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2002 Update

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following Advisory Committee Review

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THE CANADIAN CONSENSUS ON
MENOPAUSE AND OSTEOPOROSIS - 2002 UPDATE

The original Consensus document was prepared and reviewed by the Committee on Menopause and Osteoporosis, approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada, and endorsed by the Osteoporosis Society of Canada.

This 2002 Update reflects revised recommendations after the findings of the WHI study were reviewed.

CONSENSUS EDITOR
Timothy Rowe, MB, BS, FRCS, Vancouver, BC

CONFERENCE EDITORS
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June Rogers, Toronto, ON
Barbara B. Sherwin, PhD, Montreal, QC
Thirza Smith, MD, FRCS, Saskatoon, SK
Michèle A. Turek, MD, FRCP, Ottawa, ON
Chui Kin Yuen, MD, FRCS, FACOG, Winnipeg, MB

CONTRIBUTING AUTHORS
Thomas E.R. Brown, PharmD, Toronto, ON
Gisèle Bourgeois-Law, MD, FRCS, Winnipeg, MB

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Abstract

Objectives: To define the standard of care for menopausal women in Canada. To assist women and their caretakers in making informed choices to improve their quality of life by promoting health and preventing disease.

Options: The areas of perimenopause and menopause were explored under the headings of healthy living; sexual health; hormone replacement therapy in relation to cardiovascular disease, cancer, and the brain; osteoporosis; medical and special conditions; pharmacotherapy; complementary approaches; and evaluation, decision-making, and follow-up.

Outcomes: Improved health and quality of life for perimenopausal, menopausal, and postmenopausal women in Canada.

Values: References were collected through Medline searches and comparison made to existing current guidelines and consensus documents for consistency.

Evidence: The level of evidence has been determined using the criteria described by the Canadian Task Force on the Periodic Health Examination.

Benefits, Harms, and Costs: Utilization of the information and recommendations by Canadian health professionals will enhance the health and quality of life for perimenopausal, menopausal, and postmenopausal women in Canada.

Recommendations: Recommendations were grouped according to section themes. A detailed list of recommendations is available in the Executive Summary.

Validation: Recommendations were reviewed and revised by the Canadian Consensus Conference on the Menopause and the SOGC Council, and endorsed by the Osteoporosis Society of Canada.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

EXECUTIVE SUMMARY

Thirza Smith, MD, FRCSC, 1 Elizabeth Contestabile, RN, BScN2

1 Saskatoon, SK
2 Ottawa, ON

To assist women and their caregivers in making informed choices to improve their quality of life by promoting health and preventing disease.1 Canadian statistics show an increase in life expectancy for menopausal women. In 1922, a 50-year-old woman lived, on average, until age 75.2 Today, a woman the same age can expect to live until her mid-80s.3 In the year 2000, it was estimated that more than 4.75 million women (17% of the population) were aged 50 or older in Canada;4 by 2006, this number is projected to be 5.6 million.5 The increasing number of women over 70 are particularly vulnerable to conditions listed in Figure 1.

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, who have premature ovarian failure, undergo menopause before the age of 40.6 The increasing number of women dealing with conditions affected by menopause, early or otherwise (Figure 2), has resulted in a re-examination of the traditional approaches to mature women's health care. The experience and the reporting of symptoms vary widely among individuals and cultures. While usually not a serious threat to health, symptoms may negatively affect quality of life. Notably, the majority of women experience menopause as a normal event without significant difficulty.

The traditional approach of diagnosing and treating disease is no longer sufficient; health promotion and disease prevention strategies must be incorporated into every 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 as well as 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.7 Health care providers can also advocate for women
in an effort to overcome social (poverty, violence, lack of education) and geographical barriers to health.\(^8\)

Recommendations for practice must be based on scientific evidence, with ongoing research to determine the most effective interventions. Preventive health care standard strategies, including counselling, screening for diseases, and immunization, should be used regularly. While much discussion has centred on the effectiveness of hormone replacement therapy and other medications in the prevention of specific postmenopausal 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. Evidence supports counselling about such issues as smoking cessation, exercise, risk factors for falls, nutrition, alcohol use, safe driving, and use of seatbelts.\(^8\)

Recognition of the multidimensional nature of the menopause experience is essential. Physiological, psychological, developmental, and sociocultural factors must be considered. The SOGC recommends that every woman have the opportunity to make informed choices about her own health promotion, disease prevention, and quality of life issues. 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.

**METHODS**

A multidisciplinary panel of experts from across Canada was convened to review the literature to March 2001 and to update the 1998 guidelines document developed during the Canadian Consensus Conference on Menopause and Osteoporosis. The same format has been followed, but each section has been updated, some sections have been extensively rewritten, and new sections have been added on perimenopause and healthy living.\(^9\)

The panel met on three occasions: in November 2000 and February 2001 in Montreal and in April 2001 in Toronto. The panel, chaired by Robert Lea, was divided into several working groups in order to research, analyze, and prepare the draft of the thirteen sections of the document. Four senior editors were appointed to guide the process of developing final drafts.

**FIGURE I**

NUMBER OF 50-YEAR-OLD WOMEN IN 1000 WOMEN (VERTICAL AXIS) TO BE AFFECTED BY SPECIFIC DISEASES OVER THE NEXT 25 AND 35 YEARS

Source: Special tabulation, POHEM, Statistics Canada.\(^5\)
Each topic was discussed thoroughly by the entire panel. Where consensus was not reached, a majority decision was made. At times the recommendations are broad in scope, and are intended to be used as a guide in management. These were rated according to the Canadian Task Force on the Periodic Health Examination (Table 1).

SECTION A: PERIMENOPAUSE

RECOMMENDATIONS:

A1. Health care providers should not use random serum markers of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol E2 for the purpose of predicting menopause since clear markers for predicting menopause are yet to be identified. (II-2)

A2. In addition to providing effective contraception, low-dose oral contraceptives are an effective treatment for symptomatic, healthy, non-smoking perimenopausal women. (I)

A3. Using the data from studies in postmenopausal women and clinical expertise as a guide, estrogen replacement therapy (ERT) or hormone replacement therapy (HRT) may be considered as a treatment option for those perimenopausal women whose symptoms are disruptive. (III)

SUMMARY OF KEY POINTS:

A4. Perimenopause is characterized by fluctuating hormone levels, irregular menstrual cycles, and the onset of symptoms that may increase in number and severity as menopause approaches. (II-2)

A5. The perimenopause is an optimal period for preventive health care based on an individualized assessment, adoption of a healthy lifestyle, and involvement of the woman in decisions regarding treatment options and their risk-benefit assessment. (III)

SECTION B: MENOPAUSE: HEALTHY LIVING

RECOMMENDATIONS:

B1. Health care providers should encourage patients to consider lifestyle modifications such as exercise, optimal diet, and smoking cessation, as these lifestyle changes can reduce the risk of cardiovascular disease and osteoporosis. (I, II-2)

B2. The principles of health promotion and disease prevention should be encouraged in all perimenopausal and postmenopausal women. (III)

SECTION C: SEXUAL HEALTH

RECOMMENDATIONS:

C1. All health care providers dealing with menopausal women should be versed in the appropriate counselling and management of menopause and related sexual health issues. (III)

C2. In women with vaginal atrophy, health care providers may consider the use of local estrogen therapy as an effective mode of treatment or consider vaginal moisturizers as effective alternatives. (I, II-1)

C3. In women with decreased libido who have undergone bilateral oophorectomy, adding androgen to estrogen therapy has been shown to be effective in increasing libido (I). Androgen therapy may be administered to estrogen-treated postmenopausal women who have decreased libido not explained by any other factors. A risk-benefit profile has not been determined from studies with sufficiently large patient numbers. (III)

C4. Routine evaluation of hormone levels (specifically measuring serum androgen levels) in postmenopausal women with

FIGURE 2

CONDITIONS AFFECTED BY THE MENOPAUSE

<table>
<thead>
<tr>
<th>Menstrual Changes</th>
<th>Vasomotor/Flushes</th>
<th>Mood Disturbances</th>
<th>Urogenital Atrophy</th>
<th>Rate of Bone Loss</th>
<th>Fractures</th>
<th>Cardiovascular Disease</th>
<th>Alzheimer’s Disease</th>
<th>Breast Cancer</th>
<th>Colon Cancer</th>
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<td>Final Menstrual Period</td>
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<td>70</td>
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psychosexual problems is not recommended. (III) Sildenafil citrate does not appear to improve sexual response in estrogenized women (III). However, it may do so in women with decreased libido associated with use of selective serotonin re-uptake inhibitors (SSRIs) (III).

SECTION D: HRT AND CARDIOVASCULAR DISEASE RECOMMENDATIONS:

D1. Hormone replacement therapy (oral continuous-combined conjugated equine estrogens [CEE] and medroxyprogesterone acetate [MPA]) (I) or other regimens (III) should not be initiated or continued for the sole purpose of preventing future cardiovascular events (primary and secondary prevention). (I)

D2. All women should be counselled about the beneficial effects of lifestyle modifications on reducing the risk of future cardiovascular events. Appropriate modifications include consumption of a heart-healthy diet, cessation of smoking, moderate daily exercise, and maintenance of healthy body weight. (II)

D3. To prevent future cardiovascular events, women should be prescribed therapies for which there is abundant scientific evidence, such as antihypertensive and lipid-lowering medications, β-adrenergic blockers, antiplatelet agents, and angiotensin-converting enzyme (ACE) inhibitors, with due attention to the potential risks or adverse effects of any of these therapies. (I)

SECTION E: OSTEOPOROSIS RECOMMENDATIONS:

E1. Evaluation of fracture risk in postmenopausal women should include the assessment of risk factors, with bone mineral density measurement for those at increased risk.
   a) Central (hip and spine) measurements by dual energy X-ray absorptiometry (DEXA) are the most accurate and precise measurements of bone density available, making them useful for both risk assessment and follow-up. (I)
   b) Peripheral bone mass measurements (e.g., ultrasound or DEXA measurements in the radius, phalanx, or heel) is useful for fracture risk assessment, but cannot be used for follow-up. (I)

E2. Physicians should be aware that a prevalent vertebral or non-vertebral fragility fracture markedly increases the risk of future fracture. (I)

E3. Markers of bone resorption, while useful in documenting group responses in large clinical trials, have no clear place in the evaluation of follow-up of individual patients. (II)

E4. Women should be encouraged to have adequate intake of calcium and vitamin D, good nutrition and exercise, avoidance of negative lifestyle habits (smoking, alcohol). A normal exposure to estrogen during reproductive life and exercise contribute to optimal achievement and maintenance of genetically determined peak bone mass. These recommendations are applicable to all women (II); for early postmenopausal women, adequate calcium and vitamin D intake alone is not sufficient to maintain bone mass. (I)

E5. Although combination of antiresorptive therapies may be

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<thead>
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<th>TABLE 1 QUALITY OF EVIDENCE ASSESSMENT10</th>
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<td>The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.</td>
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<tr>
<td>I: Evidence obtained from at least one properly randomized controlled trial.</td>
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<td>II-1: Evidence from well-designed controlled trials without randomization.</td>
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<td>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</td>
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<tr>
<td>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940’s) could also be included in this category.</td>
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<td>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</td>
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<th>TABLE 1 CLASSIFICATION OF RECOMMENDATIONS10</th>
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<tr>
<td>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.</td>
</tr>
<tr>
<td>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</td>
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<tr>
<td>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</td>
</tr>
<tr>
<td>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</td>
</tr>
<tr>
<td>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</td>
</tr>
<tr>
<td>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</td>
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synergistic in increasing bone mineral density, their effect on fracture has not been proven. Combination therapy should be reserved for patients not responding to single-agent antiresorptive therapy. (I)

SUMMARY OF KEY POINTS:
E6. The goal of osteoporosis management is the prevention of fracture. This may or may not be associated with significant increases in bone mineral density. (I)
E7. Postmenopausal bone loss can be effectively prevented by antiresorptive therapy such as estrogen replacement, selective estrogen receptor modulator, or bisphosphonate therapy. (I)
E8. Treatment with alendronate or risedronate has been demonstrated to decrease both vertebral and non-vertebral fractures including hip fractures (I); treatment with raloxifene, or calcitonin, has been demonstrated to reduce vertebral fractures (I); treatment with estrogen or etidronate appears to reduce vertebral fracture (II). Physicians should consider a range of treatment options for osteoporosis.
E9. According to the WHI study, continuous combined HRT was effective in reducing the risk of hip fractures (5 fewer cases per 10,000 women per year). Vertebral and other fractures were also reduced.

SECTION F: UROGENITAL HEALTH
RECOMMENDATIONS:
F1. Urodynamic studies should be performed prior to incontinence surgery or when there is mixed incontinence. (II-3)

SUMMARY OF KEY POINTS:
F2. Urogenital aging may result in urinary urge and stress incontinence, recurrent urinary tract infection, and pelvic organ prolapse.
F3. There is no objective benefit from estrogen replacement therapy for postmenopausal urinary stress incontinence. (I)
F4. There is neither objective nor subjective benefit from estrogen replacement therapy for postmenopausal urge incontinence. (I)
F5. Estrogen therapy decreases the incidence of recurrent urinary tract infections in postmenopausal women. (I)

SECTION G: MEDICAL AND SPECIAL CONDITIONS
No specific recommendations.

SECTION H: HORMONES AND THE BRAIN
SUMMARY OF KEY POINTS:
H1. Estrogen positively influences brain structures and functions that are known to be critical for memory. (I)
H2. In healthy postmenopausal women, estrogen protects against the deterioration in short- and long-term memory that occurs with normal aging. (I)
H3. Estrogen replacement is associated with a reduction in the risk of developing Alzheimer’s disease in postmenopausal women (II-2), but does not affect the progression of deterioration in women with diagnosed Alzheimer’s disease. (I)
H4. Estrogen effectively enhances mood in women with dysphoria or mood lability (I), but there is no evidence that estrogen alone is an effective treatment for clinical depression. The addition of progestin may attenuate the beneficial effect of estrogen on mood and on cognition in some women. (I)
H5. At present, there is no evidence that raloxifene influences cognitive functioning or mood. (I)

SECTION I: PHARMACOTHERAPY
RECOMMENDATIONS:
I1. The route of estrogen delivery should be primarily determined by patient preference, with the objective of using the lowest effective dose. (III)
I2. Physicians should consider alternate routes of administration such as vaginal and transdermal administration. (III)
I3. Physicians should be aware that women who wish to use continuous combined HRT long term (five or more years) should be re-evaluated annually. (III)

SECTION J: HORMONE REPLACEMENT THERAPY AND CANCER
RECOMMENDATIONS:
J1. No estrogen-progestin regimen is completely protective against endometrial carcinoma, and all unscheduled uterine bleeding should be investigated. (II-3)
J2. Estrogen-progestin therapy should not be withheld from women with treated stage 1 and 2, grade 1 or 2 adenocarcinoma of the endometrium who have moderate to severe menopausal symptoms. (II-3)
J3. According to the WHI study, physicians should inform their patients that the use of estrogen-progestin treatment increases the risk of breast cancer after 5 years of use but not in a statistically significant way. The risk returns to baseline after 5 years of stopping therapy. (I)
J4. There should be increased breast surveillance for women who are at high risk of developing breast cancer when using estrogen-progestin therapy. (III)
J5. In very special circumstances, women at increased risk of developing breast cancer or who have been treated for breast cancer may be prescribed low dose estrogen-progestin therapy for severe symptoms unrelieved by effective alternative therapies, after risks and benefits have been extensively discussed. The duration of therapy should be regularly reviewed; there is no preventative role for estrogen therapy in this population. (III)
J6. Physicians should be aware that the reported effects of estrogen-progestin therapy on ovarian cancer have been inconsistent. A possible increased risk may occur in women...
on long-term estrogen-only therapy (10 or more years). (I)

SUMMARY OF KEY POINTS:
J7. Unopposed estrogen therapy substantially increases the risk of developing atypical endometrial hyperplasia (I) and endometrial carcinoma (II-2). The appropriate dose and duration of progestin therapy will reduce these estrogen-associated risks.
J8. Continuous combined HRT was associated with a reduction in the risk of colorectal cancer, which failed to reach statistical significance (6 fewer cases per 10,000 women per year). (I)

SECTION K:
MENOPAUSE: COMPLEMENTARY APPROACHES
RECOMMENDATIONS:
K1. Physicians and their patients should be more aware of complementary therapies in order to effectively consider treatment options. (III)
K2. Patients should be informed that lifestyle changes, including dietary modifications, exercise (I), reduction of stress, and cessation of smoking can benefit the emotional and physical health of women in midlife. (II-1)

SECTION L:
EVALUATION, DECISION-MAKING, AND FOLLOW-UP
RECOMMENDATIONS:
L1. The assessments recommended by the Canadian Task Force on the Periodic Health Examination should be included in the evaluation and follow-up of perimenopausal and postmenopausal women. (III)
L2. Routine abdominal or transvaginal ultrasonography of the pelvis should not be used in healthy asymptomatic postmenopausal women. (II-1)
L3. Postmenopausal women with abnormal bleeding patterns should undergo a review of their estrogen-progestin therapy administration (where appropriate), a pelvic examination, and an endometrial biopsy (II-1). Transvaginal ultrasonography is an alternative when endometrial sampling is not possible or the results are inconclusive. If the situation remains unclear, tissue sampling with or without hysteroscopy is recommended. (II)
L4. The majority of women wish to participate in the decision-making process, and health care providers should encourage them to do so. (III)
L5. Decisions should be based on an individual assessment of symptoms, risk factor analysis, and discussion of the risks and benefits of each option. The decision should be re-evaluated as new information becomes available. (III)
L6. Health care providers should actively advocate for public-funded educational programs to increase knowledge about menopause and osteoporosis for both women and their health care providers. (III)

GLOSSARY
To provide consistency and to clarify any confusion surrounding the terminology associated with the menopause, the following set of definitions published in the World Health Organization Technical Report11 are included.1

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.

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).

Simple hysterectomy:
Hysterectomy with conservation of at least one ovary. Women who undergo a simple hysterectomy will have continuing ovarian function for a variable period after surgery.

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

* These are also used by the Council of Affiliated Menopause Societies (CAMS), the International Menopause Society (IMS), and the North American Menopause Society (NAMS, www.menopause.org).
Premature menopause:
Menopause that occurs at an age more than two 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.

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REFERENCES

5. CANSIM, Matrix 6900 Ottawa: Statistics Canada. www.statscan.ca
PERIMENOPAUSE

Elizabeth Contestabile RN, BScN¹; Christine Derzko, MD, FRCSC²

¹ Ottawa ON
² Toronto ON

INTRODUCTION

Our aging population has focused attention on postmenopausal health issues. However, far less is known about the perimenopause. This transition period between reproductive and post-reproductive life is characterized by fluctuations in hormone levels, irregularities in the menstrual cycle, and several other signs and symptoms. It can be a perplexing time for women and clinicians because of insufficient data from clinical trials for the development of evidence-based treatment guidelines.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) concurs with the World Health Organization (WHO) and the North American Menopause Society (NAMS) in defining perimenopause as the two to eight years preceding menopause and the first year after the final menstrual period.¹ It typically begins in the fifth decade when the endocrinological, biological, and clinical features of approaching menopause are first noticed.²

CLINICAL AND PHYSIOLOGIC CHANGES ASSOCIATED WITH PERIMENOPAUSE

The following clinical, endocrinological, and biological changes associated with perimenopause have been identified:²⁻⁴

• menstrual cycle pattern variations
• accelerated rate of follicular depletion
• erratic variations in circulating estrogen levels (it is only in the year or so before final menses that levels fall substantially)
• lower circulating progesterone levels with short or insufficient luteal phases, often preceding anovulation
• gradually increasing serum follicle-stimulating hormone (FSH) levels, while luteinizing hormone (LH) levels remain normal
• decreased serum levels of inhibin A and B (responsible for suppression of FSH), possibly as a result of follicular aging and diminishing follicular competence.

VARIATIONS IN THE MENSTRUAL CYCLE

Longitudinal studies⁶⁻⁷ have shown that the perimenopausal transition average age of onset is 45.1 years (39-51 years) and the average duration is five years (2-8 years) (mean, 95% CI). The majority of women experience four to eight years of changes in the menstrual cycle before menopause, with only 10 percent reporting abrupt cessation of menstruation.

Three distinct stages of the menopausal transition are identified in the Seattle Midlife Women’s Health Study.⁸

1. Early menopausal transition: menstrual cycles continue to be regular, but changes in the amount and length of flow or in cycle length are noted;
2. Middle menopausal transition: onset of menstrual cycle irregularity without skipping of periods;
3. Late menopausal transition: skipping of menstrual bleeds occurs, with periods often two or more months apart.

Although there was an age progression across these stages, age was not a consistent predictor of the type of menstrual cycle change. Several patterns of cycle change were also noted, including forward progression from stage to stage, no change in stage, and switching back and forth between stages.⁸

ABNORMAL UTERINE BLEEDING

Clinicians must differentiate between irregular bleeding and abnormal uterine bleeding, a more serious concern that warrants further investigation. This topic is discussed in Section L,* as well as in SOGC guidelines for Evaluation and Management of Abnormal Uterine Bleeding.⁹ ¹⁰

FERTILITY AND PREGNANCY

Women may be uncertain about their reproductive status because of the unpredictable nature of hormone production and the irregularity of their menstrual cycles during the perimenopause. Fertility in perimenopausal women is decreased, with fewer oocytes available for recruitment and ovulation. A significant number of these oocytes are chromosomally abnormal. The result is an increase in infertility and reduced success rates with infertility treatment for women age 40 years and over.¹¹

Pregnancy in the perimenopause is associated with increased obstetrical and genetic risks, including spontaneous abortion, fetal anomalies, and perinatal and maternal mortality.¹¹

CONTRACEPTION

During perimenopause, periods of ovarian failure are interspersed with periods of ovarian function. Isolated hormone measurements are not reliable for assessing reproductive status. A laboratory marker to predict the onset of menopause has yet to be identified. Contraception should be recommended until menopause is confirmed clinically, usually when amenorrhea has been present for one year.

SYMPTOMS OF PERIMENOPAUSE

Women report increasing symptoms during the peri- and postmenopausal period (Table 1). The most prevalent symptoms attributed to fluctuating hormone production include vasomotor symptoms, breast tenderness, vaginal dryness, and sleep disturbances.

Much of the current knowledge about the symptoms associated with perimenopause and menopause is limited because study populations have consisted mainly of Caucasian women over the age of 45. These issues are being addressed in the Study of Women and Health in the Nation (SWAN), which is examining the natural history of menopause in a multiracial and multiethnic population of women 40 to 55 years of age.

VASOMOTOR SYMPTOMS

Hot flushes and night sweats are common names for the vasomotor instability reported by as many as 85 percent of perimenopausal women. Defined as recurrent, transient episodes of flushing, sweating, and a sensation of heat, flushes are often accompanied by palpitations and feelings of anxiety, and may be followed by chills. While only a minor annoyance for many, flushes cause major disruptions in sleep and daily activities in about 15 percent of perimenopausal women. These symptoms often begin before the cessation of menses, increase in frequency and intensity as menopause approaches, and persist for some time afterwards.

It has generally been assumed that vasomotor symptoms are a result of the effect of low estrogen levels at the thermoregulatory centre in the hypothalamus. This theory is supported by the demonstrated efficacy of estrogen in relieving vasomotor symptoms. However, most postmenopausal women have consistently low levels of estradiol and do not experience hot flushes after the initial transition. Similarly, prepubertal girls do not have hot flushes. An alternate hypothesis is that it is the withdrawal of estrogen, or a decreasing ability of estrogen to bind to estrogen receptors, that precipitates hot flushes. This would explain the frequent occurrence of hot flushes in the perimenopause when fluctuations from relatively high to low or normal levels of estrogen occur.

Numerous other factors contribute to hot flushes, including: epilepsy, infection, carcinoid syndromes, thyroid disease, insulinoma, pheochromocytoma, pancreatic tumours, hematologic malignancies, autoimmune disorders, and mast-cell disorders. Appropriate investigation is required when vasomotor symptoms do not respond to hormone replacement therapy (HRT). When the clinical situation is not clear, documentation of an elevated serum follicle stimulating hormone (FSH) level may be helpful for confirming menopausal change.

SLEEP DISTURBANCES

Sleep disturbances are common in the perimenopausal period, and are often related to vasomotor symptoms. The pattern of difficulty in sleeping differs from other symptoms of menopause, suggesting that it may not be a direct effect of hormonal changes but rather a result of many factors. Insomnia can 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 perimenopause, further investigation is warranted, especially for insomnia that occurs nightly and is long-lasting.

BREAST TENDERNESS

Mastalgia is often cyclic in nature, occurring in the luteal phase of the menstrual cycle, and is common in the premenopausal and early perimenopausal period. A decrease in prevalence is noted in the late perimenopause and postmenopause as ovulation ceases and cyclical hormone production stops.

UROGENITAL SYMPTOMS

Vaginal dryness is occasionally reported by perimenopausal women and may increase over time, becoming more of a concern postmenopausally. Often the first change noted is decreased lubrication with sexual arousal.

Other symptoms related to urogenital aging, such as urinary

---

**TABLE 1**

**COMMONLY REPORTED SYMPTOMS OF THE PERIMENOPAUSE**

<table>
<thead>
<tr>
<th>Associated with hormonal status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vasomotor symptoms: hot flushes, night sweats</td>
</tr>
<tr>
<td>• Vaginal dryness, dyspareunia</td>
</tr>
<tr>
<td>• Mastalgia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potentially associated with hormonal status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue, lack of energy, insomnia, sleep disturbances</td>
</tr>
<tr>
<td>• Backache, joint and muscle pain</td>
</tr>
<tr>
<td>• Mood swings, depression, irritability, anxiety, memory loss, changes in libido</td>
</tr>
<tr>
<td>• Urinary incontinence</td>
</tr>
<tr>
<td>• Headaches</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not associated with hormonal status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major depression</td>
</tr>
<tr>
<td>• Weight gain</td>
</tr>
</tbody>
</table>
incontinence, may be common but are not frequently reported unless specifically addressed during evaluation. The prevalence of stress incontinence is highest in perimenopause, while the prevalence of urge incontinence increases after menopause.21**

**SEXUAL FUNCTION**

Perimenopausal women may express concerns about changes in sexual function, including a decreased interest in and capacity for sexual activity. The level of sexual function a woman has at the time of menopause correlates with her current health and activity level, her sexual adjustment in the premenopausal years, and her personal and cultural expectations of sexual function after menopause. Ongoing population studies such as SWAN15 will help to determine the associations between menopausal status, aging, sociocultural factors, and sexual function.22†

**PSYCHOLOGICAL EFFECTS**

Depression and anxiety are more frequently reported during perimenopause. Greater psychological stress is experienced during the menopause transition than in the postmenopausal years. Transient depressed mood during the perimenopause is associated with depressed mood before menopause, a longer transition to menopause, and more severe menopausal symptoms.23,24 Current evidence does not support an association between estrogen levels during the menopausal transition and the onset of clinical depression.13,24 Women who have major depression at the time of menopause are likely to have had prior depressive episodes, postpartum affective syndromes or premenstrual dysphoric disorder.25

Women who seek care for symptoms during the perimenopausal period may be more vulnerable to symptom distress. Studies report that these women were less healthy, had more psychosomatic complaints and vasomotor reactions,23,26 and were more likely to have a history of premenstrual symptoms.25

Women who report the development or exacerbation of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PDD) may be confusing the symptoms with onset of perimenopause. Monitoring of symptoms will help to determine if they are confined to the luteal phase of the cycle and meet the criteria for PMS/PDD.25

Some of the somatic and psychological symptoms associated with the perimenopause may be difficult to differentiate from the manifestations of a depressive disorder. Clinical evaluation, including a detailed history, confirmation of perimenopausal or postmenopausal status, and the use of standardized mood-rating scales, will help to clarify the diagnosis.27

Mild depressive symptoms may respond to treatment with estrogen alone, but more severe depression or a failure to respond to estrogen treatment alone are clear indications for standard psychopharmacologic therapy.27*

**EVALUATION OF THE PERIMENOPAUSAL WOMAN**

Evaluation of the perimenopausal woman should focus on three areas: assessment of menopause status and the severity of symptoms, assessment of current health status, and assessment of risk factors for disease. Random serum measurements of FSH, lutenizing hormone (LH), and estradiol to determine menopause status are of no use in menstruating women. They may be helpful to determine menopause status in women who have undergone hysterectomy, when premature ovarian failure is suspected, or for other clinical concerns. They may also be used to predict ovarian reserve in older women desiring pregnancy. Amenorrhea in women under 50 years should not be presumed to be a result of menopause. The possibility of pregnancy and other causes should be considered. A menstrual calendar is a useful tool for monitoring bleeding patterns, for identifying abnormal uterine bleeding, and for determining the need for further investigation. The elements of a comprehensive evaluation are explained in Section L.***

---

**TABLE 2**

**NON-HORMONAL OPTIONS FOR SYMPTOM CONTROL**

| Vasomotor symptoms: | *Antidepressants*  
|                    | Clonidine  
|                    | Bellergal*  
|                    | Regular aerobic exercise  
|                    | Periodic deep breathing exercises  
|                    | Dietary phytoestrogens  
|                    | Black cohosh  
| Vaginal dryness: | Vaginal moisturizer (Replens™)  
|                    | Vaginal lubricants  
|                    | Continued regular sexual activity  
| Sleep Disturbances: | Prescription pharmacotherapy (hypnotics)19  
|                    | Valerian*  
|                    | Behavioural treatments‡  
| Mild to Moderate Depression: | Prescription antidepressants27  
|                    | Psychotherapy27  
|                    | St. John’s Wort*  

* Menopause: complementary approaches, J Obstet Gynaecol Can 2001;23(11)  
† Menopause and sexual function, J Obstet Gynaecol Can 2001;23(9):849-52  
‡ Menopause: healthy living, J Obstet Gynaecol Can 2001;23(9):842-8

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* Pharmacotherapy, J Obstet Gynaecol Can 2001;23(11).  
† Menopause and sexual function, J Obstet Gynaecol Can 2001;23(9):849-52.  
THERAPEUTIC OPTIONS FOR THE PERIMENOPAUSAL YEARS

The perimenopausal years provide an excellent opportunity to develop an individualized plan for disease prevention and health promotion. Objectives include the maintenance of optimal physical, mental, and social activity, the early detection of chronic diseases, and a smooth transition to the post-menopausal years. A comprehensive assessment, reassurance, and counselling may be all that healthy perimenopausal women require.

HEALTHY LIFESTYLE
A healthy lifestyle is a prerequisite for any program to promote health and prevent disease. The fundamentals include the avoidance of smoking, maintenance of a healthy weight, regular physical activity, a healthy diet, and limited alcohol intake. This topic is discussed in more detail in Section B.*

NON-HORMONAL THERAPIES FOR SYMPTOM CONTROL
Non-hormonal options with evidence of effectiveness in controlling symptoms are listed in Table 2.

HORMONAL THERAPIES FOR SYMPTOM CONTROL

ORAL CONTRACEPTIVE THERAPY
Low-dose oral contraceptives (OCs) containing 20 to 35 µg of ethinyl estradiol offer many benefits for the perimenopausal woman (Table 3). An OC containing 20 µg of ethinyl estradiol has been shown to provide effective contraception, reduce menstrual cycle irregularity, decrease bleeding, and relieve menopausal symptoms.28 Important additional benefits of such treatment include a decrease in the risk for ovarian and endometrial cancer, reduced dysmenorrhea, reduced menorrhagia, a lower risk of functional ovarian cysts, and possibly increased bone density.4,9,29,30 Women taking an OC may experience a return of symptoms during the hormone-free interval, although supplementation during that time with a low dose of estrogen may be helpful. Alternatively, the OC may be taken continuously.

Risks associated with the use of OCs include an increased risk for venous thromboembolism (VTE) and acute myocardial infarction.31 The risk for ischemic stroke appears to be low for users of low-dose OCs who do not have additional risk factors.32 The risk for cardiovascular disease increases further with age, smoking, a positive family history of premature heart disease or VTE, and other cardiac risk factors.31,32 After the age of 35, OC use should be considered only for healthy non-smoking women.

Oral contraceptive use is associated with a slightly increased risk of developing breast cancer, which returns to baseline 10 years after cessation. Breast cancers diagnosed in OC users tend to be less clinically advanced than those found in non-users.33 It should be noted that the risks associated with OC use have been identified from older studies and meta-analyses that usually involved younger women and higher doses of estrogen. Further studies are needed to determine the risks of low-dose OC use by perimenopausal women.

TABLE 3

EFFECTS OF ESTROGEN IN CONTROLLING MENOPAUSAL SYMPTOMS

| Vasomotor symptoms: | dose-related decrease in incidence and severity 37-40 | efficacy may be altered by the estrogen preparation, route of administration, or concomitant progestin 4 |
| Sleep disturbances: | estrogen therapy improves restlessness, ability to fall asleep and nocturnal awakenings 41 |
| Sexual function: | estrogen therapy increases blood flow to the genital area, relief of dyspareunia and vaginal dryness with either systemic or local administration 42 |
| Psychological effects: | estrogen therapy improves mood in depressed perimenopausal women, independent of its effect on flushes 43 |


FIGURE 1

ALGORITHM FOR DISCONTINUING ORAL CONTRACEPTIVES IN PERIMENOPAUSAL/MENOPAUSAL WOMEN 10

Age 51-52

Serum FSH on day 7 of pill-free week

FSH > 30 IU/L

Discontinue OC

FSH < 30 IU/L

Serum E2, FSH:LH ratio on day 7 of pill-free week

OR Continue OC x 12 months

E2 < 73 pmol/l

FSH:LH ratio > 1

Serum FSH measurements on day 7 of the pill-free interval may not have sufficient sensitivity to diagnose menopause. Figure 1 provides guidelines for discontinuing the OC and initiating HRT.

**PROGESTIN THERAPY**

Cyclic progestin therapy (5-10 mg of medroxyprogesterone acetate daily, 10-14 days of each month) has been used to regulate anovulatory bleeding and reverse endometrial hyperplasia. Synthetic progestins such as medroxyprogesterone acetate (20 mg daily by mouth) and megestrol acetate (20 mg twice daily) can offer an effective alternative for the treatment of vasomotor symptoms in postmenopausal women. A progestosterone-releasing intrauterine system (Mirena™) has been approved in Canada for contraception. It reduces the amount and duration of menstrual flow and may be an effective option for the control of menorrhagia. The progestogen-only contraceptive pill (POP) provides effective contraception for perimenopausal women without increasing risk for cardiovascular disease. Compared to the combined estrogen-progestin OC, the POP is associated with a higher rate of spotting and breakthrough bleeding, may be less effective for relief of vasomotor symptoms, and may worsen depressed mood. Progestin therapy is further discussed in Section H.*

**HORMONE REPLACEMENT THERAPY**

The use of HRT or estrogen replacement therapy (ERT) provides the most effective relief of vasomotor and other menopausal symptoms (Table 3). However, HRT and ERT have not been well studied in the perimenopausal interval. In addition, HRT and ERT cannot be assumed to provide contraception for the perimenopausal woman, and may not provide cycle control in women still having spontaneous menses.

**RECOMMENDATIONS:**

A1. Health care providers should not use random serum markers of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol E₂ for the purpose of predicting menopause since clear markers for predicting menopause are yet to be identified. (II-2)

A2. In addition to providing effective contraception, low-dose oral contraceptives are an effective treatment for symptom-atic, healthy, non-smoking perimenopausal women. (I)

A3. Using the data from studies in postmenopausal women and clinical expertise as a guide, estrogen replacement therapy (ERT) or hormone replacement therapy (HRT) may be considered as a treatment option for those perimenopausal women whose symptoms are disruptive. (III)

**SUMMARY OF KEY POINTS:**

A4. Perimenopause is characterized by fluctuating hormone levels, irregular menstrual cycles, and the onset of symptoms that may increase in number and severity as menopause approaches. (II-2)

A5. The perimenopause is an optimal period for preventive health care based on an individualized assessment, adoption of a healthy lifestyle, and involvement of the woman in decisions regarding treatment options and their risk-benefit assessment. (III)

**CONCLUSION**

Emerging evidence about perimenopause provides information about the associated clinical, endocrinological, and biological changes, as well as effective treatment options for troublesome symptoms. The clinical encounter between a woman and her health care provider presents an excellent opportunity for discussion about perimenopausal issues, individualized assessment, counselling, and shared decision-making. Continued research is needed to support further understanding and the development of evidence-based management guidelines for the perimenopause.


**REFERENCES**

13. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet...


INTRODUCTION

The transition through perimenopause and menopause provides an ideal opportunity to focus women’s attention on lifestyle choices that can improve their overall health. This is often a time of high motivation, during which health care providers can encourage lifestyle modifications involving nutrition, exercise, weight management, stress reduction, smoking cessation, and the limitation of alcohol and caffeine intake. The Nurses’ Health Study showed an 83 percent reduction in coronary events in women who adhered to a healthy lifestyle involving diet, exercise, and abstinence from smoking. The numbers of women in this category were small (3%), but they underscore the enormous potential for intervention in this area.

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 six to eight glasses of water per day (Table 1). This 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 2).

Women with medical conditions such as hypertension, dyslipidemia, and diabetes mellitus should consult a dietitian for specific dietary advice. Additional information about various nutritional issues can be obtained from resources listed at the end of this section and from the Canadian recommendations for the management and treatment of dyslipidemia.

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 the Osteoporosis Society of Canada to promote bone health. The addition of muscle-strengthening exercise involving the upper and lower limbs, abdomen, and back muscles for 30 to 60 minutes three 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. Thirty minutes of moderate aerobic exercise (which may be broken into 10 minute sessions three times daily) on most days is recommended by the Canadian Medical Association and the Heart and Stroke Foundation for its cardioprotective effects. The Health Canada Activity Guide is a useful resource.

WEIGHT GAIN

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. This weight gain is not related to hormone replacement 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.

Most menopausal women are more accepting of their body image and size, and do not pursue drastic weight-loss diets. However, many are surprised and dismayed when they experience midlife weight gain, and will seek advice from their health-care practitioner on how to minimize adverse health consequences. A recent 54 month randomized controlled trial indicated that perimenopausal weight gain and elevations in low-density lipoprotein (LDL) cholesterol could be minimized by ingestion of a low-fat diet with moderate calorie restriction, combined with a modest increase in exercise.
OBESITY
The incidence of obesity is increasing in North America, and
Health Canada now estimates that more than 40 percent of
Canadian women are overweight (with a body mass index [BMI]
> 25 kg/m²) or obese (BMI > 30 kg/m²).17 The measurement of
BMI (weight in kg divided by height in m²) is the best clinical
indicator of obesity and provides a guide for management. Other
indicators, such as a waist-hip ratio greater than 1.18 or a waist
circumference greater than 95 cm, have been associated with an
increased risk of cardiovascular disease,18 type 2 diabetes,18 and
breast cancer.19 In Canada it is estimated that the direct cost of
obesity in 1997 was more than $1.8 billion, accounting for 2.4
percent of total health care costs.20 In addition, morbidity is
increased in obese individuals because of hyperlipidemia, hyper-
tension, cholelithiasis, sleep apnea, osteoarthritis, and the stress
of social disapproval and stigmatization.20

A five to 10 percent reduction in body weight in obese individ-
uals is sufficient to reduce complications from these dis-
eases.18 The rate of angiographically significant atherosclerosis
and coronary events has been improved in one year and main-
tained over five years by intensive lifestyle modifications, includ-
ing aerobic exercise, stress-management training, smoking
cessation, group psychosocial support, and a vegetarian diet that
emphasizes whole foods and less than 10 percent fat content.6

TREATMENT
Many women are interested in preventing the comorbidities asso-
ciated with obesity, but are often unaware of the specific amount

TABLE I
DIETARY RECOMMENDATIONS FROM CANADA’S FOOD GUIDE2

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

www.hc-sc.gc.ca/hppb/nutrition/pube/foodguid/
of weight loss required to improve their health. They may also have inadequate or inaccurate information about weight-loss programs. Health care professionals play an important role in assessing individual readiness for weight management measures, in educating women about sensible approaches, and in providing long-term follow-up and encouragement.

The initial goal is to reduce body weight by approximately 10 percent from baseline over six to 12 months. The most successful treatment to date includes a controlled diet with a deficit of 500 to 1000 Kcal per day, reducing dietary fat intake to less than 30 percent of total energy intake, regular physical activity, and behaviour modification.21

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 3).22 Drug therapy (orlistat or sibutramine) 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 (Table 4).23

The National Institute of Health has a detailed website outlining the Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. It also contains BMI tables and the evidence tables used to construct the guidelines.

**STRESS**

Women face many challenging stressors during midlife and the menopausal transition. Stress significantly affects quality of life, may result in a variety of somatic symptoms, and may aggravate various underlying medical conditions. Stress has been causally related to cardiovascular disease, particularly in women. Not only has stress been reported to trigger ischemia and acute myocardial infarction (MI), but marital stress triples the risk of sudden death after an MI in women.24 Stress reduction strategies that may benefit all individuals include regular exercise, yoga, tai chi, massage, meditation, paced respiration, biofeedback, relaxation techniques, and behaviour-modification techniques. Some of these techniques have also been helpful in relieving vasomotor symptoms (Section K*).

**TABLE 2**

<table>
<thead>
<tr>
<th>DIETARY REFERENCE INTAKES (DRI) OF SELECTED NUTRIENTS²</th>
<th>DRIs</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Vitamin D  
- premenopausal  
- age 50-65  
- age 65+  
- 200 IU  
- 400 IU  
- 800 IU | Function: Required for optimal calcium absorption  
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. |
| Calcium (elemental)  
- premenopausal  
- postmenopausal  
- on anti-resorptive therapy  
- not on anti-resorptive therapy  
- 1000 mg  
- 1000 mg  
- 1500 mg | Function: Required to maintain calcium homeostasis, cellular function and bone mineralization  
Food sources: Most plentiful in milk products  
Comment: Prerequisite for effective anti-resorptive therapy |
| Iron  
- premenopausal  
- postmenopausal  
- 18 mg  
- 8 mg | Function: Required for red blood cell (RBC) formation  
Food sources: Most plentiful in red meat. Also found in fruits, vegetables and grains. |
| Vitamin B6 (serotonin)  
- 1.5 mg | Function: Needed for production of RBCs and serotonin and for metabolism of protein and fat  
Food 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  
Food 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  
Food sources: Fruits, vegetables, and grains |

* Menopause: complementary approaches,  
J Obstet Gynaecol Can 2001;23(12).
SMOKING

In 1996, Health Canada estimated that 1.7 million Canadian women smoked cigarettes, resulting in numerous adverse effects on health and quality of life (Table 5).25-27 Smoking is the single greatest preventable cause of illness and premature death, largely due to its associations with cancer and cardiovascular disease. Every 35 minutes, a Canadian woman dies from smoking-related causes, accounting for some 15,000 deaths per year.25 Of these deaths, lung cancer accounts for 36 percent, cardiovascular disease for 40 percent, and respiratory failure for 22 percent.

Reports from the Nurses’ Health Study have described a 24 percent decrease in mortality within two years of smoking cessation, reversal of cardiovascular risk within five years, and a reduction in all-cause mortality to non-smoking levels within 10 to 14 years after quitting.28 Between 1980 and 1992, 41 percent of the participants in this study stopped smoking, accounting for a 13 percent decline in their overall incidence of heart disease.29 In addition to the well-known health risks, quality of life may also be affected in menopausal women who smoke (Table 5). Higher doses of estrogen may be required to control vasomotor symptoms because of the increase in estrogen catabolism caused by smoking.26 Although oral contraceptive pills are commonly prescribed to control irregular bleeding and vasomotor symptoms during the perimenopause, they should not be used for this purpose in women who smoke or who use nicotine patches or gum.26,27

As it may take several attempts to stop smoking completely, continuing support is critical for success. A combination of behaviour modification, group support, and drug therapy appears to be most helpful (Table 6).30-33 Detailed smoking cessation guidelines are available from the Canadian Lung Association,30 Canadian Cancer Society,31 and Health Canada.32,33

ALCOHOL

Alcohol aggravates menopausal symptoms such as hot flashes, insomnia, and depression, and may contribute to weight gain by adding empty calories to the diet.34 Excess alcohol consumption is often associated with an increased risk of osteoporosis due to calcium and other nutritional deficiencies, and with an increased incidence of falls and fractures due to imbalance.35 Furthermore, the Nurses’ Health Study reported that death rates from alcohol abuse were 50 to 100 percent higher in women than in men.36 A detailed history of alcohol and other drug use or abuse is

<table>
<thead>
<tr>
<th>TABLE 3</th>
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</thead>
<tbody>
<tr>
<td><strong>INDICATIONS FOR INTERVENTION BY BMI CATEGORY</strong>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Encourage balanced diet and exercise</td>
</tr>
<tr>
<td>Healthy</td>
<td>18.5-24.9</td>
<td>Encourage balanced diet and exercise</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-26.9</td>
<td>Lifestyle (diet, exercise, behaviour therapy)</td>
</tr>
<tr>
<td>Overweight</td>
<td>27-29.9</td>
<td>Lifestyle, plus drug therapy if comorbidities* exist</td>
</tr>
<tr>
<td>Obese Class 1</td>
<td>30-35</td>
<td>Lifestyle plus drug therapy</td>
</tr>
<tr>
<td>Obese Class 2</td>
<td>35-39.9</td>
<td>Lifestyle plus drug therapy, plus surgery if comorbidities* exist</td>
</tr>
<tr>
<td>Obese Class 3</td>
<td>40</td>
<td>Lifestyle, drug therapy, and surgery</td>
</tr>
</tbody>
</table>

*Comorbidities: hypertension, diabetes, hyperlipidemia

<table>
<thead>
<tr>
<th>TABLE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHARMACOLOGIC AGENTS APPROVED FOR TREATMENT OF OBESITY</strong> (NB: Must be combined with dietary and exercise measures)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indication</th>
<th>Precautions</th>
</tr>
</thead>
</table>
| Orlistat (Xenical)  | 120 mg t.i.d. | BMI > 30 BMI > 27 with comorbidities | - decreases intestinal fat absorption  
|                     |      |            | - improves lipid and glucose levels  
|                     |      |            | - can cause oily diarrhea  
|                     |      |            | - may decrease absorption of fat-soluble vitamins, necessitating vitamin supplementation |
| Sibutramine HCl (Meridia*) | 10 mg per day (increase to 15 mg/day if no significant weight loss in 4 weeks) | BMI > 30 BMI > 27 with comorbidities | - serotonin and norepinephrine reuptake inhibitor  
|                     |      |            | - induces early satiety  
|                     |      |            | - can increase blood pressure and heart rate, requiring monitoring before and during therapy  
|                     |      |            | - contraindications: stroke, transient ischemic attacks, congestive heart failure, arrhythmia, inadequately controlled blood pressure |

* Only available in the United States
essential. It is not uncommon for women to treat mood disturbances with alcohol and other drugs.

Light to moderate alcohol consumption (1-2 drinks/day per Table 1) can decrease the risk of heart disease.35 However, this amount may also increase the risk of breast cancer.36 It therefore appears prudent to limit alcohol intake.

CAFFEINE

Caffeine ingestion may aggravate menopausal symptoms such as hot flashes and insomnia. Caffeine-containing drinks increase urinary calcium excretion, but increasing dietary calcium can counteract this. Data from observational studies suggest that consuming more than three cups of caffeinated beverages daily increases the risk of hip fracture.37 It is therefore prudent to limit the intake of caffeine-containing foods and beverages, and to encourage women to add low-fat milk to their coffee and tea as a means of increasing calcium intake (Tables 1 and 2).

RECOMMENDATIONS:

B1. Health care providers should encourage patients to consider lifestyle modifications such as exercise, optimal diet, and smoking cessation, as these lifestyle changes can reduce the risk of cardiovascular disease and osteoporosis. (I, II-2)

B2. The principles of health promotion and disease prevention should be encouraged in all perimenopausal and postmenopausal women. (III)

CONCLUSION

Science has made significant advances in the realm of life extension and aging. However, the basic premise underlying most of this research remains a simple one: individuals who maintain healthy lifestyles tend to live relatively long and healthy lives.1,6,28,29

REFERENCES


### TABLE 5

<table>
<thead>
<tr>
<th>HEALTH CONSEQUENCES OF SMOKING IN WOMEN26,27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>- coronary artery disease</td>
</tr>
<tr>
<td>- cerebrovascular disease</td>
</tr>
<tr>
<td>- peripheral vascular disease</td>
</tr>
<tr>
<td>Respiratory diseases</td>
</tr>
<tr>
<td>- chronic lung diseases, emphysema</td>
</tr>
<tr>
<td>- lung cancer</td>
</tr>
<tr>
<td>Consequences of accelerated follicular depletion or accelerated metabolism of estrogen</td>
</tr>
<tr>
<td>- increased infertility</td>
</tr>
<tr>
<td>- increased oral contraceptive failure</td>
</tr>
<tr>
<td>- earlier onset of menopause</td>
</tr>
<tr>
<td>- increased vasomotor symptoms</td>
</tr>
<tr>
<td>- increased urinary incontinence</td>
</tr>
<tr>
<td>- lower peak bone mass</td>
</tr>
<tr>
<td>- increased postmenopausal bone loss</td>
</tr>
<tr>
<td>- increased osteoporotic fractures</td>
</tr>
<tr>
<td>Connective tissue effects</td>
</tr>
<tr>
<td>- increased facial wrinkling</td>
</tr>
<tr>
<td>- accelerated macular degeneration</td>
</tr>
<tr>
<td>- premature grey hair and hair loss</td>
</tr>
<tr>
<td>- increased hearing loss</td>
</tr>
<tr>
<td>- discoloured teeth and nails</td>
</tr>
<tr>
<td>- hoarse voice</td>
</tr>
<tr>
<td>Other cancer risks</td>
</tr>
<tr>
<td>- cervical</td>
</tr>
<tr>
<td>- esophageal</td>
</tr>
<tr>
<td>- oral cavity</td>
</tr>
<tr>
<td>- laryngeal</td>
</tr>
<tr>
<td>- renal</td>
</tr>
<tr>
<td>- bladder</td>
</tr>
<tr>
<td>- leukemia</td>
</tr>
</tbody>
</table>

### TABLE 6

<table>
<thead>
<tr>
<th>PHARMACEUTICAL SMOKING CESSATION AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>Nicorette® gum</td>
</tr>
<tr>
<td>Nicorette Plus® gum</td>
</tr>
<tr>
<td>Nicoderm® patch</td>
</tr>
<tr>
<td>Nicotrol® patch</td>
</tr>
<tr>
<td>Habitrol® patch</td>
</tr>
<tr>
<td>Bupropion (Zyban®)</td>
</tr>
</tbody>
</table>


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**TABLE 7**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Organization</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart and Stroke</td>
<td>Heart and Stroke Foundation of Canada (includes heart, stroke and dietary information plus individual risk assessment and smoking cessation guidelines)</td>
<td><a href="http://www.hsf.ca">www.hsf.ca</a> (1-888-HSF-INFO)</td>
</tr>
<tr>
<td>Menopause</td>
<td>Society of Obstetricians and Gynecologists of Canada (includes Consumer Education brochures, Clinical Practice Guidelines, and Consensus Conference Reports)</td>
<td><a href="http://www.sogc.org">www.sogc.org</a></td>
</tr>
<tr>
<td></td>
<td>North American Menopause Society (includes Consensus Opinions, surveys, and Consumer Education materials)</td>
<td><a href="http://www.menopause.org">www.menopause.org</a></td>
</tr>
<tr>
<td>Nutrition</td>
<td>Canada’s Food Guide</td>
<td><a href="http://www.hc-sc.gc.ca/hppb/nutrition/">www.hc-sc.gc.ca/hppb/nutrition/</a></td>
</tr>
<tr>
<td></td>
<td>Dietitians of Canada</td>
<td><a href="http://www.hc-sc.gc.ca/hppb/la-nutrition/">www.hc-sc.gc.ca/hppb/la-nutrition/</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="http://www.dieticians.ca/eatwell">www.dieticians.ca/eatwell</a></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Osteoporosis Society of Canada (includes osteoporosis diagnosis, prevention &amp; treatment plus Calcium Calculator)</td>
<td><a href="http://www.osteoporosis.ca">www.osteoporosis.ca</a></td>
</tr>
<tr>
<td></td>
<td>National Osteoporosis Foundation (includes NOF guidelines plus professional and patient information on osteoporosis)</td>
<td><a href="http://www.nof.org/">www.nof.org/</a></td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>Canadian Lung Association (includes Smoking Cessation Support Group on the Web, information on provincial stop smoking programs)</td>
<td><a href="http://www.sk.lung.ca/smoking/">www.sk.lung.ca/smoking/</a> or <a href="http://www.lung.ca">www.lung.ca</a></td>
</tr>
<tr>
<td></td>
<td>Canadian Cancer Society (includes smoking cessation support programs &amp; links to other smoking cessation web sites)</td>
<td><a href="http://www.cancer.ca/tobacco">www.cancer.ca/tobacco</a> (1-888-939-3333)</td>
</tr>
<tr>
<td></td>
<td>Health Canada (website includes smoking cessation programs and information about smoking in Canada)</td>
<td><a href="http://www.infotobacco.com/index2.html">www.infotobacco.com/index2.html</a></td>
</tr>
<tr>
<td></td>
<td>Smoking Cessation Guidelines: from the University of Toronto Department of Family &amp; Community Medicine</td>
<td><a href="http://www.hc-sc.gc.ca/hppb/cessation/">www.hc-sc.gc.ca/hppb/cessation/</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact: Shirley Crum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-905-812-4104</td>
</tr>
<tr>
<td>Exercise</td>
<td>Health Canada Physical Activity Guide</td>
<td><a href="http://www.hc-sc.gc.ca/hppb/paguide">www.hc-sc.gc.ca/hppb/paguide</a></td>
</tr>
</tbody>
</table>


INTRODUCTION

Sexual concerns are often an issue for women in the perimenopausal years and beyond. Health care providers have to be aware of these issues and provide a nonjudgemental approach to sexual health based on mutual trust and respect. It is important to remember that personal, relationship, and societal factors play an important role in menopausal sexuality. The health care provider’s time limitations and experience and the nature of the problem may warrant referral for counselling.

EFFECTS ON SEXUALITY

HORMONAL CHANGES

Lack of estrogen leads to urogenital atrophy and resultant dyspareunia, as well as to decreased blood flow and reduced sensation. Estrogen replacement increases blood flow to the genital area and relieves vaginal dryness and dyspareunia. Through its positive effects on mood and wellbeing, estrogen replacement may also affect sexuality.

Lack of progesterone has no adverse effect on sexual function. Progestin replacement, whether cyclic or continuous, can have a negative influence on mood and wellbeing as well as cause a decrease in sexual activity when associated with frequent breakthrough bleeding. Lack of testosterone, particularly in women with surgical menopause, has been associated with decreased libido. Levels of testosterone were reduced by more than 40 percent in women undergoing bilateral oophorectomy.

HYSTERECTOMY

The majority of women experience no adverse effects on sexual function from a hysterectomy. In the two year Maryland Women’s Health Study, sexual function was not impaired and most women reported that their sexual activity and overall libido improved after hysterectomy. In many cases, freedom from heavy or irregular bleeding or from pelvic pain and dyspareunia leads to enjoyable sexual activity for the first time in many years. In a minority of women, hysterectomy can adversely affect coital function, either because of shortened vaginal length or because of a painful vaginal vault scar. For most women, orgasm is unaffected; however, orgasmic function may be altered if loss of uterine contractions leads to decreased pleasurable sensations or if loss of cervical tapping eliminates the woman’s particular trigger for orgasm. Possible changes in sexual function associated with gynaecological surgery should be discussed with patients prior to the procedure.

OOPHORECTOMY

As with hysterectomy, many women experience no adverse effects on their sexual function after oophorectomy. However, bilateral oophorectomy is associated with a reduction in serum estrogen and testosterone levels that, in some women, may lead to decreased libido or a decreased sense of wellbeing. Physicians should ask about changes in sexual function in follow-up visits after surgery.

HORMONAL TREATMENTS

Estrogen therapy increases mucosal thickness and vaginal rugation, and restores vaginal fluid volume, moisture, and pH levels. It can be administered either systemically or locally in estrogen vaginal cream, a sustained-release vaginal ring or vaginal tablets (not yet available in Canada). Some women experience troublesome atrophic urogenital symptoms despite standard systemic estrogen therapy. These symptoms respond well to the addition of vaginal estrogen therapy.

TOPICAL ESTROGEN THERAPY

Vaginally administered estrogen can be absorbed systemically, but circulating levels are only 25 percent of those seen with equivalent doses orally ingested. Daily doses of 0.3 mg conjugated estrogens or less do not produce changes in serum estrogen levels (equivalent to 0.5 g or 1/8 applicator of Premarin cream). This dose-related absorption has not been consistently proven to provide relief of vasomotor symptoms bone protection, but may be sufficient to cause endometrial hyperplasia. The vaginal ring incurs lower serum estrogen levels than vaginal estrogen cream, but the therapeutic efficacy for urogenital atrophy is equivalent. Although no data have yet been published, the fact that serum estradiol levels are undetectable 48 hours after insertion of the vaginal ring suggests its possible use in women for whom systemic estrogen therapy is contraindicated.
ANDROGEN THERAPY

A trial of androgen therapy should be considered in women with decreased libido following bilateral oophorectomy if adequate estrogen therapy has been given and the problem persists.13-15 A trial of androgen therapy may also be appropriate following natural cessation of ovarian function for women on hormone replacement therapy (HRT) with no other explanation for their loss of libido or for women with other symptoms of androgen deficiency (Table 1).16 Clinical factors rather than serum hormone levels influence the discussion of androgen supplementation. There is no role for testosterone therapy in premenopausal women.

SIDE-EFFECTS OF ANDROGEN THERAPY IN WOMEN

Symptoms of androgen excess such as hirsutism, voice changes, and clitoromegaly can occur in women treated with testosterone, and these symptoms may be irreversible. The incidence is less than five percent in women on low-dose therapy. Since androgens may have adverse effects on blood lipid levels, androgen therapy should not be given without concomitant estrogen therapy. Testosterone is partly metabolized to estrogen, and it is therefore prudent to use a progestin to protect the endometrium from hyperplasia.18

Hepatotoxicity is a theoretical concern with oral administration of methyltestosterone, but it has not been observed with the replacement doses of testosterone used in women. A recent review of the side-effects of testosterone therapy concluded that the adverse effects associated with the supraphysiologic doses used in men did not occur with the much lower doses used in combination with estrogen for HRT in women.18

ANDROGEN PREPARATIONS

There are no data on the optimal preparation, dosage, length of treatment or long-term safety of testosterone replacement. Currently used preparations and suggested dosages are listed in Table 2.

Preliminary results from the use of testosterone undecanoate (Andriol®) in women have been reported.19 To date, no hepatotoxicity has been reported with use of low-dose testosterone undecanoate. Supraphysiologic testosterone concentrations following testosterone undecanoate administration with 40 mg on alternate days have been reported, but individual variations are considerable.19 Expanded pharmacokinetic and clinical studies are required.

To reduce the risk of virilizing side-effects, clinicians may administer reduced dosages of intramuscular testosterone enanthate (Climacteron® or Delatestryl®). Use of the 1.0 ml dose recommended in the past should be discouraged, since it is associated with hirsutism and virilization.20 In order to ensure adequate estrogen for symptom relief, these testosterone enanthate preparations can be administered in combination with 0.5 ml of estradiol valerate (Delestrogen®) in the same syringe. Anecdotal reports have suggested that patients may be reluctant to discontinue androgen therapy due to its positive effect on energy and well-being.

Tibolone (Livial®) is a synthetic steroid with estrogenic, progestogenic, and androgenic properties.21 It is not currently available in Canada. Tibolone was found to have a greater positive effect on libido than an estrogen-norethisterone combination after one year of treatment.21 A comparison of tibolone and conjugated estrogen therapy over six months showed no difference between the treatments in recovery of libido.21 There was no evidence of virilizing side-effects.21

In oophorectomized women with low libido, transdermal testosterone (300 µg daily) added to estrogen replacement therapy (ERT) led to increased desire, increased frequency of sexual activity, and increased orgasmic functioning.22 Transdermal administration of testosterone appears to result in more stable serum levels than oral testosterone undecanoate23 or subcutaneous implants of testosterone.23

Further studies are necessary to determine the optimal dose, formulation, and duration of all androgen-containing treatment plans.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>SYMPTOMS OF ANDROGEN DEFICIENCY SYNDROME (ADS)17</th>
</tr>
</thead>
<tbody>
<tr>
<td>• loss of sexual desire</td>
<td>• loss of sensation in clitoris and nipples</td>
</tr>
<tr>
<td>• loss of sensation in clitoris and nipples</td>
<td>• difficulty reaching orgasm</td>
</tr>
<tr>
<td>• thinning and loss of pubic hair</td>
<td>• loss of vitality</td>
</tr>
<tr>
<td>• loss of vitality</td>
<td>• diminished sense of well-being</td>
</tr>
<tr>
<td>• reduction in muscle tone</td>
<td></td>
</tr>
</tbody>
</table>

| TABLE 2 | ANDROGEN PREPARATIONS AVAILABLE IN CANADA* |
|------------------|---------------------|---------------------|
| Preparation      | Dose                |                      |
| Oral             |                      |                      |
| Methyl testosterone (Metandren®) | 1/4 or 1/8 of a 10 mg tablet |
| Testosterone undecanoate (Andriol®) | 40 mg daily or on alternate days  |
| Intramuscular    |                      |                      |
| Testosterone enanthate (in combination with estrogen as Climacteron® injection, or without as Delatestryl®) | 0.5 ml intramuscularly every 4-6 weeks |

* Pharmacotherapy, J Obstet Gynaecol Can 2001;23(12)
MONITORING WOMEN RECEIVING ANDROGEN THERAPY

Symptoms should be re-evaluated after an initial two to three month trial of therapy. If the degree of symptom relief warrants continued androgen therapy, it is prudent to re-evaluate the lipid profile after three to six months of therapy. If the lipid profile is normal, then the guidelines from the Canadian Consensus on Cholesterol* should be followed. If the lipid profile is abnormal, then androgen therapy should be discontinued and additional investigation and possible treatment of the lipid abnormality is warranted. The results of liver function tests should remain normal.

SILDENAFIL CITRATE (VIAGRA™)

There was no increase in sexual response in a large randomized controlled trial of sildenafil citrate in estrogenized women with sexual dysfunction that included female sexual arousal disorder.24 However, sildenafil citrate therapy may benefit a subset of women experiencing delayed orgasm during therapy with selective serotonin re-uptake inhibitors (SSRIs).25

NON-HORMONAL TREATMENTS

Regular sexual activity maintains genital blood flow and helps to prevent vaginal dryness and atrophy. A lubricant can be used during sexual activity to decrease dyspareunia. A polycarbophil-based vaginal moisturizer has been shown to provide beneficial effects similar to those of vaginal estrogen cream on vaginal moisture, fluid volume, elasticity, and pH after 12 weeks of treatment.10

NON-HORMONAL SEXUAL ISSUES IN THE PERI- AND POSTMENOPAUSAL PERIOD

Numerous lifestyle and non-hormonal issues can influence sexual health. Contraception should be assumed necessary to prevent pregnancy until the diagnosis of menopause has been established. It should be remembered that women with premature menopause can occasionally retain ovarian function and spontaneous ovulation. A woman with a new sexual partner should be counselled about safe sex practices. Coital incontinence may be helped by emptying the bladder just prior to intercourse, or by using an antimuscarinic (such as oxybutynin 4 mg) one hour prior to intercourse.26

Depression may be associated with a loss of sexual interest. While antidepressants may improve libido as a function of improving the depression, many antidepressants have sexual side-effects. These include loss of libido and, in the case of selective serotonin reuptake inhibitors (SSRIs), orgasmic dysfunction. Sexual side-effects are less prevalent with certain antidepressants (nefazodone, moclobemide), but other factors may be more important in determining the appropriate choice of antidepressant. The orgasmic dysfunction but not the decreased libido induced by SSRIs can be ameliorated by using cyproheptadine two to four mg prior to sexual activity.27 Physicians should be aware of the sexual side-effects of prescribed and over-the-counter medications.28

The lack of a sexually functioning partner is the most common sexual problem in older women. Some couples are unaware of the normal changes in sexual function associated with aging, including the need in older men for direct penile stimulation to achieve an erection. As in any couple’s life as well as during menopause, relationship difficulties can also have negative effects on a woman’s sexual wellbeing.

ASSESSMENT OF SEXUAL CONCERNS IN MENOPAUSAL WOMEN

The depth of inquiry into factors listed in Table 3 should reflect the woman’s level of concern. For example, if anorgasmia is not a problem for a particular woman, nothing needs to be done apart from ensuring that it is not a symptom of an underlying medical condition. Conversely, every woman, regardless of age or health, deserves the opportunity to have her sexual concerns appropriately evaluated and treated.

REFERRAL TO A SEX THERAPIST

In most cases, a patient’s sexual concerns can be discussed by a concerned and informed family physician or gynaecologist,1 especially if a long-standing relationship exists. A referral to a specialist in sex therapy is appropriate if there continues to be no improvement in sexual issues despite adequate hormone replacement, if there are difficult relationship issues, or if there are chronic issues such as unresolved sexual abuse or sexual problems spanning most of the woman’s life or relationship.

If possible, both partners should be referred. Sexual difficulties, by their very nature, involve more than one person,

TABLE 3

<table>
<thead>
<tr>
<th>COMPONENTS OF THE SEXUAL ASSESSMENT IN PERI- AND POSTMENOPAUSAL WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libido (desire)</td>
</tr>
<tr>
<td>Arousal (lubrication)</td>
</tr>
<tr>
<td>Orgasm</td>
</tr>
<tr>
<td>Hormonal status</td>
</tr>
<tr>
<td>Lifestyle</td>
</tr>
<tr>
<td>fatigue</td>
</tr>
<tr>
<td>distractions (work, children, caring for elderly parents)</td>
</tr>
<tr>
<td>Relationship issues including abuse</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

regardless of with whom the problem originated. Referral as a couple also avoids the perception by the woman or her partner that there is something “wrong” with her and that she needs to be “fixed.”

RECOMMENDATIONS:

C1. All health care providers dealing with menopausal women should be versed in the appropriate counselling and management of menopause and related sexual health issues. (III)

C2. In women with vaginal atrophy, health care providers may consider the use of local estrogen therapy as an effective mode of treatment or consider vaginal moisturizers as effective alternatives. (I, II-1)

C3. In women with decreased libido who have undergone bilateral oophorectomy, adding androgen to estrogen therapy has been shown to be effective in increasing libido (I). Androgen therapy may be administered to estrogen-treated postmenopausal women who have decreased libido not explained by any other factors. A risk-benefit profile has not been determined from studies with sufficiently large patient numbers. (III)

C4. Routine evaluation of hormone levels (specifically measuring serum androgen levels) in postmenopausal women with psychosexual problems is not recommended. (III)

C5. Sildenafil citrate does not appear to improve sexual response in estrogenized women (III). However, it may do so in women with decreased libido associated with use of selective serotonin re-uptake inhibitors (SSRIs) (III).

J Obstet Gynaecol Can 2001;23(9):849-52

REFERENCES

HORMONE REPLACEMENT THERAPY AND CARDIOVASCULAR DISEASE
Michele A. Turek, MD, FRCPC,1 Christine Derzko, MD, FRCSC2
1 Ottawa, ON
2 Toronto, ON

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in postmenopausal women (Figure 1). Half of all postmenopausal women will develop coronary artery disease (CAD) and one-third will die from this disease. A majority of women have at least one risk factor for CAD.1 The risk for CVD rises with age and increases significantly after menopause. Premature menopause provides additional risk. These observations have prompted suggestions that estrogen-progestin treatment (EPT) might reduce CVD risk in postmenopausal women. Evidence from two randomized controlled trials (RCTs) indicates, however, that EPT is not effective for either primary or secondary prevention of CAD events in women with few or no menopausal symptoms.2,3

Estrogen has both rapid and longer-term actions on the cardiovascular system.4 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. Some estrogen effects may be beneficial (effects on lipoproteins, fibrinolysis, antioxidant, endothelial function) whereas some are considered to be detrimental (pro-inflammatory, prothrombotic).

This document reviews clinical and biological evidence about the known or potential balance of the cardiovascular benefits and risks, including the case when estrogen is taken with or without progestin shortly after the menopause for the treatment of menopausal symptoms. This type of use was not the target of either the HERS or the WHI study.2,3

EFFECTS OF ESTROGEN AND PROGESTINS

LIPOPROTEIN METABOLISM

Elevated total serum cholesterol and low-density lipoprotein cholesterol (LDL) levels are important coronary risk factors in women. Low levels of high-density lipoprotein cholesterol (HDL) are a strong independent risk factor.5 The effect of high serum triglycerides is not as clear, since this is also associated with other risk factors such as diabetes and obesity.6 Alterations in other lipid fractions, such as an increase in levels of lipoprotein(a) [Lp(a)], are also associated with the risk of CAD in women. Levels of Lp(a) are lowered with estrogen, regardless of the route of administration. In part, the beneficial effects of HRT on CVD risk can be attributed to effects of these plasma lipoproteins (Table 1).

The specific lipid effect depends on the type of hormones administered and the route of administration. For example, the addition of medroxyprogesterone acetate (MPA) attenuates the beneficial effects of estrogen on HDL, whereas the addition of micronized progesterone does not.7 Oral estrogen therapy has a greater beneficial effect upon HDL and LDL than does transdermal therapy, whereas transdermal estrogen has a more favourable effect on serum triglyceride levels (Table 1).8-10 These effects may not be clinically relevant, except in those women with hypertriglyceridaemia or low HDL levels.8

ENDOTHELIAL EFFECTS OF ESTROGEN

Endothelial function is impaired in postmenopausal women.11 Estrogen administration results in up-regulation of estrogen receptors on the vessel wall.4 Short-term estrogen administration enhances endothelial-dependent flow-mediated vasodilatation in healthy women, mediated mostly by nitric oxide (NO).12 The exposure of arterial endothelium to estrogens appears to induce an estrogen receptor-mediated antioxidant effect, which enhances the biological activity of NO. The effect of the addition of a progestin to estrogen replacement therapy (ERT) on vascular reactivity is uncertain. In addition, few studies have examined the effects of long-term estrogen in women with established atherosclerosis using standard tests of vasodilatation.4

ANTITHROMBOTIC AND PRO-INFLAMMATORY EFFECTS

C-reactive protein (CRP), an acute phase reactant protein and a marker of inflammation, is associated with future coronary events in postmenopausal women.13 HRT increases circulating levels of CRP.14 Markers of thrombosis are also adversely affected by currently used regimens of HRT (Table 2). However, serum homocysteine levels (a marker for cardiovascular risk) are lower in users of HRT.15 The effects of lower doses of oral estrogen and transdermal estrogen on inflammatory and procoagulant markers are currently being investigated.
ATHEROGENESIS

Estrogen therapy is theoretically antiatherogenic, and the results of previous studies of estrogen therapy have shown benefits in animals and humans. However, a recent placebo-controlled trial (ERA) comparing the effects of oral conjugated equine estrogens (CEE) and combined CEE-MPA therapy in postmenopausal women with established coronary disease showed no effect of either treatment on the progression of angiographically-demonstrated coronary disease over three years. Data from lipid-lowering trials indicate that lesion area, as detected angiographically, may not be a relevant endpoint when evaluating outcomes in coronary heart disease. Thus the validity and generalizability of such angiographic trials using HRT is limited.

CARDIOVASCULAR EFFECTS OF SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

In healthy postmenopausal women, raloxifene hydrochloride (Table 1) and tamoxifen citrate reduce plasma LDL levels. Raloxifene does not, however, increase total HDL levels, but, like HRT, decreases levels of Lp(a) and homocysteine. A large secondary cardiovascular prevention trial involving raloxifene (Raloxifene Use for The Heart, or RUTH) is currently in progress.

Unlike HRT, raloxifene does not result in a significant increase in CRP levels. Long-term tamoxifen administration appears to be associated with a sustained decrease in circulating fibrinogen levels. A meta-analysis of adjuvant tamoxifen trials in women with early breast cancer did not demonstrate a significant reduction in CVD mortality.

OBSERVATIONAL STUDIES

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 indicate that current users of HRT have a 40 percent lower risk of CAD than women who never used HRT. An update of this cohort study has been recently published, specifically examining the dose of estrogen and duration of use of hormones. This study found that 0.3 mg oral conjugated estrogen (CE) daily was associated with a reduction in risk of CAD similar to that seen with use of 0.625 mg CE daily (RR 0.58 vs. 0.54 respectively). However, an increased risk of stroke was observed with daily doses of 0.625 mg CE or more (RR 1.35). The duration of hormone use had little effect on overall benefit, although the authors acknowledge their limited ability to monitor the early effects following initiation of HRT. Now that RCT reports indicate that EPT is not effective for primary or secondary prevention of CAD, the observed benefit in epidemiological studies may have appeared simply because the observed EPT users in the population were healthier than non-users.

RANDOMIZED CONTROLLED TRIALS

The Heart and Estrogen/Progestin Replacement Study (HERS), a secondary prevention trial of continuous-combined estrogen and progestin (CEE and MPA), did not demonstrate any overall reduction in cardiovascular events over four years of treatment. There was an increased risk (RR 1.57) of a second
cardiovascular event in the first year of treatment, followed by a non-significant reduction in risk in the last two years (RR 0.67). The downward trend in risk was statistically significant (p < 0.009). The increased risk in the first year encompassed cardiac death, nonfatal myocardial infarction, and a three times greater risk of venous thromboembolism. In a subgroup analysis, the highest risk of cardiac events occurred in those women with low Lp(a) levels, and the greatest benefit was seen in those with the highest Lp(a) levels. \cite{29} Recently, although not a randomized trial, the Nurses’ Health Study has provided prospective cohort data regarding secondary prevention that is consistent with HERS. \cite{30} In a subject of women with previous coronary disease, there was an increase in cardiovascular events (RR 1.25 [CI, 0.78–2.00]) among short-term hormone users (defined as current use less than one year). However, there was a significant decrease in risk (RR 0.38 [CI, 0.22–0.66]) with longer-term use (defined as current hormone use more than 2 years).

Because estrogen has demonstrated beneficial effects on many cardiovascular risk factors, and because observational studies show an association between estrogen therapy and cardioprotection, the reasons for an apparent lack of benefit in randomized trials of HRT are unknown. Proposed theories include a reduced expression of estrogen receptors in atherosclerotic arteries, or the development of a milieu that enhances estrogen’s pro-inflammatory and pro-coagulant effects. Additionally, the secondary prevention trials enrolled elderly women who were postmenopausal for many years before beginning HRT. It is possible that the duration of HERS may not have been long enough to demonstrate the cardioprotection that has been shown with long-term HRT in observational cohort studies. Extended follow-up of HERS participants has shown no evidence of cardiovascular benefit associated with EPT treatment during 6.8 years of observations.\cite{31,32}

The Women’s Health Initiative (WHI)\cite{33} is a nine-year primary prevention study, with approximately 27,000 postmenopausal women randomized to treatment with placebo, CEE alone (for those without a uterus), or CEE and MPA (in those with an intact uterus). This randomized, double-blind, controlled trial recruited predominantly healthy postmenopausal women aged 50 to 79 years. There was a 1.29-fold increase in CAD events (95% CI 1.02, 1.63), with 37 events in the EPT group and 30 in the placebo group per 10,000 women per annum.\cite{34} The small number of excess events occurred despite a significant 13% reduction in low-density lipoprotein cholesterol and 7% increase in high-density lipoprotein cholesterol with EPT compared to placebo. Thus, EPT is not indicated for the primary prevention of coronary heart disease. The WHI estrogen only study continues because the benefits and risks have not yet been established.\cite{2}

Another primary prevention trial, the WISDOM study (Women’s International Study of Long Duration of Estrogen after Menopause) is also in progress.

**CLINICAL INDICATIONS AND CONTRAINDICATIONS FOR HORMONE REPLACEMENT THERAPY**

**PRIMARY PREVENTION OF ISCHEMIC (CORONARY) HEART DISEASE**

Primary prevention strategies are designed to prevent coronary disease, including myocardial infarction, angina, or angiographic evidence of coronary disease, in those healthy women who have not yet manifested the disease. The WHI study results indicate that EPT is not effective for the primary prevention of coronary artery disease (CAD). Further large long-term trials are needed to evaluate whether EPT taken soon after the menopause for symptom relief has any effect on CAD. The first line of therapy should include lifestyle modifications, the use of acetylsalicylic acid (ASA) in high-risk women, and antihypertensive and lipid-lowering agents,\cite{35} all of which have been shown in RCTs to decrease cardiovascular risk and improve outcome.

**SECONDARY PREVENTION OF ISCHEMIC (CORONARY) HEART DISEASE**

Secondary prevention strategies are designed to lower the risk of subsequent events in those women who already have manifest coronary artery disease (a history of myocardial infarction, angina with documented disease, or having undergone coronary artery bypass surgery or percutaneous coronary angioplasty). As data from the available randomized trials fail to provide evidence that starting HRT provides effective secondary prevention of CVD, it should not be initiated as a means of decreasing the risk of further cardiovascular events.

At present, proven therapies such as ASA, β-adrenergic blockers, ACE inhibitors, and lipid-lowering agents are recommended.\cite{36}

**HISTORY OF DEEP VEIN THROMBOSIS**

Postmenopausal women with a history of deep vein thrombosis (DVT) should be cautioned about the risk of venous thromboembolic events (VTEs), including pulmonary embolism, associated with use of HRT.\cite{37,39} In addition to a personal history of DVT or pulmonary embolism, other risk factors should be considered prior to initiation of HRT (Table 3). Suggested investigations for a patient with a history of idiopathic VTE are listed in Table 4.

In the WHI study, venous thromboembolism risk in the first year of use was 3.6-fold higher for EPT users compared with placebo users.\cite{2} Although the relative hazard declined with time, the overall risk during more than 5 years of use remained significantly elevated (RH 2.11, 95% CI 1.26, 3.55).

The HERS results indicated that, in postmenopausal women with known CAD, use of HRT is associated with a three times greater risk for venous thrombosis (four events per 1000 women-years).\cite{40} In HERS, most of these events occurred in women at risk for VTE because of cancer, lower extremity...
fracture, and immobilization. Such women should be informed that use of HRT confers a small excess risk of VTE, although the overall case fatality rate is low. In addition, hospital admission for medical or surgical treatment within 90 days was also found to increase the risk of VTE. HRT should therefore be avoided during this period of time.

Biochemical data suggest that transdermal estrogen therapy in women with a history of DVT may carry less risk of thrombosis than oral therapy, but clinical data are not yet available. Limited studies have reported a three to five times greater risk of VTE with use of tamoxifen, and a three times greater risk with raloxifene therapy.

PRIOR STROKE
A woman who has a stroke or transient ischemic attack (TIA) may subsequently become immobilized, increasing her risk of VTE. In these circumstances, use of HRT should be avoided. Appropriate anticoagulation may attenuate the risk of VTE.

There is no evidence to date concerning the effect of HRT or estrogen on the risk of recurrent stroke in postmenopausal women with cerebrovascular disease. In the HERS cohort, use of HRT had no effect on the risk of stroke or TIA in women with established cardiovascular disease.41 The WHI study found, however, that stroke incidence was increased among generally healthy EPT users, although the difference was not significant (29 versus 21 cases per 10,000 women per annum in EPT and placebo users, respectively). In contrast to the effect on coronary events, no early increase in the risk of stroke was found.

Once a woman becomes mobile again following a stroke or TIA, EPT may be reinstituted if there are severe menopausal

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**TABLE 3**

**CLINICAL RISK FACTORS FOR VTE**

1. Personal history of DVT or pulmonary embolism.
2. First degree family members with history of DVT or pulmonary embolism.
3. Poor obstetrical outcomes in patient or family, such as severe preeclampsia, multiple fetal losses, unexplained stillbirth, unexplained intrauterine growth retardation, unexplained severe abruptio placenta.
4. Known thrombophilia.
5. Other risk factors such as immobilization (> 48-72 hours continuously bedridden in the last month), major surgery or trauma in the previous month, previous VTE, cancer (on treatment, treated in the previous 6 months, palliative).
6. Risk factors as per HERS (see text).

**TABLE 4**

**SUGGESTED INVESTIGATIONS FOR THE PATIENT WITH A HISTORY OF IDIOPATHIC DVT**

1. PTT; INR
2. Protein C
3. Protein S
4. Antithrombin III
5. Activated protein C resistance (Factor V Leiden)
6. Lupus anticoagulant
7. Anticardiolipin antibody
8. Prothrombin gene defect
9. Homocysteine

---

**TABLE 5**

**TARGET LIPID VALUES BY LEVEL OF RISK**

<table>
<thead>
<tr>
<th>Level of risk (definition)</th>
<th>LDL-C level (mMol/L)</th>
<th>Total cholesterol: HDL-C ratio</th>
<th>Triglyceride level (mMol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high* (10-year risk of CAD &gt; 30%, or history of cardiovascular disease or diabetes)</td>
<td>&lt; 2.5</td>
<td>&lt; 4.0</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>High* (10-year risk 20-30%)</td>
<td>&lt; 3.0</td>
<td>&lt; 5.0</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Moderate** (10-year risk 10-20%)</td>
<td>&lt; 4.0</td>
<td>&lt; 6.0</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Low*** (10-year risk &lt; 10%)</td>
<td>&lt; 5.0</td>
<td>&lt; 7.0</td>
<td>&lt; 3.0</td>
</tr>
</tbody>
</table>

* start medication and lifestyle changes concomitantly if values are above target values.
** start medication if target values are not achieved after three months of lifestyle modification.
*** start medication if target values are not achieved after six months of lifestyle modification.

symptoms. Randomized trials specifically targeted to stroke prevention currently in progress will provide more information.

**HRT AND DYSLIPIDEMIA**

The choice of HRT prescribed for menopausal symptoms may be influenced by the lipid profile. A lipid screen should be repeated three to six months after beginning HRT, particularly if the initial serum triglyceride level was 2.5 mmol/L or greater. Asymptomatic (low-risk) women should undergo a full lipid screen (serum total cholesterol, HDL, LDL, triglycerides) every five years after the age of 50 or at menopause, whichever comes first. Routine screening should occur when women develop clinical evidence of CAD, peripheral vascular disease, carotid atherosclerosis, stroke, diabetes mellitus, stigmata of dyslipidemia, or more than one risk factor for CAD. Target lipid levels are determined according to a patient’s level of risk. Most women with clinical CAD or diabetes (classified as “very high risk”) will require lipid-lowering drugs. The reader is referred to the recently published lipid guidelines (Table 5).

**HYPERTENSION**

Large controlled trials such as the PEPI trial have found no significant change in blood pressure with oral administration of HRT. A study comparing transdermal and oral HRT found no change in blood pressure in treated women over two years, whereas the placebo group showed an increase. In the Nurse’s Health Study, hypertensive women who used HRT had a decreased risk of coronary artery disease. Therefore, the presence of hypertension is not a contraindication to HRT use, and it may in fact have a favourable effect on blood pressure due to beneficial changes in thromboxane and prostacyclin activity.

**RECOMMENDATIONS:**

D1. Hormone replacement therapy (oral continuous-combined conjugated equine estrogens [CEE] and medroxy-progesterone acetate [MPA]) (I) or other regimens (III) should not be initiated or continued for the sole purpose of preventing future cardiovascular events (primary and secondary prevention). (I)

D2. All women should be counselled about the beneficial effects of lifestyle modifications on reducing the risk of future cardiovascular events. Appropriate modifications include consumption of a heart-healthy diet, cessation of smoking, moderate daily exercise, and maintenance of healthy body weight. (II)

D3. To prevent future cardiovascular events, women should be prescribed therapies for which there is abundant scientific evidence, such as antihypertensive and lipid-lowering medications, b-adrenergic blockers, antiplatelet agents, and angiotensin-converting enzyme (ACE) inhibitors, with due attention to the potential risks or adverse effects of any of these therapies. (I)

**CONCLUSION**

In contrast to results obtained from earlier long-term observational studies, the available RCT data provides clear evidence that estrogen, with or without progesterin, does not reduce cardiovascular events either in healthy women or in those with established coronary disease; nor does it slow the progression of atherosclerosis as detected by angiography. The reason for the difference between observational and RCT findings appears to be the lower validity of the observational study design methodology.

Based on the available data, HRT in any form is not recommended to reduce cardiovascular events or to prevent coronary heart disease. Other proven methods for risk reduction should be strongly encouraged, including the adoption of a heart-healthy lifestyle (including daily moderate to vigorous physical activity, not smoking, maintaining a normal body mass index, and good dietary habits) and modification of cardiovascular risk factors. Evidence-based treatment, in the form of lipid-lowering therapy, ASA therapy, use of b-adrenergic blockers, and angiotensin-converting enzyme (ACE) inhibitors, should also be considered since there is reliable evidence that such treatments are effective.


**REFERENCES**

1. Heart and Stroke Foundation of Canada. The Changing Face of Heart Disease and Stroke in Canada 2000. Prepared in collaboration with Laboratory Centre for Disease Control, Health Canada; Statistics Canada; Canadian Cardiovascular Society; Canadian Stroke Society; Heart and Stroke Foundation of Canada.


INTRODUCTION

Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Loss of bone mineral density is silent until fracture occurs. Postmenopausal status and advanced age account for about 80 percent of cases of osteoporosis. Secondary osteoporosis refers to bone loss that is due to identifiable causes such as diseases, drugs or immobility.

EPIDEMIOLOGY, FRACTURE RISK

Over 70 percent of all fractures in people aged 45 or over are due to osteoporosis. It has been estimated that two million Canadian women have osteoporosis. With the aging of the Canadian population, this number will increase rapidly. Women are particularly at risk for osteoporotic fracture, having an incidence of fracture three times that of men. The average 50-year-old woman has a lifetime osteoporosis fracture risk of 17.5 percent for the hip, 15.6 percent for the vertebra, 16 percent for the distal forearm, and almost 40 percent for any site. Occult vertebral fractures are common in elderly postmenopausal women and indicate a three to five times greater risk of future vertebral fracture, as well as an increased risk of hip fracture. An incident vertebral fracture in a patient with osteoporosis confers a 20 percent risk of subsequent vertebral fracture in the following year.

SOCIAL AND MEDICAL OUTCOMES OF FRACTURE

The medical and social consequences of fractures make osteoporosis an important public health problem. About 20 percent of women and 40 percent of men die within one year after hip fracture. It has been estimated that 50 percent of women who sustain a hip fracture become functionally dependent in their daily activities, and 19 percent require long-term nursing home care because of the fracture. Vertebral fractures appear to be associated with similar five-year mortality. Only one-third of all vertebral fractures are clinically diagnosed.

In addition to health care costs, vertebral fractures cause back pain, loss of height, depression, and low self-esteem. 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 dollars in 1993. With the aging of the population, the frequency of osteoporotic fractures will increase in both men and women. In addition, it is likely that the population explosion in developing countries will change the demography of osteoporosis; for example, the incidence of hip fracture (and presumably other osteoporotic fractures) is expected to increase four-fold worldwide during the next 50 years, and the attendant costs will threaten the viability of the health care systems of many countries.

PREVENTION OF OSTEOPOROSIS

Because of the high prevalence of osteoporosis, we must adopt a cost-economic approach to preventing osteoporosis. Population strategies for primary prevention of osteoporosis, including interventions in childhood and young adult life to maximize peak bone mass and prevent premenopausal decline in bone mass, are essential.

BUILDING AND MAINTAINING SKELETAL HEALTH THROUGHOUT LIFE

Bone size, strength, and mineralization increase during development, with a peak in the third decade of life. Those with the highest peak bone mass have a protective advantage from the reductions in bone density that occur with increasing age, illness, and decreased sex-steroid activity. Genetic factors are the predominant predictors of peak bone mass, with physiological, environmental, and modifiable lifestyle factors also having a significant role.

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. 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 adults, elemental calcium intake from diet and supplements should be 1000 to 1500 mg per day. Vitamin D is required for optimal calcium absorption. A vitamin D intake of 400 to 800 IU per day has been recommended for adults, with 800 IU per day suggested for those over age 65 or with proven osteoporosis.

Physical activity early in life contributes to higher peak bone mass. Resistance and impact exercises are the most beneficial. Exercise during the middle years of life has numerous health benefits, but the effects of exercise on BMD have not been well studied. Fracture endpoint reduction is not changed by exercise interventions. Exercise during the later years can slow loss of BMD, and it may increase muscle mass and strength in frail individuals.

These recommendations regarding calcium, vitamin D, and exercise are a prerequisite for optimal antiresorptive effect, both in clinical practice and in clinical trials of fracture incidence.

**PHARMACOLOGIC PREVENTION**

Estrogen, cyclic etidronate, alendronate (5 mg daily), risedronate (5 mg daily), and raloxifene (60 mg daily) are all effective in preventing postmenopausal bone loss. Bisphosphonates may have prolonged resolution of effect, with 0.5 to two percent loss in bone density annually on discontinuation. Fracture data are not provided in prevention trials because of the low fracture rate in young patients. Differentiation and choice of therapies will depend on side effects, extraskeletal effects, cost, and patient preference.

**ASSESSING A WOMAN’S RISK FOR OSTEOPOROSIS**

All postmenopausal women should be evaluated for osteoporosis in routine postmenopausal health care. A combination of medical history, physical examination, and selected diagnostic tests may be required.

Clinically, osteoporosis should be assessed by the identification of risk factors. Established major risk factors for low bone mass include a family history of osteoporosis, use of corticosteroids, and estrogen deficiency states (Table 1). Unfortunately, clinical risk factors for predicting low bone density, even in combination, have poor sensitivity and specificity. The assessment of risk factors will only identify 30 percent of women with low bone mass at the time of menopause. However, these factors can be used to help identify a woman at high risk who may benefit from further evaluation. A physical examination should be performed, noting body habitus and any evidence of height loss or kyphosis. Physical examination

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**TABLE 1**

<table>
<thead>
<tr>
<th>Potentially Modifiable</th>
<th>Nonmodifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cigarette smoking</td>
<td>History of fracture after age 40</td>
</tr>
<tr>
<td>Low body weight (&lt;57.8 Kg)</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Estrogen deficiency due to: - Early menopause (&lt; age 45) - Bilateral oophorectomy - Prolonged premenopausal amenorrhea</td>
<td>History of hip, wrist or vertebral fracture in a first-degree relative</td>
</tr>
<tr>
<td>Low calcium intake</td>
<td>Caucasian or Asian</td>
</tr>
<tr>
<td>Glucocorticoid (prednisone &gt; 7.5 mg / day for &gt; 3 months or endogenous hypercortisolism)</td>
<td>Female sex</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>Dementia with increased likelihood of falls</td>
</tr>
<tr>
<td>Excess caffeine</td>
<td>Poor general health</td>
</tr>
<tr>
<td>Impaired caffeine</td>
<td></td>
</tr>
<tr>
<td>Recurrent falls</td>
<td></td>
</tr>
<tr>
<td>Inadequate physical activity</td>
<td></td>
</tr>
<tr>
<td>Poor health / frailty</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2**

**INDICATIONS FOR BONE DENSITOMETRY, ACCORDING TO THE OSTEOPOROSIS SOCIETY OF CANADA (1999)**

If one of the following risk factors is present:
1. Personal history of non-traumatic osteoporotic fracture after 40: wrist, shoulder, vertebrae, hip.
2. History of osteoporosis in a first-degree relative.
3. Thin build, with BMI <20/kg/m² or weight <57.8 kg.
4. Early menopause (<45 years old) or chronic hypogonadism before menopause.
5. Glucocorticoid therapy (≥7.5 mg of prednisone per day or equivalent for more than 3 months, or presence of Cushing’s syndrome).
6. Primary hyperparathyroidism.
7. Prolonged use of anticonvulsants without vitamin D supplementation (>10 years).
8. Chronic malabsorption or malnutrition (>5 years).
9. Chemotherapy, if long-term survival is expected.
10. Documented loss of height.

If two or more of the following risk factors are present:
2. History of hyperthyroidism.
3. Low calcium intake.
4. Alcoholism.

---

will also help exclude secondary causes of osteoporosis. Factors associated with an increased risk of falls, such as an impaired sensorium, muscle weakness, and instability, should be noted.

**INDICATIONS FOR DUAL ENERGY X-RAY ABSORPTIOMETRY**

BMD is only one of several determinants of fracture risk, accounting for the overlap in the distribution of BMD for individuals who have and have not sustained fractures. Nevertheless, it is the single most predictive test for the identification of a population at risk, and it has been used as the entry criterion for clinical trials of pharmacologic agents. A fragility fracture is, by itself, sufficient for the diagnosis of osteoporosis, regardless of BMD.

BMD testing is indicated only in patients in whom the information might lead to a change in management. Cost-effective BMD testing, such as dual energy X-ray absorptiometry (DEXA) of the hip and spine, is appropriate for women over the age of 65, or for women over the age of 55 with one or more additional risk factors for osteoporotic fracture besides menopause.38,39

The Osteoporosis Society of Canada (OSC) has recently updated its indications for BMD testing, summarized in Table 2.40

**ROLE OF PERIPHERAL BONE DENSITY TESTING**

Peripheral BMD can be measured by DEXA, ultrasound or single X-ray absorptiometry at several skeletal sites (radius, phalanx, calcaneus, tibia, metatarsal). These technologies are almost as accurate as DEXA of the hip and spine, in predicting future fracture risk,41,42 but they cannot be used at the present time for follow-up. Peripheral testing may play an important role for women in underserviced areas and in raising awareness about osteoporosis. However, these services may be provided by unregulated practitioners, which raises concerns about quality control.

**INTERPRETING THE RESULTS OF BMD TESTING**

A study group of the World Health Organization (WHO) has proposed guidelines for the interpretation of BMD by DEXA at the hip and spine in postmenopausal Caucasian women (Table 3).43,44 These guidelines are based on fracture prevalence in this population. Their relevance to other populations, to other BMD technologies (such as ultrasound), or to sites other than hip and spine is not determined.45 A T-score is used to compare the patient’s BMD to a normal young woman’s BMD.

In 30 percent of cases, an imperfect correlation exists between BMD measurements at different sites.46 When there are discrepancies between sites, the lowest value should be used for diagnosis. Ordinarily, BMD in the lumbar spine can be measured with more precision, and early postmenopausal changes are more readily detected there than at other sites.16

In elderly women, degenerative changes in the lumbar spine may artifactualy elevate spinal BMD.47 Therefore, the total hip BMD measurement may be the best test for assessing BMD in women over age 65. Even with a precision error as low as one percent, serial BMD measurements require a minimum follow-up interval of one to two years to detect a bone loss of two to three percent (the average loss per year for a normal woman at menopause). A longer interval (5 years) is required for repeat BMD testing when normal values are obtained.

**BLOOD AND URINE TESTS**

In patients with diagnosed osteoporosis, blood tests to rule out secondary osteoporosis are essential, and are documented in Table 4.15 Although blood and urine tests may be useful in large clinical trials to determine the level of bone turnover, they have very limited clinical utility at present. Individual patients show a large variability in tests from one day to the next.48 Markers of bone formation (such as bone specific alkaline phosphatase) and bone resorption (urinary N-telopeptide or deoxypyridinoline, urinary or serum C-telopeptide) may show elevated levels in postmenopausal women.49 The levels of markers in postmenopausal women on antiresorptive therapy may be reduced.50 Elevated marker levels cannot be used to identify patients for therapy, and in an individual patient they are not useful for monitoring the response to therapy.

<table>
<thead>
<tr>
<th>BMD T-Score* standard deviations</th>
<th>Change in fracture risk</th>
<th>WHO categorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; -1</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td>-1 to -2.5</td>
<td>4-fold increase</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>&lt; -2.5</td>
<td>8-fold increase</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>With one or more fragility fractures with or without low BMD</td>
<td>20-fold increase</td>
<td>Severe osteoporosis</td>
</tr>
</tbody>
</table>

*Results (T-score) are compared with the mean for young adult normal female controls. Derived from a WHO Study Group report. WHO Tech Rep Ser 1994;843:1-129.
Making a diagnosis of osteoporosis with plain radiographs is only possible after the loss of bone mass becomes severe. Spinal X-rays may identify vertebral compression fractures, Paget's disease, and metastatic bone disease. However, it is normally not useful, since while plain films can detect compression fractures, detection of changes of apparent bone density are not reliable until at least 30 percent of bone mineral has been lost.

**WHEN TO REFER**

In general, patients with postmenopausal osteoporosis can be effectively managed without referral. Those who may need referral include patients with complex general medical concerns in addition to osteoporosis or with secondary osteoporosis, and patients who cannot be adequately counselled by the primary physician. In addition, patients who are not responding to therapy need referral. Expertise in osteoporosis may be found with different specialists (including endocrinology, nephrology, rheumatology, geriatrics, gynaecology, and internal medicine) in different communities.

**ASSESSING THE EFFECTIVENESS OF THERAPY**

Regulatory agencies require evidence of fracture prevention for the approval of new treatments for osteoporosis. Fracture prevention is evaluated by the proportion of patients with a new fracture, or by the time to first fracture. The effectiveness of many older agents in preventing fracture cannot be determined from published reports, since the trials with these agents frequently were small, with BMD endpoints. As was seen with fluoride therapy, increases in BMD alone are not sufficient to predict fracture reduction.

**ANTIRESORPTIVE PHARMACOTHERAPY**

Therapy initiated early has the advantage of preventing deterioration in bone, but at the expense of requiring a longer duration of therapy. Treating only the elderly, in whom fractures are more common, is more cost-effective, but some elderly patients will fracture before therapy can be initiated. Treating women with a hip T-score of less than −2, or a hip T-score less than −1.5 with one or more risk factors (Table 1), would also be cost-effective. In addition, patients on long-term high-dose corticosteroid therapy and patients with prevalent fragility fractures should probably receive antiresorptive therapy. Clinical decision-making must be individualized and may vary according to other factors.

**THERAPEUTIC AGENTS**

Randomized placebo-controlled trials (RCTs) of cyclic etidronate, alendronate, risedronate, and raloxifene show increases in BMD at the spine and hip with each of these agents. Alendronate, risedronate, and raloxifene significantly reduce the risk of vertebral fractures. Despite a small increase in BMD, nasal calcitonin, has demonstrated a significant reduction in vertebral fractures. The effect of cyclic etidronate on the reduction of vertebral fractures is less well documented. Alendronate and risedronate reduce the risk of subsequent nonvertebral fractures in women with postmenopausal osteoporosis. Alendronate, risedronate, and etidronate preserve bone mass in adults with glucocorticoid-induced osteoporosis. There have been no trials showing prevention of nonvertebral fracture with bisphosphonates in women with normal bone mass. In RCTs of bisphosphonates, the rates of discontinuation due to adverse events were similar in the placebo and active treatment groups. The safety and
efficacy of this therapy in children and young adults has not been evaluated. Patients in clinical trials may not always be representative of a community population.

HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) is the traditional approach for osteoporosis prevention, as demonstrated by many studies with BMD as the primary measure.66-68 Both oral and transdermal estrogen therapy decrease bone loss.66-68 Estrogen therapy that is begun after age 60 and continued also offers bone-conserving benefit.69,70 Lower doses of estrogen taken in combination with calcium may be equally protective.71 BMD rises in women who begin estrogen therapy within five years after menopause;66-68 stabilization of BMD is expected in older women who begin therapy 10 years or more after menopause.70 Observational studies show a reduction in the rate of hip fracture in women who choose to take long-term HRT and remain on therapy.69,70 The Women’s Health Initiative randomized controlled trial is the first trial with definitive data supporting the ability of postmenopausal hormones to prevent fractures at the hip, vertebrae, and other sites.72 The additional benefits and risks of HRT are important to an individual woman in making a choice of therapy. HRT is inexpensive, and dosing is convenient.

BISPHOSPHONATES

There are two major classes of bisphosphonates approved for the prevention and treatment of osteoporosis in Canada: non-nitrogen-containing bisphosphonates such as cyclic etidronate, and nitrogen-containing bisphosphonates such as alendronate and risedronate. These classes differ in their molecular mechanism of action, and clinical trials demonstrate differences in fracture and bone density protection when compared to placebo. There have been no head-to-head trials of these agents.

NON-NITROGEN-CONTAINING BISPHOSPHONATES: CYCLIC ETIDRONATE

Trials with cyclic etidronate (etidronate 400 mg daily for two weeks every three months) were powered for BMD endpoints only.53,54,73 Discernible increases in BMD are seen in the spine and, to a lesser extent, the hip. Non-responders are frequent. Reduction in vertebral fracture risk can be seen only in high-risk subgroups of the etidronate clinical trials. Data on non-vertebral fracture prevention have only been reported from observational studies.74 It is also approved for the prevention of corticosteroid-induced osteoporosis.95 Cyclic etidronate is inexpensive and well-tolerated, with rare gastrointestinal upset and bone pain reported as side effects.54,73 It is administered either two hours before eating or two hours after eating. Low-dose cyclic therapy is required because continuous therapy impairs mineralization.75

Etidronate acts by forming toxic metabolites of adenosine triphosphate (ATP) and consequently inhibiting osteoclastic bone resorption.76 This mode of action differs from that of nitrogen-containing bisphosphonates, which act on the mevalonate acid pathway.77

NITROGEN-CONTAINING BISPHOSPHONATES: ALENDRONATE

Alendronate, in doses of 10 mg daily78 or 70 mg once weekly,79 leads to detectable increases in bone mineral density at both spine and hip. A reduction in vertebral fracture risk is seen with use of alendronate 10 mg daily, both in patients with prior vertebral fractures56 and patients with no prior vertebral fractures.59 Significant reductions in rates of non-vertebral and hip fractures are seen as soon as 12 to 18 months after commencing therapy. Alendronate is approved for the prevention and treatment of corticosteroid-induced osteoporosis. Side effects of therapy are frequently associated with misdosing. Rarely, gastrointestinal upset and bone pain occurs, but there is no impairment of mineralization.80 Studies confirm long-term efficacy and safety, with continuing increases in bone density to the end of seven years. Alendronate must be taken with water, 30 minutes before breakfast, with the patient subsequently remaining upright for 30 minutes.

The 70 mg once-weekly dosing regimen of alendronate has been shown to provide patients with a more convenient, therapeutically equivalent alternative to daily dosing.79 It may enhance compliance and long-term persistence with therapy. Dosing with 70 mg once weekly is equivalent to 10 mg daily in safety and BMD efficacy, but no fracture data is available.79

NITROGEN-CONTAINING BISPHOSPHONATES: RISEDRONATE

Administration of risedronate 5 mg daily leads to significant BMD increases at the spine and hip.60 A reduction in vertebral fracture rate is seen in patients who have prevalent vertebral fractures.60 Morphometric vertebral fracture reduction at one year of therapy has been demonstrated.57,60 Significant reductions in non-vertebral and hip fractures have been reported in a recent study;62 this is the only study recording hip fracture as a primary endpoint. Risedronate rarely causes gastrointestinal upset and bone pain. No impairment of mineralization is seen.60 It must also be taken after fasting, with water only, either 30 minutes before breakfast, or at least two hours before or after food, and the patient must subsequently remain upright for 30 minutes.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) have been an important advance in osteoporosis therapy. The goal of these agents is to maximize the beneficial effect of estrogen on bone and to minimize or antagonize the effects of estrogen on the breast and endometrium. Modest BMD increases are seen at the
**TABLE 5**

**RANDOMIZED CONTROLLED TRIALS WITH ANTIRESORPTIVE THERAPIES: PATIENTS WITH PREVIOUS VERTEBRAL FRACTURES**

<table>
<thead>
<tr>
<th>Medication</th>
<th>17 β-Estradiol (Estraderm™)</th>
<th>NS-Calcitonin (Miacalcin™)</th>
<th>Raloxifene (Evista™)</th>
<th>Alendronate Sodium (Fosamax™)</th>
<th>Risedronate (Actonel™)</th>
<th>Risedronate (Actonel™)</th>
<th>Cyclic-Etidronate (Didrocal™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT Name</td>
<td>Lufkin⁶⁸</td>
<td>PROOF⁶¹</td>
<td>MORE⁵⁸</td>
<td>FIT⁶⁶</td>
<td>VERT-NA⁵⁷</td>
<td>HiP⁶²</td>
<td>Harris⁵⁴</td>
</tr>
<tr>
<td>Duration (yrs)</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td># Patients</td>
<td>75</td>
<td>627 (1255)⁴</td>
<td>1539 (7705)⁵</td>
<td>2027</td>
<td>1641 (2458)⁶</td>
<td>9331</td>
<td>423</td>
</tr>
<tr>
<td>Study Subjects</td>
<td>65 (47–75)</td>
<td>68 (31–80)</td>
<td>71 (55–81)</td>
<td>68</td>
<td>74 (&gt; 70)</td>
<td>68.5</td>
<td>100% 1 fx</td>
</tr>
<tr>
<td>Age (range)</td>
<td>100% ≥ 1 fx</td>
<td>80% ≥ 1 fx</td>
<td>100% 1 fx</td>
<td>100% ≥ 1 fx</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Dose</td>
<td>100 µg</td>
<td>200 IU</td>
<td>60 mg</td>
<td>5 / 10 mg</td>
<td>5 mg</td>
<td>2.5 and 5 mg</td>
<td>400 mg 2wk/15wk</td>
</tr>
<tr>
<td>DEXA lumbar spine vs. placebo ⁸</td>
<td>↑ 5.1 %</td>
<td>NS</td>
<td>↑ 2.6 %</td>
<td>↑ 6.2 %</td>
<td>↑ 4.3 %</td>
<td>NA</td>
<td>↑ 4.0 %</td>
</tr>
<tr>
<td>DEXA femoral neck vs. placebo</td>
<td>↑ 2.6 %</td>
<td>NS</td>
<td>↑ 2.1 %</td>
<td>↑ 4.1 %</td>
<td>↑ 2.8 %</td>
<td>↑ 2.1% and 3.4%⁹</td>
<td>NS</td>
</tr>
<tr>
<td>Vertebral fractures vs. placebo (%) placebo/therapy ⁹</td>
<td>↓ 61%</td>
<td>↓ 33%</td>
<td>↓ 30%</td>
<td>↓ 46%</td>
<td>↓ 41%</td>
<td>N/A</td>
<td>↓ 18% (17.4 / 14.3)</td>
</tr>
<tr>
<td>Hip fractures vs. placebo</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>↓ 51% (2.2 / 1.1)</td>
<td>NS</td>
<td>↓ 30% ³⁶</td>
<td>NS</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td>↓ 53% BMD Fx T&lt;2.5 or Vfx ¹</td>
<td>Age 70–79 FN T&lt;3.0</td>
<td>↓ 40% (1.9 / 3.2)</td>
<td>+ prevalent vertebral fx ↓ 60% (2.3/5.7) Age ≥ 80 + risk factor NS (5.1 / 4.2)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral fractures vs. placebo (%) placebo/therapy</td>
<td>NS ³⁶</td>
<td>NS</td>
<td>NS</td>
<td>↓ 20% (14.7 / 11.9)</td>
<td>↓ 39% (8.4 / 5.2)</td>
<td>↓ 16% (11.2 / 9.4)</td>
<td>NS ³⁶</td>
</tr>
</tbody>
</table>

fx = fracture NS = not significant

a Individual patient BMD responses vary. Precision of DEXA LS ± 3%. Precision of DEXA total hip ± 4%.
b Fracture (fx) vs. Placebo data reported as relative risk reduction ([incidence in placebo group]/[incidence in treatment group]).
c Low recruited patient numbers preclude detection of significant non-vertebral fracture reduction.
d Other patients on 100 IU or 400 IU dose.
e Prevalent fracture 60 mg dose group.
f Trial divided into “prevalent fracture” and “no prevalent fracture” groups. Patients on 120 mg dose not included.
g Other patients on 2.5 mg dose.
h Data available on only 19% of cohort.
i Vert NA trial shows 65% reduction in vertebral fracture at 1-year. Vert MN trial (not in this table) shows similar reduction of incident vertebral fracture at 3 years (49%) as Vert NA in a high risk vertebral fracture prevalent population. Non-vertebral fracture reduction was not significant in this trial (ref: Reginster J-Y, Minne HW, Sorensen OH et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporosis Int 11:1 83-91, 2000)
j The published result in NEJM is 30%, rounded up from 28%

*This and table 6 do not allow for direct comparison of trials, as they have different inclusion criteria and parameters.*
lumbar spine and hip. Treatment with tamoxifen or raloxifene 60 mg daily has been shown to reduce vertebral fracture risk in patients with and without prevalent vertebral fracture. No reduction in rates of non-vertebral or hip fractures is seen. Side effects include leg cramps, vasomotor symptoms, and an increased risk of venous thrombosis. Raloxifene can be taken either fasting or with food.

**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. Bone mineral density stabilizes at the lumbar spine and at the hip, similar to the effect of calcium and vitamin D. A reduction in vertebral fracture rate is seen in patients with and without prior vertebral fracture. 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.

**OTHER MEDICATIONS**

Other agents in other therapeutic categories are undergoing clinical trials, or have been investigated as osteoporosis therapies. Parathyroid hormone has been demonstrated to increase bone mass and reduce fractures when given by subcutaneous injection. Fluoride is effective in increasing bone density, but paradoxically it increases fracture risk due to abnormalities in bone architecture. The cholesterol-lowering statins affect the same metabolic pathway as the nitrogen-containing bisphosphonates. There is no consistent anti-fracture efficacy of statins in observational cohorts, and controlled trials have yet to be initiated.

**COMBINATIONS OF MEDICATIONS**

The addition of bisphosphonate therapy (alendronate or cyclic etidronate) to long-term estrogen therapy in women has been shown to improve bone density; when alendronate is added to estrogen therapy, BMD increases by three percent after two years. Other indications for adding a bisphosphonate to HRT include: significant bone loss despite use of HRT, glucocorticoid therapy (at least 7.5 mg prednisone/day, or equivalent, for at least 3 months), and osteoporotic fracture in a patient on estrogen therapy. Other combinations of anti-resorptive therapies have not been investigated.

**TABLE 6**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Raloxifene (Evista&lt;sup&gt;TM&lt;/sup&gt;)</th>
<th>Alendronate Sodium (Fosamax&lt;sup&gt;TM&lt;/sup&gt;)</th>
<th>Alendronate Sodium (Fosamax&lt;sup&gt;TM&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT name</strong></td>
<td>MORE&lt;sup&gt;58&lt;/sup&gt;</td>
<td>FIT&lt;sup&gt;56&lt;/sup&gt;</td>
<td>FOSIT&lt;sup&gt;50&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Duration (yrs)</strong></td>
<td>3</td>
<td>4.2</td>
<td>1</td>
</tr>
<tr>
<td><strong># Patients</strong></td>
<td>3012 (7705)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4432</td>
<td>1908</td>
</tr>
<tr>
<td><strong>Study Subjects: Mean Age</strong></td>
<td>65 yrs (31-85 yrs)</td>
<td>68 yrs (54 - 81 yrs)</td>
<td>63 yrs (39 - 84 yrs)</td>
</tr>
<tr>
<td><strong>T-score</strong></td>
<td>T &lt; -2.5</td>
<td>T &lt; -1.8</td>
<td>T &lt; -2.0</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>60 mg</td>
<td>5/10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>DEXA – lumbar spine vs. placebo&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>↑ 2.6 %</td>
<td>↑ 6.8%</td>
<td>↑ 5%</td>
</tr>
<tr>
<td></td>
<td>[↑ 3.1%]</td>
<td>[↑ 8.3 %]</td>
<td>[↑ 5.0%]</td>
</tr>
<tr>
<td><strong>DEXA – femoral neck vs. placebo</strong></td>
<td>↑ 2.1%</td>
<td>↑ 4.6 %</td>
<td>↑ 2.4%</td>
</tr>
<tr>
<td></td>
<td>[↑ 0.8%]</td>
<td>[↑ 3.8%]</td>
<td></td>
</tr>
<tr>
<td><strong>Vertebral fractures vs. placebo&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>↓ 50%</td>
<td>↓ 44 %</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>(4.5 / 2.3)</td>
<td>(3.8 / 2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Hip fractures vs. placebo</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>(% placebo/therapy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-vertebral fractures vs. placebo</strong></td>
<td>NS</td>
<td>NS</td>
<td>↓ 47 %</td>
</tr>
<tr>
<td><strong>(absolute value placebo / therapy)</strong></td>
<td></td>
<td></td>
<td>(4.4 / 2.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> No prevalent fracture in 60 mg dose group.

<sup>b</sup> Individual patient BMD responses vary. Precision of DEXA LS ± 3%. Precision of DEXA total hip ± 4%.

<sup>c</sup> Fracture (fx) vs. Placebo data reported as relative risk reduction ([incidence in placebo group]/[incidence in treatment group]).
AGE FOR BEGINNING ANTIRESORPTIVE THERAPY

Although the management of osteoporosis should focus on prevention of the first fracture, the treatment of large numbers of young menopausal women is not cost-effective due to the low short-term incidence of fractures in this population. All women would benefit from adequate calcium, vitamin D, and lifestyle advice. It is reasonable to discuss the risks and benefits of estrogen therapy with young postmenopausal women, and reserve the assessment of osteoporosis by BMD measurement for the woman 55 years of age or older with a risk factor, or the woman 65 years of age or older with no specific risk factor (Table 2).

MONITORING TREATMENT FOR ESTABLISHED POSTMENOPAUSAL OSTEOPOROSIS

Periodic evaluation of bone density by DEXA at intervals of 1.5 to two years represents the best way to monitor the clinical response to medical intervention. Once the clinical condition is stabilized, there is no need to repeat DEXA assessments throughout life. When monitoring skeletal status with serial DEXA, it is important to understand the magnitude of biological change expected at the site measured, as well as the instrument precision at that site. The spine will change most rapidly after menopause, and with nitrogen-containing bisphosphonate therapy, the magnitude of change could be three to five percent after the first year of treatment (precision ± 3%). However, hip changes are slower (2% at one year) and machine precision is less (4%), mandating a longer interval between tests. Total hip measurements are more precise than other hip regions for following patients serially. The purpose of monitoring patients on medications that are not expected to produce detectable positive effects on BMD (calcitonin, raloxifene) is to identify any patients who may be losing bone mass on therapy.

USING BMD CHANGES TO MODIFY THERAPY

Increases in BMD on antiresorptive therapy may be more marked with one agent than another. Fracture prevention may or may not be associated with detectable increases in bone density, and a reduction in fracture risk may result from beneficial effects on bone architecture. Patients who lose bone density on therapy (by more than the precision of the instrument at that site) should have their dosing instructions reinforced, and secondary causes of osteoporosis should be excluded. The possibility of changes to therapy, or the addition of therapy, should be considered. Patients with stable or increasing bone density on therapy should continue until the clinical risk of fracture has diminished.

LENGTH OF THERAPY FOR OSTEOPOROSIS

We do not have long-term experience with most approved therapies for osteoporosis. Consequently, questions concern-

ING fracture risk in patients who discontinue therapy remain unanswered. We can advise patients that anti-fracture efficacy persists three to seven years (the length of follow-up in the clinical trials), and that bone density changes may plateau or increase slowly after the first two to three years of therapy. The decisions about duration of therapy must, however, remain clinical judgements based upon individual patient factors.

RECOMMENDATIONS:

E1. Evaluation of fracture risk in postmenopausal women should include the assessment of risk factors, with bone mineral density measurement for those at increased risk. a) Central (hip and spine) measurements by dual energy X-ray absorptiometry (DEXA) are the most accurate and precise measurements of bone density available, making them useful for both risk assessment and follow-up. (I) b) Peripheral bone mass measurements (e.g., ultrasound or DEXA measurements in the radius, phalanx, or heel) is useful for fracture risk assessment, but cannot be used for follow-up. (I)

E2. Physicians should be aware that a prevalent vertebral or non-vertebral fragility fracture markedly increases the risk of future fracture. (I)

E3. Markers of bone resorption, while useful in documenting group responses in large clinical trials, have no clear place in the evaluation of follow-up of individual patients. (II)

E4. Women should be encouraged to have adequate intake of calcium and vitamin D, good nutrition and exercise, avoidance of negative lifestyle habits (smoking, alcohol). A normal exposure to estrogen during reproductive life and exercise contribute to optimal achievement and maintenance of genetically determined peak bone mass. These recommendations are applicable to all women (II); for early postmenopausal women, adequate calcium and vitamin D intake alone is not sufficient to maintain bone mass. (I)

E5. Although combination of antiresorptive therapies may be synergistic in increasing bone mineral density, their effect on fracture has not been proven. Combination therapy should be reserved for patients not responding to single-agent antiresorptive therapy. (I)

SUMMARY OF KEY POINTS:

E6. The goal of osteoporosis management is the prevention of fracture. This may or may not be associated with significant increases in bone mineral density. (I)

E7. Postmenopausal bone loss can be effectively prevented by antiresorptive therapy such as estrogen replacement, selective estrogen receptor modulator, or bisphosphonate therapy. (I)

E8. Treatment with alendronate or risedronate has been demonstrated to decrease both vertebral and non-vertebral fractures including hip fractures (I); treatment with raloxifene, or calcitonin, has been demonstrated to reduce vertebral fractures (I); treatment with estrogen or etidronate appears to reduce vertebral fracture (II). Physicians should consider a range of treatment options for osteoporosis.

E9. According to the WHI study, continuous combined HRT was effective in reducing the risk of hip fractures (5 fewer cases per 10,000 women per year). Vertebral and other fractures were also reduced.

CONCLUSION

For premenopausal women with normal estrogen levels, no treatment except calcium and vitamin D should be offered. Bone mineral density testing should be delayed until after menopause. Patients on glucocorticoid therapy represent a different clinical situation,* and they must be investigated and appropriately treated for osteoporosis.31-36, 40-53

The best therapy is the one that takes into account the total benefits for a patient. In considering a patient's need for pharmacotherapy and choosing between the therapeutic options, an individualized approach is necessary. If the patient requires more than skeletal effects, such as relief from hot flushes, estrogen preparations may be the best option. If the patient is primarily at short-term risk for hip or non-vertebral fracture, a bisphosphonate is probably the best option. If the patient has specific intolerance to a medication, or other conditions such as a history of venous thrombosis or esophageal stricture, the clinician might favour one medication over another. Patients will also consider factors of cost, access through formularies, and dosing convenience.


REFERENCES


INTRODUCTION

Urinary complaints, including stress incontinence, urge incontinence, and recurrent urinary tract infection, 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. The female introitus, vagina, bladder, and urethra are all derived from the primitive urogenital sinus. Estrogen receptors have been found in all of these structures and possibly in the pelvic floor musculature and anorectum as well. The shared embryology of these organs accounts for their similar hormonal responsiveness.

In the markedly estrogen-reduced state of menopause, urogenital epithelial and subepithelial tissues become thinned and flattened. Urethral mucosal thickness and blood vessel engorgement decline, resulting in a reduction in mean urethral closure pressure. Urethral collagen content and elasticity also decrease, further compromising function and favouring the development of urethral sphincter incompetence. In the bladder, mucosal thinning with estrogen loss lowers the sensory threshold for detrusor contraction, resulting in irritative symptoms including urinary frequency, nocturia, and urge incontinence. Alterations in the natural vaginal and urethral flora and a rise in vaginal pH are thought to contribute to an increased incidence of lower urinary tract infection. Finally, estrogen deprivation may contribute to a loss of pelvic floor tone and collagen content, weakening musculofascial support for the pelvic organs and vaginal walls. Pelvic organ prolapse can thus be considered a consequence of urogenital aging, though this is a multifactorial problem not solely related to hypoestrogenism.

Studies of the prevalence of urogenital symptoms in postmenopausal women are limited. Affected individuals may not report symptoms, or their complaints may be deferred or ignored. The true extent of the problem of urogenital aging is therefore difficult to assess.

Symptoms related to urogenital aging may precede physical findings (Table 1). The first symptom reported is often reduced lubrication on sexual arousal. Superficial dyspareunia is common, and postcoital bleeding may occur. Additional symptoms include pruritus, dysuria, and vaginal discharge related to inflammation or infection. Urinary symptoms include incontinence, urgency, frequency, nocturia, and dysuria. Incontinence may be related to physical effort (stress) or to urgency, but is often mixed. Coital incontinence may occur, which may further contribute to sexual dysfunction. Symptoms of pelvic organ prolapse include pelvic heaviness and introital bulging. Voiding difficulty from urethral kinking or fecal incontinence can be associated with prolapse.

PHYSICAL FINDINGS

Due to a loss of rugae, the postmenopausal hypoestrogenic vagina is foreshortened, smooth, and narrowed. The vulvovaginal epithelium is comparatively pale, thin, and friable. 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. Urethral prolapse can occur. Like the vagina, the urethral and bladder mucosa appear pale and thin at the time of cystoscopy, especially in the area of the trigone.

INVESTIGATING URINARY INCONTINENCE

Urinary incontinence affects each woman’s quality of life differently. Decisions regarding investigation and treatment should be patient-motivated. After a complete history and physical examination, initial evaluation of the incontinent female should include a screening urine culture and a measurement of residual urine volume. Urine cytology and cystoscopy should be reserved for those patients with irritative symptoms, recurrent infection or hematuria. Urodynamic tests should be performed when urinary symptoms are mixed (both...
stress and urge incontinence), when there has been previous bladder neck surgery, or when there are neurologic symptoms or findings. When surgical management of stress incontinence is planned, urodynamic testing is recommended to confirm the diagnosis and to permit objective post-operative follow-up. If the practitioner is not familiar with this specialized testing, a referral to a colleague with expertise is advised.

**URODYNAMIC STUDIES**

The basis of a urodynamic study is the measurement of intravesical (bladder) pressure against volume. A pressure transducer is placed in the bladder, and the bladder is filled with water or gas. Bladder pressure is recorded to maximum bladder capacity. Provocative manoeuvres are performed, such as coughing or the Valsalva manoeuvre. The presence or absence of leakage is recorded, as is the abdominal pressure at which the leakage has occurred (the leak point pressure). Stress incontinence is diagnosed when urinary leakage occurs without an associated rise in bladder pressure. Detrusor instability is diagnosed when involuntary bladder contractions (pressure increases) occur. Sensory urgency is a diagnosis of exclusion: urgency or urge incontinence are present as symptoms, but urodynamic testing is normal. Urodynamic studies sometimes additionally include a one-hour weighed perineal pad test to quantify the volume of urine lost.

**MANAGEMENT OPTIONS FOR STRESS INCONTINENCE**

**CONSERVATIVE**

Stress incontinence can be treated successfully with physiotherapy, including pelvic floor (Kegel) exercises with or without biofeedback, weighted vaginal cones, and functional electrical stimulation. Objective response rates vary, but improvement and cure have been reported in as many as 60 percent of patients three months after completion of therapy. Patient motivation and dedicated expert staffing are imperative for success.

Clinical evidence of a clear beneficial effect of estrogen on postmenopausal urinary stress incontinence is weak, with recent data pointing to an absence of objective therapeutic benefit. A review of 66 published articles found only 23 trials appropriate for meta-analysis, of which only six were blinded and controlled. These six trials found an overall significant subjective improvement with estrogen therapy for stress incontinence, but no significant objective effect on quantitative urine loss. More recently, Jackson et al. in a large, randomized, double-blind, placebo-controlled trial, failed to demonstrate even a subjective improvement with six months of estrogen treatment. Based on current evidence, it seems unlikely that estrogen replacement therapy has a significant role to play in the treatment of urinary stress incontinence.

Other pharmacologic options for genuine stress incontinence
are directed at enhancing intrinsic urethral sphincter tone through α-adrenergic stimulation (Table 2). Success with these agents is variable,22 and serious side effects can include hypertension and cardiac arrhythmias.22 Several different anti-incontinence devices, including vaginal supportive pessaries and urethral plugs, are available in Europe, though very few are available in Canada (Table 3). These work best for those patients with mild or infrequent stress incontinence.

**Surgical**
When conservative management has failed, surgery becomes an option. Preferred surgical procedures for stress incontinence are retropubic bladder neck suspension procedures (Burch, Marshall-Marchetti-Krantz), or suburethral sling procedures, including the new tension-free vaginal tape (TVT) procedure23 that offers a minimally invasive approach under local anesthesia. In controlled trials with skilled operators, long-term objective cure rates as high as 80 to 90 percent have been reported for all these procedures.23-25 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 (Table 4).25

**Management Options for Urge Incontinence**
Detrusor instability and sensory urgency can be treated successfully with a combination of bladder drill (timed bladder emptying) and antimuscarinic agents, particularly tolterodine26 and oxybutinin (Table 5). Imipramine, a tricyclic antidepressant with anticholinergic effects, also has α-adrenergic properties which may enhance urethral sphincter tone, so it may be the drug of choice for mixed urinary incontinence. Functional electrical stimulation and, more recently, sacral nerve root modulation27 have been used with some success for recalcitrant detrusor instability. A definitive role for estrogen in the treatment of urge incontinence has not yet been established. Evidence from the randomized controlled trials performed to date28,29 and from meta-analysis31 has not demonstrated a significant benefit from estrogen for the treatment of either detrusor instability or sensory urgency. Perhaps there is a subgroup of patients who would benefit from estrogen therapy of a particular dose or type, but this is currently unknown.

**Management Options for Recurrent Urinary Tract Infection**
Estrogen replacement does have an important prophylactic role for recurrent urinary tract infection (UTI) in the 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.7 Alternatively, low-dose prophylactic antibiotics can be given once daily as suppressive therapy for three to six months, or as a single dose following intercourse, for recurrent postcoital infection. Nitrofurantoin, trimethoprim-sulfamethoxazole, and norfloxacin are commonly used.

**Table 2**
**Drug Therapy for Stress Incontinence**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine</td>
<td>30–80 mg po t.i.d./q.i.d.</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>30 mg po t.i.d./q.i.d.</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>25–75 mg b.i.d./t.i.d.</td>
</tr>
<tr>
<td>Imipramine</td>
<td>10–20 mg b.i.d.</td>
</tr>
</tbody>
</table>

**Table 3**
**Anti-Incontinence Devices**

<table>
<thead>
<tr>
<th>Vaginal (bladder neck support)</th>
<th>Urethral (plug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring pessary*</td>
<td>FemAssist™*</td>
</tr>
<tr>
<td>ContiRing™ bladder neck prosthesis</td>
<td>Reliance™</td>
</tr>
<tr>
<td>Introl™ bladder neck prosthesis</td>
<td>Impress Soft Patch™</td>
</tr>
</tbody>
</table>

* Currently available in Canada

**Table 4**
**Surgical Results for Stress Incontinence**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percent Cure</th>
<th>One Year</th>
<th>Five Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burch colposuspension</td>
<td>89</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>TVT procedure</td>
<td>90</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Modified Pereyra needle</td>
<td>65</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelly plication</td>
<td>63</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5**
**Drug Therapy for Urge Incontinence**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>2 mg po b.i.d.</td>
</tr>
<tr>
<td>Oxybutinin hydrochloride</td>
<td>2.5 mg po b.i.d./t.i.d.</td>
</tr>
<tr>
<td>Imipramine</td>
<td>10–20 mg po b.i.d.</td>
</tr>
<tr>
<td>Propantheline</td>
<td>15 mg po t.i.d./q.i.d.</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>20 mg po t.i.d./q.i.d.</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>200–400 mg po q.i.d.</td>
</tr>
</tbody>
</table>
ESTROGEN IN THE TREATMENT OF PROLAPSE

Pelvic organ prolapse is managed with a pessary or with surgery. When a pessary is used in the menopausal patient, maintenance therapy with estrogen (local or systemic) may be helpful in preventing 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. These changes are reversed in part by estrogen replacement. A similar situation may exist for the collagen of the pelvic floor and vaginal fascia if so, estrogen therapy may help to maintain existing collagen or reverse these collagen changes. Preliminary evidence points to a decrease in descent of the bladder base, demonstrated by videourodynamics, after estrogen administration in postmenopausal women. Additional unresolved questions include whether or not estrogen administered before vaginal surgery can improve tissue planes and promote mucosal healing. Mikklesen et al. reported that rates of recurrent prolapse after surgery were similar in women receiving intravaginal estradiol or placebo preoperatively.

ESTROGEN IN THE TREATMENT OF FECAL INCONTINENCE

Fecal incontinence is reported in 15 to 26 percent of women with urinary incontinence, likely because both conditions arise from pelvic floor neuromuscular dysfunction. As with urinary incontinence, fecal incontinence may be partly due to altered hormonal factors that include lower estrogen levels after menopause. Estrogen receptors are present in high number in the anorectum, suggesting that these tissues are also a target site for estrogen action. To date, limited observational data show subjective improvement in flatal incontinence and fecal staining after estrogen treatment, with objective improvement in anal resting and squeeze pressures. Further study is needed before a therapeutic role for estrogen in postmenopausal fecal incontinence can be established.

RECOMMENDATIONS:

F1. Urodynamic studies should be performed prior to incontinence surgery or when there is mixed incontinence. (II–3)

SUMMARY OF KEY POINTS:

F2. Urogenital aging may result in urinary urge and stress incontinence, recurrent urinary tract infection, and pelvic organ prolapse.

F3. There is no objective benefit from estrogen replacement therapy for postmenopausal urinary stress incontinence. (I)

F4. There is neither objective nor subjective benefit from estrogen replacement therapy for postmenopausal urge incontinence. (I)

F5. Estrogen therapy decreases the incidence of recurrent urinary tract infections in postmenopausal women. (I)

CONCLUSION

Urinary incontinence of all types is common among menopausal women. At least in part, it is the consequence of urogenital aging. Many effective treatment options are available, including both conservative (non-surgical) and surgical approaches. Based on the current available literature, however, there is no proven benefit from estrogen replacement therapy for the treatment of urinary incontinence. Estrogen replacement has a proven role as a prophylactic agent for recurrent urinary tract infection in postmenopausal women. Its role in the prevention or treatment of pelvic organ prolapse and fecal incontinence is largely unstudied and thus unknown.

Hormone replacement therapy (HRT) should be discussed with postmenopausal women who have diabetes mellitus, particularly as diabetes itself is a risk factor for cardiovascular disease. A recent study recently demonstrated an improvement in glycemic control and serum lipoproteins in postmenopausal Type II diabetics after eight weeks of conjugated estrogen (CEE) therapy. Estrogens alter glucose and insulin metabolism in different ways, depending on the compound used and the route of delivery. Estradiol-17β reduces insulin resistance through improvements in insulin sensitivity and elimination. Hypertriglyceridemia may occur in some diabetic women and, as this can be aggravated with oral estrogen therapy, the transdermal route of estrogen delivery is preferable in these cases.

At present, no data suggest that hormone replacement therapy alters the risk of developing diabetes mellitus.

**MIGRAINE**

Various internal and external factors may trigger migraine headache. Genetic predisposition may set a lower threshold for these triggers. In women, fluctuating or falling levels of estrogen appear to be a trigger: some women have a history of menstrual migraine, and migraine incidence may increase in the menopausal years. Although the influence of HRT on migraine varies with the individual woman, most evidence suggests a worsening of headaches with use of HRT. The constant daily hormone doses of a continuous-combined regimen may thus be better tolerated than those of a cyclical regimen. Transdermal estrogen may similarly afford more steady-state dosing and thus less provocation of migraine headache.

Women with a history of atypical migraines provoked by oral contraceptives will be concerned about the risk of either provoking headaches with HRT or causing a permanent neurological abnormality. There are few relevant studies for guidance. If neurological symptoms or signs develop or worsen with use of HRT, it is advisable to withdraw treatment and seek neurological consultation for assessment of any abnormality. If it is determined that this is atypical migraine, reintroduction of HRT at a lower dose may be attempted if warranted by the potential benefits. Informed consent for treatment is essential.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Data from the Nurses’ Health Study show that postmenopausal HRT is associated with a two-fold increase in the risk of developing systemic lupus erythematosus (SLE). The role of estrogen in exacerbating pre-existing SLE is unclear to date, although the large randomized placebo-controlled SELENA trial studying the safety of HRT in SLE is currently under way. HRT may also exacerbate the prothrombotic tendency that exists in patients with antiphospholipid antibody syndrome. At present, most authors recommend that HRT be used with caution in patients with active disease.

**ARTHRITIS**

**RHEUMATOID ARTHRITIS**

Hormone replacement therapy has not been shown to prevent the development of rheumatoid arthritis in postmenopausal women. Similarly, data from double-blind, randomized, controlled trials have shown no convincing effect of HRT on the clinical course or disease markers of rheumatoid arthritis. Women with rheumatoid arthritis have diminished bone mass for several reasons, including use of corticosteroids and immobility, and have an increased risk of fracture. Postmenopausal osteoporosis further exacerbates these conditions. Treatment options for osteoporosis should be strongly considered in these patients.

**OSTEOARTHRITIS**

It is still unclear if estrogen withdrawal is implicated in the development or clinical course of osteoarthritis in women, although most prospective studies suggest HRT may help prevent development of osteoarthritis in the hip and knee, and may have a beneficial modulating effect on clinical and radiological disease progression. However, while present epidemiologic evidence is strongly suggestive of a preventive and therapeutic role for HRT, data from randomized controlled trials is still lacking.
PREMATURE OVARIAN FAILURE

Premature ovarian failure (POF) affects one percent of women under the age of 40. In the absence of a clear cause, such as chromosome abnormalities, chemotherapy, radiation to the ovaries or surgical ovariectomy, a high incidence of biochemical, clinical or familial auto-immune disorders leads to the presumptive diagnosis of autoimmune POF. Evaluation for other autoimmune diseases, including thyroid, parathyroid and adrenal disorders, systemic lupus erythematosus, and diabetes mellitus, is recommended as clinically warranted. Between five and 25 percent of women with idiopathic or presumed autoimmune POF will undergo at least one spontaneous remission. In the absence of a spontaneous remission, oocyte donation offers the best potential for allowing conception. Due to the risk of premature osteoporosis, long-term HRT should be offered to all women with POF. In these younger women, higher doses of estrogen may be needed for relief of symptoms than are usually required in older postmenopausal women. As women with POF will generally be exposed to lower monthly estrogen levels but much longer duration of HRT than their non-POF peers, the long-term effects of this therapy on such disorders as breast cancer remain unclear. It seems prudent to reevaluate the individual HRT risk-benefit balance when a woman with POF enters the usual menopausal age range.

THYROID DISEASE

Autoimmune hypothyroidism is approximately ten times more common in women than in men, with an exponential rise in its occurrence after menopause. 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 estrogen replacement therapy. Since hypothyroidism in women is frequently underdiagnosed, screening strategies for those at highest risk have been proposed. Recent cross-sectional data suggest that symptoms are more frequent and cholesterol levels are higher in women with subclinical hypothyroidism. Longitudinal data suggest that there may be significant risk of cardiovascular morbidity if hypothyroidism is not treated.

Since hypothyroidism is treated with thyroxine supplements, it is also reasonable to consider the effects of thyroxine supplementation on bone density and fractures. In addition to cross-sectional reports of lower bone density in women on thyroxine, recent data suggest that risk of fracture is also increased. In a large cohort of women over 65 years of age, hip fracture risk was also increased in women with previously diagnosed Graves’ disease (RR 1.8).

Women on thyroxine supplements should be monitored by titration of serum TSH levels. Free thyroxine levels can give a less precise indication of the adequacy of thyroxine supplements. Serum total thyroxine levels should not be relied upon in women using oral estrogen, since the elevation of serum levels of thyroid binding globulin will lead to misleading elevations of total thyroxine levels, but normal free thyroxine and normal TSH levels. Thyroid nodularity becomes more prevalent in postmenopausal women than in men of similar age. The association between thyroid nodularity and estrogen withdrawal is not understood. Most of the nodules are benign, and, if palpable, should at most be investigated with fine needle aspiration biopsy.

ENDOMETRIOSIS

Combined estrogen and progestin replacement therapy in standard doses does not appear to cause regrowth of endometriosis in menopausal women, or in young women receiving estrogen-progestin “addback” therapy following medical oophorectomy with GnRH analogues. A small subgroup of women may experience recurrence of pain and other symptoms during unopposed estrogen therapy, particularly if residual disease remains following definitive surgery. In the absence of evidence from randomized studies, this appears to be one of the few clinical indications for progestin therapy following hysterectomy, either as part of a continuous-combined regimen or as progestin-only therapy. There are no convincing data to support the prophylactic use of progestin-only therapy or the withholding of estrogen for six months following definitive surgery in order to allow regression of residual disease.

There are anecdotal reports of endometrial cancer developing in residual endometriosis in women receiving unopposed estrogen therapy following abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. The available data does not indicate whether women with residual endometriosis following such surgery should be treated with combined estrogen-progestin therapy.

FIBROIDS

Although uterine fibroids do not constitute a contraindication to HRT, HRT should be used with caution in women known to have fibroids. Both estrogen and progestins can influence fibroid growth; however, the doses in conventional HRT regimens are usually not sufficient to cause enlargement of fibroids. However, rapid growth or abnormal bleeding from a submucous fibroid requires investigation and possibly surgical intervention.
**LIVER DISEASE AND GALLBLADDER DISEASE**

The use of oral estrogen may carry a 1.5- to two-fold increase in the risk of gallbladder disease. The risk of cholecystectomy appears to increase with dose and duration of use, and to persist for five or more years after stopping treatment. The transdermal route of estrogen administration had been thought to exert no effect on gallbladder disease, but a recent study documented similar changes in bile lipids and cholesterol following use of oral or transdermal estradiol, suggesting that both routes of administration may increase gallstone formation.

HRT in standard doses is not associated with significant liver injury, nor is it contraindicated in patients with chronic liver disease who have normal liver function tests. In women with pre-existing liver disease, it may be advantageous to deliver estrogen by a non-oral route in order to avoid alterations in liver metabolism.

**PREOPERATIVE STATE**

The SOGC’s Policy and Practice Guidelines Committee has drafted guidelines for prevention and treatment of thromboembolic disease in gynaecological surgery. These guidelines suggest that, in the absence of data from randomized studies, HRT should be considered as constituting a risk for postoperative venous thromboembolism. Women who undergo surgery with postoperative immobilization without discontinuing HRT should be given specific anticoagulant prophylaxis, even if the excess risk is likely to be small. In some circumstances, surgical candidates will have additional risk factors for venous thromboembolism, such as age or malignancy, and will clearly need to receive 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, improving the inflammatory and proliferative phase of wound repair, as well as tissue angiogenesis. Growth factors play an integral role in modulating wound repair. Preliminary human study shows that levels of transforming growth factor-β1 (TGF-β1) increase after HRT administration. Further investigation in this field is needed.

**MASTALGIA**

Pre-existing mastalgia is not a contraindication to the use of HRT, although it is prudent in this situation to use the lowest effective doses of estrogen and progestin. Mastalgia developing after initiation of HRT may improve with a reduction in the dose of estrogen or progestin, or both, or with use of cyclic regimens involving estrogen-free days each month.

**WEIGHT GAIN**

As women age, resting metabolic rate gradually declines and body weight tends to increase. A number of studies have shown that weight gain is greatest in the perimenopause. Although HRT is often blamed for this weight gain, combined HRT has in fact been shown to prevent an increase in central body fat mass and fat redistribution after menopause. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the mean weight gain was higher in the placebo group than in any of the HRT groups. Appropriate counselling is important, as it is estimated that as many as 20 percent of women discontinue HRT because of perceived weight gain.

**THE SKIN**

Soon after menopause, skin collagen content and skin thickness decline and abrupt increases in skin laxity and wrinkling occur. Skin elasticity is decreased. Estrogen replacement limits the extent of skin collagen loss and helps to maintain skin thickness. Significant increases in skin collagen and thickness were demonstrated in women using oral estrogen compared with use of placebo. Facial fine wrinkling has been reported to improve with estrogen therapy. Less skin extensibility was documented in postmenopausal women treated with estrogen than in untreated women, although no change in skin viscoelastic properties was found between groups.

Whether elastic fibres can be preserved or repaired with the use of HRT remains controversial. 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. Present evidence does not yet support instituting estrogen replacement for its potential benefits on skin alone. Such possible cosmetic benefits may enhance adherence to prescribed therapy.

**THE EYES**

Animal studies have shown that estrogen provides protection against cataract formation. In humans, preliminary reports have suggested a similar protective effect in postmenopausal women using estrogen. Current epidemiological evidence suggests a possible preventative role for estrogen in the development of early age-related macular degeneration. The symptom of dry eyes (keratoconjunctivitis sicca) may also be improved with the use of estrogen. Intraocular pressure decreased in a cohort of 25 postmenopausal women after 12 weeks of HRT.

ORAL HEALTH

Oral alveolar bone loss is correlated with poor oral hygiene, and also with osteoporosis. The beneficial effects on skeletal mass attributed to estrogen are also seen on oral (maxillary and mandibular) bone and teeth. Tooth loss and the need for dentures are much reduced in postmenopausal estrogen users compared to non-users: a benefit which correlates positively with the duration of estrogen use. There may also be a reduction in gingival inflammation and bleeding in women using estrogen replacement therapy.

OLDER POSTMENOPAUSAL WOMEN (60 AND OLDER)

HRT may be of particular benefit for the prevention of such age-associated conditions as osteoporosis, cognitive decline, and Alzheimer's disease. Continuous-combined therapy is the preferred regimen for the older woman with a uterus, as the return of cyclic menses is usually poorly tolerated and thus leads to poor compliance. Breakthrough bleeding on this regimen is uncommon in older hypoestrogenic women. In order to minimize mastalgia and other estrogenic side effects, it is advisable to start therapy with the lowest possible estrogen dose, given daily or on alternate days, followed by slow increases to the minimal effective dose.

There are at present no data to support reducing established doses of hormone replacement therapy simply because of a woman's advancing age. As with all patients, the decisions regarding long-term use of hormone replacement therapy must be individualized and based on good counselling provided by well-informed health care practitioners.

OTHER SPECIAL CONSIDERATIONS

Stroke, hypertension, pulmonary embolism, and the hypercoagulable state are examined in Section D.

RECOMMENDATIONS

No specific recommendations.


REFERENCES


INTRODUCTION

Although cognitive performance is thought to decline with increasing age, the available evidence suggests that age-related deficits develop only in specific skills. Whereas 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 older people to acquire, encode, and retrieve new material. Thus, the ability to learn new associations or to remember new facts becomes compromised with increasing age, regardless of gender or hormonal status.

ESTROGEN AND BRAIN FUNCTION

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. 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), contain nuclear receptors for estrogen. Estrogen also increases cerebral blood flow, modulates cerebral glucose utilization, and possesses antioxidant properties. In adult female rats, ovariectomy causes a significant decrease in the number of dendritic spines in the CA1 area of the hippocampus, and the density of spines is restored by the administration of estrogen. Thus, estrogen increases the number of synapses in this area of the brain, thereby enhancing neuronal communication and, presumably, enhancing memory functions.

ESTROGEN REPLACEMENT AS PROTECTION AGAINST COGNITIVE DECLINE IN HEALTHY WOMEN

Most but not all large epidemiological studies of elderly postmenopausal women (age approximately 65 years or older) found that women who had been taking estrogen replacement therapy (ERT) had higher scores on tests of cognitive functioning than did women of similar age who had not used ERT. Physician and patient biases may have influenced these results because of a lack of randomization. However, the majority of the randomized, prospective, double-blind, placebo-controlled trials (RCTs) have confirmed observational study findings that postmenopausal women who received treatment with estrogen performed significantly better on tests of cognitive function, especially on tests of short- and long-term verbal memory. This has clinical importance because verbal memory, which appears to be preferentially maintained by ERT is the cognitive function that shows the greatest decline with normal aging. The consistency of the RCT findings on estrogen use and cognitive function strongly suggests that ERT protects short- and long-term memory in healthy, aging postmenopausal women.

ESTROGEN REPLACEMENT AS PROTECTION AGAINST ALZHEIMER’S DISEASE

Alzheimer’s disease (AD), the most common cause of dementia, affects 1.5 to three times as many women as men, even after adjusting for increased longevity in women. Because the findings from basic neuroscience research and from RCTs in healthy postmenopausal women provide strong evidence that estrogen helps to preserve memory in aging women, much attention has recently been focused on investigating whether ERT may lower the risk of AD. Sizable cohort studies have consistently found that current estrogen use is significantly lower among women with AD than among healthy women of comparable age and education, suggesting that women taking ERT have a substantially reduced risk of AD.

In a recent community-based cohort, postmenopausal estrogen-users had a 50 percent reduction in the incidence of AD compared to non-users (OR 0.5, 95% CI = 0.2-0.9). These case-control and cohort studies suggest that ERT may reduce a woman’s risk of later developing Alzheimer’s disease by between 40 and 60 percent.

ESTROGEN REPLACEMENT AS AN EFFECTIVE TREATMENT FOR ALZHEIMER’S DISEASE

Several open-label clinical trials have reported selective cognitive improvements in women with dementia who received ERT. The findings from these early treatment studies must be interpreted cautiously, however, since the studies were uncontrolled, short-term, and relatively small. Recently, two RCTs investigated the possible benefit of ERT for women with mild to moderate Alzheimer’s disease. Women with AD who were treated with estrogen for 16 weeks showed no change in...
tests of cognitive function compared to those who were given placebo. Similarly, estrogen had no effect on slowing disease progression or improving cognitive outcomes in women with mild to moderate AD when treatment lasted for one year.

Although preliminary evidence suggests that estrogen potentiates the effect of the cholinesterase inhibitor tacrine, used to treat women with mild to moderate AD, these findings need to be replicated in controlled studies.

**ESTROGEN AND MOOD FLUCTUATIONS**

Estrogen up-regulates the serotonergic system whose dysfunction is implicated in mood disorders. In prospective, controlled studies of postmenopausal women, ERT was consistently effective in relieving dysphoric mood, but not mood disorders that met criteria for a diagnosis of clinical depression. In a recent RCT of perimenopausal women diagnosed with either major or minor depression, a full or partial therapeutic response was seen in 80 percent of women who received estradiol and 22 percent of those given a placebo. However, the finding that feelings of sadness improved while other symptoms such as disturbed sleep, feelings of unreality, emotional detachment, and somatic preoccupation were unaffected suggests that estrogen alone is not effective in alleviating the totality of symptoms that constitute a depressive syndrome. Therefore, the mood lability, dysphoria, and irritability that some women report specifically during the menopausal transition may be stabilized or alleviated by initiation of ERT.

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

Several observational studies and one randomized study show that the addition of a progestin to an estrogen replacement regimen attenuates the beneficial effect of estrogen on mood. This negative effect of progestin on mood might be mitigated by a higher estrogen-progestin dose ratio. In a recent study, the beneficial association between unopposed estrogen use and the rate of change in cognitive functioning in older women was opposed by the addition of a progestin, suggesting that combined therapy might negate the beneficial effect of estrogen on cognition. Although one study found a positive effect of a combined estrogen-androgen drug on aspects of cognition, 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. The only 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 of mood.

**SUMMARY OF KEY POINTS:**

H1. Estrogen positively influences brain structures and functions that are known to be critical for memory. (I)

H2. In healthy postmenopausal women, estrogen protects against the deterioration in short- and long-term memory that occurs with normal aging. (I)

H3. Estrogen replacement is associated with a reduction in the risk of developing Alzheimer’s disease in postmenopausal women (II-2), but does not affect the progression of deterioration in women with diagnosed Alzheimer’s disease. (I)

H4. Estrogen effectively enhances mood in women with dysphoria or mood lability (I), but there is no evidence that estrogen alone is an effective treatment for clinical depression. The addition of progestin may attenuate the beneficial effect of estrogen on mood and on cognition in some women. (I)

H5. At present, there is no evidence that raloxifene influences cognitive functioning or mood. (I)

**CONCLUSION**

Estrogen replacement prevents deterioration of aspects of cognition in older women that occurs with normal aging. There is also compelling evidence that ERT prevents or delays the onset of Alzheimer’s disease in women who are at risk for genetic or environmental reasons. However, once a woman has a diagnosis of Alzheimer’s disease, there is no evidence that ERT in the doses conventionally used for postmenopausal women will be effective in influencing the course of the disease. More definitive information on estrogen and cognition in postmenopausal women will be available in 2005 when the results of the multi-centre, randomized trials of the Women’s Health Initiative Memory Study (WHIMS) and the Women’s Health Initiative Study on Cognitive Aging (WHISCA) become available.

**REFERENCES**


**INTRODUCTION**

The first pharmaceutical agent to treat menopausal complaints was developed in the late 1920s. Since then, several discoveries have led to the development of compounds for improving the health and quality of life in postmenopausal women. No standard therapeutic regimen exists, but a variety of compounds, routes of administration, and dosages can be used to assist the individual woman desiring treatment.

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

**ESTROGENS**

The terminology of natural versus synthetic is often used to distinguish between different estrogens; however, this can be confusing or misleading. While some use the term “natural” to refer to the source of the preparation (plant or animal), others use the term to refer to the chemical structure (identical to human estrogens). However, the only truly “natural” estrogens are those produced and secreted within a woman’s body: estrone (E1) and estradiol (E2). The critical determinant of an estrogen preparation’s usefulness is not its origin, but its biological effectiveness.

The most potent naturally occurring estrogen is 17β-estradiol, followed by estrone and estriol.1 Approximate biological equivalents of the estrogens currently available for hormone replacement therapy (HRT) are listed in Table 1.2,3 These standard doses have approximately one-quarter to one-sixth the potency of the standard estrogen doses in low-dose oral contraceptive pills. Estrogen preparations used in Canada for HRT are listed in Table 2.

**ABSORPTION**

Estrone and estradiol are not readily absorbed by the gastrointestinal tract. Rapid conversion of E2 to E1 occurs in the intestinal mucosa.1 Further metabolism and conjugation occur in the liver, with glucuronidation of up to 30 percent 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.1 Estrogens may also be micronized, creating very small particles that result in an increase in surface area and rapid absorption.1 Orally ingested estrogens produce more biologically active substances in the liver than transdermal estrogens due to the “first pass” effect.1 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 and may have a favourable effect on triglycerides.1 Transdermal administration does not produce high levels of the drug in the portal circulation, which may explain why the oral and transdermal routes are associated with different effects on lipoprotein profile.1 In theory, transdermal estrogen therapy should have less effect on coagulation factors and gallbladder disease,4 but this has not yet been demonstrated clinically.

**SMOKING**

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 estrogen on lipid levels and bone mineral content.5 No difference in serum estrogen concentrations between smokers and non-smokers has been observed after transdermal therapy.5 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 17α-dihydroequilin sulphate. Conjugated equine estrogens (CEE) contain such additional bioactive estrogens as delta 8-9-dehydroestrone sulphate. Other conjugated estrogens may not be pharmacologically identical to conjugated equine estrogens, and their use could result in a change in therapeutic effectiveness.3
Estropipate

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

Estradiol

Estradiol is available in oral, transdermal, injectable, and vaginal delivery systems. To be absorbed orally, estradiol must be bound to an ethinyl group or micronized. Once absorbed, micronized estradiol is converted in the liver to estrone. In contrast, transdermal application avoids hepatic “first pass” metabolism, resulting in sustained concentrations of estradiol. Delivery systems include reservoir patches that have a pouch in which estradiol is dissolved in alcohol, and matrix patches containing an adhesive matrix in which estradiol is dissolved. Depending on the system,

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>APPROXIMATE EQUIVALENTS OF ORAL AND TRANSDERMAL ESTROGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Dose equivalent (mg)</td>
</tr>
<tr>
<td>Conjugated equine estrogens 0.625</td>
<td>0.625</td>
</tr>
<tr>
<td>Conjugated estrogen sulphate 0.625</td>
<td>0.625</td>
</tr>
<tr>
<td>Estropipate (0.75) 0.625</td>
<td>0.625</td>
</tr>
<tr>
<td>17β-estradiol 1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Ethinyl estradiol 5.0 µg</td>
<td>5.0 µg</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Dose equivalent</td>
</tr>
<tr>
<td>17β-estradiol 50 µg (patch)</td>
<td>50 µg</td>
</tr>
<tr>
<td>17β-estradiol 1.5 mg per 2 metered pumps (2.5 g of gel)</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>ESTROGEN PREPARATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Trade name</td>
</tr>
<tr>
<td>Oral (mg)</td>
<td></td>
</tr>
<tr>
<td>Conjugated equine estrogens Premarin® 0.3, 0.625, 0.9, 1.25, 2.5</td>
<td>$3.65 (0.625 mg)</td>
</tr>
<tr>
<td>Conjugated estrogens CES 0.3, 0.625, 0.9, 1.25</td>
<td>$2.32 (0.625 mg)</td>
</tr>
<tr>
<td>Congest® 0.3, 0.625, 0.9, 1.25, 2.5</td>
<td>$2.25 (0.625 mg)</td>
</tr>
<tr>
<td>PMS-conjugated 0.3, 0.625, 0.9, 1.2</td>
<td>$2.25 (0.625 mg)</td>
</tr>
<tr>
<td>Estropipate Ogen® 0.625, 1.25, 2.5</td>
<td>$4.71 (0.625 mg)</td>
</tr>
<tr>
<td>17β-estradiol (micronized) Estrace® 0.5, 1.0, 2.0</td>
<td>$5.94 (1 mg)</td>
</tr>
<tr>
<td>Esterified estrogens Neo-Estrone® 0.3, 0.625, 1.25</td>
<td>$3.30 (0.625 mg)</td>
</tr>
<tr>
<td>Transdermal twice weekly application (µg)</td>
<td></td>
</tr>
<tr>
<td>17β-estradiol Estraderm® (reservoir patch) 25, 50, 100</td>
<td>$19.50 (50 µg)</td>
</tr>
<tr>
<td>Oesclim® (matrix patch) 25, 50</td>
<td>$19.50 (50 µg)</td>
</tr>
<tr>
<td>Vivelle® (matrix patch) 37.5, 50, 75, 100</td>
<td>$19.50 (50 µg)</td>
</tr>
<tr>
<td>Estradot® (matrix patch) 37.5, 50, 75, 100</td>
<td>Pending</td>
</tr>
<tr>
<td>Transdermal weekly application (µg)</td>
<td></td>
</tr>
<tr>
<td>17β-estradiol Climara® (matrix patch) 25, 50, 75, 100 µg</td>
<td>$19.50 (50 µg)</td>
</tr>
<tr>
<td>Transdermal daily application (mg)</td>
<td></td>
</tr>
<tr>
<td>17β-estradiol Estrogel® (topical gel) 1.5 per g</td>
<td>$17.95 (2.5 g/day)</td>
</tr>
<tr>
<td>Vaginal</td>
<td></td>
</tr>
<tr>
<td>Conjugated equine estrogens Premarin® (cream) 0.625 mg per g</td>
<td>$0.34 per g (1 g = 1/4 applicator)</td>
</tr>
<tr>
<td>17β-estradiol Vagifem® (vaginal tablet) 25 µg</td>
<td>Pending</td>
</tr>
<tr>
<td>Estril® (silastic ring) 2.0 mg per ring</td>
<td>$60.00 (ring; 3 months)</td>
</tr>
<tr>
<td>Estrone Neo-Estrone cream 1.0 mg per g</td>
<td>$0.33 (1 g)</td>
</tr>
<tr>
<td>Oestrilin® 1.0 mg per g</td>
<td>$0.33 (1 g)</td>
</tr>
<tr>
<td>0.25 mg per vaginal suppository</td>
<td>$1.56 (vaginal suppository)</td>
</tr>
<tr>
<td>Injectable (mg)</td>
<td></td>
</tr>
<tr>
<td>Estradiol valerate Delestrogen® (depot injection) 10 per mL (5 mL)</td>
<td>$15.40 (5 mL)</td>
</tr>
<tr>
<td>Conjugated estrogens Premarin® 25 per mL</td>
<td>$35.62 (1 mL)</td>
</tr>
</tbody>
</table>

* calculated on wholesale base cost as of April 2001.
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 one to two minutes, where it creates its own reservoir after three to four days of use.6

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.7* Maximum protective effects are obtained with 12 to 14 days of progestin exposure per month.1

Two different classes of progestins are used in HRT:

a) 17α-hydroxyprogesterone derivatives, including medroxyprogesterone acetate (MPA), medrogesterone (metrogestone), megestrol, and progesterone
b) 19-nortestosterone derivatives (norethindrone and norethindrone acetate)

The first group of progestins primarily exhibits gestational activity, although there are some notable differences between these agents. Oral micronized progesterone does not appear to antagonize the effects of CEE on HDL-cholesterol, whereas MPA attenuates the estrogen-induced lipid effects.8 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 antimiotic effects, which may result in less menstrual bleeding.9

| TABLE 3 |

| PROGESTIN PREPARATIONS1 |

<table>
<thead>
<tr>
<th>Oral progestins</th>
<th>Trade name</th>
<th>Strengths (mg)</th>
<th>Cost a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>Gen-Medroxy®</td>
<td>2.5, 5.0, 10</td>
<td>$1.94 (5 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$2.45 (2.5 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td>Ahti-MPA®</td>
<td>2.5, 5.0, 10</td>
<td>$1.94 (5 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$2.45 (2.5 mg x 30 days)</td>
</tr>
<tr>
<td></td>
<td>Novo-Medrone®</td>
<td>2.5, 5.0, 10</td>
<td>$1.94 (5 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$2.45 (2.5 mg x 30 days)</td>
</tr>
<tr>
<td></td>
<td>Provera®</td>
<td>2.5, 5.0, 10, 100</td>
<td>$3.49 (5 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$4.41 (2.5 mg x 30 days)</td>
</tr>
<tr>
<td>Medrogesterone (metrogestone)</td>
<td>Colprone®</td>
<td>5.0</td>
<td>$2.94 (5 mg x 12 days)</td>
</tr>
<tr>
<td>Megestrol</td>
<td>Apo-Megestrol®</td>
<td>40, 160</td>
<td>$5.43 (20 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td>Megestrol-40®, Megestrol-160®</td>
<td>40, 160</td>
<td>$5.43 (20 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td>Nu-Megestrol®</td>
<td>40, 160</td>
<td>$5.43 (20 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td>Linmegestrol®</td>
<td>40, 160</td>
<td>$5.43 (20 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td>Megace®</td>
<td>40, 160, 40 per mL (liquid)</td>
<td>$8.06 (20 mg x 12 days)</td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>Prometrium®</td>
<td>100</td>
<td>$11.95 (200 mg x 12 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$14.94 (100 mg x 30 days)</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>Micronor®</td>
<td>0.35</td>
<td>$5.49 (x 12 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$13.73 (x 30 days)</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>Norlutate®</td>
<td>5.0</td>
<td>$4.23 (2.5 mg x 12 days)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injectable progestins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intrauterine progestins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel</td>
</tr>
</tbody>
</table>

The 19-nortestosterone derivatives have varying estrogenic, anti-estrogenic, and androgenic properties. These agents produce full secretory transformation, similar to the effect of MPA.\textsuperscript{10} Progestin preparations available in Canada are listed in Table 3.

**HORMONAL REGIMENS**

Regimens of HRT currently in use in clinical practice are shown in Table 6. 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.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>ANDROGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>Trade name</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>Metandren\textsuperscript{®}</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Andriol\textsuperscript{®}</td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Androderm\textsuperscript{®}</td>
</tr>
<tr>
<td>Injectable</td>
<td></td>
</tr>
<tr>
<td>Testosterone cypionate</td>
<td>Depo-testosterone Cypionate</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Delatestryl\textsuperscript{®}</td>
</tr>
<tr>
<td></td>
<td>PMS-Testosterone enanthate</td>
</tr>
</tbody>
</table>

* calculated on wholesale base cost as of April 2001

**CYCLIC ESTROGEN – PROGESTIN REGIMENS**

Estrogen and progestin have been traditionally used in a cyclical manner. In North America, cyclic therapy has consisted of estrogen taken from day one to 25 of the calendar month with the addition of a progestin for 10 to 14 days each month. This allowed for a five-day hormone-free interval; however, the rationale for this hormone-free interval is unclear. Although some women note a general reduction of mastalgia, many women report the return of distressing symptoms in the days when they are not taking hormones.\textsuperscript{7} Theoretically, eliminating the hormone-free interval may be prudent to maintain adequate estrogen concentrations in the blood and to provide maximal symptomatic relief.

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>COMBINATION PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations</td>
<td>Trade name</td>
</tr>
<tr>
<td>Oral</td>
<td>Ethinyl estradiol (EE) and norinethedrone acetate (NETA)</td>
</tr>
<tr>
<td></td>
<td>Conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA)</td>
</tr>
<tr>
<td></td>
<td>17β-estradiol (E\textsubscript{2}) and norinethedrone acetate (NETA)</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Estracom\textsuperscript{®}</td>
</tr>
<tr>
<td></td>
<td>Estalis\textsuperscript{®}</td>
</tr>
<tr>
<td></td>
<td>Estalis Sequi\textsuperscript{®}</td>
</tr>
<tr>
<td>Injectable</td>
<td>Estradiol dienanthate (ED) and estradiol benzoate (EB) and testosterone enanthate (TE)</td>
</tr>
<tr>
<td></td>
<td>Estradiol and testosterone enanthate</td>
</tr>
</tbody>
</table>

* Calculated on wholesale base cost as of April 2001
Current evidence suggests that 0.625 mg conjugated equine 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 CEE) may also be effective.11,12 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.13

Typical doses of progestins used in a cyclic regimen are listed in Table 7. When daily doses larger than 0.625 mg CEE or its equivalent are used, larger doses of progestins might be required (MPA 10 mg or equivalent daily).

The effects of administering medroxyprogesterone acetate for 14 days every three months have been investigated: the rates of endometrial hyperplasia with this regimen have been found to vary from zero to 12 percent. If this regimen is used, routine endometrial assessment for unscheduled bleeding is recommended.2*

## CONTINUOUS-COMBINED REGIMENS
An alternative to the cyclic administration of progestin in HRT is continuous daily treatment with both an estrogen and progestin. This method was developed in order to avoid the withdrawal bleeding associated with cyclic HRT regimens. Most data are derived from studies which used CEE 0.625 mg with 2.5 mg MPA per day.14,15 Other progestins can be used: their theoretical dose equivalents are listed in Table 7.

Forty percent of women receiving this therapy have irregular breakthrough bleeding during the first three to six months. The majority of women who persist with the medication (75-87%) become amenorrheic by 12 months of use; some women have breakthrough bleeding after one year.16 A recent comparison study indicated that significantly more women attained amenorrhea based on various parameters when administered continuous combined EE/NETA.17 A levonorgestrel-releasing intrauterine system is currently indicated for contraception. The device can be left in situ for five 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.18

## INDIVIDUALIZING THERAPY
The use of estrogens can result in unpleasant side effects in five to 10 percent of women using 0.625 mg CEE, or its equivalent, daily.19 Common complaints in women on therapy include mastalgia, nausea, headache, and bloating. These side effects are often dose-related, and may resolve with continued use or a decrease in dose. Since side effects may vary among currently available estrogen preparations, it is a reasonable strategy to substitute another preparation for a poorly tolerated one.

### TABLE 6
**ESTROGEN AND PROGESTIN REGIMENS**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Days per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic estrogen</td>
<td>1 to 25</td>
</tr>
<tr>
<td>Cyclic progestin</td>
<td>1 to 12–14</td>
</tr>
<tr>
<td>Continuous estrogen</td>
<td>every day</td>
</tr>
<tr>
<td>Continuous progestin</td>
<td>every day</td>
</tr>
<tr>
<td>Continuous estrogen</td>
<td>every day</td>
</tr>
<tr>
<td>Continuous progestin</td>
<td>every day</td>
</tr>
<tr>
<td>Cyclic unopposed estrogen</td>
<td>1 to 25</td>
</tr>
<tr>
<td>Continuous unopposed estrogen</td>
<td>every day</td>
</tr>
<tr>
<td>Continuous estrogen</td>
<td>every day</td>
</tr>
<tr>
<td>Long cycle progestin</td>
<td>1 to 14 (every 3 months)</td>
</tr>
</tbody>
</table>

### TABLE 7
**PROGESTINS—DOSE FOR ENDOMETRIAL PROTECTION**

<table>
<thead>
<tr>
<th>ORAL</th>
<th>CYCLIC</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>daily for at least 12 days/month (mg)</td>
<td>5–10</td>
</tr>
<tr>
<td>Medrogestone (metrogestone)</td>
<td>5–10</td>
<td></td>
</tr>
<tr>
<td>Megestrol</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>200–300**</td>
<td>100</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>0.35–0.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>2.5</td>
<td>0.5–1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRANSDERMAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethindrone acetate (NETA)**</td>
<td>250 µg</td>
</tr>
</tbody>
</table>

* Larger doses of estrogen may necessitate higher doses of progestin
** May be administered vaginally
*** Available in combination with 17β-estradiol patches

* Hormone replacement therapy and cancer, J Obstet Gynaecol Can 2001;23(12).
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 to change the preparation or route of administration. Breast tenderness or leukorrhea may require a reduction in medication dose. Switching from one progestin formulation to another may reduce these symptoms. Adverse reactions to progestins are more frequent when progestins are given with estrogen therapy.

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.

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.

ESTROGEN-ONLY THERAPY
Estrogen without the endometrial protective effect of a progestin 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. 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. Endometrial assessment, preferably by biopsy, 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 flushes. The obese patient is able to produce endogenous estrogen by peripheral conversion of androstendione to estrone in adipose tissue. In addition, obese women have low serum concentrations of sex hormone-binding globulin (SHGB), resulting in a further increase in circulating free estrogen. These women have high concentrations of unopposed free estrogen, and are at risk of developing endometrial neoplasia.

ESTROGEN-ANDROGEN HORMONE REPLACEMENT THERAPY
A woman’s total estrogen production after menopause decreases by 80 percent and androgen production decreases by as much as 50 percent. Following bilateral oopherectomy, serum estrogen and androgen concentrations drop precipitously. The potential indications for estrogen-androgen therapy are outlined in Section C, while the estrogen preparations used for HRT are listed in Table 4.

CONTRAINDICATIONS TO ESTROGEN USE
The number of contraindications continues to decrease, as both knowledge and use of estrogen replacement therapy (ERT) increase. Special considerations regarding the use of ERT are discussed in Section G.

The following conditions are usually considered absolute contraindications to ERT:
1. unexplained vaginal bleeding prior to investigation
2. acute liver disease
3. active thromboembolic disease
4. known or suspected carcinoma of the breast

The risk posed by estrogen use in a patient with a past history of thrombosis is variable. The risk of recurrence of breast cancer following estrogen therapy is also unknown. Caution is recommended in patients with a history of cardiovascular disease and hypertriglyceridemia. For all patients, 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
3. pregnancy

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

CONTRAINDICATIONS TO ANDROGEN USE
The use of androgen is contraindicated in women with extensive cardiac, hepatic or renal disease.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)
Estrogen binds intracellularly to an estrogen receptor, and the
estrogen-receptor complex in turn binds to DNA, thus activating target genes. Different estrogen receptor subtypes in different tissues have allowed the development of selective estrogen receptor modulators (SERMs), which can act as estrogen agonists in some tissues and as estrogen antagonists in other tissues. Ideally, SERMs would have favourable effects on bone and liver while being antagonistic in the uterus and breast.

**Tamoxifen**
Tamoxifen, first synthesized in 1966, has been found to have some estrogen agonist effect in the endometrium and estrogen antagonist effect in the breast. This agent is useful as adjuvant therapy in patients with estrogen receptor-positive breast cancer, and as a primary prevention in patients who are at very high risk for breast cancer. Endometrial stimulation and an increased long-term risk of endometrial carcinoma remain significant concerns regarding its use.

**Raloxifene**
Raloxifene reduces the risk of new vertebral fractures by 30 to 50 percent. No significant reduction in non-vertebral or hip fracture was seen in a very large trial. Although LDL-cholesterol levels are reduced and triglyceride levels not increased with raloxifene therapy, HDL-cholesterol levels are not increased, in contrast to the effect of oral estrogen therapy. As yet there are no data to prove any reduction in cardiovascular disease with use of raloxifene. The side effects of SERMs include exacerbation of vasomotor symptoms and vaginal dryness, leg cramps, and an increase in the risk of venous thromboembolism similar to that seen with estrogen therapy.

**CONTRAINDICATIONS TO SERMS**
Contraindications to tamoxifen and raloxifene are listed in Table 8.

**NON-HORMONAL MEDICATIONS**

**BISPHOPHONATES**
Bisphosphonates are physiologic inhibitors of crystallization. Their basic structure is phosphorus-carbon-phosphorus, which cannot be degraded in humans. Consequently, the molecules are excreted unchanged in the urine and have a half-life in the organism proportional to the affinity they have for bone. The agents with a very high affinity for bone, such as etidronate and alendronate, may have half-lives in the skeleton of up to 15 years.

Three bisphosphonates are approved for the prevention and treatment of osteoporosis: etidronate, alendronate, and risedronate. There is a need to distinguish between nitrogen-containing bisphosphonates (alendronate, risedronate) and non-nitrogen bisphosphonates (etidronate), as the molecular mechanism of action and the clinical effects of the two classes are significantly different.

Non-nitrogen bisphosphonates inhibit osteoclasts by forming toxic metabolites of adenosine triphosphate (ATP). By reason of their affinity for bone, they are selective in inhibiting osteoclast action. Etidronate is a bisphosphonate that can inhibit mineralization when given continuously; it must therefore only be given cyclically.

Nitrogen-containing bisphosphonates inhibit protein prenylation, a step along the mevalonic acid pathway.

Alendronate and risedronate have very low bioavailability, and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>• Abdominal pain • Nausea • Diarrhea</td>
<td>• Abnormalities of the esophagus • Inability to sit/stand upright for 30 minutes • Hypersensitivity to the drug • Women of childbearing potential • Renal insufficiency (&lt; 30 mL/min)</td>
</tr>
<tr>
<td>Etidronate</td>
<td>• Diarrhea • Nausea • Constipation</td>
<td>• Clinically overt osteomalacia • Hypersensitivity to the drug • Women of childbearing potential • Renal insufficiency (&lt; 30 mL/min)</td>
</tr>
<tr>
<td>Nasal calcitonin</td>
<td>• Rhinitis • Nasal dryness • Epistaxis</td>
<td>• Hypersensitivity to the drug • Women of childbearing potential</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>• Vasodilatation (flushing) • Leg cramps</td>
<td>• History of venous thromboembolic events • Hypersensitivity to the drug • Women of childbearing potential</td>
</tr>
<tr>
<td>Risedronate</td>
<td>• Abdominal pain • Nausea • Diarrhea</td>
<td>• Abnormalities of the esophagus • Inability to sit/stand upright for 30 minutes • Hypersensitivity to the drug • Women of childbearing potential • Renal insufficiency (&lt; 30 mL/min)</td>
</tr>
</tbody>
</table>
should be taken on an empty stomach to avoid binding to gastric contents and dramatically decreasing absorption. Ideally, these agents should be taken before breakfast with a large glass of water, and breakfast should be delayed for at least 30 minutes. By remaining upright, the risk of oesophageal reflux and potential irritation is minimized.

Etidronate is supplied in a combination pack. Etidronate 400 mg is taken daily at bedtime for 14 days, followed by 76 days of calcium carbonate 500 mg daily. The calcium is included to help patients remember the timing for their cyclical etidronate therapy. Calcium may be taken on days when etidronate is taken, but should be taken at a different time from the etidronate dose. Additional calcium may be required to meet patient needs on non-etidronate dosing days.30,33

Bisphosphonates such as etidronate, clodronate, pamidronate, and zoledronate are available for intravenous administration. None has yet been approved for the treatment of osteoporosis.

Side effects from bisphosphonates are rare, and in the large clinical trials the rates of side effects are essentially equivalent in bisphosphonate-treated and placebo-treated patients.34,35 Nonetheless, reflux of acid bisphosphonate may cause oesophageal irritation, especially in patients predisposed to gastric reflux. There may be differences between bisphosphonates in their potential for irritating the gastrointestinal tract. Other reported side effects include altered taste, bone pain, and hypersensitivity (Table 8).29

CONTRAINDICATIONS
Contraindications to bisphosphonates are listed in Table 8.

CALCITONIN
Calcitonin is a peptidic hormone that reduces bone resorption by inhibiting osteoclastic function. Calcitonin also provides an analgesic effect.25 In a large five-year trial, treatment with 200 IU of nasal calcitonin daily (combined with 1000 mg of calcium and 400 IU of vitamin D daily) produced a significant reduction in the risk of vertebral fractures in postmenopausal women with osteoporosis.36 The effect on other type of fractures

| TABLE 9 | DRUG INTERACTIONS25 |
| --- | --- | --- | --- | --- |
| Interacting drug | Mechanism | Effect | Management |
| Estrogens | Rifampicin | Enhanced estrogen hepatic metabolism | Decreased estrogenic activity | Inform patient of interaction and possible effects |
| | | | | |
| Warfarin | Unknown | Decrease in anticoagulant action | Monitor INR when estrogen is added or stopped |
| Progestins - MPA - Levonorgestrel - Norethindrone - Progesterone | Rifampin | Enhanced progestin Enhance hepatic metabolism | Decreased progestin activity | Inform patient of interaction and possible effects |
| Testosterone | Warfarin | Unknown | Potentiation of anticoagulant effect | Use with caution. Monitor INR if combination is used. |
| Raloxifene | Estrogens | Receptor competition | Effects of both drugs are counteracted | Concomitant administration is not recommended |
| Cholestryramine | Binding of raloxifene to cholestryramine | 60 percent decrease in raloxifene absorption and enterohepatic cycling | Take raloxifene one hour before or three hours after cholestryramine |
| Rifampin | Enhanced hepatic raloxifene metabolism | Decreased raloxifene activity | Short-term treatment only |
| Tamoxifen | Warfarin | Unknown | Potentiation of anticoagulant effect | Use with caution. Monitor INR if combination used |
| Bisphosphonates | Warfarin | Unknown | Variable elevations in INR; potentiation of anticoagulant effect | Monitor INR when a bisphosphonate is added or withdrawn |
| Divalent cations | Chelation | Decrease in bisphosphonate bioavailability | Take the bisphosphonate at least 30 minutes before any calcium tablets, calcium-rich foods or calcium-containing drugs (antacids) |
is uncertain. The most frequent side effects reported with use of nasal calcitonin are nasal dryness, epistaxis, and rhinitis.\(^{29}\)

**NEW THERAPIES**

Tibolone is a steroid with estrogenic, progestational, and androgenic activity. It has been used in Europe for treatment of menopausal symptoms and sexual functioning. It is not currently available in Canada.

In addition to new compounds, different formulations of estrogens and progestins are in development. These include transdermal delivery systems, gels, subdermal pellets for implantation, and vaginal tablets. Newer SERMs, which may have differing effects on target tissues depending on their selectivity and potency, are also in development.

**DRUG INTERACTIONS**

HRT might interact with several drugs. Table 9 lists the most important interactions. Since other interactions might occur, it is advisable to consult a pharmacist or a drug interaction reference when adding a new therapy to a patient receiving HRT or osteoporosis medications.

**RECOMMENDATIONS:**

I. The route of estrogen delivery should be primarily determined by patient preference, with the objective of using the lowest effective dose. (III)

II. Physicians should consider alternate routes of administration such as vaginal and transdermal administration. (III)

III. Physicians should be aware that women who wish to use continuous combined HRT long term (five or more years) should be re-evaluated annually. (III)

**CONCLUSION**

Several products are available to treat menopause-related problems. Every woman should be informed of the potential benefits and adverse reactions with any treatment option considered. Health professionals play a key role in providing the most current information for each patient.


**REFERENCES**


INTRODUCTION

The fact that several risk factors for breast and endometrial cancer are associated with increased endogenous estrogen exposure\(^1\)\(^-\)\(^4\) suggests that exogenous estrogen might also increase the incidence of these cancers.\(^4\) Repeated gonadotropic stimulation may also be a risk factor for ovarian cancer,\(^5\) whereas 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 mostly functions as an anti-estrogen by decreasing the number of nuclear estrogen receptors\(^6\) and introducing 17\(\beta\)-hydroxysteroid dehydrogenase.\(^7\) 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.\(^8\) Similarly, synergistic effects of progestins in combination with estrogen have been found.\(^9\)

ENDOMETRIAL CANCER

UNOPPOSED ESTROGEN

Several lines of evidence indicate that unopposed estrogen replacement therapy (ERT) increases the risk of endometrial cancer.\(^1\)\(^-\)\(^2\) Epidemiological studies have shown a five to 10-fold increased risk of endometrial cancer in women taking ERT;\(^9\) this risk is related to estrogen dose and duration of therapy.\(^10\) Furthermore, this increased risk of developing endometrial carcinoma persists for at least five years after unopposed ERT has ceased.\(^10\) In the PEPI trial, unopposed ERT has also been shown to cause atypical endometrial hyperplasia in up to 30 percent of study subjects.\(^11\)

Whereas the risk of developing endometrial cancer is significantly elevated after at least five years of therapy,\(^10\) the risk of developing invasive cancer or of dying from endometrial cancer while taking ERT remains uncertain. Although most studies report no excess deaths due to endometrial cancer among ERT users,\(^10\) one meta-analysis has shown an increased risk for late-stage, high grade invasive tumours.\(^12\)

COMBINED PROGESTIN AND ESTROGEN REPLACEMENT

Adding progestins or progesterone to an ERT regimen markedly reduces the risk of developing both endometrial hyperplasia\(^11\) and cancer,\(^10\) although no hormone replacement therapy (HRT) regimen has proven completely protective. Various regimens using different dosages of progestins for a minimum of 12 to 14 days per month\(^13\) 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,\(^14\) continuous therapy with low-dose progestin may offer endometrial protection equivalent or superior to that of cyclic therapy.

Limited experience suggests that 14 days of progestin therapy every three months may not be completely protective against atypical endometrial hyperplasia.\(^15\) Limited data also suggest that daily micronized progesterone for 25 to 30 days may be protective against hyperplasia.\(^16\) Long-term follow-up data on endometrial cancer are not yet available with these regimens.

HRT FOR WOMEN PREVIOUSLY TREATED FOR ENDOMETRIAL CANCER

HRT has traditionally been withheld from women after treatment for endometrial cancer, based on the belief that HRT might increase the risk of recurrence. This belief has never been substantiated, and two recent retrospective studies have questioned it.\(^17\)\(^,\)\(^18\) Based on these limited studies, a committee opinion of the American College of Obstetricians and Gynecologists concluded that HRT 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 percent depth of myometrial invasion.\(^19\) Estrogen administration is commonly begun postoperatively when the patient is ambulatory. It remains undetermined whether progestin should be added to the regimen in these patients. The use of androgens in these patients is controversial, because androgens may undergo aromatization to estrogen.\(^20\)
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Long-term tamoxifen users have an increased risk of endometrial cancer, and a subgroup of high-risk patients may develop cancers with a worse prognosis. However, newer SERMs such as raloxifene have no stimulatory effects on the endometrium.

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. The American College of Obstetricians and Gynecologists has issued the recommendation that women taking tamoxifen should have annual gynecological examinations, and that the indication for endometrial biopsy should be based on the presence of bleeding.

BREAST CANCER

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

Some authorities have questioned whether the association between HRT and breast cancer is real or merely the result of surveillance bias. The magnitude of this putative risk can be appreciated better by comparing it with other known risk factors for breast cancer. As illustrated in Table 1, there appears to be a greater risk of breast cancer associated with excessive alcohol consumption or with failure to exercise regularly than is associated with HRT. Data from the Nurses’ Health Study suggest that the following variables increase a woman’s risk for breast cancer: elevated serum testosterone levels, high BMI or waist-to-hip ratio, high alcohol consumption, increased breast tissue density on mammography, previous benign breast disease, and a positive family history of breast cancer.

Studies have specifically examined the effect of long-term HRT with or without progestin on breast cancer risk; of these, two case-control studies reported conflicting results, while all three prospective cohort studies reported that progestins did not alter the estrogen-related risk of breast cancer. Furthermore, most recent studies suggested that an estrogen-progestin regimen might increase the risk of breast cancer to a greater extent than estrogen alone. In one of these studies the effect was largely confined to lean women, while another suggested that a combination of estrogen and cyclical progestin was associated with a greater risk of breast cancer than that associated with a continuous-combined regimen. However, these conclusions were based on very small numbers.

According to the WHI Study the use of estrogen-progestin treatment increases the risk of breast cancer after 5 years of use, but not in a statistically significant way. The risk returns to baseline 5 years after stopping therapy.

HRT AND WOMEN WITH BENIGN BREAST DISEASE

HRT can be prescribed to women with benign breast disease.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline breast cancers per 1000 women</th>
<th>Additional cancers per 1000 women</th>
<th>Total cancers per 1000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HRT use (baseline)*</td>
<td>45</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>5 years HRT use</td>
<td>2</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>10 years HRT use</td>
<td>6</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>15 years HRT use</td>
<td>12</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (2 drinks/day)</td>
<td>27</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Lack of regular exercise (&lt; 4 hrs/week)</td>
<td>27</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Late menopause (10 yr delay)</td>
<td>13</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Body mass index (10 kg/m² increase)</td>
<td>14</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Weight gain after menopause (≥ 20 kg)</td>
<td>45</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

* Baseline or basic risk applies to all women and is due to factors that cannot be controlled (such as aging and gender). From Reid RL. Progestins in hormone replacement therapy: impact on endometrial and breast cancer. J Soc Obstet Gynaecol Can 2000;22:679. With permission.
Women with a personal history of premalignant disease of the breast are at increased risk for breast cancer. 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, compared to women with non-proliferative benign histology. These risks are not affected by the use of HRT.

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

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

**HRT AND WOMEN WITH RISK FACTORS FOR BREAST CANCER**

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

HRT 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 five percent of these women carry a specific genetic mutation (BRCA1 or 2) that confers a 60 to 80 percent lifetime risk of developing breast cancer. Some of the women may elect to undergo BPO, which raises concerns about use of HRT after surgical menopause. The effects of HRT on women carrying BRCA1 or 2 genes have not been well studied. Rebbeck *et al.* reported that ever-use or never-use of HRT was not a significant independent predictor of breast cancer outcome, in a model that included BPO. Exclusion of women who had HRT exposure after BPO did not significantly affect the risk reduction conferred by BPO. The use of newer synthetic antiestrogens such as raloxifene is an option that may also be considered for prevention of osteoporosis.

**HRT AND WOMEN WITH BREAST CANCER**

It remains unclear whether HRT can be prescribed to women previously treated for breast cancer. All women should receive expert individualized counselling which takes into account prognostic factors for breast cancer (stage of disease, estrogen receptor status of the tumour, and time since diagnosis of breast cancer), immediate quality of life issues related to estrogen deficiency, risk factors for future osteoporotic fractures, and other options for control of symptoms and disease prevention. At present, the risks and benefits of HRT in breast cancer survivors are poorly defined.

Recruitment bias is a major factor in interpreting outcome reports, and most study subjects to date had favourable prognostic factors. A mean of 7.4 percent (range 0–9%) of women with localized breast cancer showed recurrence of disease equivalent to the predicted rate of recurrence. The National Cancer Institute of the United States has initiated a randomized prospective trial of HRT following treatment of breast cancer in women with stage I and II disease to clarify some of these issues.

There is no reliable information about the influence of HRT on cancer progression in a woman found to have breast cancer while taking HRT. In general, the current practice is to stop HRT until proper staging and therapy are completed.

Breast cancer survivors frequently report such symptoms as hot flashes, vaginal dryness, and decreased libido, especially if the cancer occurred premenopausally and was followed by chemotherapy. For such patients, non-hormonal medications have been proven more effective than placebo in reducing hot flashes. Similarly, high doses of progesterins are effective in alleviating vasomotor symptoms, although their safety has not been established in women previously treated for breast cancer. Certain forms of topical estrogen therapy, such as sustained-release estradiol vaginal rings or low-dose vaginal cream (equivalent to 0.5 g or one-eighth applicator of CEE cream daily) will control hypo-estrogenic vaginal symptoms with minimal systemic absorption. The vaginal mucosa will readily absorb higher dosages of estrogenic vaginal cream. Other approaches may also be considered, including the use of lubricants or gels.

In women with reduced libido, androgen therapy may be considered, although the same concerns exist as for HRT because androgens may be aromatized into estrogens. There is presently no evidence to support or refute the usefulness of adding androgens to an HRT regimen in breast cancer survivors.

**OTHER CANCERS**

**HRT AND COLO-RECTAL CANCER**

Most case-control and cohort studies in current HRT users have shown a decrease in the incidence of colorectal cancers. 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 one year of assessment) users of HRT. According to the WHI Study, continuous-combined treatment with HRT was associated with a reduction in the risk of colorectal cancer, which failed to reach statistical significance (6 fewer cases/10,000 women/year). The benefit did not appear until after three years of use.
HRT AND OTHER CANCERS OF THE REPRODUCTIVE TRACT

There is too little information to comment on any relationship between HRT use and cancers of the cervix, vagina or vulva. A recent epidemiological study reported that long-term use of unopposed estrogens was associated with an increased risk of ovarian cancer, but data were not available on the hormone regimens used.

OTHER CANCERS PRECLUDING THE USE OF HRT

Melanoma, especially the cutaneous form, is considered to be potentially hormone-sensitive, but it is not possible to comment on any relationship between melanoma and HRT because of insufficient data, and the confounding factor of quantity of exposure to ultraviolet light.

Although OCs are associated with an increased risk of hepatocellular cancer, no data supports an association. Thyroid carcinoma is quite prevalent in postmenopausal women, but available data again shows no association between ever-use of HRT and this malignancy.

RECOMMENDATIONS:

J1. No estrogen-progestin regimen is completely protective against endometrial carcinoma, and all unscheduled uterine bleeding should be investigated. (II-2)

J2. Estrogen-progestin therapy should not be withheld from women with treated stage 1 and 2, grade 1 or 2 adenocarcinoma of the endometrium who have moderate to severe menopausal symptoms. (II-3)

J3. According to the WHI study, physicians should inform their patients that the use of estrogen-progestin treatment increases the risk of breast cancer after 5 years of use but not in a statistically significant way. The risk returns to baseline after 5 years of stopping therapy. (I)

J4. There should be increased breast surveillance for women who are at high risk of developing breast cancer when using estrogen-progestin therapy. (III)

J5. In very special circumstances, women at increased risk of developing breast cancer who have been treated for breast cancer may be prescribed low dose estrogen-progestin therapy for severe symptoms unrelieved by effective alternative therapies, after risks and benefits have been extensively discussed. The duration of therapy should be regularly reviewed; there is no preventative role for estrogen therapy in this population. (III)

J6. Physicians should be aware that the reported effects of estrogen-progestin therapy on ovarian cancer have been inconsistent. A possible increased risk may occur in women on long-term estrogen-only therapy (10 or more years). (I)

SUMMARY OF KEY POINTS:

J7. Unopposed estrogen therapy substantially increases the risk of developing atypical endometrial hyperplasia (I) and endometrial carcinoma (II-2). The appropriate dose and duration of progestin therapy will reduce these estrogen-associated risks.

J8. Continuous combined HRT was associated with a reduction in the risk of colorectal cancer, which failed to reach statistical significance (6 fewer cases per 10,000 women per year). (I)

REFERENCES

can Physiological Society, p. 615-29.


INTRODUCTION

There is a strong consumer-driven need for health care providers to be knowledgeable about complementary treatments for menopausal symptoms. While conventional hormone replacement therapy (HRT) is effective for the treatment of menopausal symptoms and prevention of such diseases as osteoporosis, adherence rates for HRT are low. Data from the Massachusetts Women’s Health Survey of 2500 postmenopausal women indicated that 20 percent of women stopped taking HRT within nine months, predominantly due to fear of cancer and dissatisfaction with uterine bleeding.1 Another 10 percent used HRT intermittently, while 20 to 30 percent never filled their prescriptions. Women frequently combined HRT with herbal remedies, yet 60 to 70 percent of them failed to inform their physicians of this use.1,2

An estimated 46 percent of the American population consulted an alternative care provider in 1997, amounting to over 600 million visits, and exceeding the number of visits to all American primary care physicians.2 In a 1997 survey conducted by the North American Menopause Society in Canada and the United States, 80 percent of respondents reported the use of interventions other than prescription medication (Table 1).3

In the largest survey to date, more than 46,000 subscribers of Consumer Reports magazine assessed standard and alternative therapies for common medical problems.4 Alternative therapies included use of megavitamins, herbal and nutritional supplements, deep-tissue massage, chiropractic manipulation, acupressure, meditation, and relaxation therapy. Almost 35 percent (more than 16,000 readers) had used alternative therapies; nine percent used them alone while 25 percent used them in combination with conventional therapies. They used alternative therapies predominantly for the relief of troublesome symptoms that had not responded to conventional therapy. In contrast to previous surveys,2 more than 60 percent of those who used alternative therapies informed their doctors about it, and were more likely to report good results when they tried alternative (especially herbal) treatments on the advice of their health professional or alternative practitioner than when they simply treated themselves. Reassuringly, for nearly all of the 43 medical conditions reported, respondents obtained the best results from prescription drugs (50% much improved) and from surgery when it was recommended (75% much improved).

As mainstream medical journals begin to publish research about alternative therapies, health care providers face both the challenge and the opportunity to incorporate evidence-based alternative therapies into their practices. Despite the clear benefits of therapies involving dietary and lifestyle modifications, adherence rates are regrettably low.

DIET AND LIFESTYLE INFLUENCE ON MIDLIFE HEALTH

Many of the leading causes of death are influenced by modifiable factors such as cigarette smoking, diet, exercise, and obesity. Cigarette smoking is a strong independent risk factor for cardiovascular disease, stroke, peripheral vascular disease, osteoporosis, and certain forms of cancer.5-8 The cardioprotective and anticancer effects of a diet low in saturated and trans-unsaturated fats and high in fibre cannot be overemphasized.5-8 Weight-bearing exercise enhances wellbeing, promotes balance and agility, and has positive effects on cardiovascular function and in the skeleton.5-8*

DIETARY PHYTOESTROGENS

Phytoestrogens are non-steroidal plant compounds with estrogen-like biological activity and a chemical structure similar to that of estrogen.9 They have mixed estrogen agonist and antagonist effects in different target tissues related to their weak competitive binding to the estrogen receptor.9-11 Phytoestrogens may also activate “orphan” receptors that are distinct from the recognized estrogen receptors (ER-α and ER-β), and may have non-receptor-mediated effects on enzyme activity, growth factor action, angiogenesis, and cell growth.9 The three principal varieties of phytoestrogens are isoflavones (genistein, daidzein), coumestans, and lignans. Phytoestrogens may possess anticancer properties, likely related to the antioxidant properties of genistein and to genistein-mediated inhibition of the enzyme tyrosine kinase, which is involved with cell growth and regulation.9-11

Phytoestrogens are present in the highest concentrations...
in soybean and linseed (flaxseed) products. In addition to the commonly known soy foods (tofu, tempeh, miso, soy milk), newer products more palatable to Western taste have been introduced. Fruits, vegetables, cereals, and seeds contain comparatively trivial amounts of phytoestrogens, although an appreciable cumulative intake may be obtained from a combination of several sources (Table 2).

Although there are few specific recommendations about dose and formulation, the epidemiological evidence regarding phytoestrogens is derived from a typical Asian diet, which contains 20 to 150 mg isoflavones, or 20 to 50 g soy protein, per day (Table 2). The recent United States Food and Drug Administration guidelines suggest a health benefit from the daily intake of approximately 50 mg isoflavones, or 25 g soy protein. The benefits attributable to phytoestrogens may be derived, at least in part, from their incorporation into a low-fat, high-fibre Asian diet. It is unknown whether increasing the phytoestrogen content in a relatively high fat, processed Western diet will have the same benefit, or whether there is any benefit from over-the-counter phytoestrogen or isoflavone supplements. The production of these supplements is currently not regulated or standardized.

The phytoestrogen or isoflavone content of foods varies significantly, due to varying conditions of cultivation and industrial processing. There may be marked individual and sex-related differences in the absorption of various phytoestrogens, and it is not clear whether interactions with other foods, or competition with exogenous or endogenous estrogens for the same receptors, will alter the potential effects of phytoestrogens.

The role of isoflavones in menopausal health has been extensively reviewed in a recent Consensus Opinion statement from the North American Menopause Society.

**LIPIDS AND CARDIOVASCULAR DISEASE**

Primate and *in vitro* studies have shown that soy protein or isoflavone extracts reduce atherosclerotic plaque progression, while human trials have shown an increase in arterial compliance with isoflavone treatment, similar to that seen in other studies of long-term estrogen use.

A meta-analysis of 38 controlled clinical trials reported a variable but significant decrease in total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels following a high dietary intake of soy protein. The proposed mechanisms are thought to involve up-regulation of LDL-cholesterol receptors, increased clearance of cholesterol, and inhibition of cholesterol synthesis.

The best evidence for the positive health effects of phytoestrogens is derived from the lipid effects. However, it seems possible that the beneficial effects are derived only from whole foods and soy proteins, because purified isoflavone extracts appear to have inconsistent or absent lipid effects.

**BONE DENSITY**

A review of randomized clinical trials involving a potent synthetic phytoestrogen derivative (ipriflavone) reported a positive effect on bone density, although the doses used were much higher than those achievable through dietary phytoestrogen intake. More recently, a large randomized trial reported no improvement in bone density and no change in vertebral fracture risk after 36 months of treatment with 600 mg ipriflavone daily versus placebo. Studies involving dietary soy proteins and isoflavone extracts have varied in their results and methodological strength. Fracture data are not available and further study is needed.

**BREAST CANCER**

Phytoestrogens appear to have antiangiogenic, antiestrogenic, and antiproliferative properties in animal models and human breast cancer cell-lines. Epidemiological evidence suggests an association between dietary phytoestrogens and a reduced breast cancer risk or improved breast cancer survival, although prepubertal exposure may be required. Case-control studies demonstrate a soy protein-related reduction in breast cancer risk, particularly in Asian and premenopausal women, although not necessarily in postmenopausal women. The use of phytoestrogen supplements

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<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
</table>
| **REPORTED PAST OR CURRENT USE OF SUPPLEMENTS OR ALTERNATIVES TO PRESCRIPTION HRT—RESULTS OF THE 1997 NORTH AMERICAN MENOPAUSE SOCIETY (NAMS) SURVEY (N = 605)**  

| Healthy Eating | 85% |
| Healthy Weight | 77% |
| Regular Exercise | 75% |
| Vitamins | 70% |
| Calcium Supplements | 58% |
| Smoking Cessation | 28% |
| Herbal Therapies | 27% |
| Relaxation/Yoga | 25% |

in women diagnosed with breast cancer is controversial, because of the potential for such compounds to bind to estrogen receptors. Prospective trials in this area are underway.

**ENDOMETRIAL CANCER**

Increasing soy product consumption has been reported to lower the risk of endometrial cancer in one case-control study.

**MENOPAUSAL SYMPTOMS**

Epidemiological data suggest that Asian women consuming diets rich in soy products experience fewer vasomotor symptoms. Several small clinical trials have reported a mild improvement in hot flushes and vaginal dryness after dietary phytoestrogen supplementation. However, the results were often not statistically significant, and they varied with regard to response, the formulation used, the duration of the treatment effect, and the presence of a control group. A Cochrane database systematic review of the topic is in progress.

**VITAMIN AND MINERAL SUPPLEMENTS**

**CALCIUM AND VITAMIN D**

Dietary calcium and vitamin D will reduce, but not prevent, postmenopausal bone loss. Both are threshold nutrients, indicating that a benefit is generally only observed following supplementation of calcium- and vitamin D-deficient populations. Postmenopausal women require 1000 to 1500 mg of elemental calcium per day. Recent evidence suggests that all adults may benefit from vitamin D supplementation of at least 400 IU per day, increasing to 800 IU after the age of 65. The addition of magnesium to the calcium supplement is not necessary, but it may counteract the constipating effects of calcium carbonate. Calcium supplementation may also be useful in the treatment of premenstrual symptoms, including negative affect, fluid retention, and pain.

**ANTIOXIDANTS**

Antioxidants are substances that protect against the effects of free radicals, the waste products formed when oxygen is used as fuel. Dietary antioxidants may protect against cardiovascular disease by altering the oxidation of LDL-cholesterol and modifying the process of atherosclerosis. Their ability to protect DNA and cell membranes from oxidative damage may also provide anti-cancer effects. Common antioxidants include selenium, flavinoids, beta-carotene, and vitamins C and E. Fruits, vegetables, and nuts are rich dietary sources of antioxidants.

Epidemiological studies have suggested an inverse relationship between antioxidant intake (dietary or supplemental) and the risk of various cancers and cardiovascular events. However, evidence from randomized controlled trials has been inconsistent or negative. A meta-analysis of four large randomized placebo-controlled trials of vitamin E showed that daily doses of 50 to 400 mg, over intervals of 1.3 to five years, had no effect on the risk of death or cardiovascular events. Similarly, other antioxidants, including vitamin C and β-carotene, have no proven cardioprotective or anti-cancer effects.

However, some of the existing trials have been criticized because of the low number of events, the duration of follow-up, the antioxidant doses used, or the possibility that individual antioxidants may require co-factors and may therefore not be effective when used in isolation. The results of major clinical trials in progress will provide more conclusive data.

---

**TABLE 2**

<table>
<thead>
<tr>
<th>ISOFLAVONE (DAIDZEIN PLUS GENISTEIN) CONTENT OF FOODS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Soybeans, green, raw</td>
</tr>
<tr>
<td>Soy flour</td>
</tr>
<tr>
<td>Soy protein concentrate (water-washed)</td>
</tr>
<tr>
<td>Soy protein isolate</td>
</tr>
<tr>
<td>Miso soup, dry</td>
</tr>
<tr>
<td>Tempeh</td>
</tr>
<tr>
<td>Soybeans, sprouted, raw</td>
</tr>
<tr>
<td>Soybean curd (fermented)</td>
</tr>
<tr>
<td>Soy cheese, unspecified</td>
</tr>
<tr>
<td>Tofu (Mori-Nu) silken, firm</td>
</tr>
<tr>
<td>Tofu (Azumaya) extra firm, steamed</td>
</tr>
<tr>
<td>Tofu yogurt</td>
</tr>
<tr>
<td>Soy hot dog, unprepared</td>
</tr>
<tr>
<td>Soy protein concentrate</td>
</tr>
<tr>
<td>(alcohol extraction)</td>
</tr>
<tr>
<td>Soy milk</td>
</tr>
<tr>
<td>Soy noodles, flat</td>
</tr>
<tr>
<td>Vegetable burgers, prepared</td>
</tr>
<tr>
<td>(Green Giant Harvest Burger)</td>
</tr>
<tr>
<td>Soylinks, cooked (Morning Star Breakfast)</td>
</tr>
<tr>
<td>Frankfurters, canned, meatless</td>
</tr>
<tr>
<td>(Worthington Foods, Loma Linda, Big Franks)</td>
</tr>
<tr>
<td>Split peas, raw</td>
</tr>
<tr>
<td>Soy sauce</td>
</tr>
<tr>
<td>(shoyu, made from soy and wheat)</td>
</tr>
<tr>
<td>Pinto beans, raw</td>
</tr>
<tr>
<td>Peanuts, all types, raw</td>
</tr>
<tr>
<td>Granola bar, snack</td>
</tr>
<tr>
<td>Chickpeas (garbanzos)</td>
</tr>
<tr>
<td>Soy sauce (made from hydrolyzed -vegetable protein)</td>
</tr>
<tr>
<td>Tea, green, Japan</td>
</tr>
<tr>
<td>Beans, kidney, red, raw</td>
</tr>
<tr>
<td>Lentils, mature, raw</td>
</tr>
<tr>
<td>Beans, kidney, red, boiled</td>
</tr>
<tr>
<td>Green snap beans, raw or boiled</td>
</tr>
<tr>
<td>Lima beans, boiled</td>
</tr>
</tbody>
</table>

Source: United States Department of Agriculture-Iowa State University (Menopause 2000;7:217). Table 2. Reprinted with permission.

VITAMIN B₆
Any effectiveness of vitamin B₆ for the treatment of perimenopausal symptoms similar to those of premenstrual syndrome (PMS) remains controversial. Conclusions from a systematic review of nine trials involving 940 patients were limited by the low quality of most of the trials, but did suggest that doses of vitamin B₆ up to 100 mg per day may have a beneficial effect on PMS and premenstrual depression. A Cochrane database systematic review of the topic is in progress. Care should be taken to calculate the total vitamin B₆ dose obtained from various sources, as doses over 100 mg per day may be neurotoxic.

HERBAL REMEDIES

QUALITY CONTROL
The use of herbal remedies to treat menopausal symptoms, or as an adjunct to HRT, is growing rapidly in Canada and the United States. Many prescription drugs originate from plant sources, including digitalis (foxglove), acetylsalicylic acid (ASA) (white willow), vincristine (periwinkle), and estrogen-progestin preparations (soybeans and Mexican wild yams). Because no therapeutic claims are made for most natural health products and herbal remedies, they are classified as food or dietary supplements, not as drugs. As such, they may be consumed as desired because of the presumed absence of pharmacologic properties. Consumers often consider them to be inherently safe, even though they may contain biologically active compounds with the potential for side effects and drug interactions.

On 26 March 1999, Health Canada's Office of Natural Health Products was created to oversee areas such as regulation, labelling, standards development, product licensing, post-approval monitoring, and research involving natural health products. However, there is still no routine surveillance by Health Canada for product quality. Several hundred herbal products have undergone scrutiny by the Therapeutic Products Program of Health Canada, and have been issued Drug Identification Numbers (DIN) or General Public numbers (GP), which indicate that there has been a review of a product's formulation, labelling, and instructions, but which do not confirm bioactivity or clinical efficacy. Because the DIN or GP does not refer to the herbal product in general but to a particular manufacturer's preparation, consumers are advised to purchase only those brands with appropriate DIN or GP labelling.

SOURCES OF ACCURATE INFORMATION
Table 3 lists general references for researching herbal remedies. The Canadian Medical Association and Canadian Pharmacists Association recently published an authoritative, practical, evidence-based guide to herbal products. It contains an extensive appendix of general references, as well as a detailed literature review on each of 57 individual herbal products. The book also provides information about reporting adverse drug reactions (ADRs) to drug products or herbal medicines via regional ADR centres, Health Canada's Web site, or the form in the Clinical Information section of the Compendium of Pharmaceuticals and Specialties (CPS).

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELECTED GENERAL REFERENCES FOR RESEARCHING HERBAL MEDICINES</strong></td>
</tr>
<tr>
<td><strong>Organization</strong></td>
</tr>
<tr>
<td>European Scientific Cooperative on Phytotherapy (ESCOP)</td>
</tr>
<tr>
<td>American Botanical Council, Austin TX</td>
</tr>
<tr>
<td>Herbal Hall</td>
</tr>
<tr>
<td>National Center for Complementary and Alternative Medicine, Bethesda MD</td>
</tr>
<tr>
<td>Office of Dietary Supplements, National Institutes of Health, Bethesda MD</td>
</tr>
</tbody>
</table>

**EFFECTIVENESS OF HERBAL REMEDIES**

Table 4 lists various herbal remedies that have been suggested for relief of menopausal symptoms. Although many of these remedies have provided short-term relief of symptoms, data on long-term symptom relief (such as urogenital aging) or disease prevention (osteoporosis, cardiovascular disease) are not yet available. In addition, many herbal products are combination products with multiple constituents, variable potential effects, and variable quality control. For the sake of clarity, this review will focus on the effects of single-agent preparations.

**BLACK COHOSH**

Remifemin®, a German-produced extract of black cohosh (*Cimicifuga racemosa*), is one of the most widely used alternatives or adjuncts to HRT for the treatment of menopausal symptoms.²⁷,²⁸ It is a traditional North American Aboriginal remedy for menopausal complaints,²⁷,²⁸ and was one of the main ingredients in the early menopausal remedy known as “Lydia Pinkham’s Compound.”²⁷,²⁸ More recently, six small clinical trials in the German literature reported a significant improvement in hot flushes and mood with its use.²⁷,²⁹ Remifemin® appeared to be superior to placebo for the relief of vasomotor symptoms, although the numbers in each treatment group were small.²⁹ No vaginal bleeding was reported in study periods of up to six months, and no endometrial thickening was observed sonographically after 12 weeks of treatment.²⁹ Endometrial biopsies were not obtained, and no long-term follow-up data are available. No estrogenic effects were noted in the uteri of immature mice or ovariectomized rats.³⁰ The compound binds competitively to estrogen receptors,³¹ and two small reports have described inhibition of proliferation in breast cancer cell lines.¹⁶,³²

Although the mechanism of action is unknown, black cohosh appears to exert estrogen-like actions in some tissues and anti-estrogenic actions in other tissues.¹⁶,²⁷-³²

**Side Effects:** Mild gastrointestinal upset and a mild decrease in blood pressure have been reported.²⁷

**Products:** Black cohosh is available in Canada as Remifemin®, standardized to contain 1 mg of triterpenes (27-deoxyacteine) per 20 mg tablet. The usual dose is two tablets daily. The onset of action appears to be two to four weeks.

---

**TABLE 4**

<table>
<thead>
<tr>
<th>Name</th>
<th>Use</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Black Cohosh (Cimicifuga racemosa, Remifemin®)**²⁷,²⁸-³²</td>
<td>Vasomotor symptoms</td>
<td>20 mg tablet twice daily</td>
<td>Side effects: mild gastrointestinal (GI) upset or hypotension. Caution: may compete with ERT for estrogen receptor, reducing effect of both therapies</td>
</tr>
<tr>
<td>**St. John’s Wort (Hypericum perforatum)**²⁷,³³-³⁶</td>
<td>Mild to moderate depression</td>
<td>300 mg three times daily</td>
<td>Side effects: GI upset (1–2%) and rare photosensitivity. Caution: possible additive effects with other antidepressants, especially from SSRIs or MAOIs. May reduce activity or serum levels of drugs using cytochrome P450 metabolism, including warfarin, digoxin, indinavir, theophylline, cyclosporin and oral contraceptives.</td>
</tr>
<tr>
<td>**Ginkgo biloba (EGb 761)**²⁷-²⁸,³⁷-³⁹</td>
<td>Memory impairment</td>
<td>120–160 mg daily in divided doses (DIN available)</td>
<td>Side effects: GI upset, headache, skin reaction. Caution: may prolong bleeding time and potentiate the action of anti-platelet or anticoagulant drugs</td>
</tr>
<tr>
<td>**Valerian (Valeriana officinalis L)**²⁷,⁴¹-⁴⁵</td>
<td>Sleep disturbances</td>
<td>400–900 mg at bedtime (DIN available)</td>
<td>Side effects: headache, excitability, cardiac disturbances. Caution: possible additive effects when combined with other sedatives or hypnotics</td>
</tr>
<tr>
<td>**Ginseng (Panax ginseng)**²⁷,⁴⁷-⁴⁹</td>
<td>Available data do not support use</td>
<td></td>
<td>No consistent quality control. No consistent dose or formulation recommendations. Caution: may potentiate the action of anti-platelet or anticoagulant drugs. May induce hypoglycemia in combination with insulin or oral hypoglycemic agents.</td>
</tr>
<tr>
<td><strong>Dong Quai</strong>²⁷,⁵⁰</td>
<td>Available data do not support use</td>
<td></td>
<td>No relief of vasomotor symptoms and no demonstrable effects on vagina or endometrium</td>
</tr>
<tr>
<td><strong>Evening Primrose Oil</strong>³⁸</td>
<td>Available data do not support use</td>
<td></td>
<td>No benefit over placebo for vasomotor symptoms</td>
</tr>
</tbody>
</table>
Impression: Remifemin® may be a useful alternative for the short-term relief of menopausal symptoms. Further study is justified, particularly to determine its effect on human endometrium, bone, lipid profiles, and breast tissue.

ST. JOHN’S WORT
Extracts of St. John’s wort (Hypericum perforatum) have been used for the treatment of mild to moderate depression since the time of Hippocrates. A Cochrane database review of 29 trials involving 2291 patients, two subsequent randomized controlled trials, and post-marketing surveillance data involving 3250 patients all indicate that St. John’s wort is superior to placebo, and as effective as standard antidepressants, in the short-term trials. A large multicentre trial of St. John’s wort sponsored by the United States National Institute of Mental Health is in progress.

The exact mechanism of action is unclear, but the compound may include interaction with gamma-aminobutyric acid, sigma and serotonin receptors.33-36

Side Effects: St. John’s wort should not be used concurrently with full doses of other prescription antidepressants because of the potential for serotonin syndrome, hypomania, or other serious interactions, particularly with drugs of the monoamine oxidase inhibitor (MAOI) and selective serotonin reuptake inhibitor (SSRI) classes. Decreased activity or decreased serum levels of warfarin, dioxigen, theophylline, indinavir, cyclosporin, and phenprocoumon, as well as breakthrough bleeding on oral contraceptives, have been reported.27 These actions are likely due to induction of hepatic cytochrome P450 activity and appear similar in magnitude to that of grapefruit juice. The most common side effects are gastrointestinal symptoms, dizziness, and restlessness occurring in one to two percent of patients, similar to placebo. Rarely, photosensitivity has been reported, possibly due to other unidentified active ingredients.27-36 The drug does not cause sedation, impair concentration or driving ability, affect libido or potentiate the effects of alcohol.27,35

Products: St. John’s wort is available in Canada as an aqueous-phenolic extract in capsules of 300 mg standardized to contain five percent hyperforin, 0.3 percent hypericin, or both. The usual dose is 900 mg per day in three divided doses, although this may be increased to 1800 mg if required and decreased to 300 to 600 mg daily for maintenance therapy. The onset of action is two to four weeks.27

Impression: St. John’s wort may be a useful herbal alternative for the short-term treatment of mild to moderate depression. Additional studies are needed to characterize the precise mechanism of action and the long-term effects of the compound.

GINKGO BILOBA
An extract of Ginkgo biloba (EGb 761) appears to be effective in the treatment of dementia, mood disorders associated with poor memory, and intermittent claudication.37 Three recent randomized controlled trials demonstrated modest but significant improvement in cognitive performance and social functioning among patients with memory impairment, Alzheimer’s disease, and multi-infarct dementia. However, the treatment effect was small and may not be clinically meaningful.

The mechanism of action of Ginkgo biloba includes antagonism of platelet-activating factor in addition to antioxidant and vasoregulatory properties, which appear to increase tolerance to cerebral hypoxia.40

Side Effects: Gastrointestinal upset, headache, and allergic skin reactions have been reported.27 Caution should be used in patients taking ASA, non-steroidal anti-inflammatory drugs (NSAIDs), and anticoagulants, as Ginkgo biloba may prolong the bleeding time.27,28

Products: Ginkgo biloba is available in Canada as an extract standardized to contain 40 mg of Ginkgo (24% ginkgo-heterosides) per capsule. The recommended dose is 120 to 160 mg per day in divided doses.

Impression: More research is needed to determine the full mechanism of action and therapeutic potential of Ginkgo biloba. To date, evidence suggests that it may be a useful alternative for some postmenopausal women experiencing difficulties with memory.

VALERIAN
Valerian (Valeriana officinalis L) has been used for over 1000 years as a tranquilizer and sedative.41-45 Five small placebo-controlled trials reported a variable decrease in sleep latency scores, improvement in sleep quality, and increase in slow-wave sleep.41-45

Side Effects: The drug is generally well tolerated, although headaches, excitability, and cardiac disturbances have been reported, possibly due to other unidentified active ingredients or inappropriate doses.28 Valerian does not appear to produce a morning hangover.27 It should not be mixed with other sedatives because of the possibility of additive effects.

Products: Valerian is available as a standardized extract of 0.8 percent valerenic acid. The studied doses are 400 to 900 mg orally at bedtime.

Impression: Valerian appears to exert a mild dose-dependent hypnotic effect, and may be useful for short-term therapy of menopausal sleep disturbances.
GINSENG

Ginseng is perhaps the most widely recognized plant used in traditional Chinese medicine. It plays a major role in the herbal health care market, although there are few well-controlled human trials.28 A large placebo-controlled trial of 384 symptomatic postmenopausal women reported no overall effect of a standardized ginseng extract (Ginsana®) on vasomotor symptoms, serum estradiol or follicle-stimulating hormone levels, endometrial thickness or vaginal maturation index. Furthermore, there was no overall difference in three standardized quality of life questionnaires, although there was significant improvement in individual subscales involving depression, general health, and positive well-being.46 A recent systematic review of randomized controlled trials involving preparations of ginseng alone found variable, but not compelling, evidence to support the use of ginseng to enhance physical performance, psychomotor performance, and cognitive function.47

Side Effects: Although ginseng is thought to be safe, adverse effects including nervousness, insomnia, dizziness, and hypertension have been reported.27,28 Ginseng preparations may prolong the bleeding time via antiplatelet activities and inhibition of thromboxane formation.27 Ginseng should therefore not be used peri-operatively or in patients taking anticoagulants, ASA, NSAIDs or other compounds such as Gingko biloba that may affect bleeding parameters. American ginseng may induce hypoglycemic reactions when used in combination with insulin or oral hypoglycemic agents.48 Siberian ginseng may falsely elevate serum digoxin levels, presumably by interfering with the digoxin assay.27

Products: Ginseng is available in a wide and confusing array of products. At least six species and varieties of the genus Panax have been used in traditional medicine (American, Korean, Sanchi, Shuzishen, Chikusetsu, Himalayan, and dwarf ginseng). Siberian ginseng is derived from a different plant (Eleutherococcus senticosus). Some products have been found to contain no ginsenosides at all. There are no consistent recommendations regarding dose.

Impression: Ginseng is commonly used for a variety of complaints, but the available evidence does not support its use for menopausal symptoms. Additional trials are required to confirm ginseng’s potential effect on general health and well-being. Poor quality control is a major problem for the consumer.

DONG QUAI

Dong quai (Angelica sinensis) is a coumarin-containing root commonly used in Chinese herbal remedies to treat a variety of gynaecologic complaints, including menopausal symptoms, premenstrual syndrome, menstrual irregularities, dysmenorrhea, and infertility. The only randomized, blinded, controlled trial to date demonstrated no difference between dong quai and placebo in the relief of vasomotor symptoms in 73 menopausal women, and no demonstrable estrogenic effects of dong quai on the endometrium or vagina.49 The available data do not support the use of dong quai in the treatment of menopausal symptoms. It remains possible that dong quai has a beneficial effect when it is incorporated into traditional herbal mixtures, rather than when it is used in isolation.27,49

ALTERNATIVES TO ESTROGEN THERAPY
FOR THE CONTROL OF HOT FLUSHES

There is widespread interest in alternatives to estrogen replacement therapy for the relief of vasomotor symptoms in women in whom estrogen therapy is not appropriate or acceptable.*

CLONIDINE

Clonidine inhibits sympathetic outflow by acting as a presynaptic CNS α2-agonist. It can decrease hot flushes.5 The initial dose is 0.05 mg twice daily, but many women require at least 0.1 mg twice daily. It may also be administered as a weekly transdermal patch (containing 2.5 mg clonidine). Frequent side effects, including dry mouth, palpitations, drowsiness, dizziness, and hypotension, limit the usefulness of this medication.

PROGESTINS

Progestins may offer an effective alternative for the treatment of vasomotor symptoms. Medroxyprogesterone acetate (150 mg IM every 3 months or 10–20 mg daily orally) and megestrol acetate (20–40 mg daily) may be used.5

ANTIDEPRESSANTS

One randomized controlled trial has reported a significant reduction in vasomotor symptoms with venlafaxine hydrochloride (Effexor®) compared to placebo.50 Dose-response studies ranging from 37.5 to 150 mg daily showed that 75 mg daily was the most effective dose. Uncontrolled pilot studies have also reported an improvement in vasomotor symptoms over baseline with use of paroxetine hydrochloride (Paxil®),51 fluoxetine (Prozac®),52 and sertraline (Zoloft®).53 Side effects include dry mouth, decreased appetite, nausea, and constipation, particularly in the initial weeks of therapy.50 There is a dose-related risk of increased blood pressure with use of venlafaxine, affecting approximately three percent of patients using daily doses of less than 100 mg.

BLACK COHOSH

Six small clinical trials in the German literature have reported a significant improvement in hot flushes and mood with use of this agent (Table 4).27,28 These reports require confirmation in larger randomized controlled trials.

* Perimenopause, J Obstet Gynaecol Can 2001;23(9):836-41, Table 2.
LIFESTYLE

Both regular aerobic exercise\textsuperscript{54,55} and periodic deep breathing exercises may result in a 40 to 50 percent reduction in hot flushes. Weight-bearing exercise also enhances well-being, promotes balance and agility, and has protective effects in the cardiovascular system and skeleton. Regrettably, few candidates persist with regular exercise programs.

BELLERGAL

Anecdotal reports suggest that Bellergal\textsuperscript{10} (a combination of phenobarbital, ergotamine, and belladonna) may be helpful for the short-term relief of vasomotor symptoms, but it can cause sedation, and has potential for habituation.\textsuperscript{5}

PHYTOESTROGENS

Several small clinical trials have demonstrated a mild improvement in hot flushes and vaginal dryness in response to dietary phytoestrogen supplementation.\textsuperscript{12} However, the results often failed to reach statistical significance and varied with regard to response, formulation used, and duration of the treatment effect. A Cochrane database systematic review of the topic is in progress.\textsuperscript{18}

VITAMIN E

Although vitamin E supplements have been used empirically to relieve hot flushes, a randomized placebo-controlled trial showed no statistical improvement in flushes among breast cancer survivors using 800 IU daily for four weeks.\textsuperscript{56} Anecdotal evidence suggests that vaginal vitamin E oil may relieve vaginal dryness, itching, and irritation.

EVENING PRIMROSE OIL

A randomized controlled trial indicated that evening primrose oil was as effective as placebo for the treatment of menopausal vasomotor symptoms.\textsuperscript{57} Although it is commonly sold for a variety of “female complaints,” the available data do not support the use of evening primrose oil for control of menopausal symptoms.

ESTRIOL

Estriol is a metabolite of estradiol that has been proposed to relieve vasomotor symptoms, when given in sufficient doses.\textsuperscript{59} However, a large Swedish case-control study\textsuperscript{58} found that use of oral estriol at doses of 1 to 2 mg daily was associated with an increased relative risk of endometrial neoplasia, suggesting that a progestin should be added to estriol therapy for endometrial protection. In contrast, there appears to be little risk of endometrial proliferation following low-dose vaginal administration of estriol.\textsuperscript{58}

There is no evidence to show that estriol provides any protection against postmenopausal breast cancer, osteoporosis, cardiovascular disease, and colon cancer.\textsuperscript{59} Tri-est (80% estriol, 10% estrone, 10% estradiol) and Bi-est (70% estriol, 30% estradiol) are available as tablets or creams from compounding pharmacies in Canada. Much of their biological activity may be derived from the more potent estrone and estradiol components. Estrogen bioavailability after topical application of the cream is uncertain, and no clinical trials regarding the efficacy of these compounds have been completed. These preparations are expensive, and they appear to offer no advantage over standard HRT.

PROGESTERONE CREAMS

Numerous different progesterone creams are available over-the-counter in the United States and many are available through compounding pharmacies in Canada or surreptitiously through health food stores. For most products, there is little consistency or quality control. The products can be categorized as follows:

1) Those that contain no progesterone, but variable amounts of progesterone precursors that are generally obtained from the inedible Mexican wild yam (\textit{Dioscorea barbascus}). There is no enzymatic process in the human body to convert these precursors into progesterone.

2) Those that contain progesterone that has been synthesized in a laboratory, often from Mexican wild yam or soy precursors. While these products contain variable amounts of chemically defined progesterone, absorption through the skin is variable and usually poor.\textsuperscript{60-62}

In a 12-week randomized trial, no progestational effect on the endometrium was noted in 21 estrogen-primed women using standardized daily doses of 16 to 64 mg of micronized progesterone cream.\textsuperscript{63} In a one-year randomized controlled trial, a daily dose of 20 mg progesterone cream produced no protective effect on bone density, yet produced a small but significant improvement in vasomotor symptoms compared to placebo.\textsuperscript{64}

Although these products claim to treat menopausal symptoms, premenstrual syndrome, and osteoporosis, the amount of progesterone absorbed from the various preparations is highly variable, and should be considered inadequate to provide endometrial or bone protection.\textsuperscript{63,64} While prescription preparations of progesterone and progestins are absorbed through the skin (norethindrone-containing patches) or vaginal mucosa (micronized progesterone tablets administered vaginally, progesterone vaginal suppositories or progesterone vaginal gel), there is insufficient evidence to conclude that transdermal absorption of the non-prescription progesterone creams is similarly effective.\textsuperscript{*}

RECOMMENDATIONS:

K1. Physicians and their patients should be more aware of complementary therapies in order to effectively consider treatment options. (III)

K2. Patients should be informed that lifestyle changes, including dietary modifications, exercise (I), reduction of stress, and cessation of smoking can benefit the emotional and physical health of women in midlife. (II-1)

CONCLUSION

Various complementary therapies can benefit the health and well-being of midlife women. Moderate or high-quality evidence exists to support the benefits of lifestyle changes and selected botanical preparations. Conversely, evidence has also accumulated to refute the putative benefits of other alternative therapies. Awareness of this information permits more effective counselling of midlife women and facilitates informed decision-making. Health care providers now face both the challenge and the opportunity to incorporate evidence-based alternative therapies into their practices and their lifestyles.


REFERENCES

14. K2. Patients should be informed that lifestyle changes, including dietary modifications, exercise (I), reduction of stress, and cessation of smoking can benefit the emotional and physical health of women in midlife. (II-1)

CONCLUSION

Various complementary therapies can benefit the health and well-being of midlife women. Moderate or high-quality evidence exists to support the benefits of lifestyle changes and selected botanical preparations. Conversely, evidence has also accumulated to refute the putative benefits of other alternative therapies. Awareness of this information permits more effective counselling of midlife women and facilitates informed decision-making. Health care providers now face both the challenge and the opportunity to incorporate evidence-based alternative therapies into their practices and their lifestyles.


REFERENCES


EVALUATION, DECISION-MAKING AND FOLLOW-UP

Jennifer M. Blake, MD, FRCSC,1 Elizabeth Contestabile, RN, BScN,2 Michel Fortier, MD, FRCSC3

1 Toronto ON
2 Ottawa ON
3 Ste-Foy QC

INTRODUCTION

Evaluation of peri- and postmenopausal women should be done in the context of overall health promotion. General recommendations for health care evaluation can be found in the Canadian Guide to Clinical Preventive Health Care,1 which has been developed and endorsed by the Canadian Task Force on the Periodic Health Examination.

The broader issues of healthy choices in menopause are described in Section B.* For women with medical concerns, the reader is directed to those sections dealing with specific medical conditions. The first two parts of this section deal with the specific considerations to incorporate into the assessment of menopausal women. The assessment will guide decisions about the range of menopausal concerns and options. A careful assessment and decision-making process can improve the likelihood that a woman will make a lasting choice, or a choice that will be reassessed appropriately.

EVALUATION

In addition to a standard clinical assessment, the history should include quality of life issues and an assessment of risk factors. The goal of risk assessment is to identify a patient’s risk for disease, to determine appropriate screening and risk reduction strategies, and to promote adherence to the recommendations.2,3

Comprehensive assessment of the peri- or postmenopausal woman includes an evaluation both of risk factors for general disease4 (Table 1) and of specific risk factors for the most prevalent diseases of the postmenopausal years, including cardiovascular disease, osteoporosis, and cancer.5 This information is obtained during the history and physical examination and from screening test results. Several specific screening examinations and tests are useful for women over the age of 50. It is appropriate to offer these or to encourage women to discuss these with their primary care provider.

The accuracy of the risk assessment depends on the reliability of the information provided by the patient, the ability of the clinician to identify the major risk factors for disease, and re-evaluation of risk factors at regular intervals. Use of a specially designed documentation form can ensure that the risk assessment is comprehensive and that the information is easy to retrieve, update, and convey to the patient.2 Compilation of a risk assessment profile identifies the areas of increased risk and provides a focus for risk-reduction strategies.

BREAST EVALUATION

BREAST CANCER RISK ASSESSMENT

The purpose of risk assessment is to identify women at high risk of developing breast cancer. Unfortunately, 76 percent of breast cancers occur in women with no identifiable risk factors.5 Women with a strong genetic predisposition for breast cancer and those identified as being at high risk can benefit from referral to dedicated clinics for closer monitoring or consideration of chemoprophylaxis.5

The Gail model6 is a risk-assessment tool that allows a woman to predict her five-year and lifetime probability of developing breast cancer compared to women of the same age with low risk factors. This mathematical model considers six factors (Table 2), but does not incorporate BRCA status or exposure to hormone supplements.7

Risk assessment tools may be helpful for women who are very concerned about breast cancer, provided that they understand the limitations of the model. Computer-based software, hand calculators, and user-friendly Internet sites are available for calculating risk.*

BREAST EXAMINATION

Breast examination by a clinician should be performed annually. In some studies it has been found to be as effective as mammography in detecting abnormalities.8,9 It additionally provides an opportunity to reinforce the importance of breast self-examination and to review the technique.

MAMMOGRAPHY

Recommendations about the appropriate frequency of mammographic examinations depend on a woman’s age and breast cancer risk.*

The effectiveness of screening mammography in influencing mortality for women aged 40 to 49 years at average risk of breast cancer is debated. Upon reaching the age of 40, Canadian women should be informed of the potential benefits and risks of screening mammography to help them decide when they wish to begin screening. Between the ages of 50 and 69, women should be offered screening every two years. After age 69, women should be screened according to clinical indications. Provincial cancer associations may have different recommendations and physicians are advised to consult their provincial cancer society for local guidelines. Higher-risk women may benefit from individualized recommendations.

**CARDIOVASCULAR EVALUATION**

**RISK ASSESSMENT**

The relationship between the major cardiovascular risk factors and the incidence of cardiovascular disease (CVD) has been established by the Framingham Heart Study. Such information is clinically useful if it identifies high-risk patients who warrant immediate attention and intervention, and if it motivates patients to adhere to risk-reduction strategies. Computer-based software, hand calculators, and Internet sites may be used for calculating CVD risk with the Framingham scoring system.*

The Working Group on Hypercholesterolemia and Other Dyslipidemias recommends that asymptomatic women over age 50 should initially be screened to obtain a fasting lipid profile (total serum cholesterol, high-density lipoprotein cholesterol, triglyceride, and low-density lipoprotein cholesterol levels), and a fasting glucose level to rule out diabetes mellitus. Thereafter, asymptomatic women should be screened every five years after the age of 50.† These issues are covered in more detail in Section D.‡

**THYROID EVALUATION**

The most recent Canadian Task Force on the Periodic Health Exam does not recommend screening for thyroid disease in asymptomatic adults.† However, the high prevalence of hypothyroidism among postmenopausal women justifies the use of a sensitive thyroid-stimulating hormone (TSH) assay if there are symptoms suggestive of thyroid disease (see Section H).‡

**BOWEL EVALUATION**

In asymptomatic patients over 40 years of age, the value of fecal occult blood testing, or sigmoidoscopic or colonoscopic visualization for the screening of bowel cancer, remains uncertain. However, patients with a personal or strong family history of Crohn’s disease, ulcerative colitis, colonic polyposis, or bowel cancer should undergo screening colonoscopy. A rectal examination should be a routine part of the physical examination.

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* [http://www.chd-taskforce.de/framingham-english.htm](http://www.chd-taskforce.de/framingham-english.htm)
BONE DENSITOMETRY
This subject is discussed in Section E.* Non-modifiable risk factors for osteoporosis should be identified (such as a history of fracture, family history of osteoporosis, prior use of corticosteroids), and modifiable behaviours discussed (diet, exercise, smoking). After menopause, the rate of bone loss varies among individuals, and bone densitometry can be useful in quantifying bone mass. Bone densitometry should be performed according to the guidelines published by the SOGC and the Osteoporosis Society of Canada.*

GENERAL GYNAECOLOGICAL ASSESSMENT
In the gynaecological assessment, the examiner must include evaluations for vulvar disease and the manifestations of urogenital aging. Screening for sexually transmitted diseases, including human immunodeficiency virus (HIV) infection, should be offered in appropriate situations.

CERVICAL ASSESSMENT
Cervical cancer screening (Pap smear) should be performed according to Health Canada guidelines from the Cervical Cancer Prevention Network,15 which are endorsed by the SOGC.† All women 18 years or older who have had sexual intercourse should be initially screened with two Pap smears, one year apart; if these smears are satisfactory, then rescreening every three years is advised until the age of 69, if they have had no significant abnormality in the past,15 but these recommendations are predicated on the presence of a system for recall and quality assurance, and currently most provinces in Canada do not have such a system. Thus annual screening is prudent.† For women 69 years of age or older who have never been screened, two Pap smears at six-month intervals are recommended, and, if normal, they do not need to have any further smears.16 Smears containing atrophic cells may be misinterpreted by the cytologist, and a course of vaginal estrogen before repeating the smear may improve accuracy.15

EVALUATION OF THE ENDOMETRIUM
DURING THE MENOPAUSAL TRANSITION
Perimenopausal women with abnormal vaginal bleeding should be appropriately investigated (Figure 1). Women who have risk factors for endometrial cancer may benefit from a baseline or screening endometrial biopsy. These risk factors include obesity, diabetes, hypertension, high alcohol intake, anovulation, prolonged oligomenorrhea or amenorrhea in an estrogenized state (for example, polycystic ovarian disease).

IN POSTMENOPAUSAL WOMEN NOT TAKING HRT
Any bleeding that occurs after 12 months of amenorrhea warrants investigation.

IN POSTMENOPAUSAL WOMEN TAKING HRT
The investigation and management of abnormal bleeding in women using hormone replacement therapy (HRT) must be individualized. Vaginal bleeding may occur because of the effects of the exogenous hormones or because of coincidental disease.

Cyclical Estrogen-Progestin
Any irregular or unscheduled bleeding should be evaluated, once proper compliance and dosage have been confirmed. Typically, the bleeding is considered reassuring if it occurs during the final days of a 12- to 14-day progestin regimen, or in the week following progestin withdrawal. Absence of withdrawal bleeding is usually not worrisome unless cervical stenosis is suspected.

Continuous-Combined Estrogen and Progestin
Irregular bleeding is common in the first six months of treatment, especially in recently menopausal women. Bleeding that persists after six months of therapy generally requires evaluation to rule out neoplasia or anatomical lesions such as polyps or fibroids. Women who continue to have irregular bleeding after one year of therapy may benefit from an increase in progestin dose or a change in regimen.

Unopposed Estrogen
Women with a uterus should only be given unopposed estrogen therapy after discussing the associated risk of endometrial neoplasia and the need for yearly endometrial assessment. The Postmenopausal Estrogen/Progestin Interventions (PEPI) study showed that 10 percent of women taking unopposed estrogen therapy will develop complex or atypical endometrial hyperplasia within one year of beginning treatment.17

TAMOXIFEN
The place of transvaginal ultrasonography or endometrial sampling in the early detection of endometrial cancer in women taking tamoxifen is undetermined.18 The American College of Obstetricians and Gynecologists has recommended that women taking tamoxifen have annual gynaecologic examinations, and that further evaluation be based on symptoms.19

METHODS OF ENDOMETRIAL EVALUATION
Endometrial Biopsy
Histological evaluation of the endometrium has been the gold standard to rule out endometrial neoplasia.20 An endometrial biopsy can usually be performed as an office procedure, although a paracervical nerve block may occasionally be required. Plastic semi-rigid cervical dilators may be used in the office. Only in rare circumstances is a general anesthetic necessary for sampling of the endometrium.

† http://www.hc-sc.gc.ca/hppb/ahc/cervicalcancer/index.html
Transvaginal Ultrasound and Saline Infusion Sonography
Assessment of endometrial thickness by transvaginal ultrasound (TVU) is an alternative screening tool when biopsy is not acceptable or possible. It may also detect or suggest the presence of focal lesions such as submucosal myomas or endometrial polyps. While a thickened endometrium (more than 5 mm in diameter) warrants further evaluation to rule out endometrial neoplasia, the low positive predictive value of the test means that the results of the additional tests will usually be normal. There are no comparable data using abdominal ultrasound screening for endometrial abnormalities, nor should ultrasonography of the pelvis be routinely performed in postmenopausal women. The infusion of saline into the uterine cavity during ultrasonography (SIS) may result in better assessment of the endometrial cavity, allowing differentiation of focal lesions from diffuse endometrial thickening.

Hysteroscopy With or Without D&C
Unsatisfactory results, or persistent unexplained bleeding after endometrial biopsy or TVU, warrant further investigation by means of hysteroscopy with directed biopsy or possibly dilation and curettage (D&C). Hysteroscopy is particularly useful in identifying and removing endometrial polyps and submucosal fibroids, which can easily be missed during a non-directed endometrial biopsy or D&C.

Putting it All Together: Evaluation + Risk Assessment + Clinical Interpretation
Despite the evidence that HRT is beneficial to the health of menopausal women, only a small percentage of Canadian women will use long-term HRT. The reasons cited for discontinuing HRT are listed in Table 3.
In order to increase adherence to any therapy, menopausal women need careful counselling and follow-up. The maximum benefit of therapy, for example, prevention of osteoporosis, depends on continued use. Alternative regimens of hormone administration make it possible to adjust a regimen individually to achieve the desired outcome.
Bone densitometry may be useful as a decision-making tool for promoting both initiation of and adherence to therapy.
Knowledge of risk is one of the factors that can help in adherence to a decision. The challenge of patient evaluation is to combine various individual risks in a clinically useful way that assists with decision-making. A decision model has been developed to compare the effects of alendronate therapy, raloxifene therapy, and HRT on risks of hip fracture, coronary heart disease, breast cancer, and life expectancy, according to an individual woman's risk factors.

**DECISION-MAKING RESOURCES**

Few clinicians have the time necessary to fully educate each woman in their practice about the wide range of options available in menopause, yet education about menopause is a prerequisite for informed decision-making. Several useful booklets and other resource materials are available to assist the clinician. Patients can study these on their own time, and return to their clinician to formulate a plan (Table 4).

**SHARED DECISION-MAKING**

A woman's decision-making regarding HRT is primarily her own, but appears to be influenced by factors beyond risk and benefit assessment. Physicians' prescribing habits vary by geographic region, and female physicians are more likely to prescribe HRT than are male physicians. Risk factors presented by the patient may be less influential than the prevailing view of the physician about the benefit of HRT in general. Clinical tips to help establish an appropriate system of management are listed in Table 5.

**PREVENTION DECISIONS AND TREATMENT DECISIONS**

Decisions to use HRT for the relief of symptoms are generally straightforward, entailing short-term use of medication. Preventive benefits are only measured after long-term exposure, and are measured by their impact on a population, rather than on an individual.

Preventive decision-making involves four considerations:

1. Perceived susceptibility to the preventable condition
2. Perceived severity of the preventable condition
3. Perceived likelihood of benefiting from the intervention
4. Risk of harm from the intervention.

Perception drives decision-making. Perceptions are formed by a complex interaction of factual knowledge, personal experience, vivid anecdotes, social supports, and socially held beliefs. The Internet is a new source of opinion that also colours perception. Each woman will apply her own weighting, based on personal context and various social factors, in arriving at a decision. A process to explore each dimension, enabling misconceptions to be corrected, is most likely to lead to a sense of confidence in the decision.

**HIDDEN AGENDAS**

Women may hesitate to disclose benefits they hope to achieve from HRT that may not be on the physician's list, such as concern with skin aging. A decision to accept risks based on such goals needs to be considered in the context of the relevant literature and the end-points used.

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**TABLE 3**

**REASONS FOR DISCONTINUING HRT**

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of cancer (especially breast)</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Lack of information about benefits/risks</td>
</tr>
<tr>
<td>Unnatural to take hormones</td>
</tr>
<tr>
<td>PMS-like symptoms</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Complicated regimens</td>
</tr>
</tbody>
</table>

**TABLE 4**

**DECISION-MAKING RESOURCES**

<table>
<thead>
<tr>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision Tree on ERT/HRT Recommendation for Health Care Professionals published by the North American Menopause Society²⁹</td>
</tr>
<tr>
<td>Decision aid Making Choices: Hormones after Menopause, developed at the Ottawa Health Decision Centre in 1996²⁰,³¹</td>
</tr>
<tr>
<td>SOGC brochures:</td>
</tr>
<tr>
<td>Menopause: Let's Talk About It</td>
</tr>
<tr>
<td>Osteoporosis: Let's Talk About It</td>
</tr>
<tr>
<td>Drug Therapy for Menopause and Osteoporosis: Let's Talk About It</td>
</tr>
<tr>
<td>Heart Disease: Let's Talk About It</td>
</tr>
<tr>
<td>Hormones and Breast Cancer: Let's Talk About It</td>
</tr>
<tr>
<td>Your Guide to Menopause</td>
</tr>
</tbody>
</table>

**TABLE 5**

**CLINICAL TIPS FOR PRACTICE**

- Negotiate the decision-making process and confirm that the process may require several office visits
- Suggest decision aids, reading materials, and Internet resources
- Suggest interaction with other health care professionals who have special knowledge (e.g., nurses, physiotherapists, dieticians, and pharmacists)
- Engage the patient in the choice, to facilitate adherence to the decision
- Plan certain criteria for each individual to follow (e.g., frequency of hot flushes, bone density)
- Provide the framework for monitoring (e.g., follow-up visits, a schedule for mammography)
FOLLOW-UP

Involving the woman in the decision-making process, anticipating start-up problems, and arranging suitable follow-up all facilitate adherence to treatment. The regular follow-up schedule should include, as a minimum, one follow-up visit three to six months after initiating therapy, followed by annual visits.

RECOMMENDATIONS:
L1. The assessments recommended by the Canadian Task Force on the Periodic Health Examination should be included in the evaluation and follow-up of peri-menopausal and postmenopausal women. (II-1)
L2. Routine abdominal or transvaginal ultrasonography of the pelvis should not be used in healthy asymptomatic postmenopausal women. (II-1)
L3. Postmenopausal women with abnormal bleeding patterns should undergo a review of their estrogen-progestin therapy administration (where appropriate), a pelvic examination, and an endometrial biopsy (II-1). Transvaginal ultrasonography is an alternative when endometrial sampling is not possible or the results are inconclusive. If the situation remains unclear, tissue sampling with or without hysteroscopy is recommended. (II)
L4. The majority of women wish to participate in the decision-making process, and health care providers should encourage them to do so. (III)
L5. Decisions should be based on an individual assessment of symptoms, risk factor analysis, and discussion of the risks and benefits of each option. The decision should be re-evaluated as new information becomes available. (III)
L6. Health care providers should actively advocate for public-funded educational programs to increase knowledge about menopause and osteoporosis for both women and their health care providers. (III)


REFERENCES


In addition to previous corrections appearing in the chapters on Pharmacotherapy and Complementary Approaches, revised recommendations and relevant statements throughout the text have been incorporated in answer to the WHI study on continuous-combined HRT. Changes have been made to the chapters on Hormone Replacement Therapy and Cardiovascular Disease, Osteoporosis, and Hormone Replacement Therapy and Cancer.