-old woman is evaluated for a 1-year history of dyspareunia. She has tried using lubricants, but she still has discomfort and has lost interest in sexual intercourse. She reports vaginal itching but no vaginal discharge, bleeding, or odor. She reached menopause 2 years ago and notes occasional hot flushes, but they are not troublesome. There is no history of sexual trauma, sexually transmitted infection, or pelvic surgery. She reports no marital problems. Medical history is otherwise remarkable for hypertension. Her only medication is benazepril.

On physical examination, the patient is afebrile, blood pressure is 130/78 mm Hg, pulse rate is 72/min, and respiration rate is 14/min. BMI is 27. The general medical examination is unremarkable. On pelvic examination, she can only tolerate insertion of a narrow speculum, and the vaginal mucosa is pale and dry with smooth vaginal walls and decreased rugae. There is scant vaginal discharge. Bimanual examination is normal.

Microscopic evaluation of a vaginal preparation reveals no hyphae, yeast, or clue cells.

Which of the following is the most appropriate management?

(A) Discontinue benazepril

(B) Systemic estrogen and progestin therapy

(C) Topical testosterone

(D) Topical vaginal estradiol

A 57-year-old woman is evaluated for a 2-month history of bothersome hot flushes multiple times daily, with night sweats disrupting sleep about two to three times nightly. She also reports irritability and mood lability and reports worsening vaginal dryness with dyspareunia. Her last menstrual period was 13 months ago. Medical history is significant only for hypothyroidism. Personal and family histories are negative for breast and ovarian cancer. Her only medication is levothyroxine. Mammography and cervical cancer screening are up to date.

On physical examination, vital signs are normal. The general medical examination is unremarkable. Breast examination is negative. On pelvic examination, the vaginal mucosa is pale with decreased rugae with petechial hemorrhages present. Decreased vaginal lubrication is noted.

Which of the following is the most appropriate next step in management?

A. Measure serum follicle-stimulating hormone level

B. Measure serum estradiol level

C. Prescribe estradiol-progestin combination

D. Prescribe low-dose paroxetine

E. Prescribe vaginal estradiol cream

Question 49

A 77-year-old man is evaluated for a 6-month history of fatigue, weakness, and erectile dysfunction. He previously had an enjoyable sex life with his wife but more recently has experienced low interest in sexual activity. He is unable to engage in his regular exercise routine due to reduced energy and muscle weakness. He reports no weight loss or depressed mood.

On physical examination, the patient is afebrile, blood pressure is 142/88 mm Hg, and pulse rate is 90/min. BMI is 32. Examination of the heart and lungs is normal. Musculoskeletal and nervous system examinations are normal. Normal-appearing testes and circumcised penis are noted.

Laboratory studies show an 8:00 AM serum total testosterone level of 195 ng/dL (6.8 nmol/L). Serum thyroid-stimulating hormone level is within normal limits.

Which of the following is the most appropriate next step in management?

A. **Begin testosterone replacement therapy**

B. **Measure follicle-stimulating hormone and luteinizing hormone levels**

C. **Measure prolactin level**

D. **Obtain a pituitary MRI**

E. **Repeat 8:00 AM testosterone level**

Question 30

A 28-year-old man is evaluated for fatigue and erectile dysfunction. His symptoms have been progressive over the past year. He notes decreased libido and reports loss of morning erections. He also feels tired, has difficulty concentrating, and notes diffuse joint aches. He believes he has less strength and has had to decrease his level of exercise.

Medical history is unremarkable. He had normal puberty and normal growth. He takes no medications.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 108/72 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 23. The liver edge is palpable 4 cm below the costal margin. The penis is normal, and the testes are normal volume but soft and freely mobile without masses. Visual fields are intact.

Laboratory studies:	
Follicle-stimulating hormone	3.0 mU/mL (3.0 U/L)
Luteinizing hormone	2.2 mU/mL (2.2 U/L)
Prolactin	12 ng/mL (12 µg/L)
Testosterone, total (8 AM)	178 ng/dL (6.2 nmol/L)
Testosterone, total (8 AM), repeated	162 ng/dL (5.6 nmol/L)
Thyroid-stimulating hormone	2.3 µU/mL (2.3 mU/L)

Pituitary MRI is normal.

Which of the following is the most appropriate next step in management?

A. **Begin testosterone replacement therapy**

B. **Karyotyping**

C. **Serum ferritin level and transferrin saturation**

D. **Testicular ultrasound**

Resources

- Endocrine Society Clinical Guidelines

Main Resources

SPECIAL FEATURE

Clinical Practice Guideline

Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

Cynthia A. Stuenkel, Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, and Richard J. Santen

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Objective: The objective of this document is to generate a practice guideline for the management and treatment of symptoms of the menopause.

Participants: The Treatment of Symptoms of the Menopause Task Force included six experts, a methodologist, and a medical writer, all appointed by The Endocrine Society.

Evidence: The Task Force developed this evidenced-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews of published data and considered several other existing meta-analyses and trials.

Consensus Process: Multiple e-mail communications, conference calls, and one face-to-face meeting determined consensus. Committees of The Endocrine Society, representatives from endorsing societies, and members of The Endocrine Society reviewed and commented on the drafts of the guidelines. The Australasian Menopause Society, the British Menopause Society, European Menopause and Andropause Society, the European Society of Endocrinology, and the International Menopause Society (co-sponsors of the guideline) reviewed and commented on the draft.

Conclusions: Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms and other symptoms of the climacteric. Benefits may exceed risks for the majority of symptomatic postmenopausal women who are under age 60 or under 10 years since the onset of menopause. Health care professionals should individualize therapy based on clinical factors and patient preference. They should screen women before initiating MHT for cardiovascular and breast cancer risk and recommend the most appropriate therapy depending on risk/benefit considerations. Current evidence does not justify the use of MHT to prevent coronary heart disease, breast cancer, or dementia. Other options are available for those with vasomotor symptoms who prefer not to use MHT or who have contraindications because these patients should not use MHT. Low-dose vaginal estrogen and ospemifene provide effective therapy for the genitourinary syndrome of menopause, and vaginal moisturizers and lubricants are available for those not choosing hormonal therapy. All postmenopausal women should embrace appropriate lifestyle measures. ***J Clin Endocrinol Metab* 100: 3975–4011, 2015)**

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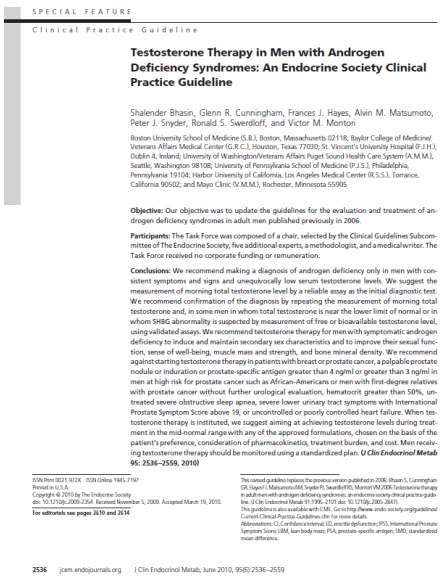
Abbreviations: BZA, bazedoxifene; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DVT, deep vein thrombosis; EPT, estrogen plus progestogen therapy; ET, estrogen therapy; GSM, genitourinary syndrome of menopause; HR, hazard ratio; MetS, metabolic syndrome; MHT, menopausal hormone therapy; MI, myocardial infarction; MPA, medroxyprogesterone acetate; OTC, over the counter; PE, pulmonary embolism; POI, primary ovarian insufficiency; QOL, quality of life; RCT, randomized controlled trial; SERM, selective estrogen receptor modulator; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; VMS, vasomotor symptoms; VTE, venous thromboembolism; VVA, vulvovaginal atrophy.



SPECIAL FEATURE

Clinical Practice Guideline

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

Shalender Bhasin, Glenn R. Cunningham, Frances J. Hayes, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, and Victor M. Montori

Boston University School of Medicine (S.B.), Boston, Massachusetts 02118; Baylor College of Medicine/Veterans Affairs Medical Center (G.R.C.), Houston, Texas 77030; St. Vincent's University Hospital (F.J.H.), Dublin 4, Ireland; University of Washington/Veterans Affairs Puget Sound Health Care System (A.M.M.), Seattle, Washington 98108; University of Pennsylvania School of Medicine (P.J.S.), Philadelphia, Pennsylvania 19104; Harbor University of California, Los Angeles Medical Center (R.S.S.), Torrance, California 90502; and Mayo Clinic (V.M.M.), Rochester, Minnesota 55905

Objective: Our objective was to update the guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men published previously in 2006.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, a methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

Conclusions: We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and, in some men in whom total testosterone is near the lower limit of normal or in whom SHBG abnormality is suspected by measurement of free or bioavailable testosterone level, using validated assays. We recommend testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or prostate-specific antigen greater than 4 ng/ml or greater than 3 ng/ml in men at high risk for prostate cancer such as African-Americans or men with first-degree relatives with prostate cancer without further urological evaluation, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan. ***J Clin Endocrinol Metab* 95: 2536–2559, 2010)**

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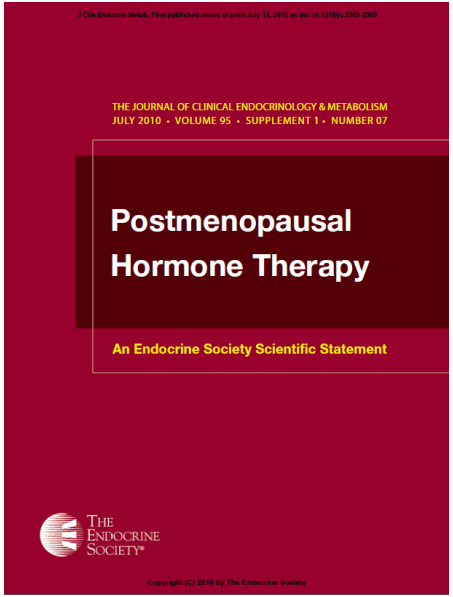
doi: 10.1210/jc.2009-2354 Received November 5, 2009. Accepted March 19, 2010.
For editorials see pages 2610 and 2614

This revised guideline replaces the previous version published in 2006: Bhasin S, Cunningham GR, Hayes F, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM 2006 Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 91:1995–2101 doi: 10.1210/jc.2005-2847).
This guideline is also available with J CME. Go to http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm for more details.
Abbreviations: CI, Confidence interval; ED, erectile dysfunction; IPSS, International Prostate Symptom Score; LBM, lean body mass; PSA, prostate-specific antigen; SMD, standardized mean difference.



J Clin Endocrin Metab. First published ahead of print July 14, 2010 as doi: 10.1210/jc.2009-2509

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Postmenopausal Hormone Therapy

An Endocrine Society Scientific Statement

THE ENDOCRINE SOCIETY®

Objectives

- To determine biochemically and clinically if hormone replacement therapy is needed in males and females
- Understand the risk of replacement in males
- Understand the risk of replacement in females
- To know how to treat the biochemical goals of treatment for hormone replacement in males and females

Hypogonadism

- In males, it describes a variety of medical conditions that makes the individual lack the ability to produce either sperm or testosterone
- In females, it describes a variety of medical conditions that makes the individual unable to produce estrogen; hallmarked by not starting or stopping menses

Prevalence of Hypogonadism

- Male hypogonadism: A rare disorder, universal screen has been studied and not cost effective, prevalence greatly varies based on study populations and screening protocols

- Female hypogonadism: Premenopausal a rare disorder, no universal screening in youth, but with time and longevity all women progress to menopause (average age in the US approximately 51.3 years)

Failure to Initiate Puberty

- In males, they lack muscle and height development; usually reported by the lack of adrenarche
- In females, they lack of development of secondary characteristics of adrenarche and thelarche; but most commonly present with lack of menarche

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Two Classes of Hypogonadism

- Primary Failure: The gonads (testes or ovaries) do not function properly
- Secondary Failure: An outside influence is preventing the gonads from working properly (e.g. hypothalamic hypogonadism, antibody blockade, pituitary disordered, chronic illness, obesity, chronic opioid use, hemochromatosis, HIV, sleep apnea and irregular sleep, ESRD on HD, etc.)

Clinical Work Up Of Hypogonadism

- History
- History
- History

Clinical Work Of Hypogonadism

- History
  - Did the patient go through puberty?
  - Did the patient go through adrenarche?
  - Did the patient reproduce?
  - Did the symptoms happen suddenly or over a long period of time?
  - Was there associated events? (illness, trauma)
  - Are there secondary reasons for failure?

Symptoms of Male Hypogonadism

- Decrease libido
- Decreased muscle strength
- Cessation of androgen dependent hair growth
- Breast changes
- Fatigue
- Hot Flashes

Symptoms of Female Hypogonadism

- Cessation of menses
- Decreased libido
- Vaginal dryness or dyspareunia
- Fatigue
- Breast changes
- Hot Flashes

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Signs of Male Hypogonadism

- Prepubertal development
- Testicular atrophy
- Breast tissue changes
- Visual field loss
- Eunuchcoid body habitus
- Increased fractures

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Signs of Female Hypogonadism

- Prepubertal development
- Decreasing density of breast tissue
- Vaginal atrophy
- Visual field loss
- Increased fractures

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Screening For Hypogonadism

- In general, this should not be done!
  - No universally excepted method of screening
  - Labs are variable and can be inaccurate
  - Lack of understanding of long term consequences of long term androgen and estrogen deprivation on mortality
  - The benefits and adverse consequences of supplementation in generally asymptomatic or not clinically impaired individuals is unclear

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Searching For Hypogonadism

- Condition to consider evaluation associated with androgen and estrogen dysfunction:
  - Sellar disease, surgery, or radiation
  - Chronic opioid or glucocorticoid medications
  - HIV associated weight loss
  - ESRD on HD
  - Infertility
  - Unexpected osteoporosis
  - Type 2 diabetes

Assessing Male Hypogonadism

- Total Testosterone: Collected first thing in the morning is currently the best method
- If abnormal, the standard of practice is to repeat the test
- If abnormal, repeat **twice in the morning (or after routine waking time)**; then further evaluation is warranted

Assessing Male Hypogonadism

- Free and Bioavailable Testosterone – is not recommended or accurate
  - –Analog method: Most common method, but is inaccurate andnot recommended
  - –Calculated methods: Dependent on quality of sex hormone globulin, and total testosterone measurements. They are inaccurate
  - –Equilibrium dialysis method: Most accurate method by using sex hormone globulin, total testosterone, and albumin. In most situations, send this out to the lab.

Assessing Male Hypogonadism

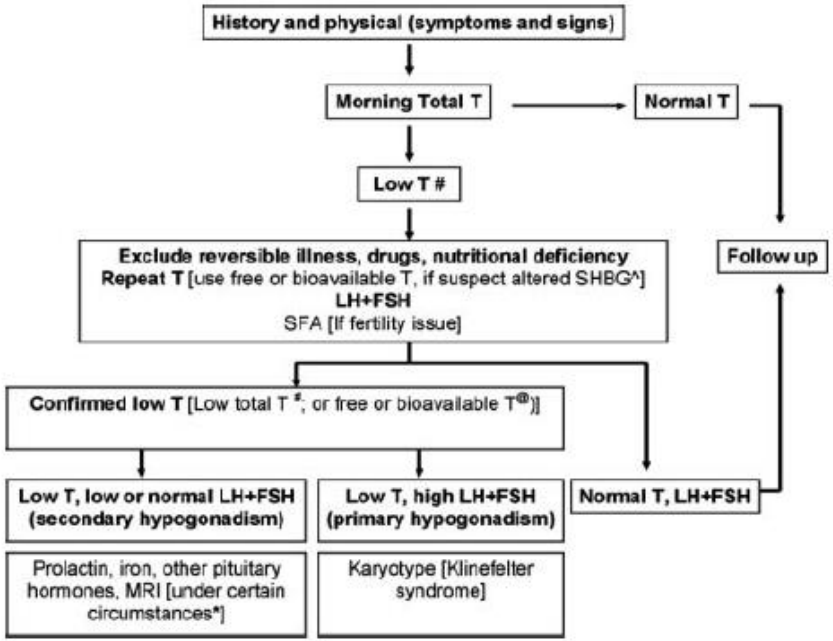

FIG. 1. An approach for the diagnostic evaluation of adult men suspected of having androgen deficiency. #, In some laboratories, the lower limit of the normal testosterone range in healthy young men is approximately 280–300 ng/dl (9.8–10.4 nmol/liter); however, this range may vary in different laboratories. Use the lower limit of the range established in your reference laboratory. @, In some reference laboratories, the lower limit of the normal free testosterone range in healthy young men is approximately 5–9 ng/dl (0.17–0.31 nmol/liter) using equilibrium dialysis or calculated from total testosterone and SHBG; however, this range may vary in different laboratories, depending on the specific equilibrium dialysis or calculated from total testosterone and SHBG assays and the reference population used. Use the lower limit of the range established in your reference laboratory. ^, Conditions in which SHBG levels may be altered are listed in Table 2. *, Perform pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor or infiltrative disease if severe secondary hypogonadism (serum T $<$ 150 ng/dl), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect, such as headache, visual impairment, or visual field defect are present. SFA, Seminal fluid analysis; T, testosterone; MRI, magnetic resonance imaging.

Assessing Female Hypogonadism

- Complicated by the variation of estrogen levels that occur in females during the reproductive cycle in premenopausal women
- Laboratory evaluations usually start with Estradiol, Follicle Stimulating Hormone(FSH), and Luteinizing Hormone(LH) levels

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Assessing Female Hypogonadism

- Some conditions to consider in females other than hypogonadism:
  - Endocrine: Thyroid hormone excess, carcinoid syndrome, pheochromocytoma
  - Dietary: alcohol, additives, spicy food
  - Anxiety
  - Infections
  - Mastocytosis

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Replacing Androgens in Males

- Several preparations
  - Intramuscular (200-300mg testosterone enanthate every 2-3 weeks, or 75-100mg Q 1 week)
  - Transdermal Patches
  - Transdermal Gel
  - Buccal
  - Pellets

Replacing Estrogen in Females

- Several preparations
  - Intramuscular
  - Oral tablets
  - Transdermal Gel
  - Transdermal Spray
  - Transdermal Patch
  - Pellets (generally for contraception only)
  - Local vaginal cream or ring

Replacing Progesterone in Females

- Several preparations
  - –Oral tablets
  - –Transdermal Patch
  - –Local vaginal gel
  - –Intrauterine

Replacing Estrogen and Progesterone in Females

- Several preparations:
  - Oral tablets
  - Transdermal Patch

Androgens Replacement in Males

- Who to Treat:
  - Known testicular failure
  - Pituitary and brain lesions causing secondary hypogonadism
  - People with secondary causes that will not be cured with relief of the underlying problem

Associated Conditions Recommending No Androgen Supplementation

- Metastatic prostate cancer
- Breast cancer
- Prostate nodules
- High PSA (>4ng/ml)
- Hematocrit (>50%)
- Severe benign prostatic hypertrophy
- Uncontrolled congestive heart failure

Replacing Estrogens in Females

- First, is a uterus present or not present?
- If a uterus is present, then one must consider progesterone to treat the growth and vascularization of the uterus from the estrogen replacement

Associated Conditions Recommending No Estrogen or Progesterone Supplementation

- Breast cancer of moderate to high risk
- Endometrial Cancer
- Increased cardiovascular risk (history of peripheral vascular disease, deep vein thrombosis, myocardial infarction, stroke etc.)

Replacing Estrogens in Females

- **First uterus present or no uterus present**
- If premenopausal age (<51.3yo, particularly<40yo), then likely needs a replacement
  - Even if for no symptomatic reason, still likely needs replacement to retain good bone health
- If wanting menopausal hormone therapy (MHT), then needs an in depth evaluation and discussion
- If >60yo or 10 years since normal menopause, then likely does not need hormone replacement

Menopausal Hormone Therapy

- In the past, the Women's Health Initiative study discourages MHT due to increases in breast cancer, endometrial cancer, and cardiovascular disease, but…
  - Generally, this risk was greater in those ladies starting MHT at age 60 or greater, and those on progesterone
  - So what about those less than 60 or close to time of menopause?

Menopausal Hormone Therapy 50-59 years old

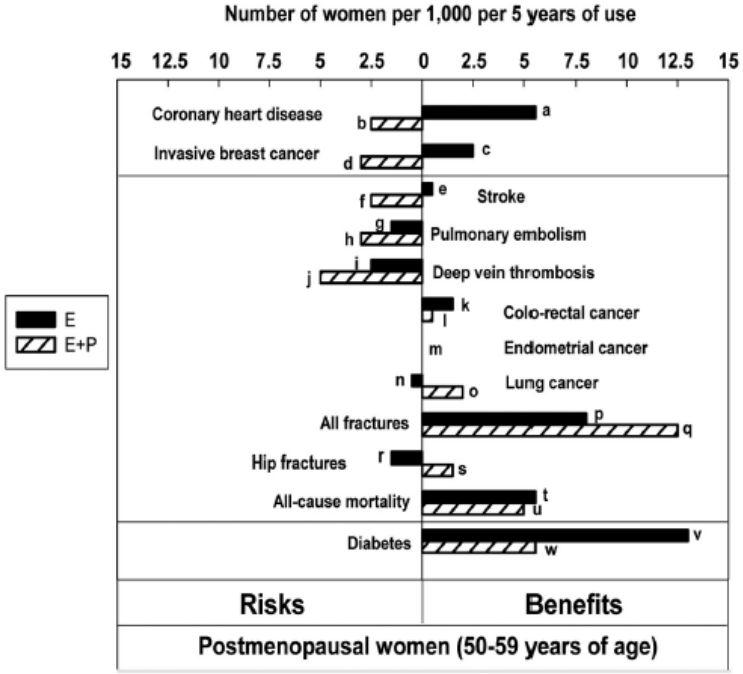

Figure 3. Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50–59 years during intervention phase of WHI. One set of analyses examined the risks and benefits of these agents in women ages 50–59 years. This figure plots these data, which are expressed here as excess risks and benefits per 1000 women using MHT for 5 years. Because women deciding to use MHT are more likely to continue this for a period of years rather than 1 year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure are statistically significant. Nonetheless, this figure represents the best estimates that are available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in The Endocrine Society Scientific Statement (38). The HR (95% CI) values for the bars in the figure are listed here with reference to the alphabetical designations shown next to the bars: a, HR, 0.60 (0.35–1.04); b, HR, 1.34 (0.82–2.19); c, HR, 0.82 (0.50–1.34); d, HR, 1.21 (0.81–1.80); e, HR, 0.99 (0.53–1.85); f, HR, 1.51 (0.81–2.82); g, HR, 1.53 (0.63–3.75); h, HR, 2.05 (0.89–4.71); i, HR, 1.66 (0.76–3.67); j, HR, 3.01 (1.36–6.66); k, HR, 0.71 (0.30–1.67); l, HR, 0.79 (0.29–2.18); m, HR, 1.00 (ns-ns); n, HR, 1.12 (0.45–2.75); o, HR, 0.62 (0.30–1.29); p, HR, 0.90 (0.72–1.11); q, HR, 0.82 (0.68–1.00); r, HR, 5.01 (0.59–42.9); s, HR, 0.17 (0.02–1.45); t, HR, 0.70 (0.46–1.09); u, HR, 0.67 (0.43–1.04); v, HR, 0.83 (0.67–1.04); and w, HR, 0.85 (0.66–1.09). [RJ Santen, et al: Competency in menopause management: whither goest the internist? *J Womens Health (Larchmt)*. 2014;23(4): 281–285, courtesy of Mary Ann Liebert, Inc].

Menopausal Hormone Therapy 50-59 years old

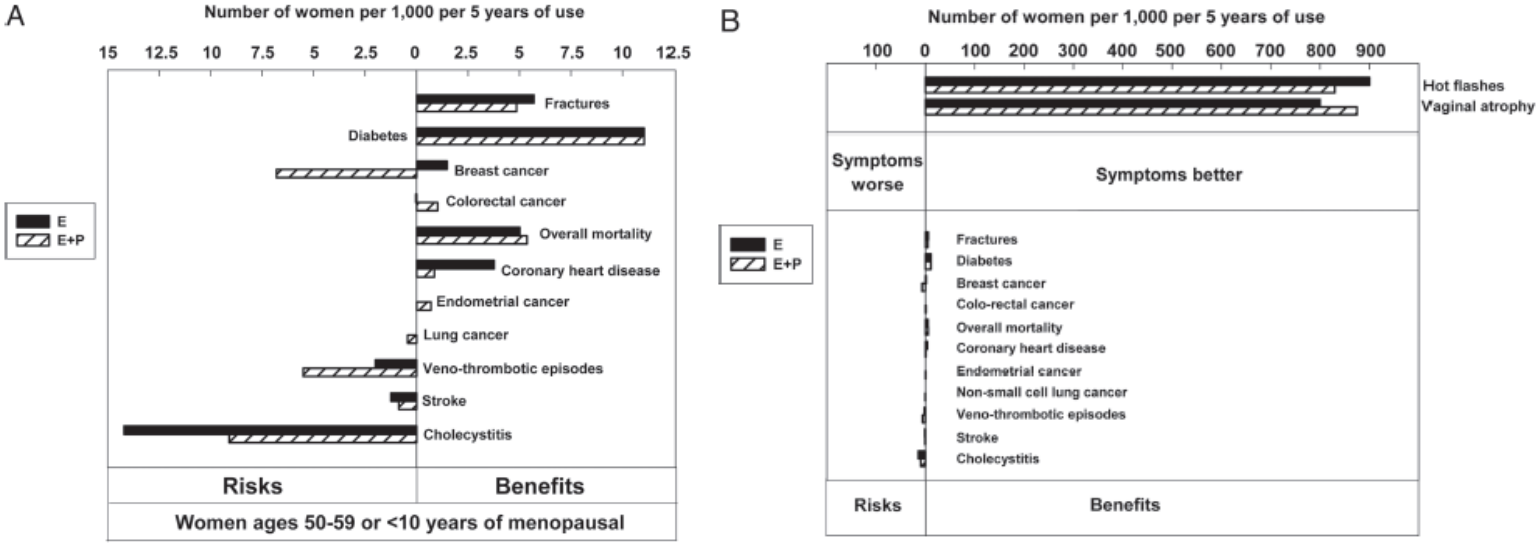

FIG. 5. A, Risks and benefits of MHT in women starting MHT between the ages of 50 and 59 yr or less than 10 yr after the start of menopause. Data are expressed as the attributable (excess) risk or benefit for a woman taking E alone as MHT for 5 yr. B, Number of women per 1000 taking MHT for 5 yr who are expected to have improvement of symptoms of vaginal atrophy or hot flashes. Design of panels A and B is the same. Note that the data regarding risks and benefits in the bottom of panel B represent those illustrated in panel A, where they are illustrated in expanded form so that they can be clearly seen. The purpose of reproducing these data in the bottom of panel B is to compare the number of women benefiting from relief of symptoms of hot flashes and vaginal atrophy with the number of women experiencing other risks and benefits. Fig. 5B is based on data in Refs. 270, 295, and 508. *Solid black bars*, E alone; *hatched bars*, E+P.

Menopausal Hormone Replacement In Women With Symptoms

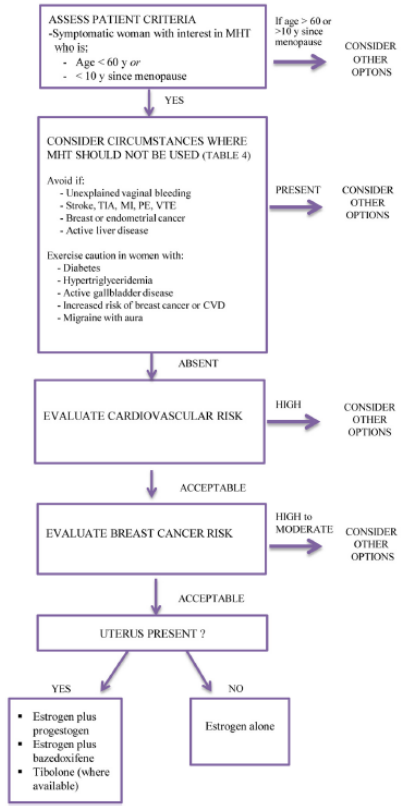

Figure 2. Approach to the patient with VMS contemplating MHT. TIA, transient ischemic attack.

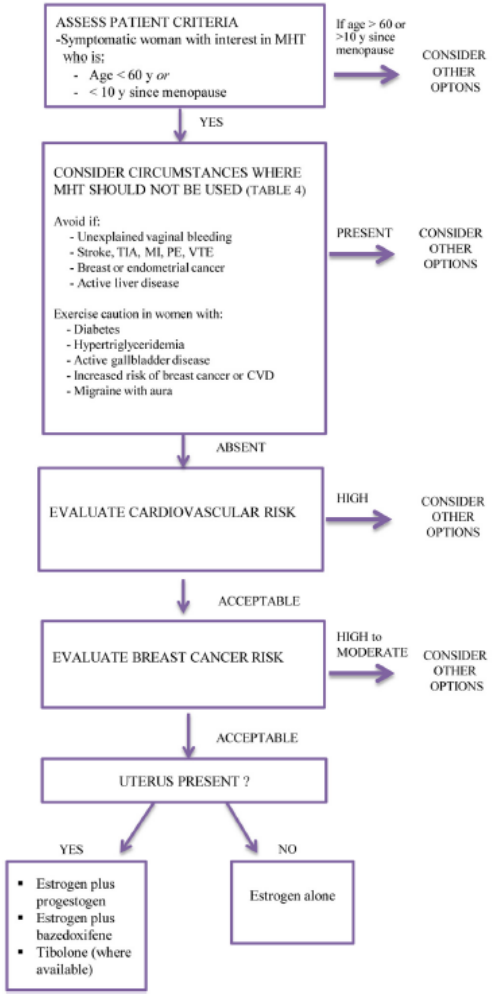

Figure 2. Approach to the patient with VMS contemplating MHT. TIA, transient ischemic attack.

Treatment Of Vaginal Dryness, Dyspareunia, and Genital Urinary Complaints and Menopause

- Consider local placement and preparations with an estrogen cream, gel, or ring
  - –Gives relief without systemic side effects or exposure

Alternative Treatment of Hot Flashes

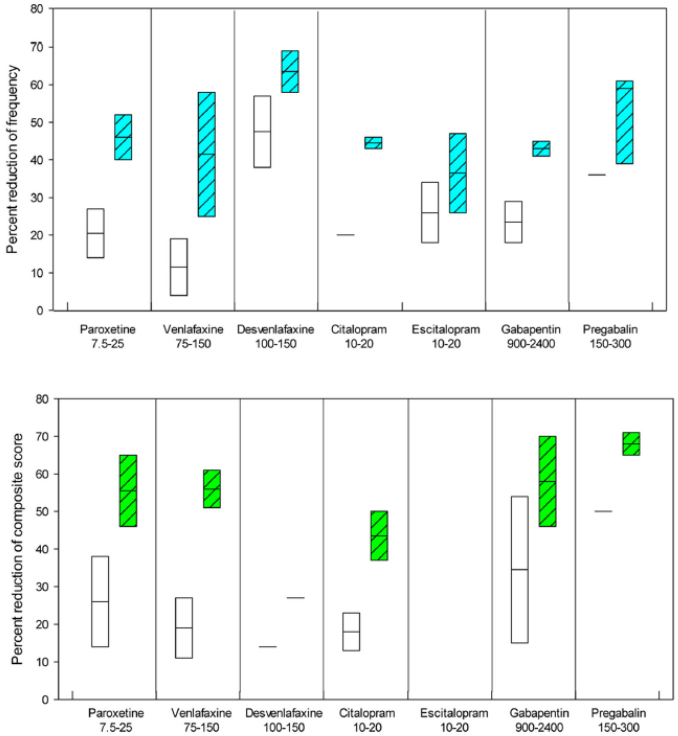

Figure 4. Hot flash frequency and composite score with nonhormonal prescription therapies for relief of VMS. Upper panel, Effect on frequency of VMS; lower panel, effect on composite score (severity times frequency; best representation of effect); open bars, placebo; colored bars, therapies; length of bars, ranges in studies; horizontal bar, means. All of these agents are generally well tolerated (226). Hypersensitivity or prior adverse drug reactions to each of these agents represent contraindications. For the SSRI/SNRIs, prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are also contraindications. SSRI/SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRI/SNRIs, or poorly controlled hypertension. These agents uncommonly induce suicidal thoughts within the first few months of treatment. Preliminary evidence suggests a possible increase in risk of bone fracture. Gabapentin and pregabalin may increase suicidal thoughts and behaviors, cause drowsiness or dizziness, and impair balance and coordination. Pregabalin may impair memory and concentration. Clonidine is contraindicated in patients with low blood pressure and may cause lightheadedness, hypotension, headache, and constipation; sudden cessation of treatment can be associated with significant increments in blood pressure (63).

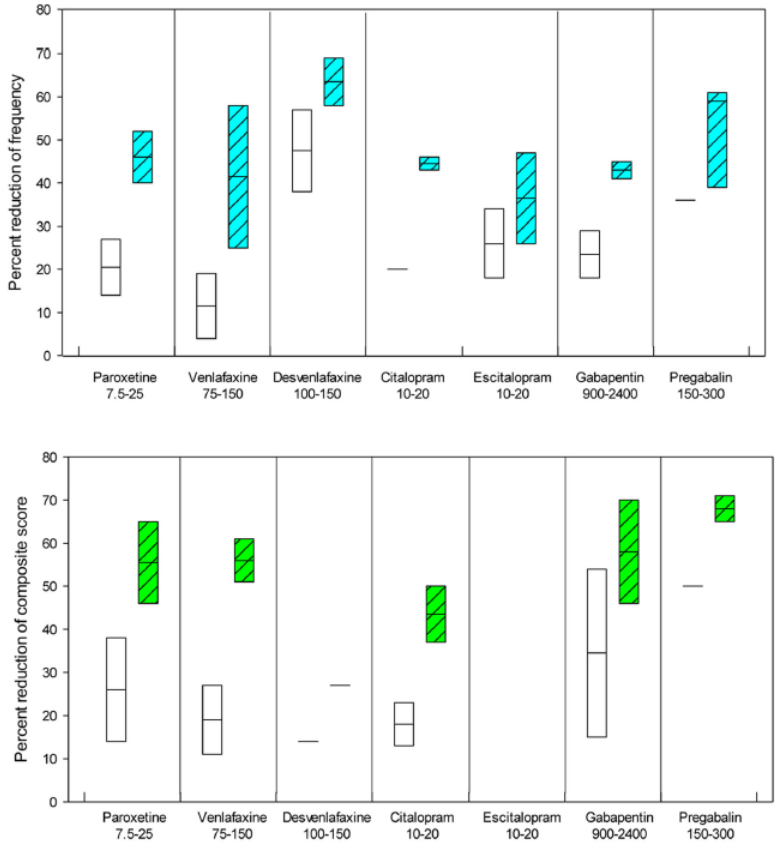

Figure 4. Hot flash frequency and composite score with nonhormonal prescription therapies for relief of VMS. Upper panel, Effect on frequency of VMS; lower panel, effect on composite score (severity times frequency; best representation of effect); open bars, placebo; colored bars, therapies; length of bars, ranges in studies; horizontal bar, means. All of these agents are generally well tolerated (226). Hypersensitivity or prior adverse drug reactions to each of these agents represent contraindications. For the SSRI/SNRIs, prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are also contraindications. SSRI/SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRI/SNRIs, or poorly controlled hypertension. These agents uncommonly induce suicidal thoughts within the first few months of treatment. Preliminary evidence suggests a possible increase in risk of bone fracture. Gabapentin and pregabalin may increase suicidal thoughts and behaviors, cause drowsiness or dizziness, and impair balance and coordination. Pregabalin may impair memory and concentration. Clonidine is contraindicated in patients with low blood pressure and may cause lightheadedness, hypotension, headache, and constipation; sudden cessation of treatment can be associated with significant increments in blood pressure (63).

Alternative Treatment of Hot Flashes

- Agents studied with generally no benefits:
  - Black cohosh
  - Omega-3 fatty acids
  - Acupuncture
  - Exercise

How To Evaluate Treatment

- Follow up at least every 3-6 months and monitor symptoms and clinical effects
- Monitor hormone labs; treat until clinical effect is achieved, and not to exceed mid normal level of the hormone range
- Watch LFT’s, hematocrit, and PSA in men
- Screen for osteoporosis in the beginning, and get bone mineral density every 2 years

Problems With Long Term Androgen Replacement in Males

- Unmask prostate malignancy
- Increase benign prostatic hypertrophy
- Erythrocytosis
- Deep Vein Thrombosis
- Acne
- Gynecomastia
- **Testicular atrophy and dependence**

Problems With Long Term Hormone Replacement in Females

- If the uterus is present, then vaginal bleeding and endometrial malignancy may occur
- Symptoms persist
- Breast tenderness
- Triglyceride elevation (particularly with oral supplementation)
- Gall bladder disease
- Breast endometrial malignancy (particularly with progesterone medications)
- Deep Vein Thrombosis

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Comparison of Traditional HT with “bioidentical hormone” therapy

Characteristics	Traditional Hormones	Many “bioidentical hormones”
Molecular Structure	Similar or identical to human	Identical to human
FDA Oversight	Yes	No
Dosage	Monitored; accurate and consistent	Not monitored; may be inaccurate or inconsistent
Purity	Monitored; pure	Not monitored; may be impure
Safety	Tested; risk known	Not FDA monitored; risk unknown
Efficacy	Tested and proven	Not FDA tested; unproven
Scientific Evidence	Existent; conclusive	Insufficient

A 53-year-old woman is evaluated for a 1-year history of dyspareunia. She has tried using lubricants, but she still has discomfort and has lost interest in sexual intercourse. She reports vaginal itching but no vaginal discharge, bleeding, or odor. She reached menopause 2 years ago and notes occasional hot flushes, but they are not troublesome. There is no history of sexual trauma, sexually transmitted infection, or pelvic surgery. She reports no marital problems. Medical history is otherwise remarkable for hypertension. Her only medication is benazepril.

On physical examination, the patient is afebrile, blood pressure is 130/78 mm Hg, pulse rate is 72/min, and respiration rate is 14/min. BMI is 27. The general medical examination is unremarkable. On pelvic examination, she can only tolerate insertion of a narrow speculum, and the vaginal mucosa is pale and dry with smooth vaginal walls and decreased rugae. There is scant vaginal discharge. Bimanual examination is normal.

Microscopic evaluation of a vaginal preparation reveals no hyphae, yeast, or clue cells.

Which of the following is the most appropriate management?

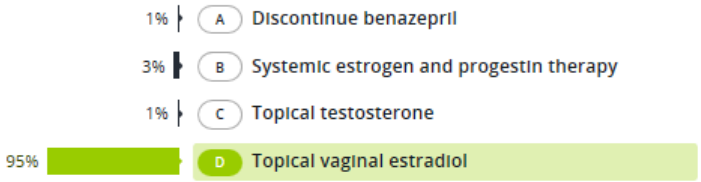
A. Discontinue benazepril

B. Systemic estrogen and progestin therapy

C. Topical testosterone

D. Topical vaginal estradiol

Which of the following is the most appropriate management?



Answer & Critique

Correct Answer: D

Educational Objective: Treat genitourinary syndrome of menopause.

The most appropriate management of this woman with dyspareunia due to genitourinary syndrome of menopause is topical vaginal estradiol. Symptoms of atrophic vaginitis affect 10% to 40% of postmenopausal women and include vaginal dryness, dyspareunia, vulvovaginal irritation, and itch. The associated dyspareunia may lead to avoidance of sexual activity due to discomfort. Treatment for genitourinary syndrome of menopause may include hormone-free vaginal moisturizers, which may control symptoms in some women. If symptoms persist with lubricant use, topical estradiol is useful in alleviating vaginal symptoms. A low-dose tablet containing 25 µg of 17-β estradiol is available; it is generally inserted nightly for 2 weeks and then twice weekly on nonconsecutive nights to restore vaginal epithelium. Concurrent progestin is generally not indicated for women with an intact uterus who use low-dose vaginal estrogen alone, as systemic absorption is minimal.

Key Point

Vaginal estrogen therapy is effective in treating women who have moderate to severe symptoms of genitourinary syndrome of menopause that have not responded to lubricants.

Several classes of medication may exacerbate vaginal dryness, including antiestrogens (tamoxifen, aromatase inhibitors), progestins, antihistamines, and anticholinergics. However, ACE inhibitors, such as benazepril, are not associated with vaginal dryness.

Systemic estrogen therapy with a patch, gel, or tablet may be used in conjunction with vaginal estrogen to treat vasomotor symptoms or for other indications, along with concurrent progestin treatment in patients with an intact uterus. Moderate to severe vasomotor symptoms can be treated with systemic hormone therapy in the appropriate risk-stratified patient; however, this patient's hot flush symptoms are tolerable and do not warrant systemic hormone therapy.

This patient's decreased interest in sexual intercourse is likely related to her dyspareunia and not decreased libido. Additionally, topical or systemic testosterone is not currently FDA approved for treatment of decreased libido in women, and its use for this purpose is discouraged by the Endocrine Society until long-term safety data can be established.

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Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause. 2013 Sep;20(9):888-902; quiz 903-4.

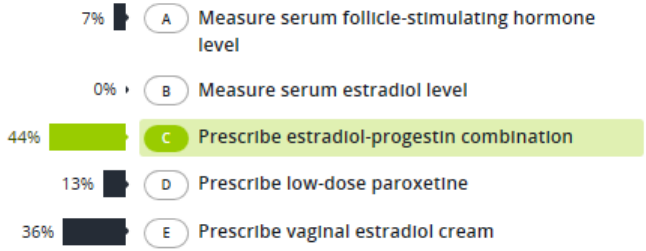
A 57-year-old woman is evaluated for a 2-month history of bothersome hot flushes multiple times daily, with night sweats disrupting sleep about two to three times nightly. She also reports irritability and mood lability and reports worsening vaginal dryness with dyspareunia. Her last menstrual period was 13 months ago. Medical history is significant only for hypothyroidism. Personal and family histories are negative for breast and ovarian cancer. Her only medication is levothyroxine. Mammography and cervical cancer screening are up to date.

On physical examination, vital signs are normal. The general medical examination is unremarkable. Breast examination is negative. On pelvic examination, the vaginal mucosa is pale with decreased rugae with petechial hemorrhages present. Decreased vaginal lubrication is noted.

Which of the following is the most appropriate next step in management?

- A **Measure serum follicle-stimulating hormone level**
- B **Measure serum estradiol level**
- C **Prescribe estradiol-progestin combination**
- D **Prescribe low-dose paroxetine**
- E **Prescribe vaginal estradiol cream**

Which of the following is the most appropriate next step in management?



Answer & Critique

Correct Answer: C

Educational Objective: Treat vasomotor symptoms in a low-risk menopausal woman.

Educational Objective: Treat vasomotor symptoms in a low-risk menopausal woman.

The most appropriate management of this patient is a combination of oral estradiol and progestin. Severe vasomotor symptoms are best treated with systemic hormone therapy. An individualized approach based on personal risk factors (including age, time since menopause, and absence of increased risk for cardiovascular disease, thromboembolism, or breast cancer) suggests that this patient is an appropriate candidate. The absolute risks associated with hormone therapy use in healthy women younger than 60 years are low, as are the risks of adverse cardiovascular events if time since menopause is less than 10 years. Estradiol can be administered orally or transdermally in gel, patch, or spray; progestin is needed to prevent endometrial proliferation in this patient with an intact uterus.

Key Point

The absolute risks for use of hormone therapy in healthy women younger than 60 years are low, as are the risks of adverse cardiovascular events if time since menopause is less than 10 years.

Treatment should begin with the lowest effective dose needed to achieve symptom relief. Systemic hormone therapy treats the symptoms present in this patient, including severe hot flushes, vaginal atrophy, and mood swings. Dose, duration, and route of systemic hormone therapy should be based on symptom response, individualized risk stratification, and patient preference. Because treatment duration greater than 5 years is associated with increased breast cancer risk, the need for treatment should be reassessed annually.

A patient who is amenorrheic for more than 12 months is, by definition, menopausal. Therefore, measuring a serum follicle-stimulating hormone level will not alter management and represents unnecessary and low value care.

Measurement of serum estrogen levels in this patient would not be helpful in guiding therapy. The treatment of vasomotor symptoms in a menopausal patient is based on clinical presentation and response to treatment, and laboratory studies are not routinely indicated before starting therapy.

Low-dose selective serotonin reuptake inhibitors (SSRIs) such as paroxetine have been shown to alleviate vasomotor symptoms. However, nonhormonal agents such as SSRIs or gabapentin will not alleviate this patient's symptoms of vaginal atrophy and dyspareunia.

Vaginal estradiol will alleviate symptoms of vaginal atrophy; however, local therapy will not relieve her severe hot flushes and mood changes. Therefore, systemic hormone therapy is a better choice for this patient.

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Manson JE. Current recommendations: what is the clinician to do? Fertil Steril. 2014 Apr;101 (4):916-21. PMID: 24680650

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Question 49

A 77-year-old man is evaluated for a 6-month history of fatigue, weakness, and erectile dysfunction. He previously had an enjoyable sex life with his wife but more recently has experienced low interest in sexual activity. He is unable to engage in his regular exercise routine due to reduced energy and muscle weakness. He reports no weight loss or depressed mood.

On physical examination, the patient is afebrile, blood pressure is 142/88 mm Hg, and pulse rate is 90/min. BMI is 32. Examination of the heart and lungs is normal. Musculoskeletal and nervous system examinations are normal. Normal-appearing testes and circumcised penis are noted.

Laboratory studies show an 8:00 AM serum total testosterone level of 195 ng/dL (6.8 nmol/L). Serum thyroid-stimulating hormone level is within normal limits.

Which of the following is the most appropriate next step in management?

A. Begin testosterone replacement therapy

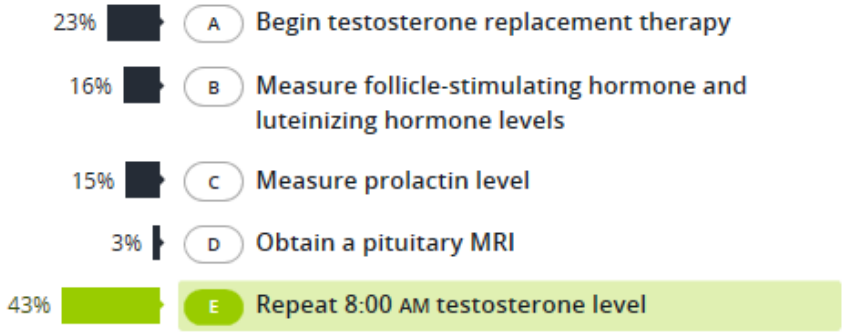
B. Measure follicle-stimulating hormone and luteinizing hormone levels

C. Measure prolactin level

D. Obtain a pituitary MRI

E. Repeat 8:00 AM testosterone level

Which of the following is the most appropriate next step in management?



Answer & Critique

Correct Answer: E

Educational Objective: Evaluate a patient for hypogonadism.

Educational Objective: Evaluate a patient for hypogonadism.

A repeat testosterone level is appropriate for this older patient with fatigue, weakness, and erectile dysfunction (ED). Men with specific signs and symptoms of androgen deficiency should be evaluated by measuring morning total testosterone level as the initial diagnostic test. Men with low or low-normal testosterone levels should have confirmatory testing before initiating testosterone therapy, and further evaluation of the cause of hypogonadism should be pursued before treatment is started, if indicated. If the repeat serum total testosterone level is more equivocal (200-350 ng/dL [6.9-12.1 nmol/L]) or if a sex hormone–binding globulin abnormality is likely in the patient being evaluated, a serum free testosterone level by equilibrium dialysis or a calculated serum free testosterone level can determine whether hypogonadism is truly present.

Key Point

Men with low or low-normal testosterone levels should have confirmatory morning serum total testosterone testing before initiating testosterone therapy, and further evaluation of the cause of hypogonadism should be pursued before treatment is started.

When hypogonadism is confirmed, the next step is to determine whether the patient has primary or secondary hypogonadism by measuring the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Primary hypogonadism is indicated by supranormal LH and FSH levels. If secondary hypogonadism is confirmed by inappropriately normal or low LH and FSH levels, measurement of the serum prolactin level to evaluate for hyperprolactinemia and iron saturation level (transferrin saturation and ferritin levels) to exclude hemochromatosis should be performed to assess for the possible cause. In addition, the presence of any additional pituitary hormone deficiencies should be assessed.

An MRI of the pituitary gland should be ordered to exclude hypothalamic or pituitary masses as the cause of decreased gonadotropin production and secretion if any symptoms consistent with mass effect are present, including headaches, visual field changes, a serum total testosterone level less than 150 ng/dL (5.2 nmol/L), an increased prolactin level, or any additional pituitary hormonal deficiencies.

Testosterone replacement in older men should be given only in the setting of hypogonadism that is based on symptoms (such as decreased libido and generalized muscle weakness) and morning serum total testosterone levels lower than 200 ng/dL (6.9 nmol/L) on at least two separate occasions. Therefore, this patient needs confirmation on repeat testing before considering testosterone replacement therapy.

Bibliography

Heidelbaugh JJ. Management of erectile dysfunction. Am Fam Physician. 2010 Feb 1;81(3):305-12. PMID: 20112889

Question 30

A 28-year-old man is evaluated for fatigue and erectile dysfunction. His symptoms have been progressive over the past year. He notes decreased libido and reports loss of morning erections. He also feels tired, has difficulty concentrating, and notes diffuse joint aches. He believes he has less strength and has had to decrease his level of exercise.

Medical history is unremarkable. He had normal puberty and normal growth. He takes no medications.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 108/72 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 23. The liver edge is palpable 4 cm below the costal margin. The penis is normal, and the testes are normal volume but soft and freely mobile without masses. Visual fields are intact.

Laboratory studies:	
Follicle-stimulating hormone	3.0 mU/mL (3.0 U/L)
Luteinizing hormone	2.2 mU/mL (2.2 U/L)
Prolactin	12 ng/mL (12 µg/L)
Testosterone, total (8 AM)	178 ng/dL (6.2 nmol/L)
Testosterone, total (8 AM), repeated	162 ng/dL (5.6 nmol/L)
Thyroid-stimulating hormone	2.3 µU/mL (2.3 mU/L)

Pituitary MRI is normal.

Which of the following is the most appropriate next step in management?

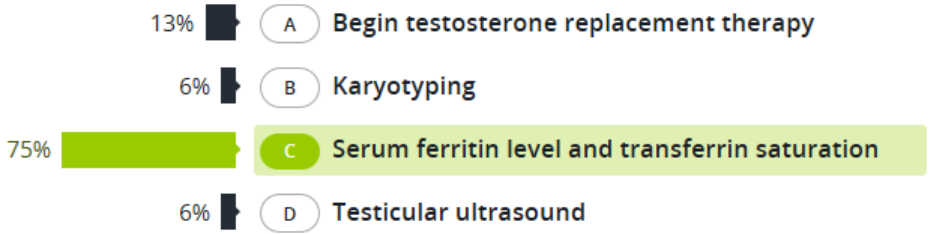
A. **Begin testosterone replacement therapy**

B. **Karyotyping**

C. **Serum ferritin level and transferrin saturation**

D. **Testicular ultrasound**

Which of the following is the most appropriate next step in management?



Answer & Critique

Correct Answer: C

Educational Objective: Identify hemochromatosis as a cause of hypogonadotropic hypogonadism.

The patient has a clinical history suspicious for hemochromatosis and should be further evaluated by measuring serum transferrin saturation and ferritin levels. The patient has hypogonadism based on his clinical symptoms of decreased libido and erectile dysfunction, associated with a low morning serum testosterone level. A hypogonadotropic etiology is indicated by his low luteinizing and follicle-stimulating hormone levels. Causes of hypogonadotropic hypogonadism include infiltrative diseases such as hemochromatosis, sarcoidosis, cancer metastatic to the pituitary, and lymphoma. Pituitary tumors that impair gonadotropin function may also be a cause. This patient has several clinical findings suggestive of possible hemochromatosis, including a report of arthralgia and hepatomegaly on physical examination. Therefore, the next step in evaluation of this patient's hypogonadotropic hypogonadism is measurement of serum ferritin level and transferrin saturation to evaluate for possible hemochromatosis.

Key Point

Patients with symptoms of hypogonadotropic hypogonadism should have serum transferrin saturation and ferritin concentration levels measured to identify hemochromatosis prior to initiating any therapy.

The cause of hypogonadism must be evaluated prior to the initiation of testosterone replacement. If testosterone therapy is started without testing for hemochromatosis, the diagnosis may be missed.

Although genetic disorders such as Klinefelter syndrome (47,XXY) may cause hypogonadism, patients with this syndrome have hypergonadotropic hypogonadism with elevated luteinizing and follicle-stimulating hormone values, unlike this patient. Therefore, karyotyping is not indicated.

A testicular ultrasound is used to evaluate the cause of primary testicular failure and is not indicated in the evaluation of hypogonadotropic hypogonadism. This patient's low gonadotropin levels indicate either a hypothalamic or pituitary disorder, instead of testicular disease. Although hemochromatosis may also directly affect testicular function in addition to its central hypogonadal effect, testicular ultrasound is not helpful in establishing the diagnosis of hemochromatosis as a cause of hypogonadism.

Bibliography

Bacon BR, Adam PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 Practice guidelines by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328-43. PMID: 21452290

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In Conclusion:

- Primary failure and pituitary secondary gonad failure happens infrequently males
- Hormone replacement therapy, when needed, is of medical benefit particularly in the young with regard to bone health
- Menopausal Hormone Therapy (MHT) can be considered in women with symptoms age <60 and less than 10 years after menopause
- There are risks of hormone replacement therapy, and in males include developing dependence or testicular atrophy
- Hormone replacement is a science and art that requires monitoring if initiated
- The are alternatives to MHT in women with hot flashes

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Thank You!

Questions?

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  - St. Clair Shores, MI 48084
  - Phone: 586-443-2380
  - Fax: 586-443-2381

- Call Beaumont Health system and ask to have him paged
  - 248-898-5000

1. Evaluate the patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
2. Monitor testosterone level 3 to 6 months after initiation of testosterone therapy:
   Therapy should aim to raise serum testosterone level into the mid-normal range.
   - Injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/liter) or <400 ng/dl (14.1 nmol/liter), adjust dose or frequency.
   - Transdermal patches: assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range.
   - Buccal testosterone bioadhesive tablet: assess level immediately before or after application of fresh system.
   - Transdermal gels: assess testosterone level any time after patient has been on treatment for at least 1 wk; adjust dose to achieve serum testosterone level in the mid-normal range.
   - Testosterone pellets: measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
   - Oral testosterone undecanoate[a]: monitor serum testosterone level 3 to 5 h after ingestion.
   - Injectable testosterone undecanoate: measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.
3. Check hematocrit at baseline, at 3 to 6 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.
5. In men 40 yr of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3 to 6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
6. Obtain urological consultation if there is:
   - An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment.
   - A PSA velocity of >0.4 ng/ml · yr using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 yr).
   - Detection of a prostatic abnormality on digital rectal examination.
   - An AUA/IPSS of >19.
7. Evaluate formulation-specific adverse effects at each visit:
   - Buccal testosterone tablets: inquire about alterations in taste and examine the gums and oral mucosa for irritation.
   - Injectable testosterone esters (enanthate, cypionate, and undecanoate): ask about fluctuations in mood or libido, and rarely cough after injections.
   - Testosterone patches: look for skin reaction at the application site.
   - Testosterone gels: advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel.
   - Testosterone pellets: look for signs of infection, fibrosis, or pellet extrusion.

[a] Not approved for clinical use in the United States.

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TABLE 7. Some recommended regimens[a] for testosterone replacement therapy

150 to 200 mg administered every 2 wk, or 75–100 mg of testosterone enanthate or cypionate administered im weekly
One or two 5-mg testosterone patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas
5 to 10 g of testosterone gel applied daily over a covered area of skin
30 mg of a bioadhesive, buccal testosterone tablet applied to buccal mucosa twice daily
Testosterone pellets (dose and regimen vary with the formulation used)

[a] Formulations available in other countries but not in the United States include: 1) oral testosterone undecanoate (typically used at a dose of 40 to 80 mg orally two or three times daily with meals); 2) two testosterone matrix patches 30, 45, or 60 cm^2 applied every 2 d; 3); injectable testosterone undecanoate 1000 mg followed by a second 1000-mg injection 6 wk later, and then 1000 mg every 10 to 14 wk. Physicians in countries where these formulations are available should follow the approved drug regimens. See Tables 6 and 8 for additional safety and pharmacokinetics information.

Table 5. Commonly Prescribed Hormone Therapies

Preparation	Doses	Comments
Systemic estrogen therapies[a]		
Oral estrogen tablets		
Micronized E2	0.5, 1.0, 2.0 mg/d	
Estradiol valerate[b]	1.5 mg/d	
CEE	0.3, 0.45, 0.625 mg/d	Higher doses available Preparation used in WHI
Transdermal estrogens		
Estradiol patch	0.025 to 0.1 mg once or twice weekly depending on preparation 0.014 mg/wk	Corresponds to 0.5 to 2.0 mg estradiol tablets Diffusion can be different from one patch to another Preserved bone in women >60 y old
Estradiol percutaneous gel	0.25–1.5 mg qd	Corresponds to 0.5 to 2.0 mg estradiol tablets Can be transferred to persons and pets by skin contact
Estradiol transdermal spray	1.5 mg qd	Estradiol via spray Can be transferred to persons and pets by skin contact
Vaginal ring		
Estradiol acetate	0.05–0.10 mg/d	Systemic levels of estradiol provide relief of VMS; 90-d duration/ring
Progestogen therapies		
Oral progestin tablets		
Medroxyprogesterone acetate	2.5, 5, 10 mg/d	Utilized in WHI
Norethindrone	0.35 mg/d	
Neta	5.0 mg/d	
Megestrol acetate	20, 40 mg/d	
Dydrogesterone[b]	10 mg/d	
Chlormadinone acetate[b]	5, 10 mg/d	
Medrogestone[b]	5 mg/d	
Nomegestrol acetate[b]	3.75, 5 mg/d	
Promegestone[b]	0.125, 0.25, 0.5 mg/d	
Oral progesterone capsule		
Micronized progesterone	100, 200 mg/d	In peanut oil; avoid if peanut allergy. May cause drowsiness and should be taken at bedtime
Intrauterine system progestin[c]		
LNorg	20 μg released/d 6 μg/d	IUD for 5-y use IUD for 3-y use
Vaginal gel progesterone[c]	4%, 8%	45- or 90-mg applicator
Combination hormone therapies		
Oral		
CEE + MPA	0.3–0.625 mg/1.5–5 mg/d	Cyclic or continuous
E2 + Neta	0.5–1 mg/0.1–0.5 mg/d	Continuous
E2 + drospirenone	0.5–1 mg/0.25–1 mg/d	Continuous
E2 + norgestimate	1 mg/0.09 mg/d	Cycle 3 d E alone, 3 d E + progesterone
E2 + dydrogesterone[b]	1–2 mg/5–10 mg/d	Cyclic and continuous
E2 + cyproterone acetate[b]	2 mg/1 mg/d	Continuous
E2 + MPA[b]	1–2 mg/2–10 mg/d	Continuous
CEE + BZA[d]	0.45 mg/20 mg/d	Continuous
Transdermal		
E2 + Neta	50 μg/0.14–0.25 mg/patch	Twice weekly
E2 + LNorg	45 μg/0.015 mg/patch	Once weekly

Abbreviations: IUD, intrauterine device; E, estrogen; E2, 17-β estradiol; LNorg, levonorgestrel; Neta, norethindrone acetate or norethisterone