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Canadian Consensus Conference on Menopause, 2006 Update

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Outcomes: Prescription medications, complementary and alternative medicine (CAM), and lifestyle interventions are presented according to their efficacy in treating menopausal symptoms.

Evidence: MEDLINE and the Cochrane database were searched for articles from March 2001 to April 2005 in English on subjects related to menopause, menopausal symptoms, urogenital and sexual health, mood and memory, hormone therapy, CAM, and on specific medical considerations that affect the decision of which intervention to choose.

Values: The quality of evidence is rated using the criteria described in the report of the Canadian Task Force on the Periodic Health Examination. Recommendations for practice are ranked according to the method described in this report (see Table 1).

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RECOMMENDATIONS

I. General Recommendations

1. Health care providers should discuss and encourage initiation of healthy lifestyle choices in menopausal women. (II-2A)
2. The primary indication for hormone therapy (HT) should be for the management of moderate to severe menopausal symptoms. (IA)
3. HT should not be prescribed for primary or secondary prevention of cardiovascular disease (CVD) or for primary prevention of dementia. (IA)
4. Local estrogen therapy (ET) is recommended if HT is prescribed for vulvovaginal symptoms alone. (IA)
5. HT should be prescribed for the appropriate duration to achieve treatment goals while taking into consideration risks and benefits and the woman's quality of life. (IIIB)
6. HT should be prescribed at the lowest effective dose, although the long-term risk/benefit ratio of lower dose HT has not been demonstrated. (IIIC)
7. The primary indication for progestin use should be endometrial protection in women using systemic estrogen therapy who have an intact uterus. (IA)
8. HT may be prescribed for an extended period, following proper counselling, if the woman decides that for her the benefits outweigh the risks (II-2A). Periodic re-evaluation is strongly recommended (IIIC).

ABSTRACT

Objective: To provide guidelines for health care providers on the management of menopause in asymptomatic healthy women as well as in women presenting with vasomotor symptoms, urogenital, sexual, and mood and memory concerns and on specific medical considerations, and cardiovascular and cancer issues.

Key words:

Menopause, estrogen, progestin, androgen, complementary therapies, vasomotor symptoms, urogenital symptoms, mood, memory, estrogen replacement therapy, hormone replacement therapy, cardiovascular diseases, cancer

This guideline reflects emerging clinical and scientific advances as of the date issued and are subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local Institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations*
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from 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 support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canadian Communication Group; 1994. p. xxvii.

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

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.

9. Androgen therapy may be considered for selected women with acquired sexual desire/interest disorders after comprehensive assessment, systemic estrogen therapy and appropriate counselling (II-1B) Androgen therapy is still investigational and long-term safety data are lacking (IIIB).
10. Health care providers may offer identified complementary and alternative medicine with demonstrated efficacy for mild menopausal symptoms. (IB)

II. Specific Recommendations

Chapter 1: Introduction:

No Recommendations

Chapter 2: Menopause and Age-Related Concerns

1. Lifestyle modifications, including reducing core body temperature, regular exercise, weight management, smoking cessation, and controlled breathing may be recommended to reduce mild vasomotor symptoms. (IC)
2. Health care providers should offer HT (ET/estrogen-progestin therapy) 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 especially during the transition phase. (IA)
4. Non-hormonal prescription therapies, including antidepressant agents, gabapentine, clonidine, and bupropion, can be prescribed as alternatives to HT to reduce vasomotor symptoms. (IB)
5. Complementary and alternative medicine, including black cohosh, red clover (derived isoflavone, and vitamin E) may be recommended for the reduction of mild vasomotor symptoms (IB). Long-term efficacy and safety data are still lacking.
6. Any unexpected bleeding that occurs after 12 months of amenorrhea is considered postmenopausal bleeding and should be investigated. (IA)

7. If prescribing HT to older postmenopausal women, low or ultra-low dose ET is preferred. (IB)

Chapter 3: Urogenital Concerns

1. Conjugated estrogen (CE) cream, an intravaginal sustained-release estradiol ring, or estradiol vaginal tablets are recommended as effective treatment for vulvovaginal atrophy. (IA)
2. Routine progestin co-therapy 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 vulvovaginal atrophy including dryness and dyspareunia. (IA)
5. Effective surgical treatment options, including Burch colposuspension and the TVT procedure, are recommended for the treatment of stress urinary incontinence. (IA)
6. Effective non-surgical treatment 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, can be recommended for the treatment of stress urinary incontinence. (II-1B)
7. Lifestyle modification, bladder drill (II-1B), and antimuscarinic therapy (IA) are recommended for the treatment of urge urinary incontinence.
8. ET should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence. (IA)
9. Vaginal estrogen therapy can be recommended for the prevention of recurrent urinary tract infections in postmenopausal women. (IA)

Chapter 4: Sexual Concerns

1. 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)
2. For women with vaginal atrophy, local estrogen should be prescribed to improve vulvovaginal atrophy-associated dyspareunia. (IA)
3. 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)
4. Any investigational testosterone therapy included in the management of selected women with acquired sexual desire/interest disorder, typically associated with an arousal disorder, should only be initiated by clinicians experienced in women's sexual dysfunction and with informed consent from the woman. The investigational nature, lack of long-term safety data, need for systemic estrogen therapy, and careful follow-up must be explained. (IC)

Chapter 5: Mood and Memory

1. Estrogen alone may be offered as an effective treatment for depressive disorders in perimenopausal women and may augment clinical response to antidepressant treatment, specifically SSRIs (IB). The use of antidepressant medication, however, is supported with the 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 developing dementia in postmenopausal women or for retarding the progression or deterioration in women with diagnosed Alzheimer's disease. (IB)

Chapter 6: Prescription Drugs

No Recommendations

Chapter 7: Complementary and Alternative Medicine

No Recommendations

Chapter 8: Specific Medical Considerations

1. HT should be offered to women with premature ovarian failure (POF) or early menopause (IA), and its use can be recommended until the age of natural menopause (IIIC).
2. ET can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (IA)
3. Menopausal women undergoing pelvic surgery should be given appropriate thromboembolic prophylaxis. (IA)
4. Health care providers may prescribe HT to diabetic women for the relief of menopausal symptoms. (IA)

Chapter 9: 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 consider other evidence-based therapies and interventions to effectively reduce the risk of CVD events in women with or without vascular disease. (IA)

Chapter 10: Cancer

1. All unscheduled uterine bleeding should be investigated because no estrogen-progestin regimen is completely protective against endometrial carcinoma. (IA)
2. Estrogen-progestin therapy may be offered to women with low-grade adenocarcinoma of the endometrium who have moderate to severe menopausal symptoms. (IB)
3. 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)
4. Health care providers may prescribe HT for menopausal symptoms in women at increased risk of breast cancer with appropriate counselling and surveillance (IA) (in women in the Women's Health Initiative [WHI] study with high Gail scores were at no greater risk of breast cancer than women with low risk scores).
5. 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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Knowledge and attitudes about the menopausal transition have changed markedly in the past 5 years. The results of large and expensive randomized controlled trials have provided new information about the risks and benefits of hormone therapy (HT). Legitimate concerns have been raised about the designs of these studies and the applicability of data to younger menopausal women, but there is no doubt that practice with respect to hormonal therapy in menopause has shifted.

While the 1990s were characterized by great expectations for HT to provide preventive benefits, current thinking emphasizes lifestyle choices for health promotion and disease prevention; reserving hormonal therapy for symptomatic women, or for short-term use. The US Preventive Services Task Force has reviewed the relevant issues for chronic disease prevention, and concluded (Grade D) that "overall, the harmful effects of [hormone therapy] are likely to exceed chronic disease prevention in most women."¹ They specifically excluded symptomatic use of HT from this recommendation, and they acknowledged the importance of clinical decision making in assessing the risks and benefits of HT.

Sound evidence increasingly convinces us of the benefits of healthy lifestyle, diet, and exercise in reducing the risk of serious illness, including heart disease² and cancer.³ Several lines of evidence also point to the importance of early childhood health in determining risk of adult disease.^{4,5} More women entering menopause today have had the advantage of growing up with access to better nutrition, preventive health care, and information about healthy living. Over the past 25 years, the risk of heart disease, for example, has progressively fallen.⁶

Many women today enter menopause in unprecedented states of health. Yet at the same time, levels of obesity are rising and physical inactivity is an ongoing concern. In our increasingly diverse society, we are challenged to find answers that are applicable to heterogeneous populations of women. Women are well read and informed about menopause, but have had their trust eroded. They seek thoughtful expert guidance, but wish to make their own choices.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) published its first Menopause Consensus Report in 1994,⁷ and has published 2 updates since then, most recently in 2002.⁸

This updated consensus document attempts to address the concerns of women and their healthcare providers. The expert consensus panel was composed of endocrinologists, gynaecologists, public health and family physicians, a cardiologist, and a psychiatrist. Osteoporosis was taken on by a

separate group. The consensus panel reviewed all pertinent evidence published in peer-reviewed journals since the last consensus update of 2002. The publications were rated according to level of evidence. The panel reached its conclusions through face-to-face meetings, exchange of information via email, and by teleconferences.

After a comprehensive introduction, the first part of the consensus focuses on the concerns, expressed and unexpressed, that women may have about menopause.⁹ The following sections deal with the concerns that providers may have in assisting women with specific medical conditions, or in sorting through controversial areas in menopause. Helpful resources for women are listed throughout, and key references for physicians are highlighted. Evidence-based recommendations summarize key points.

We hope that this consensus update will help women and health care providers to better understand menopause and act with best evidence for future health.

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Introduction

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The purpose of this chapter is to provide an overview of the new context in which caregivers must place the management of postmenopausal women.

Menopause is a biological process that occurs as part of aging in women. Aging is the natural progression of changes in structure and function of body systems that occurs as a function of the progress of time and in the absence of disease.

1. DEFINITIONS

The following definitions, published in the World Health Organization Technical Report Series,¹ are generally accepted:

Natural Menopause

The permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect one year or more after the event. An adequate independent biological marker for the event does not exist, and there is no place for performing serial measurements of serum estradiol or follicle-stimulating hormone (FSH) in an attempt to specify whether or not the FMP has passed.

Perimenopause

Includes the period immediately prior to menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause. The term "climacteric" should be abandoned to avoid confusion.

Menopausal Transition

Reserved for that time before the FMP when variability in the menstrual cycle is usually increased.

Premenopause

The whole of the reproductive period prior to menopause.

Induced Menopause

Cessation of menstruation that follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (by chemotherapy or radiation).

Postmenopause

The period of time dating from the FMP, regardless of whether the menopause was induced or spontaneous.

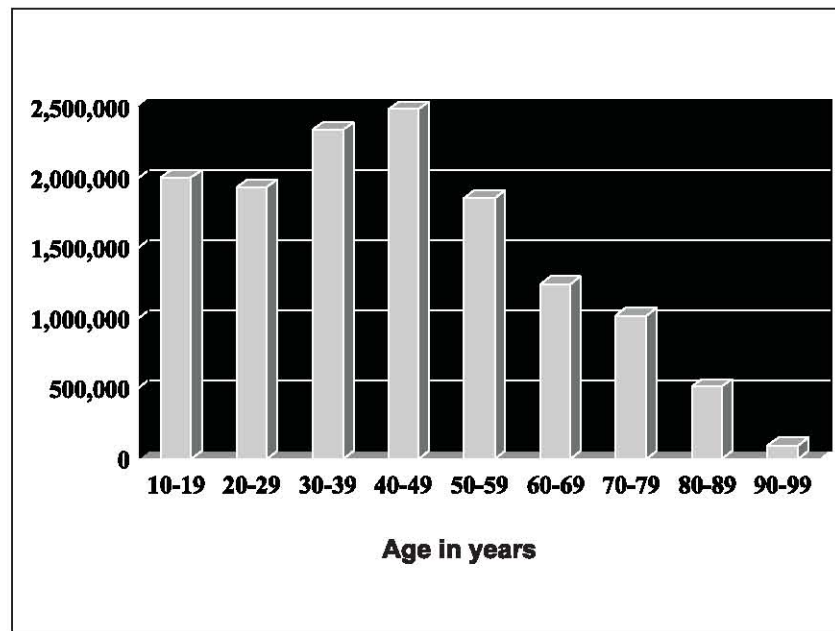
Premature Menopause

Menopause that occurs at an age less than 2 standard deviations below the mean age of menopause in the reference population. In practice, without reliable estimates of the distribution of age at natural menopause in developing countries, the age of 40 years is used frequently as an arbitrary cut-off point, below which menopause is said to be premature. Premature menopause may be spontaneous, a manifestation of autoimmune disorder, induced by medical disease, medication, irradiation, or surgery. Or, it may simply be menopause occurring at the outer limits of the normal curve.

Premature Ovarian Failure (POF)

POF is characterized by amenorrhea and consistently high FSH levels in women under 40.² Presumptive autoimmune ovarian failure is not absolute; spontaneous remissions may be experienced by between 5% and 25% of all women with presumed POF.

It should be noted that menopause is a point in time, according to the above definition. It is therefore, imprecise to describe a woman as "menopausal"; the correct descriptions would be to describe a woman who has not reached menopause as either "premenopausal" (if she has continuing normal ovarian function), "perimenopausal" (if she has any of the endocrinological, biological, and clinical features

Figure 1.1. Canada's female population by age group (2001 census)⁵.

of approaching menopause), or “postmenopausal” (if she has passed the final menstrual period).

2. DEMOGRAPHICS

In the 2005 Canadian census, the total number of women over the age of 50 was over 5.5 million,³ and it has been estimated that the number of women in this age group will reach 6.9 million by the year 2016, and 7.9 million by the year 2026—at which point they will comprise 22% of the Canadian population.⁴

The median age of the female population has been in the 40 to 49-year age bracket since 2001 (Figure 1.1).^{3,5}

The average age of menopause in Canada is 51, and Figure 1.1 shows that there is a large cohort of women in Canada who will reach this age in the coming decade. The average age at menopause of 51 years has remained remarkably constant throughout the centuries, apparently unaffected by improving nutrition and reduction of disease. However, certain chemotherapeutic agents, radiation, smoking, and hysterectomy can contribute to an earlier onset of menopause.⁶ Many younger women have had their ovaries surgically removed, and a smaller number spontaneously undergo menopause before the age of 40.⁶

Canadian statistics show an increase in life expectancy for postmenopausal women. In 1922, a 50-year-old woman lived, on average, until age 75.⁷ Today, a woman the same age can expect to live until her mid-80s.⁸ The increasing numbers of women over 70 are particularly vulnerable to conditions shown in Figure 1.2.

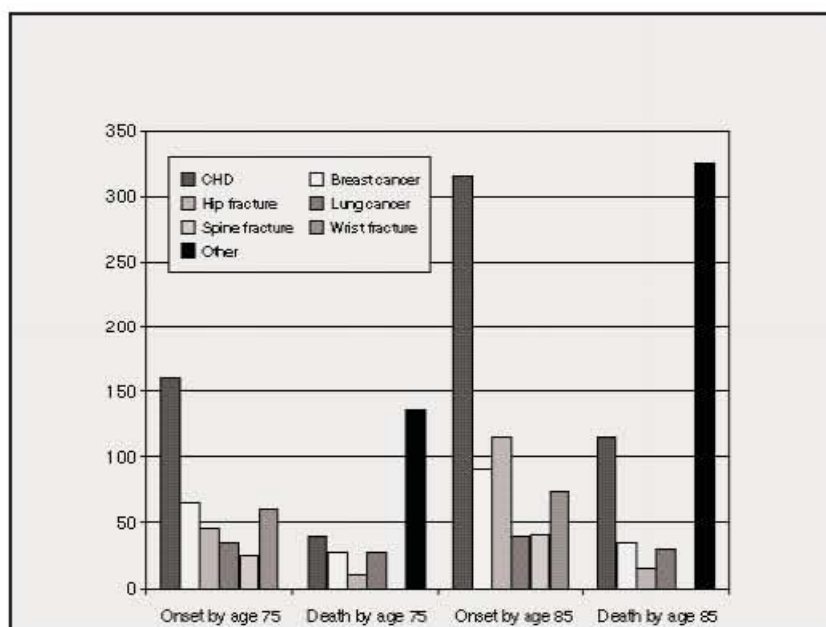
Although the age at which menopause occurs in an individual woman is primarily determined genetically, it may also be associated with external factors. Most prominent among these is cigarette smoking, which will reduce the age of menopause proportionally to the number of cigarettes smoked and the duration of smoking; on average, women who smoke experience menopause two years earlier than non-smokers.⁹ Other factors that are less clearly associated with an earlier menopause include nulliparity,¹⁰ exposure to toxic chemicals, treatment of malignancy with chemotherapy or pelvic radiation, epilepsy,¹¹ and medically treated depression.¹² Conditions that may delay menopause include obesity,¹³ multiparity,¹⁴ alcohol use,¹⁵ and high cognitive scores in childhood.¹⁶

No evidence has been identified to link age at menopause with the use of oral contraceptives, age at menarche, marital status, or ethnicity.

3. MENOPAUSE IN THE CANADIAN CONTEXT

The issue of menopause and postmenopausal health in women is of significance to society in general because of the universality of menopause—it affects all women—and because of the unprecedented increase in the number of postmenopausal women in Canada. Moreover, rising life expectancy means that not only are there increasing numbers of postmenopausal women, but also an increasing proportion of them are in the late postmenopausal years. The relevance to public health of any adverse effects of menopause is of potentially great importance to any society, and

Figure 1.2. Number of 50-year-old women (per 1000 women) affected by specific conditions by age 75 and by age 85. CHD: coronary heart disease.



Source: Special tabulation, POHEM, Statistics Canada.⁴

potentially more so in a society with a universal health care system such as Canada's.

The menopausal transition may be a time of major symptoms with a significantly adverse effect on quality of life, and these symptoms may require medical assessment with or without prescription of medical therapy. Nevertheless, the experience and the reporting of symptoms vary widely among individuals and cultures. Notably, the majority of women experience menopause as a normal event without significant difficulty, and these largely asymptomatic women will, therefore, not be seen by a physician for the purpose of detecting disease and relieving symptoms.

The traditional approach of diagnosing and treating disease is thus no longer sufficient; health promotion and disease prevention strategies must be incorporated into every physician's practice.

Health promotion and disease prevention provide the foundation for the comprehensive management of women's health, and are critical strategies for the responsible allocation of limited health care resources. It is also important to recognize that medical care determines only a small portion of the health of a society. Both individual and population- or society-based initiatives must be developed for effective health promotion.

Consideration must be given to the determinants of health, including the social and physical environment, individual genetic and physiologic characteristics, in combination with

lifestyle and behaviour. By focusing on disease prevention and early intervention, health care providers can help women to avoid much disability. Health care providers can also advocate on behalf of women in an effort to overcome social (poverty, violence, lack of education) and geographical barriers to health.

Recommendations for practice are evidence-based, with research continuously in progress to determine the most effective interventions. Standard strategies for preventive health care, including counselling, screening for diseases, and immunization, must be used regularly. While discussion has focused on the effectiveness of medical therapy in postmenopausal women for the alleviation of symptoms and the prevention of specific conditions such as osteoporosis, the effectiveness of a healthy lifestyle in disease prevention cannot be ignored. Women must be informed about the effect of lifestyle on the modifiable risk factors for disease, and encouraged to make the necessary changes.

An individualized approach to comprehensive care, based on the identified benefits and risks combined with regular reassessment and re-evaluation, will ensure that a woman's changing needs are met.

4. MENOPAUSE AND DIET

Canada's Food Guide recommends a diet rich in plant-based foods, low in saturated and trans-fatty acids, high in dietary fibre, and accompanied by 6 to 8 glasses of

Table 1.1. Dietary recommendations from Canada's food guide*

Food groups	Servings per day	Comments
Fruits & vegetables	5-10 1 serving = 1 medium-sized fruit or vegetable; 250 mL (1 cup) salad; 125 mL (½ cup) juice	- Rich sources of antioxidants, vitamins, and fibre - Choose dark green and orange fruits and vegetables when possible
Grains & cereals	5-12 1 serving = 1 slice bread; ½ pita or bun; 30 g (¼ cup) cold cereal; 250 mL (1 cup) rice or pasta	- High-fibre diet reduces cardiovascular and cancer risk - Choose whole grain and enriched products when possible
Meat & alternatives	2-3 1 serving = 50 to 100 g (2-3.5 oz.) beef, poultry, fish; 250 mL (1 cup) legumes; 100 g (1/3 cup) tofu; 30 mL (2 tbsp) peanut butter	- Choose lean meats, poultry and fish plus dried peas, beans, lentils and soy products when possible - Cold water fish are high in omega-3 fatty acids
Milk products	2-4 1 serving = 250 mL (8 oz) milk; 175 g (¾ cup) yogurt; 50 g (2 oz) cheese	- High sources of calcium - Milk is the only dairy product fortified with Vitamin D - Choose lower fat dairy products
Other foods & beverages		
Oils & fats		- Obtain 10 percent of total calories from saturated fat - Use olive or canola oil
Sugar		- Avoid animal fats, hydrogenated oils, and trans-fatty acids - Minimize use of products that are mostly sugar (jams, syrup, honey, candies)
Alcohol	1 serving: 150 mL (5 oz) wine; 350 mL (1 bottle) beer; 50 mL (1.5 oz) liquor; 11-15 g alcohol	- Limit intake to 1-2 drinks/day for cardioprotective effects - Breast cancer risk is increased with 2 drinks/day
Caffeine		2-3 caffeinated beverages/day allowable in calcium-sufficient individuals - Caffeine may contribute to bone resorption in calcium-deficient individuals

*Source: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index_e.html

water per day (Table 1.1).¹⁷ Although there is no scientific evidence for a benefit from this level of daily fluid intake, to rely on thirst as a stimulus for fluid intake may result in a deficiency because the sensation of thirst may decline with age. The recommended diet provides adequate nutrients and vitamins for most menopausal women, unless specific diseases or malabsorption problems are present. It may, however, be difficult to obtain optimal amounts of select

nutrients such as calcium, vitamin D, and folate from diet alone (Table 1.2).

Women with medical conditions such as hypertension, dyslipidemia, and diabetes mellitus should consult a dietitian for specific dietary advice.¹⁸⁻²⁰

Diet and Heart Disease

Since the risk of coronary heart disease (CHD) in women shows a consistent rise after the menopause, using any

Table 1.2. Dietary reference Intakes (DRI) for selected nutrients*

Vitamins and minerals	DRI	Comments
Vitamin D		Function: Required for optimal calcium absorption
• Premenopausal	200 IU	Sources: Daily intake of 3-4 oz fish or one litre fortified milk, or exposure to 15-20 minutes sunshine without sunscreen Caution: Deficiency common in northern climates (including all of Canada), elderly and housebound. Supplements often required to achieve adequate intake in these circumstances
• age 50-65	400 IU	
• age 65 +	800 IU	
Calcium (elemental) premenopausal		Function: Required to maintain calcium homeostasis, cellular function and bone mineralization
Postmenopausal	1 000 mg	Sources: Most plentiful in milk products Comment: Prerequisite for effective anti-resorptive therapy
• on antiresorptive therapy	1 000 mg	
• not on anti-resorptive therapy	1 500 mg	
Iron		Function: Required for red blood cell (RBC) formation
• premenopausal	18 mg	Sources: Most plentiful in red meat. Also found in fruits, vegetables, and grains
• postmenopausal	8 mg	
Vitamin B6 (serotonin)	1.5 mg	Function: Needed for production of RBCs and serotonin and for metabolism of protein and fat Sources: Whole grains, green vegetables, beans, nuts, meats Caution: Doses 100 mg may be neurotoxic
Vitamin B12 (cyanocobalamin)	2.4 µg	Function: Needed for RBC formation and neurological function Sources: Milk products and protein-rich foods Caution: Absorption decreases with age and gastric hypoacidity
Folate (folic acid)	400 µg	Function: B vitamin that affects cell division and RBC formation and lowers homocysteine levels Sources: Fruits, vegetables, and grains

*Source: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index_e.html

means possible to lower the risk is desirable. Observational studies show a relationship between serum cholesterol levels and CHD,²¹ and dietary measures to lower serum cholesterol are an important part of the prevention of CHD.²² Evidence from the Nurses' Health Study suggests that replacing saturated fat and trans-fatty acids in the diet with nonhydrogenated, monounsaturated, and polyunsaturated fats may be more effective in reducing the risk of CHD than reducing overall fat intake in women.²³ The intake of omega-3 fatty acids is linked to a reduction in risk of CHD²⁴; potential dietary sources of these fatty acids are coldwater fish (salmon, tuna, and halibut), flaxseeds, and flaxseed oil. The American Heart Association recommends that women limit total fat intake to not more than 30% of total calories, and polyunsaturated fat to 10% of total calories, with the remaining fat intake being made up from sources of monounsaturated fat, such as olive oil or canola oil.²⁵

Other dietary strategies to reduce the risk of CHD in women include increasing intake of flavonoids^{26,27} (found in fruits and vegetables, especially broccoli, and in tea),

dietary folate²⁸ (fruit and vegetables, grains) through regulation of circulating homocysteine, and soy products,²⁹ as sources of isoflavones.

Diet and Osteoporosis

A woman's genetically determined peak bone mass requires an adequate intake of calories, calcium and protein. Minimising the rate of subsequent bone loss 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 further. Other dietary content has not been shown to influence the rate of loss of bone mineral density.

Adequate and appropriate nutrition is important for all individuals, but diet alone is not sufficient to prevent bone loss in women who experience early menopause.³⁰ Supplementation of calcium and vitamin D may be necessary, especially in those with low intake of dairy products. Calcium is the most important specific nutrient for attaining peak bone mass and preventing and treating osteoporosis. For older women, elemental calcium intake from diet and

Table 1.3. Indications for Intervention by BMI category⁴⁰

Category	IMC	Intervention
Underweight	18.5	Encourage balanced diet and exercise
Healthy	18.5–24.9	Encourage balanced diet and exercise
Overweight	25–26.9	Lifestyle (diet, exercise, behaviour therapy)
Overweight	27–29.9	Lifestyle, plus drug therapy if comorbidities* exist
Obese class 1	30–35	Lifestyle plus drug therapy
Obese class 2	35–39.9	Lifestyle plus drug therapy, plus surgery if comorbidities* exist
Obese class 3	40	Lifestyle, drug therapy, and surgery

*Comorbidities: hypertension, diabetes, hyperlipidemia

supplements should be 1000 mg per day in premenopausal women, increasing to 1500 mg per day in postmenopausal women.³⁰ Vitamin D is required for optimal calcium absorption. A vitamin D intake of 400 IU per day has been recommended for women up to the age of 50, increasing to 800 IU per day in women over age 50.³⁰

Diet and Cancer

It has been estimated that 30% to 40% of all cancer could be prevented over time by the combination of following a recommended diet, participating in regular physical activity, and maintaining an appropriate body weight.³¹ Many aspects of a woman's diet have a role in cancer risk, especially the consumption of red meat and animal fat, and the consumption of fruit and vegetables. Canada's Food Guide recommends daily consumption of between 5 and 10 servings of fruit and vegetables, especially dark green and orange vegetables, and between 5 and 12 servings of grains and cereals. The consumption of fruit and vegetables by Canadians has increased by approximately 40% since the 1960s, and this has likely contributed to reduced risk of some cancers, particularly of the gastrointestinal tract.³²

Associations between aspects of diet and risk of breast cancer have come under recent scrutiny, with particular emphasis on dietary intake of fat and intake of isoflavones. Dietary intervention studies have, to date, shown inconclusive results.

Alcohol intake, however, has been implicated in several forms of cancer. Drinking 2 standard drinks per day increases the risk of cancer of the oral cavity, larynx, and esophagus. Alcohol consumption is a known risk factor for breast cancer and, to a lesser extent, colorectal cancer.³³

Weight Management

The International Agency for Research on Cancer attributes one-quarter to one-third of cancers of the breast, colon, uterus, esophagus, and kidney to physical inactivity and

excess body weight.³⁴ In particular, excess body weight is associated with increased risk of cardiovascular disease, type II diabetes and breast cancer; other morbidities associated with obesity are hypertension, hyperlipidemia, cholelithiasis, osteoarthritis, sleep apnea, and stress from social stigmatization.³⁵

Conversely, women whose weight is below normal have an increased risk of osteoporosis, and this will be more significant if the low body weight was associated premenopausally with amenorrhea.³⁶

Perimenopausal weight gain is common but not inevitable. The average amount of weight gained during the perimenopause ranges from 2.25 to 4.19 kg.³⁷ This weight gain is not related to hormone therapy or menopause itself, but to an age-associated reduction in the metabolic rate resulting from the shift in ratio of fat-to-lean body composition.³⁸

The preferred indicator of obesity, and guide for weight management, is the body mass index (BMI: body weight in kg divided by height in m²). The Canadian Community Health Survey (2000–2001) indicated that approximately 50% of women aged 45 to 64 years are either overweight (BMI 25–29.9) or obese (BMI 30 or greater).³⁹ Because of the known associations between excess body weight and morbidity, reducing excess weight is desirable.

The initial goal is to reduce body weight by approximately 10% from baseline over 6 to 12 months. Individual and group support (dietitians, Weight Watchers, Overeaters Anonymous, Take Off Pounds Sensibly [TOPS]), medication, and surgery all play a role in facilitating weight loss. The level of intervention required depends on the BMI category and the presence of comorbidities (Table 1.3).⁴⁰ Drug therapy (orlistat in Canada; phentermine HCl, and sibutramine are also available in the US) should only be used when diet and exercise have failed in individuals with a BMI greater than 30 or BMI greater than 27 with comorbidities.⁴¹

Table 1.4. Selected resources

Topic	Organization	Website*
Sexual health	The Society of Obstetricians and Gynaecologists of Canada	http://www.sexualityandu.ca
Breast cancer risk	National Cancer Institute Breast Cancer Risk Assessment Tool Harvard Center for Cancer Prevention	http://brca.nci.nih.gov/brc/ http://www.yourdiseaserisk.harvard.edu
Heart and stroke	Heart and Stroke Foundation of Canada (includes heart, stroke and dietary information plus individual risk assessment and smoking cessation guidelines)	http://www.hsf.ca (1-888-HSF-INFO)
Menopause	Society of Obstetricians and Gynaecologists of Canada (includes consumer education brochures, clinical practice guidelines, and consensus conference reports) North American Menopause Society (includes consensus opinions, surveys, and consumer education materials)	http://www.sogc.org http://www.menopause.org
Nutrition	Canada's Food Guide to Healthy Eating	http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index_e.html
Osteoporosis	Osteoporosis Canada (includes osteoporosis diagnosis, prevention and treatment plus Calcium Calculator)	http://www.osteoporosis.ca
Weight control	National Heart, Lung and Blood Institute (includes BMI calculator, evidence tables, tip sheets)	http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/index.htm
Exercise	Public Health Agency of Canada Physical Activity Guide	http://www.phac-aspc.gc.ca/pau-uap/paguide/

*All websites accessed on December 7, 2005

5. MENOPAUSE AND EXERCISE

The simplest and most effective way to maintain good health is through regular exercise. Among the many benefits of exercise are improvements in serum lipids and weight, and protection from cardiovascular disease, diabetes, and breast cancer.

Women who exercise regularly report lower levels of stress, lighter periods, and fewer menopausal symptoms. Regular exercise can also decrease bone loss, improve balance and strength, and provide protection from falls and fractures.

Exercise must be tailored to a woman's age, ability, and individual preference. A sedentary woman should be advised to start slowly and progress gradually. A minimum of 20 to 30 minutes of weight-bearing exercise on most days is recommended by Osteoporosis Canada to promote bone health.³⁰ The addition of muscle-strengthening exercise involving the upper and lower limbs, abdomen, and back muscles for 30 to 60 minutes 3 times per week can help to improve bone mass and decrease back pain. Flexibility training (stretch classes, tai chi, yoga) improves balance and helps to prevent muscular injuries and falls.⁴² Thirty minutes of moderate aerobic exercise (which may be broken into 10-minute sessions 3 times daily) on most days is recommended by the Canadian Medical Association and the Heart and Stroke Foundation for its cardioprotective effects. Health Canada's Physical Activity Guide is a useful

resource.⁴³ Table 1.4 lists selected resources for assisting the maintenance of good health.

ROLE OF HEALTH CARE PROVIDERS

Women in menopause are ready to make positive changes in their lives,⁴⁴ and life transitions are opportune times to make lifestyle changes. Not only is there evidence that healthy lifestyle leads to better outcomes, but there also is good evidence to demonstrate that an intervention by a physician and other health care providers increases the likelihood that a patient will make a healthy change.⁴⁵ Providing women with advice, encouragement and support, and trusted educational resources are all strategies that can benefit the menopausal woman, and are fundamental to any other medical advice that may be appropriate.

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Menopause and Age-Related Concerns

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INTRODUCTION

Menopause transition may raise several concerns for health care providers involved in women's health.

Women may experience changes in their physical and psychological status related to hypoestrogenism and aging. This chapter will address some of the most frequent concerns that bring women to our offices. Urogenital complaints, sexual health, mood, and cognition will be addressed in other chapters.

I: VASOMOTOR SYMPTOMS

The vasomotor symptoms associated with menopause are commonly termed hot flashes and night sweats. Hot flashes are characterized by the sudden onset of intense warmth that begins in the chest and may progress to the neck and face.¹ They are often accompanied by anxiety, palpitations, and profuse sweating. Vasomotor symptoms may interfere with a woman's ability to work, her social life, her sleep pattern, and her general perception of health.

NATURAL HISTORY

Vasomotor symptoms are an early, readily apparent sign of menopause transition. Their maximal prevalence is during the first 2 years postmenopause, after which the prevalence declines over time. Most women experience hot flashes for 6 months to 2 years, although some women have them for 10 years or longer. A Swedish study found that about 9% of 72-year-old women have hot flashes.² The Massachusetts Women's Health Study, a longitudinal study of 454 women, found that about 75% of women experienced hot flashes during the transition from perimenopause to postmenopause, which lasted a median time of 3.8 years.³ The Study of Women's Health Across the Nation (SWAN) demonstrates different prevalence rates of hot flashes among racial/ethnic groups. According to this multiethnic cross-sectional survey of more than 16 000 women aged 40 to 55, African-American women report hot flashes most frequently, followed by Hispanics, Caucasians, Chinese, and Japanese.⁴ Recent data from

SWAN indicate that differences in body mass index (BMI) may be a more important predictor than ethnic difference.⁵

Various factors are predictors of an increased frequency of vasomotor symptoms. A high BMI (27 kg/m²) seems to be associated with an increased frequency of vasomotor symptoms.⁴ A history of premenstrual complaints is significantly associated with hot flashes in perimenopausal women. According to data from the Melbourne Health Project, approximately 47% of transitional women with a history of moderate to severe premenstrual complaints experienced hot flashes compared with 32% of women without a history of premenstrual complaints.⁶ Warm, ambient air temperature increases a woman's core body temperature and makes her more likely to reach the sweating threshold. In SWAN, cigarette smoking, low socioeconomic status, and less physical activity increased the relative risk of hot flashes.⁴ After bilateral oophorectomy, acute symptoms are more frequently found and may be worse than for women experiencing spontaneous menopause. Over time, the prevalence of symptoms becomes similar to that of women who have reached menopause naturally.⁷

The precise cause of vasomotor symptoms is not known, although they appear to have a hypothalamic origin. Menopause, however, is not the only condition associated with hot flashes and night sweats. Other conditions and drugs that can result in hot flashes are presented in Table 2.1. Dysfunction of central thermoregulatory centres caused by changes in estrogen levels at the time of menopause has long been postulated to be the cause of hot flashes. While it is well known that hot flashes occur with estrogen withdrawal at menopause, estrogen is not the only etiologic factor. It seems that in symptomatic postmenopausal women, hot flashes are triggered by small elevations in core body temperature within a reduced thermoneutral zone. Complex neuroendocrine pathways involving norepinephrine, serotonin, estrogens, testosterone, and endorphins govern regulation in the thermo-regulatory area of the central nervous system and are possible targets where dysfunction may occur in individuals with vasomotor symptoms.⁸

TREATMENT

Multiple treatments have been used to relieve hot flashes, including lifestyle modifications, non-prescription, and prescription therapies. Prescription therapies may be grouped as hormonal or non-hormonal agents. Multiple placebo-controlled trials have shown about 25 to 30% reduction in hot flashes within 4 weeks of placebo treatment.¹ Moreover, a Cochrane review of estrogen therapy compared to placebo for the treatment of hot flashes has shown that placebo may cause a vasomotor symptom reduction of up to 50%.⁹ These results highlight the importance of applying appropriate scientific scrutiny to anecdotal reports and uncontrolled trials that claim the efficacy for treatment of hot flashes.

Lifestyle Modifications

When choosing a therapy for vasomotor symptoms, we must consider the severity of hot flashes, mainly determined by their impact on quality of life. We must also take into account the health status and personal choice. The first line of approach for addressing mild vasomotor symptoms is lifestyle modification, including manipulating the environment and changing behaviours.

Remembering the pathophysiology of hot flashes, it seems rational to assume that practices that lower core body temperature may be beneficial. An observational study has shown that lowering air temperature reduces vasomotor symptoms.¹⁰ Women report that using a fan, keeping cool by dressing in layers, and consuming cold food and drinks may help prevent hot flashes. Conversely, hot foods or drinks and alcohol should be avoided. Women should also be encouraged to quit smoking and to exercise regularly. A weight reduction program should be recommended to overweight women. However, no randomized controlled trials have examined the efficacy of exercise, weight reduction programs, or smoking cessation in managing vasomotor symptoms. Investigators have examined the role of relaxation training and controlled breathing in small groups of women with mild to moderate hot flashes. After a short period of training, the intervention objectively decreased vasomotor symptoms by 50% to 60% and may be an effective alternative or adjuvant treatment for some women.^{11,12}

Non-Prescription Therapies

Canadian women between 45 and 64 years old are significant users of complementary and alternative medicine¹³ (Please also refer to Chapter 7). Herbs most frequently used for menopausal problems include black cohosh, chaste tree berry, dong quai, ginseng, evening primrose oil, red clover, Chinese herb mixtures, and liquorice. Evidence is generally lacking regarding efficacy and long-term safety of these agents and study populations often only include women

Table 2.1 Potential Causes of Hot Flashes and Abnormal Sweating

Drugs	Tamoxifen
	Raloxifene
	Diltiazem
	Amyl nitrate
	Nicotinic acid
	Levodopa
	Bromocriptine
	Selective serotonin reuptake inhibitors (SSRIs)
	Thyroid diseases
	Epilepsy
Diseases	Insulinoma
	Pheochromocytoma
	Carcinoid syndromes
	Leukemia
	Pancreatic tumours
	Autoimmune disorders
	Mast-cell disorders

experiencing mild symptoms. Black cohosh and products that contain phytoestrogens are the only complementary and alternative medicine (CAM) that have shown some benefits for treatment of menopausal symptoms.^{14,15}

Black Cohosh

In a recent review of complementary and alternative medicine, 3 of the 4 randomized controlled trials found black cohosh to be beneficial for treating hot flashes.¹⁵ Neither the identity of active compounds nor the mechanism of action of black cohosh is known. No clinical trials have lasted for more than 6 months. There are no published data from human trials about long-term safety, particularly regarding endometrial or breast stimulation. Recently, a few cases of hepatotoxicity have been reported. A recent case report described a fulminant liver failure in a 50-year-old woman taking black cohosh for the relief of menopausal symptoms.¹⁶ Although black cohosh may be useful for menopausal symptoms, long-term use cannot be presumed to be safe until appropriate safety studies are conducted.

Red Clover-Derived Isoflavone

Red clover contains several phytoestrogen compounds, including the isoflavones daidzein and genistein. Only 1 small randomized, double-blind, placebo-controlled trial reported that after 8 weeks of Promensil (a red clover extract) at 80 mg per day hot flashes were marginally reduced.¹⁷ However, other well-designed studies did not find any benefit of red clover supplements over placebo.^{15,18}

Soy-Derived Isoflavone

Randomized controlled clinical trials have shown that, in general, hot flashes are not reduced or are only slightly diminished in women who consume soy foods or soy extracts when compared with controls.^{15,18}

Vitamin E

Tocopherol (vitamin E) has also been reported as an agent that improves vasomotor symptoms. A randomized, double-blind, placebo-controlled crossover study tested moderate-dose vitamin E (800 UI/d) in 120 women with a history of breast cancer. On crossover analysis, a slight decrease in hot flash frequency (1 less hot flash per day) favoured vitamin E treatment. No adverse effect of therapy was observed, but at the end of the study, subjects did not prefer vitamin E use over placebo.¹⁹ A recent randomized, double-blind, placebo-controlled international trial in patients with vascular disease or diabetes mellitus has demonstrated that long-term vitamin E supplementation may increase the risk of heart failure.²⁰

Progesterone Creams

Topical wild yam and micronized progesterone creams have been promoted for hot flashes as well as many other conditions. However, convincing evidence about efficacy and safety are lacking. Serum levels of progesterone after transdermal application of creams are insufficient to prevent estrogenic stimulation of the endometrium. Therefore, progesterone cream should not be used as the progestin component of combined hormone therapy.¹⁵

Acupuncture

Acupuncture is another non-pharmacological treatment used to relieve hot flashes. At the moment, there is not enough evidence to recommend acupuncture for the treatment of vasomotor symptoms.¹⁵

Prescription Therapies: Hormonal

Many women suffer from persistent vasomotor symptoms that respond only to prescription therapy. The most commonly prescribed hormone is estrogen (ET), either alone or combined with a progestin (EPT) for women with a uterus. Other hormones that may be used are progestins alone and oral contraceptives, particularly for perimenopausal women. For a complete list, please refer to Chapter 6.

Hormone Therapy

A meta-analysis conducted by the Cochrane Group of 21 randomized, double-blind, placebo-controlled trials found that systemic ET/EPT significantly reduced both hot flash frequency and severity compared with placebo. Overall hot flash frequency was reduced by 77% relative to placebo, while symptom severity was reduced by 87%.⁹ In a recent report of secondary endpoints evaluated in the Women's Health Initiative (WHI) study, 85.7% of subjects on EPT compared with

57.7% of women on placebo had relief of hot flashes. The relief of night sweats was also more pronounced in the EPT group (77.6% compared with 57.4%).²¹ There are many Health Canada—approved systemic ET/EPT preparations, routes of administration, regimens, and doses. No evidence indicates that one product or regimen is superior to another for symptom relief. Patch and gel formulations are equally effective in treating vasomotor symptoms and the effects are comparable to those achieved by oral ET/EPT.²² For a complete list of estrogens and progestins formulations, please refer to Chapter 6.

A dose-response relationship seems to exist with estrogen therapy alone that does not exist with a combined estrogen-progestin therapy. A large randomized, multicentre, placebo-controlled trial showed that the reduction in vasomotor symptoms was similar with conjugated estrogens (CE) 0.625 mg per day and medroxyprogesterone acetate (MPA) 2.5 mg per day and all lower combination doses. However, CE 0.625 mg per day alleviated hot flashes more effectively than the lower doses of CE alone.²³ Moreover, a trial of 4 weeks or longer of ET/EPT may be required to get the full effect on vasomotor symptoms. The principal indication for the use of a combined regimen (EPT) is the presence of a uterus. However, a systemic progestin may be added to an ET regimen if a hysterectomized woman presents persistent vasomotor symptoms on standard or higher doses of estrogens (equal or higher than CE 0.625 mg/d or equivalent).

Currently, it seems preferable to use the lowest dose of oral or transdermal HT that adequately controls vasomotor symptoms, but low-dose preparations should not yet be emphasized as being safer than traditional doses.²⁴

SOGC Clinical Tip

Levonorgestrel Intra-Uterine System (IUS-LNG 20 mcg/d, Mirena) may be used for the prevention of endometrial hyperplasia or cancer in women using ET. When comparing a regimen of regular doses of ET with IUS-LNG 20 mcg per day to a standard oral or transdermal EPT regimen, two 1-year studies demonstrated similar endometrial responses (endometrial thickness and histology).^{25,26} However, subjects in the IUS-LNG group presented more days of bleeding during the first 3 months, but the difference between groups disappeared by 6 months.²⁵ A new frameless intrauterine drug delivery system (LNG 10 mcg/d) is under evaluation and seems well tolerated and effective in suppressing the endometrium during ET.²⁷

SOGC Clinical Tip

Women's preference is the main factor determining the choice of ET delivery route. However, the transdermal route may be preferred in women with specific medical conditions. For women with elevated triglyceride levels, transdermal ET seems preferable, since oral ET has a potentially negative effect on triglyceride levels.²⁸

Transdermal ET/EPT may show advantages over oral ET/EPT in women with diabetes or metabolic syndrome as well as women with hypertension. For a detailed discussion concerning HT and women with pre-existing medical conditions, please refer to Chapter 8.

Transdermal ET/EPT is also a good choice for women with malabsorption syndromes or other gastrointestinal conditions such as gastroesophageal reflux.

Since transdermal ET avoids the hepatic first-pass, there is no increase in sex-hormone binding globulin (SHBG), allowing more circulating free testosterone.^{29,30} Women complaining of decreased sexual desire may therefore benefit from the transdermal route.

SOGC Clinical Tip

Oral MPA (Provera) 20 mg per day, intramuscular MPA (Depo-Provera) 150 mg every 1 to 3 months, and oral megestrol acetate (Megace) 20 mg per day are available in Canada and may be used in symptomatic women who cannot or do not want to use ET. The side effects profile of those regimens may be a problem for some women. Micronized progesterone (Prometrium) 200 mg per day has a better side effects profile and a beneficial effect on sleep, but evidence of efficacy for vasomotor symptom treatment is lacking. Progestins alone should not be used in women with breast cancer. The uncertainty about breast cancer risk with progestins should be addressed when counselling women. Progestins

Progestins alone may be considered as an alternative treatment for hot flashes if the benefit-risk profile is acceptable to the woman. The question of whether a progestin alone increases the risk of breast cancer is unanswered. MPA has been shown in several trials to relieve hot flashes in healthy women as well as in women with breast or endometrial cancer. Both intramuscular (DMPA 150 mg) and oral forms

(MPA 20 mg/d) have demonstrated efficacy.^{31,32} Another oral progestin, megestrol acetate, has also been studied for treating hot flashes. A randomized, placebo-controlled, double-blind crossover trial of 97 postmenopausal women with a history of breast cancer receiving 20 mg per day of megestrol acetate has shown a 85% reduction of hot flashes.³³

Oral Contraceptives

Low-dose oral contraceptives (OCs) are commonly prescribed for women who need both contraception and therapy to relieve hot flashes. Two studies of perimenopausal women have shown a reduction of vasomotor symptoms with an OC containing 0.02 mg or 0.03 mg of ethinyl estradiol.^{34,35} Contraindications to the use of OCs include a history of thromboembolic events, cardiovascular disease, migraine, hormone-sensitive carcinoma, jaundice, and liver disease. Smokers over age 35 should not use OCs.³⁶ Perimenopausal women may also take advantage of several non-contraceptive benefits when using OCs. For a review of OC use during menopausal transition, please refer to the Canadian consensus on contraception.³⁷

Prescription Therapies: Non-Hormonal

For women with moderate to severe hot flashes for whom hormones are not an option, other prescription medications have shown some effectiveness in relieving hot flashes. Some of these drugs were studied in women with a history of breast cancer. Data obtained from cancer survivors can probably be extrapolated to other populations of women. In Canada, Bellergal and Dixarit (clonidine) are the only two non-hormonal medications approved for the treatment of vasomotor symptoms.

Antidepressant Agents

Newer antidepressant agents have become the most promising class of non-hormonal treatment of vasomotor symptoms. These agents affect the release and reuptake of neurotransmitters, principally serotonin and norepinephrine, at multiple sites in the central nervous system. Venlafaxine is the first antidepressant drug to undergo clinical investigation for the treatment of hot flashes. This agent inhibits both serotonin and norepinephrine reuptake. A double-blind, placebo-controlled trial in which 191 women were randomized to placebo or to 1 of 3 venlafaxine doses (37.5 mg, 75 mg, or 150 mg) has shown a significant reduction of hot flashes with all 3 doses compared to placebo.³⁸ More than 60% reduction of hot flash score was reached with both 75 mg and 150 mg. Subjects treated with venlafaxine experienced adverse effects more frequently than did placebo-treated patients. For the treatment of hot flashes, venlafaxine should be started at 37.5 mg per day and increased up to 75 mg per day after 1 week, if the hot flashes are not optimally reduced. There is no reason to use a higher

dose of venlafaxine for the treatment of vasomotor symptoms, because side effects increase without additional benefit for vasomotor symptoms.

Other antidepressant agents, paroxetine and fluoxetine, both selective serotonin reuptake inhibitors (SSRIs), have demonstrated some efficacy in the treatment of vasomotor symptoms. Randomized, double-blind, placebo-controlled trials have shown a 50% to 60% decrease in hot flashes with controlled-release paroxetine 12.5 mg per day or 25 mg per day and fluoxetine 20 mg per day.^{39,40} Results from a pilot uncontrolled study also support the use of paroxetine (20 mg/d) for vasomotor symptom therapy.⁴¹ However, the long-term efficacy of antidepressant agents in the management of hot flashes is questioned. A recent 9-month trial, showed no benefit of fluoxetine compared to placebo for vasomotor symptom treatment.⁴²

SOGC Clinical Tip

Venlafaxine (Effexor) should be started at 37.5 mg per day for a week and increased up to 75 mg per day if well tolerated. Higher doses are not useful for the treatment of vasomotor symptoms. Venlafaxine as well as SSRIs should be slowly tapered to minimize the occurrence of discontinuation symptoms. It is prudent to reduce the antidepressant dose by 25% per week.

Gabapentin

Gabapentin is a (γ -aminobutyric acid (GABA) analogue that is used to treat a variety of neurologic disorders including epilepsy and neuropathic pain. Its precise mechanism of action is unclear. After a few case reports of reduced hot flashes in patients using gabapentin for neurologic conditions, RCTs have been initiated. Gabapentin 900 mg per day, in 3 divided doses, has reduced hot flashes by 50% in a randomized, double-blind, placebo-controlled trial.⁴³ Gabapentin was relatively well tolerated in this trial, with dizziness and light-headedness being the major adverse effects observed.

SOGC Clinical Tip

Gabapentin (Neurontin) should be started at 300 mg daily and increased to 300 mg 3 times a day over 3 to 7 days. Somnolence and dizziness are the principal side effects. Discontinuation of gabapentin should be done over a 1-week period.

Clonidine

An old antihypertensive drug, clonidine, is a well known non-hormonal therapy for hot flashes. An 8-week trial found that oral clonidine 0.1 mg per day marginally reduced

hot flashes in 194 women (by 38% versus 30% for placebo).⁴⁴ However, clonidine was associated with more side effects than placebo, including dizziness, dry mouth, drowsiness, and constipation.

SOGC Clinical Tip

Dixarit 0.05 mg twice a day is a labelled vasomotor treatment in Canada. It should be stopped if no benefit is noted after 2 to 4 weeks of treatment or if a woman experiences side effects including dizziness, dry mouth, drowsiness, and constipation.

Bellergal

Bellergal is an older sedative containing phenobarbital and belladonna. Clinical trials of this combination showed small benefit favouring Bellergal over placebo.¹ However, this combination is associated with several adverse effects, including dry mouth, constipation, and sedation.

In summary, vasomotor symptoms are normally a transitory phenomenon, but they may impair the quality of life of perimenopausal and postmenopausal women. The most effective treatment is HT, but several prescription and non-prescription therapies are available for women who cannot or do not want to use HT (see Table 2.2). For a complete list of prescription drugs, please refer to Chapter 6.

II: SLEEP

Sleep difficulty is one hallmark of the menopause transition. In general, women report more problems with sleep than men, and aging influences the quantity and quality of sleep for both sexes. A community-based survey in a multiethnic sample of more than 12 000 Caucasian, African American, Chinese, Japanese, and Hispanic women aged 40 to 55 years has shown a 38% rate of sleep disturbances. Age-adjusted rates were highest in the late perimenopausal and surgically postmenopausal groups. Other factors associated with sleep difficulty were ethnicity, higher education, vasomotor symptoms, psychosocial symptoms, increase in perceived stress, less physical activity, smoking, and arthritis. Among ethnic groups, Japanese women have the lowest rate (28%) and Caucasian women the highest (40%).⁴⁵

Two major sleep disorders occur during menopause: sleep apnea and insomnia. Both sleep-onset insomnia and sleep-maintenance insomnia are increased during perimenopause and menopause.⁴⁶ Menopause is a classic example in which a woman may wake up repeatedly with hot flashes but, secondarily, she has difficulty falling back to sleep.

Moreover, mood disorders, which may be associated with menopause transition, may be intertwined with sleep disorders. Sleep diaries of depressed people indicate that cycles of insomnia precede depression.⁴⁷

Table 2.2 Management of Vasomotor Symptoms

Type of Intervention	Intervention	Magnitude of Effect	Level of Evidence
Lifestyle modifications	Reducing core body temperature	↓	II-3
	Regular exercise	↓	II-3
	Smoking cessation	?	II-3
	Controlled breathing	↓	I
Non-prescription therapies	Black cohosh	↔ or ↓	I
	Red clover-derived isoflavones	↔ or ↓	I
	Soy-derived isoflavones	↔	I
	Vitamin E	↓	I
	Progesterone cream	↔	I
	Acupuncture	↔	I
	ET/EPT	↓↓↓	I
Prescription therapies: hormonal	Progestins	↓↓ to ↓↓↓	I
	Oral contraceptives	↓ to ↓↓	I
	Venlafaxine	↓↓	I
Prescription therapies: non-hormonal	Paroxetine	↓↓	I
	Fluoxetine	↓ or ↔	I
	Gabapentin	↓ to ↓↓	I
	Clonidine	↓	I
	Bellergal	↓ to ↓↓	I

Magnitude of effect::

↓: Less than 50% reduction of vasomotor symptoms

↓↓: More than 50% reduction of vasomotor symptoms

↓↓↓: More than 80% reduction of vasomotor symptoms ↔: Neutral (no more efficient than placebo)

↔: neutral (no more efficient than placebo)

?: Unknown or controversial

ET/EPT: estrogen therapy/estrogen progestin therapy.

It is well known that changes in hormonal pattern affect sleep. Progesterone seems to have an anxiolytic effect, although the exact mechanism is unclear. Progesterone also has an impact on breathing: it is a respiratory stimulant and has been used to treat mild obstructive sleep apnea. Estrogen has been shown to decrease sleep latency, decrease the number of awakenings, increase total sleep time, and decrease the number of cyclic spontaneous arousals. In addition to its prevention of hot flashes, estrogens have a significant effect on core body temperature during sleep.⁴⁶

Difficulty sleeping may interfere with quality of life and result in excessive daytime fatigue, irritability, and impaired learning and cognition. Since there are many possible causes of insomnia other than those specifically associated with menopause transition, further investigation is warranted, especially for insomnia that occurs nightly and is long-lasting.⁴⁶ Table 2.3 lists other well-known causes of insomnia. If an underlying cause of sleep problems is found, the treatment should be directed toward the cause.

After menopause, the prevalence of sleep apnea is increased.⁴⁸ The weight gain commonly seen after menopause as well as the loss of respiratory drive from loss of progesterone in postmenopause might be reasons for sleep-disordered breathing after menopause. Treatment of sleep-disordered breathing can include continuous positive airway pressure (CPAP), dental appliances, or surgery, and should be done under appropriate medical surveillance. Behavioural therapy, including an exercise program that leads to weight loss, might be appropriate in some patients, particularly those with excessive fat around the neck. Data on the efficacy of HT for the treatment of sleep-disordered breathing are conflicting.^{49,50}

When women suffer from idiopathic insomnia, the improvement of sleep hygiene should be the initial therapy (dark, quiet room with no television, etc.). Behavioural therapy is the first choice for long-term treatment. Effective behavioural therapies include bedtime rituals, relaxation therapy, biofeedback, and cognitive behavioural therapy.

Table 2.3 Causes of insomnia

Medical conditions	Depression
	Neurologic disorders
	Restless legs syndrome
	Hyperthyroidism
	Cushing syndrome
	Overactive bladder
Medications	Selective serotonin reuptake inhibitors (SSRIs)
	Adrenergic agents
	Corticosteroids
	Ginkgo biloba
	Ginseng
Stimulants	Cigarettes
	Caffeine
	Alcohol
	Chocolate

Non-prescription therapies, including valerian, phytoestrogens, and St. John's Wort, may help for mild sleep problems.

Non-specific treatments, such as hypnotics and antidepressants, may be used in selected patients. HT is an appropriate consideration for most women with sleep disorders who experience vasomotor symptoms. For a combined estrogen/progestin regimen, micronized progesterone seems to better improve the quality of sleep of postmenopausal women compared with MPA.⁵¹ Currently, there are conflicting data regarding the efficacy of HT in menopausal sleep problems not associated with vasomotor symptoms.

III: WEIGHT GAIN

Menopausal transition weight gain is common but not inevitable. The average amount of weight gained during the transition ranges from 2.25 kg to 4.19 kg.⁵² As women age, resting metabolic rate gradually declines and body weight tends to increase until old age.⁵³ Moreover, there is a shift in the ratio of fat-to-lean body composition. Women's experience of weight gain has led to the prevalent patient perception that HT causes weight gain. Randomized trials demonstrate that short- and long-term administration of HT does not appear to influence body composition or body weight to any detectable degree.⁵⁴ In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the mean weight gain was higher in the placebo group than in any of the HT groups.⁵⁵ Appropriate counselling is important, as it is estimated that as many as 20% of women discontinue HT because of perceived weight gain.⁵⁶

The most powerful modifier of weight gain in menopausal women is physical activity. The longitudinal examination of the relation of ageing, menopausal status, and physical activity to weight, in women participating in an observational study of menopausal transition (SWAN), has shown that maintaining or increasing participation in regular physical activity contributes to prevention or attenuation of gains in weight and waist circumference.⁵⁷ A recent 5-year RCT indicated that menopausal transition weight gain can be minimized by ingestion of a low-fat diet (25% total fat, 7% saturated fat, and 100 mg of dietary cholesterol) with moderate calorie restriction (1300 kcal/d), combined with a modest increase in exercise (energy expenditure of 1000 to 1500kcal/wk).⁵⁸

IV: ACHES AND PAINS

Joint pain is a common complaint during the menopausal transition. In a recent survey of 293 women aged 45 to 50 years, 54% of them reported joint pain during the month preceding the survey.⁵⁹ There is little information regarding the effects of HT on these symptoms. However, joint pain caused by osteoarthritis may be minimized by HT,⁶⁰ but results of studies, mostly observational, are conflicting. Currently, HT appears to have no role in the prevention or treatment of osteoarthritis,⁶¹ but may have some benefit for aches and pains. In a recent report of secondary endpoints evaluated in the WHI study, women taking EPT had fewer musculoskeletal symptoms compared to women on placebo (less joint pain: 47.1% versus 38.4%; and less general aches or pains: 49.3% versus 43.7%).²¹

Glucosamine, a non-prescription remedy, is widely used for musculoskeletal problems. A recent Cochrane database review has shown a modest reduction of pain and functional impairment resulting from osteoarthritis with the Rotta preparation of glucosamine.⁶² As a first-line therapy, physical activity should probably be recommended to women with non-specific musculoskeletal pain.

V: SKIN CHANGES

Changes in the skin with ageing occur gradually and are most noticeable on the face and sun-exposed areas. With ageing, the skin becomes more dry, wrinkled, and unevenly pigmented. It is often difficult to separate chronologic ageing changes and environmental insult such as smoking and sun exposure. It is also difficult to differentiate age-related skin changes from changes related to declining hormonal secretion and menopause. However, soon after menopause, skin collagen content and skin thickness decline⁶³ and abrupt increases in skin laxity and wrinkling occur.⁶⁴ Skin elasticity is decreased.⁶⁵

Estrogen therapy limits the extent of skin collagen loss and helps to maintain skin thickness.⁶⁴ Significant increases in

skin collagen and thickness were demonstrated in women using oral estrogen compared with use of placebo.⁶⁶ Facial fine wrinkling has been reported to improve with estrogen therapy.^{67,68} Less skin extensibility was documented in postmenopausal women treated with estrogen than in untreated women, although no change in other skin viscoelastic properties was found between groups.⁶⁴ Whether elastic fibres can be preserved or repaired with the use of HT remains controversial.⁶⁵ Preliminary evidence suggests that estrogen has a beneficial effect on at least some of the mechanical properties of the skin, so that it may slow the progress of intrinsic cutaneous aging. Recent studies show no difference in wound healing after laser skin resurfacing for premenopausal women compared to postmenopausal women with or without HT.⁶⁹

Present evidence does not support instituting estrogen therapy for its potential benefits on skin alone.

VI: EYE CHANGES

Ophthalmic changes are noted in postmenopausal women. These changes result mostly from the natural process of aging and from changes in hormonal profile. With aging, intraocular pressure increases, tear film function declines, and visual performance is decreased.^{70–72}

Cataracts are the leading cause of visual impairment in older adults. Cataract incidence increases significantly with advancing age. There is a relationship between low serum levels of estrogen, menopausal symptoms (in women ages 31–54), and the occurrence of cataracts.⁷³ Estrogen receptors have been detected in ocular tissue.⁷⁴ Older studies have suggested a protective effect in postmenopausal women using estrogen,^{75–76} but data from the Salisbury Eye Evaluation study suggest no evidence of protection against the incidence or progression of lens opacities with HT.⁷⁷

Recent case-control studies show an improvement in tear production and visual function with HT.^{78,79} However, an RCT did not show modification of intraocular pressure in women using HT compared to women not treated with HT.⁷⁸

Older epidemiological evidence suggests a possible preventive role for estrogens in the development of early age-related macular degeneration (AMD).⁸⁰ A recent study also showed a decrease in the incidence of AMD with HT (odds ratio, 0.5; 95% confidence interval, 0.30–0.98).⁸¹ However, a conflicting study has been published involving older French women with no beneficial effect of HT on AMD.⁸²

In conclusion, HT may have beneficial effects on ophthalmic health, but evidence is lacking to support the use of HT in prevention or treatment of eye disorders.

Table 2.4 Causes of abnormal uterine bleeding in perimenopausal and postmenopausal women⁸³

Perimenopausal women	Postmenopausal women
Anovulation	Endometrial atrophy
Endometrial polyps	Vaginal atrophy
Uterine fibroids	Endometrial hyperplasia and cancer
Adenomyosis	Endometrial polyps
Endometrial hyperplasia and cancer	Hormonal effect
Vulvar, vaginal, and cervical lesions	Vulvar, vaginal, or cervical lesions

VII: ORAL HEALTH

Oral alveolar bone loss of the maxilla and mandible is correlated with poor oral hygiene and with osteoporosis.⁸³ Hormone therapy has a positive effect on the alveolar bone of postmenopausal women.⁸⁴ The beneficial effects on skeletal bone mass attributed to estrogen are also seen on oral (maxillary and mandibular) bones and teeth. A 3-year double-blind, randomized, placebo-controlled study showed hormone therapy increased total femur and femoral trochanter bone density and oral bone mass in postmenopausal women.⁸⁵ Hormone therapy is a protective factor in dental pain and decreases tooth mobility and depth of periodontal pockets. Response to hormone therapy may be related to estrogen receptors in gingiva and periodontal ligaments.⁸⁶

Tooth loss and the need for dentures are much reduced in postmenopausal estrogen users compared to non-users: a benefit which correlates positively with duration of estrogen use. If a woman has ever taken ET, her risk of losing all her teeth is cut to two thirds the risk of a woman who has never used estrogen. Long-term users (15+ years) have half the risk of becoming toothless.⁸⁷

There may also be a reduction in gingival inflammation and bleeding in women using estrogen therapy.⁸⁸ However, some middle-aged and elderly women report a burning mouth, and this is positively correlated with anti-hypertensives, sedatives, and hormone therapy.⁸⁹

In summary, HT seems to have beneficial effects on oral and dental health, but use of HT for oral benefits only is not advisable.

VIII: ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding (AUB) is a frequent complaint during menopausal transition and may be related to multiple etiologies (see Table 2.4). The most frequent cause of bleeding during the menopausal transition is dysfunctional uterine bleeding resulting from anovulation. As dysfunctional uterine bleeding is a diagnosis of exclusion, evaluation of a perimenopausal woman with AUB is warranted. The evaluation should be done principally by a careful history and physical examination, followed, if needed, by appropriate investigations, such as blood tests, pelvic ultrasound, sonohysterogram, endometrial biopsy, and hysteroscopy.^{90,91}

Any bleeding that occurs after 12 months of amenorrhea is considered postmenopausal bleeding and should be investigated as such. Table 2.4 displays the most common causes of postmenopausal bleeding.

IX: OLDER POSTMENOPAUSAL WOMEN WITH PERSISTENT SYMPTOMS

One quarter of women who discontinue hormone therapy are still symptomatic with hot flashes or sleep disturbance, or feel that their quality of life was better with therapy than without.⁹² Some women over 60 years old wish to restart therapy after discussing the risks and benefits. A study of initial start-up in 66-year-olds showed that 40% discontinued therapy due to side effects on standard doses and particularly disliked unwanted cyclic bleeding.⁹³ An RCT of the safety and effectiveness of unopposed ultra-low-dose transdermal estradiol (0.014 mg/d) for postmenopausal women aged 60 to 80 with an intact uterus showed an increased bone mineral density (BMD) and decreased bone turnover without causing endometrial hyperplasia.⁹⁴ After 2 years of this ultra-low-dose ET, the treatment and placebo groups had similar rates of endometrial hyperplasia, endometrial proliferation, and vaginal bleeding.⁹⁵ Ultra-low-dose unopposed estrogens are promising, but we must keep in mind that lower than standard doses of unopposed estrogen are clearly associated with increased endometrial cancer risk, and hyperplasia risk increases after 60 years of age.^{96,97} Currently, ultra-low doses of estrogen are not available in Canada.

SOGC Clinical Tip

To minimize the incidence of mastalgia (perhaps as high as 25–76%), breakthrough bleeding, and other estrogenic side effects, it is advisable to start therapy with the lowest possible estrogen dose in older women, given daily or on alternate days, followed by slow increases to the minimal effective dose. For women 60 years of age and older on HT who elect to continue HT, it is probably advisable to taper the dose until the minimal effective dose is reached. When using CE 0.3 mg or equivalent doses of other estrogens in older women with a uterus, it is preferable to use a combined (EPT) regimen. The decision regarding long-term use of HT must be individualized and based on detailed counselling about risks and benefits.

RECOMMENDATIONS

1. Lifestyle modifications, including reducing core body temperature, regular exercise, weight management, smoking cessation, and controlled breathing may be recommended to reduce mild vasomotor symptoms. (IC)
2. Health care providers should offer HT (ET/estrogen-progestin therapy) 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 especially during the transition phase. (IA)
4. Non-hormonal prescription therapies, including antidepressant agents, gabapentine, clonidine, and bellergal, can be prescribed as alternatives to HT to reduce vasomotor symptoms. (IB)
5. Complementary and alternative medicine, including black cohosh, red clover (derived isoflavone), and vitamin E, may be recommended for the reduction of mild vasomotor symptoms (IB). Long-term efficacy and safety data are still lacking.
6. Any unexpected bleeding that occurs after 12 months of amenorrhea is considered postmenopausal bleeding and should be investigated. (IA)
7. If prescribing HT to older postmenopausal women, low or ultra-low dose ET should be preferred. (IB)

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Urogenital Concerns

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INTRODUCTION

Urogenital complaints, including vulvovaginal atrophy, stress incontinence, urge incontinence, and recurrent urinary tract infection (UTI), are common among women in their postmenopausal years. They result at least partly from urogenital aging, a progressive and variable condition that occurs as a result of both estrogen deprivation and tissue aging itself.

PATHOPHYSIOLOGY

The female introitus, vagina, bladder, and urethra are all derived from the primitive urogenital sinus, so it is not surprising that these structures possess hormonal sensitivity and demonstrate hormone receptor activity. At the introitus, estrogen and progesterone receptors have been identified and are predominantly vaginal in location,¹ whereas the majority of androgen receptors are found in the vulva.² Preliminary evidence suggests that progesterone (but not estrogen) receptor number is decreased in menopause.³ Estrogen and progesterone receptors have also been found in the pelvic floor musculature and endopelvic fascia⁴ as well. The shared embryology of these organs accounts for their similar hormonal responsiveness, including their shared marked susceptibility to the estrogen (and possibly also androgen) deprivation that occurs as part of menopause.

In the hormone-deprived state of menopause, the urogenital epithelial and subepithelial tissues undergo atrophic change. The connective tissue components of the vaginal mucosa, including collagen, elastin, and smooth muscle, all degenerate. Vaginal length and diameter shrink, the vaginal fornices disappear, and the rugal folds of the vagina are lost.⁵ Blood flow to the vagina is reduced,⁶ causing decreased transudation during sexual arousal and increased tissue susceptibility to trauma (Figure 3.1). Vulvar sensitivity to pressure and light touch declines.⁷ The vaginal mucosa becomes thinner and less cellular, and glycogen production declines,⁵ decreasing the colonization of lactobacilli and thus lactic acid production. The usual acidity of the vagina, which serves as a potent defence mechanism, is lost, leading to an overgrowth of enteric organisms in the

vaginal and urethral flora, and an increased susceptibility to vulvovaginal and/or lower UTI.⁸

Similarly, urethral mucosal and submucosal thickness decline in the estrogen-deprived state of menopause, as do the collagen content and elastin.⁹ Such changes result in a reduction in mean urethral closure pressure.¹⁰ In the bladder, mucosal thinning with estrogen loss is thought to lower the sensory threshold for detrusor contraction, putatively resulting in irritative symptoms including urinary frequency, nocturia, and urge incontinence.¹¹ Investigators have observed decreased pelvic floor tone¹² and collagen content¹³ in the estrogen-deficient state, suggesting that urogenital aging may contribute to the development of pelvic organ prolapse. Studies on human tissues have not consistently documented the presence of progesterone receptors in either the bladder or the urethra.¹ If progesterone receptors are indeed present in the human urinary tract, their number is low.¹⁴ The decline in progestin levels associated with menopause would thus not be expected to exert any significant influence on urethral or bladder function.

PREVALENCE

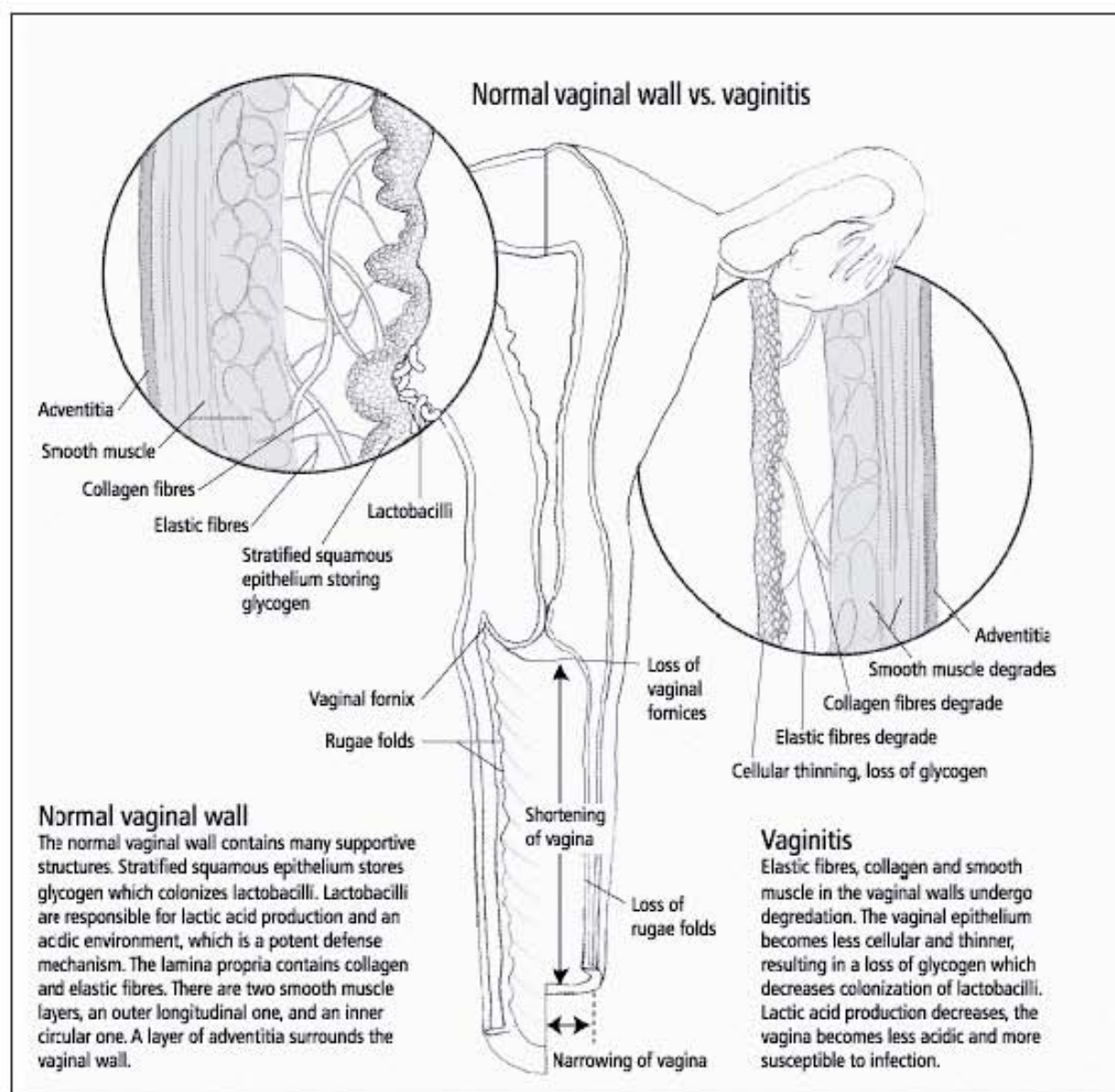
Although urogenital atrophy is an inevitable consequence of aging and menopause, not all women are symptomatic. Of those women who experience troublesome symptoms, only a minority will consider their complaints to be chronic and severe.¹⁵ The onset of symptoms is often insidious, and can occur long after the resolution of other menopausal symptoms, such as hot flashes. Symptoms may also occur in perimenopausal women who do not have visible signs of vulvovaginal atrophy. Smokers may be at higher risk.¹⁶

SOGC Clinical Tip

Postmenopausal women need to be asked about the symptoms of urogenital aging. Many women will not spontaneously report urogenital symptoms unless directly questioned, and will therefore needlessly suffer in silence.

Large cohort studies of menopausal women (age range, 50–85 years) have reported the prevalence of symptoms of

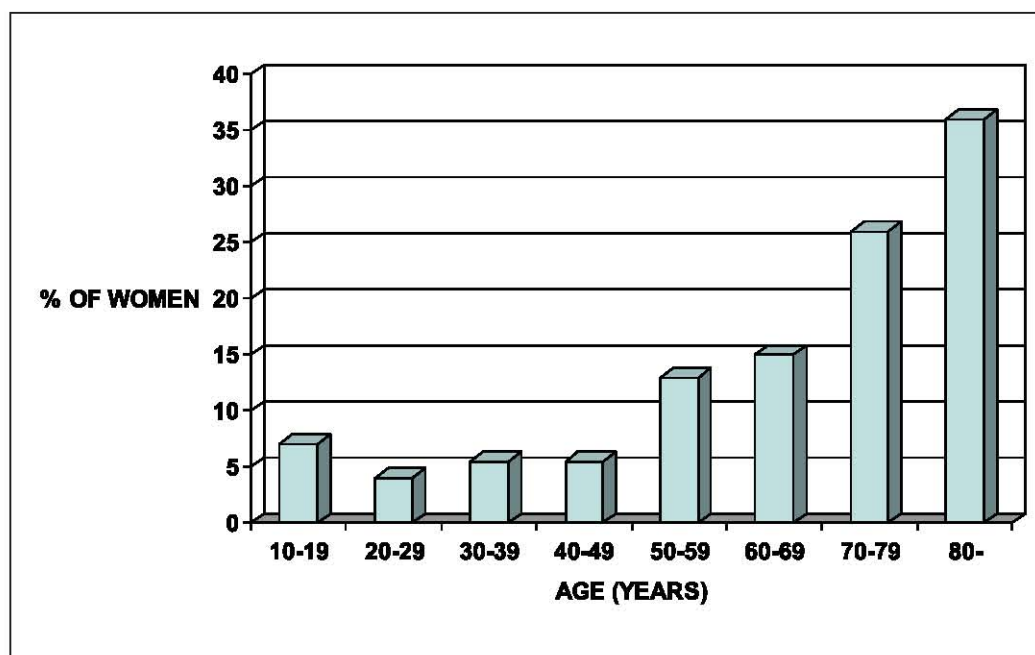
Figure 3.1. Vaginitis: vaginal atrophic vaginitis



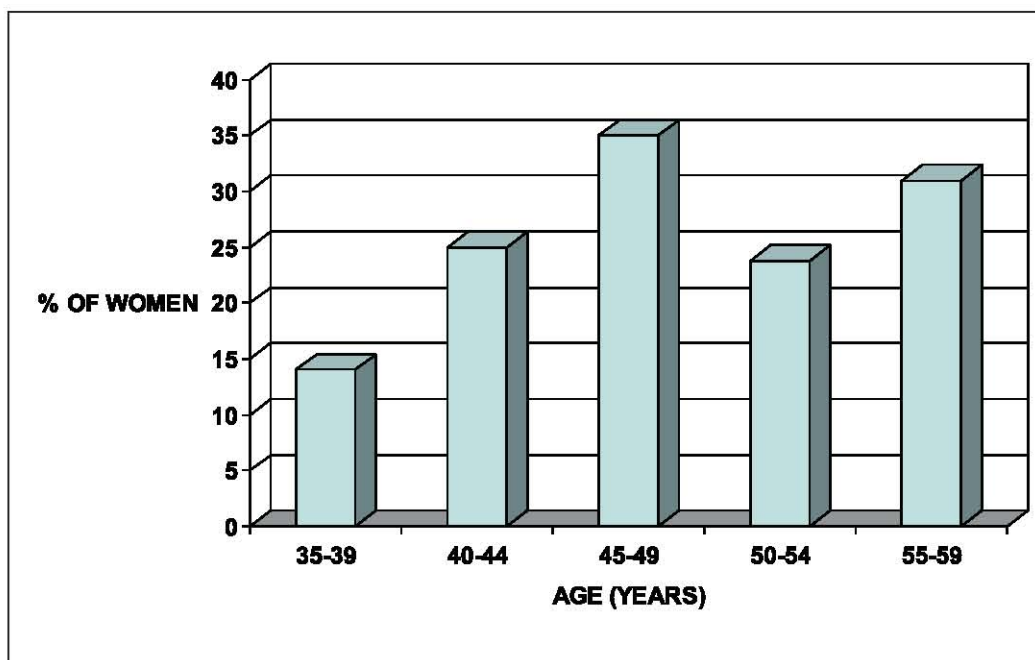
From: Johnston BL. The recognition and management of atrophic vaginitis. *Gynecol & Aging* 2003;5(7):9-15

vaginal atrophy, including vaginal dryness from 27% to 55%^{15,17,18} and dyspareunia from 32% to 41%.^{17,18} Investigators using questionnaires often report higher rates of vaginal atrophy than clinical experience would suggest, perhaps indicating that many women will admit to this problem only in an anonymous format. In one survey, although half of the respondents noted moderate to severe vaginal

discomfort, only one-third of this subgroup had sought medical care for their symptoms.¹⁵ Contrary to the assumptions of health care providers that women receiving systemic hormone therapy will not experience symptoms of vaginal atrophy, it is estimated that approximately 40% of women taking adequate doses of oral hormone therapy (HT) have persistent vaginal dryness.⁵

Figure 3.2. Prevalence of urge incontinence by age

From: Drutz H, Bachmann G, Bouchard C, Morris B. Towards a better recognition of urogenital aging. *J Soc Obstet Gynaecol Can* 1996;18:1017-31.

Figure 3.3. Prevalence of stress incontinence by age

From: Drutz H, Bachmann G, Bouchard C, Morris B. Towards a better recognition of urogenital aging. *J Soc Obstet Gynaecol Can* 1996;18:1017-31.

Table 3.1. Symptoms of urogenital aging

Vulvovaginal	Urinary	Prolapse
• Dryness • Pruritus • Dyspareunia • Thin discharge • Post-coital bleeding	• Dysuria • Hematuria • Frequency / nocturia • Urgency	• Pelvic heaviness • Introital bulge • Incomplete emptying on voiding • Constipation • Low back pain

SOGC Clinical Tip

Urogenital atrophy is not a problem only seen in menopausal women. Any prolonged estrogen-deficient state can result in atrophic change in the urogenital tract, including prolonged lactation, hypothalamic amenorrhea, premature ovarian failure after chemotherapy or radiation, or anti-estrogenic medication use (e.g., tamoxifen).

The estimated prevalence of culture-proven UTI in postmenopausal women 60 years of age or older ranges from 4% to 15%.¹⁹

Urinary incontinence of all forms has been reported in 10% to 30% of postmenopausal women,^{20,21} compared with only 1% to 5% of men of similar age. In fact, prevalence estimates for urinary incontinence are consistently higher in women than in men, at all ages, perhaps suggesting a hormonal role in etiology (though none has been clearly proven). The prevalence of urge incontinence seems to increase with the number of years after menopause (Figure 3.2). In contrast, the prevalence of stress incontinence is highest in the perimenopausal years, with no marked increase thereafter²² (Figure 3.3).

SYMPTOMS

Symptoms related to urogenital aging may precede physical findings. The first symptom reported is often reduced lubrication on sexual arousal.²³ Dyspareunia is common, and postcoital bleeding may occur.²³

SOGC Clinical Tip

Dyspareunia is only one part of the spectrum of urogenital aging. Many postmenopausal women who are not coitally active suffer from urogenital aging, with complaints including vulvar soreness, discharge, urinary urgency and frequency, and/or recurrent lower UTI.

Additional symptoms include pruritus, dysuria, and vaginal discharge related to inflammation or infection.²³ Urinary symptoms include incontinence, urgency, frequency, nocturia, and dysuria.²⁴ Incontinence may be related to physical effort (stress) or to urgency, but is often mixed. Coital incontinence has been reported in 11% of women complaining of urinary incontinence,²⁵ which may further contribute to sexual dysfunction.²³ Symptoms of pelvic organ prolapse include pelvic heaviness and introital fullness.²⁶ Voiding difficulty from urethral kinking²⁷ or anal incontinence²⁸ can be associated with prolapse. (Table 3.1)

EVALUATION

The cornerstone of clinical evaluation of urogenital health in menopausal women is the pelvic examination. Due to a loss of rugae, the postmenopausal vagina is foreshortened, smooth, and narrowed. The vulvovaginal epithelium is comparatively pale, thin, and friable. Submucosal petechial hemorrhages may be visualized with speculum insertion. Decreased tissue elasticity may cause introital narrowing and limited vaginal mobility. Pelvic floor relaxation with prolapse of the vaginal walls or uterus is often present. Estrogen deficiency results in a relative degree of narrowing and retraction of the urethral meatus toward the introitus.²³ Urethral prolapse can occur with resultant postmenopausal bleeding. Like the vagina, the urethral and bladder mucosa appear pale and thin at the time of cystoscopy, especially in the area of the trigone.

Laboratory markers of urogenital atrophy include a vaginal pH greater than 5.0 and a change in the maturation index of the vaginal wall towards a predominance of basal cells,²⁹ reflecting superficial thinning of the mucosa. Culture of the vagina may reveal growth of enteric organisms not normally found in the vagina.

Initial evaluation of the incontinent female should include a screening urine culture and a measurement of residual urine volume (by post-void catheterisation or pelvic ultrasound). Urine cytology and cystoscopy should be reserved for those patients with irritative symptoms, recurrent infection, or persistent hematuria. Though urodynamic testing is not always necessary, it should be considered when urinary

**Table 3.2. Local estrogen therapy
Recommended dosing (efficacy and safety)**

CE Cream	0.5 g cream (1/4 applicator) 3 times weekly
Estradiol Ring	2 mg ring q3 months
Estradiol Tablet	25 µg twice weekly

CE: conjugated estrogen

symptoms are mixed (both stress and urge incontinence), when there has been previous bladder neck surgery, or when there are neurologic symptoms or findings.³⁰ When surgical management of stress incontinence is planned, urodynamic testing is recommended to confirm the diagnosis and to permit objective post-operative follow-up.³¹

VULVOVAGINAL ATROPHY TREATMENT

Lifestyle Modification

Since a decline in estrogen levels is the primary etiology behind vulvovaginal atrophy, lifestyle factors that accelerate this decline should be avoided. While evidence concerning the association between smoking and vaginal atrophy is conflicting, smoking cessation should be encouraged for a constellation of reasons.³² Continued regular vaginal coitus provides protection from urogenital atrophy, presumably by increasing the blood flow to the pelvic organs.³³ Masturbation has also been shown to increase genital blood flow in menopausal women and may help maintain urogenital health.³⁴ Research has failed to demonstrate any beneficial effect of dietary estrogen³⁵ or supplements, such as dong quai,³⁶ on vaginal atrophy.

Vaginal Moisturizers

Polycarbophil gel (Replens), the only true vaginal moisturizer available in Canada, has been demonstrated through clinical trials to have a beneficial effect equivalent to that of local hormone therapy, including increases in vaginal moisture and vaginal fluid.³⁷ It cannot reverse vulvovaginal atrophy. In prospective randomized studies, when compared with local HT, polycarbophil gel resulted in equivalent subjective improvement of vaginal itching, irritation, and dyspareunia, though, as expected, no objective vaginal cytologic change was seen.³⁸

Vaginal Lubricants

There are several lubricants currently available to women in Canada. While vaginal lubricants can be used to decrease immediate irritation during coital activity, there is no evidence that these products have any long-term therapeutic effect.

Systemic Hormone Therapy

Systemic hormone therapy is indicated for women who are seeking to treat a variety of symptoms associated with the estrogen deprivation of menopause. A woman who is experiencing general symptoms of menopause, such as hot flashes and sleep disturbance in association with vaginal atrophy, may choose systemic hormone therapy. However, the systemic route in some women is not an effective means of relieving vulvovaginal atrophy.^{5,39}

SOGC Clinical Tip

Systemic hormone therapy alone may not adequately treat the symptoms of urogenital aging. If the sole reason for systemic hormone therapy is for symptomatic vaginal atrophy, vaginal estrogen therapy is more appropriate. Additional vaginal estrogen therapy may be needed for symptomatic women who use systemic hormone therapy for its other benefits.

Local Hormone Therapy

The goal of local hormone therapy is to provide sufficient estrogen to reverse atrophic changes in the local tissues and relieve associated symptoms, while at the same time avoiding systemic effects. At present, there are 3 modalities for providing local estrogen available in Canada: estrogen cream, an estradiol-containing vaginal ring, and estradiol-containing vaginal tablets. All of these modalities have been proven to effectively treat vulvovaginal atrophy.³⁹⁻⁴² A recent comprehensive Cochrane Review noted equal efficacy of all vaginal estrogens (conjugated estrogen [CE] cream, ring, tablet) over placebo or non-hormonal moisturizer.⁴³

SOGC Clinical Tip

Because of its ability to improve vaginal blood flow and lubrication, vaginal estrogen therapy helps prevent vaginal ulceration and/or infection from pessary use in postmenopausal women. Anecdotally, pessaries fit better in a well-estrogenized rather than an atrophic vagina, so therapy may improve pessary fitting and retention.

Systemic absorption of estrogen can occur in women who use local estrogens, especially at the beginning of treatment when the vaginal epithelium is thin.⁴⁴ However, no cases of atypical endometrial hyperplasia or endometrial carcinoma causally associated with the use of any local estrogen have been reported in the literature despite extensive and long-term clinical use. Recommendations for annual endometrial surveillance by ultrasound or endometrial biopsy, and the use of low-dose progestin co-therapy, in

asymptomatic (i.e., non-bleeding) women using appropriate doses of vaginal estrogens, are not supported by evidence⁴⁵ (Table 3.2).

Selective Estrogen Receptor Modulators

Where tamoxifen increases the vaginal maturation index,⁴⁶ raloxifene does not modify the vaginal index of the vaginal epithelium, nor has it been associated with increased frequency or severity of vaginal complaints during clinical trials.⁴⁷ Two studies examining the concomitant use of raloxifene with CE vaginal cream or polycarbophil gel found that raloxifene did not negatively affect the therapeutic benefit of CE cream on the vaginal mucosa.^{47,48}

STRESS URINARY INCONTINENCE TREATMENT

Lifestyle Modification

Modifiable factors such as chronic cough, excessive fluid and/or caffeine consumption, or infrequent voiding should first be corrected. In some cases, physical activity patterns can be adjusted. For obese women, even a body mass index (BMI) reduction of as little as 5% of total BMI can result in significant subjective improvement in urine loss.⁴⁹

Though avoiding intercourse is a common strategy employed by women with coital incontinence, such an approach is hardly a solution. More than 90% of women complaining of coital incontinence have underlying urethral sphincter weakness (i.e., stress incontinence) on urodynamic testing.²⁵ The management of this problem, therefore, is similar to that for stress incontinence in general.

Non-Surgical Treatment

Stress incontinence can be treated successfully with physiotherapy, including pelvic floor (Kegel) exercises with or without biofeedback,⁵⁰ weighted vaginal cones,⁵¹ and functional electrical stimulation.⁵² Objective response rates vary, but improvement and cure have been reported in as many as 60% of women 3 months after completion of therapy.^{47,49} Patient motivation and dedicated expert staffing are imperative for success.

Several different anti-incontinence devices, including vaginal supportive pessaries and urethral plugs, have been used for the treatment of stress incontinence. These devices have moderate success in appropriately selected patients, though long-term compliance is discouraging.⁵³ Farrell et al.⁵⁴ reported cure or improvement in 59 of 100 women with urinary incontinence with or without prolapse at a mean of 11 months after initial pessary fitting. Traditionally, pessaries have been thought to be most successful in women with mild to moderate symptoms, but in this study, the severity of symptoms and the type of pessary used did not affect the success of treatment. Intravaginal pessaries should thus be viewed as a reasonable initial approach for women with

stress incontinence, and ideally always tried before an operative solution is sought.

Pharmacologic Treatment

Clinical evidence of a clear beneficial effect of estrogen on postmenopausal urinary stress incontinence is increasingly weak, with recent data pointing to an absence of objective therapeutic benefit. Jackson et al.,⁵⁵ in a large, randomized, double-blind, placebo-controlled trial, failed to demonstrate even a subjective improvement with 6 months of estrogen treatment. In 2003, a Cochrane Review⁵⁶ was able to identify only 15 small trials evaluating the role of estrogen against placebo for the treatment of all urinary incontinence. Just over 350 women were included in each treatment arm. Overall, approximately 50% of estrogen-treated women reported improvement or cure as compared to 25% in those who received placebo. The effect was largest in those women with pure urge incontinence. However, more recent observations from large randomized controlled trials have suggested an increased incidence of urinary incontinence (especially stress incontinence) in users of combined estrogen-progestin therapy⁵⁷ and unopposed estrogen therapy⁵⁸ as compared to placebo. Clearly, the data is conflicting; but at present, when all the data is considered, it seems unlikely that estrogen therapy has a significant role to play in the treatment of urinary stress incontinence, or in fact urinary incontinence in general.

There are few effective pharmacologic options for stress urinary incontinence. Alpha-adrenergic agonists (to enhance intrinsic urethral sphincter tone) have been tried. Success with these agents is variable,⁵⁹ and serious side effects can include hypertension and cardiac arrhythmias.⁵⁶ More recently, duloxetine, a selective serotonin-norepinephrine reuptake inhibitor, has been shown to provide significant benefit over placebo for mild to moderate stress incontinence in over 50% of recipients, with an acceptable safety and side effect profile.⁶⁰ At the time of this publication, however, duloxetine is not yet available in Canada.

Surgical Treatment

When non-surgical management has failed, surgery becomes an option. Preferred surgical procedures for stress incontinence include the Burch retropubic colposuspension, or suburethral sling procedures, including the tension-free vaginal tape (TVT) procedure that offers a minimally invasive approach without the need for general anesthesia. Though objective long-term (i.e., greater than 5- to 10-year) data regarding the success of these procedures is limited, objective cure rates over shorter durations of time (6 months to 2 years) as high as 80 to 90% have been reported for all these procedures.^{61,62} In 2004, 2-year results from an RCT comparing the Burch colposuspension and the TVT procedure were published. Data analysis at 2 years

using available data (not using intention-to-treat analysis, with pre-op failures considered cured) documented equivalent success rates with both procedures (81% vs. 82%), but improved quality of life even at 2 years in theTVT group, an important comparative advantage.⁶³ Needle suspension procedures, such as Pereyra and particularly the anterior colporrhaphy with Kelly plication, are to be discouraged, as their long-term success is comparatively less.⁶⁴

URGE URINARY INCONTINENCE TREATMENT

Lifestyle Modification

Urge urinary incontinence can be treated successfully by lifestyle modification, including bladder drill (timed bladder emptying), trigger avoidance, and fluid and caffeine restriction.⁶⁵

Non-Surgical Treatment

Functional electrical stimulation and, more recently, sacral nerve root modulation⁶⁶ have been used with some success for recalcitrant urge incontinence.

Pharmacologic Treatment

Antimuscarinic agents have also been shown to be effective, particularly tolterodine and oxybutynin.⁶⁷ Study results vary depending on the outcome measures used, but in general, approximately 30% of patients receiving drug therapy regain urinary continence in all circumstances, and between 50% to 80% of treated subjects experience subjective improvement.⁶⁴ Long-acting forms of both agents are currently available. Most recently, a transdermal oxybutynin patch has been added. These newer options offer similar efficacy to the older immediate-release agents with a decreased side effect profile.⁶⁴ Side effects, including dry mouth and confusion, are particularly important considerations with use in the elderly, so antimuscarinics must be used in this population with some caution and long-acting or transdermal agents are best. Imipramine, a tricyclic antidepressant with anticholinergic effects, also has alpha-adrenergic properties which may enhance urethral sphincter tone, so it may be the drug of choice for mixed urinary incontinence.⁶⁸

As discussed above, a definitive role for estrogen in the treatment of urge incontinence has not yet been established. Evidence from earlier meta-analysis⁶⁹ and from more recent RCTs^{54,70} has not demonstrated a significant benefit from estrogen for the treatment of urge incontinence. Perhaps there is a subgroup of patients who would benefit from estrogen therapy of a particular dose or type, but this is currently unknown.

RECURRENT URINARY TRACT INFECTION TREATMENT

Lifestyle Modification

While a Cochrane Review of the effect of the consumption of cranberry juice on the risk of UTI found the evidence to be inconclusive,⁷¹ a recent clinical trial found that a cranberry-lingonberry juice concentrate reduced the risk of UTI.⁷²

Non-Hormonal Treatment

Alternatively, for recurrent UTI, low-dose prophylactic antibiotics can be given once daily as suppressive therapy for 3 to 6 months, or as a single dose following intercourse, for recurrent postcoital infection. Nitrofurantoin, trimethoprim-sulfamethoxazole, and norfloxacin are commonly used.

Hormonal Treatment

Estrogen therapy does have an important prophylactic role for recurrent urinary tract infection in menopause. In a randomized, double-blind study, the incidence of recurrent UTI in postmenopausal women treated with intravaginal estrogen compared to placebo was significantly reduced to 0.5 episodes per patient year from 5.9 in women treated with placebo.⁷³ As expected, the authors also observed a significant decrease in vaginal pH in study participants treated with estrogen, as well as the reappearance of vaginal lactobacilli in 61% of treated women compared to no reappearance of vaginal lactobacilli in the placebo group.⁷⁰ Ericksen has shown a similar beneficial prophylactic effect for postmenopausal urinary tract infection using a sustained-release intravaginal estradiol ring as compared with a placebo ring.⁷⁴ Challenging these robust findings, Brown et al.⁷⁵ reported no reduction in the incidence of UTI with oral HT in participants in the HERS study, though clearly the HERS study population was a select group and its results cannot be generalized on this issue.

PELVIC ORGAN PROLAPSE TREATMENT

Pelvic organ prolapse is usually managed with a pessary or with surgery. When a pessary is used in the menopausal patient, maintenance therapy with estrogen (local or systemic) may help prevent vaginal ulceration and infection. The value of estrogen itself in maintaining or improving pelvic support remains unclear, although the presence of estrogen receptors in the endopelvic fascia and pelvic floor musculature suggests a potential beneficial effect. Skin thickness and dermal collagen content decline after menopause.⁷⁶ These changes are reversed in part by estrogen therapy. A similar situation may exist for the collagen of the pelvic floor and vaginal fascia,⁷⁷ and if so, estrogen therapy may help to maintain existing collagen or reverse these

collagen changes. Furthermore, estrogen therapy in rats has been shown to exert a neuroregenerative effect after crush injury,⁷⁸ perhaps suggesting that estrogen could help prevent neurodegeneration in the pelvic floor of humans. Additional unresolved questions include whether or not estrogen administered before vaginal surgery can improve tissue planes and promote mucosal healing. Mikkelsen et al.⁷⁹ reported that rates of recurrent prolapse after surgery were similar in women receiving intravaginal estradiol or placebo preoperatively.

SOGC Clinical Tip

There is no cure for urogenital aging. For any of the symptoms of urogenital aging, successful treatment mandates chronic therapy. If treatment is discontinued, be it lifestyle change or pharmacologic therapy, the symptoms inevitably will recur and persist.

RECOMMENDATIONS

1. Conjugated estrogen (CE) cream, an intravaginal sustained-release estradiol ring, or estradiol vaginal tablets are recommended as effective treatment for vulvovaginal atrophy. (IA)
2. Routine progestin co-therapy 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 vulvovaginal atrophy including dryness and dyspareunia. (IA)
5. Effective surgical treatment options, including Burch colposuspension and the TVT procedure, are recommended for the treatment of stress urinary incontinence. (IA)
6. Effective non-surgical treatment 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, can be recommended for the treatment of stress urinary incontinence. (II-1B)
7. Lifestyle modification, bladder drill (II-1B), and antimuscarinic therapy (IA) are recommended for the treatment of urge urinary incontinence.
8. ET should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence. (IA)
9. Vaginal estrogen therapy can be recommended for the prevention of recurrent UTIs in postmenopausal women. (IA)

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Sexual Concerns—Menopause and Sexual Function

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INTRODUCTION

Health practitioners dealing with mid-aged and older women should be aware of the appropriate assessment and management of sexual health issues.

Challenges to the assessment and management of women's sexual concerns postmenopause include the following:

1. sexuality is a biopsychosocial entity that requires more than medical knowledge
2. many physicians receive minimal training in assessment and management of sexual dysfunction
3. many studies in this area were based on a conceptualization of sexual response more typical of men's experience.

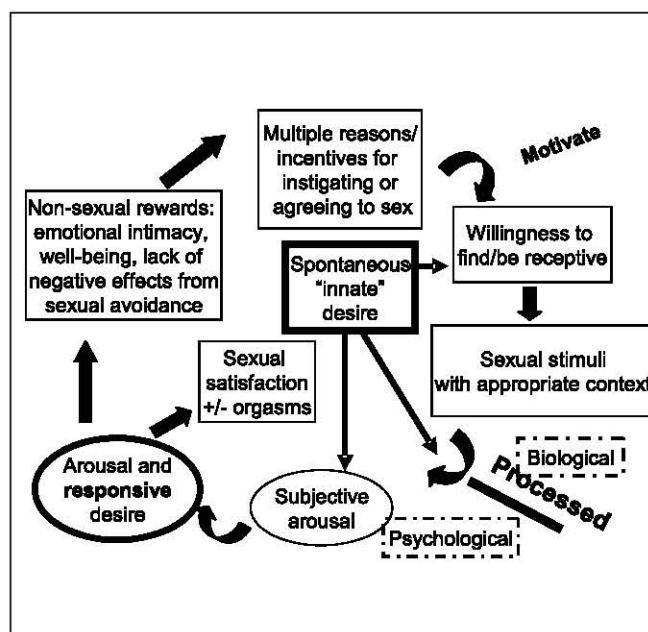
Most mid-aged and older women consider their sexuality moderately or very important. Sexual enjoyment for the majority appears resilient to the loss of sex hormones associated with the inevitable gradual decline in adrenal androgens, variable decline in ovarian androgens, plus cessation of ovarian estrogen production. Thus the various epidemiologic studies have not shown definite increase in sexual problems with age—though the studies are conflicting^{1–3}—and women may or may not be distressed by any given problem.¹

However, one large longitudinal study of women transitioning menopause identified reduction in desire and responsiveness both with age and with menopausal status. Rather than by testosterone or estradiol levels, protection from sexual dysfunction was afforded by positive feelings for the partner and by emotional and mental well-being.⁴ Rather than any physiological aspect of the sexual response, mental well-being and feelings for the partner generally and at the time of sexual interaction appear to protect from distress about sex.⁵

WOMEN'S SEX RESPONSE CYCLE

The current conceptualization of women's sexual response is shown in Figure 4.1. Women initiate or accept sexual activity for a variety of reason—often to do with enhancing emotional closeness with the partner.⁶ Sexual desire as in sexual thinking and fantasizing may be absent initially.^{6–9}

Figure 4.1 The blended sex response cycle



Sexual stimulation in an appropriate context can lead to subjective arousal/excitement and enjoyment, thereby precipitating sexual desire^{10,11} (see Figure 4.1). Emotional and sexual satisfaction increase subsequent motivation. Feelings for her partner and the woman's own emotional well-being modulate her sexual motivation and her arousability. The latter is also influenced by her ability to focus on stimuli and not be distracted, her sense of sexual self-confidence, and the expectation of a rewarding outcome. Any initial, apparently—spontaneous/intrinsic sexual desire augments the cycle as shown in Figure 4.1.

Biological factors also modulate arousability and therefore motivation, as well as intrinsic desire. Fatigue, depression,¹² medications (including antidepressants), and, less commonly, thyroid disorder or hyperprolactinemia may contribute. The role of reduced androgen activity is an area of current research. Thus sexual response is truly biopsychosocial.¹⁰

Table 4.1. (Part 1). Biopsychosocial Assessment of the Couple Together

Sexual problem in each partner's own words	Clarify further with direct questions. Offer potential explanations but do not ask leading questions.
Duration, consistency, priority	Ask how long problems have existed, whether problems are present in all situations and which problem is most severe.
Context of sexual problems	Explore various contexts of sexual problems, including emotional intimacy with partner, activity/behaviour just prior to sexual activity, privacy, safety, birth control, risk of sexually transmitted diseases (STDs), usefulness of sexual stimulation, sexual skills of partner, sexual communication, time of day.
Rest of each partner's sexual response	Ask about the following currently and prior to the onset of the sexual problems: sexual motivation, subjective arousal, enjoyment, orgasm, pain, erection, and ejaculation in male partner.
Reaction of each partner to sexual problems	Establish how each partner has reacted emotionally, sexually, and behaviourally.
Previous help	Ask about compliance with any prior recommendations and their effectiveness.
Reason for presenting now	Ask what precipitated this request for help.

Table 4.1. (Part 2). Assessment of Each Partner Alone

Partner's own assessment of the situation	Sometimes it is easier to acknowledge symptoms (e.g., total lack of desire) in the partner's absence.
Sex response with self-stimulation	Ask whether he or she has sexual thoughts and fantasies.
Past sexual experiences*	Ask about positive and negative aspects.
Developmental history*	Explore relationships to others in the home while growing up, losses, traumas, how they coped, to whom (if anyone) he or she was close, who showed him or her affection, whom did he or she feel loved and respected by. Clarify whether some of these themes are playing out now in the current sexual relationship.
Sexual, emotional and physical abuse*	Ask about potential abuse, and explain that abuse questions are routine and do not necessarily imply causation of the problems.

*These items may sometimes be omitted (e.g., for a recent problem after decades of healthy sexual function).

SEXUAL FUNCTION AND ANDROGEN

There is minimal evidence that serum levels of testosterone-free, calculated free, total, or bioavailable) correlate with sexual function. The 2 larger studies of 2961 and 1021 women show no correlation.^{13,14} Studies comprising 141, 40, 41, and 483 women show no correlation.^{9,15-17} Two small studies comprising 18 and 30 women showed some evidence of correlation.^{18,19}

Intracellular Androgen Activity

Importantly, serum levels of testosterone do not reflect intracellular testosterone production whereby dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), and androstenedione are converted within cells to either testosterone or estradiol, with less than 10% of testosterone spilling back into the bloodstream to be measured.²⁰ Until a measure of total androgen activity, such as measurement of various glucuronides, is widely applied to both women with and without sexual problems, the concept of "androgen insufficiency" remains imprecise.^{14,20}

Reduction in Androgen Status in Mid-Aged and Older Women

Where total testosterone may be increased and free testosterone little changed in postmenopausal compared with premenopausal women,²¹ intracellular production of testosterone decreases markedly with age due to reduced adrenal androgen precursors.²⁰ Moreover, levels of sex hormone-binding globulin (SHBG) are typically higher postmenopause, they increase less when obesity is present.²¹ Surgical menopause will deprive women of all ovarian androgen production as may some forms of premature ovarian failure and chemotherapy-induced menopause. This variable ovarian androgen decline, coupled with the "normative" reduction of adrenal precursors, may cause women to be particularly vulnerable to sexual symptoms.

SEXUAL FUNCTION AND ESTROGEN

Estrogen affects sexual motivation indirectly in that the insomnia, irritability, altered skin sensitivity, and vasomotor symptoms of estrogen deficiency may reduce sexual

SOGC Clinical Tip

Etiological domains include those to do with the current context (e.g., lack of the type of stimuli the particular woman needs—commonly insufficient non-physical stimuli and insufficient physical but non-genital stimuli), inappropriate timing (e.g., late at night when exhausted), as well as interpersonal factors (e.g., finding the partner's behaviour unattractive, lack of trust, lack of emotional closeness, unhealthy balance of power within the relationship).

Medical etiological factors underlying women's sexual problems include depression, fatigue, medications with sexually negative effects—most commonly selective serotonin reuptake inhibitors (SSRIs) but also gonadotropin-releasing hormone (GnRH) agonists, and narcotics, as well as endocrine factors including low thyroid, low estrogen, low androgen, high prolactin. Vulnerability to sexual dysfunction may stem from experiences in childhood or adolescence including emotional and physical sexual abuse, as well as lack of nurturing/safety/freedom to express emotions. Personal psychological factors could be relevant (e.g., difficulties relinquishing control, high anxiety, perfectionist tendencies to self-monitor during sex, suppressed anger causing other emotions also to be suppressed).

motivation. It also remains possible that benefit from androgen supplementation is due to increased estradiol activity from SHBG reduction. There is direct involvement of estrogen in the genital vasocongestive response to sexual stimulation. Although measured increases in genital vasocongestion response to erotic stimuli are similar in pre- and postmenopausal women,²² baseline measures of genital congestion are lower in postmenopausal women, such that lubrication could be insufficient for comfortable intercourse or digital vaginal stimulation. Similarly, postmenopausal vulval atrophy may be associated with loss of sexual sensitivity, reduced engorgement of vulval structures and pain with the stimulation. A recent analysis of 438 Australian women transitioning menopause showed that estrogen levels did have a direct effect on sexual function in the areas of response and freedom from dyspareunia. However, the estrogen effect was of lesser importance than that of prior level of sexual function, a change in partner, and the women's feelings for her partner—again, demonstrating the powerful effects of psychosocial factors on sexual function. From this same study, it was also suggested (by means of looking at the subgroup of 77 women who were receiving hormonal therapy) that the level of estradiol in the blood needed to produce a minimal clinically relevant difference in sexual response is twice that needed to improve dyspareunia.¹⁷ Of note, however, is the fact that the vast majority of women, who were on various forms of oral estrogen, the activity of which is not reflected by estradiol levels and the other forms of estrogen, particularly estrone, were not measured.

THE NATURE AND ETIOLOGY OF WOMEN'S SEXUAL PROBLEMS

Women's sexuality is highly contextual. Untoward past and present circumstances may underlie apparent dysfunction—there being nothing intrinsically wrong with the sex response system. The “dysfunction” is then logical, adaptive,⁵ and it may be distressing. Sexual desire and response tend to be suppressed in a global way—women rarely present with discreet problems in one phase of the sex response cycle,^{1,23} and phases change with time.

ASSESSMENT OF SEXUAL PROBLEMS

Menopause allows an opportunity to enquire about sexual difficulties. Given the importance of the interpersonal relationship and any partner sexual dysfunction, whenever possible (and relevant), it is recommended that both partners be interviewed—alone as well as together.

Table 4.1 refers to questions to ask the couple as well as those to ask each partner alone.

Detailed Assessment for Complaint of Chronic Dyspareunia

Table 4.2 clarifies the detailed assessment of chronic dyspareunia by history.

Physical Exam

A full physical exam including pelvic exam is usually included as part of good medical care. However, the detailed genital and pelvic exam is mandatory for the assessment of dyspareunia and also necessary for the assessment of genital arousal disorder. Table 4.3 outlines the genital pelvic exam.

Table 4.2. Assessment of chronic dyspareunia: history

Ask if vaginal entry is possible at all (i.e., with finger, penis, speculum, tampon).
Ask if subjective sexual arousal (excitement) is experienced when intercourse is attempted and as it progresses.
Ask exactly when the pain is experienced:
▪ with attempted full entry of penile head
▪ with partial entry of penis or dildo
▪ with deep thrusting
▪ with penile movement
▪ with the man's ejaculation
▪ with the woman's subsequent urination
▪ for hours or minutes after attempted or completed intercourse or other vaginal stimulation attempts
Ask whether on some occasions there is less/no pain and, if so, what is different about those times.

Table 4.3. Genital pelvic exam

External genitalia	Sparsity of pubic hair suggests low adrenal androgens Vulval skin disorders, for example, lichen sclerosis causing soreness with sexual stimulation (e.g., when it involves the clitoral hood) Cracks/fissures in the interlabial folds suggest chronic candidiasis Labial abnormalities may cause embarrassment/sexual hesitancy (e.g., particularly long labia or asymmetry).
Introitus	Vulval atrophy Lichen sclerosis Signs of recurrent splitting of posterior fourchette Abnormalities of hymen Adhesions of the labia minora Swellings in area of major vestibular glands, Allodynia (pain sensation from touch stimulus) of Skene's duct openings and of crease between outer hymenal edge and inner edge of labia minora – typical of vulvar vestibulitis syndrome, as causes of introital dyspareunia. Cystocele, rectocele, prolapse interfering with the woman's sexual self-image Abnormal vaginal discharge associated with burning dyspareunia.
Internal exam	Hypertonicity of pelvic muscles, associated with mid-vaginal dyspareunia Tenderness (trigger points) on palpating deep levator ani due to underlying hypertonicity Vaginal atrophy as causes of deeper dyspareunia.
Full bimanual exam	Presence of nodules and/or tenderness in the cul-de-sac, fornices, along uterosacral ligament Retroverted fixed uterus Tenderness palpating anterior or posterior vaginal wall are suggestive of bladder or rectal pathology as causes of deeper dyspareunia.

REVISED DEFINITIONS OF WOMEN'S SEXUAL DISORDER/DYSFUNCTION

An international committee organized by the American Foundation of Urological Disease recently recommended revisions to the DSM-IV's definitions of women's sexual disorders. Despite the known common global suppression of response, especially in mid-aged women, the individual phase disorders were preserved (see Table 4.4).²⁴

MANAGEMENT OF LOW SEXUAL DESIRE/INTEREST AND SUBJECTIVE SEXUAL AROUSAL

Studies of women (pre- and postmenopause) with chronic complaints of low arousal show increases in genital congestion in response to erotic stimuli identical to those of control women.²² The major issue for women with combined and subjective arousal disorders is their lack of subjective arousal from any stimuli—physical or non-physical. Sexual

Table 4.4. Revised DSM-IV definitions of women's sexual dysfunction

Diagnosis	Definition	Comments
Sexual desire/interest disorder	Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies, <i>and</i> a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to become sexually aroused are scarce or absent. The lack of interest is beyond a normative lessening with life cycle and relationship duration.	Minimal spontaneous sexual thinking or desiring of sex ahead of sexual experiences does not necessarily constitute disorder. Additional lack of responsive desire is integral to the diagnosis.
Sexual arousal disorders (combined and subjective)	Absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation and variable awareness of vulval swelling and lubrication.	There is minimal sexual excitement (subjective arousal) from any type of stimulation – erotic material, stimulating the partner, genital and nongenital stimulation. Awareness of the reflexive genital vasocongestion is variable.
Genital arousal disorder	Absent or impaired genital sexual arousal – minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. <i>Subjective sexual excitement still occurs from non-genital sexual stimuli.</i>	Subjective arousal (sexual excitement) from non-genital stimuli (erotica, stimulating the partner, receiving breast stimulation, kissing) is key to this diagnosis. Early studies indicate reduced vasocongestion in some but not all cases. Loss of sexual sensitivity of physiologically congested tissues accounts for others.
Orgasmic disorder	Despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation.	Women with arousal disorders frequently do not experience orgasm. Their correct diagnosis is one of an arousal disorder.
Vaginismus	Persistent or recurrent difficulties in allowing vaginal entry of a penis, finger, or any object despite the woman's expressed wish to do so. There is often (phobic) avoidance and anticipation/fear/experience of pain, along with variable and involuntary pelvic muscle contraction. Structural or other physical abnormalities must be ruled out/addressed.	Confirmation of this diagnosis is not possible until there has been therapy sufficient to allow a careful introital and vaginal examination. It is a presumptive diagnosis initially.
Dyspareunia	Persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse.	There are many causes, including vulvar vestibulitis and vulval atrophy from estrogen deficiency.

experiences which fail to arouse do not trigger desire, such that desire/interest disorder and arousal disorders are typically comorbid.^{1,23}

SOGC Clinical Tip

Women complaining of difficulties with desire and arousability frequently have histories of depression and others exhibit mood instability, low self-esteem, a tendency to anxiety, and depressive thinking.²³ Depression itself is commonly associated with sexual difficulties even before the prescribing of antidepressants.¹² Addressing these women's mental health and self-esteem issues should be one focus of therapy.

Other areas of managing low desire and low subjective arousal are shown in Table 4.5.

Psychological factors reducing the woman's arousability that involve past negative sexual experiences, including abuse or expected negative outcome from partner sexual dysfunction, may require appropriate referral. Benefit from treating a male partner's erectile dysfunction can result in reversal of the woman's complaints—including difficulties with sexual arousal, lubrication, orgasm, satisfaction, and pain.²⁵ There are no approved non-hormonal medications for loss of subjective arousal and desire. Only one study supports the investigational use of bupropion.²⁶

Table 4.5. Areas of Management of Low Desire and Low Subjective Arousal

- Mental health issues – identify/refer
- Interpersonal issues – identify/refer
- Lack of needed sexual stimuli – give information
- Inappropriate timing of sexual interactions – give information
- Factors to do with privacy as well as protection from unwanted pregnancy and from STDs – give information
- Partner sexual dysfunction – treat/refer

Investigational Systemic Androgen Therapy

Although testosterone has been in clinical use since the 1930s, only recently has there been scientific study of physiological supplementation, measuring improvements in arousability/response as well as improvements in spontaneous desire. Recent randomized controlled trials of 24 weeks, administering systemic transdermal testosterone to high premenopausal levels, have shown increased arousability and response^{27,28,29,30,31} and increased measures of desire in the (non-published) questionnaire used in the most recent studies, when compared with estrogen alone. These studies recruited women reporting loss of sexual desire since surgical menopause. Despite the diagnostic focus, all studies showed improvement in sexual response as well as the latter 4 showing increase in desire, illustrating the globally reduced response in women complaining of “low desire.” Note that all women were estrogenized.

Needed Safety Data

Long-term prospective safety and efficacy data for various formulations of systemic estrogen therapy prescribed for sexual symptoms occurring at menopause are lacking. Similarly, safety and efficacy data for administering testosterone at levels close to the upper limit of normal for premenopausal women, along with systemic estrogen, are inadequate—being only short term. Nonphysiological administration of testosterone without estrogen to postmenopausal women is totally without any safety/efficacy data.

Levels of endogenous bioavailable estradiol and testosterone positively correlate with insulin resistance, independent of central adiposity and body-mass index (BMI).^{32,33} The previously mentioned data from the Study of Women's Health Across the Nation (SWAN) showed robust correlation between low SHBG (thereby freeing serum testosterone) and metabolic syndrome.¹³ The free androgen index was also positively associated with the presence of metabolic syndrome. Exogenous testosterone may increase visceral adiposity as shown by CT scan.³⁴ Postmenopausal

estrogen therapy has been shown to have beneficial³⁵ and detrimental³⁶ effects on glucose metabolism.

Table 4.6 lists factors contributing to the current clinical dilemma.

SOGC Clinical Tip

The possibility of increasing androgen availability by changing from oral to transdermal estrogen, thereby lowering SHBG, should first be explored.³⁹

SOGC Clinical Tip

For all women, whether naturally or surgically menopausal, complaining of loss of sexual arousability and desire, careful assessment of interpersonal and intrapersonal factors must first be done and identified difficulties addressed before investigational testosterone therapy is discussed. Limitations in the longer-term outcome data must be explained if systemic estrogen/androgen are prescribed. The investigational nature of this therapy must be explained and informed consent obtained.

The transdermal route appears to be safer, serum testosterone levels (calculated free t, total T) are needed to detect inadvertent supraphysiological dosage.

Table 4.7 lists potential risks of long-term androgen administration.

Supraphysiological levels of testosterone, typically found with the use of intramuscular formulations and with oral testosterone undecanoate should be avoided (see Table 4.8). A transdermal route is preferable. Ongoing clinical trials involve the use of testosterone gel containing 1.9 mg testosterone⁴⁰ as well as testosterone patches containing 300 µg daily.^{27–31}

Unfortunately, achieving high premenopausal levels of testosterone (the aim of current RCTs) is not necessarily physiological. Compared to a woman in her 30s, an older woman has relative intracellular testosterone deficiency due to markedly reduced adrenal precursors. The phenomenon of intracellular production of testosterone (and estrogen) in target tissues allows local androgen action. Supplementing exogenous testosterone exposes all cells to higher concentrations. Therefore ongoing clinical monitoring of testosterone therapy is essential.

Table 4.6. Factors Contributing to Current Dilemma Concerning Androgen Therapy

- The need for (time-consuming) comprehensive biopsychosocial assessment.
- Unavailability of any accepted measures of total androgen activity.
- Presence of expected long-term dysfunction from presumed hormonal lack, but absence of long-term safety data on hormone administration.
- The need for concomitant systemic estrogen therapy, with documented risk if started some years postmenopause, and without long-term safety data when started for sexual symptoms at the time of menopause.
- Current lack of formulations of systemic androgen for women.
- Lack of sensitive accurate assays of testosterone levels to monitor testosterone supplementation³⁷ (assays designed for higher male range)
- For clear-cut situations of androgen deficiency (e.g., hypothalamic pituitary disease), adrenal disease, bilateral salpingo-oophorectomy (especially in younger women), premature menopause (especially from chemotherapy), *long-term* systemic estrogen and androgen would appear logical but is without scientific study in the long term.³⁸

Although serum levels of testosterone are not recommended in assessment of women's sexual problems, some form of biochemical monitoring is necessary given variable absorption. The majority of assays of testosterone (total, free, bioavailable) are not reliable in the female range,³⁷ a calculated free T based on a reliable assay for total T is currently recommended for monitoring of investigational therapy.³⁷ Follow-up includes:

- measurement of lipids, hematocrit;
- examination of upper abdominal obesity, hirsutism, acne, scalp hair loss, clitoromegaly, breast changes;
- mammography, uterine ultrasound.

SOGC Clinical Tip

There is level I evidence of modest benefit from testosterone supplementation to carefully selected estrogenized women with surgical menopause recruited for reasons of low desire. However, no actual recommendation can currently be given. This is due to lack of long-term safety/efficacy data and the presence of permanent androgen lack, the inability to determine which women are androgen deficient, and the current guideline to stop estrogen as soon as possible. There are no data on prescribing testosterone without estrogen.

MANAGEMENT OF SEXUAL PAIN

The history and exam may have identified definitive cause of sexual pain (see Tables 4.2 and 4.3).

Local estrogen formulations include vaginal cream, tablets, or a silicone ring placed high in the vagina, releasing estradiol over the subsequent 12 weeks, at which time it is replaced. Systemic absorption is least with the ring and limited to the first few days after insertion; systemic absorption is also insignificant with the tablets when used every 3 days.^{47,48}

Table 4.7. Potential Risks From Long-Term Androgen Therapy

- Risks from concomitant long-term estrogen
- Potential increase in insulin resistance and increase in upper abdominal obesity
- Hirsutism, acne, loss of scalp hair
- Clitoromegaly and voice-deepening
- Fluid retention
- Endometrial and breast hyperplasia/neoplasia
- Reduced HDL cholesterol if methyl testosterone (available in the US) is used
- Sleep apnea
- Emotional lability
- Unknown (due to lack of long-term data)

SOGC Clinical Tip

Specifically, loss of vaginal elasticity with thinning of the vaginal epithelium, reduced lubrication, and lost vulval sexual sensitivity, all associated with vulvovaginal atrophy affecting 10%–30% of postmenopausal women,^{2,45} may be improved with local estrogen.⁴⁶

Vulvar vestibulitis is seen in mid-life women as well as younger women.⁴⁹ At present, a number of therapies address various aspects of the central and peripheral sensitization associated with neurogenic inflammation leading to the discreet areas of allodynia around the introital rim.⁵⁰ These include chronic pain medications such as anticonvulsants and tricyclic antidepressants, topical local anaesthetics, topical anti-inflammatories such as cromoglycate, and sexual and psychotherapy (see Figure 4.2). There are no evidence-based recommendations.

Figure 4.2

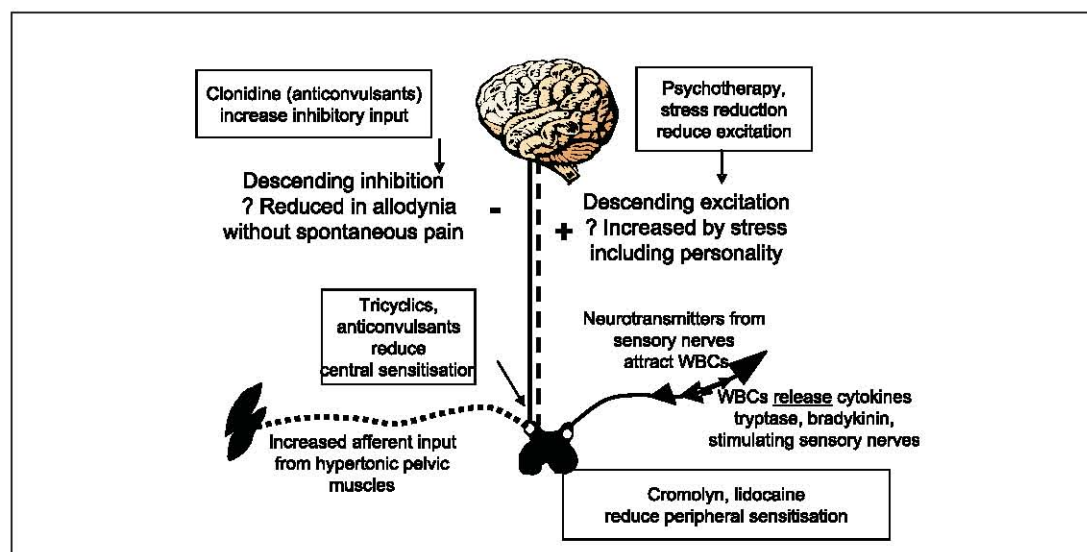


Table 4.8. Testosterone Formulations

- Homemade creams, tablets, gels have variable absorption and lack efficacy data.
- Testosterone undecanoate leads to supraphysiological levels.⁴¹
- Climacterone, for which there are level I data, leads to cumulative supraphysiological testosterone levels.⁴²
- Intramuscular testosterone, even at 25 mg dose, leads to supraphysiological levels.⁴³
- Estratest (CE plus methyl testosterone; unavailable in Canada) reduces HDL cholesterol (level I efficacy data from 1 study).⁴⁴
- Methyl testosterone is no longer available and had the same lipid risk.
- Topical vulvar testosterone cream is used to restore reduced vulval sexual sensitivity but is without scientific study.

Table 4.9. Management of Orgasmic Disorder

- Consider antidepressant therapy (replace serotonergic antidepressant and/or add bupropion).⁵²
- Possibly refer for relationship issues, especially regarding trust.
- Give information about the need for more prolonged and more direct vulval and clitoral stimulation associated with aging.
- Consider *investigational* use of phosphodiesterase inhibitors (PDEs) for neurological disease (e.g., multiple sclerosis, spinal cord injury).

Hypertonicity of pelvic muscles is thought to partially contribute in many women, such that pelvic muscle physiotherapy may be recommended.⁵¹

Figure 4.2. is a schematic of proposed pathophysiological mechanisms underlying the chronic pain of vulvar vestibulitis syndrome and therapeutic interventions.

Pain relief may be partial and/or delayed, so it is important to assist the couple to create rewarding erotic sexual interactions that do not involve anything entering the vagina. Normalizing non-penetrative sex to both partners may be necessary. Chronic dyspareunia leads to lost arousability and lack of desire at any stage in the sexual experience if the painful component—intercourse—persists.

MANAGEMENT OF LACK OF ORGASM DESPITE HIGH AROUSAL (ORGASMIC DISORDER)

More often a lifelong concern, orgasmic disorder may be acquired in mid- or later life. Management will focus on one or more of the areas shown in Table 4.9.

Ask whether the woman can experience orgasms with self-stimulation. If she can, this would direct therapy toward interpersonal issues (e.g., trust +/- the need for the woman guide her partner regarding the specific type of stimulation she requires).

SOGC Clinical Tip

The majority of mid-aged women presenting with loss of orgasm have an arousal disorder.

Loss of genital sexual sensitivity and response may predominate, or, more commonly, there is a global lack of mental subjective sexual excitement, as well as apparent loss of the body's former response. In either case, the diagnosis is arousal disorder rather than orgasmic disorder.

MANAGEMENT OF GENITAL AROUSAL DISORDER

The underlying pathophysiology of the “genital deadness,” despite local estrogen therapy, reported by some otherwise healthy mid-life and older women is unclear. Limited research with vaginal photoplethysmography suggests some have demonstrably reduced genital congestion in response to erotic stimuli which produce subjective sexual arousal.⁵³ This subgroup with subjective arousal but impaired genital congestion may benefit from phosphodiesterase inhibitors (PDEIs).⁵³ Others appear to have lost sexual sensitivity of physiologically congested vulvar tissues (such that PDEIs would be of no benefit). Any role of topical vulval testosterone awaits scientific study. Women with genital arousal disorder associated with neurological disease or autonomic nerve damage from radical pelvic surgery may benefit from PDEIs.⁵⁴

RECOMMENDATIONS

1. A biopsychosexual assessment preferably of both partners (when appropriate), identifying intrapersonal, contextual, interpersonal, and biological factors is recommended prior to treatment of women's sexual problems. (IIIA)
2. For women with vaginal atrophy, local estrogen should be prescribed to improve vulvovaginal atrophy-associated dyspareunia. (IA)
3. 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)
4. Any investigational testosterone therapy included in the management of selected women with acquired sexual desire/interest disorder, typically associated with an arousal disorder, should only be initiated by clinicians experienced in women's sexual dysfunction and with informed consent from the woman. The investigational nature, lack of long-term safety data, need for systemic estrogen therapy, and careful follow-up must be explained. (IC)

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Mood and Memory

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INTRODUCTION

Many women experience physical, emotional, and cognitive changes during the transition into menopause.

Common symptoms include those associated with estrogen depletion, such as vasomotor symptoms, in addition to mood disturbances and cognitive difficulties.¹ The physical changes have been addressed elsewhere in the guidelines and will not be reviewed in this chapter. Although still controversial,² the time surrounding menopause appears to be a period of increased risk for the development of depressive symptoms, as suggested by community-based studies and clinic-based surveys (gynaecology clinics).³⁻⁷ The most prevalent mood symptoms during the perimenopause include irritability, tearfulness, anxiety, depressed or labile mood, lack of motivation or energy, and poor concentration and sleep.⁸ Although these aforementioned symptoms have been linked to fluctuations in estradiol,⁹ others have proposed alternative explanations. Depressive symptoms have been postulated to occur as a result of sleep disturbances associated with vasomotor symptoms (clinical application of the domino theory)¹⁰ as well as secondary to psychosocial and cultural factors such as lifestyle and diet.¹¹⁻¹²

SOGC Clinical Tip

Perimenopausal women may complain of many symptoms commonly seen during perimenopause, but if they describe suicidal ideation they should be referred for an evaluation of major depression.

The relationship between perimenopause and mood disorders is even less well understood; although in a subgroup of vulnerable women, there may be a relationship between estrogen depletion, estrogen deficiency, or change in estrogen levels.^{8,13-14} Associated risk factors for development of depression during the perimenopausal period include a history of depressive disorders, poor physical health, and life stressors (lack of employment and social support), history of surgical menopause, and a long perimenopausal

transition.^{3,15-18} Thus although depressive symptoms are common, most women do not develop depressive disorders (characterized by a significant number of symptoms causing clinically significant distress or impairment) during perimenopause.

SOGC Clinical Tip

Depressive symptoms may worsen in women with major depression during perimenopause. Such perimenopausal women who have been stable on an antidepressant may become symptomatic once again. Always ask about current and past psychiatric treatment during your medical workup.

Although cognitive performance is thought to decline with increasing age, not just during perimenopause, the available evidence suggests that age-related deficits develop only in specific skills. Where no changes in performance are seen in tasks involving very short-term memory or in distant, remote memory in aging individuals, there are decreases in the ability of some older people to acquire, encode, and retrieve new material.¹⁹ Thus the ability to learn new associations or to remember new facts can become compromised with increasing age, regardless of gender or hormonal status. This chapter reviews current evidence for the use of hormones, with a primary focus on estrogen, to treat depressed mood or cognitive decline in perimenopausal and menopausal women.

ESTROGEN AND BRAIN FUNCTION

Estrogen has multiple effects on brain function and structure. Estrogen influences on neurotransmitter systems can occur through genomic effects²⁰ or through direct membrane effects.²¹ The genomic effect is slow (hours to years) and the membrane effect is rapid (minutes to hours). Estrogen can also affect the excitability of neurons, presumably through G-protein dependent mechanisms.²²⁻²³ Overall estrogens exert a positive effect on serotonergic activity: increased synthesis of serotonin, up regulation of 5-HT₁ receptors, down regulation of 5-HT₂ receptors, decreased

monoamine oxidase (MAO) activity,²⁴ and modulation of binding affinity of 5-HT receptors.²⁵ Estrogen affects not only the serotonergic system but also other neurotransmitter systems. Estrogen increases the activity of nor-adrenaline, acts as a cholinergic agonist, decreases dopamine D2 receptor sensitivity and can act as an adjunct agonist of γ -aminobutyric acid (GABA).^{14,24} Several different effects of estrogen on brain structure and function could explain its ability to maintain aspects of memory. For example, estrogen potentiates neurite outgrowth, dendritic spine formation, and synapse formation.²⁶ Regions of the brain responsible for learning and memory, including the basal forebrain (the origin of ascending cholinergic pathways) and the hippocampus (a critical brain structure involved in memory), contain nuclear receptors for estrogen.²⁷ Estrogen also increases cerebral blood flow,²⁸ modulates cerebral glucose utilization,²⁹ and possesses antioxidant properties.³⁰ Although still not well understood, estrogen has many effects in the brain that could explain its effects on both mood and memory.

ESTROGEN AND MOOD

Estrogen Monotherapy

Studies of Perimenopausal and Postmenopausal Women with Depressed Mood

Although there are more than 20 placebo-controlled trials testing estrogen's efficacy for treating depressed mood in perimenopausal or menopausal women, a consensus does not exist regarding estrogen's therapeutic efficacy. Limiting factors that also hinder comparisons across trials include heterogeneity in study design and population, degree of mood disturbance, the use of various measures to determine that disturbance, and the inclusion of women with concurrent psychiatric illness. It has been argued that trials employing parenteral or transdermal 17β -estradiol most reliably detect a drug-placebo difference and that these delivery systems may therefore be more effective in treating depressed mood.³¹ A quantitative review of 26 studies examining the effect of hormones on mood using broad inclusion criteria and including non-placebo controlled trials, found the overall mean effect size of hormone therapy (HT) to improve mood was 0.68 (variance = 0.14, $P < 0.00$). Interestingly, the mean effect size for studies using estrogen without progesterone was 0.69 (variance = 0.21, $P < 0.00$).³² The mean effect size was larger among perimenopausal than postmenopausal women and was reduced in studies that included both perimenopausal and menopausal women. Moreover, treatment for longer than eight months was associated with greatest improvement. As the above effect sizes are moderate to large, the results bode well for estrogen. Unfortunately, the inclusion of subjects who were

either not depressed or experiencing only mild levels of depression limit the generalizability of the meta-analysis to women with depressed mood or mild depressive symptoms, not to women with major depressive disorder.

SOGC Clinical Tip

A trial of HT can be suggested to a woman with perimenopausal symptoms that include mild depressive symptoms if she does not have a history of depression. Women who have a history of depression should be evaluated for the necessity of an antidepressant.

Interestingly, following the publication of the results of the Women's Health Initiative (WHI) that found that HT should not be used for primary prevention,³³ many women discontinued their use of HT. A recent study has noted that since that publication the numbers of prescriptions for serotonergic antidepressants has statistically significantly increased in women. Although this is an observational study with limitations, it does suggest that these antidepressants are being prescribed for symptoms previously controlled by HT (i.e., hot flashes and depressed mood).³⁴

SOGC Clinical Tip

There is evidence that some antidepressant medications can be used to treat hot flashes (i.e., venlafaxine, paroxetine). Initially, the flashes may seem to intensify rather than be ameliorated with treatment. Rather than discontinue treatment or increase the dose, provide psychoeducation to the woman and encourage her to continue the antidepressant trial.

Studies in Women With Depressive Disorder

There are a limited number of studies examining the role of estrogen in the treatment of major depressive disorder. When Soares et al.³⁵ examined the efficacy of 17β -estradiol under placebo-controlled conditions in a mixed sample of 50 perimenopausal women with syndromal and subsyndromal depression, remission of the depressive disorder was observed in 68% of women in the estradiol group versus 20% in the placebo group ($P < 0.001$). Depression scores dropped from 25 to 9 for the estradiol group versus 22 to 16 for the placebo group after 12 weeks of treatment ($P = 0.02$). Moreover, the antidepressant benefit of estradiol was sustained after a 4-week washout period. The treatment was well tolerated and adverse events were rare. Although this study showed estradiol is an effective antidepressant for women in perimenopause, only half the sample met criteria

for major depressive disorder (26/50), and over half experienced depression for the first time. The generalizability of these results is thus limited to perimenopausal women with first-onset minor levels of depression. Despite the need for trials with large sample sizes, there is now accumulating evidence with four small studies (two randomized controlled trials [RCTs]) demonstrating that estradiol is effective for the treatment of depressive disorders during perimenopause.³⁵⁻³⁸ Moreover, two of the above studies also indicated that the antidepressant effect of estrogen appeared independent from the effects mediated through the alleviation of vasomotor symptoms.^{35,36} Studies that have examined the effect of estrogen on postmenopausal women with depressive disorders, however, have not shown benefit.³⁸⁻⁴⁰

Estrogen Augmentation

Estrogen has also been used to augment antidepressant treatment in women whose depression has been resistant to antidepressant medication. There are no prospective RCTs using HT to augment selective serotonin reuptake inhibitors (SSRIs). Four studies examining non-randomized HT use to improve antidepressant response were positive^{37,41-43} and two were negative.⁴⁴⁻⁴⁵ Although the results are mixed, the evidence suggests that estrogen may augment clinical response to SSRI antidepressant treatment in some women.

SOGC Clinical Tip

Close collaboration with psychiatric colleagues should become a standard of care for the treatment of perimenopausal women with depressive symptoms.

ESTROGEN AND COGNITION

Estrogen Therapy as Protection Against Cognitive Decline in Healthy Women

The issue of whether estrogen therapy (ET) can improve cognitive functioning in healthy postmenopausal women remains controversial with conflicting evidence. While some⁴⁶⁻⁴⁹ large epidemiological studies of elderly postmenopausal women (age approximately 65 years or older) found that women who had been taking estrogen had higher scores on tests of cognitive functioning than did women of similar age who had not used ET, others have not.⁵⁰ The results from randomized, prospective, double-blind, placebo-controlled trials⁵¹⁻⁵⁸ have also not consistently found that postmenopausal women who received treatment with estrogen performed significantly better on tests of cognitive function, although the results were stronger for tests of short- and long-term verbal memory. Indeed, a recent meta-analysis indicated that estrogen may improve specific cognitive domains (i.e., verbal memory

and selected executive cognitions such as vigilance, reasoning, motor speed, and verbal function).⁵⁹ Although a recent review⁶⁰ found little evidence for an effect of ET or HT on overall cognitive function, an effect for some cognitive abilities (i.e., verbal memory) was found. Further, another meta-analysis concluded that HT has small and inconsistent effects that include enhancement of verbal memory, abstract reasoning, and information processing.⁶¹ However, a subgroup of women, free from probable dementia at baseline, from the Women's Health Initiative Study and aged 65 years or older taking estrogen plus progestin, were followed for 4.2 years (Women's Health Initiative Memory Study [WHIMS]).⁶² HT did not improve cognitive function when compared with placebo. Moreover, a small increased risk of clinically meaningful cognitive decline occurred in the HT group. Women in the ET alone group (5.4 years of mean follow-up) also did not benefit. In fact, ET had an adverse effect on cognition, greater among women with lower cognitive function at initiation of treatment.⁶³ Regardless of the methodological concerns that have been raised for WHIMS,⁶⁴ and the finding that hormone treatment did not show a beneficial effect for estrogen, the effects of HT or ET may depend on the woman's age. The aforementioned results apply to postmenopausal women. There is a serious lack of data on the cognitive effects of estrogen on perimenopausal women. The effects of HT may also depend on the type of menopause (surgical or natural), the therapeutic intervention used (estrogen with or without a progestin, with Premarin the most widely used having the least effect), mode of delivery (transdermal, oral, intramuscular), dosage and duration, and the presence or absence of perimenopausal or menopausal symptoms.

Estrogen Therapy as Protection Against Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia, affects 1.5 to 3 times as many women as men, even after adjusting for increased longevity in women.⁶⁵ Because the findings from basic neuroscience research and from RCTs in healthy postmenopausal women provided some evidence that estrogen helps to preserve memory in aging women, much attention has recently been focused on investigating whether ET may lower the risk of AD. Cohort and case-control studies^{66,67} have suggested that women taking ET have a substantially reduced risk of developing AD. However, a large population-based, case-control study (Framingham Heart Study) in menopausal women did not find that ET use reduced the risk of developing dementia.⁶⁸ The results from WHIMS showed that not only did HT not prevent mild cognitive impairment in women aged 65 years or older, but also an increased risk for probable dementia among HT users, compared with placebo.⁶⁹ The results of the ET alone group also showed that ET did not reduce

dementia or mild cognitive impairment incidence but in fact increased the risk for both.⁷⁰

Estrogen Therapy as an Effective Treatment for Alzheimer's Disease

Several open-label clinical trials have reported selective cognitive improvements in women with dementia who received ET.⁷¹⁻⁷³ The findings from these early treatment studies must be interpreted cautiously, however, since the studies were uncontrolled, short-term, and relatively small. Two RCTs investigated the possible benefit of ET for women with mild to moderate AD.^{74,75} Women with AD who were treated with estrogen for 16 weeks showed no change in tests of cognitive function compared with those who were given placebo.⁷⁴ Similarly, estrogen had no effect on slowing disease progression or improving cognitive outcomes in women with mild to moderate AD when treatment lasted for 1 year.⁷⁵ A recent review concluded neither ET nor HT is currently indicated for cognitive improvement or maintenance for women with AD, but that different preparations could have different effects.⁷⁶

PROGESTINS, TESTOSTERONE, SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS) AND MOOD OR COGNITION

Several observational studies and one randomized study show that the addition of a progestin to ET attenuates the beneficial effect of estrogen on mood.⁷⁷ The meta-analysis reviewing the effects of hormones on depressed mood found lower effect sizes for studies that used the combination of estrogen and progesterone or progesterone only.³² This negative effect of progestin on mood might be mitigated by a higher estrogen-progestin dose ratio.

In terms of the effects of progestins on cognition, the beneficial association between unopposed estrogen use and the rate of change in cognitive functioning in older women was found to be opposed by the addition of a progestin,⁷⁸ suggesting that combined therapy might negate the potential beneficial effect of estrogen on cognition. Recall, however, that the results from WHIMS for the ET group alone showed ET had an adverse effect on cognition. Although one study found a positive effect of a combined estrogen-androgen drug on aspects of cognition,⁵² it is not known whether this was a direct effect of the androgen, or whether it occurred due to the aromatization of testosterone to estrogen.

Treatment with testosterone has been found to improve depressed mood and anxiety among postmenopausal women with decreased testosterone levels.⁷⁹

The adrenal androgen dehydroepiandrosterone (DHEA) has also been found to have antidepressant effects in a small placebo-controlled trial with 22 patients (10 women);⁸⁰

most recently a small, randomized, double-blind, placebo-controlled, cross-over treatment study with 23 men and 23 women found that DHEA was an effective treatment for mid-life-onset depressive disorders.⁸¹

A randomized study of raloxifene, a selective estrogen receptor modulator, showed that treatment of postmenopausal women for one year was not associated with any change in their scores on tests of cognitive functioning or decline in mood.⁸² In a recent pilot study, postmenopausal women with treatment-resistant depression (TRD) were randomly assigned to raloxifene for 8 weeks or placebo for 4 weeks followed by raloxifene for 4 weeks. Although both groups showed significant improvement, there was a trend for greater reduction in depression scores, higher change in depression scores, and remission in the 8-week group.⁸³ A larger trial with a longer treatment period will be needed to determine if raloxifene will be an effective adjunctive treatment to antidepressants for postmenopausal women with TRD. Although the study examining the effect of raloxifene (60 mg) on cognitive function on 50 postmenopausal women was negative,⁸⁴ the most recent data, based on a large sample size, was not. The Multiple Outcomes of Raloxifene Evaluation (MORE) RCT randomized postmenopausal women with osteoporosis to either raloxifene (60 or 120 mg) or placebo; development of mild cognitive impairment and dementia was a secondary outcome. After three years, 5386 women were screened for dementia; raloxifene at a dose of 120 mg per day resulted in a reduced risk of cognitive impairment in postmenopausal women.⁸⁵

More research is certainly needed to determine the effects of progestins, testosterone, and serms on cognition and mood.

HORMONES AND ANXIETY

Research has recently started to examine anxiety disorders during peri- and postmenopause. In fact, in perimenopausal women, vasomotor symptoms can be mistaken for panic or anxiety attacks. Although high levels of FSH can help to identify symptomatic perimenopausal woman, elevated rates of anxiety symptoms have also been reported during perimenopause and may be associated with very high levels of FSH.⁸⁶

Research has been sparse with conflicting results; a large population-based survey of 8000 Scottish women⁸⁷ aged 44 to 54 years found that 23% of women surveyed identified anxiety as a problem, but 2 prospective studies following women before and after menopause found no significant increase in anxiety symptoms.^{88,89} The Epidemiologic Catchment Area Study (ECA) did not report increased panic attack rates in women aged 45 to 64 or over age 65 (6-month prevalence, 4.5%–7.9% and 0%–3.7 respectively;

overall lifetime prevalence, 9.7%).⁹⁰ In a recently published large cross-sectional survey of 3369 community-dwelling postmenopausal women taking part in the Myocardial Ischemia and Migraine Study⁹¹ (ancillary study of the Women's Health Initiative), panic attacks were found to occur commonly, with 9.8% of women reporting full-blown attacks and 8.1% with limited symptom attacks, the highest rates occurring in women aged 50 to 59 (all attacks 17.9%; 95% confidence interval, 16.6%–19.2%). Interestingly, there was no significant association of panic attacks with self-reported use of HT. The panic attacks were found to be associated with stressful life events, medical comorbidity, and functional impairment. It is not known however if the onset of the panic attacks in the aforementioned cross-sectional study was pre- or postmenopausal. Although controversial, it has been proposed that panic disorder may have a bimodal distribution with a second peak occurring between ages 45 to 54.⁹²

Although estrogen may have anxiolytic effects through genomic means,⁹³ there has been little clinical research. ET has been found to reduce subclinical anxiety symptoms^{94,95} and estrogen may blunt autonomic responses to stress in postmenopausal women.⁹⁶ There have been no published clinical trials evaluating the effect of estrogen on anxiety disorders to date in peri- or postmenopausal women. Although preclinical studies^{97,98} suggest that progesterone is an anxiolytic, the effect of progesterone on anxiety disorders has not been studied. More research is warranted to investigate hormonal treatments for anxiety symptoms.⁹⁹

RECOMMENDATIONS

1. Estrogen alone may be offered as an effective treatment for depressive disorders in perimenopausal women and may augment clinical response to antidepressant treatment, specifically SSRIs (IB). The use of antidepressant medication, however, is supported with the 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 developing dementia in postmenopausal women or for retarding the progression or deterioration in women with diagnosed AD. (IB)

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Therapeutics: Prescription Drugs

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INTRODUCTION

The first pharmaceutical agent to treat menopausal complaints was developed in the late 1920s. Since then, a number of discoveries led to the development of compounds for improving the health and quality of life in menopausal women. No standard therapeutic regimen exists, but a variety of compounds, routes of administration, and dosages can be used to optimize an individual's therapy.

Every woman should be informed of the potential benefits and adverse reactions associated with each treatment option she considers. It is the responsibility of the health care professional to provide the most current information.

ESTROGENS

To distinguish between different estrogens, the terminology of natural versus synthetic is often used; however, this can be confusing or misleading. While some have used the term "natural" to refer to the source of the preparation (i.e., plant or animal), others have used the term to refer to the chemical structure (i.e., identical to human estrogens). However, the only truly "natural" estrogens are those produced and secreted within a woman's body (i.e., estrone and estradiol). The critical determinant of an estrogen preparation's usefulness is not its origin, but its biological effectiveness. The most potent naturally occurring estrogen is 17 β -estradiol, followed by estrone and estriol.¹

Estrone and estradiol are not readily absorbed by the gastrointestinal tract. Rapid conversion of estradiol to estrone occurs in the intestinal mucosa.¹ Further metabolism and conjugation occur in the liver, with glucuronidation of up to 30% of the initial oral dose occurring in the "first pass" through the liver, followed by rapid urinary and biliary excretion.¹ To enhance oral bioavailability and prevent degradation, estrogens can be conjugated and delivered as sodium sulphates, or stabilized by adding piperazine or an ester group. Estrogens may also be micronized, creating

very small particles that result in an increase in surface area and rapid absorption.¹

The estrogen preparations used in Canada for hormone therapy (HT) are listed in Table 6.1.

Orally ingested estrogens produce a number of biologically active substances in the liver due to the important "first pass" effect. Oral administration is associated with rapid increases in levels of high-density lipoprotein (HDL) cholesterol and triglycerides, whereas transdermal estrogen therapy has less effect on the lipoprotein profile. Transdermal administration does not produce high levels of the drug in the portal circulation; this may explain why the oral and transdermal routes are associated with different effects on the lipoprotein profile.¹ In theory, transdermal estrogen therapy should have less effect on coagulation factors and gall bladder disease,² but clinical evidence of this has not yet been demonstrated. Refer to chapter 2 for more information regarding the differences between the transdermal versus oral route of administration.

Smoking increases the clearance of estrogen in the liver. Much lower serum concentrations of estrone and estradiol have been found in smokers than in non-smokers after oral administration of estrogen, with a consequent reduction in the effect of treatment on lipid levels and bone mineral content. No difference in serum estrogen concentrations between smokers and non-smokers has been observed after transdermal therapy.³

Conjugated Estrogens

Conjugated estrogens are a blend of estrogens that can be chemically produced or derived from plant or animal sources. Under current Canadian regulations, conjugated estrogen tablets must contain specific proportions of sodium estrone sulphate, sodium equilin sulphate, and 17 α -dihydroequilin sulphate. Conjugated equine estrogens (CEE), in our document referred to as conjugated estrogens (CEs), contain such additional bioactive estrogens as delta 8-9-dehydroestrone sulphate. Other CEs

Table 6.1. 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	
	PMS-conjugated estrogens CSD	0.3, 0.625, 0.9, 1.25	
Estropipate	Ogen	0.625, 1.25, 2.5	
17 β -estradiol (micronized)	Estrace	0.5, 1.0, 2.0	
Esterified estrogens	Neo-Estrone	0.3, 0.625, 1.25	
Transdermal twice weekly (μg)			
17 β -estradiol	Estraderm	25, 50, 100	
	(reservoir patch)		
	Oesclim (matrix patch)	25, 50	
	Estradot (matrix patch)	25, 37.5, 50, 75, 100	
Transdermal weekly (μg)			
17 β -estradiol	Climara (matrix patch)	25, 50, 75, 100	
Transdermal daily			
17 β -estradiol	Estrogel (topical gel)	0.06%	
Vaginal			
Conjugated estrogens	Premarin (cream)	0.625 mg/g	0.5–2.0 g/d
17 β -estradiol	Estring (silastic ring)	2.0 mg/ring	
	Vagifem (vaginal tablet)	25 μ g	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	

may not be pharmacologically identical to conjugated equine estrogens, and their use could result in a change in therapeutic effectiveness.⁴

Estropipate

Estropipate contains estrone that has been solubilized by sulphate and stabilized by piperazine. A tablet containing 0.75 mg of estropipate contains 0.625 mg of sodium estrone sulphate.

Estradiol

Estradiol is available in oral, transdermal, injectable, and vaginal delivery systems. To be absorbed orally, estradiol

must be micronized. Once absorbed, estradiol is converted in the liver to estrone.¹ By contrast, transdermal application avoids hepatic “first pass” metabolism, resulting in sustained concentrations of estradiol.^{1,5} Delivery systems include reservoir patches that have a pouch in which estradiol is dissolved in alcohol. Matrix patches contain an adhesive matrix in which the estradiol is dissolved. Depending on the system, patches must be changed once or twice weekly. Estradiol is also available in a gel formulation that is applied to the skin daily. This product is absorbed into the skin in 1 to 2 minutes and serum concentrations reach steady state after the third daily administration.

Table 6.2. Progestin preparation

	Trade name	Strength	Comment
Oral			
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	Mirena Intrauterine System (IUS)	52 mg per IUS	

PROGESTINS

Progestin Addition To Estrogen Therapy

The addition of a progestin to estrogen therapy has been shown to reduce, but not eliminate, the estrogen-attributable risk of endometrial hyperplasia or cancer in a dose- and duration-dependent fashion (see chapter 10).⁶ Maximum protective effects are obtained with 12 to 14 days of progestin exposure per month.¹

Two different classes of progestins are used in HT:

1. 17 α -hydroxyprogesterone derivatives (including medroxyprogesterone acetate [MPA], megestrol, and progesterone);
2. 19-nortestosterone derivatives (norethindrone and norethindrone acetate).

17 α -hydroxyprogesterone derivatives primarily exhibit progestational activity, although there are some notable differences between these agents.

For example, oral micronized progesterone does not appear to antagonize the positive effects of CE on HDL cholesterol, whereas MPA attenuates the estrogen-induced lipid effects.⁷ Additionally, differences in bleeding patterns may occur. A full secretory transformation occurs with the use of MPA, while daily doses of less than 300 mg of micronized progesterone have antimitotic effects only, which may result in less menstrual bleeding.⁸

The 19-nortestosterone derivatives have varying estrogenic, anti-estrogenic, and androgenic properties. These agents produce full secretory transformation, similar to the effect of MPA.⁹ The progestin preparations available in Canada are listed in Table 6.2.

Table 6.3. Combination products

	Trade name	Strengths	Comment
Oral			
Ethinyl estradiol (EE) and norethindrone 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 + 1mg DRSP	Approval pending
Transdermal			
17β-estradiol (E ₂) and norethindrone acetate	Estracomb	50 g E ₂ + 250 µg NETA	
	Estalis	50 g E ₂ + 250 µg NETA 50 g E ₂ + 140 µg NETA	
	Estalis Sequi	50 g E ₂ +	
		50 g E ₂ + 250 µg NETA or 50 g E ₂ + 140 µg NETA	
Injectable			
Estradiol dienanthate (ED), estradiol benzoate (EB), and testosterone enanthate (TE)	Climacteron	7.5 ED + 1 EB + 150 mg TE/mL	
Estradiol-testosterone enanthate (TE)	Neo-Pause	6.5 + 100 mg TE/mL	

HORMONAL REGIMENS

There are many regimens of HT used in clinical practice. Regimens containing both estrogen and progestin should always be offered unless the woman has had a hysterectomy, in which case the endometrial protective effects of progestin will not be necessary. Refer to Table 6.3 for currently available combination products.

Cyclic Estrogen-Progestin Regimens

Estrogen and progestin have traditionally been used in a cyclical manner. In North America, cyclic therapy has consisted of estrogen taken from day 1 to day 25 of the calendar month with the addition of a progestin for 10 to 14 days each month. This allowed for a 5-day hormone-free interval. The rationale for this hormone-free interval is unclear. Although some women note a reduction of breast tenderness, many women report the return of distressing symptoms in the days when they are not taking hormones.⁶ Theoretically, eliminating the hormone-free interval may be

prudent to maintain adequate estrogen concentrations in the blood and to provide maximal symptomatic relief.

Current evidence suggests that 0.625 mg of conjugated estrogens (or equivalent) daily is the standard effective dose for prophylaxis of osteoporosis, although lower doses (0.5 mg oral micronized estradiol, 0.3 mg CE) may also be effective.^{10,11}

Cyclical combined estrogen and progestin therapy generally involves 12 to 14 days of progestin use per month. Whitehead et al. demonstrated the critical importance of the duration of progestin therapy in stabilizing the endometrium and reducing the risk of hyperplasia.¹²

Typical doses of progestins used in a cyclic regimen are listed in Table 6.4. When daily doses larger than 0.625 mg of CE or its equivalent are used, larger doses of progestins might be required (10 mg MPA or equivalent daily).

The effects of administering MPA for 14 days every 3 months have been investigated; the rates of endometrial hyperplasia with this regimen have been found to vary widely (from 0% to 12%). If this regimen is used, routine

Table 6.4. Progestin dosages for endometrial protection

	Cyclic 10–14 d/mth (mg)	Continuous daily (mg)
Oral		
Medroxyprogesterone acetate	5–10*	2.5
Medrogestone (medrogestone)	5–10*	
Megestrol	20	
Micronized progesterone	200–300* [†]	100
Norethindrone	0.35–0.7*	0.35
Transdermal		
Norethindrone acetate [‡]	0.14 or 0.25	0.14
Intrauterine		
Levonorgestrel IUS		52 mg/IUS

*Larger 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.

endometrial assessment for unscheduled bleeding is recommended (see chapter 10).⁵

Continuous-Combined Regimens

An alternative to the cyclic administration of progestin in HT is continuous daily treatment with both an estrogen and a progestin. This method was developed to avoid the withdrawal bleeding associated with cyclic HT regimens. Most data are derived from studies that used 0.625 mg CE with 2.5 mg MPA per day.^{13–14} Other progestins can be used.

Forty percent of women receiving this therapy have irregular breakthrough bleeding during the first 3 to 6 months. The majority of patients who persist with the medication become amenorrheic by 12 months of use; some women have breakthrough bleeding after 1 year.¹⁵

The levonorgestrel-releasing intra-uterine system (Mirena) is currently indicated for contraception. The device can be left in situ for 5 years and, as with other continuous progestin use, breakthrough bleeding may occur during the first months of use.² Current research suggests potential for use of such a device in postmenopausal women, in combination with systemic estrogen administration.¹⁶ See Table 6.4 for a complete list of progestin dosages and regimens.

Individualizing Therapy

The use of estrogens can result in unpleasant side effects in 5% to 10% of women using 0.625 mg of CE, or its equivalent, daily.¹⁷ Common complaints in women on therapy include breast tenderness, nausea, headache, and bloating. These side effects are often dose related, and may resolve with continued use or a decrease in dose. Because the side effects vary among currently available estrogen preparations, substituting another preparation for a poorly tolerated one is a reasonable strategy.

Estrogen doses may be titrated to achieve control of symptoms. Residual vasomotor symptoms or vaginal dryness may indicate a need to increase the dose, or change the preparation or route of administration, whereas breast tenderness or leukorrhea may require a reduction in dose. Adverse reactions to progestins are more frequent when progestins are given with estrogen therapy.¹⁸ Side effects of progestins include alterations in mood, breast tenderness, and bloating. Switching from one progestin formulation to another may reduce these symptoms.²

Cyclic progestin-associated side effects may be reduced or eliminated by switching to a continuous-combined regimen. Like estrogens, each progestin preparation has a different side effect profile. For example, micronized progesterone can cause sedation, and should therefore be administered at bedtime. The micronized progesterone formulation Prometrium contains peanut oil and is contraindicated in women allergic to peanuts.

Estrogen-Only Therapy

This is recommended only in women who do not have a uterus. The role of unopposed estrogen in the development of endometrial neoplasia has been well documented.⁷ Infrequently, a woman with a uterus may elect to take unopposed estrogen, usually because of previous bleeding problems or adverse progestin-related side effects. However, these women need close follow-up and evaluation (see Chapter 10). Endometrial assessment should be performed annually, and may also be prudent as a baseline in women with other risk factors for endometrial cancer.

Progestin-Only Therapy

Progestins can be used to control vasomotor symptoms in women with contraindications to estrogen. Schiff et al. demonstrated the efficacy of MPA 20 mg daily in controlling vasomotor symptoms, while Loprinzi et al. used megestrol 20 mg twice daily to relieve hot flashes.^{19,20}

An obese woman is able to produce endogenous estrogen by peripheral conversion of androstenedione to estrone in adipose tissue.²¹ In addition, obese women have low serum concentrations of sex hormone-binding globulin (SHBG), resulting in a further increase in circulating free estrogen.²¹ These women have high concentrations of unopposed free

Table 6.5. Androgen preparations

Androgen	Trade Name	Strength (mg)
Oral		
Testosterone undecanoate	Andriol	40
Transdermal		
Testosterone	Androderm	12.2/patch
	AndroGel	2.5 g/packet, 5 g/packet, and 1.25 g/actuation (60 actuations)
Injectable		
Testosterone cypionate	Depo-Testosterone (Cypionate)	100 per mL (10 mL)
	Testosterone cypionate	100 per mL (2 mL and 10 mL)
Testosterone enanthate	Delatestryl	200 per mL (5 mL)
	PMS-Testosterone enanthate	200 per mL (10 mL)
Estradiol dienanthate (ED), estradiol benzoate (EB), and testosterone enanthate (TE)	Climacteron	7.5 ED + 1 EB + 150 mg TE/mL

estrogen; they are at risk of developing endometrial neoplasia and may have to take a progestin.

Estrogen-Androgen Hormone Therapy

Following menopause, a woman's total estrogen production decreases by 80% and androgen production decreases by as much as 50%.² Following bilateral oophorectomy, serum estrogen and androgen concentrations drop precipitously. The potential benefits of androgen treatment have been observed with the administration of relatively large doses of androgens. Androgen therapy is associated with virilizing effects (acne, alopecia, and hirsutism) and an adverse effect on the cholesterol-lipoprotein profile; potential benefits from this therapy must be weighed against the unwanted effects.²²

Potential indications for estrogen-androgen therapy are outlined in Chapter 4, while the androgen preparations used for HT are listed in Table 6.5.

CONTRAINDICATIONS TO ESTROGEN USE

The number of contraindications continues to decrease, as both knowledge and use of ET increase. Special considerations regarding the use of ET are discussed in Chapter 8.

The following conditions are usually considered absolute contraindications to estrogen replacement therapy:

1. unexplained vaginal bleeding prior to investigation;
2. acute liver disease; and
3. active thromboembolic disease.

The risk posed by estrogen use in a woman with a history of thrombosis is variable (see Chapter 8). The risk of recurrence of breast cancer following estrogen therapy is also unknown (see Chapter 10). Caution is recommended in women with a history of cardiovascular disease and hypertriglyceridemia (see Chapter 9). For all women, the severity of menopausal symptoms must be considered in light of the known risks and potential benefits of therapy.

CONTRAINDICATIONS TO PROGESTIN USE

The contraindications to use of progestins are:

1. known or suspected carcinoma of the breast;
2. undiagnosed vaginal bleeding; and
3. pregnancy.

There is insufficient evidence to support a contraindication to the use of progestins in patients with a history of thromboembolic disorders.

CONTRAINDICATIONS TO ANDROGEN USE

The use of androgen is contraindicated in women with extensive cardiac, hepatic, or renal disease.²³

DRUG INTERACTIONS

Hormone therapy might interact with several drugs. It is advisable to consult a pharmacist or a drug interaction reference when adding a new therapy to a woman receiving HT.

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Complementary and Alternative Medicine

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INTRODUCTION

Women between 45 and 64 years old are significant users of complementary and alternative medicine (CAM).¹⁻⁴ There is a strong consumer-driven need for substantial information regarding CAM, and health care providers should be prepared to answer patients enquiries and guide them into using products which actually have efficacy and safety data to back up their often exaggerated product claims.

The 1997 North American Menopause Survey (NAMS) found that 80% of respondents reported the use of interventions other than prescription medications. Many women report using complementary and alternative medicine for menopausal symptoms which include hot flashes, joint pain, sleep problems, forgetfulness, mood difficulties, and fatigue.^{3,5} The challenge for health care providers is to incorporate evidence-based non-prescription therapeutics into our practices as consumer demand increases for alternative treatments of their menopausal symptoms.

There is no question that the modification of diet and lifestyle can positively influence mid-life health. There are clear benefits of therapies involving dietary and lifestyle changes. Factors such as obesity, diet, exercise, and cigarette smoking affect the general health of all menopausal women. The cardio protective and anti-cancer effects of a diet low in saturated and trans-unsaturated fats and high in fibre has been shown to be beneficial.^{2,6-8} Cigarette smoking is a strong independent risk factor for cardiovascular disease, stroke, peripheral vascular disease, osteoporosis, and certain cancers.^{2,6-8} Weight-bearing exercise enhances well-being, promotes balance and agility, and has positive effects on bones and cardiovascular function.⁹ These are standard recommendations for a healthy lifestyle and prevention of heart disease and cancer. Bandolier's Summary of Advice on Healthy Living is a simple, concise summary of 10 lifestyle tips to decrease your risk of heart disease and cancers. Further details for healthy living can be found on the Bandolier home page at www.eBandolier.com. The general principles of healthy living can have a positive effect on hot flashes in menopausal women,¹⁰ as cigarette smoking and less

physical activity and a higher BMI (≥ 27) have been shown to increase the relative risk of hot flashes.¹¹ The menopausal transitional weight gain can be minimized with moderate caloric restriction combined with a modest increase in exercise.¹² The challenge is that despite the clear benefits of dietary and lifestyle modifications, adherence rates are often low. Therefore, a menu of alternative treatments for menopausal symptoms is required to meet the needs of all menopausal women.

HERBAL REMEDIES

The Natural Health Products regulations under the Natural Health Products Directorate (Health Canada) has changed the status of natural health products and remedies from food or dietary supplements to drugs. (See Table 7.1 for information on the Health Directorate.) Natural health products include herbs, vitamins, minerals, and homeopathics. Their mandate is "to ensure that all Canadians have ready access to natural health products that are safe, effective, and of high quality, while respecting the freedom of choice and philosophical and cultural diversity."

Health care providers and patients can report any adverse reactions. The forms for reporting can be found in the CPS. Consumers are advised to purchase only those brands with appropriate drug identification numbers (DINs) to ensure that they are getting a product that has been reviewed with regard to the product's formulation, labelling, claims, and instructions.

Tables 7.1 and 7.2 list selected general references for researching natural health products.

NON-PRESCRIPTION THERAPIES

Historically there have been a variety of herbal treatments that have been used to control menopausal symptoms.

Some of these remedies have provided short-term relief of symptoms, however data on long-term symptom relief, such as urogenital aging or disease prevention (osteoporosis and cardiovascular disease), is not available. As well, evidence is generally lacking regarding efficacy and long-term safety of herbal agents, and study populations usually only

Table 7.1. Recommended websites

Organization	Website*
Therapeutics Products Directorate (Health Canada)	http://www.hc-sc.gc.ca/ahc-asc/branch-dirigen/hpfb-dgpsa/tpd-dpt/index_e.html Issues advisories on products
American Botanical Council	http://www.herbalgram.org An on-line resource for herbal news and information
CAMline	http://www.camline.org An evidence-based website on complementary and alternative medicine for health care professionals and the public
Cochrane Collaboration Consumer Network	http://www.cochrane.org/consumers/homepage.htm Informs about consumer involvement in the Cochrane Collaboration
European Scientific Cooperative on Phytotherapy (ESCOP)	http://www.escop.com/ An organization that aims to advance the scientific status of phytomedicines
Memorial Sloan-Kettering Cancer Center	http://www.mskcc.org/mskcc/html/11570.cfm Provides information for oncologists and healthcare professionals, including a clinical summary for herbs, botanicals, and other products; details about constituents, adverse effects, interactions, and potential benefits or problems; and evaluations of alternative or unproved cancer therapies, as well as products for sexual dysfunction
National Centre for Complementary and Alternative Medicine, National Institutes of Health	http://nccam.nih.gov/ Explores complementary and alternative healing practices in the context of rigorous science
Canadian Health Network	http://www.canadian-health-network.ca/ Public Health Agency of Canada website with detailed information on many health topics, including complementary and alternative health
Passeport Santé (French Only)	http://www.passeportsante.net/fr/Accueil/Accueil/Accueil.aspx Aims to promote health and prevent illness through a combination of CAM and conventional medicine
The Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine	http://cpmcnet.columbia.edu/dept/rosenthal/ Promotes an inclusive medical system by using scientific inquiry to ensure that the valuable health practices of other cultures are better understood and integrated with Western medical practices

*Websites were accessed on December 5, 2005.

suffered mild symptoms. Black cohosh and foods that contain phytoestrogens do show some promise for treatment of menopausal symptoms.¹³ The phytoestrogen or isoflavone content of foods varies significantly. The epidemiological evidence regarding phytoestrogens is derived from a typical Asian diet, which is also a low-fat diet. It is unknown whether a typical North American diet will benefit from the addition of a diet rich in phytoestrogens. A recent systematic review of phytoestrogens for the treatment of menopausal symptoms concluded that “the available evidence suggests that phytoestrogens available as soy foods, soy extracts, and red clover extracts do not improve hot flashes or other menopausal symptoms.”¹⁴

Tables 7.3 and 7.4 focus on the single-agent preparations that are the most commonly used for short-term relief of menopausal symptoms. The tables are organized to distinguish between those agents with available data and agents without available data to support their use (lack of efficacy or safety concerns).

COMPLEMENTARY APPROACHES

There are other non-herbal approaches to handle menopausal symptoms. Lifestyle modification, including practices that lower core body temperature, such as using a fan, dressing in layers, and consuming cold food and drinks, may temporarily help with night sweats and flushing. Relaxation techniques can decrease symptoms.^{10,33} Meditation,

Table 7.2. Selected Reference Texts

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exercise, smoking cessation, and weight loss may be helpful.^{10,11,33} Acupuncture has been shown to be an alternative treatment of vasomotor symptoms in postmenopausal women in a few small studies.^{34,35} At present, there is not enough evidence to recommend acupuncture for the treatment of vasomotor symptoms (NAMS position statement).³⁶ Reflexology has not been shown to be effective in controlling symptoms of menopause.³⁷

CONCLUSION

Non-prescription therapeutics including some herbal and complementary treatments can help with the symptoms of menopause. However, health care providers and consumers should be aware that despite the potential usefulness of many of these therapies, scientific research in the area of complementary and alternative therapies is limited at this time. It is important to note that there is no long-term safety data on herbal remedies. Consumers should be made aware that natural products do have side effects and can cause adverse reactions not unlike pharmaceutical therapies. There is also the potential for serious drug interactions. Awareness of evidence-based complementary and alternative therapies allows the health care provider to offer safe non-pharmaceutical choices of treatment to women with menopausal symptoms.

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Table 7.3. Selected Non-Prescription Therapies for Menopausal Symptoms

Name	Use	Dose	Comments
Black cohosh (cimifuga racemosa, remifemin) ^{13,15}	Vasomotor symptoms	20 mg tablet twice daily	Side effects: nausea, vomiting, bradycardia, hypotension, increased perspiration Interactions: anesthetics, antihypertensives, sedatives (may increase hypotensive effect) Estrogen supplements, hormonal contraceptives (may increase effects or compete with ERT for estrogen receptors, reducing effects of both therapies) Contraindications: Patients with a history of estrogen-dependent tumours (estrogen receptor-positive breast cancer), uterine cancer, or thromboembolic disorders Special considerations: Monitor blood pressure closely in hypertensive patients on an anti-hypertensive or sedative. Discontinue black cohosh 2 weeks before surgery to avoid hypotensive reactions with anesthetics.
Red clover-derived isoflavone (Promensil) ^{13,14,16}	Vasomotor symptoms	80 mg tablet daily (DIN available)	Side effects: breast tenderness, breast enlargement, weight gain Interactions: anticoagulants (heparin, warfarin), antiplatelet drugs (aspirin, clopidogrel, ticlopidine), increase risk, of bleeding hormonal contraceptives increase effects by increasing estrogen components. Contraindications: Patients with estrogen receptor-positive neoplasia Special considerations: Use cautiously in patients susceptible to bleeding problems or those on anticoagulants. Discontinue red clover-derived isoflavone 2 weeks before surgery.
Vitamin E (tocopherol) ^{17,18}	Vasomotor symptoms	800 IU daily DIN available)	Slight decrease in hot flash frequency (1 less hot flash per day). Long-term use of vitamin E of doses 400 IU increases all-cause mortality.¹⁸ Side effects: Vitamin E has anticoagulant properties. Increased risk for hemorrhagic stroke. Interactions: May displace other fat-soluble antioxidants disrupting the natural balance of antioxidant systems. Special considerations: Use cautiously in patients susceptible to bleeding problems or those on anticoagulants. Discontinue 2 weeks before surgery.
St. John's Wort (hypericum perforatum) ^{15,19,20}	Mild to moderate depression	300 mg 3 times daily (DIN available)	Side effects: dizziness, restlessness, sleep disturbance, dry mouth, constipation, nausea, diarrhea, phototoxicity of skin, allergic hypersensitivity. Interactions: alcohol, MAO inhibitors, SSRIs, narcotics, over-the-counter cold and flu medications, sympathomimetics, tyramine-containing foods, digoxin, warfarin, theophylline, indinavir, cyclosporin, drugs metabolized by CYP3A reduces their activity Contraindications: MAO inhibitors, SSRIs, history of allergy to St. John's Wort Special considerations: Exercise caution when using with drugs metabolized by CYP3A (reduces their activity).
Valerian (valerian officinalis) ^{15,21-25}	Sleep disturbances	400–900 mg at bedtime (DIN available)	Side effects: excitability, headache, cardiac disturbances, blurred vision, nausea, hepatotoxicity, hypersensitivity reactions Interactions: alcohol, CNS depressants, additive effects with sedatives or hypnotics. Contraindications: patients with hepatic dysfunction, patients on other sedatives, hypnotics or those with alcohol dependency Special considerations: Discontinue 2 weeks prior to surgery

Table 7.4. Products Where Available Data Does Not Support Use for Menopausal Symptoms

Name	Use	Dose	Comments
Kava (kavapyrone) ^{15,26-28}	Anxiety	70–110 mg t.i.d. (No agreed-upon standards exist. Formulations of kava vary in their actual content.)	Side effects: headache, dizziness, changes in judgment and motor reflexes, vision changes, hypertension, diarrhea, liver damage including hepatitis and liver failure, blood dyscrasias (decreased platelet and lymphocyte counts), weight loss, shortness of breath, hypersensitivity reactions of the skin, reddened eyes, galactorrhea and breast engorgement Interactions: alcohol (increases kava toxicity), alprazolam (may cause coma), benzodiazepines (causes additive sedative effects), digoxin (increases digoxin toxicity), levodopa (increases parkinsonian symptoms), phenobarbital (additive effects). Contraindications: Avoid administration with psychotropic drugs. Use cautiously in patients with neutropenia, renal disease or thrombocytopenia. Do not use in patients with liver disease. Special considerations: Safety information has not been routinely collected. Significant adverse reactions may occur with long-term use. Caution patient to avoid alcohol and other CNS depressants, as they enhance kava's sedative and toxic effects. Absorption of kava may be enhanced if taken with food.
Soy-derived isoflavones, genistein, and daidzein ^{13,14}	Vasomotor symptoms	25–40 mg daily	Randomized, controlled clinical trials have shown that hot flashes are not reduced or only slightly diminished in women who consume soy extracts or soy foods. ^{13,14} Side effects: breast tenderness, breast enlargement, flatulence Interactions: Administration of levothyroxine concurrently with soy protein results in decreased absorption of levothyroxine. Do not administer together. Contraindications: Patients who are sensitive to soy products and those with estrogen dependent tumours.
Chaste tree (Vitex) ¹⁵	Vaginal dryness, depression, mastalgia	20 mg capsule daily	Human data supporting claims are sparse.
DHEA ¹⁵	Vasomotor symptoms	Variable	DHEA doses over 25 mg/d should be avoided in women because of reports of irreversible voice changes and hirsutism. Data lacking about proper dose and long-term effects. Side effects: headache, acne, hair loss, hirsutism, oily skin
Wild yam ²⁹	Menopausal symptoms	Variable (topical)	Little effect on symptoms
Ginkgo biloba ³⁰	Memory impairment	120–240 mg in divided doses (DIN available)	Available data does not support use in healthy adults with normal cognition. Side effects: headache, GI upset, insomnia, skin reaction, bleeding Interactions: anticoagulants, antiplatelets, insulin, oral hypoglycemics (causes elevated blood glucose levels)
Ginseng (Panax ginseng) ^{15,31}	Cognitive function	No consistent dose recommendations	Available data does not support use. No consistent quality control. No consistent dose or formulation recommendations. Side effects: headache, insomnia, nervousness, epistaxis, hypertension, palpitations, GI upset, mastalgia, vaginal bleeding, pruritus Interactions: anticoagulants, insulin, diabetic drugs Contraindications: MAO inhibitors
Dong quai ^{15,31}	Vasomotor symptoms	500 mg t.i.d.	Available data does not support use Side effects: bleeding, increased skin photosensitivity, diarrhea Interactions: anticoagulants, antiplatelets
Evening primrose oil ^{13,32}	Vasomotor symptoms	3–4 g/d	Available data does not support use. No benefit over placebo for vasomotor symptoms. Side effects: headache, nausea, rash Interactions: phenothiazines (increased risk of seizures)

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Specific Medical Considerations

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WOMEN WITH PREMATURE OVARIAN FAILURE, PREMATURE, OR EARLY MENOPAUSE

Much attention has been paid to the risks and benefits of hormone therapy (HT) in older postmenopausal women, and to changes in the paradigm for HT in women at physiologic menopause, leading to confusion about the health and management issues for women undergoing an early onset of menopause. Women may experience premature menopause (prior to the age of 40) because of premature ovarian failure (POF), or through damage of ovarian function. Similarly women may experience an earlier menopause (ages 40–45) through normal distribution around the mean, or because of ovarian damage. These conditions require specific assessment and management.

Premature Ovarian Failure

Diagnosis

POF is not early menopause; it affects 1% of women under the age of 40.¹ A definition of POF is amenorrhea and consistently high follicle-stimulating hormone (FSH) levels in women under 40. In the absence of a clear cause, such as chromosomal abnormalities or induced menopause, a high incidence of biochemical, clinical or familial autoimmune disorders leads to the presumptive diagnosis of autoimmune POF.¹ Evaluation for other autoimmune disorders including thyroid, parathyroid, and adrenal disorders; systemic lupus erythematosus; and diabetes mellitus is recommended. The diagnosis can be extremely distressing to the woman affected, and clinicians must exercise sensitivity in communicating with women about this condition and its potential health implications. Spontaneous remissions may be experienced by between 5% and 25% of all women with presumed POF. The use of the term menopause in particular has a connotation of premature aging and may lead to confusion. The preferred diagnostic description is therefore POF.^{2,3}

Management

Due to the risk of health consequences such as osteoporosis and sexual dysfunction, long-term HT should be offered to all women with POF.⁴ In younger women, higher doses of

estrogen, and possibly androgen, than are usually required in older postmenopausal women may be needed to relieve symptoms. Oral contraceptives may be used to achieve symptom relief. Women with POF appear to be at risk of premature cardiovascular disease. In women of normal karyotype, new research shows that there is an early onset of endothelial dysfunction associated with POF, which is restored to normal by HT within 6 months of treatment.⁵ Women with POF on HT will be exposed to lower monthly estrogen levels than if they had spontaneous menstrual cycles. Recommendations to use HT, for symptoms only and for the shortest duration possible in the lowest dose, are not applicable. HT would normally be offered until the usual menopausal age, thereafter as a matter of a decision between a woman and her physician.

Many women with POF will have fertility concerns. In the absence of a spontaneous remission, oocyte donation offers the best potential for allowing conception.⁶

Induced and Early Menopause

Induced menopause, whether from surgery, ionizing radiation, or chemotherapy is unlike natural menopause in that the ovarian sources of androgen and estrogen are removed prematurely and simultaneously. This may have different physiologic effects on rate of loss of bone mass, rates of atherosclerosis, vulvo-vaginal atrophy, and libido than natural menopause.

USE OF HT IN CANCER SURVIVORS

With the exception of meningioma, breast, and widespread endometrial cancer, there is no biological evidence that HT may increase the risk of recurrence.⁷ Thrombosis risk should be assessed as some cancers are known to increase risk of venous thromboembolic disease (VTE).⁸

Gynecologic Conditions

Endometriosis

Combined HT in standard doses does not appear to cause regrowth of endometriosis in postmenopausal women, nor in women receiving estrogen-progestin “add-back” therapy

following medical oophorectomy with gonadotropin-releasing hormone (GnRH) analogues.⁹ A small subgroup of women may experience recurring pain and other symptoms during unopposed ET, particularly if residual disease remains following definitive surgery.

In a prospective randomized trial of HT among women with endometriosis who underwent bilateral salpingo-oophorectomy (BSO), there was no recurrence at 45 months in those who did not receive HT. There was recurrence of 0.9% per year in those on HT. If more than 3 cm peritoneal involvement was detected at the initial surgery, there was a 2.4% recurrence per year, and if there was incomplete surgery, there was a 22.2% recurrence.¹⁰

In the absence of evidence from randomized studies, symptomatic endometriosis, or large residual volumes of endometriosis may be an indication for progestin therapy following hysterectomy, either as part of a continuous-combined regimen or as progestin-only therapy.¹¹

There are case reports of endometrial cancer developing in residual endometriosis in women receiving unopposed estrogen therapy, as well as in obese women with high endogenous estrogens, following abdominal hysterectomy and BSO for endometriosis.¹²⁻¹⁶

Women with a history of endometriosis can be offered HT for menopausal symptoms, using the lowest effective dose of ET. There are no convincing data to support the routine use of combined estrogen-progestin rather than ET for women with a history of endometriosis, nor is there evidence that use of progestin-only therapy or the withholding of estrogen for 6 months following definitive surgery will reduce the risk of recurrence or malignancy. This remains a matter of clinical judgment and informed choice.¹⁷

Fibroids

Although uterine fibroids do not constitute a contraindication to HT, both estrogen and progestin can influence fibroid growth. The doses in conventional HT regimens are usually not sufficient to cause enlargement of fibroids. HT use for more than 5 years is associated with a 1.7-fold increased risk of subsequent leiomyomas only among those with a low body mass index.¹⁸ However, rapid growth or abnormal bleeding from a pre-existing submucous fibroid requires investigation and possibly surgical intervention. Leiomyoma cells convert circulating androstenedione into estrone via aromatase and then into the active E2 via 17 β -hydroxysteroid dehydrogenase type 1. In situ estrogen plays a role in growth in hypoestrogenic conditions such as natural menopause. Aromatase inhibitors may in the future be used therapeutically to inhibit both leiomyomatous and ovarian estrogen production.¹⁹

Early onset of menopause arising spontaneously exposes women to a greater risk of estrogen-deficiency related

changes. Unlike women with POF, they are not at increased risk of autoimmune or associated disorders.¹ Conversely, women with early menopause are at very low risk for age-related conditions such as deep venous thrombosis (DVT) or stroke. For these reasons, current recommendations to use HT in typical menopause, for symptoms only and for the shortest duration possible in the lowest dose, are not applicable to these distinct populations.

Preoperative State

The SOGC's Policy and Practice Guidelines Committee has drafted guidelines for the prevention and treatment of VTE in gynaecological surgery.²⁰ These guidelines suggest that, in the absence of data from randomized studies, hormone therapy should be considered as constituting a risk for post-operative VTE. Women who undergo pelvic surgery should be given appropriate thromboembolic prophylaxis.^{8,21} Transdermal estrogens may have less impact on coagulation factors than oral estrogens,²² but are not an alternative to accepted means of thrombo-prophylaxis.

Wound Healing

Venous ulcers, pressure sores, and burns occur frequently in elderly institutionalized women. Animal and limited human studies suggest that wound healing may accelerate with estrogen replacement therapy (ERT), improving the inflammatory and proliferative phase of wound repair, as well as tissue angiogenesis.²³ Growth factors play an integral role in modulating wound repair and may be enhanced by ET.²⁴ HT may have a protective effect on the occurrence of venous ulcers of the lower limbs.²⁵ Further investigation in this field is needed. HT is not currently indicated for wound healing, nor for prophylaxis.

Metabolic and Endocrinologic Conditions

Diabetes Mellitus

Diabetes is associated with a number of adverse health risks, notably cardiovascular disease.²⁶ The incidence of diabetes is increasing, excess weight and inactivity are 2 contributing factors. This section reviews the evidence surrounding HT and diabetes.

HT AND THE INCIDENCE OF DIABETES.

Recent analysis of the HER Study data suggests that HT reduces the risk of developing diabetes (Level 1). The incidence of developing diabetes was 6.2% in the HT group and 9.5% in the placebo group. In women with coronary disease, HT reduced the incidence of diabetes by 35%.²⁷

METABOLIC EFFECTS OF HORMONAL THERAPY

In postmenopausal type II diabetics, an improvement in glycemic control and serum lipoproteins was demonstrated after 8 weeks of conjugated estrogen (CE) therapy.²⁸ Estrogens alter glucose and insulin metabolism in different ways, depending on the compound used and route of

delivery.²⁹ Estradiol-17 β reduces insulin resistance through improvements in insulin sensitivity and elimination. Diabetic women in the NHANES III project currently taking HT have better glycemic control and lipoprotein profiles.³⁰ HT was significantly associated with decreased HgA1C levels in a multiethnic population of 15 435 women with type II diabetes.³¹ This provides reassurance regarding the metabolic effects of hormone therapy in diabetic women.

CARDIOVASCULAR DISEASE

Evidence for the impact of HT on the risk of cardiovascular disease in postmenopausal diabetic women is inconsistent. The Women's Health Initiative (WHI) trial did not show any difference between coronary heart disease (CHD) risk in diabetic and non-diabetic women.³² Diabetic women on HT may benefit from the addition of statins.³³

HORMONE THERAPY—DIFFERENCES BETWEEN REGIMENS

Several studies have demonstrated increased levels of triglycerides, C-reactive protein, and coagulation factor³⁴ in women treated with CE and medroxyprogesterone acetate (MPA). In diabetic women, there may be advantages in minimizing these metabolic effects.

TRANSDERMAL ROUTE OF DELIVERY

Hypertriglyceridemia can be aggravated with oral estrogens and may be an underlying health concern in some diabetic women. Transdermal delivery does not have this effect, and appears to be preferable.

ALTERNATIVE ORAL REGIMENS

There has been limited research into alternative oral formulations of HT on lipoproteins and coagulation factors.³⁵

LOW-DOSE HORMONE THERAPY

Recent work shows preservation of beneficial lipid profile and vascular vasodilatation with low-dose CE in non-diabetic women and absence of inflammatory and clotting changes that were observed with high-dose CE.³⁶ Continuous combined HT in postmenopausal women with type II diabetes showed beneficial effects on lipoprotein concentrations and improved some markers of coagulation and glycemic control.³⁷

There may be more suitable regimens, routes of delivery, and dosages than the conventional CE and MPA for women at high risk of CVD, but there is no clinical evidence of superiority of any single approach. This area requires more study.

Hypoactive Thyroid Disease

Autoimmune hypothyroidism is approximately 10 times more common in women than in men, with an exponential rise in its occurrence after menopause.³⁸ It is unclear whether this increase has any relationship to the withdrawal of circulating estrogen at menopause, or whether the incidence is lower in women who use HT.

Women with thyroid disease are at an increased risk of osteoporosis. The use of thyroxine is associated with an increased risk of osteoporosis,³⁹ and recent data suggest that risk of fracture is also increased. Hip fracture risk was also increased in women with previously diagnosed Graves disease (relative risk [RR], 1.8).⁴⁰ Bone density should therefore be monitored.

Elevation of serum levels of thyroid-binding globulin (TBG) occurring with oral HT reduces free thyroxine levels. Transdermal estrogen may be preferred in hypothyroidism since it does not alter TBG.⁴¹

Gallbladder and Liver Disease

GALLBLADDER DISEASE

Current use of oral estrogen may carry a 1.8-fold increased risk of gallbladder (GB) disease in the cohort Nurses' Health Study.⁴² Long-term use of more than 5 years carried a 2.5-fold increase in risk compared to non-use. The risk of cholecystectomy appears to increase with dose and duration of use, and to persist for 6.8 years after stopping treatment.⁴³ Other risk factors for GB disease include obesity and central adiposity. The transdermal route of estrogen administration in the past was thought to exert no effect on GB disease. A recent study documented similar changes in bile lipids and cholesterol following use of oral or transdermal E2, suggesting that both routes of administration may increase gallstone formation.⁴⁴

The WHI has now reported biliary tract outcomes. This RCT of oral HT also found a 2-fold greater risk for GB disease or GB problems resulting in surgery, and a higher risk for cholecystitis and cholelithiasis with estrogen and with estrogen and progestin.⁴⁵

CHRONIC LIVER DISEASE

HT is not contraindicated in patients with chronic liver disease who have normal liver function tests.⁴⁶ In women with pre-existing liver disease, such as primary biliary cirrhosis, it may be advantageous to deliver estrogen by a transdermal route in order to avoid alterations in liver metabolism.⁴⁷

Hepatic hemangiomas and adenomas are influenced by both endogenous and exogenous female sex hormones and only enlarge significantly in a few patients. Routine liver ultrasound follow-up in those women on HT with these hemangiomas appears appropriate since 23% enlarged on HT compared to 10% of those in controls.⁴⁸ Hormone therapy is not advised in women with hepatic adenomas.

Migraine

Various internal and external factors may trigger migraine headache. Genetic predisposition may set a lower threshold for these triggers.⁴⁹ In women, fluctuating or falling levels of estrogen appear to be a trigger.⁵⁰ Some women have a history of menstrual migraine, and migraine incidence may

increase in the menopausal years.⁵¹ In perimenopause, a minority seems to be more susceptible to fluctuating hormone levels in the menstrual cycle.⁵²

A population based study examined the relationship between migraine and hormone therapy in postmenopausal women. The odds ratio for migraine was 1.42 (95% confidence interval [CI], 1.24–1.62) for women who were current users of HT compared with women who had never used HT.⁵³ Although the influence of HT on migraine varies with the individual woman, most evidence suggests a worsening of headaches with use of HT.⁵⁴ Conversely, there appears to be a decrease in risk for migraine without aura in postmenopausal women.⁵⁵ The constant daily hormone doses of a continuous-combined regimen are better tolerated than a cyclical regimen.⁵⁶ Transdermal estrogen may similarly afford more steady-state dosing and thus less provocation of migraine headache.^{57,58} Women with a history of atypical migraines provoked by oral contraceptives will be concerned about the risk of either provoking headaches with systemic HT or causing a permanent neurological abnormality. There are few relevant studies for guidance.

If neurological symptoms or signs develop or worsen with use of HT, it is advisable to withdraw treatment and seek neurological consultation for assessment of any abnormality. If it is determined that this is an atypical migraine, reintroduction of HT at a lower dose may be attempted if warranted by the potential benefits.⁵⁴ Informed consent for treatment is essential.

Connective Tissue Disorders

Systemic Lupus Erythematosus

A modest decrease in disease activity is seen in systemic lupus erythematosus (SLE) after natural menopause.⁵⁹ Data from the Nurses' Health Study show that postmenopausal HT is associated with a 2-fold increase in the risk of developing SLE.⁶⁰ The role of estrogen therapy in exacerbating pre-existing SLE is unclear to date, although the large randomized controlled trial (SELENA) studying the safety of HT in SLE is currently under way.⁶¹

HT may also exacerbate the prothrombotic tendency that exists in patients with antiphospholipid antibody syndrome.⁶¹ At present, most authors recommend that HT be used with caution in patients with active disease. Patients with inactive or stable/moderate disease and at low risk for thrombosis may benefit from HT without a change in disease activity.⁶² A 1-year transdermal estrogen and oral MPA RCT prevented bone loss at the lumbar spine and femur in postmenopausal women with SLE with no increase in disease activity.⁶³

Rheumatoid Arthritis

Hormone therapy has not been shown to prevent the development of rheumatoid arthritis (RA) in postmenopausal women.^{64,65} Similarly, data from double-blind RCTs have shown no convincing effect of HT on the clinical course or disease markers of RA.^{66,67} A prospective cohort study showed estrogen and other female reproductive risk factors are not strongly associated with the development of RA in elderly women.⁶⁸ Women with RA have diminished bone mass for several reasons, including use of corticosteroids and immobility. They also have an increased risk of fracture.⁶⁷ These risks are further exacerbated by postmenopausal osteoporosis. Other treatment options for osteoporosis should be strongly considered in these patients.

RECOMMENDATIONS

1. HT should be offered to women with POF or early menopause (IA), and its use can be recommended until the age of natural menopause (IHC).
2. ET can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (IA)
3. Menopausal women undergoing pelvic surgery should be given appropriate thromboembolic prophylaxis. (IA)
4. Health care providers may prescribe HT to diabetic women for the relief of menopausal symptoms. (IA)

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Cardiovascular Disease

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INTRODUCTION

More women entering menopause today have had the advantage of growing up with access to better nutrition, preventive health care, and information about healthy living. Over the past 25 years, the risk of heart disease, for example, has progressively fallen.¹ In spite of these advances in health status, cardiovascular disease (CVD) is still a leading cause of morbidity and mortality in postmenopausal women.

SOGC Clinical Tip

The onset of menopause is an ideal time to address CVD risk and to calculate such risk using the Framingham score. Such a risk score can be used to counsel a woman about the importance of CVD, initiate lifestyle changes, and guide pharmacotherapy.

Half of all postmenopausal women will develop coronary artery disease (CAD) and one-third will die from this disease. A majority of Canadian women (80%) have at least one risk factor for CAD.² The risk for CVD rises with age and increases significantly after menopause. The incidence of CAD may lag behind men by as much as 10 to 15 years until well into the seventh decade. Stroke is also a leading cause of death and disability for women, especially in older postmenopausal women. This translates into a substantial effect on mortality for Canadian women (38 345 deaths in 2000).³ Although premature menopause is identified as a risk factor for cardiovascular mortality,⁴ this association may be affected by other confounders such as major cardiovascular risk factors.^{5,6} Nevertheless, these observations have prompted suggestions that hormone therapy (HT) might reduce CVD risk in postmenopausal women.

SOGC Clinical Tip

A majority of Canadian women (80%) have at least one risk factor for CVD.

Estrogen has both rapid and longer-term actions on the cardiovascular system.⁷ These rapid actions are non-genomic and cause vasodilatation. The longer-term actions are genomic, mediated by estrogen receptors, and affect vascular injury responses and atherosclerosis. Thus estrogen may promote cardio-protective effects by reducing LDL cholesterol, raising HDL cholesterol, inhibiting oxidation of LDL particles, improving endothelial function and lowering levels of factors such as Lp(a), fibrinogen, and plasminogen-activator inhibitor type 1.^{8,9} On the other hand, adverse physiological effects on inflammation (as measured by C-reactive protein) and markers of thrombosis may counteract the beneficial effects and may also be important in the observed increased risk of stroke and venous thromboembolism.¹⁰ In contrast to oral hormone therapy, transdermal estrogen does not have significant effects on some markers of thrombosis or inflammation.¹¹ The addition of progestins modulates estrogen's cardiovascular effects;¹² however, non-androgenic progestins may have fewer adverse effects.¹³ Altogether, these surrogate measures had provided over-all substantial biological plausibility concerning a favourable role for HT in the prevention of CVD.¹² These experimental results and observational studies had provided the bulk of the evidence for a protective or beneficial role for HT in CVD until the results of randomized controlled trials (RCTs) were published or other surrogate endpoints (such as angiographic assessment of coronary atherosclerosis or carotid intima-media thickness) were reported.

Observational studies of primary prevention of CVD have consistently shown that postmenopausal women who use estrogen with or without a progestin have a lower rate of coronary events than those who do not. Results from the Nurses' Health Study of more than 116 000 women over more than 20 years indicate that current users of HT have a 40% lower risk of CAD than women who never used HT¹⁴⁻¹⁷; these data were also been confirmed in earlier meta-analyses. A more recent meta-analysis of these observational studies, however, did not show any evidence of overall protection from CVD once results were controlled for confounding factors such as socioeconomic status,

education, and major coronary risk factors.¹⁸ As detailed in several articles, there may be a number of explanations (both methodological and biological) for the apparent divergent findings of observational studies and RCTs, including the fact that benefit in these observational epidemiological studies may have occurred because the HT users in the population were healthier than non-users.¹⁹⁻²²

SOGC Clinical Tip

HT has complex and often competing cardiovascular, biochemical, and physiological effects that are modulated by the type of HT and a woman's own cardiovascular risk.

CLINICAL TRIALS IN WOMEN WITH KNOWN CORONARY ARTERY DISEASE

The first randomized trial with clinical endpoints, The Heart and Estrogen/Progestin Replacement Study (HERS), a secondary prevention trial of continuous-combined conjugated estrogen (CE) and progestin (MPA), did not demonstrate any overall reduction in cardiovascular events (nonfatal MI and heart disease deaths) over 4 years of treatment.²³ This lack of benefit occurred despite improved surrogate endpoints as had been seen in the PEPI trial.¹² There was an increased risk (relative risk [RR], 1.57) of a second cardiovascular event in the first year of treatment that was not found in subsequent years 4 and 5. However, extended follow-up of HERS participants did not show evidence of cardiovascular benefit associated with EPT treatment during 6.8 years of observations.²⁴

Other secondary prevention trials followed the initial HERS results, some using different formulations of HT or endpoints. The Estrogen Replacement and Atherosclerosis study (ERA) compared the effects of oral CEs and combined CE-MPA therapy in postmenopausal women with established coronary disease. This trial showed no effect of either treatment on the progression of angiographically demonstrated coronary disease over 3 years.²⁵ The Women's Angiographic Vitamin and Estrogen Trial (WAVE), using a 2x2 factorial design of vitamins and CE or CE plus MPA in women with coronary disease, reported greater angiographic progression of atherosclerosis and an increase in clinical CVD events in those women on HT.²⁶ In the Estrogen in the Prevention of Reinfarction Trial (ESPRIT-HRT), there was no difference in CVD events or all-cause mortality at 2 years in women treated with estradiol valerate or placebo post-myocardial infarction.²⁷ Transdermal estradiol with or without norethindrone was not found to be beneficial in preventing CVD events in women with proven coronary disease after more than 2 years in the Papworth HRT Atherosclerosis Study.²⁸ The

Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) did not demonstrate a significant effect on progression of coronary atherosclerosis in women treated with 17 β -estradiol with or without MPA.²⁹ These secondary prevention trials initiated therapy in most women who were many years postmenopausal and excluded women who had vasomotor symptoms.

SOGC Clinical Tip

HT does not prevent CAD but does increase the risk of cardiovascular events in the first year of treatment in older postmenopausal women.

CLINICAL TRIALS IN WOMEN WITHOUT KNOWN CORONARY ARTERY DISEASE

Non-invasive B-mode ultrasonographic measurement of progression of carotid artery intima-media thickness is a useful surrogate end point for clinical coronary events because it can measure clinically relevant effects on atherogenesis.³⁰ Two trials have assessed the effects of 17 β -estradiol using this technique in healthy, but high risk, women. In the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), 222 postmenopausal women were randomized to 2 years of treatment with micronized 17 β -estradiol or placebo.³¹ For these women with elevated LDL cholesterol but no pre-existing coronary disease, treatment with 17 β -estradiol reduced the rate of progression in carotid intima-media thickness (0.0053 mm difference in thickness). In those women who did not use lipid-lowering medication, the difference (benefit of unopposed ERT) in the average rates of atherosclerosis progression was even greater ($P = 0.002$). However, the Postmenopausal Hormone Replacement against Atherosclerosis (PHOREA) trial found no effect of 17 β -estradiol combined with a progestin on progression of carotid intima-media thickness in a study of 321 postmenopausal women followed for one year.³² Other modalities that can non-invasively evaluate atherosclerosis, including CT scan for coronary calcification and MRI, as well as methods to measure endothelial dysfunction, require further assessment in randomized clinical studies.^{30,33} Although such small trials do suggest interesting mechanistic data, randomized clinical trials are thought to provide the strongest evidence for HT and CVD outcomes.

The NHLBI-sponsored landmark Women's Health Initiative (WHI) trial was the first randomized primary prevention trial of HT designed to provide CVD event outcomes. The Women's Health Initiative Estrogen + Progestin trial randomized 16 608 postmenopausal women with intact uteri to CE 0.625 mg per day with MPA 2.5 mg per day or

placebo.³⁴ One primary outcome was a composite of nonfatal MI and coronary death, for which there was no cardiac protection observed among women assigned to HT (hazard rate [HR], 1.24; 95% confidence interval [CI], 1.00–1.54).³⁵ However, there was risk in the first year of treatment (HR, 1.81; 95% CI, 1.09–3.01). The companion Women's Health Initiative estrogen-alone trial randomized 10 739 women with prior hysterectomy to CE or placebo.³⁶ There was no coronary disease benefit (HR, 0.91; 95% CI, 0.75–1.12) after 6.8 years of follow-up. Overall, the absolute risk for coronary events is low, but there may be an early hazard effect as was seen in HERS. As with the secondary prevention trials, these 2 large primary prevention trials were conducted in predominantly asymptomatic older postmenopausal women. There are no RCTs specifically addressing CVD outcomes with HT for younger perimenopausal women.

CLINICAL TRIALS IN PERIPHERAL ARTERIAL DISEASE

There have been no clinical trials of HT with peripheral arterial disease outcomes as a primary outcome. There was no protection against peripheral artery disease (carotid disease, lower extremity arterial disease, abdominal aortic aneurysm) in the WHI Estrogen and Progestin Trial.³⁷ Similarly, HT was neutral in the prevention of peripheral arterial disease in women with coronary disease in the HERS trial.³⁸

CLINICAL TRIALS IN STROKE

Observational studies of HT (predominantly with estrogen) have provided inconsistent evidence for protection against stroke, although the large Nurses' Health Study had found a dose-response relation between estrogen and risk of stroke and an association between the use of progestin and stroke.¹⁷ Both arms of the WHI have found an increased risk of stroke: HR 1.41 (95% CI, 1.07–1.85) for the combined trial and HR 1.39 (95% CI, 1.10–1.77) for the estrogen-alone study.^{34,36} This risk was seen in both arms and implies that it is the estrogen component that may be responsible. The increased risk was confined to ischemic as opposed to hemorrhagic stroke. In the HERS cohort, although a secondary outcome, use of HT had no effect on the risk of stroke or transient ischemic attack (TIA) in women with established cardiovascular disease; the reported HR was 1.23 (95% CI, 0.89–1.70).³⁹ The Women's Estrogen for Stroke Trial (WEST), an RCT of 17 β -estradiol in postmenopausal women with a previous history of stroke or TIA, did not find a reduction in risk of recurrent stroke after 2.8 years of treatment.⁴⁰ A meta-analysis of randomized trials of HT reported an HR of 1.30 (95% CI, 1.13–1.47) for total stroke, with those taking HT having a worse outcome.⁴¹ All indicate that postmenopausal HT is

not effective for reducing the risk of a recurrent stroke among women with established vascular disease or for preventing a first stroke.

VENOUS THROMBOSIS

Observational studies have shown at least a 2-fold increased risk for venous thromboembolism (deep venous thrombosis and pulmonary embolism) in postmenopausal women prescribed HT.^{42–44} In the WHI combined study, the overall risk of venous thromboembolism during more than 5 years of use was significantly elevated (HR, 2.06; 95% CI, 1.57–2.70).⁴⁵ There was an additive risk of this HT regimen with known risk factors of thrombosis such as increasing age, overweight, and obesity, as well as Factor V Leiden, thus highlighting the interaction of such risk factors. In the WHI estrogen-alone arm, this risk was attenuated with an overall HR of 1.33 (95% CI, 0.99–1.79).³⁶ The HERS results indicated that, in postmenopausal women with known CAD, use of HT is associated with a 3-times greater risk for venous thrombosis (HR, 2.7; 95% CI, 1.4–5.0).⁴⁶ In HERS, most of these events occurred in women at risk for venous thromboembolic disease (VTE) because of cancer, lower extremity fracture, and immobilization. Biochemical data and some clinical studies suggest that transdermal estrogen therapy may carry less risk of thrombosis than oral therapy.^{47,48}

SOGC Clinical Tip

HT (with estrogen) increases the risk of stroke and venous thromboembolism, especially in older postmenopausal woman with risk factors for these conditions.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) are non-hormonal agents that bind to estrogen receptors and may produce either estrogen-agonistic or estrogen-antagonistic effects, depending on the target tissue.⁴⁹ One SERM, raloxifene, did not show any increase in CVD.⁵⁰ Raloxifene, similar to oral estrogen, increases the risk for venous thromboembolism. There are no completed clinical trials of selective estrogen receptor modulators with primary cardiovascular outcomes.

CONCLUSION

CVD is the leading cause of death and an important contributor to morbidity and disability in women. It is largely preventable. Stroke, in particular, is especially prevalent in older postmenopausal woman. Efforts should focus on reducing the risk of CVD among women in known and effective ways. Unfortunately, there are persisting data

indicating that CVD is undertreated in women or that women do not recognize the importance of CVD.⁵¹⁻⁵³ Women should receive counselling about lifestyle modifications (smoking cessation, maintenance of a normal body weight, regular moderate to vigorous physical activity, and consumption of a heart-healthy diet) because of the beneficial effects of these strategies. In addition, pharmacotherapy of hypertension and dyslipidemias should be used when indicated. For women who already have established heart disease or who have been identified as high risk according to risk calculations such as the Framingham score, lifestyle modification, including control of hypertension and diabetes, assume heightened importance because of their greater mortality associated with acute coronary events, such as myocardial infarction and worse outcomes from stroke.^{30,54} Therapy with anti-platelet agents (such as acetylsalicylic acid, beta blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering medications) is recommended when indicated and is amply supported by evidence of benefit. More research is required to clarify the role of HT and CVD outcomes in recently menopausal women, as well as the contribution of different formulations and doses of estrogen and progestin to the risk of CAD, stroke, and venous thromboembolism.

SOGC Clinical Tip

Women on HT who experience a cardiovascular event such as myocardial infarction, stroke, or venous thromboembolism should be advised to discontinue such therapy. Should significant vasomotor symptoms require continuation of HT, then the lowest dose for the shortest time should be considered. Cardiovascular risk factors in particular should be addressed and treated as per guidelines.

RECOMMENDATIONS

1. Health care providers should not initiate or continue HT for the sole purpose of preventing CVD (CAD and stroke). (IA)
2. Health care providers should abstain from prescribing HT in women at high risk for VTE. (IA)
3. Health care providers should consider other evidence-based therapies and interventions to effectively reduce the risk of CVD events in women with or without vascular disease. (IA)

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Cancer

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INTRODUCTION

The fact that several risk factors for breast and endometrial cancer are associated with increased endogenous estrogen exposure¹⁻⁴ suggests that exogenous estrogen might also increase the incidence of these cancers. Estrogens are generally accepted as promoters of endometrial and breast epithelial cell proliferation, but their actions within the ovaries are less well known.

The association between progesterone, progestins, and cancer remains controversial. In the endometrium, progesterone functions mostly as an anti-estrogen by decreasing the number of nuclear estrogen receptors⁵ and introducing 17 β -hydroxysteroid dehydrogenase.⁶ Most in vitro studies of cancer cell lines and cultured normal cells show progesterone to have an inhibitory effect on proliferation in the breast, but in vivo experiments with normal breast tissue show a high mitotic index during the luteal phase.⁷ Similarly, synergistic effects of progestins in combination with estrogen have been found.⁸

ENDOMETRIAL CANCER: UNOPPOSED ESTROGEN

Several lines of evidence indicate that unopposed estrogen replacement therapy (ET) increases the risk of endometrial cancer.^{1,2} Epidemiological studies have shown a 5- to 10-fold increased risk of endometrial cancer in women taking ET; this risk is related to estrogen dose and duration of therapy.⁹ Furthermore, this increased risk of developing endometrial carcinoma persists for at least 5 years after unopposed ET has ceased.⁹ In the PEPI trial, unopposed ET (0.625 mg) resulted in atypical endometrial hyperplasia in up to 30% of study subjects.¹⁰ Where the risk of developing endometrial cancer is significantly elevated after at least 5 years of unopposed ET,⁹ the risk of developing invasive cancer or of dying from endometrial cancer while taking ET is low. Most studies report no excess deaths due to endometrial cancer among ET users,⁹ although one meta-analysis has shown an increased risk for late-stage, high-grade invasive tumours.¹¹

SOGC Clinical Tip

In most circumstances, women with a uterus who choose to use HT should be advised to use combined estrogen/progestin therapy to reduce the risk of endometrial neoplasia.

Recent interest in lower doses of estrogen has provided insight into the endometrial effects of these formulations. Low-dose unopposed estrogen (0.3 mg conjugated estrogen [CE]) resulted in endometrial hyperplasia in only 2% to 3% of women treated for 2 years,¹² whereas ultralow-dose unopposed transdermal estrogen (14 μ g) used for 2 years resulted in only one case of hyperplasia among 188 women treated—a rate similar to that in placebo users.¹³

SOGC Clinical Tip

Though unopposed estrogen at very low doses probably carries a low risk of endometrial neoplasia, limited data support the safety of such an approach.

COMBINED PROGESTIN AND ESTROGEN THERAPY

Adding progestins or progesterone to an ET regimen markedly reduces the risk of developing both endometrial hyperplasia¹⁰ and cancer,⁹ although no hormone therapy (HT) regimen has proven completely protective. Various regimens using different dosages of progestins for a minimum of 12 to 14 days per month¹⁴ have been proposed. While the dose of progestin should be individualized, as a general rule, higher progestin doses should accompany higher-dose estrogen administration. In keeping with the observation that the duration of progestin therapy is more important than the actual dose,¹⁵ continuous therapy with low-dose progestin may offer endometrial protection equivalent or superior to that of cyclical therapy.

Limited experience suggests that 14 days of progestin therapy every 3 months may not be completely protective against atypical endometrial hyperplasia.¹⁶ Limited data also

suggest that daily micronized progesterone for 25 to 30 days may be protective against hyperplasia.¹⁷ Long-term follow-up data on endometrial cancer are not yet available with these regimens. Use of lower-than-standard estrogen doses for relief of vasomotor symptoms¹² and for their bone-sparing effects¹⁸ may allow the reduction or elimination of progestin therapy when coupled with careful endometrial surveillance.¹³ Long-term safety data employing low-dose unopposed estrogen are not yet available. Several small studies have evaluated the use of systemic ET in conjunction with a levonorgestrel releasing intrauterine system.¹⁹⁻²¹ This approach is associated with higher rates of unpredictable bleeding at the outset but may afford excellent endometrial protection without the need for systemic progestin exposure.

HT FOR WOMEN PREVIOUSLY TREATED FOR ENDOMETRIAL CANCER

Based on the belief that HT might increase the risk of recurrence, HT has traditionally been withheld from women after treatment for endometrial cancer. This belief has never been substantiated, and two recent retrospective studies have questioned it.^{22,23} Based on these limited studies, a committee opinion of the American College of Obstetricians and Gynecologists concluded that HT may be used by women who have been treated for endometrial cancer and who fall into a low-risk group, defined as women with stage I disease, grade 1 or 2 histology, and less than 50% depth of myometrial invasion.²⁴ Estrogen administration is commonly begun postoperatively when the woman is ambulatory. It remains undetermined whether progestin should be added to the regimen in these women. The use of androgens in these women is controversial because androgens may undergo aromatization to estrogen.²⁵

SOGC Clinical Tip

Women with a history of early stage (stage I), low grade (grade 1 or 2) endometrial cancer may take HT to control distressing vasomotor symptoms.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Long-term tamoxifen users have an increased risk of endometrial cancer,²⁶ and a subgroup of high-risk patients may develop cancers with a worse prognosis.²⁶ However, newer selective estrogen receptor modulators (SERMs), such as raloxifene, have no stimulatory effects on the endometrium.²⁷ There is insufficient evidence regarding the value of routine transvaginal ultrasonography or endometrial sampling for the early detection of endometrial cancer in women using tamoxifen.²⁸ The American College of Obstetricians and Gynecologists has issued the

recommendation that women taking tamoxifen should have annual gynaecological examinations, and that the indication for endometrial biopsy should be based on the presence of bleeding.²⁹

SOGC Clinical Tip

Since long-term tamoxifen users are at increased risk of endometrial cancer, any vaginal bleeding in a current or former user warrants sampling of the endometrium (endometrial biopsy).

BREAST CANCER

Factors that influence breast cancer are listed in Table 10.1.³⁰ Based on a reanalysis of over 90% of the epidemiological studies published on this subject, current users of HT and those who ceased HT 1 to 4 years prior to the study had a small increase in relative risk of breast cancer, comparable to the effect of a delayed menopause.³¹ The combined analysis reported no increased risk for HT use of less than 5 years.³¹ For women who had used HT for 5 years or longer, the average relative risk of breast cancer increased by approximately 2% per year of use.³¹ Translated into real estimates, this relative risk for breast cancer with HT would account, after 5, 10, or 15 years of use, for an excess of 2, 6, or 12 cases per 1000 HT users respectively. Within 5 years of discontinuation of HT use, the increased relative risk virtually disappeared.³¹

The magnitude of this risk can be appreciated better by comparing it with other known risk factors for breast cancer. As illustrated in Table 10.1,³⁰ there appear to be comparable or greater risks for breast cancer, associated with excessive alcohol consumption,³² failure to exercise regularly,^{33,34} late childbearing and failure to breastfeed,³⁵ and postmenopausal obesity,³⁶ than is associated with HT.

Table 10.2 also illustrates this issue.

SOGC Clinical Tip

The increased risk for breast cancer after 5 years of combined estrogen/progestin therapy is similar in magnitude to other lifestyle variables such as fewer pregnancies and reduced breastfeeding, postmenopausal obesity, excessive alcohol or cigarette use, and lack of regular exercise.

SOGC Clinical Tip

The increased risk associated with hormone use returns to normal within 5 years of stopping hormone therapy.

Table 10.1. Risk Factors for Breast Cancer

Factor	Baseline Breast Cancers* per 1000 women	Additional Cancers per 1000 Women	Total Cancers per 1000 Women
No HT use (baseline)*	45	0	45
5 years HT use	45	2	47
10 years HT use	45	6	51
15 years HT use	45	12	57
Alcohol consumption (2 drinks/d)	45	27	72
Lack of regular exercise (hr/wk)	45	27	72
Late menopause (10-y delay)	45	13	58
Body mass index (10 kg/m ² increase)	45	14	59
Weight gain after menopause (≥ 20 kg)	45	45	90
Late childbearing and reduced breastfeeding	45	45	90

*Baseline or basic risk applies to all women and is due to factors that cannot be controlled (such as aging and gender). Increases are estimates based on published data indicating relative risk associated with lifestyle choices.

Modified with permission from Reid RL. Progestins in hormone replacement therapy: impact on endometrial and breast cancer. *J Soc Obstet Gynaecol Can* 2000;22:679.

Several studies have specifically examined the effect of long-term HT with or without progestin on breast cancer risk. Case control studies revealed contradictory findings about whether progestins augmented the breast cancer risk,^{37,38} whereas prospective cohort studies found the addition of progestin failed to alter the estrogen-related risk of breast cancer.³⁹⁻⁴¹ Two recent studies add further evidence for an adverse effect of a combined estrogen-progestin regimen on breast cancer risk.^{42,43}

The Million Women Study⁴³ was a large observational study that reported breast cancer incidence in 870 000 UK women followed with screening mammograms for both hormone users and non-users. This trial is noteworthy for its large numbers and adjustments for the well-recognized factors associated with risk of breast cancer. No increase in risk of breast cancer was measured in past users of any hormone preparation, regardless of length of time since discontinuation and of duration of use. The time passed since discontinuation of therapy in the study ranged from less than 5 years to 10 or more years (with the exception of discontinuation in the year previous to diagnosis). Based on an average follow-up of 2.6 years, the relative risks for invasive breast cancer were: 1.00 (95% confidence interval [CI], 0.96–1.04) for women who never used estrogen, 1.01 (95% CI, 0.95–1.08) for women who had used estrogen at some point in the past, 1.30 (95% CI, 1.22–1.38) for women who currently used estrogen only, and 2.00 (95% CI, 1.91–2.09) for women who currently used estrogen plus progestin.

This study has been widely criticized for potential biases that may have confounded results.^{44, 45}

In the WHI CE/medroxyprogesteron acetate (MPA) study,⁴² no increased risk of invasive breast cancer was seen in the 75% of women who had never used HT before starting the trial; however, in the remaining women, HT increased the risk of breast cancer after 5 years of use by 8 additional cases for every 10 000 women using combined hormones for 1 year (hazard rate [HR], 1.24; 95% CI, 1.02–1.5). This risk returned to baseline 5 years after stopping therapy. Both size and stage of breast cancer suggested that women on HT had more advanced tumours, though no increase in in situ breast cancers accompanied this finding. In the CE alone WHI study, there was a reduced detection of breast cancer, which was not statistically significant (HR, 0.77; 95% CI, 0.59–1.01) in the women assigned to CE.

Though it may be tempting to speculate that the additional progestin in the CE/MPA WHI trial accounted for the increased risk of breast cancer, the authors of that trial point out that baseline characteristics of the two patient populations were quite different, making such head-to-head comparisons problematic.

SOGC Clinical Tip

The only large RCT comparing users and non-users of HT in menopause revealed a small increase in the risk of breast cancer with use of combined estrogen/progestin therapy, but not with estrogen-only therapy after 5 years of use.

Table 10.2. Cumulative absolute risk and additional risk of breast cancer with duration of use of hormone replacement therapy

Age at Calculation (years)	Age Range (years)	Risk with no hormone replacement therapy		Additional risk (%) with combination therapy* years of use				% With estrogen-only therapy			
		Ratio [†]	%	3 years	5 years	10 years	15 years	3 years	5 years	10 years	15 years
40	40–79	1 in 14	7.21	0.18	0.38	1.18	2.22	0.05	0.12	0.34	0.64
45	45–79	1 in 15	6.76	0.26	0.52	1.45	2.54	0.07	0.15	0.41	0.73
50	50–79	1 in 16	6.10	0.31	0.60	1.59	2.82	0.09	0.18	0.45	0.81
55	55–79	1 in 19	5.30	0.33	0.64	1.76	3.17	0.09	0.19	0.50	0.91
60	60–79	1 in 23	4.44	0.37	0.73	2.01	3.51	0.10	0.21	0.57	1.00
65	65–79	1 in 29	3.48	0.42	0.84	2.19	3.27	0.12	0.25	0.62	0.91
70	70–79	1 in 42	2.37	0.47	0.88	1.84	—	0.13	0.25	0.50	—
75	75–79	1 in 88	1.14	0.43	0.58	—	—	0.12	0.14	—	—

* The additional risk for a specific formulation and duration of use can be added to the baseline risk with no hormone therapy to provide an estimate of a woman's specific cumulative absolute risk of breast cancer from a specific age to age 79 years.

† The ratio is calculated as the reciprocal of the cumulative absolute breast cancer risk (%) of non-users.

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HT AND WOMEN WITH BENIGN BREAST DISEASE

HT can be prescribed to women with benign breast disease. Women with a personal history of premalignant disease of the breast are at increased risk for breast cancer.⁴⁶ The relative risk of developing breast cancer is 1.8 in women with a history of proliferative breast disease without atypical hyperplasia, and 3.6 in those with atypical hyperplasia,⁴⁷ compared with women with non-proliferative benign histology. These risks are not affected by the use of HT.^{47,48}

RISK OF BREAST CANCER IN WOMEN CONSIDERING HT WITH A HISTORY OF ORAL CONTRACEPTIVE USE

Previous use of oral contraceptives (OCs) does not further increase the HT-related risk for breast cancer. Neither long-term past use nor use prior to menopause confers any appreciable increase in the risk of HT-related breast carcinoma.^{49,50}

HT AND WOMEN WITH RISK FACTORS FOR BREAST CANCER

HT can be prescribed for women with a family history of breast cancer after proper counselling. Women with a history of breast cancer in a first-degree relative carry a 2 to 4 times increased risk of developing breast cancer.⁵⁰ This risk increases even further if two first-degree relatives are affected or if the cancer occurs premenopausally.⁵¹ The available data suggest that the addition of HT does not

further increase this risk.^{51–53} HT can also be prescribed to women with a genetic predisposition to breast or ovarian cancer, after bilateral prophylactic oophorectomy (BPO) and after proper counselling. Three to 5% of these women carry a specific genetic mutation (BRCA1 or 2) that confers a 60% to 80% lifetime risk of developing breast cancer.⁵⁴ Some of the women may elect to undergo BPO, which has been shown to reduce the subsequent risks for both breast and ovarian cancer,⁵⁵ which raises concerns about use of HT after surgical menopause. The effects of HT on women carrying BRCA1 or 2 genes have not been well studied. Rebbeck et al.⁵⁶ reported that ever-use or never-use of HT was not a significant independent predictor of breast cancer outcome, in a model that included BPO. Exclusion of women who had HT exposure after BPO did not significantly affect the risk reduction conferred by BPO.

A more recent decision analysis assumed that hysterectomy was not used in conjunction with BPO (which is seldom the case) and accordingly modelled risks as per the combined estrogen/progestin arm of the WHI. Even assuming the risks of the estrogen/progestin arm of the WHI (which were greater than the risks in the estrogen-only arm of the WHI), the authors concluded that BPO improved life expectancy in women with BRCA1/2 mutations irrespective of whether HT was used after oophorectomy.⁵⁷ Their opinion was that after BPO, women should decide on use of hormones based on quality-of-life decisions.

SOGC Clinical Tip

Women with a family history of breast cancer are no more likely to experience breast cancer if they choose to use HT to control menopausal symptoms.

SELECTIVE ESTROGEN RECEPTOR MODULATORS AND BREAST CANCER

An overview of 4 primary prevention trials with tamoxifen given for 5 or more years (National Surgical Adjuvant Breast and Bowel Project [NSABP],⁵⁸ International Breast Cancer Intervention Study^{1,59} Royal Marsden Hospital tamoxifen randomized chemoprevention trial,⁶⁰ and the Italian randomized trial among hysterectomized women⁶¹) concluded that women randomly assigned to tamoxifen had a 36% reduction in the incidence of ductal carcinoma-in-situ (DCIS) and a 46% reduction in invasive breast cancer.⁶² ER-positive tumours were reduced by 48% in the overview, but no significant reduction was observed in the incidence of ER-negative tumours.⁶² The excess of serious side effects in women taking tamoxifen (116 events) almost offset the reduction in cancer incidence (176 cases). The incidence of endometrial cancer was increased 2.4-fold, deep venous thrombosis 1.9-fold, and cerebral vascular accident 1.5-fold.

The possible preventive effects of a second-generation SERM, raloxifene, on breast cancer were assessed in a secondary analysis of the MORE trial.⁶³ This revealed a significant reduction of breast cancer in women randomly assigned to receive raloxifene. Raloxifene reduced the incidence of all breast cancers by 62%, invasive breast cancer by 72%, and invasive ER-positive breast cancer by 84%. Similar to findings for tamoxifen in the NSABP P-1 trial, there was no reduction of ER-negative tumours.⁶⁴ Unlike tamoxifen in the NSABP P-1 trial, no reduction in DCIS was observed for women randomly assigned to raloxifene. Women randomly assigned to raloxifene had a 3-fold increase in thromboembolic events but no increase in uterine bleeding or uterine cancer.

SOGC Clinical Tip

The SERM raloxifene, when used for bone protection, reduces the subsequent risk for breast cancer with no increase in the risk of endometrial neoplasia.

HT AFTER BREAST CANCER

Some 30 000 premenopausal women with a diagnosis of breast cancer are rendered acutely symptomatic subsequent to chemotherapy-induced ovarian failure each year in North America. There are over 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 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 those who do not.⁶⁵⁻⁶⁷ Data from the first randomized clinical trials to examine this issue have recently appeared. The HABITs trial from Scandinavia found that women who used hormones after a diagnosis of breast cancer had a higher recurrence risk than did women assigned to placebo. Among 434 women randomized to the study, there were 26 recurrences in women assigned to HT and 6 recurrences in women receiving placebo.⁶⁸ Surprisingly, a concurrent study being conducted in Sweden failed to find any adverse effect of HT, leaving this issue unresolved.⁶⁹ Both studies were stopped prematurely on the basis of the HABITs trial findings and the concern that ongoing recruitment would no longer be possible because of the adverse publicity about the HABITs trial preliminary findings.

Women who wish to consider HT for quality-of-life issues after a diagnosis of breast cancer should understand that a definitive answer to the question of whether HT will influence prognosis is lacking. 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 non-HT therapies exist for some menopausal symptoms (like topical estrogen for urogenital atrophy). If these options are unsuitable and quality of life is seriously impaired, then individual women with low risk of tumour recurrence may still wish to explore the option of HT.

SOGC Clinical Tip

Women with a history of breast cancer may still use local intravaginal estrogen to treat symptoms of urogenital atrophy.

OTHER CANCERS**HT and Colorectal Cancer**

Most case-control and cohort studies in current HT users have shown a decrease in the incidence of colorectal cancers.⁷⁰⁻⁷¹ Moreover, two recent meta-analyses summarizing the results of these studies show that the risk is reduced by one-third in current and recent (within 1 year of assessment) users of HT.⁷⁰⁻⁷¹ According to the WHI CE/MPA trial,⁴⁵ continuous-combined treatment was associated with a statistically significant reduction in the risk of colorectal

cancer (HR, 0.56; 95% CI, 0.38–0.81) amounting to 6 fewer cases per 10 000 women per year.

In the WHI CE-alone trial, no significant differences were found in the rates of colorectal cancer for women assigned to CE versus those assigned to placebo. The absolute risk of colorectal cancer observed in the study was 17 cases per 10 000 women per year in the CE group and 16 cases per 10 000 women per year in the placebo group. A direct head-to-head comparison of the results from the CE-alone and CE/MPA trials cannot be made, however, because the trials enrolled women with different baseline characteristics (e.g., hysterectomized vs. non-hysterectomized; greater degree of obesity in CE-alone participants), which may correspond with differing risk profiles.

HT and Ovarian Cancer

Combined OCs are known to reduce the risk of ovarian cancer by 50%.⁷² It may seem surprising, therefore, that several observational studies suggest a slightly increased risk of ovarian cancer in women using estrogen-only therapy, an effect that is thought to be either duration-dose related^{73–77} or cumulative-dose related.⁷⁸ The net effect of HT is, therefore, likely to be small and clinically insignificant.

The WHI investigators reported a small, nonsignificant increase in ovarian cancer risk in women assigned to receive CE/MPA, compared with those assigned to placebo (HR, 1.58; 95% CI, 0.77–3.24; 95% CI, 0.59–4.23).⁴² Average follow-up time for the women included in this analysis was 5.6 years. The annual incidence rate for ovarian cancer observed among the total study population was 34 cases per 100 000 person-years. This rate is lower than the NCI SEER population-based rate of 45 cases per 100 000 person-years in women in the same age range as the WHI participants. The WHI investigators found no differences between treatment groups in histology, grade, or stage of disease at diagnosis. In addition, no significant interactions between group assignment and any of the following variables were observed: age, race/ethnicity, body mass index, family history of breast or ovarian cancer, family history of colorectal cancer, prior use of OCs, prior exposure to estrogen alone, or prior use of CE/MPA.

In summary, the incidence of ovarian cancer among CE/MPA users in the WHI was somewhat greater than that observed in the placebo group, although the difference in incidence rates was small and not statistically significant. The authors concluded that continuous combined CE/MPA may increase the risk of ovarian cancer. However, they added that due to the low rates of ovarian and other gynaecologic cancers in the study population and the limited precision of the risk estimates, “the results should not have an appreciable influence on most women’s

decision-making when seeking relief for moderate to severe vasomotor symptoms.”⁴²

Other Cancers

There is too little information to comment on any relationship between HT use and cancers of the cervix, vagina, or vulva.⁷⁹

SOGC Clinical Tip

Combined HT is associated with a reduced risk of colorectal cancer and a possible small increase in the risk of ovarian cancer. These effects are very small, however, and should not impact decision-making about the use of HT for distressing vasomotor symptoms.

RECOMMENDATIONS

1. All unscheduled uterine bleeding should be investigated because no estrogen-progestin regimen is completely protective against endometrial carcinoma. (IA)
2. Estrogen-progestin therapy may be offered to women with low-grade adenocarcinoma of the endometrium who have moderate to severe menopausal symptoms. (IB)
3. 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)
4. Health care providers may prescribe HT for menopausal symptoms in women at increased risk of breast cancer with appropriate counselling and surveillance (IA) (in women in the Women’s Health Initiative [WHI] study with high Gail scores were at no greater risk of breast cancer than women with low risk scores).
5. 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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Canadian Consensus Conference on Osteoporosis, 2006 Update

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RECOMMENDATIONS:

1. The goals of osteoporosis management should be fracture risk assessment and prevention of fracture (IB). Bone mineral density should not be viewed as the only indicator for management success because therapy may or may not be associated with significant increases in BMD. (IA)
2. Physicians should be aware that a prevalent vertebral or non-vertebral fragility fracture markedly increases the risk of future fracture. (IA)
3. Fragility fracture after the age of 40, over 65 years of age without fragility fracture, low BMD, and family history of osteoporotic fracture (especially maternal hip fracture) should be recognized as the key risk factors for fragility fractures. Systemic glucocorticoid use of more than 3 months duration should be considered as another major risk factor. (IA)
4. Evaluation of osteoporosis in postmenopausal women should include the assessment of clinical risk factors for low BMD and BMD testing. (IB)
5. Central (hip and spine) measurements by dual energy X-ray absorptiometry (DXA) should be used for both risk assessment (IA) and follow-up (IB), as they provide the most accurate and precise measurements of BMD.
6. Further evidence should be collected to determine the role of peripheral BMD measurements (e.g., ultrasound or DXA measurements in the radius, phalanx, or heel) in clinical practice. (II-2D)
7. Postmenopausal women with historical height loss greater than 6 cm, prospective height loss greater than 2 cm, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with a specific request to rule out vertebral fractures. (IA)
8. Until more data becomes available on other clinical applications, bone turnover markers can be used to rapidly assess adherence and effectiveness of pharmacological interventions. (IB)

ABSTRACT

Objective: To provide guidelines for the health care provider on the diagnosis and clinical management of postmenopausal osteoporosis.

Outcomes: Strategies for identifying and evaluating high-risk individuals, the use of bone mineral density (BMD) and bone turnover markers in assessing diagnosis and response to management, and recommendations regarding nutrition, physical activity, and the selection of pharmacologic therapy to prevent and manage osteoporosis.

Evidence: MEDLINE and the Cochrane database were searched for articles in English on subjects related to osteoporosis diagnosis, prevention, and management from March 2001 to April 2005. The authors critically reviewed the evidence and developed the recommendations according to the *Journal of Obstetrics and Gynaecology Canada's* methodology and consensus development process.

Values: The quality of evidence is rated using the criteria described in the report of the Canadian Task Force on the Periodic Health Examination. Recommendations for practice are ranked according to the method described in this report.

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Key Words: Osteoporosis, prevention, treatment, diagnosis, bone mineral density, dual energy X-ray absorptiometry, bone turnover markers, vertebral fractures, fragility fractures, antiresorptive, hormone therapy, selective estrogen receptor modulator, bisphosphonates, calcitonin, anabolic, bone forming agent

Calcium and Vitamin D

9. Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin D3 (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs). (IB)

Hormone Therapy

10. Hormone therapy (HT) should be prescribed to symptomatic postmenopausal women as the most effective therapy for symptom relief (IA) and a reasonable choice for the prevention of bone loss and fracture (IA). The risks should be weighted against the benefits if estrogen therapy is being used solely for fracture prevention. (ID)

Bisphosphonates

11. Treatment with alendronate or risedronate should be considered to decrease vertebral, non-vertebral, and hip fractures. (IA)
12. Treatment with etidronate can be considered to decrease vertebral fractures. (IB)

Selective Estrogen Receptor Modulators

13. Treatment with raloxifene should be considered to decrease vertebral fractures. (IA)

Calcitonin

14. Treatment with calcitonin can be considered to decrease vertebral fractures and to reduce pain associated with acute vertebral fractures. (IB)

Parathyroid Hormone

15. Treatment with teriparatide should be considered to decrease vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. (IA)

Combination Therapy

16. Although combination of antiresorptive therapies may be synergistic in increasing bone mineral density, the anti-fracture effectiveness has not been proven; therefore, it is not recommended. (ID)

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INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by a low BMD and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.¹ The condition is usually painless until a fracture occurs. Because of its association with fractures, osteoporosis is a major public health hazard with high morbidity, mortality, and social costs. Recent advances in measuring BMD have provided strategies to assess the presence and extent of early and asymptomatic osteoporosis.

EPIDEMIOLOGY

Osteoporosis is a major public health problem in Canada and its prevalence is increasing as the population ages.² According to results from BMD assessments in the Canadian Multicentre Osteoporosis Study (CaMos), the prevalence of osteoporosis in Canadian women aged 50 years and over was 12.1% at the lumbar spine and 7.9% at the femoral neck, with a combined prevalence of 15.8%.³ The prevalence of osteoporosis increases with age from approximately 6% at 50 years of age to over 50% above 80 years of age.⁴ In light of these statistics and the aging of the population, it comes as no surprise that osteoporosis will be an even greater problem in the future.

Based on fracture data, it has been estimated that approximately 1 in 4 women and 1 in 8 men in Canada have osteoporosis.^{5,6} The public health and clinical importance of osteoporosis lies in the fractures that occur. Conservative

estimates have suggested that a 50-year-old Caucasian woman has a remaining lifetime fragility fracture risk of 40% (for hip, vertebra, or wrist).⁷

SOGC Clinical Tip

Osteoporosis Canada (former Osteoporosis Society of Canada) recommends that all postmenopausal women older than 50 years be assessed for the presence of risks factors for osteoporosis.

Social and Medical Outcomes of Fracture

The medical and social consequences of fractures make osteoporosis an important public health problem. About 20% of women and 40% of men die within 1 year after a hip fracture.⁸ It has been estimated that 50% of women who sustain a hip fracture become functionally dependent in their daily activities, and 19% require long-term nursing home care because of the fracture.⁸ Vertebral fractures appear to be associated with similar 5-year mortality.⁹⁻¹¹ Only one-third of all vertebral fractures are clinically diagnosed.¹² In addition to health care costs, vertebral fractures cause back pain, loss of height, depression, and low self-esteem.¹³ Wrist and other fractures have considerable morbidity that is not usually captured in osteoporosis cost estimates. The total costs of osteoporosis are difficult to assess and are based on many assumptions. It is estimated that the total acute care costs attributable to osteoporosis in Canada (hospitalization, outpatient care, and drug therapy) approached \$1.3 billion in 1993.³

It is also well-known that the burden of illness associated with hip fracture extends beyond the initial hospitalization. The levels of health services used were assessed in a study of women aged 50 years and over who had been admitted to an acute care facility for hip fracture in the Hamilton-Wentworth region in Ontario from April 1, 1995 to March 31, 1996.¹⁴ The mean 1-year cost of hip fracture for the 504 study patients was \$26 527 (95% confidence interval [CI], \$24 564–\$28 490). One-year costs were significantly ($P < 0.001$) different for patients who returned to the community (mean = \$21 385), versus those who were transferred (mean = \$44 156) or readmitted (mean = \$33 729) to long-term care facilities. Initial hospitalization represented 58% of the 1-year cost for the community-dwelling patients, compared with 27% of the cost for the long-term care residents. Only 59.4% of the community-dwelling patients resided in the community 1 year following fracture, and 5.6% of patients who survived their first fracture experienced a subsequent hip fracture. Annual economic implications of hip fracture in Canada are \$650 million and are expected to rise to \$2.4 billion by 2041.¹⁴

Table 11.1. Recommended Calcium and Vitamin D Intake From All Sources^{39*}

Calcium	
Children (4–8)	800 mg
Adolescents (9–18)	1300 mg
Premenopausal women	1000 mg
Men < 50	1000 mg
Menopausal women	1500 mg
Men > 50	1500 mg
Pregnant or lactating women	1000 mg
Vitamin D	
< age 50	400 IU
> age 50	800 IU

All sources means total diet and supplement.

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BONE HEALTH

Osteoporosis is a disease with its roots in childhood as bone size, strength, and mineralization peak in one's 20s. Those with the highest peak bone mass have an advantage as reductions in bone density occur with advancing age and menopause. Peak bone mass, while largely genetically determined, is not always met. This can be a result of inadequate calcium and vitamin D intake, poor nutrition, lack of physical exercise, smoking, and other environmental, physiologic, and lifestyle factors. Refer to Table 11.1 for calcium and vitamin D recommendations.

RECOMMENDATIONS:

1. The goals of osteoporosis management should be fracture risk assessment and prevention of fracture (IB). BMD should not be viewed as the only indicator for management success because therapy may or may not be associated with significant increases in BMD. (IA)
2. Physicians should be aware that a prevalent vertebral or non-vertebral fragility fracture markedly increases the risk of future fracture. (IA)
3. Fragility fracture after the age of 40, being over 65 years of age, low BMD, and family history of osteoporotic fracture (especially maternal hip fracture) should be recognized as the key risk factors for fragility fractures. Systemic glucocorticoid use of more than 3 months duration should be considered as another major risk factor. (IA)
4. Evaluation of osteoporosis in postmenopausal women should include the assessment of clinical risk factors for low BMD and BMD testing. (IB)
5. Central (hip and spine) measurements by DXA should be used for both risk assessment (IA) and follow-up (IB), as they provide the most accurate and precise measurements of BMD.
6. Further evidence should be collected to determine the role of peripheral BMD measurements (e.g., ultrasound or DXA measurements in the radius, phalanx, or heel) in clinical practice. (II-2D)
7. Postmenopausal women with historical height loss greater than 6 cm, prospective height loss greater than 2 cm, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with a specific request to rule out vertebral fractures. (IA)
8. Until more data becomes available on other clinical applications, bone turnover markers can be used to rapidly assess adherence and effectiveness of pharmacological interventions. (IB)

Calcium

Adequate dietary calcium intake is necessary for mineralization of the skeleton and attainment of peak bone mass. In postmenopausal women, calcium supplements slow bone loss and improve BMD.¹⁵ Increasing dietary calcium through dairy products has also been associated with increasing BMD.¹⁶ There are many forms of calcium supplements available and while they may differ in qualities such as absorption, calcium carbonate, being least expensive, could be a cost effective option in older populations.¹⁷

Vitamin D

The prevalence of vitamin D deficiency in Canada is high.⁵ The northern latitude makes it difficult to raise vitamin D levels sufficiently in the summer to maintain adequate levels throughout the winter. This is especially true for housebound and institutionalized people. In elderly men and women with vitamin D insufficiency, vitamin D supplementation probably reduces vertebral fractures and may also impact non-vertebral fractures.^{18,19}

Recent evidence suggests that routine supplementation with calcium (1000 mg/d) and vitamin D₃ (800 IU/d), either alone or in combination, is not effective in reducing the risk of fractures among community-dwelling older women with at least one self-reported risk factor for hip fracture. It is also not effective in preventing further fractures in elderly men and women who had a recent fragility fracture.^{20,21}

Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium

Table 11.2. WHO Diagnostic Categories for BMD in Postmenopausal Caucasian Women³⁷

1.	Normal: BMD or BMC not more than 1 SD below the peak bone mass or young adult mean (T-score above -1).
2.	Osteopenic: BMD or BMC between 1 and 2.5 SD below the young adult mean (T-score between -1 and -2.5).
3.	Osteoporosis: BMD or BMC 2.5 SD or more below the young adult mean (T-score at or below -2.5).
4.	Severe osteoporosis (established osteoporosis): BMD or BMC 2.5 SD or more below the young adult mean (T-score at or below -2.5) and the presence of one or more fragility fractures.

WHO: World Health Organization; BMD: bone mineral density; BMC: bone mineral content; SD: standard deviation.

(1000 mg/d) and vitamin D₃ (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs). Muscle strength, which may reduce the risk of falling, is also affected by vitamin D (dose equivalent to 800 IU/d),¹⁹ but this has been recently challenged. Osteoporosis prevention and treatment requires adequate vitamin D intake.

CALCIUM AND VITAMIN D RECOMMENDATION

9. Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin D₃ (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs). (IB)

Exercise

Physical activity early in life contributes to higher peak bone mass, with resistance and impact exercises showing most benefit.²²⁻²⁵ In postmenopausal women, BMD at the spine can be positively affected by aerobics, resistance, and weight-bearing exercise.²⁶⁻²⁸

Walking also appears to benefit the hip BMD. Walking may be the most cost-effective exercise that is easily accessible to the population.²⁸ Trials of exercise in older community-dwelling women with osteoporosis produce variable results in terms of improved strength and balance.²⁹ Exercise interventions that increase strength and improve balance can reduce falls, but there is not yet evidence of fracture reduction in exercise trials. Women should be encouraged to perform fast walking in a safe environment as a means of improving bone health.

Nutrition

Optimal bone health requires good overall nutrition. Malnutrition is associated with an increased risk of osteoporosis.³⁰ Body mass index (BMI) ≤ 20 kg/m² is associated with increased risk of fracture.³¹ Elderly community-dwelling women are at risk of malnutrition for many reasons. Weight gain in underweight community-dwelling women is associated with increased BMD.³² High protein and high sodium diets increase calcium excretion and increase markers of

bone resorption.³³ Weight loss in overweight postmenopausal women with a normal calcium intake may also result in inadequate calcium absorption.³⁴ A caffeine intake of over 4 cups of coffee per day has been associated with an increased risk in hip fracture.³⁵

Osteoporosis has been added to the negative effects of smoking. Smokers have significantly lower bone mass compared with non-smokers. This effect appears to be dose dependent and may be partially reversible by smoking cessation. The negative effect of smoking is even more pronounced at the hip, where it is estimated that smoking increases lifetime fracture risk by 31% in women and 40% in men.³⁶

DEFINITIONS

The WHO has proposed 4 diagnostic categories for postmenopausal Caucasian women combining BMD (or bone mineral content [BMC] measured at any site and osteoporotic fracture in a stratified definition of osteoporosis (Table 11.2).³⁷ The choice of this 2.5 standard deviation cut-off by the WHO was based on epidemiological data showing that over 50% of the individuals who have already sustained a fragility fracture were at or below this level of BMD.

A US National Institutes of Health (NIH) consensus conference defined osteoporosis as “. . . a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality.”³⁸ The only clinically applicable index of bone quality at present is a patient's history of a fragility fracture. Fragility fractures are associated with significant morbidity, increased mortality, and staggering medical expenses. In the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of low BMD.

This definition recognizes that there is a strong association between BMD and the likelihood of fracture in untreated postmenopausal women, but that other factors independent of BMD influence fracture risk as well: rate of bone loss, breakdown of bone architecture, ineffective repair of fatigue damage, geometric aspects of skeletal structure such

Table 11.3. Risk Factors That Identify who Should be Assessed for Osteoporosis³⁹

Major Risk Factors	Minor Risk Factors
Age 65 years	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy 3 months	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight 57 kg
Osteopenia apparent on X-ray film	Weight loss 10% of weight at age 25
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45)	

Osteoporosis Canada has taken the position that "BMD testing is appropriate for targeted case-finding among women under the age of 65 and for all women age 65 and older because of the high risk of osteoporosis and fracture after that age."³⁹

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as hip axis length, frequency and type of falls, and life expectancy. Therefore, the WHO definition is important for assessing the number of affected individuals but should not be used as the sole indication for treatment. In fact, treatment could be justified regardless of the BMD level in patients who have already sustained a fragility fracture and in glucocorticoid-treated patients.³⁹ Furthermore, Osteoporosis Canada has recently proposed that an individual's 10-year absolute fracture risk, rather than BMD alone, be used for fracture risk categorization.⁴⁰

ASSESSMENT

Women at Risk of Low Bone Mineral Density

Osteoporosis Canada recommends that all postmenopausal women older than 50 be assessed for the presence of risks factors for osteoporosis.³⁹ There are two stages of assessment in identifying high-risk individuals for osteoporosis: risk factors identifying those who should be assessed with a BMD test, and the risk factors identifying those at risk of osteoporotic (fragility) fracture who should be considered for therapy.³⁹

SOGC Clinical Tip

Among the major factors identifying those who should be assessed with a BMD test, the most relevant are: age > 65 years; fragility fracture after age 40, including wrist, vertebral, and hip fractures; family history of osteoporotic fracture (especially maternal hip fracture); and systemic glucocorticoid therapy of > 3 months.

It is important to assess for the presence of one major or two minor risk factors for osteoporosis (Table 11.3) to identify who should have a BMD test.

There are a number of decision tools that have been developed to aid physicians in selecting patients for BMD testing using a variety of combinations of risk factors.⁴¹⁻⁴⁴ Recent evidence from multiple sources confirms that each tool identifies over 90% of women aged 45 years or older with primary osteoporosis.⁴⁵⁻⁴⁷ However, these tools have poor specificity in that a significant portion of identified women (30% to 60%) will have normal BMDs upon testing.⁴⁵⁻⁴⁷

Women at Risk of Fragility Fracture

It is critical to recognize that low BMD is one of the most significant risk factors for predicting future fragility fractures. Equally important is the presence of a previous fragility fracture. Despite availability of different evaluation techniques and diagnostic modalities, it has been estimated that only 5% to 25% of Canadian women with fragility fractures are subsequently investigated for osteoporosis, and only half of those receive treatment.^{48,49}

Fragility fracture is defined as a fracture that occurs spontaneously or following a minor trauma, such as a fall from standing height (e.g., a fall from roller skates or ice skates); a fall from a sitting position; a fall from laying down on a bed or a reclining deck chair from less than a meter high; a fall after having missed 1 to 3 steps in a staircase; a fall after a movement outside of the typical plane of motion; or coughing. Some studies have considered fractures that occur as a result of any fall from a height of less than a meter, such as

after having missed 1 to 3 steps in a staircase, as fragility fractures.⁵⁰⁻⁵⁵

Measurement of height loss is a good clinical indicator of vertebral fracture.⁵⁶ Klotzbuecher et al.⁵⁷ performed a meta-analysis of the risk of future fracture, given the history of prior fracture, and concluded that women with prior fracture had a 2- to 10-fold risk of another fracture, compared with those without fracture. This risk was reported to further increase with the number of prior vertebral fractures.

MONITORING: CENTRAL DXA, RADIOGRAPHS, AND BONE TURNOVER MARKERS

Depending on the clinical situation, central DXA scans (lumbar spine and hip) may be repeated in 1 to 3 years. This is usually done to monitor the response to a pharmacologic therapy or to document the stability of bone density in untreated patients at risk for bone loss and to improve adherence to therapy.⁵⁸ Whenever possible, the patient's initial and follow-up scans should be done on the same instrument, using the same procedure. The reader is referred to the recommendations for BMD reporting in Canada, recently published by Osteoporosis Canada.⁴⁰

SOGC Clinical Tip

Depending on the clinical situation, central DXA scans (lumbar spine and hip) may be repeated in 1 to 3 years, on the same instrument, using the same procedure.

Role of Peripheral Bone Mineral Density Testing

Peripheral BMD can be measured by DXA, ultrasound, or single X-ray absorptiometry at several skeletal sites (radius, phalanx, calcaneus, tibia, metatarsal). These technologies are predictive of hip fracture in women over the age of 65, but they cannot be used at the present time for follow-up.^{59,60} Peripheral testing may play an important role for women in underserved areas and in raising awareness about osteoporosis. However, these services may be provided by unregulated practitioners, raising concerns about quality control.

Radiographs

There is renewed interest in vertebral fractures resulting from osteoporosis. The presence of a vertebral fracture increases the risk of a second vertebral fracture at least 4-fold over 3 years.⁶¹ A study of the placebo group in a recent major clinical trial showed that 20% of subjects experiencing a vertebral fracture during the period of observation had a second vertebral fracture within 1 year.⁶²

Vertebral fractures are also indicators of increased risk of fragility fractures at other sites, such as the hip.⁶³

Postmenopausal women with historical height loss greater than 6 cm, prospective height loss greater than 2 cm, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with specific request to rule out vertebral fractures.⁵⁶

SOGC Clinical Tip

Measurement of height loss is a good clinical indicator of vertebral fracture.

Spinal radiographs remain the best method for assessing the presence of vertebral fractures with no satisfactory alternative currently available.⁶⁴ The role of vertebral fracture assessment (VFA) on DXA to define vertebral dimensions without distortion due to parallax is being established.

For the initial assessment of spinal osteoporotic fractures, both the antero-posterior (AP) and lateral projections of both the thoracic and lumbar spines is advised. For follow-up, only the lateral radiographs of the thoracic and lumbar spines are required, as these are the most effective in the detection of osteoporotic fractures.

SOGC Clinical Tip

Antero-posterior (AP) and lateral projections of both the thoracic and lumbar spine radiographs remain the best method for assessing the presence of vertebral fractures with no satisfactory alternative currently available.

Bone Turnover Markers

Bone turnover markers have emerged as powerful tools to help in the management of osteoporosis since they provide information that is different and complementary to BMD measurements.⁶⁵ Because of the coupling between resorption and formation in the remodelling cycle, both markers of bone formation (within 3 to 6 months) and bone resorption (within 1 to 3 months) will decrease or increase in parallel, in response to antiresorptive and anabolic drug therapies. Bone formation markers include serum osteocalcin, bone alkaline phosphatase (BAP), and the C- and N-terminal propeptides of type I collagen (PICP, PINP). Bone resorption markers include urinary hydroxyproline, urinary pyridinoline (PYR), urinary deoxypyridinoline (D-PYR), as well as urinary collagen type I cross-linked N-telopeptide (uNTx), and urinary and serum collagen type I cross-linked C-telopeptide (uCTx and sCTx).

Large prospective population studies in untreated subjects have shown that increased bone remodelling and, more

specifically, an increase in bone resorption markers, are associated with increased vertebral and non-vertebral fractures independently of BMD on a group basis, but their measurements cannot yet be recommended to predict fracture risk on an individual basis.^{39,66,67} Currently, bone turnover markers cannot be recommended for the prediction of bone loss.⁶⁸

The ability to monitor treatment with bone turnover markers to rapidly assess adherence and effectiveness of pharmacological interventions represents the most promising clinical application.⁶⁵ Given the paucity of data, the clinical utility of bone turnover marker changes under anabolic agents is yet to be determined. Currently approved osteoporosis therapies are mostly antiresorptive and produce a rapid reduction of bone turnover that reaches nadir levels in 3 to 6 months, followed by a plateau. For the clinician, the primary concern is the early identification of non-responders, that is, of patients who fail to demonstrate the expected decrease in bone remodelling and, therefore, the expected reduction in fracture risk. The optimal threshold of bone marker change that will lead to the maximal fracture reduction is yet to be defined. However, recent findings from a large fracture trial indicate no further anti-fracture benefit with further decreases in bone resorption markers below a decrease of 55% to 60% for uCTX and 35% to 40% for uNTx.⁶⁹ Further research is needed to establish the cut-offs of each bone turnover markers based on the probability of fracture in large clinical trials of each therapeutic regimen.

To reduce the impact of circadian variability on clinical interpretation of bone turnover markers, it is essential that the timing of sample collection is tightly controlled: early morning (serum before 9:00 AM; first or second morning voided urine, with creatinine correction) after an overnight fast.⁶⁸ In addition, it should be noted that abnormal bone turnover marker values may indicate that a fracture has occurred within the previous 3 months, resulting in accelerated local bone metabolism.⁷⁰

Recent developments using an electrochemiluminescence automated method (Elecys, Roche Diagnostics) to measure N-MID Osteocalcin and PINP (bone formation) and sCTX (bone resorption) with excellent intra- and interassay precisions (CV $\approx$ 5–8%) have improved the ability of bone turnover markers to monitor the individual response to antiresorptive or bone-forming therapies.⁷¹

THERAPEUTICS AGENTS

For a summary of hormonal preparations, refer to chapter 6 of the Canadian Consensus Conference on Menopause, 2006 Update.

SOGC Clinical Tip

Routine supplementation with calcium (1000 mg/d) and vitamin D3 (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs).

For an overview of non-hormonal osteoporosis therapies, refer to Tables 11.4 and 11.5.

Hormone Therapy

Since the publication of results from the 2 hormone randomized controlled clinical trials of the Women's Health Initiative (WHI),^{72,73} guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC)⁷⁴ and a position statement from the North American Menopause Society (NAMS),⁷⁵ recommended the use of HT in postmenopausal women for moderate to severe symptoms of menopause.

The estrogen and progestin component of WHI randomized controlled trials is the first trial with definitive data supporting the ability of conjugated equine estrogens and progestins to prevent clinical fractures at the hip, vertebrae, and other sites, in a population of postmenopausal women not selected for osteoporosis based on BMD testing.⁷² Similar results for prevention of fractures were demonstrated in the estrogen component trial of WHI.⁷³

For symptomatic menopausal women choosing HT as a therapeutic option,⁷⁶ osteoporosis prevention can still be considered as a secondary benefit due to the positive effect ovarian hormones have on BMD. This is supported by results of many studies with BMD as the primary measure.⁷⁷⁻⁷⁹ Both oral and transdermal estrogen therapy (ET) decrease bone loss.⁷⁷⁻⁷⁹ Lower doses of estrogen taken in combination with calcium may also prevent BMD loss.⁸⁰ BMD rises in women who begin ET within five years after menopause.⁷⁷⁻⁷⁹ Postmenopausal treatment with unopposed very-low-dose transdermal estradiol (0.014mg/day) has also been shown to increase BMD and decrease markers of bone turnover without causing endometrial hyperplasia.⁸¹ There is no published data for fracture reduction with these lower doses of estrogen.

SOGC Clinical Tip

For symptomatic menopausal women choosing HT as a therapeutic option, osteoporosis prevention can still be considered as a secondary benefit due to the positive effect ovarian hormones have on BMD.

Table 11.4. Common side effects and contraindications of drugs used in osteoporosis

Drug (trade name)	Common side effects	Contraindications and precautions
Alendronate (Fosamax)	- Abdominal pain - Nausea - Diarrhea	- Abnormalities of the esophagus - Inability to sit/stand upright for 30 minutes - Hypersensitivity to the drug - Women of childbearing potential - Renal insufficiency (# mL/min)
Cyclical etidronate (Didrocal)	- Diarrhea - Nausea - Flatulence	- Clinically overt osteomalacia - Hypersensitivity to the drug - Women of childbearing potential - Renal insufficiency (mL/min)
Nasal calcitonin (Miacalcin NS)	- Rhinitis - Nasal dryness - Epistaxis - Abdominal pain	- Hypersensitivity to the drug - Women of childbearing potential
Raloxifene (Evista)	- Vasodilatation (flushing) - Leg cramps	- History of venous thromboembolic events - Hypersensitivity to the drug - Women of childbearing potential
Risedronate (Actonel)	- Abdominal pain - Hypertension - Joint problems	- Abnormalities of the esophagus - Inability to sit/stand upright for 30 minutes - Hypersensitivity to the drug - Women of childbearing potential - Renal insufficiency (mL/min)
Teriparatide (Forteo)	- Nausea - Dizziness - Leg cramps	- Hypersensitivity to the drug - Pre-existing hypercalcemia - Severe renal insufficiency - Bone metastases or history of bone cancer - Patients at increased risk of developing osteosarcoma that should not be treated with teriparatide: - Paget's Disease - Unexplained elevations of alkaline phosphatase - History of internal or external radiotherapy of the skeleton

HORMONE THERAPY RECOMMENDATION

10. HT should be prescribed to symptomatic postmenopausal women as the most effective therapy for symptom relief (IA) and a reasonable choice for the prevention of bone loss and fracture (IA). The risks should be weighted against the benefits if estrogen therapy is being used solely for fracture prevention. (ID)

Bisphosphonates

Bisphosphonates are naturally occurring analogues of pyrophosphate that bind to hydroxyapatite crystals in bone. There are 3 oral bisphosphonates approved in Canada for the prevention and treatment of osteoporosis: etidronate, alendronate, and risedronate. Etidronate is a non-nitrogen

containing bisphosphonate and has largely been replaced by the more potent nitrogen-containing bisphosphonates alendronate and risedronate.⁹⁵

Eetidronate

Cyclical etidronate is currently prescribed as 400 mg daily for 14 days followed by 76 days of calcium. A meta-analysis of 13 RCTs (of which 6 were placebo controlled) of cyclical etidronate found BMD increased by 4.06% ($P < 0.01$) at the lumbar spine and 2.35% at the femoral neck ($P < 0.01$). There was evidence for the reduction of vertebral fractures (37% reduction; $P = 0.02$) but not for non-vertebral fractures ($P = 0.97$).^{88,96}

TABLE 11.5. Non-hormonal osteoporosis medications

Treatment	Regimen
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)
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
Prevention	Regimen
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.

Alendronate

The most commonly prescribed alendronate dose is currently 70 mg once weekly or 10 mg daily. A meta-analysis included 11 randomized placebo-controlled trials of 12 855 postmenopausal women.⁹⁷ These trials were of at least 1-year duration and used daily doses ranging from 5 to 40 mg. BMD increases were dose dependant, particularly for doses 10 mg or greater. Three years of therapy with alendronate resulted in BMD increases of 7.48% ($P < 0.01$) in the lumbar spine and 5.6% ($P < 0.01$) in the total hip. The pooled relative risk reduction for vertebral fractures with doses of 5 mg or greater was 48% ($P < 0.01$); and in those who were treated with doses of 10 mg or greater, the relative risk reduction in non-vertebral fracture was 49% ($P < 0.01$).⁹⁷

In postmenopausal women with a prevalent vertebral fracture from the vertebral fracture arm of the Fracture Intervention Trial (FIT), treatment with alendronate reduced the incidence of hip fractures by 51% ($P = 0.047$) over 3 years.⁹⁸ In a post hoc pooled analysis of the vertebral fracture and clinical fracture arms of FIT, alendronate reduced the relative risk of hip fracture by 53% ($P = 0.005$) over 3 to 4 years in postmenopausal women with a prevalent vertebral fracture or a femoral neck BMD T-score of -2.5 or less.⁹⁹ In this post hoc analysis, alendronate has been found to reduce fractures both in high risk women with vertebral fractures and those with osteopenia.⁹⁹ Furthermore, clinical vertebral fracture rate reduction (59%; $P < 0.001$) was demonstrated as early as one year into the study.⁹⁹ In a more recent post

hoc analysis of a subgroup of women who had T-scores of -1.6 to -2.5, there was a relative risk reduction in clinical and radiographic fractures of 60 ($P = 0.005$) and 43% ($P = 0.002$) respectively, compared with placebo with 3 years of therapy.¹⁰⁰ Fractures appear to remain significantly reduced up to 7 years on therapy, with BMD increases of 11.4% at the lumbar spine.¹⁰¹

SOGC Clinical Tip

Alendronate (Fosamax) has been found to reduce fractures both in high-risk women with vertebral fractures and those with osteopenia. The most commonly prescribed alendronate doses are currently 70 mg once weekly or 10 mg daily.

Risedronate

Risedronate is prescribed either at 35 mg once weekly or 5 mg daily. A meta-analysis of eight randomized placebo-controlled trials of 14 832 postmenopausal women with osteoporosis examined the efficacy of risedronate in doses ranging from 2.5 to 5 mg daily in trials of at least 1-year duration. A dose-dependant improvement was associated with the 5 mg dose. BMD increased by 4.54% at the lumbar spine ($P < 0.01$) and 2.75% ($P < 0.01$) at the femoral neck. Patients taking 5 mg of risedronate daily demonstrated relative risk reduction of 38% ($P = 0.01$) in vertebral fractures and of 32% ($P < 0.01$) in non-vertebral fractures, compared with those taking placebo.¹⁰²

A significant reduction in new vertebral fractures in high-risk women with osteoporosis and vertebral fractures (61–65%) has been observed within the first year of therapy in the VERT trials.^{103,104} These risk reductions have subsequently been demonstrated in individuals with and without vertebral fractures.¹⁰⁵ In addition, non-vertebral fractures were reduced by 74% within 1 year of risedronate therapy.¹⁰⁶ A post hoc analysis of the VERT trials has also demonstrated risedronate efficacy at reducing relative risk for clinical vertebral fractures (80% reduction, $P < 0.05$; 1 [0.1%] risedronate patient versus 12 [1.0%] placebo patients) in just 6 months.¹⁰⁷

A similar post hoc analysis combining BMD and VERT trials demonstrated a significant reduction in relative risk for non-vertebral fractures (66% reduction, $p < 0.05$) as early as 6 months.¹⁰⁶

BMD continues to increase with long-term use. The mean increase from baseline in lumbar spine BMD over 5 years was 9.3% ($P < 0.001$).¹⁰⁸ The relative risk of new vertebral fractures was significantly reduced with risedronate treatment in years 4 and 5 by 59% ($P = 0.01$). The mean increase from baseline in lumbar spine BMD over 7 years was 11.5% ($P < 0.05$).¹⁰⁹

In a large RCT designed to determine hip fracture efficacy, risedronate was shown to reduce hip fracture rates in those with low femoral neck BMD by 40% ($P = 0.009$) and prior vertebral fractures by 60% ($P = 0.003$).¹¹⁰ Nonskeletal clinical risk factors (other than low BMD) did not identify a population that benefited from treatment, although it did identify a population at increased risk of hip fracture.

SOGC Clinical Tip

A significant reduction in new vertebral fractures in high-risk women with osteoporosis and vertebral fractures has been observed within the first year of therapy with risedronate (Actonel). Risedronate is prescribed either at 35 mg once weekly or 5 mg daily.

Tolerability and Safety

Adverse effects from bisphosphonates are rare, and in a meta-analysis of cyclical etidronate,⁹⁶ alendronate,⁹⁷ and risedronate,¹⁰² there was no difference in withdrawals, compared with placebo for adverse events. The most frequent concerns associated with cyclical etidronate are diarrhea, nausea, and, rarely, osteomalacia if cyclical therapy is not used.

Nitrogen containing bisphosphonates (alendronate and risedronate) may be associated with gastrointestinal side effects in patients with prior upper gastrointestinal disease, concomitant nonsteroidal anti-inflammatory drug use, and those already using antireflux medications.^{111,112}

Once weekly bisphosphonates may reduce adverse effects and increase adherence. Once weekly alendronate (70 mg) and risedronate (35 mg) have been found to be equivalent to daily dosing at the lumbar spine, hip, and total body BMD.^{113–115} Increasing age and the presence of non-vertebral fractures have been found to be independent predictors of adherence in postmenopausal women.¹¹⁶

To minimize the risk for esophagitis, patients must take bisphosphonates on an empty stomach with a full glass of water, then remain upright and avoid food, beverage, and other medications for 30 minutes. Patients who have mechanical problems of the esophagus, renal dysfunction (creatinine clearance < 30 mL/min), hypersensitivity to the drug, or suffer from hypocalcemia should avoid bisphosphonates.⁹⁵

BISPHOSPHONATES RECOMMENDATIONS

11. Treatment with alendronate or risedronate should be considered to decrease vertebral, non-vertebral, and hip fractures. (IA)
12. Treatment with etidronate can be considered to decrease vertebral fractures. (IB)

NEWER AGENTS, COMBINATION THERAPY

Selective Estrogen Receptor Modulators

SERMs consist of a group of structurally diverse compounds that are distinguished from estrogen by their ability to interact with estrogen receptors, but act either as an estrogen agonist or antagonist depending on the particular environment. A receptor changes its shape when a SERM binds to it, and its particular shape determines which gene it will activate. Subsequently, the activated genes will produce proteins that regulate different processes in the body, such as bone remodelling. Presently, raloxifene is the only SERM approved in Canada for the management of osteoporosis. Raloxifene exhibits agonist effects on the bone and cardiovascular system and antagonist effects on the breast and uterus.

The anti-fracture efficacy of raloxifene is well established by the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a large RCT of postmenopausal women with or without prevalent vertebral fractures with BMD scores of -2.5 and lower in either the lumbar spine or the hip. Raloxifene is efficacious (vertebral fracture reduction of 30% in women with and 55% in women without prevalent fractures in 3 years),^{82,83} sustainable (50% in fourth year versus 55% in years 0–3),⁸⁴ fast acting (68%, $P = 0.01$, in a 1-year post hoc analysis).⁸⁵ The risk reduction for non-vertebral fractures in the overall MORE population is not significant, but a reduction of 47% ($P = 0.04$) is noted in a post hoc analysis of patients with severe (semi-quantitative grade 3)

prevalent vertebral fractures.⁸⁶ In another post hoc analysis of postmenopausal women without baseline vertebral fracture who are osteopenic at the total hip by NHANES III criteria, treatment with 60 mg per day of raloxifene significantly reduced the risk of new vertebral fractures (47% reduction) and new clinical vertebral fractures (75% reduction).⁸⁷

A meta-analysis of seven randomized placebo-controlled trials of raloxifene found BMD increased by 2.51% ($P < 0.01$) at the lumbar spine and 2.11% at the total hip ($P < 0.01$). There was evidence for the reduction of vertebral fractures (40% reduction; $P = 0.01$) but not for non-vertebral fractures ($P = 0.24$).⁸⁸

In the prevention trials, it was reported that fewer women in the raloxifene treatment group progressed from normal to osteopenia, and from osteopenia to osteoporosis.⁸⁹

In addition to its skeletal effects, the MORE trial demonstrates that raloxifene reduces breast cancer by 76% in postmenopausal women with osteoporosis.⁹⁰ The recent results of Continuing Outcomes of Raloxifene Evaluation (CORE), the extension arm of the MORE trial, confirm that the breast cancer reduction effect in osteoporotic women lasts up to 8 years, with a reduction rate of 66%.⁹¹

Unlike the HERS and WHI trials, which indicated an increased risk of cardiovascular events, the MORE trial did not demonstrate harmful effects of raloxifene on the cardiovascular system. In fact, in a subset of women at high risk of cardiovascular diseases, it may have a beneficial effect.⁹²

Until more results are published in the STAR and RUTH trials, raloxifene is not recommended for prevention of breast cancer or cardiovascular diseases.

SOGC Clinical Tip

Because of its vertebral fracture efficacy data and its additional extraskeletal benefits, raloxifene (Evista) 60 mg daily is recommended to prevent and treat osteoporosis in younger, asymptomatic postmenopausal women.

Tolerability and Safety

The side effects of raloxifene are minimal, with increased incidence of leg cramps and hot flashes (especially in the younger postmenopausal women). The incidence of deep venous thrombosis doubles, but the absolute incidence is small. Venous thromboembolism is a serious side effect associated with raloxifene, although it is reported infrequently: 1.44 and 3.32 events per 1000 woman-years for placebo and raloxifene 60 mg per day.⁹⁰ The magnitude of the relative risk is similar to that observed with both HRT

or HT^{72,93} and tamoxifen.⁹⁴ Patients are advised to stop using raloxifene a few days prior to major surgeries or long-haul international travel.

SELECTIVE ESTROGEN RECEPTOR MODULATORS RECOMMENDATION

13. Treatment with raloxifene should be considered to decrease vertebral fractures. (IA)

Calcitonin

Calcitonin is a hormone, produced in the thyroid gland, which is effective in specifically inhibiting osteoclastic bone resorption. Poor oral absorption necessitates either subcutaneous or intranasal administration. Nasal spray calcitonin 200 IU is approved for the treatment of postmenopausal osteoporosis.¹²⁹ BMD stabilizes at the lumbar spine and at the hip, similar to the effect of calcium and vitamin D.¹²⁹

A meta-analysis of 30 RCTs (of which 15 were placebo controlled) of calcitonin found a significant relative risk reduction of 21% ($P = 0.05$) in vertebral fractures but not in non-vertebral fractures ($P = 0.12$).⁸⁸

In the PROOF study, nasal salmon calcitonin significantly reduced vertebral fractures by 33% to 36% using a daily dose of 200 IU in postmenopausal women with and without prior vertebral fracture.¹²⁹ No anti-fracture effect has been shown with 100 IU or 400 IU doses, and there is no significant reduction in rates of non-vertebral or hip fracture. Some women report the side effect of rhinorrhea. Nasal spray calcitonin has a possible analgesic effect that may be useful in managing the pain of acute vertebral compression fractures. Nasal spray dosing is convenient and flexible.

SOGC Clinical Tip

Nasal spray calcitonin 200 IU (Miacalcin) is approved for the treatment of postmenopausal osteoporosis and has a possible analgesic effect that may be useful in managing the pain of acute vertebral compression fractures.

WHEN TO INITIATE THERAPY

Previous guidelines from the Osteoporosis Society of Canada (now called "Osteoporosis Canada") advised to consider pharmacologic intervention based on an individual's lowest BMD T-score not adjusted for age, as a marker of relative fracture risk and a threshold that varies based on the absence or presence of fragility fracture and other risk factors for fracture.³⁹

Table 11.6. Ten-year fracture risk for women⁴⁰

Age (years)	Low risk <10%	Moderate risk 10%–20%	High risk >20%
Lowest T-Score Lumbar spine, total hip, femoral neck, trochanter			
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

Although this was major progress compared with the thresholds derived from the WHO, there were still several weaknesses associated with that system:

1. On its own, a T-score is not the optimal diagnostic parameter for clinical decision making.¹³⁰
2. More than half of the osteoporotic fractures occurred in women with a BMD-T score of -1.0 to -2.5, in a large longitudinal observational study in the US.¹³¹
3. Absolute fracture risk can vary substantially within any WHO category due to modification of risk by other factors such as age and sex.¹³²

Therefore, the OSC now proposes that age, sex, fracture history, and glucocorticoid use be incorporated into the assessment of fracture risk.⁴⁰ Additional clinical variables may be included in the absolute fracture risk estimate in the future when the methods are more firmly established and validated. The OSC recommends using the lowest BMD T-score to determine a person's 10-year absolute fracture risk: combined risk for fractures of the hip, spine, forearm, and proximal humerus⁴⁰ (Table 11.6).

There are 3 categories for absolute risk: low (less than 10%), moderate (10% to 20%), and high (over 20%). Fragility fracture after age 40 or glucocorticoid use increase risk categorization to the next level: from low risk to moderate risk, or from moderate risk to high risk.

Co-therapy with bisphosphonates should be initiated in women (with or without HT) receiving or planning to receive a daily dose of prednisone of > 7.5 mg (or equivalent) for more than 3 months.³⁹ Pharmacological intervention should be considered in women at high risk of fracture, particularly those known to have low BMD or prevalent fragility fracture. However, not all clinical risk factors for fracture are amenable to pharmacotherapy. For example, in a

non-osteoporotic individual with high risk of falling, a fall prevention program could be preferred to pharmacotherapy.

In low-risk women, the therapeutic intervention could be limited to counselling about bone hygiene, that is, nutrition (adequate calcium and vitamin D through diet and/or supplements), physical exercise, and risk-factor modification (smoking, alcohol, weight).

In moderate-risk women, pharmacological intervention could be considered on the basis of a woman's perception of a serious threat arising from the disease (e.g., strong family history of osteoporotic fracture), or on the basis of the extra skeletal benefits associated with some therapeutic options such as raloxifene; either of these will lead to an improved persistence.

LENGTH OF THERAPY

This issue is simple for teriparatide, the only anabolic agent currently available in Canada. According to its labelling, the duration of treatment with teriparatide is limited to 18 months in Canada. However, for the antiresorptives, there is no current definitive answer to this question. Anti-fracture efficacy has been evaluated in placebo-controlled trials of 3,^{82,96,97,102,103,104} 4,^{84,97,102} or 5 years duration.^{72,73,108,133}

The antiresorptive drugs appear to be safe up to 5,^{72,73} 7,¹⁰⁹ 8,⁹¹ and 10 years¹³⁴ for HT, risedronate, raloxifene, and alendronate, respectively. Except for a rapid loss of hip fracture protection after estrogen discontinuation,¹³⁵ no fracture data are available after discontinuation of any of the other antiresorptive drugs.

CALCITONIN RECOMMENDATION

14. Treatment with calcitonin can be considered to decrease vertebral fractures and to reduce pain associated with acute vertebral fractures. (IB)

Parathyroid Hormone

Parathyroid hormone (PTH) and its analogues represent a new class of anabolic agents for the treatment of severe osteoporosis. Unlike current antiresorptive agents, which act primarily by inhibiting bone resorption and remodelling to increase bone mass, PTH directly stimulates osteoblast activities and markedly increases bone formation to a greater extent than bone resorption.

Teriparatide (recombinant human PTH(1-34), the only approved drug in this class, is an analog of parathyroid hormone which has shown a significant relative risk reduction in vertebral (65%; $P < 0.001$) and non-vertebral fractures (53%; $P = 0.02$).¹¹⁷

Teriparatide is administered as a daily subcutaneous injection of 20 mcg and is approved for therapy of up to 18 months. This regimen increased lumbar spine BMD by 9.7% ($P < 0.001$), total hip BMD by 2.6% ($P < 0.001$), and femoral neck BMD by 2.8% ($P < 0.001$).¹¹⁷

Jiang et al. conducted a histomorphometric study of paired bone biopsies from the teriparatide clinical trial. Women receiving teriparatide had significant increases in cancellous bone volume and cancellous trabecular number and connectivity density, as well as an increase in cortical thickness.¹¹⁸

This unique improvement of bone microarchitecture illustrates the bone forming properties of teriparatide and distinguishes it from the maintenance observed with bisphosphonates.¹¹⁹

Because of its cost and its unique anabolic property, teriparatide is usually reserved for patients with severe osteoporosis.

SOGC Clinical Tip

Teriparatide (Forteo) is administered as a daily subcutaneous injection of 20 mcg and is approved for therapy of up to 18 months. It is recommended for patients with prior fragility fractures; patients with very low BMD, below -3 to -3.5; or patients who continue to fracture or to lose BMD while taking antiresorptive therapy.

Tolerability and Safety

No major adverse reactions have been associated with teriparatide. Compared with placebo, teriparatide 20 µg per day has a higher incidence of nausea, dizziness, and leg

cramps. Hypercalcemia is an occasional occurrence, but is rarely clinically significant.¹¹⁷ Teriparatide produced osteosarcoma in rats who received the drug at doses 3 to 58 times higher than the human therapeutic dose for virtually their entire lifespan, that is, from the age of 8 weeks to 2 years.¹²⁰ Reported osteosarcomas in Fischer 344 rats are unlikely to predict an increased risk for osteosarcoma subsequent to the therapeutic use of teriparatide in women with severe osteoporosis at the dosage recommended in the product monograph, namely 20 µg per day subcutaneously for 18 months.

Teriparatide should not be used in patients with metabolic bone diseases other than osteoporosis (osteomalacia, primary or secondary hyperparathyroidism, Paget's disease of the bone, hypercalcemia), in patients with cancer or are at risk for bone metastasis, or in patients who have previously undergone bone radiation therapy. Teriparatide is also contraindicated in children and adolescents as well as during pregnancy and while breastfeeding. Known allergy to the product or its excipient also contraindicates its use. Safety of teriparatide use in the presence of renal impairment has not been established and, consequently, is not recommended.

PARATHYROID HORMONE RECOMMENDATION

15. Treatment with teriparatide should be considered to decrease vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. (IA)

Combination Therapy

Combination of Antiresorptives

The addition of bisphosphonate therapy (alendronate, risedronate, and cyclic etidronate) to long-term ET in women has been shown to improve bone density; when alendronate is added to ET, BMD increases by 3% after 2 years.^{121,122} Other combination therapies (e.g., calcitonin and estrogen, raloxifene and alendronate), also increase bone density. However, fracture data are lacking. Because of the additional cost and side effects and the lack of fracture efficacy, combination therapies are usually not recommended.

Combination of PTH Therapy and Antiresorptives

It appears that bisphosphonates may slightly blunt the effect of PTH therapy if they are given concurrently or preceding PTH therapy.¹²³ There is good evidence that giving bisphosphonates after a course of PTH therapy will enhance and maintain the bone mass.¹²⁴ Estrogen and raloxifene do not appear to have the blunting effect on PTH therapy.¹²⁵⁻¹²⁸ Fracture data are lacking and combination therapies are usually not recommended. Sequential

therapies preceding or following PTH treatment are useful in maintaining and enhancing bone mass.

When HT is used for symptomatic treatment of postmenopausal women, the addition of bisphosphonates or PTH is indicated in the following situations: significant bone loss despite use of HT; glucocorticoid therapy (at least 7.5 mg prednisone/day, or equivalent, for at least 3 months); and osteoporotic fracture in a woman on HT.

COMBINATION THERAPY RECOMMENDATION

16. Although combination of antiresorptive therapies may be synergistic in increasing BMD, the anti-fracture effectiveness has not been proven; therefore, it is not recommended. (ID)

SUMMARY

Osteoporosis and its consequent increase in fracture risk is a major health concern for postmenopausal women, and has the potential to reach epidemic proportions. Low BMD, clinical risk factors for fragility fractures, indices of vertebral fracture such as height loss and kyphosis, and radiographic vertebral fractures are combined in a new paradigm to estimate the 10-year fracture risk and develop treatment protocols for the most at risk women.

Well-designed RCTs have proven the efficacy of drugs such as bisphosphonates, calcitonin, estrogen and progestin therapy, SERMs, and recombinant human PTH (1-34) to treat osteoporosis. These studies also proved undoubtedly that drug therapies for osteoporosis can reduce risk of fractures and improve quality of life. However, the studies' beneficial results are obtained under ideal conditions; but in real life, effectiveness (efficacy in real practice) matters more than efficacy. Compliance with and adherence to a specific drug may influence effectiveness. Finally, adequate calcium and vitamin D through diet and/or supplements are essential adjuncts to osteoporosis prevention and treatment.

CONCLUSION

In this document, we have outlined clinical decision making to manage postmenopausal women: diagnosis, risk assessment, appropriate investigations, non-pharmacologic and pharmacologic treatments, and monitoring of response to therapy.

We hope this information will assist you in your clinical practice, particularly in selecting the appropriate postmenopausal women to be tested and treated for osteoporosis, as well as the investigations and therapeutic options best suited for postmenopausal patients with osteoporosis.

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