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Menopause and Osteoporosis Update 2009

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LA SOCIÉTÉ DES OBSTÉTRICIENS ET GYNÉCOLOGUES DU CANADA

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Menopause and Osteoporosis Update 2009

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Abstract

Objective: To provide updated guidelines for health care providers on the management of menopause in asymptomatic healthy women as well as in women presenting with vasomotor symptoms or with urogenital, mood, or memory concerns, and on considerations related to cardiovascular disease, breast cancer, and bone health, including the diagnosis and clinical management of postmenopausal osteoporosis.

Outcomes: Lifestyle interventions, prescription medications, and complementary and alternative therapies are presented according to their efficacy in the treatment of menopausal symptoms. Strategies for identifying and evaluating women at high risk of osteoporosis, along with options for the prevention and treatment of osteoporosis, are presented.

Evidence: MEDLINE was searched up to October 1, 2008, and the Cochrane databases up to issue 1 of 2008 with the use of a controlled vocabulary and appropriate key words. Research-design filters for systematic reviews, randomized and controlled clinical trials, and observational studies were applied to all PubMed searches. Results were limited to publication years 2002 to 2008; there were no language restrictions. Additional information was sought in BMJ Clinical Evidence, in guidelines collections, and from the Web sites of major obstetric and gynaecologic associations world wide. The authors critically reviewed the evidence and developed the recommendations according to the methodology and consensus development process of the Journal of Obstetrics and Gynaecology Canada.

Values: The quality of the evidence was rated with use of the criteria described by the Canadian Task Force on Preventive Health Care. Recommendations for practice were ranked according to the method described by the Task Force. See Table.

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Key Words: Menopause, estrogen, vasomotor symptoms, urogenital symptoms, mood, memory, cardiovascular disease, breast cancer, osteoporosis, fragility fractures, bone mineral density, lifestyle, nutrition, exercise, estrogen therapy, complementary therapies, bisphosphonates, calcitonin, selective estrogen receptor modulators, antiresorptive agents

Summary Statements and Recommendations

Chapter 1: Towards a Healthier Lifestyle

No recommendations.

Chapter 2: Vasomotor Symptoms

1. Lifestyle modifications, including reducing core body temperature, regular exercise, weight management, smoking cessation, and avoidance of known triggers such as hot drinks and alcohol may be recommended to reduce mild vasomotor symptoms. (IC)
2. Health care providers should offer HT (estrogen alone or EPT) as the most effective therapy for the medical management of menopausal symptoms. (IA)
3. Progestins alone or low-dose oral contraceptives can be offered as alternatives for the relief of menopausal symptoms during the menopausal transition. (IA)
4. Nonhormonal prescription therapies, including treatment with certain antidepressant agents, gabapentin, clonidine, and bellergal, may afford some relief from hot flashes but have their own side effects. These alternatives can be considered when HT is contraindicated or not desired. (IB)
5. There is limited evidence of benefit for most complementary and alternative approaches to the management of hot flashes. Without good evidence for effectiveness, and in the face of minimal data on safety, these approaches should be advised with caution. Women should be advised that, until January 2004, most natural health products were introduced into Canada as “food products” and did not fall under the regulatory requirements for pharmaceutical products. As such, most have not been rigorously tested for the treatment of moderate to severe hot flashes, and many lack evidence of efficacy and safety. (IB)
6. Any unexpected vaginal bleeding that occurs after 12 months of amenorrhea is considered postmenopausal bleeding and should be investigated. (IA)
7. HT should be offered to women with premature ovarian failure or early menopause (IA), and it can be recommended until the age of natural menopause (IIIC).
8. Estrogen therapy can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (IA)

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care*

Quality of evidence assessment†	Classification of recommendations‡
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. Can Med Assoc J 2003;169(3):207-8.

†The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.*

‡Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.*

Chapter 3: Cardiovascular Disease (CVD)

1. Health care providers should not initiate or continue HT for the sole purpose of preventing CVD (coronary artery disease and stroke). (IA)

2. Health care providers should abstain from prescribing HT in women at high risk for venous thromboembolic disease. (IA)

3. Health care providers should initiate other evidence-based therapies and interventions to effectively reduce the risk of CVD events in women with or without vascular disease. (IA)

4. Risk factors for stroke (obesity, hypertension, and cigarette smoking) should be addressed in all postmenopausal women. (IA)

5. If prescribing HT to older postmenopausal women, health care providers should address cardiovascular risk factors; low- or ultralow-dose estrogen therapy is preferred. (IB)

6. Health care providers may prescribe HT to diabetic women for the relief of menopausal symptoms. (IA)

Chapter 4: Hormone Therapy and Breast Cancer

1. Health care providers should periodically review the risks and benefits of prescribing HT to a menopausal woman in light of the association between duration of use and breast cancer risk. (IA)

2. Health care providers may prescribe HT for menopausal symptoms in women at increased risk of breast cancer with appropriate counselling and surveillance. (IA)

3. Health care providers should clearly discuss the uncertainty of risks associated with HT after a diagnosis of breast cancer in women seeking treatment for distressing symptoms. (IB)

Chapter 5: Urogenital Health

Urogenital concerns

1. Conjugated estrogen cream, an intravaginal sustained-release estradiol ring, or estradiol vaginal tablets are recommended as effective treatment for vaginal atrophy. (IA)

2. Routine progestin cotherapy is not required for endometrial protection in women receiving vaginal estrogen therapy in appropriate dose. (IIIC)

3. Vaginal lubricants may be recommended for subjective symptom improvement of dyspareunia. (IIIC)

4. Health care providers can offer polycarbophil gel (a vaginal moisturizer) as an effective treatment for symptoms of vaginal atrophy, including dryness and dyspareunia. (IA)

5. As part of the management of stress incontinence, women should be encouraged to try nonsurgical options, such as weight loss (in obese women), pelvic floor physiotherapy, with or without biofeedback, weighted vaginal cones, functional electrical stimulation, and/or intravaginal pessaries. (II-1B)

6. Lifestyle modification, bladder drill (II-1B), and antimuscarinic therapy (IA) are recommended for the treatment of urge urinary incontinence.

7. Estrogen therapy should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence but may be recommended before corrective surgery. (IA)

8. Vaginal estrogen therapy can be recommended for the prevention of recurrent urinary tract infections in postmenopausal women. (IA)

9. Following treatment of adenocarcinoma of the endometrium (stage 1) estrogen therapy may be offered to women distressed by moderate to severe menopausal symptoms. (IB)

Sexual concerns

10. A biopsychosexual assessment of preferably both partners (when appropriate), identifying intrapersonal, contextual, interpersonal,

and biological factors, is recommended prior to treatment of women's sexual problems. (IIIA)

11. Routine evaluation of sex hormone levels in postmenopausal women with sexual problems is not recommended. Available androgen assays neither reflect total androgen activity, nor correlate with sexual function. (IIIA)
12. Testosterone therapy when included in the management of selected women with acquired sexual desire disorder should only be initiated by clinicians experienced in women's sexual dysfunction and with informed consent from the woman. The lack of long-term safety data and the need for concomitant estrogen therapy mandate careful follow-up. (IC)

Chapter 6: Mood, Memory, and Cognition

1. Estrogen alone may be offered as an effective treatment for depressive disorders in perimenopausal women and may augment the clinical response to antidepressant treatment, specifically with SSRIs (IB). The use of antidepressant medication, however, is supported by most research evidence (IA).
2. Estrogen can be prescribed to enhance mood in women with depressive symptoms. The effect appears to be greater for perimenopausal symptomatic women than for postmenopausal women. (IA)
3. Estrogen therapy is not currently recommended for reducing the risk of dementia developing in postmenopausal women or for retarding the progression of diagnosed Alzheimer's disease, although limited data suggest that early use of HT in the menopause may be associated with diminished risk of later dementia. (IB)

Chapter 7: Bone Health

1. The goals of osteoporosis management include assessment of fracture risk and prevention of fracture and height loss. (1B)
2. A stable or increasing BMD reflects a response to therapy in the absence of low trauma fracture or height loss. Progressive decreases in BMD, with the magnitude of bone loss being greater than the precision error of the bone densitometer, indicate a lack of response to current therapy. Management should be reviewed and modified appropriately. (1A)
3. Physicians should identify the absolute fracture risk in postmenopausal women by integrating the key risk factors for fracture; namely, age, BMD, prior fracture, and glucocorticoid use. (1B)
4. Physicians should be aware that a prevalent vertebral or nonvertebral fragility fracture markedly increases the risk of a future fracture and confirms the diagnosis of osteoporosis irrespective of the results of the bone density assessment. (1A)
5. Treatment should be initiated according to the results of the 10-year absolute fracture risk assessment. (1B)

Calcium and vitamin D

6. Adequate calcium and vitamin D supplementation is key to ensuring prevention of progressive bone loss. For postmenopausal women a total intake of 1500 mg of elemental calcium from dietary and supplemental sources and supplementation with 800 IU/d of vitamin D are recommended. Calcium and vitamin D supplementation alone is insufficient to prevent fracture in those with osteoporosis; however, it is an important adjunct to pharmacologic intervention with antiresorptive and anabolic drugs. (1B)

Hormone therapy

7. Usual-dosage HT should be prescribed for symptomatic postmenopausal women as the most effective therapy for menopausal symptom relief (1A) and a reasonable choice for the prevention of bone loss and fracture. (1A)
8. Physicians may recommend low- and ultralow-dosage estrogen therapy to symptomatic women for relief of menopausal symptoms (1A) but should inform their patients that despite the fact that such therapy has demonstrated a beneficial effect in osteoporosis prevention (1A), no data are yet available on reduction of fracture risk.

Bisphosphonates

9. Treatment with alendronate, risedronate, or zoledronic acid should be considered to decrease the risk of vertebral, nonvertebral, and hip fractures. (1A)
10. Etidronate is a weak antiresorptive agent and may be effective in decreasing the risk of vertebral fracture in those at high risk. (1B)

Selective estrogen receptor modulators

11. Treatment with raloxifene should be considered to decrease the risk of vertebral fractures. (1A)

Calcitonin

12. Treatment with calcitonin can be considered to decrease the risk of vertebral fractures and to reduce pain associated with acute vertebral fractures. (1B)

Parathyroid hormone

13. Treatment with teriparatide should be considered to decrease the risk of vertebral and nonvertebral fractures in postmenopausal women with severe osteoporosis. (1A)

Preamble

Menopause is a critical phase in the lives of women. It evokes discussion, controversy, and concern among women and their health care providers about how best to deal with acute symptoms and what changes or interventions are best for optimization of long-term health. In 2009, as the largest demographic from the "baby-boomer" generation reaches age 50 years, we will begin a period of historic demand for menopausal counselling.

Women entering menopause are highly motivated to make changes to optimize their health. Thus, health care providers have a unique opportunity to review a woman's lifestyle choices and medical options and to make recommendations that will maintain or improve her quality of life. This opportunity requires that health care providers avail themselves of the available scientific information on aging and familiarize themselves with the emerging information.

The appropriateness of offering HT as an option to menopausal women has come under the spotlight with conflicting reports of benefits and risks and confusion about how these compare. This document will provide the reader with an update about the controversies surrounding HT for menopausal women and will try to bring balance and perspective to the risks and benefits to facilitate informed discussion about this option.

In 2006, the SOGC published a detailed update from the Canadian Consensus Conference on Menopause that highlighted recommendations for counselling and care of menopausal women.[1] Few of these recommendations have changed, although new data have allowed some additional insights, which are reflected in the recommendations of the current report.

The current consensus document was developed after a detailed review of publications pertaining to menopause, osteoporosis, and postmenopausal HT. Published literature was identified through searching PubMed (up until February 7, 2008) and the databases of the Cochrane Library (issue 1, 2008), with the use of a combination of controlled vocabulary (e.g., Hormone Replacement Therapy, Cardiovascular Diseases, Mental Health) and key words (e.g., hormone replacement therapy, coronary heart disease, mental well-being). Research-design filters for systematic reviews, randomized and controlled clinical trials, and observational studies were applied to all PubMed searches. Results were limited to publication years 2002 to 2008; there were no language restrictions. Additional information was sought in *BMJ Clinical Evidence,* in guidelines collections, and from the Websites of major obstetric and gynaecologic associations world wide.

Abbreviations Used in This Guideline

BMD	bone mineral density
BMI	body mass index
CAD	coronary artery disease
CEE	conjugated equine estrogens
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
HABITS	hormonal replacement therapy after breast cancer—Is it safe?
HERS	Heart and Estrogen/progestin Replacement Study
HR	hazard ratio
HT	hormone therapy
IMT	intima–media thickness
MORE	Multiple Outcomes of Raloxifene Evaluation
MPA	medroxyprogesterone acetate
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SERM	selective estrogen-receptor modulator
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAR	Study of Tamoxifen and Raloxifene
WHI	Women's Health Initiative
WHIMS	Women's Health Initiative Memory Study
WISDOM	Women's International Study of long Duration Oestrogen after Menopause

REFERENCE

1. Bélisle S, Blake J, Basson R, Desindes S, Graves G, Grigoriadis S, et al. Canadian Consensus Conference on Menopause, 2006 update. J Obstet Gynaecol Can 2006;28(2 Suppl 1):S1-S112.

Towards a Healthier Lifestyle

In 2009, as the largest demographic from the "baby-boomer" generation reaches age 50 years, a period of historic demand for menopausal counselling will begin, along with an unprecedented opportunity to influence patterns of disability and death in the later decades of life. As outlined in the following chapters of this update to the Canadian Consensus Conference on Menopause[1] and the Canadian Consensus Conference on Osteoporosis,[2] many of the risk factors for the conditions prevalent among older women are modifiable through changes in lifestyle.

LIFESTYLE AND CARDIOVASCULAR HEALTH

Women entering menopause today have had the advantages of growing up with access to better nutrition, a greater focus by society and by health care professionals on preventive health care, and much improved access to information about healthy living. Over the past 25 years, the risk of heart disease has progressively fallen.[3] Still, CVD remains the leading cause of death and an important contributor to illness and disability among women: half of all postmenopausal women will have CVD, and a third will die from it. The risk of CVD rises with age and increases significantly after menopause.

The INTERHEART study, an RCT examining modifiable risk factors across many populations, determined that the main risks for CVD are modifiable and that for women 94% of CVD risk could be attributed to modifiable factors.[4] Factors identified in that study as contributing substantially to increased CVD risk included diabetes mellitus, hypertension, abdominal obesity, current smoking, and psychosocial stress. Each of these risks can be reduced through appropriate choices, interventions, or both. Available evidence demonstrates that initiation of HT should be done with caution in women with distressing vasomotor symptoms who are more than a decade after menopause because of the association with an increased risk of adverse cardiac events. Attention to correction of underlying cardiovascular risk factors before initiation of HT would be important in these isolated cases.

Stroke is also a leading cause of disability and death among women, especially postmenopausal women. Risk factors for stroke (obesity, hypertension, smoking, and diabetes) are common among North American women as they enter menopause, and certain segments of the population, such as African-Americans, are more likely to manifest these risk factors. HT appears to slightly increase the risk of ischemic stroke, and caution should be taken to manage hypertension and other risk factors in women seeking treatment for distressing vasomotor symptoms.[5] Clearly, risk factors for stroke should be addressed in all menopausal women and particularly in those seeking HT.

The mainstay for CVD prevention will remain a lifelong pattern of healthy living incorporating a balanced, heart-healthy diet, moderate exercise, maintenance of a healthy body weight, avoidance of smoking, limited consumption of alcohol, and attention to treatment of known risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus.

OTHER BENEFITS OF LIFESTYLE MODIFICATION

The benefits of a healthy lifestyle extend well beyond optimizing cardiovascular health. For best preservation of memory and cognition, women should be advised about the importance of good overall health, including good cardiovascular health, exercise,[6] avoidance of excessive alcohol consumption, and measures to reduce the risk of diabetes and hypertension, as well as maintenance of an active mind.

The risk of breast cancer associated with postmenopausal HT is the health risk of greatest concern to women and to their physicians. Singletary[7] tried to place various breast cancer risk factors into perspective, noting that HT, as a risk, rates about the same as early menarche, late menopause, and a variety of lifestyle-associated risks, such as excessive alcohol consumption and failure to exercise. Attention should be directed to modifiable risk factors, such as smoking, sedentary lifestyle, excessive intake of alcohol, and postmenopausal weight gain.[8] Reduction of dietary fat intake was not associated with any reduction in breast cancer risk in the WHI[9] but may help prevent cardiovascular diseases and possibly ovarian cancer.[10]

Adequate calcium and vitamin D intake is necessary to attain and maintain normal bone quantity and quality and thus achieve optimal bone strength. But an exercise program is also essential to the prevention and treatment of osteoporosis. A comprehensive calculation of the 10-year absolute fracture risk, available from the World Health

Organization,[11] includes current tobacco smoking and alcohol intake of 3 or more units daily among the risk factors now added to the traditional risk factors of age, low BMD, prior fracture, and glucocorticoid use. Younger individuals at a low risk of fracture are appropriately managed with lifestyle changes and strategies designed to prevent bone loss, with an emphasis on regular exercise and reduced consumption of alcohol (to less than 2 drinks/d) and coffee (to less than 4 cups/d). Smoking cessation should also be strongly advised.

Some of the risk factors for urinary incontinence are modifiable with lifestyle changes. Those identified include obesity, amount and type of fluid intake, and smoking. For obese women (mean baseline BMI, 38.3 kg/m^2), even a reduction in BMI of as little as 5% can result in significant subjective improvement in urine loss.[12] The effect of BMI and weight gain was assessed in 30 000 women with new-onset urinary incontinence in the Nurses' Health Study II.[13] Increasingly higher BMI was related to increasing odds of incontinence developing (P for trend < 0.001). The increases were similar for all incontinence types. The odds of incontinence also increased with increasing adult weight gain (P for trend < 0.001): the OR for at least weekly incontinence developing was 1.44 (95% CI, 1.05 to 1.97) among women who had gained 5.1 to 10 kg since early adulthood and 4.04 (95% CI, 2.93 to 5.56) among women who had gained more than 30 kg compared with women who had maintained their weight within 2 kg. In the same population, physical activity was associated with a significant reduction in the risk of urinary incontinence developing. The results appeared to be somewhat stronger for stress urinary incontinence than for urge urinary incontinence.[14]

MENOPAUSE AND DIET

Canada's Food Guide

Since 1942, *Canada's Food Guide* has provided advice on food selection and nutritional health. With the February 2007 launch of the latest version, *Eating Well with Canada's Food Guide,*[15] come 2 major changes: the guide now offers information on the amount and types of food recommended according to age and sex, and it emphasizes the importance of combining regular physical activity with healthy eating. With the growing concern about the rates of overweight and obesity among Canadians, providing advice on portion size and the quality of food choices was a key consideration in this revision of the guide. The new guide was developed through widespread consultation with approximately 7000 stakeholders, including dietitians, scientists, physicians, and public health personnel with an interest in health and chronic disease prevention. It is available in 13 languages, and a version has been specially tailored for First Nations, Inuit, and Métis people.

The guide encourages Canadians to focus on vegetables, fruit, and whole grains, to include milk, meat, and their alternatives, and to limit foods that are high in calories, fat (especially trans fats), sugar, and salt. The enhanced, interactive Web component, "My Food Guide," helps users personalize the information according to age, sex, and food preferences; it includes more culturally relevant foods from a variety of ethnic cuisines. To build a customized plan for healthy choices in both nutrition and physical activity after menopause, a woman can start by choosing "Female" and age "51 to 70." She learns that she should be consuming each day 7 servings of vegetables and fruits, 6 of grain products, 3 of milk and alternatives, and 2 of meat and alternatives. Within each food group, she is invited to choose 1 to 6 examples. For the first group, vegetables and fruits, the long, colourfully illustrated list (with serving sizes and notes about acceptable alternatives) is headed by 3 general recommendations: eat at least 1 dark green and 1 orange vegetable a day, prepare vegetables and fruits with little or no added fat, sugar, and salt, and have vegetables and fruits more often than juice. The vegetables and fruits are grouped in 2 lists, 1 of dark green and orange choices and the other of additional choices. After making selections and clicking on "Next," the woman is presented with the other categories of food in turn and then categories of physical activity. At the end a colourful PDF of "My Food Guide" is produced; it can be printed or saved on one's computer. This summary reiterates the tips for each food category and the portion size for each choice, notes that "age 50 or over, include a vitamin D supplement of 10 μg (400 IU), and recommends "Build 30 to 60 minutes of physical activity into your day every day."

Also on the guide's website is "My Food Guide Servings Tracker". This tool helps users keep track of the amount and type of food eaten each day and to make comparisons with the recommendations. Tips about food and physical activity are reiterated on the sheet that is printed out. A recent RCT has shown that people trying to lose weight who use a dietary log will lose twice as much weight as those who do not keep track of their food intake.[16] Those studied, at an average age of 55 years, were overweight or obese. All participants were asked to revise their diets to include less fat, more vegetables, fruits, and whole grains, to increase their exercise, and to attend meetings that encouraged calorie restriction, moderate-intensity physical activity, and dietary approaches to reduce hypertension.

Linked to the Food Guide website is the site for EATracker (Eating and Activity Tracker),[17] a tool developed by the Dietitians of Canada to provide even more detailed

Selected resources

Topic	Organization and details	Website*
Breast cancer risk	US National Cancer Institute: Breast Cancer Risk Assessment Tool	www.bcra.nci.nih.gov/brc
Disease risk and prevention	Siteman Cancer Center, Washington University School of Medicine: Your Disease Risk (health tool, originally developed at the Harvard Center for Cancer Prevention, which covers cancer, diabetes, heart disease, osteoporosis, and stroke)	www.yourdiseaserisk.wustl.edu
Exercise	Public Health Agency of Canada: Physical Activity Guide	www.phac-aspc.gc.ca/pau-uap/paguide/
Heart disease and stroke	Heart and Stroke Foundation of Canada: information on heart disease, stroke, nutrition, physical activity, smoking cessation, and stress reduction	www.hsf.ca
Menopause	Society of Obstetricians and Gynaecologists of Canada: clinical practice guidelines, consensus conference reports, and educational material for consumers	www.sogc.org www.menopauseandu.ca
Nutrition	Health Canada: Eating Well with Canada's Food Guide	www.healthcanada.gc.ca/foodguide
	Dietitians of Canada: EATracker (Eating and Activity Tracker)	www.dietitians.ca/public/content/eat_well_live_well/english/eatracker/index.asp
Osteoporosis	Osteoporosis Canada: information on diagnosis, prevention, and treatment	www.osteoporosis.ca
Sexual health	Society of Obstetricians and Gynaecologists of Canada: news and information on sexual-health issues, including a section for women over 50 years of age	www.sexualityandu.ca
Weight control	US National Heart, Lung, and Blood Institute: Aim for a Healthy Weight (Obesity Education Initiative: information for patients and the public and for health professionals)	www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/index.htm

*Last accessed September 1, 2008.

nutritional information and guidance as one progresses through an attempt to make healthy changes in both eating and physical activity.

As Dr David Butler-Jones, Chief Public Health Officer for Canada, said at the launch of the new food guide, "By increasing their levels of physical activity, improving eating habits, and achieving healthy weights, Canadians can help ensure good health and prevent many chronic diseases, including some cancers, type 2 diabetes, cardiovascular disease and stroke."

Diet and Heart Disease

Observational studies show a relationship between serum cholesterol levels and CVD.[18] Dietary measures to lower those levels are an important part of the prevention of CVD.[19] Evidence from the Nurses' Health Study suggests that replacing dietary saturated fat and trans fatty acids with nonhydrogenated, monounsaturated, and polyunsaturated fats may be more effective in reducing the CVD risk than reducing overall fat intake in women.[20] The intake of omega-3 fatty acids is linked to a reduced risk of CVD;[21] potential dietary sources of these fats include cold water fish (salmon, tuna, and halibut), flax seeds, and flax seed oil. *Canada's Food Guide* recommends limiting the amount of saturated fat and trans fatty acids used each day and including 30 to 45 mL (2 to 3 tablespoons) of unsaturated fat each day to get the fat that is needed; this amount includes oil used for cooking, salad dressings, margarine, and mayonnaise. Having 2 servings of fish a week is also recommended.

Other dietary strategies to reduce the CVD risk include increasing the intake of flavonoids[22,23] (found in vegetables, fruits, and tea), dietary folate[24] (found in vegetables, fruits, and grains), and soy products[25] (sources of isoflavones).

Diet and Bone Health

Minimizing the rate of bone loss with age requires adequate nutrition and, in particular, adequate intake of calcium and vitamin D. If dietary intake is reduced in order to lower dietary fat content, calcium intake may need to be supplemented. Diet alone is not sufficient to prevent bone loss in women with early menopause. [26] Supplementation of both calcium and vitamin D may be necessary, especially in those with low intake of dairy products.

For postmenopausal women the SOGC recommends a total intake of 1500 mg of elemental calcium from dietary and supplemental sources and, to ensure optimal calcium absorption, supplementation with 800 IU/d of vitamin D (twice as much vitamin D as recommended in *Canada's Food Guide*) for women 50 years of age or older.

Diet and Cancer

It has been estimated that 30% to 40% of all cancer could be prevented with a healthy diet, regular physical activity, and maintenance of an appropriate body weight.[27] Possible associations between aspects of diet and breast cancer have come under scrutiny, with emphasis on intake of fat and isoflavones. Reduction of dietary fat intake in the WHI was not associated with any reduction in breast cancer risk,[9] although it may have a benefit in preventing ovarian cancer.[10]

MENOPAUSE AND EXERCISE

In addition to protecting against CVD, diabetes, and breast cancer, regular physical exercise can reduce levels of stress and menopausal symptoms, decrease bone loss, and improve balance and strength.

Thirty minutes of moderate aerobic exercise (even in 10-minute sessions) is recommended for its cardioprotective effects. A minimum of 20 to 30 minutes of weight-bearing exercise on most days, along with muscle-strengthening exercise involving the arms and legs, abdomen, and back for 30 to 60 minutes 3 times per week can improve bone mass and decrease back pain. Flexibility training can improve balance and will thus help to prevent falls and protect against fractures.

ROLE OF HEALTH CARE PROVIDERS

Not only is there evidence that a healthy lifestyle leads to better outcomes, but also there is good evidence that intervention by health care providers increases the likelihood that a patient will make a healthy change. Women in menopause are ready to make positive changes in their lives,[28] and life transitions are opportune times to make lifestyle changes. Providing advice, encouragement, and support, as well as trusted educational resources (Table), is a fundamental adjunct to any other medical advice that may be appropriate.

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Vasomotor Symptoms

Vasomotor symptoms affect 60% to 80% of women entering menopause.[1] Hot flashes are common in the perimenopausal transition, when ovarian activity may be intermittent, and they have also been documented during the luteal and menstrual phases of the cycle in women with premenstrual dysphoric disorder.[2] Although most postmenopausal women (60%) experience hot flashes for less than 7 years, up to 15% report that hot flashes persist for 15 years or more.[3] The symptoms that can accompany hot flashes (including sweating, palpitations, apprehension, and anxiety) contribute to the woman's discomfort, inconvenience, and distress, particularly when these episodes occur very frequently. They can be a significant contributor to sleep disturbance. In Western societies, hot flashes are a chief menopausal complaint leading women to seek either over-the-counter remedies or medical treatment, which supports the belief that this symptom represents a significant disruption in the quality of life.[3]

Normally the body maintains an optimal temperature for metabolic activity through vasodilatation and sweating when overheated and shivering when cold.[4] Postmenopausal women are thought to have narrowing of this "thermoneutral zone" such that small changes in temperature can evoke the regulatory response of sweating or shivering.[4] Risk factors for hot flashes include obesity and cigarette smoking[5] and, along with a variety of known triggers (alcohol, warm ambient environment, hot drinks), form the basis for lifestyle recommendations to reduce vasomotor symptoms.

Since the report about risks associated with HT from the WHI in 2002, many physicians have abandoned the prescription of HT for vasomotor symptoms in favour of recommending lifestyle changes and cooling devices that can be purchased through the Internet. Unfortunately, many women find that these approaches afford little relief and have turned to unproven and often untested complementary and alternative therapies.

Herbal remedies have become a multi-billion-dollar business in North America,[6] yet few of those promoted for vasomotor symptoms have met the rigorous testing criteria required of pharmaceutical products by the US Food and Drug Administration. The current regulatory requirement for pharmaceutical products with purported benefit for hot flashes is that participants in clinical trials must experience on average 7 hot flashes per day or 50 per week. Most reported studies of herbal products have been open label and conducted in women with as few as 1 or 2 hot flashes per day.

Recent reports caution about potential adverse safety profiles of marketed herbal products, and cautions have appeared about interactions of natural health products (NHPs) with pharmaceutical and anesthetic agents.[7–9] New Canadian legislation in January 2004 removed NHPs from the food category and placed them into a special drug category to allow regulation of manufacturing, labelling, and indications for use.[10] To date, little appears to have been accomplished in the regulation of NHPs in Canada.

Several recent systematic reviews have examined options for treatment of moderate to severe vasomotor symptoms.[11–16] None of these found any single complementary therapy to have proven efficacy for moderate to severe hot flashes, and the most recent review[15] concluded by stating that "although individual trials suggest benefits from certain therapies, data are insufficient to support the effectiveness of any complementary and alternative therapy in this review for the management of menopausal symptoms." A direct head-to-head comparison of HT versus black cohosh, soy, or multibotanicals showed only the HT to have an effect greater than that of placebo.[17]

The *Medical Letter* in 2004 and another systematic review of estrogen versus placebo in the treatment of hot flashes concluded that no therapeutic agent was as effective as estrogen.[18,19] MPA and estrogen were shown to have comparable efficacy in a 1-year randomized double-blind trial.[20] Nonhormonal options that have shown some efficacy for relief of vasomotor symptoms include bellergal,[21] clonidine,[22] SNRIs[23] or their active metabolites such as desvenlafaxine succinate,[24] and gabapentin.[25,26]

Recommendations

1. Lifestyle modifications, including reducing core body temperature, regular exercise, weight management, smoking cessation, and avoidance of known triggers such as hot drinks and alcohol may be recommended to reduce mild vasomotor symptoms. (IC)

2. Health care providers should offer HT (estrogen alone or EPT) as the most effective therapy for the medical management of menopausal symptoms. (IA)

3. Progestins alone or low-dose oral contraceptives can be offered as alternatives for the relief of menopausal symptoms during the menopausal transition. (IA)

4. Nonhormonal prescription therapies, including treatment with certain antidepressant agents, gabapentin, clonidine, and bellergal, may afford some relief from hot flashes but have their own side effects. These alternatives can be considered when HT is contraindicated or not desired. (IB)

5. There is limited evidence of benefit for most complementary and alternative approaches to the management of hot flashes. Without good evidence for effectiveness, and in the face of minimal data on safety, these approaches should be advised with caution. Women should be advised that, until January 2004, most natural health products were introduced into Canada as "food products" and did not fall under the regulatory requirements for pharmaceutical products. As such, most have not been rigorously tested for the treatment of moderate to severe hot flashes, and many lack evidence of efficacy and safety. (IB)

6. Any unexpected vaginal bleeding that occurs after 12 months of amenorrhea is considered postmenopausal bleeding and should be investigated. (IA)

7. HT should be offered to women with premature ovarian failure or early menopause (IA), and it can be recommended until the age of natural menopause (IIIC).

8. Estrogen therapy can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (IA)

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Cardiovascular Disease

CORONARY ARTERY DISEASE

Controversy and confusion persist about the effects of postmenopausal HT on CVD. Since the publication of the SOGC's Canadian Consensus Conference on Menopause in 2006,[1] several publications have shed additional light on this subject.

The INTERHEART study, an RCT examining modifiable risk factors across many populations, determined that the main risks for CVD are modifiable and that for women 94% of CVD risk could be attributed to modifiable factors.[2] Factors identified in that study as contributing to increased CVD risk included diabetes mellitus (OR, 2.37), hypertension (OR,1.91), abdominal obesity (OR, 1.62), current smoking (OR, 2.87), and psychosocial stress (OR, 2.67). Each of these substantial risks can be reduced through appropriate choices, interventions, or both.

Our understanding of the effect of hormones on cardiovascular function continues to unfold. Well known are the systemic effects on lipids, hemostasis, and carbohydrate metabolism.[3] Other direct effects of estrogen include modulation of blood vessel reactivity in the short term and vascular structural remodelling in the long term. The structural remodelling of the blood vessels includes changes in the lumen, overall diameter, and relative intimal and medial areas of smooth muscle. These changes arise from hypertrophy and hyperplasia of the vascular cells and increased synthesis of the extracellular matrix. Estrogen has both rapid (nongenomic) and longer-term (genomic) effects on the blood vessel wall. Both types of effects are estrogen-receptor-mediated, although only the genomic effects result from alterations in gene expression.[4,5] Recently obtained in vitro evidence suggests that a cholesterol metabolite (27-hydroxycholesterol) may compete for the estrogen receptor in blood vessels and negate or neutralize certain receptor-mediated actions of estrogen.[6] The development of atherosclerosis and thrombosis is a complex process, now thought to include inflammation within the arterial wall. Oral, but not transdermal, estrogen has been shown to increase the plasma concentration of CRP, a marker of inflammation, which points to the complexity required in any model designed to explain the actions of estrogen on the cardiovascular system.[7–9]

There is now ample evidence that HT has no role in reducing future risks of CVD events in women with established CAD. The HERS secondary prevention trial demonstrated no benefit and an increased risk of early adverse cardiac events in women with known CVD who were randomly assigned to receive CEE and MPA.[10] Other research in women with angiographically proven CAD has confirmed that HT fails to delay the progression of disease.[11–13]

The data on the role of HT for primary prevention of CVD have been the primary reason for the ongoing debate. Whereas data from a variety of sources (epidemiologic studies, observational studies, and clinical trials examining surrogate endpoints) suggested a possible cardioprotective role for estrogen,[14,15] the WHI cast doubt on the value of HT in this situation. The first publication from the WHI reported that combined estrogen/progestin therapy increased the risk of myocardial infarction and stroke.[16] The subsequently published "adjudicated" findings showed no statistically significant overall increase in the incidence of coronary events or death among users of the combination of CEE and MPA (EPT).[17] There was, however, a significant elevation in the incidence of cardiovascular events in EPT users compared with women receiving a placebo in the first year of therapy but not thereafter: in year 1 the attributable risk of nonfatal myocardial infarction was 21 per 10 000 woman-years. The estrogen-only arm of the trial demonstrated no evidence of coronary artery benefit or risk, although the authors concluded that "there was a suggestion of lower coronary heart disease risk in women aged 50–59 at baseline" (HR, 0.63 [95% CI, 0.36 to 1.08]).[18,19] This finding was evident only in a subgroup analysis and therefore should be considered only "hypothesis-generating." Subsequent subgroup analysis demonstrated a reduction in the total mortality rate in the age group 50 to 59 years (HR, 0.70 [95% CI, 0.51 to 0.96]).[20]

Those who accept that the results of the WHI effectively contradict the numerous observational and clinical studies suggesting cardioprotective effects of HT point out that observational studies are potentially fraught with bias. Women who seek HT are better educated and of higher socioeconomic status; thus, they have greater access to other health care resources, from which they may receive treatment for other cardiovascular risk factors, such as diabetes, hypertension, and hypercholesterolemia.[21,22] Those

who adhere to HT for its putative merits in disease prevention are more likely to adhere to other wellness advice: they tend to be leaner, to exercise more often, and to consume more alcohol, which, by itself, affords a degree of cardioprotection. Women who become sick with other conditions are more likely to stop HT, so that there appear to be more deaths in nonusers or past users than in current users. These and other biases of observational studies, some claim, could explain the discrepant findings of the WHI that failed to confirm a cardioprotective benefit of HT in menopausal women.

However, while acknowledging the potential for bias in observational studies, many within the scientific community point out that there are still not RCT data available that refute the preponderance of experimental and clinical trial data suggesting cardioprotective benefits for HT when started early in postmenopausal women.

Conclusions about the role of HT for primary cardioprevention based on the WHI findings have been challenged because of the greater ages of the participants and the time since loss of ovarian estrogen production (an average of 13 years).[23] Time since menopause has been shown to correlate with extent of subclinical atherosclerosis as determined by carotid IMT in populations of women with natural and surgical menopause.[24] WHI subsamples were weighted heavily in favour of the inclusion of minority women to strengthen the study of intervention effects on certain intermediate effects, and many of the modifiable risks for CVD identified in the INTERHEART study were present in such women. With close to 70% of women in the WHI over the age of 60 years at enrolment, it seems likely that a substantial proportion of the WHI population would have had subclinical CVD. The early increase in the incidence of cardiac events reported in the EPT arm of the WHI, with no overall difference in the cardiovascular mortality rate, is similar to the effect of HT started in older women in the HERS secondary prevention trial.[10] In the EPT arm of the WHI trial the RR for CAD was 1.68 in the first 2 years after the start of HT, 1.25 in years 2 to 5, and 0.66 beyond 5 years.

Lobo et al[25] looked elsewhere for data on immediate cardiovascular risks of HT when started in newly menopausal women. Using data from 2 pivotal clinical trials in which all adverse events were recorded for 4065 young, healthy postmenopausal women started on HT, these investigators found no increase in the incidence of either myocardial infarction or stroke in the year after initiation of therapy. These women were not followed for long enough to determine whether there might be longer-term benefit or risk.

A "critical-window" or "critical-timing" hypothesis was subsequently advanced as a way to try to explain how the use of HT at the onset of menopause could be cardioprotective whereas later initiation could cause adverse coronary events as seen in the WHI.[26–29] This theory suggests that the prothrombotic or plaque-destabilizing effects of HT in women with established CAD may account for an initial increase in the incidence of coronary artery events in older women but that the healthy coronary arteries of younger women benefit from the anti-atherogenic effects of estrogen. Recently a contributory mechanism for this dichotomous effect of HT has been postulated with the discovery that 27-hydroxycholesterol, an abundant cholesterol metabolite found in atherosclerotic lesions, acts as a competitive antagonist of estrogen receptor action in the vasculature. According to this theory, 27-hydroxycholesterol accumulations in atherosclerotic lesions might account for the loss of estrogen protection from vascular disease in older women.[6]

To further explore the critical-timing hypothesis, Salpeter et al[30] performed a meta-analysis of 23 RCTs with 39 049 women followed for 191 340 woman-years to assess the effect of HT for at least 6 months on the incidence of CHD events including myocardial infarction and death in younger and older postmenopausal women. They found that HT significantly reduced the incidence of CHD events when initiated in younger (OR, 0.68 [95% CI, 0.48 to 0.96]) but not older (OR, 1.03 [95% CI, 0.91 t01.16]) menopausal women. The authors concluded that the reduced cardiac event rate for younger women seen in this meta-analysis of RCTs paralleled that seen in the observational Nurses' Health Study, which followed a cohort of 120 000 women below the age of 55 years. After adjustment for potential confounding variables, such as age, cardiovascular risk factors, and socioeconomic status, HT use was found to be associated with a 40% reduction in the incidence of CHD events.[14] Similarly, the findings in older women paralleled those of the HERS[10] and WHI[16] trials, in which initiation of HT in older women was associated with an increase in the incidence of adverse CHD events in the first year only.

In another meta-analysis of RCTs, Salpeter et al[31] examined the effects of HT on mortality in 30 trials and 26 708 women. They found an overall OR for total mortality associated with HT of 0.98 (95% CI, 0.87 to 1.12). Hormone replacement reduced the mortality rate in the younger group (OR, 0.61 [95% CI, 0.39 to 0.95]) but not in the older group (OR, 1.03 [95% CI, 0.90 to 1.18]).

Subgroup analysis within the Nurses' Health Study[32] and in the WHI[20] also demonstrated no increase in the incidence of cardiac events and possible cardioprotection among the recently menopausal cohort, which strengthens the hypothesis about a critical window for initiation of HT after onset of menopause. The observational arm of the WHI reported

lower rates of cardiac events in 17 503 current users of EPT (62% had used EPT for more than 5 years at enrolment) than in 35 551 age-matched controls (OR 0.71).[33]

Grodstein et al[32] re-examined the observational data from the Nurses' Health Study to determine the effect of different ages at initiation of HT on the incidence of cardiac events. For women beginning HT near the onset of menopause, both estrogen therapy alone (RR, 0.66 [95% CI, 0.54 to 0.80]) and EPT (RR, 0.72 [95% CI, 0.56 to 0.92]) were associated with a significantly reduced risk of CHD. No significant benefit was observed in women starting HT beyond age 60 or more than 10 years after menopause.

Rossouw et al[20] performed a secondary analysis of the WHI data to determine the impact of years since menopause and age at the time of HT initiation on cardiovascular outcomes. The HR for adverse cardiovascular outcomes was 0.76 in women starting HT less than 10 years after menopause, 1.10 for women starting 10 to 20 years since menopause, and 1.28 for women starting more than 20 years after menopause (*P* for trend, 0.02). The HR for total mortality among the women aged 50 to 59 years who were randomly assigned to HT was significantly reduced, at 0.76 (95% CI, 0.51 to 0.96). In their concluding remarks the authors stated: "We did not identify any subgroup with reduced risk of CHD, although total mortality was reduced among women aged 50 to 59 years. The absence of excess absolute risk of CHD and the suggestion of reduced total mortality in younger women offers some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms."

Ideally this critical-timing hypothesis would be tested in an RCT designed for that specific purpose rather than through post-hoc and subgroup analysis of the data from other trials.[34] (Cardiac event rates are very low in women between the ages of 50 and 59 years, and a properly designed RCT to determine whether HT is truly cardioprotective in this population would have some significant hurdles. Depypere et al[35] estimated that large numbers of women would be needed in any RCT designed to assess possible cardioprotective benefits of HT in newly menopausal women. To prove a significant decrease in 10-year mortality starting with a normal population with an average age of 55 to 59 years, the numbers needed for hypothetical reductions of 30%, 20%, and 10% would be, respectively, 18 514, 44 072, and 185 936. Newly menopausal women are more likely to be symptomatic, and many may not agree to be randomly assigned to HT or placebo therapy. Long-term adherence is likely to be a problem: a survey of hormone use in the United States before the WHI revealed that only 3% of women using EPT and only 10% using estrogen alone stayed on their HT for more than 5 years.[36] The challenges and costs of such an initiative would be staggering.

Researchers have used other noninvasive techniques to examine progression of CVD in women with and without HT at different stages of menopause. However, these methods have involved surrogate markers for endpoints and are not solely relied upon in the cardiovascular field to prove efficacy of any medical intervention.

Carotid IMT has been followed as an early marker of atherosclerotic disease.[15,37,38] Espeland,[37] in the Asymptomatic Carotid Artery Progression Study, compared carotid IMT by ultrasonography. In the placebo group, IMT progressed among estrogen nonusers and regressed in estrogen users. Hodis et al,[15] in a 2-year RCT in healthy postmenopausal women without pre-existing CVD, found that IMT progressed (by an average of 0.0036 mm/yr) in the group treated with placebo and regressed (by an average of 0.0017 mm/yr) in the group treated with unopposed estrogen ($P = 0.046$). Dwyer et al[38] evaluated carotid IMT to examine the relationship between subclinical atherosclerosis and years since hysterectomy. Among women who had undergone bilateral oophorectomy, IMT was significantly increased in relation to years since hysterectomy. No similar increase in IMT was seen in women with intact ovaries.

In women more remote from menopause no similar benefit in the progression of atherosclerosis was seen with the use of estrogen or a combination of estrogen and progestin: Hodis et al,[11] in the Women's Estrogen–Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), evaluated the effectiveness of therapy with estradiol alone or with sequential MPA on the progression of angiographically demonstrated coronary artery stenosis by means of computed tomography[39] in 169 older postmenopausal women and reported no benefit from HT.

Coronary artery calcium scores generated by means of electron-beam computed tomography have been shown to correlate with coronary artery plaque burden as assessed pathologically and to have significant predictive value for subsequent cardiac events in symptomatic and asymptomatic adults.[40,41] A recent meta-analysis of predictive utility concluded that this score is an independent predictor of subsequent CAD events.[42] An expert advisory panel cautioned that most of the data on these scores come from studies on men; data for women must be interpreted with caution at this time.[43]

With these caveats in mind, it is of interest to consider recent studies of these scores as a surrogate endpoint for CAD in women using or not using HT.[44–47] Each study demonstrated evidence of reduced subclinical vascular disease among women who were compliant with HT. The WHI investigators[47] performed a substudy on 1064 women

aged 50 to 59 years in the estrogen-only arm of the WHI. Coronary artery calcium scores were significantly lower among the women randomly assigned to estrogen therapy than among the women assigned to placebo after a mean of 7.4 years of treatment. In women who remained at least 80% adherent to the treatment protocol the OR for a high score in users compared with nonusers was 0.39 ($P = 0.004$).

Two additional RCTs will attempt to provide more definitive evidence for or against the cardioprotective effect of HT started at the time of menopause. The Kronos Early Estrogen Prevention Study (KEEPS) is a multicentre 5-year clinical trial that will evaluate the effectiveness of 0.45 mg/d of CEE, 50 μg/wk of transdermal estradiol (both in combination with cyclic oral micronized progesterone, 200 mg/d for 12 days each month), and placebo in preventing the progression of carotid IMT and the accrual of coronary calcium in women aged 42 to 58 years who are within 36 months of their final menstrual period.[48] A total of 720 women were to be enrolled in 2005, with an anticipated closeout of the trial in 2010.

The National Institute on Aging's Early versus Late Intervention Trial with Estradiol (ELITE) is designed to test the hypothesis that 17 β-estradiol therapy will reduce the progression of early atherosclerosis if initiated soon after menopause, when the vascular endothelium is relatively healthy, versus later, when the endothelium has lost its responsiveness to estrogen. The participants (n = 504) are randomly assigned according to the number of years since menopause (less than 6 versus 10 or more) to receive either 17 β-estradiol, 1 mg/d orally, or a placebo. Women with a uterus also use 4% vaginal progesterone gel or a placebo gel the last 10 days of each month; the gel is distributed along with the randomly assigned treatment so that only women exposed to estradiol receive active progesterone. Ultrasonography is performed at baseline and every 6 months throughout the 2 to 5 (average 3) years of treatment to measure the rate of change in the thickness of the carotid artery.

PREMATURE LOSS OF OVARIAN FUNCTION AND CVD

Large numbers of women continue to face early loss of ovarian function either due to surgical oophorectomy or chemotherapy-associated ovarian failure. It is well known that this loss of exposure to estrogen results in premature onset of menopausal symptoms and accelerated bone loss that can lead to osteoporosis. Several studies have suggested that women after bilateral oophorectomy had a greater risk for coronary artery disease.[49–54] The Women's Health Initiative also examined coronary artery calcium scores in women after bilateral oophorectomy and found that women who did not receive HT had twice the risk of coronary artery calcium compared to women who received HT within 5 years of their surgery.[55] Their conclusion that "the findings are consistent with the thesis that estrogen deficiency associated with bilateral oophorectomy is related to an increased burden of calcified plaque in the coronary arteries that can be countered by the use of HT" further supports the need for ET following premature loss of ovarian function at least until the natural age of menopause if estrogen is not contraindicated for other reasons.

STROKE

Risk factors for stroke (obesity, hypertension, smoking, and diabetes) are common among North American women as they enter menopause. Certain segments of the population are more likely to manifest these risk factors. For this reason, the WHI sought to include large subsamples of different ethnic and minority groups: 73% of women entering that trial were classified as being in the Framingham medium-risk (36%) or high-risk (37%) category for stroke.[56]

Studies of HT (predominantly with estrogen) have provided inconsistent evidence about the effects on the risk of stroke. The large observational Nurses' Health Study found a dose–response relationship between the use of estrogen and stroke, as well as an association between the use of progestin and stroke.[57] Lobo[25] found no increased risk of stroke in pooled data from 4065 newly menopausal women started on a range of doses and regimens involving CEE with or without progestin in 2 pivotal clinical trials. Both arms of the WHI reported an increased risk of ischemic stroke across all age groups (HR, 1.44 [95% CI, 1.09 to 1.90] for the EPT trial and 1.55 [95% CI, 1.19 to 2.01] for the estrogen arm).[56] In the estrogen arm the stroke risk appeared to be lower in women aged 50 to 59 years (HR, 1.09) than in women 60 to 69 years (HR, 1.72) or 70 to 79 years (HR, 1.52), but because of the small numbers in the youngest subgroup definitive conclusions could not be reached. In the EPT arm the HR was actually greatest in the youngest group. The increased risk of stroke was restricted to the ischemic variety. Among the various racial and ethnic groups, black women had the highest risk of stroke (HR, 2.52 [CI, 1.05 to 6.08]). In the WISDOM trial[58] there was no excess incidence of cerebrovascular accidents among 2196 women randomly assigned to EPT compared with 2189 randomly assigned to placebo therapy, with an average of 1 year of follow-up. A meta-analysis of RCTs performed before the WISDOM trial found an HR of 1.30 (95% CI, 1.13 to 1.47) for total stroke.[59]

It is important to note that the absolute level of risk of ischemic stroke due to HT in younger menopausal women is low. The additional risk conferred by the use of HT was

found to be 8/10 000 woman-years in the EPT arm of the WHI[56] and 13/10 000 woman-years in the estrogen arm.[60]

Clearly risk factors for stroke should be addressed in all menopausal women and particularly in those seeking HT for distressing vasomotor symptoms. There is no evidence that HT has any role in the treatment or the primary or secondary prevention of stroke.

DIABETES AND METABOLIC SYNDROME

The results of large RCTs have suggested that HT reduces the incidence of new-onset diabetes mellitus. Women receiving active treatment in the EPT arm of the WHI had an annualized incidence of diabetes requiring treatment of 0.61% versus 0.76% in placebo-treated women. This translated into a 21% reduction (HR, 0.79 [95% CI, 0.67 to 0.93]) in incident treated diabetes, or 15 fewer cases per 10 000 women per year of therapy.[61] A similar risk reduction was noted in the HERS trial (HR, 0.65 [95% CI, 0.48 to 0.89]).[62] In the estrogen arm of the WHI there was a 12% reduction (HR, 0.88 [95% CI, 0.77 to 1.01]) in incident diabetes, or 14 fewer cases per 10 000 women per year of therapy. It is unclear whether the mechanism for this benefit is through lesser centripetal weight gain, reduced insulin resistance in women receiving combined EPT, or some other factor.

A meta-analysis of 107 trials examining components of the metabolic syndrome concluded that HT reduced abdominal obesity, insulin resistance, new-onset diabetes, lipid levels, and blood pressure in women without diabetes and reduced insulin resistance and fasting glucose levels in women with diabetes.[63]

There is inadequate evidence to recommend HT solely to prevent or ameliorate diabetes.

VENOUS THROMBOEMBOLISM

Oral HT results in an increased risk of venous thromboembolism that is greatest in the first few years after the start of therapy. In the WHI the HR was 4.0 in year 1 and fell to 1.04 by year 6.[64,65] Analysis of the WHI data confirmed other factors that contribute to the risk of venous thromboembolism. Compared with women aged 50 to 59 years, those aged 60 to 69 years had a doubling of risk (HR, 2.03; 95% CI, 1.43 to 2.88), and those aged 70 to 79 years had an almost 4-fold increase in risk (HR, 3.72; 95% CI, 2.57 to 5.36). Being overweight doubled the risk (HR, 1.96; 95% CI, 1.33 to 2.88), and obesity tripled it (HR, 3.09; 95% CI, 2.13 to 4.49). Although the highest risks were in women who were carriers of the Leiden factor V gene defect, screening is not recommended for this condition on the basis of low cost-effectiveness. Calculations suggest that screening of 795 women would be required to prevent 1 episode of venous thromboembolism in 5 years.[66]

The greatest risk factor for venous thromboembolism is advancing age: a large population study revealed that the absolute incidence is 2 to 3/10 000 for women aged 50 to 54 years and increases to 20 to 30/10 000 at age 80.[67] In the EPT arm of the WHI the absolute incidence of venous thromboembolism among hormone users was 8/10 000 for those aged 50 to 59 years and of normal weight; in comparison, the incidence was 89/10 000 woman-years among obese women aged 70 to 79 years.[64] The incidence in the placebo users in the estrogen arm of the WHI was higher than the incidence in placebo users in the EPT arm. The investigators attributed this difference to greater age and more obesity in the population under study. The overall risk was lower with estrogen therapy alone (HR, 1.32 [95% CI, 0.99 to 1.75]) than with EPT (HR, 2.06 [95% CI, 1.57 to 2.70]). The risk attributable to HT was not synergistic with the other risk factors of obesity or advancing age.[65]

The Estrogen and Thromboembolism Risk (ESTHER) Study, a multicentre case–control evaluation of the risk of thromboembolism in postmenopausal estrogen users, reported more risk associated with oral than with transdermal estrogen therapy.[68] Differences in lipid and coagulation responses to oral and transdermal routes have led to the suggestion that the route of HT might be selected on the basis of individual risk profiles.[69,70]

SUMMARY: HORMONE THERAPY AND CARDIOVASCULAR DISEASE

The mainstay for CVD prevention will remain a lifelong pattern of healthy living incorporating a balanced, heart-healthy diet, moderate exercise, maintenance of a healthy body weight, avoidance of smoking, limited consumption of alcohol, and attention to treatment of known risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus.

In the first decade after menopause the cardiovascular risks from initiating HT for distressing vasomotor symptoms are very small. Uncertainty remains about whether early initiation of estrogen therapy may even afford protection from atherosclerosis. Although additional evidence about the effects of estrogen on atherosclerosis may accrue when the KEEPS and ELITE RCTs are completed, it is unlikely that we will have good RCT data on the clinical endpoints of interest (myocardial infarction and stroke) because of the challenges and costs of mounting a long-term trial in newly menopausal women willing to be randomly assigned and to adhere to active treatment or placebo therapy. In light of the available alternative strategies for enhancing cardiac health in menopausal women, HT should not be used for primary or secondary cardioprotection.

Available evidence demonstrates that initiation of HT should be done with caution in women with distressing vasomotor symptoms who are more than a decade after menopause because it may be associated with an increased risk of adverse cardiac events. Attention to correction of underlying cardiovascular risk factors before initiation of HT would be important in these isolated cases.

Hypertension and other risk factors for stroke are common in postmenopausal women. HT appears to slightly increase the risk of ischemic stroke, and caution should be taken to manage hypertension and other risk factors in women seeking treatment for distressing vasomotor symptoms.[71]

Recommendations

1. Health care providers should not initiate or continue HT for the sole purpose of preventing CVD (coronary artery disease and stroke). (IA)
2. Health care providers should abstain from prescribing HT in women at high risk for venous thromboembolic disease. (IA)
3. Health care providers should initiate other evidence-based therapies and interventions to effectively reduce the risk of CVD events in women with or without vascular disease. (IA)
4. Risk factors for stroke (obesity, hypertension, and cigarette smoking) should be addressed in all postmenopausal women. (IA)
5. If prescribing HT to older postmenopausal women, health care providers should address cardiovascular risk factors; low- or ultralow-dose estrogen therapy is preferred. (IB)
6. Health care providers may prescribe HT to diabetic women for the relief of menopausal symptoms. (IA)

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Hormone Therapy and Breast Cancer

The risk of breast cancer associated with postmenopausal HT is the risk of greatest concern to women and to their physicians. The SOGC's Canadian Consensus Conference on Menopause in 2006 recognized an increased risk of breast cancer detection after 5 years of EPT, with an RR consistently at about 1.3 over many clinical trials and epidemiologic studies.[1] The increased risk of breast cancer detection after the use of unopposed estrogen appears to be slightly lower than that after EPT.[2]

Given that most women using HT for symptomatic relief use it for less than 5 years[3] and that the risk of breast cancer returns to normal shortly after discontinuation of HT[4] the consensus has been that short-term use of HT for relief of disruptive vasomotor symptoms carries little appreciable risk for the average woman entering menopause.[2] Longer-term use of HT has been considered a matter for discussion between an individual woman and her physician, with account taken of the potential benefits to her quality of life and bone health as well as the potential risks. The current update does not deviate from these positions but attempts to describe factors that contribute to risk.

The increased risk of breast cancer detection reported for combined HT in the WHI[5] (HR, 1.24 [95% CI, 0.75 to 2.05]) was consistent with the risks described in other large cohort studies and in the collaborative reanalysis.[4] The risk for invasive breast cancer an average of 2.4 years after the WHI trial closed was not significantly increased (HR, 1.27 [95% CI, 0.91 to 1.78]).[6]

Although women with prior hormone use enrolled in the WHI showed an increase in risk after 3 years of EPT, women who had not used HT before enrolment showed no increase in the risk of breast cancer during the 5 years of the study. The WHI investigators have recently examined breast cancer risk according to the "gap time" between natural menopause and initiation of HT in the WHI RCT and observational trials. Their results suggest that a longer gap might have conferred some protection and that women initiating HT at menopause and remaining on it for longer periods would be at increased risk.[7]

The HR of 1.24 from the WHI was widely reported as a 24% increase, which is meaningless without information on the background risk of breast cancer by age group. Unfortunately, this reporting scared many women and their health care providers, some of whom thought that 24% of hormone users would get breast cancer. In reality, the 24% increased risk of breast cancer reported by the media translated into an absolute increased risk of only 8 additional cases per 10 000 hormone users per year in the older age-mix of the WHI. This level of risk is actually lower than that previously reported from the collaborative reanalysis.[4] According to the classification of adverse events of the Council for International Organizations of Medical Sciences, this level of risk is "rare" (Table 4.1).

Many other factors modify breast cancer risk to a similar or greater extent. For example, early menarche, late menopause, postmenopausal obesity, and certain lifestyle choices such as delaying first pregnancy until after age 30, choosing not to breastfeed, failing to exercise regularly, and consuming excessive amounts of alcohol all carry similar risks, with HRs around 1.3.[9] Accumulating evidence suggests that shift work resulting in light exposure at night may be another lifestyle factor that increases breast cancer risk.[10] Although these risks are statistically significant, clinically significant RRs in epidemiologic terms are generally considered those that are greater than 3. Major risk factors for breast cancer have risk estimates that range from 3 for some instances of positive family history to 5 for women with past breast biopsy findings of atypia and to 200 for premenopausal women with a mutation in a BRCA gene.[9] A recent comprehensive analysis of breast cancer articles in the media found that news articles were much more likely to focus narrowly on pharmaceutical products, such as hormones, with little if any coverage of other equally important risk factors or preventive strategies related to lifestyle.[11]

The estrogen-only arm of the WHI did not show an increased risk of breast cancer; in fact, there was a nonsignificant decrease in the risk of breast cancer among women using estrogen alone for the 7.2 years (HR, 0.82 [95% CI, 0.65 to 1.04]). Many of the women in the estrogen-only arm were overweight: 45% had a BMI greater than 30, and 36% had a BMI between 25 and 30. The facts that obese women have an increased risk of breast cancer and show little added risk when exposed to exogenous HT[4,12] might account, in part, for the fact that no increase in breast cancer risk was observed in this population.

Other research supports the fact that the effect of estrogen alone on breast cancer is small and is usually undetectable

Table 4.1. Risk classification of adverse events according to the Council for International Organizations of Medical Sciences[8]

Very common	> 1/10
Common	1 to 10/100
Uncommon	1 to 10/1000
Rare	1 to 10/10 000
Very rare	< 1/10 000

with short-term exposure.[13,14] A Finnish study using the national medical reimbursement register found that estradiol therapy for more than 4 years resulted in 2 to 3 extra cases of breast cancer per 1000 women followed over 10 years.[13] As in the WHI, no increase in the risk of breast cancer was observed among the women who used estrogen for less than 5 years (standardized incidence ratio for < 5 years, 0.93 [95% CI, 0.80 to 1.04]). Beyond 5 years, systemic estradiol therapy was associated with an increased risk (standardized incidence ratio, 1.44 [95% CI, 1.29 to 1.59]). Zhang et al[14] conducted a prospective cohort analysis with data from the Harvard Women's Health Study and reported that consistent current users of conjugated estrogen compared with "never users" showed no significant increase in breast cancer risk after a mean of 10 years of follow-up (HR, 1.13 [95% CI, 0.77 to 1.64]). Similarly, Li et al,[15] in a population-based case–control study, found no increase in the risk of breast cancer in women who had used unopposed estrogen for up to 25 years.

There is limited evidence that women with higher endogenous estrogen levels have a greater risk of breast cancer.[16] Risks that are thought to be related to increased estrogen exposure, such as longer number of menstrual years and obesity, do not appear to be additive. This is thought to be why obese women show little if any increase in the risk of breast cancer with HT.[4,12] There is also considerable evidence that breast cancer risk is influenced as much, or more, by local estrogen production within the breast tissue through conversion of androgens to estrogen by local aromatase activity.[17,18] In spite of the markedly different circulating levels of estrogen in pre- and postmenopausal women, the concentrations of E2 in breast cancer tissue do not differ between these 2 groups of women, an indication that uptake from the circulation may not contribute significantly to the total content of E2 in breast tumours but, rather, that de novo biosynthesis (peripheral aromatization of ovarian and adrenal androgens) plays a more significant role.[19] This may account for the paradoxic finding of relatively low breast cancer risks associated with exogenous estrogen therapy[14,15,20,21] and the fact that agents that block aromatase activity or estrogen receptors in the breast (SERMs) have proven useful for breast cancer prevention and therapy.[22,23]

Data from the WISDOM trial, the British trial that was halted for lack of enrolment in the wake of the WHI, have now been analyzed. In this study, there were no statistically significant differences between the EPT users and the placebo users in the numbers of breast or other cancers (HR, 0.88 [95% CI, 0.49 to 1.56]) after a median follow-up period of 11.9 months (6498 woman-years).[24]

Two meta-analyses subsequent to the WHI, looking at both cohort and controlled trial data, have provided strong statistical evidence that EPT carries a statistically significant risk for breast cancer that is greater than the risk attributable to estrogen therapy alone.[21,25]

The Million Women Study recruited 1 084 110 women between 1996 and 2001 from those invited by the British National Health Service Breast Screening Programme to have screening mammography every 3 years; about half had ever used postmenopausal HT.[26] The study data were recorded from questionnaires returned before mammography, and the women were followed to determine cancer incidence and death rates. The study is noteworthy for its large numbers and adjustments for the well-recognized factors associated with risk of breast cancer. Data on breast cancer were analyzed for 828 923 women. No increase in risk of breast cancer was found in past users of any hormone preparation, regardless of time since discontinuation, from less than 5 years to 10 or more years, and regardless of duration of use. Current HT use was reported to increase the RR of incident breast cancer in estrogen-only users to 1.3 and in EPT users to 2.0. The finding of a greater risk with EPT than with estrogen alone is consistent with the WHI findings.

The most surprising findings in the Million Women Study were the timelines reported from HT initiation until breast cancer detection and death from breast cancer: a mean of 1.2 years from recruitment to diagnosis and 2.4 years from recruitment to death.[26] An understanding of tumour growth rates based on the concept of tumour doubling time suggests that for a breast cancer each doubling would take 50 to 100 days[27] and that 30 to 35 doublings are required for a tumour size of 1 cm.[28] In other words, 5 to 10 years is required for a cancerous breast cell to grow to a tumour of detectable size. Both the collaborative reanalysis[4] and the WHI[5] detected no increase in the risk of breast cancer with HT for less than 5 years. The unusually rapid appearance of tumours attributed to HT and other methodologic issues in data collection and analysis in the Million Women Study have led some epidemiologists to question this study's conclusions.[29–31]

Li et al[32] conducted a population-based case–control study in the Seattle–Puget Sound region of the United States to examine the association between HT and different types of breast cancer. Women aged 55 to 74 years with lobular (324), ductal–lobular (196), or ductal (524) breast cancer diagnosed from 2000 to 2004 were compared with 469 controls through interviews to determine risk factors for breast cancer and prior hormone exposure. The investigators reported that there is an elevated risk of breast cancers with a lobular component (these account for about 16% of invasive carcinomas in the United States) after 3 years of combined HT. The authors hypothesized that EPT use may stimulate the growth of foci of lobular carcinoma that would have remained small or perhaps clinically undetectable in the absence of EPT exposure. Li et al[33] had previously reported that the age-adjusted incidence rates of ductal carcinoma in the United States remained largely constant between 1987 and 1999, at 153.8 to 155.3/100 000; the proportional change was 1.03 (95% CI, 0.99 to 1.06), whereas the proportion of breast cancers with a lobular component increased from 9.5% to 15.6% over the same period. Rates of lobular cancer and mixed ductal–lobular cancer appeared to be selectively increased in hormone users in the Million Women Study.[25] The finding that lobular breast cancer rates have increased in Geneva, a population with high HT usage, compared with the Netherlands, a population with low HT usage, also supports a differential effect of hormones on this cancer subtype.[34]

Although estrogen and progesterone have been targeted as responsible for breast cancer, there is in fact considerable debate as to whether the apparent associations between HT and breast cancer are due to the facilitated detection of pre-existing small carcinomas because of more rapid growth under HT stimulation or to de novo development of malignant breast tumours brought about by an increased frequency of initiating mutations.[29] There is no question that estrogen and progesterone have a role in the cell division and replication that lead to the development of mature breast tissue. And, although epidemiologic and basic science data suggest that endogenous estrogen is potentially carcinogenic,[19] proof for humans is lacking. Studies that report the rapid appearance of breast cancers after initiation of HT lend support to the hypothesis that HT is speeding up the growth and detection of pre-existing tumours.[28,35] In support of this hypothesis are data indicating better outcomes for women whose cancers were detected while on hormone therapy.[36,37]

Return of the breast cancer risk to baseline shortly after discontinuation of HT has been consistently reported in observational studies. Ravdin et al[38] reported a sharp decrease in breast cancer incidence rates from 2002 to 2003 in the Surveillance, Epidemiology, and End Results (SEER) cancer registries of the United States; the authors speculated that this was a direct effect of the reduced use of HT after a July 2002 report from the WHI. It is clear that the age-standardized incidence rate of invasive breast cancer in the 9 oldest SEER cancer registry areas began to decrease in 1999, well before any publications from the WHI, although the trend through 2003 was not statistically significant.[39] Other research, such as the Kaiser Permanente Northwest database analysis,[40] has suggested that any changes in breast cancer incidence are more likely to reflect a combination of mammographic screening effects and changes in use of menopausal HT.

The downturn in breast cancer incidence since 1999 follows an 18-year period (1980 to 1998) in which breast cancer incidence rates increased by almost 40%. Any analysis of the effects of mammography on breast cancer incidence must acknowledge that putative effects of mammography will necessarily be superimposed upon and preceded by long-term birth cohort patterns due to generational changes in reproductive behaviour;[39,41,42] that is, a birth cohort from the 1940s might collectively make different reproductive choices (fewer pregnancies, less breast-feeding) than their predecessors.[43]

Most of the increase that occurred during the 1980s has been attributed to increased detection of localized disease and tumours less than 2 cm in diameter by the widespread introduction of screening mammography.[5] Along with increases in incidence rates of early-stage tumours were declines in rates of late-stage disease and deaths from breast cancer, consistent with effective early detection and improved treatment over time.

However, the disparity between the dramatic rise in the incidence of early-stage tumours and the more modest declines in the incidence of late-stage disease and death have raised questions about whether many mammography-detected early-stage lesions might never have progressed to late-stage cancer and as such would never have posed a threat to life.[5,44–46] The negative connotation of the word "carcinoma" in the term ductal carcinoma in situ, despite the fact that the implications of this diagnosis remain uncertain,[47] has been identified as a cause for misperception of cancer risk and unnecessary anxiety.[48] The number of women considering themselves to be breast cancer "survivors" (like the number of men "surviving" prostate cancer) continues to rise as early-stage lesions of questionable clinical significance receive cancer treatment.[49]

It would be surprising if pre-existing breast cancer "disappeared," allowing for a rapid decrease in the incidence of breast cancer within 6 to 12 months of the WHI publication. Women who stop HT may be less likely to have regular

mammography, and recent US data indeed confirm a decline in rates of mammography. A population-based study that was able to monitor mammography rates concluded that less mammography alone could not explain the declining detection of breast cancer.[50] Other analyses have suggested that saturation in screening mammography.[51] may explain the downturn in breast cancer diagnosis since 1999, while acknowledging that decreased hormone use could further impact breast cancer rates in the future.[33,39,40]

Progestins are currently class-labelled according to their effect on the endometrium. There are considerable differences between progestins. Although many studies have been unable to distinguish between the progestins used, often because of relatively low numbers of users of products other than MPA, the E3N cohort study in France,[52] following 80 377 women for 12 years, found that risk varied between the progestins used. The incidence of breast cancer was not increased in users of estrogen and progesterone (OR, 1.00 [95% CI, 0.83to 1.22]) but was increased in users of estrogen with a variety of other progestogens (OR, 1.69 [95% CI, 1.50 to 1.91]).

There is no consistent evidence to favour either continuous or cyclic sequential regimens for estrogen and progestin.

Increased breast density has been found to be an independent risk factor for breast cancer.[53,54] Women receiving postmenopausal HT in the WHI were found to have increased breast density and a greater frequency of abnormal mammograms compared with those receiving placebo.[55] Even though breast density can be increased by the use of estrogen with a progestin,[56] it has never been shown that an acquired increase in density, as in hormone treatment, increases breast cancer risk.[57,58]

Estrogen alone and low-dose or transdermal combination therapy appear to have a lesser impact on breast density.[59, 60] There is conflicting epidemiologic evidence as to whether transdermal estrogen therapy may be associated with a lesser risk of breast cancer.[21,61] There is no clinical trial evidence of a decreased risk of breast cancer in women using transdermal estrogen therapy.[13]

Two large prospective studies examined the effect of HT on the diagnostic accuracy of screening mammography; neither found an adverse effect of HT.[62,63] Other studies have indicated a 15% to 20% decrease in mammographic sensitivity in hormone users who have dense breasts.[64–67] The WHI reported more recalls due to false-positive results in HT users.[20,68] Women using EPT had an 11% greater risk of an abnormal mammogram after 5 years ($P < 0.001$). Biopsies in women on combined HT were less likely to yield a diagnosis of cancer even though breast cancers were slightly more common in that group. After discontinuation of combined HT, the adverse effect on mammography persisted for at least 12 months.[69]

There remains no consensus on whether cancers detected in women using HT are more or less advanced. The WHI had contradictory findings: among users of HT, invasive cancers were larger and more advanced at diagnosis, whereas in situ cancers were no more advanced, compared with the tumours of women not using HT.[5] Other studies have not shown this contradiction.

Women choosing to use HT for relief of distressing vasomotor symptoms need to understand that short-term hormone use is unlikely to appreciably alter their personal risk of breast cancer.[2] A large survey conducted across the United States before the first publication of the WHI revealed that only 3% of women using combined EPT and 10% of women using estrogen alone after hysterectomy adhered to therapy for more than 5 years.[3] The 40% to 50% of women who continue to experience distressing vasomotor symptoms when they stop HT need to consider their personal risk profiles before deciding to remain longer on HT.

The risk of breast cancer appears to be greater with EPT than with estrogen alone. There is as yet insufficient evidence to support progesterone over various progestogens, but there is both clinical and basic science evidence accumulating to suggest that there may indeed be clinically important differences between progestins with respect to the breast. The risk of breast cancer has been found to return to baseline after cessation of therapy. Women at risk of breast cancer may wish to know about chemoprevention agents, particularly raloxifene.

Putting risks into perspective is important. Although most women perceive breast cancer to constitute their greatest lifetime medical risk, there is ample evidence that this perception is distorted and that women are at far greater lifetime risk of death from cardiovascular diseases.[70–72] The likelihood of developing and dying from breast cancer for each decade is contrasted with the likelihood of dying from other causes in Table 4.2.

Singletary[9] tried to place various breast cancer risk factors into perspective, noting that HT, as a risk, rates about the same as early menarche, late menopause, and a variety of lifestyle-associated risks, such as excessive alcohol consumption and failure to exercise. Attention should be directed to modifiable risk factors, such as smoking, sedentary lifestyle, excessive intake of alcohol, and postmenopausal weight gain.[12] Reduction of dietary fat intake in the WHI was not associated with any reduction in breast cancer risk,[73] although this dietary modification may afford other benefits for prevention of cardiovascular diseases and possibly ovarian cancer.[74] Analysis of modifiable risk factors that could be altered after

menopause has been attained suggest that "a substantial fraction of postmenopausal breast cancers (34%) may be avoided by purposeful changes in lifestyle later in life."[75]

HORMONE THERAPY IN WOMEN WITH A FAMILY HISTORY OF BREAST CANCER

Family history by itself can provide useful information about a woman's personal risk of breast cancer. Women with a single first-degree family member (mother, sister, or daughter) in whom breast cancer was diagnosed after age 50 years have little increase in risk over the approximately 12% risk of the general population. Having 2 such relatives doubles a woman's lifetime risk (to approximately 24%). Those with first-degree relatives in whom breast cancer was diagnosed before age 50 years have a risk of 24% with 1 relative and 48% with 2 relatives.

In a study designed to address the safety of HT in women with a positive family history, the use of hormones was found not to be associated with an increase in the overall risk of breast cancer, yet was associated with a reduced overall mortality rate.[76] Similar conclusions were drawn from the collaborative reanalysis.[4] This is hardly surprising, since the influence of genetic factors is so large that it generally overshadows any small potential increment resulting from lifestyle or hormonal exposure.

HORMONE THERAPY IN BREAST CANCER SURVIVORS WITH VASOMOTOR SYMPTOMS

Some 30 000 premenopausal women with a diagnosis of breast cancer are rendered acutely symptomatic by chemotherapy-induced ovarian failure each year in North America. There are more than 2.5 million breast cancer survivors in North America, many of whom have been unable to achieve a satisfactory quality of life because alternative approaches to relieving vasomotor symptoms remain largely unsatisfactory.

A limited number of observational studies have reported on outcomes in women who choose to use HT after breast cancer compared with outcomes in women who do not choose HT. When compared with "low risk" controls, women using HT in these studies have not had a worse outcome.[77,78]

Data from the first RCTs to examine this issue have recently been reported. The HABITS trial in Scandinavia found that women who used HT after a diagnosis of breast cancer had a higher recurrence risk than did women assigned to placebo.[79] Of the 447 women randomly assigned, 442 could be followed for a median of 4 years: 39 of the 221 women in the HT arm and 17 of the 221 women in the control arm experienced a new breast cancer event (HR, 2.4 [95% CI, 1.3 to 4.2]). Cumulative incidence rates at 5 years were 22.2% in the HT arm and 8.0% in the control arm. The new breast cancer events in the HT arm were mainly local events, and according to the investigators there was no convincing evidence for a higher breast cancer mortality rate associated with HT exposure.

Table 4.2. Risk of breast cancer developing and causing death in the subsequent decade

	Rate per 1000 population		
Age (years)	Cases of breast cancer	Deaths from breast cancer	Deaths from all causes
40–49	15	2	21
50–59	28	5	55
60	37	7	126
70	43	9	309
80	35	11	670

Reproduced by permission, with modifications, from Fletcher et al.[70]

At the time the initial results of the HABITs trial were reported, in 2004,[80] a concurrent study of HT after breast cancer was being conducted in Sweden (the Stockholm Trial). Owing to the adverse findings in the HABITS trial the Stockholm Trial was prematurely closed, even though it had failed to find any adverse effect of HT. The Stockholm trial followed 378 women for a median of 4.1 years: there were 11 new breast cancer events and 2 breast cancer deaths among 188 women assigned to the HT arm, compared with 13 new breast cancer events and 4 breast cancer deaths among 190 women in the non-HT arm.[81] The RR associated with random assignment to the HT arm was not elevated, at 0.82 (95% CI,0.35 to 1.9). Possible explanations for the discrepant findings of these 2 RCTs include the fact that more node-positive tumours were evident in the HABITS trial, more women in the Stockholm Trial were treated with tamoxifen, and different progestin regimens were used in the 2 trials. The HABITs investigators concluded that further data from RCTs are needed to define the impact of specific HT regimens and accompanying circumstances (e.g., type or stage of tumour, or HT used for a limited time or during tamoxifen treatment) on the risk of recurrence of breast cancer after HT exposure.

Women who wish to consider HT for improved quality of life after a diagnosis of breast cancer should understand that a definitive answer to the question of when HT will influence prognosis is lacking. The results of observational studies, which are fraught with potential biases, have been reassuring; however, a single RCT suggested that HT had an adverse effect on recurrence rates. Alternative,

nonhormonal agents exist for the treatment of many menopausal symptoms (e.g., SSRIs for hot flashes and topical estrogen for urogenital atrophy). If these options are unsuitable and quality of life is seriously impaired, then individual women with a low risk of tumour recurrence may still wish to explore the option of HT.

SELECTIVE ESTROGEN-RECEPTOR MODULATORS AND BREAST CANCER

Raloxifene has been approved in the United States for both the treatment and the prevention of osteoporosis. In the pivotal osteoporosis prevention trial MORE, women assigned to raloxifene rather than to placebo demonstrated a 72% reduction in the incidence rate of invasive breast cancer at 4 years.[82] The MORE trial was not designed to measure the reduction in breast cancer incidence in women at increased risk, so in 1999 the National Surgical Adjuvant Breast and Bowel Project initiated the STAR trial. In this study, postmenopausal women aged at least 35 years and at increased risk for breast cancer were randomly assigned to either tamoxifen or raloxifene for 5 years and were required to complete follow-up examinations for at least 7 years. The STAR trial found that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer and was associated with a lower risk of thromboembolic events and cataracts but a higher, though not statistically significant, risk of noninvasive breast cancer.[83] The risk of other cancers, fractures, ischemic heart disease, and stroke was similar for the 2 drugs.[22] Raloxifene has now been approved in the United States for use in preventing breast cancer in women at high risk.

Recommendations

1. Health care providers should periodically review the risks and benefits of prescribing HT to a menopausal woman in light of the association between duration of use and breast cancer risk. (IA)
2. Health care providers may prescribe HT for menopausal symptoms in women at increased risk of breast cancer with appropriate counselling and surveillance. (IA)
3. Health care providers should clearly discuss the uncertainty of risks associated with HT after a diagnosis of breast cancer in women seeking treatment for distressing symptoms. (IB)

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Urogenital Health

UROGENITAL ATROPHY

Urogenital aging is, in part, related to estrogen deficiency. Significant physiologic changes occur to the female anatomy during menopause because of estrogen loss. The vulva loses most of its collagen and adipose tissue in response to estrogen loss. Oriba and Maibach[1] showed that, when lipids in the stratum corneum are lost, the barrier function they provide is lost, and the vulvar tissue loses its ability to retain water: it becomes flattened and thin. Glandular secretions also diminish. The prepuce of the clitoris atrophies, exposing the gland to irritation from clothing, prolonged sitting, and sexual contact. The vaginal surface becomes thinner, less elastic, and more friable. Fewer secretions are produced, and production is delayed longer during sexual stimulation.

In a longitudinal, population-based study of 438 women aged 45 to 55 years, Dennerstein et al[2] found that the percentage of women reporting vaginal dryness increased progressively as women approached and passed through menopause: from 3% in premenopause to 25% by 1 year and 47% by 3 years after menopause. Women who smoke have higher rates of vaginal atrophy.[3] In the WHI, the following prevalence rates were found: dryness, 27.0%; irritation or itching, 18.6%; discharge, 11.1%; and dysuria, 5.2%.[4]

Recurrent urinary tract and vaginal infections are more likely in estrogen-deficient women. Both systemic and local estrogen therapy will correct vaginal health,[5] but only local therapy reduces the frequency of recurrent urinary tract infection.[6–8]

Local lubricants can alleviate dryness and discomfort but do not reverse the histologic changes associated with urogenital aging.[9,10] Intravaginal estrogen therapy can be used for vaginal dryness either alone or in addition to systemic estrogen replacement therapy. Up to 40% of women receiving systemic therapy do not get an adequate effect of estrogen on the vaginal mucosa.[11]

Estrogen placed in the vagina can have systemic effects if given in sufficient quantity.[12] In a low dose it may be transiently absorbed in the first 7 to 14 days because the thinned epithelium of the hypoestrogenic vagina presents a minimal barrier to absorption.[13] Generally after treatment for 1 to 2 weeks the systemic level of estrogen is once again at the pretreatment level.

Recently there has been evidence that when women with breast cancer have endogenous estrogen levels maximally suppressed by use of an aromatase inhibitor, systemic absorption of vaginal estrogen, even though very low, can be detected with conventional assays.[14] Data on this finding are very limited at present. A large cohort study demonstrated no difference in the outcome of breast cancer for women choosing to receive local vaginal estrogen therapy, although it is likely that few women in this study were receiving aromatase inhibitors.[15] This suggests caution in prescribing these products if the intent of aromatase therapy is to completely suppress endogenous estrogen.[16]

URINARY INCONTINENCE

Urgency incontinence affects 10% of women by age 50, 15% by age 60, 25% by age 70, and 35% after age 80.[17] The costs of urinary incontinence are enormous, not only in terms of lost personal freedom but also in terms of expenditures on the sanitary products needed to deal with accidental leakage.[18]

In the HERS trial,[19,20] during 4.2 years of treatment, 64% of women randomly assigned to HT compared with 49% of those assigned to placebo therapy reported weekly incontinence ($P < 0.001$). The higher risk of incontinence in the HT group was evident at 4 months, persisted throughout the treatment period, and was independent of age. The ORs for weekly incontinence during HT compared with placebo therapy were 1.5 for urge incontinence (95% CI, 1.2 to 1.8; $P < 0.001$) and 1.7 for stress incontinence (95% CI, 1.5 to 2.1; $P < 0.001$). Four years of HT caused an excess risk of 12% for weekly urge incontinence and 16% for weekly stress incontinence.

In the WHI, urinary incontinence developed at a significantly higher rate among continent women taking CEE alone or with MPA than among continent women taking a placebo.[21] In addition, incontinence worsened in women taking CEE alone or with MPA compared with those taking a placebo. The authors concluded that the oral estrogen formulations used in the study increased the risk of urinary incontinence and therefore should not be used to treat it. It is clear that further research is needed.[22]

Goldstein et al[23] followed 619 postmenopausal women (mean age, 53 years) who had undergone hysterectomy and were randomized to 1 of 4 treatment groups. The researchers found that those taking CEE reported a significantly higher rate of new incontinence over 3 years (7%) than those taking a placebo (1.3%) or raloxifene (0.6%).

Although basic science in this area is limited, the results of a recent placebo-controlled, randomized clinical trial of estrogen alone may allow some theoretical explanation.[24] Women receiving 2 mg of estradiol valerate orally for 6 months showed significant decreases in total periurethral collagen. Profound effects on collagen metabolism were observed and included stimulation of collagen degradation via increased activity of matrix metalloproteinase-2. According to the authors, connective tissue is crucial to the integrated action of the suburethral vaginal wall, the pubourethral ligaments, the pubococcygeus muscles, and the paraurethral connective tissues; consequently, degradation of this connective tissue may contribute to the development of urethral hypermobility, intrinsic urethral sphincter dysfunction, or both, thus setting the stage for stress urinary incontinence. However, other work offers conflicting evidence. Using Doppler imaging, Jarmy-Di Bella et al[25] found that HT (unopposed or combined) for 3 months improved periurethral vessel number and blood flow. Such changes would be expected to improve urethral sphincter function and promote continence, not worsen it.

Clearly, the etiology of female urinary incontinence is complex and multifactorial, and the influence of hormone factors on urethral and bladder function is still poorly understood. In contrast to the reports cited above, others have shown an absence of estrogen effect on incontinence. Jackson et al,[26] in a randomized, double-blind, placebo-controlled trial, failed to demonstrate even a subjective improvement with 6 months of estrogen treatment. In another placebo-controlled trial, Waetjen et al[27] found that 2 years of transdermal treatment with estradiol did not significantly change the frequency of incontinence symptoms or the risk of at least weekly incontinence developing, compared with placebo treatment.

In 2003, a Cochrane Review was able to identify only 15 small trials evaluating the role of estrogen against placebo for the treatment of all urinary incontinence.[28] Just over 350 women were included in each treatment arm. Overall, approximately 50% of the estrogen-treated women reported improvement or cure as compared with 25% of those who received placebo. The effect was largest in the women with pure urge incontinence.

Clearly, the data are conflicting, but when all the data are considered it seems unlikely that estrogen replacement therapy has a significant role to play in the treatment of urinary stress incontinence or urinary incontinence in general. Our current understanding of hormonal factors in female urinary incontinence remains incomplete.

Other modifiable risk factors for urinary incontinence that have been identified include obesity, amount and type of fluid intake, smoking, major depression, and the use of certain medications. A list of drug classes that may cause incontinence is available online from the National Association for Continence.[29]

The effect of body habitus on urinary incontinence has been more clearly elucidated than the effect, if any, of hormones. For obese women (mean baseline BMI, 38.3 kg/m^2), even a reduction in BMI of as little as 5% can result in significant subjective improvement in urine loss.[30] The effect of BMI and weight gain was assessed in 30 000 women with new-onset urinary incontinence in the Nurses' Health Study II.[31] Increasingly higher BMI was related to increasing odds of incontinence developing (P for trend < 0.001). The OR for at least monthly incontinence developing was 2.11 (95% CI, 1.84 to 2.42) among the women with a BMI of 35 kg/m^2 or greater compared with lean women (those with a BMI of 21 to 22.9 kg/m^2). The increases were similar for all incontinence types. The odds of incontinence also increased with increasing adult weight gain (P for trend < 0.001): the OR for at least weekly incontinence developing was 1.44 (95% CI, 1.05 to 1.97) among women who had gained 5.1 to 10 kg since early adulthood and 4.04 (95% CI, 2.93 to 5.56) among women who had gained more than 30 kg compared with women who had maintained their weight within 2 kg. In the same population, physical activity was associated with a significant reduction in the risk of urinary incontinence developing. The results appeared to be somewhat stronger for stress urinary incontinence than for urge urinary incontinence.[32]

Recommendations

Urogenital concerns

1. Conjugated estrogen cream, an intravaginal sustained-release estradiol ring, or estradiol vaginal tablets are recommended as effective treatment for vaginal atrophy. (IA)
2. Routine progestin cotherapy is not required for endometrial protection in women receiving vaginal estrogen therapy in appropriate dose. (IIIC)
3. Vaginal lubricants may be recommended for subjective symptom improvement of dyspareunia. (IIIC)
4. Health care providers can offer polycarbophil gel (a vaginal moisturizer) as an effective treatment for symptoms of vaginal atrophy, including dryness and dyspareunia. (IA)
5. As part of the management of stress incontinence, women should be encouraged to try nonsurgical options,

such as weight loss (in obese women), pelvic floor physiotherapy, with or without biofeedback, weighted vaginal cones, functional electrical stimulation, and/or intravaginal pessaries. (II-1B)

6. Lifestyle modification, bladder drill (II-1B), and antimuscarinic therapy (IA) are recommended for the treatment of urge urinary incontinence.

7. Estrogen therapy should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence but may be recommended before corrective surgery. (IA)

8. Vaginal estrogen therapy can be recommended for the prevention of recurrent urinary tract infections in postmenopausal women. (IA)

9. Following treatment of adenocarcinoma of the endometrium (stage 1) estrogen therapy may be offered to women distressed by moderate to severe menopausal symptoms. (IB)

Sexual concerns

10. A biopsychosexual assessment of preferably both partners (when appropriate), identifying intrapersonal, contextual, interpersonal, and biological factors, is recommended prior to treatment of women's sexual problems. (IIIA)

11. Routine evaluation of sex hormone levels in postmenopausal women with sexual problems is not recommended. Available androgen assays neither reflect total androgen activity, nor correlate with sexual function. (IIIA)

12. Testosterone therapy when included in the management of selected women with acquired sexual desire disorder should only be initiated by clinicians experienced in women's sexual dysfunction and with informed consent from the woman. The lack of long-term safety data and the need for concomitant estrogen therapy mandate careful follow-up. (IC)

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Mood, Memory, and Cognition

MOOD

Depression occurring coincident with the menopausal transition has long been recognized; however, we still lack a clear understanding of the contribution of various factors.[1,2] Some investigators have attributed such depression to the hormonal fluctuations of the menopause and likened this period to the "window of vulnerability" that appears to form the basis for menstrual cycle-related mood disorders and postpartum depression. Although it has been tempting to speculate that intense vasomotor symptoms and sleep disruption in the early menopausal years trigger a "domino effect" leading to deterioration of mood, there is ample evidence that depression can occur in the absence of vasomotor symptoms and sleep disturbance. Other investigators have attributed menopausal depression to the "empty-nest syndrome" and the other stressors that accompany aging (such as physical discomforts, changing body image, altered sexual function, and the dual challenges of launching children to independence and caring for elderly parents). With unprecedented numbers of women about to enter the menopause in the peak demographic of the "baby-boomer" generation, a better understanding of the factors that account for perimenopausal depression assumes increasing importance.

Earlier population-based studies[3,4] and a recent systematic review of cohort studies[5] (failed to detect a link between the menopausal transition and new-onset depression, whereas some other studies appear to have established a more definitive link.[6–9]Each of these studies found contributory factors in additional to stage of menopause that figure into the development of perimenopausal depression (including vasomotor symptoms, life stress, history of depression in a family member, postpartum blues, a high body mass index, and sexual abuse).[9] It is hardly surprising that a myriad of factors could play a role in the development of depression.

Limited clinical-trial data have confirmed that transdermal estrogen may be effective for treating major depressive episodes in perimenopausal women[10,11] but not postmenopausal women.[12] Psychotherapy and judicious use of antidepressants will remain the mainstay of treatment for depression; however, in cases of resistant depression at the onset of menopause, HT may be appropriate.

MEMORY AND COGNITION

Changes in memory and cognition are common concerns among menopausal women. Memory loss has entered into the cultural vernacular and has been reported by women in population studies in both North America and Australia. A wealth of basic science research has documented important neuroprotective effects of estrogen; however, the clinical research conducted to date has not yielded conclusive answers regarding the precise effects of menopause and HT on the gradual cognitive decline associated with aging.

Epidemiologic studies have been unable to document cognitive decline in women throughout the menopausal transition. Spatial and semantic memory seem to be relatively unaffected, whereas episodic memory and, in particular, verbal fluency may show deterioration. This is consistent with women's experience of having difficulties with word finding and recall. More critical executive functions of the brain do not seem to be impaired. The general lack of discernible cognitive impairment is important and should be seen as reassuring to women concerned about the prognostic significance of mild verbal changes, such as word recall.

The evidence for a role of estrogen, as opposed to a simple effect of aging, can be deduced from studies looking at the effect of hormone replacement or estrogen deprivation. There have been several excellent review articles on the subject of cognition and estrogen since the last consensus update.[13–15]

The WHIMS trials of estrogen plus a progestin and of estrogen alone were 2 large RCTs conducted in older postmenopausal women.[16,17] Administration of HT was accompanied by an increased risk of cognitive decline. Various explanations have been advanced to explain this worrisome finding, the most prevalent being the theory that memory is related to cardiovascular health and that the cognitive decline mirrors the increased risk of coronary heart disease observed in older postmenopausal women in the WHI,[18] the other that there may exist a critical window for neuroprotection. The clinical importance of these studies is that they showed no benefit, and the potential for harm, in administering HT to older postmenopausal women. There is some evidence that a progestin may attenuate some of the potential benefit of estrogen, but this would not modify the conclusion that HT should not be administered to elderly

women for the purpose of preventing dementia. The risk of cognitive decline was particularly increased in women over the age of 65 years, and the adverse effect of CEE therapy was more pronounced among women with lower cognitive function at baseline ($P < 0.01$) and among women receiving MPA as well as estrogen compared with those receiving estrogen alone. After exclusion of women with baseline impairment, the HR was 1.77 (95% CI, 0.74 to 4.23; $P = 0.20$) in the estrogen-alone trial and 2.19 (95% CI, 1.25 to 3.84; $P = 0.006$) in the pooled trials. In the estrogen-alone trial, mild cognitive impairment was diagnosed in 76 participants in the CEE group and 58 in the placebo group (HR, 1.34 [95% CI, 0.95 to 1.89]). In the estrogen-plus-progesterone trial the HR was similar (1.25 [95% CI, 0.97 to 1.60]).

Henderson et al[19] in 2007 reanalyzed data from the WHIMS trial to ascertain whether prior hormone exposure influenced rates of dementia and Alzheimer's diseases. All-cause dementia was significantly less likely to develop in women reporting prior HT (106 cases; pooled adjusted HR, 0.54 [95% CI, 0.32 to 0.91]). For the 53 women in whom Alzheimer's disease developed, the pooled adjusted HR was 0.36 (95% CI, 0.16 to 0.85); for those with non-Alzheimer dementia, the HR was 0.70 (95% CI, 0.36 to 1.39).

In the Women's Estrogen for Stroke Trial, however, in which estradiol was administered for stroke prevention, there was generally no impact of estrogen therapy, except in women with normal function at baseline, who had less decline in cognitive domains (RR, 0.46 [95% CI, 0.24 to 0.87]).[20]

There is accumulating evidence that there may be a critical window of opportunity for neuroprotection. Sherwin[21] demonstrated efficacy of estrogen replacement for maintenance of verbal memory after oophorectomy. In studies in which a protective effect of estrogen has been found, the women were younger (mean age 45 years), and specific tests of verbal memory were performed. Since women tend to spontaneously report problems with verbal memory, more global tests of cognitive function may have failed to detect a deficit with menopause. Sherwin argues that verbal memory should be specifically measured and that the studies failing to assess verbal memory were not appropriately designed to address menopause and memory.

In a recent analysis of women who had participated in RCTs of estrogen therapy for the prevention of osteoporosis, the women randomized to HT had a lesser risk of cognitive impairment than those receiving placebo. Bagger et al[22] found that early administration of estrogen was associated with significantly improved performance in cognitive testing 5, 11, and 15 years later; this study was limited by the absence of baseline cognitive testing. In a short-term trial of estrogen replacement therapy, Dunkin et al[23] found that recently menopausal women were more likely to respond than those who were in late postmenopause.

Case–control studies of women who underwent oophorectomy before menopause have recently shown a small increase in the risk of dementia and parkinsonism. Among 813 women who underwent unilateral oophorectomy and 676 who underwent bilateral oophorectomy before the onset of menopause, compared with 1472 referent women, the HR for cognitive impairment or dementia was 1.46 (95% CI, 1.13 to 1.90; adjusted for education, type of interview, and history of depression); the risk increased with earlier age at oophorectomy (test for linear trend; adjusted $P < 0.0001$).[24] And among 1252 women who underwent unilateral oophorectomy and 1075 who underwent bilateral oophorectomy before the onset of menopause, compared with 2368 referent women, the HR for parkinsonism was 1.68 (95% CI, 1.06 to 2.67; $P = 0.03$); the risk similarly increased with earlier age at oophorectomy (test for linear trend; $P = 0.01$).[25]

These studies are important in documenting that women who lose ovarian function at an early age and are not given hormone replacement may indeed be at increased risk of a deleterious impact, but no studies have directly addressed this critical question. For women undergoing age-appropriate menopause the evidence is less clear. Of particular clinical importance is the finding that HT administered after age 65 years does not appear to benefit women and may contribute to cognitive decline A better understanding of the factors, or cofactors, that placed the older women in the WHIMS trial at increased risk of dementia would be helpful in identifying women for whom HT may not be advisable.

Women experiencing verbal memory changes at menopause can be advised that there is no apparent association between verbal memory change and global cognitive decline. For best preservation of memory and cognition, women should be advised about the importance of good overall health, including good cardiac and vascular health, exercise,[26] maintenance of an active mind, avoidance of excessive alcohol consumption, and measures to reduce the risk of diabetes and hypertension. HT is not indicated for neuroprotection. Two clinical trials in progress may shed additional light on this question. Clinical studies support basic science research suggesting that ultralow-dosage estrogen therapy may be sufficient for neuroprotection.[27] We can expect better evidence to guide practice in the next few years.

Recommendations

1. Estrogen alone may be offered as an effective treatment for depressive disorders in perimenopausal women and may augment the clinical response to antidepressant treatment, specifically with SSRIs (IB). The use of

antidepressant medication, however, is supported by most research evidence (IA).

2. Estrogen can be prescribed to enhance mood in women with depressive symptoms. The effect appears to be greater for perimenopausal symptomatic women than for postmenopausal women. (IA)

3. Estrogen therapy is not currently recommended for reducing the risk of dementia developing in postmenopausal women or for retarding the progression of diagnosed Alzheimer's disease, although limited data suggest that early use of HT in the menopause may be associated with diminished risk of later dementia. (IB)

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Bone Health

INTRODUCTION

Osteoporosis is defined as an impairment in bone strength due to an abnormal quantity or quality of bone, or both. Quantity is measured from BMD. Quality is affected by many factors, including the degree of mineralization, the connectivity of the bony trabeculae, the quality of the collagen fibres, and the health of the bone cells. The 3 types of bone cells are osteoblasts, osteoclasts, and osteocytes. The osteocytes function as "mechanostats," sensing the degree of microdamage and triggering remodelling in areas of stress and strain, thus allowing continual renewal, repair, and replacement of bone. This process of remodelling maintains bone strength.

Adequate calcium and vitamin D intake is necessary to attain and maintain normal bone quantity and quality and thus achieve optimal bone strength. Early assessment of skeletal health and then initiation of calcium and vitamin D supplementation and an exercise program are essential in the prevention and treatment of osteoporosis. Individuals at increased risk for fracture should also be offered pharmacologic therapy to reduce the risk. Identifying absolute fracture risk by age, BMD, previous fracture history, and previous use of glucocorticoid therapy is now recommended, as this enables more appropriate quantification of the risk and targets treatment to those at greatest risk.

RISK ASSESSMENT AND MANAGEMENT

Bone strength is determined from bone density and bone quality. Bone densitometry provides information on BMD and is valuable in identifying the risk of fracture. Major and minor risk factors for osteoporosis have been well identified (Table 7.1), and the presence of 1 major risk factor or 2 minor risk factors in a postmenopausal woman justifies bone densitometry.[1]

In 2005, Osteoporosis Canada recommended identifying absolute fracture risk by integrating the key risk factors for fracture; namely, age, BMD, prior fracture, and glucocorticoid use.[2] The 10-year risk of fragility fractures is thus determined (Table 7.2) and defined as high if it is greater than 20%, moderate if it is 10% to 20%, and low if it is less than 10%.[2] The additional effect of a pre-existing fragility fracture or glucocorticoid use moves the patient 1 risk category higher. These guidelines were based on Swedish data. A more comprehensive calculation of the 10-year absolute fracture risk, now available from the World Health Organization, incorporates additional risk factors: parental history of hip fracture, current tobacco smoking, rheumatoid arthritis or other secondary causes of bone loss, and alcohol intake of 3 or more units daily.[3]

It is recommended that absolute fracture risk data be used in determining who should be treated, as this will target pharmacologic therapy at those at an increased risk of fracture. Younger individuals at a low risk of fracture are appropriately managed with lifestyle changes and prevention strategies designed to prevent bone loss.

Pharmacologic therapy is recommended if the 10-year absolute fracture risk is greater than 20% (high). In those with a moderate risk, management decisions should be individualized. Those with a low risk should have further evaluation, with exclusion of secondary causes of bone loss and implementation of prevention strategies based on ensuring adequate calcium and vitamin D supplementation. It is also important to emphasize regular exercise and reduced consumption of alcohol (to less than 2 drinks/d) and coffee (to less than 4 cups/d). Smoking cessation should also be strongly advised. Such patients may benefit from additional prevention options, such as raloxifene therapy, particularly for those at an increased risk of breast cancer. Low-dose bisphosphonate therapy has been shown to prevent bone loss in postmenopausal women with osteopenia. HT for postmenopausal symptoms has also been shown to protect against osteoporosis and osteoporotic fractures.

For those at high fracture risk, intervention is advised with raloxifene or bisphosphonate therapy administered orally or intravenously. Individuals at very high risk should be considered for treatment with an anabolic agent, particularly if fractures have occurred during antiresorptive therapy or if significant bone loss has occurred despite antiresorptive therapy. A more detailed evaluation should take place to ensure compliance and the absence of secondary causes of osteoporosis before anabolic therapy is considered.

Table 7.1. Risk factors for osteoporosis

Major risk factors	Minor risk factors
Age > 65 years	Rheumatoid arthritis
Vertebral compression fracture	History of clinical hyperthyroidism
Fragility fracture after age 40 years	Long-term anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy for > 3 months	Smoking
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight ≤ 57 kg
Osteopenia apparent on radiograph	Weight loss 10% of weight at age 25 years
Hypogonadism	Long-term heparin therapy
Early menopause (before age 45 years)	

Reproduced by permission, with modifications, from Brown et al.[1]

Table 7.2. New system for predicting the 10-year absolute fracture risk in women

	10-year risk: lowest T-score*		
Age (years)	Low (< 10%)	Moderate (10% to 20%)	High (> 20%)
50	> –2.3	–2.3 to -3.9	< –3.9
55	> –1.9	–1.9 to -3.4	< –3.4
60	> –1.4	–1.4 to -3.0	< –3.0
65	> –1.0	–1.0 to -2.6	< –2.6
70	> –0.8	–0.8 to -2.2	< –2.2
75	> –0.7	–0.7 to -2.1	< –2.1
80	> –0.6	–0.6 to -2.0	< –2.0
85	> –0.7	–0.7 to -2.2	< –2.2

* L1–4 (minimum 2 valid vertebrae), total hip, trochanter and femoral neck

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ADVANCES IN PHARMACOLOGIC THERAPY

In addition to adequate calcium, vitamin D, and exercise, options for the prevention and treatment of osteoporosis include antiresorptive and anabolic agents.[4]

Antiresorptive (anticatabolic) agents inhibit osteoclast activity and reduce bone turnover.[4,5] The various agents have different mechanisms of action. Bisphosphonates reduce the rate of bone turnover, providing a longer time for bone to mineralize. Bisphosphonate therapy is thus associated with modest increases in BMD. Estrogen acts through the estrogen receptors on both osteoblasts and osteoclasts, suppressing receptor activator of nuclear factor κB ligand (RANKL)-induced osteoclast differentiation and thereby decreasing bone remodeling.[6] Raloxifene, a SERM, can bind to estrogen receptors, with tissue-specific agonist or antagonist effects. Raloxifene decreases bone remodelling in addition to its extraskeletal effects. Osteoclastic bone resorption is also inhibited by calcitonin acting on calcitonin receptors.

These antiresorptive agents are effective in reducing fracture risk by approximately 30% to 50% in postmenopausal women. However, fractures still occur, and more effective options are desirable, particularly for severe disease states. Anabolic therapy can make major improvements in the quality and quantity of bone and are therefore a welcome addition to the antiresorptive options currently available.

Anabolic therapy can increase the production of bone matrix by enhancing osteoblastic function. The resulting reduction in the risk of fracture is approximately 65% over 18 months in postmenopausal women with osteoporosis.[7] The currently approved anabolic agent is teriparatide (recombinant human parathyroid hormone [PTH] 1–34). Strontium ranelate, which has antiresorptive properties, appears to also have anabolic properties; approval of this agent for the treatment of postmenopausal osteoporosis is expected in Canada before the end of 2008.

CALCIUM AND VITAMIN D SUPPLEMENTATION

The effectiveness of calcium and vitamin D supplementation in preventing hip fractures was evaluated in the WHI. The trial involved 36 282 postmenopausal women who daily received either 1000 mg of elemental calcium as calcium carbonate and 400 IU of vitamin D, or a placebo, for an average of 7 years.[8] Patients were allowed to

take additional daily supplements of up to 1000 mg of calcium and 600 IU of vitamin D; approximately 38% of subjects took more than 1200 mg of elemental calcium daily. Personal use of bisphosphonates, calcitonin, SERMs, and estrogen therapy was also permitted. The calcium and vitamin D study arm overlapped with the HT arm; thus, approximately 51% of women were receiving estrogen.

Treatment compliance was poor: by the end of the study, only 59% of the women were taking 80% or more of their supplementation. As compared with those taking placebo, the women taking 1000 mg of calcium and 400 IU of vitamin D daily showed a 1.06% increase in hip BMD ($P < 0.01$). In the treatment-compliant group, the HR for hip fracture was 0.71 (95% CI, 0.52 to 0.97), representing a statistically significant 29% reduction in hip fracture risk among the women taking 80% or more of their calcium and vitamin D supplements. Estrogen use was associated with a 42% reduction in hip fracture risk. A small, but significant, 17% increase in the risk of renal stones was noted in the treatment group as compared with the placebo group; the HR was 1.17 (95% CI, 1.02 to 1.34). Clinicians must therefore ensure that patients are not inadvertently using excessive calcium supplementation and that the patients' urinary calcium excretion is normal, particularly if they have a history of renal stones.

Inadequate blood levels of vitamin D were also noted in the WHI study and may have contributed to the findings. In the nested case–control study, the mean serum 25-hydroxyvitamin D level at baseline was 46.0 nmol/L in the women who had sustained hip fractures as compared with 48.4 nmol/L in their controls ($P = 0.17$).[8] Vitamin D supplementation of more than 600 IU daily may have reduced the fracture risk, as has been demonstrated in other clinical trials.

Ensuring adequate vitamin D supplementation is a key component of therapy in the prevention and treatment of osteoporosis. Although it might not be sufficient as the sole means of therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin D_3 (800 IU/d) is still recommended as a mandatory adjunct to the main pharmacologic agents (antiresorptive and anabolic drugs). Vitamin D in doses of 800 IU daily has been shown to be effective in reducing the risk of falls by 49% over a 12-week period of therapy.[9] (Vitamin D supplementation at a dose of 10 000 IU once weekly has been suggested for women unable to take daily supplements of vitamin D in areas where such a preparation is available. Doses of 100 000 IU of vitamin D_3 given orally every 4 months have been shown to be effective in reducing the risk of osteoporotic fractures.[10]

HORMONE THERAPY

Estrogen Therapy

Estrogen therapy has significant antiresorptive effects. Specifically, it enhances the osteoblastic production of osteoprotegerin, which has antiosteoclastic properties because of its ability to bind to RANKL and subsequently to block the RANKL/RANK interaction required for osteoclast recruitment and activation.[11,12] In the WHI, a primary prevention trial, the estrogen-only arm demonstrated a 30% to 39% reduction in fracture rates.[13] This trial therefore confirmed the antifracture effects of HT suggested by previous clinical trials.[14,15]

Combined estrogen and progestogen therapy (EPT)

The EPT arm of the WHI had similar results: an increase in total hip BMD, together with a 34% reduction in hip and vertebral fractures and a 24% reduction in total osteoporotic fractures.[16] In early postmenopausal women, EPT resulted in increases in BMD of 2% to 3% at the hip and spine over 2 years of therapy.[14] A decline in the markers of bone turnover in response to HT was also seen in early postmenopausal women.[15]

Low- and ultralow-dose hormone therapy

HT (estrogen alone or EPT) is still considered the most effective therapy for the medical management of menopausal symptoms. Bone protection with HT at a usual dosage is considered an added benefit. Recent studies, designed to test various dosages of estrogen for bone protection have shown a linear dose response of the skeleton from the lowest to the highest dosages tested.[14,17,18] These RCTs have shown that low-dosage estrogen therapy can prevent postmenopausal osteoporosis, and ultralow-dosage estrogen therapy has beneficial skeletal effects. However, no fracture trial has yet been carried out with low- and ultralow-dosage HT. A low dose is 0.3 mg of conjugated estrogen or its equivalent (e.g., 0.5 mg of micronized estradiol); half this amount is considered ultralow.[19]

SELECTIVE ESTROGEN-RECEPTOR MODULATORS

This class of agents demonstrates tissue-specific estrogen-agonistic or estrogen-antagonistic effects.[20] In the MORE trial, patients treated with 60 or 120 mg of raloxifene daily for 4 years demonstrated reductions of 36% and 43% reduction, respectively, in the risk of vertebral fractures.[21] However, no significant effect on the risk of nonvertebral fractures was noted); this may have been the result of multiple factors, including the very low incidence of nonvertebral fractures in the placebo arm of the trial, as compared with incidence rates seen in the RCTs of other antiresorptives.

In the STAR trial, which involved 19 747 postmenopausal women at increased risk of breast cancer, the breast cancer risk reduction effects of 60 mg of raloxifene daily were equivalent to those of 20 mg of tamoxifen daily over 5 years.[22] Both drugs reduced the risk of breast cancer by approximately 50%. Raloxifene had with a better overall safety profile than tamoxifen, with 36% fewer uterine cancers and 29% fewer deep vein thromboses.

BISPHOSPHONATES

Nitrogen-containing bisphosphonates (alendronate, risedronate, and zoledronic acid) provide antiresorptive effects by binding to the calcium hydroxyapatite crystal at sites of bone resorption, where the bone matrix is exposed.[23] The bisphosphonate is buried under the newly formed bone, where it lies inert and has no skeletal effects. During bone resorption, the drug is released from the bone matrix and is ingested by osteoclasts. It inhibits farnesyl diphosphate synthase (FDPS), a key enzyme in the cholesterol synthesis pathway involved in post-translational modification of important signalling molecules (Ras, Rac, Rho, and Rab). The FDPS inhibition disrupts several pathways involved in cytoskeletal organization, cell survival, and cell proliferation, leading to osteoclast deactivation and apoptosis.[24] The result is reduced bone turnover and enhanced bone mineralization because of the extended time available for mineral accumulation. With the normalization of bone remodelling to premenopausal levels, overall bone strength is improved.[24,25] However, adherence to oral bisphosphonate therapy is mandatory to achieve a reduction in fracture risks: low adherence may compromise therapeutic effectiveness.[26]

Alendronate

Alendronate reduces the risk of vertebral fractures in postmenopausal woman with and without previous vertebral fractures, as has been demonstrated in the Fracture Intervention Trial (FIT).[27–29] Several trials have shown that alendronate use reduces bone resorption and improves BMD.[29,30]

A combined analysis of the data for 3658 patients in the FIT osteoporotic cohort that had a pre-existing fracture or a femoral neck BMD T-score of–2.5 or less at baseline demonstrated a statistically significant decrease in the incidence of symptomatic vertebral fractures of 55% ($P = 0.003$). The incidence of hip fractures was reduced by 63% at 1.5 years ($P = 0.014$) and by 54% at 36 months ($P = 0.005$).[21]

The FIT Long-term Extension study found that increases in BMD continued at the lumbar spine and hip through 10 years of alendronate treatment, with an associated fracture risk reduction.[29] Bone biopsies performed after 10 years of alendronate treatment revealed double fluorescent tetracycline label in all samples, indicating ongoing bone remodelling and an absence of "frozen" bone.[29] These data provide reassurance that long-term alendronate therapy can safely reduce the risk of vertebral and nonvertebral fractures.

Alendronate, taken orally, has been approved for the prevention of osteoporosis at a daily dose of 5 mg and for the treatment of osteoporosis at a daily dose of 10 mg or a weekly dose of 70 mg.

Risedronate

Risedronate maintains bone mass and preserves bone microarchitecture.[31] A number of studies in postmenopausal women have shown that this agent significantly reduces the risk of vertebral and nonvertebral fractures.[32–34] Data from the Vertebral Efficacy with Risedronate Therapy trials indicated that 5 mg of risedronate daily reduced the incidence of new fractures within 6 months of the start of therapy and significantly lowered the risk of new vertebral fractures within 1 year.[32–34] The reduction in risk was maintained for up to 7 years of treatment.[35] In a study of 9331 elderly women at high risk, risedronate reduced the risk of nonvertebral fractures after 3 years of treatment and also reduced the risk of hip fractures.[36]

Another study, involving early postmenopausal women, demonstrated that 5 mg of risedronate daily increased BMD at the lumbar spine by more than 5% during 2 years of treatment ($P < 0.05$) as compared with both baseline and placebo.[37] Other studies have confirmed those findings and shown that risedronate prevents bone loss and preserves trabecular architecture in early postmenopausal women.[38] In addition, key clinical trials have shown that reductions in vertebral fracture risk with risedronate are independent of increases in BMD.[39]

Various oral dosage regimens of residronate are approved for prevention and treatment of osteoporosis: 5 mg daily, 35 mg weekly, or a new 75-mg pill taken on 2 consecutive days each month.

Zoledronic acid

Zoledronic acid is the most potent bisphosphonate available.[40,41] It contains 2 nitrogen atoms in the R2 side chain. The intravenous administration of 4-mg doses has been approved for the prevention and treatment of metastatic bone disease and hypercalcemia related to malignant disease. Zoledronic acid, 5 mg intravenously on an annual basis, has been approved in Canada for the treatment for Paget's disease and postmenopausal osteoporosis.

The phase III RCT Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)

Pivotal Fracture Trial (PFT) evaluated the effects of zoledronic acid, given as a single 5-mg intravenous infusion annually, on fracture incidence in men and women 50 years of age or older who had already sustained a low-trauma hip fracture.[42] Compared with placebo, zoledronic acid reduced the 3-year risk of vertebral fracture by 70% (RR, 0.30 [95% CI, 0.24 to 0.38]) and the 3-year risk of hip fracture by 41% (HR, 0.59 [95% CI, 0.42 to 0.83]). Increases in BMD were significantly greater and height loss reduced in the group receiving zoledronic acid.

Bisphosphonate advantages and disadvantages

A major advantage of oral bisphosphonate therapy is ease of administration and excellent tolerability. The most common side effects are abdominal pain and dysphagia. However, in the RCTs conducted to date, the incidence rates of upper gastrointestinal side effects of both alendronate and risedronate have been comparable to those of placebo.[43]

Intravenous administration of bisphosphonates has a number of advantages, including less frequent dosing and less potential for gastrointestinal side effects as compared with oral administration. Intravenous therapy also has assured compliance if the patient attends the physician's office for the infusion on an annual basis.

Recently, reports of mandibular or maxillary osteonecrosis as a rare complication of bisphosphonate use have been published.[44] Osteonecrosis of the jaw (ONJ) is an avascular bone necrosis that may occur in patients at risk for this condition. Most of the reports have been associated with frequent high-dose intravenous administration of pamidronate or zoledronic acid in patients with a history of breast cancer or myeloma. Many of these patients have been receiving concomitant chemotherapy, radiation therapy, or both, which are risk factors for avascular bone necrosis. The condition has been most commonly reported in high-risk individuals after dental surgery, such as tooth extraction.[45] The condition has seldom been reported with alendronate and risedronate use[44] and has not been seen in any of the clinical trials conducted to date, which represent prospective data obtained on more than 100 000 patients treated with aminobisphosphonates for an average of 3 years. All published case reports have been anecdotal. In a retrospective chart review by the M.D. Anderson Cancer Center of 4000 cancer patients treated with zoledronic acid, pamidronate, or both, ONJ was identified in 0.825% of the patient population.[46] The HORIZON PFT trial found that the incidence of ONJ was similar in the treatment and placebo groups: 1 case in each group. The cases were validated by an adjudication committee.

Current international guidelines recognize ONJ as a very rare condition, limited mostly to the oncology population receiving high-dose intravenous bisphosphonate therapy. Prospective data in oncology and nononcology populations are needed to better understand the underlying pathophysiology of ONJ so that appropriate decisions can be made regarding prevention, diagnosis, and management,[47] as well as to determine the true incidence. At present, evidence indicates that if there is a link between bisphosphonates and ONJ, it is very weak, and the risk of bisphosphonate-associated ONJ may be less than 1 in 100 000.[47] It is important for all Canadians to visit their dentist, as recommended by the Canadian Dental Association, every 6 months to ensure that dental hygiene is maintained, as this is a cornerstone in the prevention and treatment of ONJ.

CALCITONIN

Calcitonin, a hormone produced in the thyroid gland, inhibits osteoclastic bone resorption. Its poor oral absorption necessitates either subcutaneous or intranasal administration. Administration of 200 IU by nasal spray is approved for the treatment of postmenopausal osteoporosis. With this treatment, BMD stabilizes at the lumbar spine and at the hip, an effect similar to that of calcium and vitamin D.[48] A meta-analysis of 30 RCTs of calcitonin therapy (of which 15 were placebo-controlled) found a significant RR reduction of 21% ($P = 0.05$) for vertebral fractures but not for nonvertebral fractures ($P = 0.12$).[49] In the Prevent Recurrence of Osteoporotic Fractures study, salmon calcitonin (200 IU administered by nasal spray) significantly reduced the incidence of vertebral fractures by 33% to 36% in postmenopausal women with and without prior vertebral fracture.[48] This treatment may have an analgesic effect, which could be useful in managing the pain of acute vertebral compression fractures.

DENOSUMAB

Denosumab is a fully human monoclonal antibody against RANKL; it binds to human RANKL, thus preventing osteoclast activation and consequently reducing bone resorption. It is administered by subcutaneous injection twice yearly and is currently in phase III clinical trials. In a phase II study it was shown to be well tolerated and had an effect on bone turnover similar to that of alendronate.[50] It also decreases bone turnover and increases BMD in both osteoporosis patients and cancer patients.[50,51]

ANABOLIC AGENTS

Until recently, pharmaceutical treatment of postmenopausal osteoporosis was limited to the use of antiresorptive agents. The availability of anabolic agents represents a major advance, as these agents substantially

improve the quality and the quantity of bone, significantly increasing bone strength.

Teriparatide (PTH)

In an RCT involving postmenopausal women with fragility fractures, subcutaneous administration of teriparatide, 20 μg daily for 21 months, led to a 9% increase in lumbar-spine BMD and improved femoral-neck and whole-body BMD.[7] Risks for vertebral and nonvertebral fractures were reduced by 65% and 53%, respectively. Evidence for the anabolic effects of teriparatide on bone microarchitecture has been found in bone biopsy specimens from patients treated with teriparatide, which have shown dramatic increases in the thickness, density, and number of trabeculae and increases in cortical thickness and bone size.[52] A reduction in back pain has also been noted with teriparatide use.

Teriparatide is well tolerated, with only minor adverse events such as nausea, headaches, and transient mild hypercalcemia.[53] A dose- and duration-dependent relationship between teriparatide and osteosarcoma was noted in rats receiving nearly lifelong exposure to high doses of teriparatide, 5 μg/kg or more daily.[54] These doses are much higher than the 20 μg (approximately 0.28 μg/kg) daily dose used in humans. Osteosarcoma has not been seen in humans or in studies with monkeys. To date, about 300 000 people have been treated with teriparatide, and 1 case of osteosarcoma has occurred, which is comparable to the background incidence of osteosarcoma of 1 in 250 000.

Strontium ranelate

Strontium ranelate has demonstrated antiresorptive effects and also appears to have anabolic properties. It has not been associated with an increased risk of osteosarcoma. It is incorporated into bone and accumulates in the skeleton because of its physical and chemical similarities to calcium.[55–57]

A phase III trial involving 1649 postmenopausal women demonstrated a 49% reduction in the incidence of new vertebral fractures at 1 year among those given strontium ranelate, 2 g daily, as compared with those receiving placebo.[58] A 16% reduction in the incidence of nonvertebral fractures among those receiving strontium ranelate was also noted.[59] Women at high risk of fracture demonstrated an even greater reduction in the risk of hip fracture, 36% ($P = 0.046$).[1] Side effects associated with strontium ranelate have been limited to nausea and diarrhea during the first few months of therapy.[57]

SUMMARY

Osteoporotic fractures result in significantly increased mortality rates and are associated with significant morbidity. Effective options for the prevention and treatment of osteoporosis are available in Canada. Anabolic therapy now complements antiresorptive therapy and increases our ability to reduce fracture risk significantly. Strontium ranelate is expected to be available in Canada in late 2008, and research is promising further advances, including RANKL inhibitors and other molecules that act on the anabolic pathway and should become clinically available in the near future.

Recommendations

1. The goals of osteoporosis management include assessment of fracture risk and prevention of fracture and height loss. (1B)
2. A stable or increasing BMD reflects a response to therapy in the absence of low trauma fracture or height loss. Progressive decreases in BMD, with the magnitude of bone loss being greater than the precision error of the bone densitometer, indicate a lack of response to current therapy. Management should be reviewed and modified appropriately. (1A)
3. Physicians should identify the absolute fracture risk in postmenopausal women by integrating the key risk factors for fracture; namely, age, BMD, prior fracture, and glucocorticoid use. (1B)
4. Physicians should be aware that a prevalent vertebral or nonvertebral fragility fracture markedly increases the risk of a future fracture and confirms the diagnosis of osteoporosis irrespective of the results of the bone density assessment. (1A)
5. Treatment should be initiated according to the results of the 10-year absolute fracture risk assessment. (1B)

Calcium and vitamin D

6. Adequate calcium and vitamin D supplementation is key to ensuring prevention of progressive bone loss. For postmenopausal women a total intake of 1500 mg of elemental calcium from dietary and supplemental sources and supplementation with 800 IU/d of vitamin D are recommended. Calcium and vitamin D supplementation alone is insufficient to prevent fracture in those with osteoporosis; however, it is an important adjunct to pharmacologic intervention with antiresorptive and anabolic drugs. (1B)

Hormone therapy

7. Usual-dosage HT should be prescribed for symptomatic postmenopausal women as the most effective therapy for menopausal symptom relief (1A) and a reasonable choice for the prevention of bone loss and fracture. (1A)

8. Physicians may recommend low- and ultralow-dosage estrogen therapy to symptomatic women for relief of menopausal symptoms (1A) but should inform their patients that despite the fact that such therapy has demonstrated a beneficial effect in osteoporosis prevention (1A), no data are yet available on reduction of fracture risk.

Bisphosphonates

9. Treatment with alendronate, risedronate, or zoledronic acid should be considered to decrease the risk of vertebral, nonvertebral, and hip fractures. (1A)

10. Etidronate is a weak antiresorptive agent and may be effective in decreasing the risk of vertebral fracture in those at high risk. (1B)

Selective estrogen receptor modulators

11. Treatment with raloxifene should be considered to decrease the risk of vertebral fractures. (1A)

Calcitonin

12. Treatment with calcitonin can be considered to decrease the risk of vertebral fractures and to reduce pain associated with acute vertebral fractures. (1B)

Parathyroid hormone

13. Treatment with teriparatide should be considered to decrease the risk of vertebral and nonvertebral fractures in postmenopausal women with severe osteoporosis. (1A)

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Appendix

Estrogen preparation

Estrogen	Trade name	Strengths	Comment
Oral (mg)			
Conjugated estrogens	Premarin	0.3, 0.625, 0.9, 1.25	
	CES	0.3, 0.625, 0.9, 1.25	
	Congest	0.3, 0.625, 0.9, 1.25	
Estropipate	Ogen	0.625, 1.25, 2.5	
17β-estradiol (micronized)	Estrace	0.5, 1.0, 2.0	
Esterified estrogens	Neo-Estrone	0.3, 0.625	
Transdermal twice weekly (μg)			
17β-estradiol	Estraderm (reservoir patch)	25, 50, 100	
	Oesclim (matrix patch)	25, 50	
	Estradot (matrix patch)	25, 37.5, 50, 75, 100	
Transdermal weekly (μg)			
17β-estradiol	Climara (matrix patch)	25, 50, 75, 100	
Transdermal daily			
17β-estradiol	Estrogel (topical gel)	2.5 g/ 2 pumps	
Vaginal			
Conjugated estrogens	Premarin (cream)	0.625 mg/g	0.52.0 g/d
17β-estradiol	Estring (silastic ring)	2.0 mg/ring	
	Vagifem (vaginal tablet)	25 μg	Initial dose: 1 vaginal tablet/d for 2 wk Maintenance dose: 1 vaginal tablet twice per wk, with 3- or 4-d interval
Estrone	Neo-Estrone (cream)	1.0 mg/g	
Injectable (mg)			
Conjugated estrogens	Premarin	25	

Progestin preparation

	Trade name	Strength	Comment
Oral (mg)			
Medroxyprogesterone acetate	Apo-Medroxy	2.5, 5, 10	
	Gen-Medroxy	2.5, 5, 10	
	Medroxy 2.5	2.5	
	Medroxy 5	5	
	Novo-Medrone	2.5, 5, 10	
	PMS-Medroxyprogesterone	2.5, 5, 10	
	Ratio-MPA	2.5, 5, 10	
	Provera	2.5, 5, 10, 100	
	Provera Pak	5, 10	Provera Pak 5 mg contains 14 tablets Provera Pak 10 mg contains 10 tablets
Megestrol	Apo-Megestrol	40, 160	
	Megestrol-40 Megestrol-160	40, 160	
	Nu-Megestrol	40, 160	
	Linmegestrol	40, 160	
	Megace	40, 160	
	Megace OS	40 per mL (liquid)	
Micronized progesterone	Prometrium	100	
Norethindrone	Micronor	0.35	
	Norlutate	5	
Injectable			
Medroxyprogesterone acetate	Depo-Provera	50 per mL (5 mL) 150 per mL (1 mL)	
Progesterone	Progesterone Injection	50 per mL (10 mL)	
Implant			
Progestogen	Implanon	40 g/d	Approval pending
Intrauterine			
Levonorgestrel	Minera Intrauterine System (IUS)	52 mg per IUS	

Combination products

	Trade name	Strengths
Oral		
estradiol	ActivelleLD	0.5 mg estradiol
norethindrone acetate acetate (NETA)		0.1 mg NETA once daily
estradiol	Activelle	1 mg estradiol
norethindrone acetate acetate (NETA)		0.5 mg NETA once daily
Ethinyl estradiol (EE) and norinthedrone acetate (NETA)	FemHRT	5 µg EE + 1 mg NETA (1 tablet)
Conjugated estrogens (CE) and medroxyprogesterone acetate (MPA)	Premplus	0.625 mg CE + 2.5 mg MPA (2 tablets)
		0.625 mg CE + 5 mg MPA (2 tablets)
17β-estradiol (E_2) and drospirenone (DRSP)	Angeliq	1 mg E_2 + 1 mg DRSP
Transdermal		
17β-estradiol (E_2) and norinthedrone acetate	Estacomb	50 µg E_2 + 250 µg NETA
	Estalis	50 µg E_2 + 250 µg NETA
		50 µg E_2 + 140 µg NETA
	Estalis Sequi	50 µg E_2 + 250 µg NETA
		50 µg E_2 + 140 µg NETA
17β-estradiol (E_2) and levonorgestrel (LNG)	Climara Pro (matrix patch)	45 µg E_2 + 15 µg LNG once a week

Progestin dosages for endometrial protection

	Cyclic 10–14 d/mth (mg)	Continuous daily (mg)
Oral		
Medroxyprogesterone acetate	5–10*	2.5
Medrogesterone (medrogestone)	5–10*	
Megestrol	20	
Micronized progesterone	200–300*/†	100
Norethindrone	0.35–07*	0.35
Transdermal		
Norethindrone acetate‡	0.14 or 0.25	0.14
Intrauterine		
Levonorgestrel IUS		52 mg/IUS

*Large doses of estrogen may necessitate higher doses of progestin while ultralow-dose (0.014 mg/d) may require lower doses of progestin.

†May be administered vaginally.

‡Available in combination with 17-estradiol reservoir patches.

Nonhormonal osteoporosis medications

	Regimen
Treatment	
Alendronate (Fosamax)	10 mg daily
	70 mg once weekly
Cyclical etidronate* (Didrocal)	400 mg daily for 2 weeks followed by 500 mg calcium daily for 76 days in a 3-month kit (Didrocal)
Fosavance 70/2800	70 mg/2800 IU vitamin D3
Fosavance 70/5600	70 mg/5600 IU vitamin D3
Nasal calcitonin (Miacalcin NS)	200 IU daily, intranasally via alternating nostrils
Parathyroid hormone	20 µg subcutaneously daily
Raloxifene (Evista)	60 mg daily
Risedronate (Actonel)	5 mg daily
	35 mg once weekly
Risedronate plus Calcium carbonate (Actonel plus calcium)	35 mg once-a-week + 1250 mg calcium carbonate
Teriparatide (Forteo)	20 µg injectable daily
Prevention	
Alendronate (Fosamax)	5 mg daily
Cyclical etidronate* (Didrocal)	400 mg daily for 2 weeks followed by 500 mg calcium daily for 76 days in a 3-month kit (Didrocal)
Raloxifene (Evista)	60 mg daily
Risedronate (Actonel)	5 mg daily

*Etidronate alone (Didronel) is only available as a 200 mg tablet.

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Dr Reid: Speaker or consultant to Wyeth, Bayer, Organon, Proctor and Gamble, Novo Nordisk; advisory boards: Paladin, Wyeth; research support: Organon, Bayer.

Dr Blake: Speaker or consultant to Wyeth, Merck, Glaxo Smith Kline, Bayer; advisory boards: Bayer, Wyeth and Lilly, Novo Nordisk.

Dr Abramson: Speaker or consultant to Abbott, Astra Zeneca, Boehringer Ingelheim, Bristol Myer Squibb, Dupont, Eli Lilly, Lifespeak, Norvartis, Fournier, Merck Frosst, Pfizer, Servier, Schering, Sanofi-Aventis; advisory boards: Astra Zeneca, Boehringer-Ingelheim, Novartis, Pfizer, Sanofi-Aventis; research support: Astra Zeneca, Boehringer Ingelheim, Merck.

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NOTES

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