

## SPECIAL FEATURE

# The North American Menopause Society Recommendations for Clinical Care of Midlife Women

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for the NAMS Recommendations for Clinical Care of Midlife Women Working Group

In celebration of the 25th anniversary of The North American Menopause Society (NAMS), the Society has compiled a set of key points and clinical recommendations for the care of midlife women. NAMS has always been a premier source of information about menopause for both healthcare providers and midlife women. At this special time in the history of the Society, we wished to provide a succinct guide to improve the understanding and management of women's health at this critical stage of life. In addition to covering the key topics of vasomotor symptoms, osteoporosis, and vulvovaginal health, this guide includes information and recommendations for care on more than 50 important topics, including sexual function, cognition, cardiovascular health, thyroid disease, and cancers. Additional sections review basic physiology, counseling issues, screening tests, and complementary and alternative medicine.

The basis for these key points and clinical recommendations is the NAMS premier textbook, *Menopause Practice: A Clinician's Guide*. Published originally in 2000 and updated approximately every three years to remain current, this clinical practice textbook provides in-depth coverage of all areas of interest to clinicians who care for women at midlife. Each topic is written by an expert in the field, including internationally recognized gynecologists, internists, medical and reproductive endocrinologists, cardiologists, neurologists, psychiatrists, psychologists, dermatologists, oncologists, and counselors. Relevant research is described in detail, and each topic is accompanied by an extensive list of references. NAMS Recommendations for the Clinical Care of Midlife Women, published in this edition of *Menopause*, will be freely available on the NAMS website to promote high-quality care for women throughout the world. These recommendations provide a brief overview of each topic presented in the textbook. Clinicians who wish to learn more about a given topic area, review relevant research, and access related references are encouraged to expand their knowledge by purchasing *Menopause Practice: A Clinician's Guide*, 5th edition, available through the NAMS website.

NAMS Recommendations for the Clinical Care of Midlife Women was developed by asking each author of every section of the textbook to submit a brief summary of their topic, including several key points and recommendations for clinical care. Each topic was carefully reviewed, edited, and approved

by an Editorial Panel, with final review and approval by the 2013-2014 NAMS Board of Trustees. The Editorial Panel was comprised of experts in midlife women's health from a wide range of specialties who devoted significant time and effort to ensuring the accuracy and relevance of each key point and clinical recommendation. Every clinical recommendation is accompanied by a level of evidence, and the strength of each recommendation is based on the highest level of evidence found in the data.

Recommendations are provided and graded according to the following categories:

- Level I—based on good and consistent scientific evidence.
- Level II—based on limited or inconsistent scientific evidence.
- Level III—based primarily on consensus and expert opinion.

We hope that these evidence-based recommendations will be a valuable resource for clinicians and further the mission of NAMS, at its 25th anniversary, to promote the health and quality of life of all women during midlife and beyond.

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**CHAPTER 1: MENOPAUSE****OVERVIEW OF MENOPAUSE****Key Points**

1. Menopause is a normal physiologic event, defined as the final menstrual period (FMP) and reflecting loss of ovarian follicular function.
2. *Spontaneous* or *natural* menopause is recognized retrospectively after 12 months of amenorrhea. It occurs at an average age of 52 years, but the age of natural menopause can vary widely from 40 to 58 years. *Induced menopause* refers to the cessation of menstruation that occurs after either bilateral oophorectomy or iatrogenic ablation of ovarian function (eg, by chemotherapy or pelvic radiation).
3. The Stages of Reproductive Aging Workshop (STRAW) established a nomenclature and a staging system for the female reproductive aging continuum in 2001, which was revised in 2011 with the STRAW + 10 staging system.
4. According to STRAW + 10, the term *menopause transition* refers to the span of time when menstrual cycle and endocrine changes occur, beginning with variation in the length of the menstrual cycle and ending with the FMP.
5. *Primary ovarian insufficiency* describes a transient or permanent loss of ovarian function leading to amenorrhea in women aged younger than 40 years. This condition affects approximately 1% of women. *Early menopause* describes menopause occurring in women aged 40 to 45 years and is experienced by approximately 5% of women. *Premature menopause* can be used to refer to definitive cases of menopause before age 40, such as with the surgical removal of both ovaries.
6. By the year 2025, the number of postmenopausal women is expected to rise to 1.1 billion worldwide.

**Recommendations for Clinical Care**

1. Menopause can be viewed as a sentinel event that affords a unique opportunity for a dialogue between women and their healthcare providers to evaluate and improve health-related practices. (Level II)
2. Menopause counseling, including discussion of physiologic changes, assessment of menopause-related symptoms and treatment options, review of screening recommendations, and discussion of disease risk-reduction strategies and psychosocial issues, facilitates informed decision making among midlife and older women. (Level II)
3. By considering women's concerns, values, and preferences, menopause practitioners have the potential to enhance women's sense of well-being, not only at menopause but for the remainder of their lives. (Level III)

## OVARIAN AGING AND HORMONE PRODUCTION

### Key Points

1. The menopause transition reflects the natural decline of ovarian follicular estrogen production. It is characterized by a number of menstrual cycle changes, with increasing episodes of amenorrhea. As ovarian production of estradiol diminishes further, complete absence of menstrual bleeding ensues.
2. Menopause is defined retrospectively as the final menstrual period, occurring on average at age 52 years and diagnosed after 12 consecutive months of amenorrhea.
3. Symptoms of the menopause transition, primarily vasomotor symptoms (VMS), cluster in the 2-year window immediately before and after the FMP, but may continue for many years in some women.
4. Characteristic changes in the hypothalamic-pituitary-ovarian (HPO) axis during the menopause transition result from decreased ovarian feedback of inhibin and estradiol and are manifested primarily as elevations in follicle-stimulating hormone (FSH). Although central mechanisms may contribute to reproductive aging, they are less well characterized.
5. Adrenal changes concurrent with the menopause transition include elevations in serum cortisol and transient elevations in dehydroepiandrosterone sulfate, androstenediol, and other adrenal androgens.
6. Understanding sex steroid receptor function facilitates development of pharmacologic agents that selectively manipulate these receptors and effect a diverse array of clinical outcomes.

### Recommendations for Clinical Care

1. The onset and course of the menopause transition is best determined by menstrual-cycle monitoring with a paper or electronic menstrual calendar designed for this purpose. (Level I)
2. Given the erratic nature of ovarian function during the menopause transition, hormonal measurements are difficult to interpret and in most instances should be avoided. (Level II)
3. Although determinants of ovarian reserve, including levels of antimüllerian hormone (AMH), cycle day-3 FSH and estradiol, and ovarian antral follicle count, are available, their clinical use is best confined to counseling women seeking fertility rather than predicting time to menopause. (Level I)
4. In healthy nonsmokers, low-dose oral contraceptives may be considered for the treatment of heavy or irregular bleeding during the menopause transition. These improve bleeding in part by reducing wide excursions in HPO hormone secretion. (Level I)
5. As bothersome VMS may begin well before the cessation of menses, healthcare providers should ask their midlife patients about VMS and provide information regarding therapeutic options, even if they are still cycling. (Level II)

6. Given that ovulatory cycles occur during the menopause transition, contraception is recommended until women have experienced 12 months of amenorrhea. (Level I)
7. The risk of endometrial pathology is increased at the menopause transition because serum estrogen concentrations are intermittently elevated and ovarian progesterone production is diminished. Any heavy or irregular bleeding at midlife should be thoroughly evaluated. (Level I)

## PREMATURE MENOPAUSE AND PRIMARY OVARIAN INSUFFICIENCY

### Key Points

1. *Natural menopause* occurs at approximately age 52 years. *Premature menopause* is a general term used to describe menopause that occurs before age 40 years.
2. *Primary ovarian insufficiency* (POI) is the preferred term for premature ovarian failure, because this condition can be transient and can wax and wane.
3. Primary ovarian insufficiency can arise from either decreased ovarian reserve or from ovarian follicular dysfunction. Although the etiology of POI is often idiopathic, it may be caused by genetic abnormalities, metabolic disturbances, pelvic surgery, radiation therapy, chemotherapy, or immune disorders.
4. Treatment for menopausal symptoms associated with POI can include hormonal and nonhormonal approaches.

### Recommendations for Clinical Care

1. Evaluation of POI is warranted for any woman aged younger than 40 years who misses three or more consecutive menstrual cycles. (Level I)
2. The baseline evaluation should include assays for human chorionic gonadotropin (hCG), FSH, estradiol, prolactin, and thyroid-stimulating hormone (TSH). The diagnosis of POI is confirmed by two elevated FSH levels drawn at least 1 month apart. (Level I)
3. Further assessment of ovarian reserve with an AMH level and/or vaginal ultrasound determination of antral follicle count can be helpful in counseling and management. (Level II)
4. For women with suspected POI, additional evaluation should include a karyotype and testing for a fragile X premutation, thyroid peroxidase antibodies, adrenal antibodies, fasting glucose, and serum calcium and phosphorus levels. Given that autoimmune endocrinopathies can evolve over time, ongoing surveillance in addition to baseline assessment is advised. (Level II)
5. In women anticipating cancer treatment during the reproductive years, urgent referral to a fertility specialist should be considered for counseling regarding future childbearing and fertility-preservation options. Fertility counseling later in the course of cancer treatment is also important. (Level II)

- Hormone therapy or estrogen-containing hormonal contraception, if not contraindicated, is advised to treat menopause symptoms and preserve bone mineral density in women with premature menopause or POI. (Level I)

## CHAPTER 2: MIDLIFE BODY CHANGES

### VULVOVAGINAL CHANGES

#### Key Points

- Postmenopausal estrogen loss and aging accompanied by physiologic, vascular, neurologic, and histologic changes may result in vulvovaginal symptoms, including irritation, burning, itching, vaginal discharge, postcoital bleeding, and dyspareunia.
- Genitourinary syndrome of menopause (GSM), a syndrome that encompasses symptomatic vulvovaginal atrophy (VVA), may have a significant impact on the quality of life of midlife women, with effects on sexual function and interpersonal relationships.
- Women of any age with low estrogen levels, including women with primary ovarian insufficiency, premature menopause, hypothalamic amenorrhea, or hyperprolactinemia; during lactation; or after treatment with gonadotropin-releasing hormone (GnRH) agonists/antagonists or aromatase inhibitors, may experience symptoms of GSM/VVA.
- The presentation, diagnosis, and treatment of vulvovaginitis caused by candida, bacterial vaginosis, or trichomoniasis in postmenopausal women are the same as in premenopausal women.
- Vulvar dystrophies (including lichen sclerosis, lichen planus, and squamous cell hyperplasia/lichen simplex chronicus) and vulvar dysplasia or cancer may present with vulvovaginal symptoms, with pelvic examination revealing focal lesions, white plaques, denuded areas, or skin thickening.

#### Recommendations for Clinical Care

- All perimenopausal and postmenopausal women should be asked about vulvovaginal and urinary symptoms at every comprehensive visit. (Level II)
- Examination of the postmenopausal vulva and vagina should include visual inspection for plaques, skin thickening, discoloration, or lesions. White, pigmented, or thickened vulvar or vaginal lesions should be biopsied to obtain an accurate diagnosis and to rule out a premalignant or malignant condition. (Level I)
- Any bleeding in a postmenopausal woman, including postcoital bleeding, requires a thorough evaluation. (Level I)

### BODY WEIGHT

#### Key Points

- The average amount of weight gained over the menopausal transition is 5 lb (2.3 kg). Weight gain is more

likely to be related to aging and lifestyle changes than to menopause itself.

- Obesity is associated with a variety of adverse health conditions and more severe vasomotor symptoms during the menopause transition.
- A daily caloric deficit of 400 kcal to 600 kcal, regular physical activity, low fat intake, consumption of fruits and vegetables, and ongoing behavior support all have been associated with sustained weight loss.
- The implementation of the American Heart Association's general diet and lifestyle recommendations may decrease the risk of cardiovascular and noncardiac disease.
- Pharmacologic options for weight loss include phentermine HCl, diethylpropion, orlistat, lorcaserin, and phentermine/topiramate extended release.
- Surgical options for weight loss include restrictive procedures, malabsorptive procedures, and mixed procedures; bariatric surgery generally effects greater weight loss in the morbidly obese and higher rates of resolution of comorbid conditions than lifestyle or pharmacologic options.

#### Recommendations for Clinical Care

- All adults should be screened for obesity and offered intervention based on their body mass index (BMI) and the presence of comorbidities. (Level I)
- Pharmacologic intervention should be considered as part of a comprehensive program including diet and physical activity in women with a BMI greater than 30 kg/m<sup>2</sup> or BMI greater than 27 kg/m<sup>2</sup> with comorbidities. (Level II)
- Bariatric surgery should be considered for women with a BMI of 40 kg/m<sup>2</sup> or higher or a BMI greater than 35 kg/m<sup>2</sup> with comorbidities who have failed conservative measures. (Level II)

### SKIN

#### Key Points

- Skin changes associated with menopause include decreased skin thickness and elasticity, loss of collagen, increased laxity, and wrinkling.
- More marked aging of the skin occurs with exposure to certain environmental factors, principally chronic sun exposure and smoking. Signs of skin aging include wrinkling, dyspigmentation, telangiectasias, roughness, and dryness.

#### Recommendations for Clinical Care

- Healthcare providers should encourage women to reduce sun exposure and not smoke to minimize adverse skin changes caused by environmental factors and aging. (Level I)
- To reduce photo damage to the skin, women should be advised to avoid midday sun, use sunscreen consistently, wear protective hats and clothing, and avoid tanning salons. (Level I)

## HAIR

### Key Points

1. Hair changes, including hair loss and excessive hair growth, are common during the menopause transition and postmenopause.
2. Multiple factors, including hormonal changes at menopause, genetic predisposition, and stress, contribute to midlife hair changes.
3. Female pattern hair loss (FPHL), also known as androgenetic alopecia, and telogen effluvium are the most common patterns of hair loss.
4. The increase in the ratio of androgen to estrogen during the midlife transition may influence hair changes in women. This is evidenced by the increase in hair density that can be attained with antiandrogen treatments in some women.

### Recommendations for Clinical Care

1. Before initiating treatment for hair loss or hirsutism, a thorough clinical history is required, including the onset, duration, pattern, and amount of hair loss or excess hair growth. Medical conditions and medications may contribute to hair loss or hirsutism and should be reviewed. Testing for androgen excess, chronic iron deficiency, or thyroid disorders may be indicated. (Level I)
2. Topical minoxidil 5% used once daily is an FDA-approved treatment of FPHL. Minoxidil combined with an antiandrogen such as spironolactone is commonly used in women with FPHL, although there is limited evidence to support this approach. (Level II)
3. Women with FPHL and measurable androgen excess respond differently to antiandrogen therapy compared with women with FPHL and normal androgen levels. The efficacy of antiandrogens in either group of women remains unproven because there have been no large randomized, controlled trials (RCTs) investigating antiandrogens in perimenopausal or postmenopausal women with FPHL. (Level II)
4. Hormone therapy (HT) supports hair growth as it supports other skin structures, but hair loss is not an indication for HT use. (Level II)
5. Antidandruff shampoos such as ketoconazole 2% and zinc pyrithione 1% may be used to promote scalp hair growth. Camouflaging topical sprays or keratin fibers may be used as an alternative to achieve sufficient density for the frontal hair loss in FPHL. (Level II)
6. Treatment for hirsutism focuses on a combination of hormonal therapies, peripheral androgen blockage, and mechanical depilation. Eflornithine hydrochloride is an FDA-approved topical cream that reduces the growth of unwanted facial hair in women. Waxing, bleaching, shaving, and laser treatment are other options for managing hirsutism. (Level II)

## EYES

### Key Points

1. One of the most common ocular complaints associated with menopause is dry eyes. Women report worse dry eye symptoms and more impact of these symptoms on daily life than do men.
2. Effective treatments for dry eyes include topical lubricants, punctal occlusion, and anti-inflammatory agents.
3. The prevalence of cataracts is higher in postmenopausal women than men of the same age.
4. The relationship between menopausal hormone therapy and glaucoma risk is complex, and further study is needed.
5. Age-related macular degeneration (AMD) is the leading cause of blindness in the United States. Although women are not at increased risk of AMD compared with men, there are more women than men with AMD due to their greater longevity.

### Recommendations for Clinical Care

1. Healthcare providers should ask midlife women about eye symptoms, encourage regular eye exams, and refer for ophthalmologic consultation when indicated. (Level I)
2. As menopausal HT increases the risk of dry eye symptoms, women on HT with bothersome dry eyes should be informed of this association. (Level III)

## EARS

### Key Points

1. Hearing impairment increases beyond age 50 years and is associated with depression and social withdrawal.
2. Hearing loss can result from a variety of causes, including aging, head injuries, tumors, infections, ear wax, lengthy exposure to very loud noises, and possibly loss of reproductive hormones.
3. It is unclear whether the menopause transition acts as a trigger for more rapid progression of hearing loss.
4. Physiologic levels of estrogen may preserve hearing, but estrogen-progestogen hormone therapy may have a small negative effect.

### Recommendations for Clinical Care

1. Women experiencing hearing loss at midlife should undergo a thorough evaluation, with treatment provided if indicated (Level I).

## TEETH AND ORAL CAVITY

### Key Points

1. Tooth loss is associated with decreased skeletal bone mineral density (BMD), especially in the upper jaw.
2. Women with low BMD are more susceptible to periodontal disease.
3. Long-term oral bisphosphonate use may delay healing in alveolar bone, especially when periodontal disease also is present.

4. Estrogen deficiency is associated with gingival thinning and recession. Hormonal fluctuations also may increase periodontal inflammation and susceptibility to oral lesions.

#### Recommendations for Clinical Care

1. Midlife women should undergo regular dental and periodontal examinations, with cleanings and dental treatments as needed. (Level I)
2. Women should maintain good oral hygiene beyond menopause, including the regular use of fluoride-containing toothpaste and/or mouth rinses. (Level I)
3. Postmenopausal women should maintain bone health as part of supporting dental and periodontal health. They should inform their dental care providers of the results of BMD testing and the use of related medications. (Level II)

### CHAPTER 3: CLINICAL ISSUES

#### DECLINE IN FERTILITY

##### Key Points

1. Fertility declines with increasing age, notably after age 35 years, or approximately 15 years before menopause. Age-related declines in fertility have been confirmed in epidemiologic studies as well as by the observation of declining pregnancy rates with advancing age in cycles of donor insemination and in vitro fertilization (IVF).
2. Advanced maternal age ( $\geq 35$  years) is associated with increased risks for spontaneous miscarriage (50% by age 45 years), chromosomal abnormalities in the fetus, and other pregnancy complications including premature labor, fetal mortality, and the need for cesarean delivery.
3. Diminished ovarian reserve is associated with decreased oocyte quality, oocyte quantity, and ability to conceive. There is no single ideal test for assessing ovarian reserve. Options include measurement of FSH and estradiol levels on cycle day 3, clomiphene citrate challenge testing, ovarian antral follicle count by transvaginal ultrasound, and AMH levels.
4. Age-related anatomic changes such as fibroids, tubal disease, or endometriosis may contribute to decreased fertility with advancing age.
5. For women with infertility due to advanced reproductive age, controlled ovarian hyperstimulation with intrauterine insemination and IVF may increase the likelihood of pregnancy. For women with significantly decreased ovarian reserve, IVF with oocyte donation and adoption are options for family building. Gestational carriers may be advised for women at high risk for adverse outcomes during pregnancy.
6. The success of infertility treatment depends on the woman's age, ovarian reserve, general health, indications for treatment, and the treatment modality used, with success rates decreasing with increasing age.

#### Recommendations for Clinical Care

1. Women should be counseled about the increased risk of infertility and adverse pregnancy outcomes with advancing age. (Level II)
2. Fertility treatment with a woman's own oocytes generally is not advised after age 43 years because of the extremely low likelihood of a successful pregnancy. Any fertility treatment, including donor-oocyte IVF, is not recommended after age 50 years because of increased risks associated with pregnancy. (Level II)
3. The success of oocyte-donation IVF in women in their 50s and even early 60s confirms that pregnancy is possible in women with a normal uterus, regardless of age or the absence of oocytes. (Level II)
4. In older women undergoing oocyte-donation IVF, single-embryo transfer should be strongly considered because of the risks associated with multiple births. (Level II)
5. Women of advancing age considering donor-oocyte IVF should be counseled about parenting issues and health concerns specific to their age and the age and health of their partners. (Level II)

#### UTERINE BLEEDING

##### Key Points

1. Approximately 90% of women experience 4 to 8 years of menstrual cycle changes before natural menopause, which may include heavier flow of longer duration resulting in anemia, avoidance of activities (including sex), and diminished quality of life.
2. Early perimenopause is characterized by disturbances in the timing and regulation of ovulation, whereas late perimenopause is characterized by decreased ovulation. Prolonged anovulation may lead to unopposed estrogen exposure, increasing the risk of endometrial hyperplasia and cancer.
3. Approximately 80% of women treated for heavy menstrual bleeding have no anatomic pathology. In addition to perimenopausal anovulation, irregular bleeding can be caused by anovulation associated with thyroid abnormalities, hyperprolactinemia, or polycystic ovarian syndrome. Anatomic causes of abnormal uterine bleeding (AUB) include polyps, fibroids, endometritis, endometrial hyperplasia, and cancer.
4. Evaluation of AUB may include the following laboratory tests, based on the clinical situation: complete blood count, pregnancy test, coagulation profile, sexually transmitted infection panel, liver function tests, and levels of thyroid-stimulating hormone, prolactin, follicle-stimulating hormone, estradiol, progesterone, testosterone, and dehydroepiandrosterone sulfate. Procedures may include cervical cytology, transvaginal ultrasonography, saline infusion sonohysterography, office hysteroscopy, office endometrial sampling, and dilation and curettage.

5. Medical management is the least invasive and least expensive means of controlling heavy and/or irregular uterine bleeding, although adverse effects and poor compliance may limit success. Nonhormonal agents used to manage AUB include nonsteroidal anti-inflammatory agents, tranexamic acid, and desmopressin for women with an underlying bleeding disorder.
6. Hormonal options for managing AUB include low-dose oral contraceptives, cyclic oral progestogens, depot medroxyprogesterone acetate injections, the levonorgestrel-releasing intrauterine system, and gonadotropin-releasing hormone (GnRH) agonists. The use of GnRH agonists is limited by their expense and resulting hot flashes and bone loss. Estrogen-containing contraceptives generally should not be used in women aged older than 35 years who smoke or in perimenopausal women at increased risk for cardiovascular disease. Management of AUB represents off-label use for most hormonal therapies.
7. Surgical options for managing AUB include endometrial ablation techniques, polypectomy, myomectomy, and hysterectomy. Although endometrial ablation represents a relatively effective and safe intervention, women must be informed that these procedures may impede the diagnosis of endometrial cancer later in life because of reduced bleeding, an early sign of cancer, and difficulty sampling the endometrium. Minimally invasive surgical approaches, including hysteroscopy and laparoscopy, are often an option.

#### Recommendations for Clinical Care

1. Pregnancy must be excluded in any sexually active woman of reproductive age who presents with AUB. (Level I)
2. Perimenopausal women with AUB and postmenopausal women with any bleeding require a comprehensive evaluation. (Level I)
3. Once pathology has been excluded, management of AUB may be medical (hormonal and/or nonhormonal) or surgical. Management should be individualized based on personal preferences, the need for contraception, menopause status, underlying medical problems, and the degree of bleeding and its impact on a woman's health and quality of life. (Level II)

#### VASOMOTOR SYMPTOMS

##### Key Points

1. Hot flashes occur in up to 75% of women. Although most women experience them for 6 months to 2 years, some women may experience bothersome hot flashes for 10 years or longer.
2. Lifestyle changes, including keeping body temperature low, maintaining a healthy body weight, refraining from smoking, exercising regularly, and practicing relaxation techniques, may provide some relief.
3. Nonprescription remedies such as soy, isoflavone supplements, black cohosh, vitamin E, and omega-3 fatty

acids are generally low risk but with efficacy generally similar to placebo.

4. Menopausal hormone therapy is the most effective treatment for vasomotor symptoms. Options include systemic estrogen, estrogen-progestogen, estrogen-bazedoxifene, progestogen alone, or combined oral contraceptives in women requiring contraception.
5. The selective estrogen receptor modulator bazedoxifene combined with conjugated estrogen is FDA approved for the treatment of hot flashes.
6. Custom-compounded *bioidentical hormones* are not recommended because of lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures.
7. Selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors that have been shown to be more effective than placebo for hot flashes include paroxetine, escitalopram, venlafaxine, and desvenlafaxine; paroxetine 7.5 mg is the only SSRI approved by FDA for this indication.
8. Gabapentin and clonidine reduce hot flashes but have not been approved by FDA for this indication.

#### Recommendations for Clinical Care

1. Treatment for hot flashes should be considered if symptoms are bothersome, disrupt sleep, or adversely affect quality of life. Therapy should be tailored to the individual woman's medical history, treatment goals, and personal attitudes toward menopause and medication use. (Level I)
2. The decision to initiate therapy for hot flashes, the type of therapy elected, and the duration of treatment should be individualized for each woman, with consideration given to comorbid conditions, the severity of symptoms, and the potential risks of treatment. (Level II)
3. The need for treatment should be periodically evaluated as most women will experience improvement in vasomotor symptoms over time. The need for extended treatment of persistent, bothersome hot flashes requires an individualized assessment of risks and benefits. (Level II)

#### GENITOURINARY SYNDROME OF MENOPAUSE/ SYMPTOMATIC VULVOVAGINAL ATROPHY

##### Key Points

1. Genitourinary syndrome of menopause (GSM) is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired sexual function; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTIs).

2. Symptoms of GSM/VVA can have a negative effect on quality of life that may extend to activities of daily living, exercise, sexual function, and interpersonal relationships.
3. Treatment for GSM/VVA includes nonhormonal vaginal lubricants and moisturizers, low-dose vaginal estrogen therapy (ET), systemic ET (when being prescribed for treatment of bothersome vasomotor symptoms), and ospemifene (an oral estrogen agonist/antagonist).
4. Low-dose vaginal ET results in minimal systemic absorption.
5. Vaginal ET, but not systemic ET, reduces the risk of recurrent UTIs.

#### Recommendations for Clinical Care

1. Healthcare providers should ask all perimenopausal and postmenopausal women about vulvovaginal and urinary symptoms at every comprehensive visit. (Level II)
2. Women with GSM/VVA should consider nonhormonal vaginal lubricants and moisturizers as initial therapy. (Level II)
3. Low-dose vaginal ET (available as a cream, tablet, or ring) is a highly effective treatment for persistent symptoms of GSM/VVA. (Level I)
4. The estrogen agonist/antagonist ospemifene is an oral agent for the treatment of moderate to severe dyspareunia due to GSM/VVA. (Level I)
5. Progestogen therapy for endometrial protection is not recommended with the use of low-dose vaginal ET, although studies of endometrial safety with vaginal ET do not extend beyond 1 year. (Level I)
6. Postmenopausal women with recurrent UTIs may consider treatment with low-dose vaginal ET or prophylactic antibiotics. (Level I)
7. Any bleeding in a postmenopausal woman, including postcoital bleeding, requires a thorough evaluation. (Level I)
8. All women with GSM/VVA should be counseled about available management strategies and provided with information about the efficacy, risks, and benefits of non-hormonal and hormonal interventions. (Level II)

#### URINARY INCONTINENCE

##### Key Points

1. Approximately 50% of midlife women report urinary incontinence, but embarrassment and lack of awareness about effective treatment options prevent many women from seeking treatment.
2. Although the prevalence of urinary incontinence increases with age, there is no strong association between urinary incontinence and menopause.
3. Stress incontinence (leakage with increases in intra-abdominal pressure) is related to poor urethral support, urethral sphincter weakness, and/or dysfunction of the pelvic floor muscles, whereas urgency incontinence (leakage with a sense of urinary urgency) is caused by uninhibited contractions of the detrusor muscle.

4. Evaluation of urinary incontinence should focus on defining the type(s) of incontinence a woman experiences so that type-specific treatments can be offered.

#### Recommendations for Clinical Care

1. Healthcare providers should ask midlife women about bothersome urinary incontinence symptoms at every comprehensive visit. (Level II)
2. Most stress incontinence can be successfully treated with behavioral therapies (eg, weight loss), pelvic floor muscle therapy (Kegel exercises, physical therapy), and pessaries. (Level II)
3. Surgery for stress incontinence (most commonly midurethral slings) has a success rate of approximately 85%, although long-term (>5 years) effectiveness is not well established. (Level I)
4. Most urgency incontinence can be successfully managed with behavioral therapies (eg, caffeine and fluid restriction), bladder retraining, and anticholinergic medications. (Level I)
5. Vaginal estrogen therapy may improve symptoms of irritative voiding and urinary urgency. (Level II)
6. Botox injections and sacral neuromodulation treatments are generally reserved for urgency incontinence symptoms associated with detrusor overactivity after more conservative treatment options have failed. (Level I)

#### SEXUAL FUNCTION

##### Key Points

1. Sexual problems are highly prevalent in midlife women and often associated with distress.
2. Hormonal changes at menopause as well as other physiological, psychological, sociocultural, interpersonal, and lifestyle factors contribute to midlife sexual problems.
3. Dyspareunia due to vaginal atrophy is an important and treatable cause of sexual problems after menopause.
4. Although testosterone levels decline with age, an association between low testosterone levels and impaired female sexual function has not been demonstrated.

#### Recommendations for Clinical Care

1. Healthcare providers should ask midlife women about sexual concerns at every comprehensive visit. (Level II)
2. Counseling and sex therapy, with a focus on modifying sexual technique, increasing sexual novelty, and enhancing the partner relationship and communication, are effective interventions for many individuals and couples with sexual problems. (Level II)
3. Symptomatic vulvovaginal atrophy may be treated with vaginal moisturizers, lubricants, low-dose vaginal estrogen therapy, and ospemifene. Choice of therapy depends on the severity of symptoms and the woman's medical history and personal preferences. Dyspareunia independent of VVA may improve with pelvic floor physical therapy. (Level II)

4. Treatment of underlying depression and anxiety and adjustment of antidepressant medication may be helpful for problems of sexual interest and arousal. Bupropion and PDE-5 inhibitors may have a role in the treatment of SSRI-induced sexual dysfunction. (Level II)
5. There is some evidence to support the use of testosterone therapy in carefully selected postmenopausal women with female sexual interest/arousal disorder (previously known as hypoactive sexual desire disorder) and no other etiology for their sexual problem, although a formulation designed for women and long-term safety data are lacking. (Level I)

## SLEEP DISTURBANCE

### Key Points

1. Chronic sleep disturbance can have important consequences for daytime functioning, overall well-being, health, and public safety.
2. Women undergoing the menopause transition are more likely to report reduced sleep quality, and those with hot flashes are more likely to report disturbed sleep and meet criteria for chronic insomnia.
3. Primary sleep disorders of insomnia, sleep apnea, and restless legs syndrome are common in midlife women.
4. Sleep disturbance is a common symptom of clinical depression, which occurs more frequently during the menopause transition.
5. Women with vasomotor symptoms report improved sleep quality when they receive hormonal and nonhormonal medication treatments for hot flashes.
6. Cognitive-behavior therapy (CBT) is a safe and effective treatment for insomnia.

### Recommendations for Clinical Care

1. Women reporting disturbed sleep during midlife should be evaluated, and the specific causative condition should be identified and treated. (Level II)
2. Women with bothersome nighttime hot flashes may experience improved sleep quality when their hot flashes are treated with hormonal or nonhormonal medications. (Level I)
3. Pharmacologic sleep aides are effective treatments for insomnia and sleep disturbance, but their use should be time limited. Behavioral strategies, including sleep hygiene and CBT, also are effective. (Level I)
4. Women whose sleep disturbance may be attributable to clinical depression, sleep apnea, or restless legs syndrome/periodic limb movement disorder should be referred for diagnosis and treatment. (Level II)

## HEADACHE

### Key Points

1. The World Health Organization ranks headache disorders in the top five most disabling conditions for women.
2. Although most primary headaches are tension type, the majority of women who present to an outpatient clinic

- with a chief complaint of headache meet the criteria for migraines, and half do not receive appropriate treatment.
3. Certain headache characteristics should trigger heightened concern and consideration of further investigation. These include “worst ever,” new onset at age older than 50 years, sudden onset during activity, increased frequency or severity, and associated nocturnal awakening. A headache accompanied by stiff neck, high fever, confusion, dizziness, weakness, or focal neurologic signs generally requires further evaluation, as does a headache in the setting of malignancy, immunosuppression, or systemic infection.
  4. Migraines without aura are much more common than migraines with aura. Women with migraine without aura often experience improvement in headache frequency and severity with menopause. Improvement with menopause is less likely in those whose headaches are associated with aura.
  5. Migraine with aura is associated with a significant increased risk of stroke, especially in women who smoke or use oral contraceptives.

### Recommendations for Clinical Care

1. Nonsteroidal anti-inflammatory drugs are generally the most effective therapy for tension-type headaches, whereas tricyclic antidepressants are most effective for prophylaxis. (Level II)
2. Migraines should be considered more frequently in the differential of headache when accompanied by nausea, vomiting, photophobia, or phonophobia. (Level I)
3. Women with migraines should keep a diary of their potential triggers to identify possible avoidance strategies for prevention. (Level I)
4. Combination oral contraceptives should be avoided in women with migraines with significant comorbidities for stroke, including those with aura at any age, those without aura who are older than 35 years, and those who smoke. (Level I)
5. Postmenopausal women with migraines and bothersome vasomotor symptoms may use hormone therapy at doses typically prescribed for midlife women. Hormone therapy may improve or worsen headaches. Continuous rather than cyclic HT is advised because changes in hormone levels may trigger a headache. (Level II)
6. Women with migraines with aura should be advised to stop smoking. (Level I)

## COGNITION

### Key Points

1. Symptoms of poor concentration, poor memory, and trouble multitasking are common during the menopause transition and early postmenopause.
2. Memory performance and processing speed decline slightly during the menopausal transition but appear to return to premenopausal levels after menopause.

Menopausal symptoms may be associated with cognitive complaints.

3. Cognitive symptoms can be influenced by sleep disturbances, depressed mood, hot flashes, fatigue, physical symptoms, medication use, and a variety of midlife stressors.
4. Hormone therapy does not substantially affect memory, attention, or higher order cognitive skills.
5. Early removal of the ovaries is associated with an increased risk of dementia that may be offset by use of estrogen therapy until the typical age at menopause.
6. Combined HT begun after age 65 years increases the risk of dementia.

#### Recommendations for Clinical Care

1. For midlife women with cognitive symptoms, healthcare providers should explain that such symptoms are common and appear to improve after the menopausal transition. They should review medication use and evaluate and treat, as appropriate, sleep disturbances, depressed mood, hot flashes, fatigue, physical symptoms, and situational stressors. (Level II)
2. Healthcare providers should consider additional evaluation for midlife women with cognitive impairment, cognitive symptoms accompanied by functional impairment, or a family history of dementia beginning before age 60 years. (Level II)
3. Women who undergo oophorectomy before age 48 years may be advised that taking ET until the typical age at menopause appears to lower the risk of dementia later in life. (Level II)
4. In perimenopausal and postmenopausal women, HT should not be used to improve cognitive skills. (Level III)
5. In older postmenopausal women, HT should not be used to prevent dementia or treat Alzheimer disease. (Level I)
6. Interventions that reduce cardiovascular risk, including smoking cessation, weight management, regular aerobic exercise, and control of diabetes, hypertension, and hyperlipidemia, also may reduce the risk of cognitive decline. (Level II)

#### PSYCHOLOGICAL SYMPTOMS

##### Key Points

1. Most women do not become clinically depressed during the menopause transition; however, psychological symptoms, including depressed mood, anxiety, and decreased sense of well-being are common.
2. Women with a history of a mood or anxiety disorder and early childhood stressful life events are at higher risk of increased psychological symptoms during the menopause transition. A history of premenstrual syndrome or postpartum depression is a strong risk factor for mood symptoms at midlife.
3. Life stressors are common at midlife and often coincide with the menopause transition.

#### Recommendations for Clinical Care

1. Healthcare providers should screen for psychological symptoms at midlife and treat psychological problems when indicated or provide appropriate referrals. (Level II)
2. Mild depressive symptoms respond well to psychotherapy. Moderate or severe depressive symptoms generally require pharmacologic treatment in addition to psychotherapy. (Level I)
3. Nonpharmacologic methods, including counseling and stress-reduction techniques, should be considered to reduce the adverse effects of stressors that commonly occur at midlife. (Level II)
4. Education is key in helping women understand and cope with mood symptoms related to the menopause transition. (Level II)

#### SEXUALLY TRANSMITTED INFECTIONS

##### Key Points

1. Although most sexually transmitted infections (STIs) occur in younger women, perimenopausal and postmenopausal women remain susceptible to infections, especially given that sexual activity may cause micro-abrasions in delicate, atrophic genital tissues, increasing exposure to pathogens.
2. Human papillomavirus (HPV) is the most common STI in the United States.
3. Risk factors for midlife women for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) include sexual activity outside of a long-term mutually monogamous relationship, seeking evaluation and/or treatment for STIs, and injection-drug use, among others.
4. Baby boomers (those born between 1945 and 1965) are at the highest risk of hepatitis C infection, with infection rates five times that of other birth cohorts.
5. Gonorrhea and chlamydia are best detected by nucleic acid amplification tests. Detection rates are equivalent using a vaginal swab or endocervical sample. Urine tests are acceptable but may miss up to 10% of infections.
6. Women with HIV have unique gynecologic problems that can include an earlier and more symptomatic perimenopausal transition.

#### Recommendations for Clinical Care

1. Midlife women at high risk for STIs, including those with a new sexual partner or multiple sexual partners or whose partner has multiple sexual partners, should be screened for STIs. (Level I)
2. Clinicians should utilize the evidence-based guidelines from the Centers for Disease Control and Prevention regarding the management of STIs. (Level I)
3. All adults should be screened at least once in their lifetime for HIV. (Level I)
4. Pap screening every 3 years or Pap and HPV co-testing every 5 years is recommended for women aged 30 to 65 years. Women aged older than 65 years

- may discontinue screening if they 1) have no history of a high-grade dysplasia in the past 20 years, 2) are not immunosuppressed, 3) were not diethylstilbestrol exposed, and 4) have had at least three normal Pap tests (or two Pap/HPV co-tests) since age 55 years. (Level I)
- Older women with and without risk factors for hepatitis B who have never received the hepatitis B vaccination should be counseled regarding the benefits of vaccination. (Level I)
  - All women with diabetes and chronic liver disease should be vaccinated against hepatitis B. (Level I)

## CHAPTER 4: DISEASE RISK

### CARDIOVASCULAR HEALTH

#### Key Points

- Cardiovascular disease (CVD) is the leading cause of death in women worldwide.
- Major risk factors for CVD in women include age, hypertension, dyslipidemia, diabetes mellitus (DM), family history of premature CVD, smoking, sedentary lifestyle, and poor diet. Novel risk factors for CVD include a history of a pregnancy complicated by preeclampsia, gestational diabetes, or hypertension.
- Hormonal changes associated with menopause can result in an accelerated increase in low-density lipoprotein cholesterol (LDL-C) in the year following menopause.

#### Recommendations for Clinical Care

- All women should be encouraged to reduce their risk for CVD, including heart attack and stroke, by engaging in regular exercise, consuming a healthy diet, achieving a normal body weight, and not smoking.
- Healthcare providers should evaluate all women for CVD risk using the American College of Cardiology-American Heart Association (ACC-AHA) risk assessment tool and manage risks accordingly. (Level II)
- Treatment of blood pressure (BP) is recommended in women aged younger than 60 years for systolic BP (SBP) > 140 mm Hg or diastolic BP (DBP) > 90 mm Hg. In women aged older than 60 years, treatment is recommended for SBP > 150 mmHg or DBP > 90 mm Hg. (Level II)
- Updated ACC-AHA guidelines on the treatment of dyslipidemia recommend statin therapy for women with 1) existing atherosclerotic CVD (ASCVD), 2) LDL-C 190 mg/dL or greater, 3) aged 40 to 75 years with DM, and 4) aged 40 to 75 years with an estimated 10-year ASCVD risk of 7.5% or higher, based on the use of a novel risk calculator for myocardial infarction and stroke. There is some controversy regarding use of the ASCVD risk calculator as an indication for statin therapy. (Level II)
- Aspirin therapy should be considered for women 1) aged 65 years and older without known CVD, 2) any

age with established CVD, and 3) any age with an estimated 10-year CVD risk of 10% or higher. (Level II)

- Available evidence does not support the use of systemic hormone therapy for the prevention or treatment of CVD. However, age and time since menopause are critical modifiers of the effect of systemic HT on CVD, with more favorable effects observed for women aged 50 to 59 years and within 10 years of menopause at treatment initiation. (Level I)

### DIABETES MELLITIS

#### Key Points

- Prediabetes and diabetes are highly prevalent in midlife women and the prevalence is increasing.
- Glucose metabolism worsens with weight gain and aging. Evidence that hormonal changes at menopause contribute to a worsening of glucose metabolism is inconsistent.
- Cardiovascular disease is the leading cause of death in women and the risk of CVD is higher in women with diabetes.

#### Recommendations for Clinical Care

- Screening for diabetes with glycated hemoglobin (Hb A<sub>1c</sub>), fasting plasma glucose, or an oral glucose tolerance test should be considered for all women aged 45 years and is strongly recommended if women are overweight or obese. (Level I)
- Optimal glucose control (eg, target Hb A<sub>1c</sub> <7%) is recommended to reduce the risk of vascular complications of diabetes. Lifestyle modifications addressing diet and exercise are first-line strategies for controlling glucose. Metformin therapy is the preferred initial pharmacologic strategy for type 2 diabetes. (Level I)
- Regardless of LDL-C level, statins are recommended for all women with diabetes aged between 40 and 75 years to reduce atherosclerotic CVD risk. (Level I)
- Controlling blood pressure through pharmacologic and nonpharmacologic means is also recommended to reduce cardiovascular events in women with diabetes. Target BP for women with diabetes is below 140/80 mm Hg. (Level I)
- Women with diabetes should be advised to stop smoking.

### OSTEOPOROSIS

#### Key Points

- Postmenopausal osteoporosis is a common condition that leads to an increased risk of fracture. It can be diagnosed and treated before any fracture occurs.
- The diagnosis of osteoporosis is established by measurement of bone mineral density by dual-energy x-ray absorptiometry (DXA) of the spine, hip, and/or forearm (T-score of -2.5 or lower) or by the presence of a low-trauma or fragility fracture.

3. Many conditions, diseases, and medications contribute to bone loss and increased fracture risk.
4. Current FDA-approved pharmacologic options for the prevention of postmenopausal osteoporosis include estrogen therapy, estrogen-progestogen therapy, and an estrogen agonist/antagonist (bazedoxifene) combined with estrogen (BZA-CE). Pharmacologic options approved for the treatment of postmenopausal osteoporosis include denosumab, teriparatide, and calcitonin. Pharmacologic options approved for the prevention and treatment of postmenopausal osteoporosis include bisphosphonates and the estrogen agonist/antagonist raloxifene. There are no prospective studies comparing these drugs for antifracture efficacy.
5. Pharmacotherapy reduces fracture risk in patients with osteoporosis, but the antifracture efficacy of pharmacotherapy in women with low bone mass (osteopenia) without fractures is less strong.
6. Pharmacologic therapy must be individualized based on risk-benefit assessments and patient preference.

#### Recommendations for clinical care

1. It is important to identify and address potential factors that contribute to bone loss and increased fracture risk by a careful history, physical examination, and basic laboratory testing. (Level II)
2. All postmenopausal women should be encouraged to obtain adequate calcium and vitamin D, engage in regular exercise, stop smoking, limit alcohol intake, and modify their environments to reduce the risk of falls. (Level I)
3. Bone mineral density testing is recommended for all women aged 65 years and older, with consideration for earlier testing in women with clinical risk factors for fracture, including low body weight, history of prior fracture, family history of osteoporosis, smoking, excessive alcohol intake, or long-term use of high-risk medications (eg, glucocorticoids). (Level I)
4. After initial BMD testing, the need for additional testing and the optimal interval for repeat testing should be individualized based on the baseline BMD, therapeutic interventions initiated, and fracture risk. (Level II)
5. Healthcare providers should consider treating women with osteoporosis or low bone mass who have either a 10-year probability of a hip fracture of 3% or higher or a 10-year probability of a major osteoporosis-related fracture of 20% or higher, based on the US-adapted World Health Organization algorithm (ie, using the FRAX<sup>®</sup> Web-based tool). (Level I)
6. There is considerable controversy regarding the optimal duration of bisphosphonate therapy and the length of a *drug holiday*, both of which should be based on an individualized assessment of risk and benefit. (Level II)
7. Healthcare providers should individualize treatment based on an assessment of the potential benefits and risks of therapy for each patient and the effectiveness

of a given osteoporosis treatment on reduction of vertebral and nonvertebral fractures. (Level I)

#### GALLBLADDER DISEASE

##### Key Points

1. Gallbladder disease occurs twice as frequently in women as in men.
2. Risk factors for gallstones include obesity, increased parity, weight-loss diets, bariatric surgery, and oral estrogen use.
3. Oral contraceptives and oral menopausal hormone therapy increase biliary cholesterol saturation, a prerequisite for cholesterol gallstone formation.
4. Warning signs for gallbladder disease include abdominal pain, nausea, vomiting, fever, jaundice, dark urine, and light stools.
5. In the Women's Health Initiative (WHI), combined estrogen-progestogen therapy (EPT) was associated with an increased absolute risk of 27 cases of gallbladder disease per 1,000 women after 5.6 years' use, whereas estrogen-only therapy resulted in an increased absolute risk of 45 additional cases per 1,000 women after 7 years.
6. The risk of gallbladder disease associated with HT appears greater with oral than with transdermal estrogen use.

##### Recommendations for Clinical Care

1. Hormone therapy should be administered with caution to women who have gallstones or a history of gallbladder disease. (Level I)
2. An increased risk of gallbladder disease should be included in discussions of the risks and benefits of HT. (Level II)
3. Transdermal ET is associated with lower risk of gallbladder disease than oral ET. (Level II)

#### ARTHRITIS AND ARTHRALGIA

##### Key Points

1. Osteoarthritis is predominantly a degenerative arthritis and a disease of aging. It is not associated with involvement of organs outside of the musculoskeletal system or systemic symptoms. Treatment is directed at palliating pain and maintaining function.
2. Rheumatoid arthritis is a systemic inflammatory arthritis that requires aggressive treatment with immunomodulating drugs. Current therapies generally can control the disease and progression to disabling joint destruction is uncommon.
3. Fibromyalgia is a chronic, painful process that does not affect the joints but rather is characterized by diffuse pain felt largely in the musculature. Treatment requires multiple modalities, including exercise, physical therapy, and neuroactive medications.

### Recommendations for Clinical Care

1. With more than 100 forms of arthritis, a specific diagnosis is the first step toward appropriate treatment. As many forms of arthritis have similar features and *gold standard* diagnostic tests generally are lacking, the diagnosis is determined on the basis of clinical experience and may require observation over time. (Level III)
2. Effective therapy of osteoarthritis includes palliation of pain and maintenance of function and mobility, with assist devices when necessary. Treatment should incorporate appropriate exercise regimens and analgesic medications, which may include nonsteroidal anti-inflammatory drugs and neuroactive medications. Complementary approaches are widely used and may provide significant pain relief, although their incremental benefit beyond placebo remains controversial. (Level I)
3. Rheumatoid arthritis is a serious progressive disease that should be treated with the intention of achieving remission. With the use of appropriate modern medications and biologics, most patients can expect to live a normal functional life. (Level I)
4. Fibromyalgia and myofascial pain syndromes require multidisciplinary therapeutic plans, including exercise regimens, physical therapy, and neuroactive medications; conventional analgesics and opiates have little efficacy for this condition. (Level II)

### THYROID DISEASE

#### Key Points

1. Thyroid disorders are common in women and often are associated with symptoms similar to those of the menopause transition.
2. As women age, thyroid disorders can be associated with significant morbidity and potentially increased mortality.
3. Subclinical thyroid disorders are common, although clinical trial evidence justifying benefits of treatment is lacking.
4. Overtreatment of hypothyroidism or hyperthyroidism can result in untoward effects and undesired extremes of thyroid hormone.

### Recommendations for Clinical Care

1. Current recommendations do not consistently support screening of all women for thyroid disorders; however, a high index of suspicion is merited in midlife and postmenopausal women. Measurement of thyroid stimulating hormone is the initial step in assessing thyroid function. (Level II)
2. Treatment of hypothyroidism includes administration of thyroxine (dose depending on age and comorbidities) with TSH monitoring every 6 to 8 weeks, targeting the TSH to within the normal range. (Level I)
3. Treatment of hyperthyroidism is more complex and is probably best approached in consultation with an endocrinologist. (Level II)

4. Diagnosis of subclinical thyroid disorders requires repeated monitoring because laboratory testing often returns to normal with continued observation. (Level II)
5. When treating subclinical thyroid disorders, care must be exercised not to overtreat and induce the opposite thyroid condition. (Level I)
6. The thyroid examination should evaluate for the presence of thyroid nodules. If present, referral for further evaluation is usually indicated. (Level I)

### EPILEPSY

#### Key Points

1. Menopause generally occurs earlier in women with epilepsy than in women in the general population. The earlier occurrence of menopause correlates with the total number of lifetime seizures but also may be affected by antiepileptic drugs, especially those that may affect estrogen levels by inducing the hepatic CYP450 isoenzyme (eg, phenytoin, phenobarbital).
2. Because reproductive steroids have neuroactive properties, and a subset of women with epilepsy have seizures that are hormonally sensitive (eg, catamenial epilepsy), clinicians should be aware that hormonal changes that occur during perimenopause and menopause may result in changes in seizure frequency and patterns.
3. Anovulatory cycles that characterize perimenopause and feature unopposed estrogen effects are associated with a greater frequency of generalized convulsive seizures than are ovulatory cycles.

### Recommendations for Clinical Care

1. Cyclic natural progesterone supplementation and cycle suppression with gonadotropin-releasing hormone agonists or depomedroxyprogesterone acetate have been proposed as interventions to reduce the frequency of hormonally sensitive seizures, but efficacy remains unproven. (Level II)
2. One antiepileptic drug, gabapentin, may be particularly effective in lessening some autonomic symptoms of menopause such as warmth, hot flashes, and night sweats. (Level I)
3. Because antiepileptic drugs can accelerate vitamin D metabolism and contribute to osteoporosis, postmenopausal women with epilepsy require adequate intake of calcium and vitamin D and may benefit from closer monitoring of bone mineral density. (Level II)

### ASTHMA

#### Key Points

1. Asthma is more prevalent in women than men, and its severity can vary with the menstrual cycle in women prior to menopause.
2. The incidence of asthma does not clearly increase after menopause, but lung volumes tend to decline, and pulmonary symptoms, including wheezing, become more prevalent.

3. Asthma that has its onset after menopause tends not to be associated with atopy and can be particularly severe.
4. The effect of hormone therapy on asthma is unclear. Several large observational studies have shown an association between current HT use and asthma risk, whereas several small interventional trials have demonstrated neutral to beneficial effects of HT on airway function and clinical course.

#### Recommendations for Clinical Care

1. Healthcare providers should be aware that asthma presenting after menopause is not necessarily associated with atopy and may be less responsive to anti-inflammatory treatments than asthma that presents earlier in life. (Level II)
2. Hormone therapy should not be initiated or withheld because of asthma. (Level II)

### BREAST CANCER

#### Key Points

1. Breast cancer incidence rates have been increasing in North America for decades, and the most important risk factor, other than being a woman, is age.
2. Nulliparity, late age at first birth, excess alcohol consumption, obesity, a family history of breast cancer in first-degree relatives, *BRCA* gene mutations, biopsied benign breast disease, and atypical ductal hyperplasia all increase the risk of breast cancer.
3. Breast cancer risk is increased in postmenopausal women by the use of combined estrogen-progestogen hormone therapy for more than 3 to 5 years. The use of estrogen-alone therapy in women without a uterus for up to 7 years does not increase breast cancer risk, although long-duration estrogen-alone use appears to increase breast cancer risk.
4. Selective estrogen receptor modulators (estrogen agonist/antagonists) reduce the incidence of primary breast cancer in high-risk women. Tamoxifen reduces the risk of breast cancer in premenopausal and postmenopausal women. Raloxifene reduces the risk of breast cancer in postmenopausal women.
5. In postmenopausal women, aromatase inhibitors (AIs), including anastrozole and exemestane, reduce breast cancer recurrence, improve survival, and reduce breast cancer risk in women at high risk. Aromatase inhibitors are not yet approved for breast cancer prevention.
6. Breast cancer mortality has been declining for several decades due to early detection through wider application of mammographic screening, more effective use of hormone-modulating therapies for early disease, and adjuvant chemotherapy for advanced disease.

#### Recommendations for Clinical Care

1. Routine screening for breast cancer is indicated for midlife women. There is considerable controversy regarding the age at which breast cancer screening should begin and end and the frequency of screening. Current

guidelines generally include mammograms every 1 to 2 years, starting at age 40 to 50 years and continuing until age 70. Magnetic resonance imaging is recommended for women at high risk for breast cancer. (Level I)

2. Genetic testing for *BRCA* mutations should be recommended for women at high risk for breast cancer on the basis of family history. (Level I)
3. Weight gain is associated with an increased risk of breast cancer recurrence, and a low-fat diet is associated with improved survival in women with certain types of breast cancer, so weight control and a low-fat diet may be advised for women with breast cancer. (Level II)
4. Women at increased risk for breast cancer should be counseled regarding the potential benefits and risks of tamoxifen and raloxifene for breast cancer risk reduction. (Level I)

### ENDOMETRIAL CANCER

#### Key Points

1. Endometrial cancer (endometrioid, type-I) is a relatively common cancer among postmenopausal women.
2. In the United States, survival after diagnosis of endometrial cancer is lower in black women than in white women.
3. The presenting symptom of endometrial cancer is typically abnormal uterine bleeding.
4. The principal risk factors for endometrial cancer are age (>50 years), hyperestrogenic endometrial milieu, diabetes mellitus, and obesity.
5. The precursor of endometrial cancer is atypical endometrial hyperplasia.
6. The main route of spread for endometrial cancer is contiguous extension into the myometrium.
7. Posttreatment recurrences occur in women with high-grade tumors or with deep myometrial invasion and usually involve the vaginal apex.

#### Recommendations for Clinical Care

1. In postmenopausal women, any bleeding should be promptly and thoroughly evaluated. A thickened endometrium must be biopsied. Transvaginal ultrasonography, hysteroscopy, and sonohysterography are useful to identify focal abnormalities. (Level I)
2. Postmenopausal woman with an intact uterus using systemic estrogen-only therapy are at risk of developing endometrial hyperplasia and cancer. Treatment with adequate progestogen reduces the risk of endometrial cancer in women using ET. Women using estrogen combined with bazedoxifene do not require a progestogen. (Level I)
3. Atypical endometrial hyperplasia should be treated with hysterectomy and bilateral salpingo-oophorectomy. Conservative management with progestogen therapy and close follow-up may be an option for reliable younger women seeking to preserve fertility or for poor surgical candidates. (Level I)

4. Endometrial cancer is treated with hysterectomy, bilateral salpingo-oophorectomy, and dissection of pelvic and para-aortic lymph nodes. Staging and projected prognosis are based on surgical findings. Women with advanced endometrial cancer ( $\geq 50\%$  myometrial invasion) will usually require adjuvant therapy. (Level I)

## CERVICAL CANCER

### Key Points

1. When detected at an early stage, the 5-year survival rate for women with cervical cancer is 92%. In women aged older than 65 years with cervical cancer, 42% had never been screened.
2. Risk factors for cervical cancer include human papillomavirus (HPV) infection, sexual intercourse at an early age, multiple sexual partners, smoking, and immunocompromised states, including HIV infection.
3. Almost all cervical cancers are related to infection by the sexually transmitted, high-risk (oncogenic) types of HPV. Two vaccines are available to prevent infection with the HPV types that cause most cervical cancers.

### Recommendations for Clinical Care

1. Vaccination for HPV is recommended for girls aged 13 to 26 years and for boys aged 13 to 21 years. Women immunized against HPV should follow routine cervical cancer screening guidelines. (Level I)
2. Cervical cancer screening should start at age 21 and is recommended every 3 years for women aged 21 to 29 years. For women aged 30 to 65 years, co-testing with cervical cytology and HPV testing every 5 years is advised, although screening with cytology alone every 3 years is acceptable. (Level I)
3. Women who have had a hysterectomy for benign disease with removal of the cervix should no longer be screened for cervical cancer, unless there is a history of cervical dysplasia (cervical intraepithelial neoplasia [CIN] 2 or higher). (Level I)
4. Women with a history of cervical cancer, HIV infection, immunocompromised state, or diethylstilbestrol exposure in utero require increased screening. (Level I)
5. Screening should be discontinued after age 65 years in women with adequate negative prior screening and no history of CIN2 or higher in the past 20 years. (Level I)
6. Abnormal uterine bleeding or a cervical abnormality identified during a pelvic examination may be a sign of cervical cancer and should be promptly evaluated. (Level I)

## OVARIAN CANCER

### Key Points

1. Ovarian cancer is the tenth most common cancer in US women, but the fifth most common cause of cancer death.

2. Risk factors for epithelial ovarian cancer include genetic predisposition (*BRCA* mutations, Lynch syndrome), older age, nulligravidity, endometriosis, early menarche, and late menopause.
3. Protective factors include oral contraceptives and tubal sterilization, each of which decrease risk by 50%.
4. In normal-risk women, ovarian cancer screening with cancer antigen-125 or ultrasound is not effective and is not recommended.
5. Signs of ovarian cancer are subtle and include early satiety, abdominal bloating, abdominal pain, pelvic pain, and urinary frequency occurring daily for weeks.
6. Women with suspected ovarian cancer should undergo definitive surgical procedures with gynecologic oncologists as outcomes are superior.

### Recommendations for Clinical Care

1. Women should be informed of the symptoms of ovarian cancer and advised to inform their healthcare providers if daily symptoms persist. (Level III)
2. Family history of breast, ovarian, colon, and pancreatic cancers suggestive of increased hereditary risk should prompt referral for genetic counseling. (Level II)
3. Ovarian cancer screening should not be performed in normal-risk women. In high-risk women, screening may be offered, but risk-reducing surgery (bilateral salpingo-oophorectomy or possibly bilateral salpingectomy) or medications (eg, oral contraceptives) should be considered to decrease ovarian cancer risk. (Level I)

## LUNG CANCER

### Key Points

1. Smoking prevalence has been decreasing as a result of increased tobacco control, increased tobacco prices, and more laws prohibiting smoking in many locations.
2. Lung cancer takes many years to develop, with an average age of diagnosis of 71 years. It is the leading cause of cancer death among white, black, Asian/Pacific Islander, and American Indian/Alaska Native women and the second most common cause of cancer death among Hispanic women.
3. Most lung cancers are believed to be caused by cigarette smoking. Other risk factors include exposure to asbestos, radon, second-hand smoke, and other environmental agents. Among nonsmokers, women are more likely than men to develop lung cancer. Smoking cessation reduces lung cancer incidence.
4. Studies on the effect of hormone use on lung cancer incidence and survival are limited, with inconsistent results. Large observational studies have shown protective effects of oral contraceptives and hormone therapy on lung cancer risk. However, in the Women's Health Initiative, use of estrogen-progestogen therapy was associated with an increased risk of death from lung cancer, with an additional 9 cases per 1,000 women after 5.6 years of use plus 2.4 years of additional

follow-up. An increased risk of lung cancer was not seen with the use of estrogen alone. Additional research is needed on the association between hormones and lung cancer.

### Recommendations for Clinical Care

1. Women should be asked about smoking at all comprehensive visits and smoking cessation advised. (Level I)
2. Women using HT, particularly those who smoke, should be informed that EPT was associated with a small increased risk of death from lung cancer in the WHI, with no increased risk associated with the use of estrogen alone. (Level II)
3. The US Preventive Services Task Force recommends annual screening for lung cancer with low-dose computed tomography in women aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery. (Level I)

## COLORECTAL CANCER

### Key Points

1. Colorectal cancer is a leading cause of death for women.
2. Risk factors for colorectal cancer include age, smoking, presence of colorectal polyps, inflammatory bowel disease (eg, ulcerative colitis or Crohn disease), family history of colorectal cancer, personal history of breast cancer, and certain genetic diseases (eg, Lynch syndrome/hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis).
3. Colon cancer has been linked to a high-fat, low-fiber diet and to a high intake of red or processed meat.
4. Screening for colorectal cancer has been shown to detect asymptomatic, early stage disease and improve mortality. Colonoscopy is the most accurate diagnostic test for colorectal cancer and allows for concurrent removal of polyps and biopsy of suspicious lesions. General screening guidelines include an initial colonoscopy at age 50, with repeat testing every 10 years until age 75. If polyps or other abnormalities are identified during screening, more frequent surveillance is recommended. Other methods to screen for colorectal cancer include annual high-sensitivity fecal occult blood testing, sigmoidoscopy, computed tomographic colonography, and double-contrast barium enema.

### Recommendations for clinical care

1. Women should be advised to not smoke and to eat a low-fat, high-fiber diet with limited intake of red or processed meat for overall health and possible colorectal cancer risk reduction (Level II)

2. Women should be screened for colorectal cancer, generally with an initial colonoscopy at age 50 and repeat testing every 10 years, until age 75. (Level I)
3. Women at increased risk for colorectal cancer, including those with inflammatory bowel disease, colorectal polyps, or a family history of colorectal cancer, should be screened more frequently. (Level I)

## PANCREATIC CANCER

### Key Points

1. Pancreatic cancer is the fourth leading cause of cancer death in US women.
2. There is no clear association between pancreatic cancer risk and reproductive factors or use of oral contraceptives or hormone therapy.
3. Smoking is the only well-established risk factor for pancreatic cancer, but other probable risk factors include age, high-fat diet, alcohol intake, type 2 diabetes mellitus, chronic pancreatitis, and obesity.
4. Pancreatic cancer does not cause symptoms until advanced stages, and there are no effective methods for early detection; presenting signs include jaundice and thromboembolic events.

### Recommendations for Clinical Care

1. Encourage smoking cessation and a healthy lifestyle for overall health and possible pancreatic cancer risk reduction. (Level II)
2. A midlife woman presenting with thromboembolic disease should be evaluated for the possibility of pancreatic cancer. (Level II)

## SKIN CANCER

### Key Points

1. Skin cancer is the most common form of cancer and includes basal and squamous cell carcinomas and melanoma.
2. Common risk factors for skin cancer include advancing age, chronic or intense exposure to ultraviolet radiation (typically from the sun or tanning beds), family history of skin cancer, and chronic immunosuppression.
3. Sun exposure is the most preventable risk factor for all types of skin cancer, including melanoma.
4. Some common benign skin growths associated with maturing skin such as seborrheic keratoses and capillary hemangiomas can mimic skin cancers.

### Recommendations for Clinical Care

1. All women should be assessed for skin cancer risk and be examined regularly for skin cancer and skin cancer precursors. (Level I)
2. Women should be instructed in skin self-examination to promote early detection of skin cancer. Potential signs of skin cancer include new or changing moles and lesions that bleed, ulcerate, or fail to heal. (Level II)

3. Photoprotective measures should be advised to reduce a woman's risk of skin cancer, including avoiding midday sun, using sunscreen consistently, wearing protective hats and clothing, and avoiding tanning salons. (Level I)

## CHAPTER 5: CLINICAL EVALUATION AND COUNSELING

### HISTORY AND PHYSICAL EXAM

#### Key Points

1. The health evaluation at the time of the menopause transition should be tailored to the individual woman based on her medical, social, and family history, as well as on her symptoms and quality-of-life goals.
2. Sexual and psychological histories are an important part of the assessment of women during the menopause transition.
3. The evidence supporting various aspects of the physical exam, including the clinical breast exam and bimanual pelvic exam, is limited and contradictory.

#### Recommendations for Clinical Care

1. A thorough history and focused physical exam can guide clinicians and their patients in managing the symptoms of the menopause transition and providing guidance to support enhanced health for women as they age. (Level II)
2. The evaluation and counseling of a midlife woman should be individualized based on her underlying health, risk factors, and symptoms. (Level II)

### DIAGNOSTIC AND SCREENING TESTS

#### Key Points

1. The focus of healthcare visits for midlife women is to promote a healthy lifestyle while addressing symptoms and screening for cancer, cardiovascular disease, and other diseases associated with aging.

#### Recommendations for Clinical Care

1. Although routine screening guidelines are available, screening should be individualized, based on a woman's personal and family history, physical examination findings, lifestyle choices, genetics, and other specific risk factors. (Level II)
2. Hormone measurements to determine menopause status are not routinely indicated as menstrual cycle changes are generally the best predictor of menopause stage. Follicle stimulating hormone and antimüllerian hormone levels reflect ovarian reserve and may be indicated if menopause symptoms are atypical or occur at an early age. Salivary testing of reproductive hormones is inaccurate and never indicated. (Level II)
3. Abnormal bleeding requires evaluation, and multiple methods are available, including transvaginal ultrasound, endometrial biopsy, saline infusion sonography, hysteroscopy, and dilation and curettage. Assessing endometrial

thickness by transvaginal ultrasound is an appropriate initial step, with endometrial biopsy and further evaluation indicated for a thickened endometrium (>5 mm) or persistent bleeding regardless of endometrial thickness. (Level I)

4. Cardiovascular screening should include a history and physical examination with measurement of height, weight, waist circumference, and blood pressure. A fasting lipid profile and chemistry panel may be indicated. An electrocardiogram is not recommended for routine screening but may be indicated on the basis of history and physical examination findings. (Level II)
5. Routine screening for thyroid disease is not indicated; however, midlife women with symptoms, including hot flashes, irregular menses, weight gain, or depression, should be screened for thyroid disease with a thyroid-stimulating hormone level. (Level II)
6. Testing for sexually transmitted infections should be performed on the basis of history and level of risk. (Level II)
7. Routine screening for cancer of the breast, cervix, and colon is indicated for midlife women. There is considerable controversy regarding the age at which breast cancer screening should begin and end and the frequency of screening. Current guidelines generally include mammograms every 1 to 2 years, starting at age 40 to 50 years until age 70; Pap smears every 3 years or every 5 years with human papillomavirus co-testing until age 65; and colonoscopy every 10 years, starting at age 50 until age 75. (Level II)
8. Routine screening for ovarian cancer is not indicated. (Level I)

### COUNSELING ISSUES

#### Key Points

1. Social, cultural, racial, and ethnic differences affect the way women experience the menopause transition, the frequency and severity of menopause-related symptoms, attitudes toward menopause, and use of available therapies.
2. Lesbian women often have special health concerns, and healthcare providers should know a woman's sexual orientation to provide optimal care.
3. Violence toward women is a serious public health concern. Studies confirm that women are often not asked about intimate partner violence (IPV) by clinicians. Women who are victims of IPV and sexual violence are at increased risk for serious acute and chronic health problems.
4. Although each woman's experience of menopause is different, the menopause transition and postmenopause are important periods for all women to implement behavioral changes to ensure healthy aging.

#### Recommendations for Clinical Care

1. Delivery of healthcare at midlife must respect each woman as a unique individual. Although some women

view menopause as a natural phase of life, others may see their symptoms as a medical condition requiring treatment. Clinicians should ask women directly about their view of menopause, as a woman's beliefs will impact the effectiveness of counseling. (Level III)

2. When counseling a woman regarding treatment for menopause-related symptoms, the clinician should review all available options and encourage the woman to take an active role in the decision-making process. (Level II)
3. Women generally appreciate language free of heterosexual assumptions. Asking all women the open-ended question, "Do you have sex with men, women, or both?" provides a nonjudgmental environment for women to discuss their sexuality. (Level III)
4. Healthcare providers should screen for IPV and sexual violence. An environment of openness, safety, and trust will help facilitate disclosure. Displaying posters and print materials about IPV and sexual violence in public and private areas in the office educates women about options and available resources. Many women are not aware of community outreach groups, safe shelters, or the full range of services available. (Level II)
5. Effective counseling requires that the clinician
  - Develop satisfactory relationships through communication and listening
  - Provide all information necessary for an informed decision
  - Provide unbiased, factual, and comprehensive information on the risks and benefits of any therapeutic initiative
  - Elicit and include the woman's preferences in any recommendations
  - Understand the woman's comprehension of instructions and ability to follow them
  - Periodically evaluate treatment continuance and adjust regimens as needed (Level III)

## QUALITY-OF-LIFE ASSESSMENT TOOLS

### Key Points

1. A midlife woman's quality of life (QOL) is not determined solely by her general health and menopause-related symptoms. Quality of life includes a woman's perception of her life status within her culture and value system and is influenced by her goals, expectations, and concerns.
2. Quality-of-life scales are important additions to research in the field of menopause.
3. Quality-of-life scales can be categorized as general (Short Form-36, EuroQOL), menopause specific (Greene Climacteric Scale, Women's Health Questionnaire, Menopause Symptom List, Menopause Rating Scale), or combined (UQOL, MENQOL).
4. Assessment of a woman's perceived QOL is valued as a therapeutic outcome and may be a determinant of her adherence to a recommended plan of care.

## Recommendation for Clinical Care

1. Quality-of-life scales are not only useful research tools but also may be used to assess a midlife woman in the clinical setting. (Level II)

## CHAPTER 6: COMPLEMENTARY AND ALTERNATIVE MEDICINE

### INTEGRATIVE MEDICINE

#### Key Points

1. A National Institutes of Health survey found that 36% of Americans use some form of complementary and alternative medicine (CAM). When megavitamin use and prayer for health reasons are included in the definition of CAM, the percentage rises to 62%.
2. Increased dietary soy (legumes, soy, tofu), isoflavone products, and other forms of phytoestrogens reduce menopause symptoms, although clinical trials demonstrate benefit generally similar to that of placebo.
3. Acupuncture reduces hot flashes and improves sleep patterns in postmenopausal women, although clinical trials demonstrate benefit generally similar to that of sham acupuncture.
4. Regular consumption of soy isoflavones in the diet may offer breast cancer protection if exposure occurs during breast development. Soy isoflavones also may inhibit the progression of atherosclerosis if initiated within 5 years after the onset of menopause.

#### Recommendations for Clinical Care

1. Healthcare providers should ask midlife women about CAM usage and utilize available resources to guide them regarding the efficacy and safety of available treatments. (Level III)
2. CAM approaches, including acupuncture, herbal products, dietary soy, and isoflavone products, may be offered to treat vasomotor symptoms, although clinical trials generally demonstrate benefit for menopausal symptoms similar to that of placebo. (Level II)
3. There are no data that soy, phytoestrogens, or isoflavone products increase the risk of breast or endometrial cancer, although women with breast or endometrial cancer should consider consulting their oncologists before using them. (Level II)

### HERBS

#### Key Points

1. Marketed herbal products are regulated in the United States as dietary supplements. Many manufacturers employ rigorous quality-control measures and produce high-quality products, whereas others produce poorer-quality products with regard to purity and levels of active compounds.
2. The German Federal Institute for Drugs and Medical Devices approved black cohosh for menopause-related

complaints, premenstrual syndrome, and dysmenorrhea. Although several of the plant's constituents have been identified, its precise mechanism of action is unknown.

3. St. John's wort, also known as *Hypericum perforatum*, is the most popular herbal treatment for mild depression. Several studies of St. John's wort showed improvement in mood and anxiety disorders in perimenopausal and postmenopausal women. The herb kava also may reduce anxiety.
4. The efficacy of black cohosh for the treatment of hot flashes is similar to that of placebo.
5. Vitex, also known as chasteberry, is commonly used for premenstrual syndrome, irregular menstruation, and cyclical mastalgia.

#### Recommendations for Clinical Care

1. Because some herbal products may affect the metabolism of drugs or increase bleeding, healthcare providers should ask midlife women about their use of herbal remedies and dietary supplements, particularly if a medical procedure or drug therapy is planned. (Level II)
2. St John's wort may be advised for mild mood symptoms in midlife women. (Level II)

## CHAPTER 7: NONPRESCRIPTION OPTIONS

### GOVERNMENT REGULATIONS FOR DIETARY SUPPLEMENTS

#### Key Points

1. Regulation of prescription drugs as well as over-the-counter (OTC) drugs by FDA is explicit and defined by federal statutes contained in the 1938 Federal Food, Drug, and Cosmetic Act (FDCA). This Act is continually being amended and updated. New prescription drug marketing approval and postmarketing safety monitoring are the core responsibilities of the Center for Drug Evaluation and Research (CDER) at FDA.
2. As a result of the passage of the Dietary Supplement Health and Education Act of 1994, the regulation of dietary supplements by FDA is extremely limited, except in cases of clear danger to public health. This amendment to the 1938 FDCA defined dietary supplements as foods rather than drugs, allowing dietary supplement manufacturers to claim health benefits that would otherwise have been illegal under the FDCA.
3. The authority and ability of FDA to regulate prescription drugs *custom compounded* by pharmacies for individual patients (as opposed to manufacturing of prescription drugs by commercial drug manufacturers) has been disputed for decades. Recent concerns about drug purity and safety claims for some compounded drugs have resulted in new enforcement authority for FDA to inspect pharmacies and remove products from the market. In general, it is the responsibility of individual state medical and pharmacy boards to regulate the compounded drug industry.

4. The practice of medicine, including the ability of healthcare providers to prescribe drugs and advertise their products and services is not regulated by FDA but rather by individual state medical boards.

### VITAMINS AND MINERALS—CALCIUM

#### Key Points

1. Calcium is the most abundant mineral in the human body, occurring predominantly in bones and teeth.
2. The importance of adequate calcium intake for skeletal health is well established; randomized clinical trials of calcium in combination with vitamin D demonstrate a role in fracture prevention.
3. The main dietary sources of calcium are dairy products (including milk, cheese, and yogurt), which provide an average of 70% of the total calcium intake in midlife and older women.
4. Calcium requirements for skeletal maintenance in women fluctuate throughout life but increase after menopause due to increased bone resorption and decreased intestinal calcium absorption, both of which are associated with decreased ovarian estrogen production.
5. Supplemental calcium but not dietary calcium has been linked to an increased risk of kidney stones. Recent studies also have raised the possibility that calcium supplements may increase the risks of cardiovascular disease, but the research to date is inconsistent and inconclusive.

#### Recommendations for Clinical Care

1. The Institute of Medicine (IOM) 2011 report set the Recommended Dietary Allowances (RDA) for calcium at 1,000 mg per day for women aged 50 years and younger and 1,200 mg per day for those aged older than 50 years. (Level I)
2. The IOM also set the tolerable upper intake level (intakes above which adverse events may occur) at 2,500 mg per day for women aged 50 years and younger and 2,000 mg per day for those aged older than 50 years. (Level II)
3. Many women can meet the RDA for calcium by eating calcium-rich foods. For those who cannot eat (or do not enjoy) dairy products, other dietary sources of calcium include bone-containing fish such as sardines or salmon, calcium-fortified juices and cereals, tofu, broccoli, collard greens, and kale. (Level I)
4. Calcium supplements should be considered if diet does not provide the recommended amount of calcium. Many women, however, are taking excessive doses of supplemental calcium and may need only about 500 mg per day in supplements to reach the RDA. (Level II)

### VITAMINS AND MINERALS—VITAMIN D

#### Key Points

1. Vitamin D is a sterol-like compound that increases the intestinal absorption of calcium and is essential for bone health.

- The main sources of vitamin D are cutaneous synthesis following ultraviolet-B exposure; foods such as fortified dairy products, fatty fish, and some mushrooms; and supplements.
- Risk factors for vitamin D deficiency/insufficiency include limited sun exposure, older age, dark skin pigmentation, obesity, low dietary intake of vitamin D, malabsorption syndromes, selected medications (anti-convulsants, antituberculous therapy), and renal or hepatic disease.
- Observational studies suggest an association between low vitamin D levels and nonskeletal health outcomes, including heart disease, cancer, and diabetes, but evidence from randomized trials is sparse, inconsistent, and does not prove a cause-and-effect relationship.
- Magnesium is present in a wide variety of foods. The richest dietary sources are nuts, legumes, certain seeds, various marine fish, and dairy products.
- Magnesium salts taken orally tend to have a cathartic effect.

#### Recommendations for Clinical Care

#### Recommendations for Clinical Care

- The Recommended Dietary Allowances for vitamin D were set by the Institute of Medicine (IOM) in 2011 at 600 IU per day for adult women aged 70 years and younger and 800 IU per day for women aged older than 70 years. The IOM also set the tolerable upper intake level (intakes above which adverse events may occur) at 4,000 IU per day. (Level I)
- Other guidelines for vitamin D intake in women have been proposed by other professional organizations and have generally ranged from 800 IU to 2,000 IU per day. (Level II)
- The blood concentration of 25-hydroxyvitamin D (25OHD) is a marker of vitamin D exposure. The IOM recommends achieving a 25OHD level of 20 ng/mL (50 nmol/L) or higher, but several other professional organizations recommend levels of 30 ng/mL (75 nmol/L) or higher. (Level II)
- The IOM has specified that 25OHD levels above 50 ng/mL (125 nmol/L) may be associated with adverse health effects. (Level II)
- Although universal screening of the population for vitamin D deficiency is not recommended, vulnerable populations at increased risk (the elderly or institutionalized, patients with medical conditions such as malabsorption or osteoporosis, patients taking anti-convulsants or other selected medications) may benefit from screening as well as from vitamin D supplementation. (Level II)

- The Institute of Medicine's daily recommended intake of magnesium for women is 320 mg per day. The evidence supporting recommended intakes of magnesium is considered weak because there are no well-accepted indicators of optimal magnesium status. (Level III)
- Although the clinical significance of low intake is less clear than for many other nutrients, it would be desirable to improve magnesium intake status for most adults. The median magnesium intake in US adult women is approximately 230 mg per day. It has been estimated that about 60% to 70% of the US population has an intake below the recommended level. (Level II)
- Magnesium supplementation may be indicated for patients with malabsorption conditions, including celiac disease, and in patients with excessive magnesium loss caused by gastrointestinal disease (eg, diarrhea, vomiting). (Level II)

#### OTHER VITAMINS AND MINERALS

##### Key Points

- A healthy diet that includes vegetables, fruits, low-fat dairy products, whole grains, chicken, fish, and nuts is associated with reduced rates of diabetes, hypertension, cardiovascular disease, colorectal adenoma, and colorectal cancer.
- Vitamin and antioxidant supplements do not appear to prevent cardiovascular disease, breast cancer, cataracts, or mortality, and there is a potential for harm with high intake of certain vitamins and supplements.
- Several meta-analyses have indicated that various B vitamin supplements are not protective against cardiovascular events or cognitive decline, whereas there is conflicting evidence concerning B vitamins and cancer.

#### Recommendations for Clinical Care

- The importance of a healthy, nutrient-rich diet that includes increased consumption of vegetables, fruits, low-fat dairy products, whole grains, chicken, fish, and nuts should be promoted at every comprehensive visit. (Level II)
- Recent evidence suggests that the use of multivitamins or individual vitamins may not reduce the risk of various chronic diseases in most healthy individuals, so midlife women should be advised to limit the use of supplements and instead try to improve their diets. (Level II)

#### OTHER SUPPLEMENTS

##### Key Points

- Coenzyme Q10 has been used for heart failure, hypertension, and statin-induced myopathies; however, study

#### VITAMINS AND MINERALS—MAGNESIUM

##### Key Points

- Magnesium has an important role in bone health and is a necessary cofactor for numerous enzymes involved in energy metabolism.
- Manifestations of severe magnesium deficiency include impaired calcium homeostasis, a higher risk of hypertensive vascular disease, excessive platelet aggregation/thrombosis, and osteoporosis.

results are inconsistent. Coenzyme Q10 is superior to placebo for migraine prophylaxis.

2. Most of the cardiovascular and triglyceride-lowering benefits of omega-3 fatty acids are seen with fish oils.
3. Clinical trial evidence supports the use of glucosamine sulfate in improving pain and function in patients with osteoarthritis (OA). The benefit of chondroitin in improving OA symptoms is unclear.
4. Studies with S-Adenosyl Methionine (SAME) have shown benefit in mild to moderate depression.

#### Recommendations for Clinical Care

1. Coenzyme Q10 may be considered for migraine prophylaxis. (Level II)
2. Omega-3 fatty acids from fish oils may be used to lower triglyceride levels, with the greatest benefit seen in patients with very high triglyceride levels. (Level II)
3. Glucosamine sulfate may be used to improve symptoms and function in patients with OA. The need to use chondroitin in combination with glucosamine is unclear. (Level II)
4. SAME may be of benefit in the treatment of mild to moderate depression, although studies in severe depression are lacking. (Level II)

### OVER-THE-COUNTER HORMONES

#### Key Points

1. Over-the-counter hormone preparations containing dehydroepiandrosterone (DHEA), melatonin, and topical progesterone are regulated as dietary supplements in the United States, whereas in Canada, all but melatonin are sold as prescription drugs.
2. The evidence of efficacy of OTC topical progesterone cream for menopause symptoms is limited, and because dose and absorption vary among formulations, OTC topical progesterone typically does not provide adequate levels for endometrial protection with systemic estrogen use.
3. Dehydroepiandrosterone has been studied for a variety of conditions, including sexual function, depression, aging, and well-being, with inconclusive results.
4. The effects of melatonin on sleep and behavioral sedation are inconsistent; however, evidence supports favorable effects for circadian-rhythm sleep disorders.

#### Recommendations for Clinical Care

1. Over-the-counter topical progesterone cream should not be used to provide endometrial protection with estrogen use, and any benefit for menopause symptoms is unproven. (Level III)
2. The role of oral DHEA in improving mood, sexual function, and general well-being remains unproven. (Level III)
3. Melatonin supplementation may have a role for circadian-rhythm sleep disorders, including shift work and jet lag. (Level II)

## CHAPTER 8: PRESCRIPTION THERAPIES

### CONTRACEPTIVES

#### Key Points

1. Despite a decline in fertility, women of older reproductive age who do not wish to conceive should use effective contraception until 1 year after the final menstrual period.
2. Long-acting reversible contraceptive methods, which include the copper intrauterine device (IUD), the levonorgestrel intrauterine system, and the etonogestrel subdermal implant, provide superior contraceptive effectiveness (equivalent to sterilization) and higher continuation rates compared to shorter-acting methods.
3. Although no contraceptive methods are contraindicated on the basis of age alone (except for the use of oral contraceptives in heavy smokers aged older than 35 years), women of older reproductive age may have medical conditions that increase the risks associated with certain methods, rendering them inappropriate.
4. Additional benefits of combined estrogen-progestogen contraceptives for perimenopausal women include management of vasomotor symptoms and abnormal uterine bleeding.

#### Recommendations for Clinical Care

1. Evidence-based guidelines from the Centers for Disease Control and Prevention represent a valuable resource for clinicians and women of older reproductive age when selecting appropriate contraceptive methods and managing contraceptive issues. (Level II)
2. Contraceptive methods that contain estrogen should be used with caution in women of older reproductive age who smoke, are obese, or have other risk factors for cardiovascular disease. In most cases, progestogen-only methods and the copper IUD provide effective, safe alternatives. (Level II)
3. The higher-dose levonorgestrel intrauterine system can be used as a first-line treatment for heavy menstrual bleeding and is an effective reversible alternative to endometrial ablation and hysterectomy. (Level I)
4. Combination hormonal contraceptives provide important noncontraceptive benefits, including treatment of irregular uterine bleeding, reduction of vasomotor symptoms, decreased risk of ovarian and endometrial cancer, and maintenance of bone mineral density. (Level II)

### ESTROGEN THERAPY AND ESTROGEN-PROGESTOGEN THERAPY

#### Key Points

1. Treatment of moderate to severe vasomotor symptoms is the primary indication for hormone therapy. The benefits outweigh the risks for most healthy, symptomatic women aged younger than 60 years or within 10 years of the final menstrual period.

2. Progestogen therapy (progesterone and synthetic progestins) is an option to treat hot flashes, but it is not as effective as estrogen, and long-term safety data are limited. Its primary use in postmenopausal women is to reduce the risk of endometrial cancer associated with unopposed estrogen therapy (ET).
3. An increased risk of breast cancer was seen with 3 to 5 years of estrogen-progestogen therapy use in the Women's Health Initiative, whereas no increased risk of breast cancer was seen with 7 years of ET use, allowing for more flexibility in duration of ET use in women without a uterus.
4. Both transdermal ET and low-dose oral ET have been associated with a lower risk of venous thromboembolism and stroke compared with standard-dose oral ET in observational studies, but evidence from randomized, controlled trials is lacking.
5. A combination of the selective estrogen receptor modulator bazedoxifene with conjugated estrogen is approved for the treatment of vasomotor symptoms and prevention of osteoporosis in women with a uterus.
6. Systemic HT and low-dose vaginal ET are very effective treatments for moderate to severe symptoms of vulvar and vaginal atrophy (vaginal dryness, dyspareunia, and atrophic vaginitis). The estrogen agonist/antagonist ospemifene is a new oral agent approved for this indication.

#### Recommendations for Clinical Care

1. The lowest dose of HT should be used for the shortest duration needed to manage menopausal symptoms. Individualization is important in the decision to use HT and should incorporate the woman's personal risk factors and her quality-of-life priorities in this shared decision. (Level II)
2. Extended duration of HT use might be appropriate in symptomatic women or for the prevention of osteoporosis, if alternative therapies are not tolerated. A careful assessment of individual benefits and risks is advised in these cases. (Level III)
3. The use of custom-compounded bioidentical HT is not recommended, given limited product quality control and lack of evidence that it is safe or effective. (Level III)
4. When ET is considered solely for treatment of moderate to severe symptoms of vulvar and vaginal atrophy, the use of low-dose vaginal ET rather than systemic ET is advised due to its greater safety profile. (Level II)
5. Women with primary ovarian insufficiency or early menopause without contraindications to HT should consider the use of HT or combined estrogen-progestogen contraceptives until the average age of natural menopause (52 years). Longer duration may be considered for symptomatic women. (Level II)
6. Hormone therapy should not be prescribed for chronic disease prevention. (Level I)

## COMPOUNDED HORMONE THERAPY

### Key Points

1. The term *custom-compounded hormone therapy* describes the mixing of hormones by a pharmacy based on a prescription reportedly customized for an individual woman, often based on blood or salivary hormone levels. These HT products typically contain one or more hormones in differing amounts in addition to other ingredients to create a cream, gel, lozenge, tablet, spray, or skin pellet.
2. Although the term *bioidentical hormones* is often used to describe custom-compounded HT products as they typically contain only hormones structurally identical to those produced by a woman's ovaries during the reproductive years, the term was invented by marketers and has no clear scientific meaning.
3. Use of custom-compounded HT has increased significantly since the initial publication of the Women's Health Initiative as women seek alternative therapies.
4. Compounding pharmacies are regulated by state pharmacy boards, with little oversight by FDA.
5. Compounded hormones are not tested for safety and efficacy as are FDA-approved commercially manufactured HT products.
6. Compounded hormones do not routinely include the product information sheet required by FDA of commercially manufactured HT products.
7. Advertising and promotional claims regarding the efficacy and safety of compounded hormones are not validated by medical evidence.
8. Consumers generally are unaware of the limited control FDA exercises over the marketing and safety monitoring of compounded hormones.

### Recommendations for Clinical Care

1. Prescription of custom-compounded HT is not advised due to lack of quality control and regulatory oversight of these products, with concerns regarding product efficacy and safety. (Level I)
2. The use of serum or salivary hormone levels is not recommended to assist in the management of HT as these levels are of no value in either selecting initial medication dosages or monitoring therapy for menopausal symptoms. (Level II)
3. Women requesting bioidentical or custom-compounded HT should be encouraged to use FDA-approved HT products that are biochemically identical to the hormones naturally produced by the ovaries during reproductive life (eg, estradiol and progesterone). Approved HT products are available in a wide range of doses, which may be adjusted to meet the individual needs of each woman. (Level II)

## ANDROGENS

### Key Points

1. Androgen levels decline in women with aging but do not change across the menopause transition.

Androgen levels are significantly lower in women with primary ovarian insufficiency and following bilateral oophorectomy.

2. There is evidence to support the use of testosterone therapy in carefully selected postmenopausal women with female sexual interest/arousal disorder (previously known as hypoactive sexual desire disorder) and no other identified etiology for their sexual problem.
3. The long-term risks of androgen therapy in women, including possible effects on the risk of cardiovascular disease or breast cancer, are unknown.
4. There is no evidence to support the use of dehydroepiandrosterone for the management of female sexual interest/arousal disorder. Research is ongoing regarding the use of vaginal DHEA in postmenopausal women with symptomatic vulvovaginal atrophy and associated decreased libido.
5. There are currently no androgen-containing prescription products government-approved for the treatment of female sexual interest/arousal disorder in the United States or Canada.

#### Recommendations for Clinical Care

1. A trial of testosterone therapy may be considered in carefully selected postmenopausal women with female sexual interest/arousal disorder and no other etiology for their sexual problems. Women must be informed of potential adverse effects and unknown long-term risks. (Level I)
2. Women using testosterone should be monitored for adverse effects, including facial hair, acne, voice changes, clitoromegaly, and adverse changes in lipids or liver function tests. Blood testosterone levels should be checked intermittently to ensure that levels remain in the normal range for reproductive-aged women. (Level II)
3. Formulations of testosterone approved for the treatment of men increase the risk of excessive dosing when prescribed for women. (Level II)
4. There is currently no role for the use of DHEA in the treatment of female sexual disorders. (Level I)

### SELECTIVE ESTROGEN RECEPTOR MODULATORS

#### Key Points

1. Selective estrogen receptor modulators (SERMs) are compounds that act as estrogen agonists in some tissues and as estrogen antagonists in others. Different SERMs provide different tissue-specific actions, allowing for individualization depending on the medical needs of the postmenopausal women.
2. SERMs available in the United States and Canada include tamoxifen, approved for prevention and treatment of breast cancer; toremifene, approved for treatment of breast cancer; raloxifene, approved for prevention and

treatment of osteoporosis and prevention of breast cancer; and ospemifene, approved for treatment of dyspareunia due to postmenopausal vaginal atrophy.

3. The first tissue-selective estrogen complex (TSEC) is a pairing of conjugated estrogens with the SERM bazedoxifene, approved for the treatment of vasomotor symptoms and the prevention of osteoporosis in women with a uterus. Bazedoxifene provides endometrial protection, so a progestogen is not needed.
4. In addition to its known benefit for prevention and treatment of breast cancer, tamoxifen is an estrogen agonist in bone and reduces bone loss in postmenopausal women at the spine and hip. Adverse effects include an increased risk of uterine cancer, venous thromboembolic events (VTEs), and cataracts.
5. Raloxifene increases bone mineral density and decreases the risk of osteoporotic vertebral, but not hip or nonvertebral, fractures. Raloxifene also reduces the risk of invasive breast cancer in postmenopausal women at increased risk for breast cancer. Raloxifene increases the risk of VTEs but does not increase the risk of uterine cancer.
6. Ospemifene improves vaginal pH, vaginal maturation index, and dyspareunia due to vulvovaginal atrophy in postmenopausal women. No trials have evaluated ospemifene's effects on the prevention or treatment of breast cancer or osteoporosis.

#### Recommendations for Clinical Care

1. The decision to initiate or continue therapy with a SERM or TSEC should be individualized based on the clinical needs of the postmenopausal woman, her medical history, and the known risks and benefits of each agent. (Level II)
2. SERMs may be used to prevent breast cancer (tamoxifen, raloxifene), treat breast cancer (tamoxifen, toremifene), prevent and treat osteoporosis (raloxifene), and treat moderate to severe dyspareunia due to vaginal atrophy (ospemifene). (Level I)
3. The TSEC bazedoxifene combined with conjugated estrogens may be used in women with a uterus to treat moderate to severe vasomotor symptoms and prevent osteoporosis. (Level I)
4. SERMs should not be used in women at high risk of thrombosis because they increase the risk of VTEs, similar to oral estrogen therapy. (Level I)

### SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

#### Key Points

1. Several selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) decrease the frequency and severity of vasomotor symptoms in postmenopausal women.

2. The SSRI, paroxetine, is the first nonhormonal medication to be government approved for the treatment of vasomotor symptoms. The approved dose (paroxetine 7.5 mg) is lower than the doses of paroxetine approved for the treatment of depression.
3. Although randomized controlled trials demonstrate efficacy greater than placebo for other SSRIs and SNRIs, including venlafaxine and escitalopram, and other doses of paroxetine, these formulations are not currently approved for the treatment of vasomotor symptoms.
4. Some SSRIs and SNRIs inhibit the cytochrome P450 enzyme system and may render tamoxifen less effective.

### Recommendations for Clinical Care

1. Midlife women with bothersome vasomotor symptoms may consider the use of an SSRI or SNRI for the treatment of vasomotor symptoms; paroxetine 7.5 mg is the only non-hormonal agent government approved for this indication. (Level I)
2. Women using tamoxifen for the prevention or treatment of breast cancer should avoid the use of paroxetine for management of vasomotor symptoms. (Level II)
3. Use of an SSRI or SNRI for the treatment of vasomotor symptoms should be individualized, based on a woman's medical history, personal preferences, and the overall risk-benefit assessment. (Level II)

**DISCLOSURES:** NAMS is committed to ensuring balance, independence, and objectivity in all its educational activities. All those involved in the development of *Recommendations for Clinical Care of Midlife Women* were required to disclose financial relationships they or their spouse/partner have had during the last 12 months with a commercial interest whose products or services are discussed. Disclosures are noted in parentheses after each contributor.

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