Clinical practice guidelines for the diagnosis and management of osteoporosis

Scientific Advisory Board,* Osteoporosis Society of Canada

Objective: To recommend clinical practice guidelines for the assessment of people at risk for osteoporosis, and for effective diagnosis and management of the condition.

Options: Screening and diagnostic methods: risk-factor assessment, clinical evaluation, measurement of bone mineral density, laboratory investigations. Prophylactic and corrective therapies: calcium and vitamin D nutritional supplementation, physical activity and fall-avoidance techniques, ovarian hormone therapy, bisphosphonate drugs, other drug therapies. Pain-management medications and techniques.

Outcomes: Prevention of loss of bone mineral density and fracture; increased bone mass; and improved quality of life.

Evidence: Epidemiologic and clinical studies and reports were examined, with emphasis on recent randomized controlled trials. Clinical practice in Canada and elsewhere was surveyed. Availability of treatment products and diagnostic equipment in Canada was considered.

Values: Cost-effective methods and products that can be adopted across Canada were considered. A high value was given to accurate assessment of fracture risk and osteoporosis, and to increasing bone mineral density, reducing fractures and fracture risk and minimizing side effects of diagnosis and treatment.

Benefits, harms and costs: Proper diagnosis and management of osteoporosis minimize injury and disability, improve quality of life for patients and reduce costs to society. Rationally targeted methods of screening and diagnosis are safe and cost effective. Harmful side effects and costs of recommended therapies are minimal compared with the harms and costs of untreated osteoporosis. Alternative therapies provide a range of choices for physicians and patients.

Recommendations: Population sets at high risk should be identified and then the diagnosis confirmed through bone densitometry. Dual-energy x-ray absorptiometry is the preferred measurement technique. Radiography can be an adjunct when indicated. Calcium and vitamin D nutritional supplementation should be at currently recommended levels. Patients should be counselled in fall-avoidance techniques and exercises. Immobilization should be avoided. Guidelines for management of acute pain are listed. Ovarian hormone therapy is the therapy of choice for osteoporosis prevention and treatment in postmenopausal women. Bisphosphonates are an alternative therapy for women with established osteoporosis who cannot or prefer not to take ovarian hormone therapy.

Validation: These guidelines were reviewed and approved by the Scientific Advisory Board of the Osteoporosis Society of Canada, in consultation with individual family and general practitioners.

Sponsors: These guidelines are based on the consensus statements on osteoporosis prevention and management, published by the Scientific Advisory Board of the Osteoporosis Society of Canada in 1996. Sponsors of this publication are Procter & Gamble Pharmaceuticals Canada Inc., Eli Lilly Canada, Inc., Wyeth-Ayerst Canada Inc., Merck Frosst Canada Inc. and the Dairy Bureau of Canada.

*Members of the Scientific Advisory Board are listed at the end of this article.

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This supplement has not been peer reviewed.

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Osteoporosis Society of Canada

La Société de l'Ostéoporose du Canada

Society of Obstetricians and Gynaecologists of Canada

La Société des obstétriciens et gynécologues du Canada

As the population ages, diagnosis and treatment of diseases associated with advancing age become more pertinent to the front-line practitioner. Osteoporosis is already a serious public health problem and promises to become significantly larger if effective prevention and corrective treatment are not pursued. To date, much of osteoporosis diagnosis and management has been research-based. There is an urgent need to set down guidelines to facilitate assimilation of the results of this research into clinical practice.

Diagnosis and management of any widespread disease must address efficacy in an environment of cost containment. For osteoporosis, this is difficult because data on cost are limited and often not comparable. Nevertheless, the costs implied by these guidelines have been uppermost in our minds throughout the development process.

The guidelines concentrate on a two-step diagnostic approach: first, to identify specific population sets at risk for osteoporosis; and second, to confirm or deny the existence of osteoporosis through bone densitometry in people in these sets. More frequent use of densitometry in Canada is very controversial, but there is no other way to evaluate risk of fracture appropriately. Without knowing the real risk, how can one ensure the appropriate frames of reference for treatment?

The treatment of confirmed osteoporosis is standard: in addition to ensuring adequate calcium and vitamin D intake and physical activity, ovarian hormone therapy (OHT) remains the best option for those who will accept it, tolerate it and benefit from it. A great challenge in preventing and even treating osteoporosis, though, is assessing a woman's risk for fracture at the time of menopause and offering OHT in a schedule that is effective and acceptable to her. These guidelines also discuss newer alternatives, such as bisphosphonates, for patients for whom OHT is recommended but who will not or cannot take it, and for those with severe osteoporosis for whom more rapid restoration of bone density is essential to prevent further fragility fractures.

Medicine remains a balance of science and art. The science of osteoporosis management discussed in this document still requires the art of medicine to apply it to individual patients. These guidelines are meant to provide primary care physicians with some colours to fill their palette.

Development of the guidelines

The need for a set of current guidelines for medical practitioners in the diagnosis and management of osteoporosis was identified by members of the Scientific Advisory Board (SAB) of the Osteoporosis Society of Canada (OSC). Following two OSC consensus conferences in 1993 and 1995 and the approval of the consensus statements presented at these conferences, a subgroup of the SAB met to identify which sections were appropriate for inclusion in the guidelines.

Sections were written by a specialist working group. The working group comprised rheumatologists, nephrologists, gynecologists, geriatricians, endocrinologists, radiologists and OSC executive members.

Each section was reviewed by individual family practitioners and subsequently tested in a focus-group setting with general practitioners and family practitioners. Modifications and recommendations arising from these processes were incorporated into the second revision. A second review was undertaken with family practitioners in a focus group setting. A third review incorporated focus-group recommendations. The guidelines received the approval of the SAB and the OSC Board of Directors. Fig. 1 provides an algorithm for managing osteoporosis when bone densitometry is unavailable, and Fig. 2 provides one for managing osteoporosis when bone densitometry is accessible.

Definition of osteoporosis

Osteoporosis is characterized by low bone mass and deterioration of bone tissue, leading to increased bone fragility and risk of fracture.[1,2] The World Health Organization (WHO) has defined osteoporosis as a bone-mineral-density measurement (T score) of more than 2.5 standard deviations (SDs) below the mean for young adults.[1,2] Bone densitometry reports refer to Z scores or T scores. The Z score (age-matched control) compares the patient with a population adjusted for age, sex and weight; the T score (young normal control) compares the patient with a sex-adjusted population at peak bone mass.

Based on this definition, clinicians may consider a bone to be osteoporotic if it has sufficiently decreased density that it would be unable to withstand the traumas of normal activities, or if there has already been spontaneous or nontraumatic fracture.

Burden of illness

Osteoporosis is a major health and economic problem. One in four women over 50 years of age[3] and one in eight men over 50[1,3] are believed to have osteoporosis.[3] Osteoporosis increases in prevalence with age in both sexes. An estimated 1.4 million Canadians are affected.

The US National Osteoporosis Foundation has estimated that 70% of hip fractures are the result of osteoporosis.[4] There were estimated to be over 21 000 osteoporosis-related hip fractures in Canada in 1993.[5]

Women's mortality rates from osteoporotic fractures are greater than the combined mortality rates from cancers of the breast and ovaries.[6,7] Up to 20% of women[8] and 34% of men[9] who fracture a hip die in less than a year.[9-11]

One Canadian survey has estimated the 1993 total

acute health care costs (hospitalization, outpatient care, drug therapy) attributable to osteoporosis at $465 million.[5] When long-term facility care and chronic hospital care are included, the total reaches $1.3 billion.[5]

Vertebral and wrist fractures are also common in osteoporosis. Yet possibly half of vertebral fractures do not come to clinical attention.[12] As a result, the annual incidence of vertebral fractures in the general population has not been directly measured.[13]

With Canada's elderly population increasing, the number of people with osteoporosis is growing rapidly. Moreover, the rate of fractures may be increasing much faster than can be accounted for by population aging.[7,13,14] This trend may reflect changes in physical activity,[15] altered nutrition, increased tobacco and alcohol consumption, and other environmental factors.[16]

Identifying patients at risk

Bone mass and risk of fracture

The likelihood of osteoporosis developing is deter-

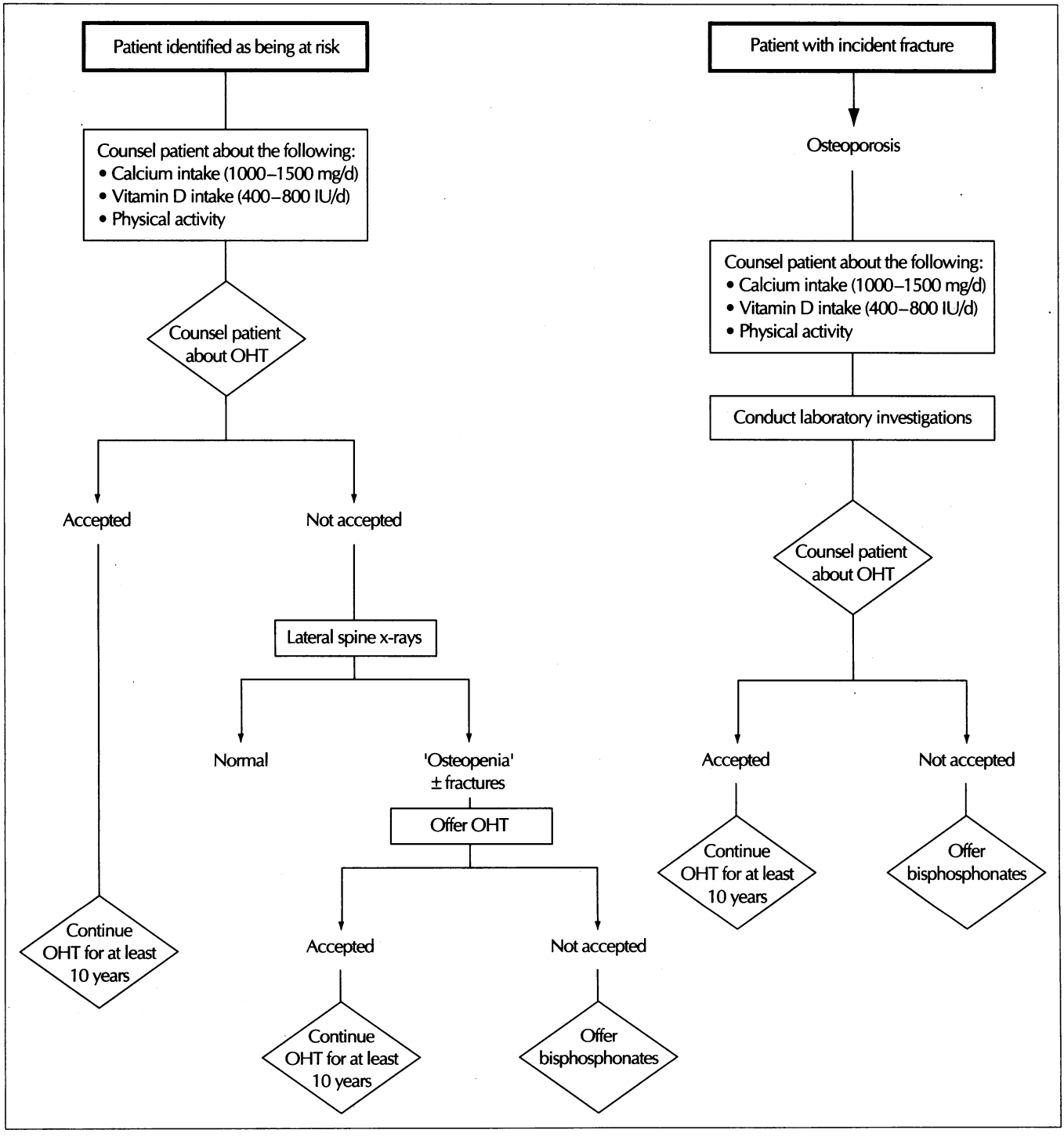
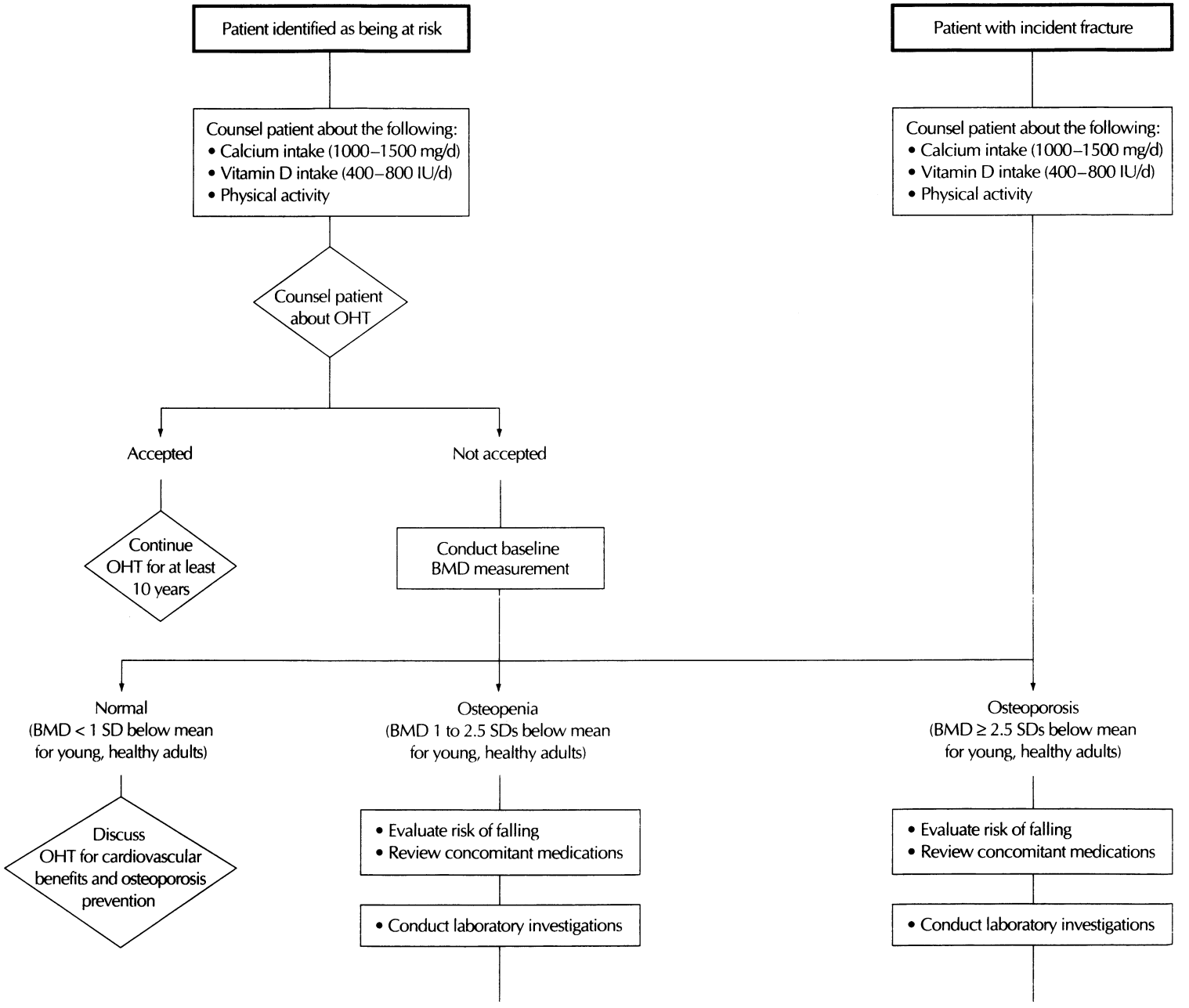


Fig. 1: Algorithm for managing osteoporosis in the absence of bone densitometry.


Patient identified as being at risk
Counsel patient about the following:
• Calcium intake (1000–1500 mg/d)
• Vitamin D intake (400–800 IU/d)
• Physical activity
Counsel patient about OHT
Accepted
Not accepted
Continue OHT for at least 10 years
Conduct baseline BMD measurement
Patient with incident fracture
Counsel patient about the following:
• Calcium intake (1000–1500 mg/d)
• Vitamin D intake (400–800 IU/d)
• Physical activity
Normal (BMD < 1 SD below mean for young, healthy adults)
Osteopenia (BMD 1 to 2.5 SDs below mean for young, healthy adults)
Osteoporosis (BMD ≥ 2.5 SDs below mean for young, healthy adults)
Discuss OHT for cardiovascular benefits and osteoporosis prevention
• Evaluate risk of falling
• Review concomitant medications
• Conduct laboratory investigations
• Evaluate risk of falling
• Review concomitant medications
• Conduct laboratory investigations

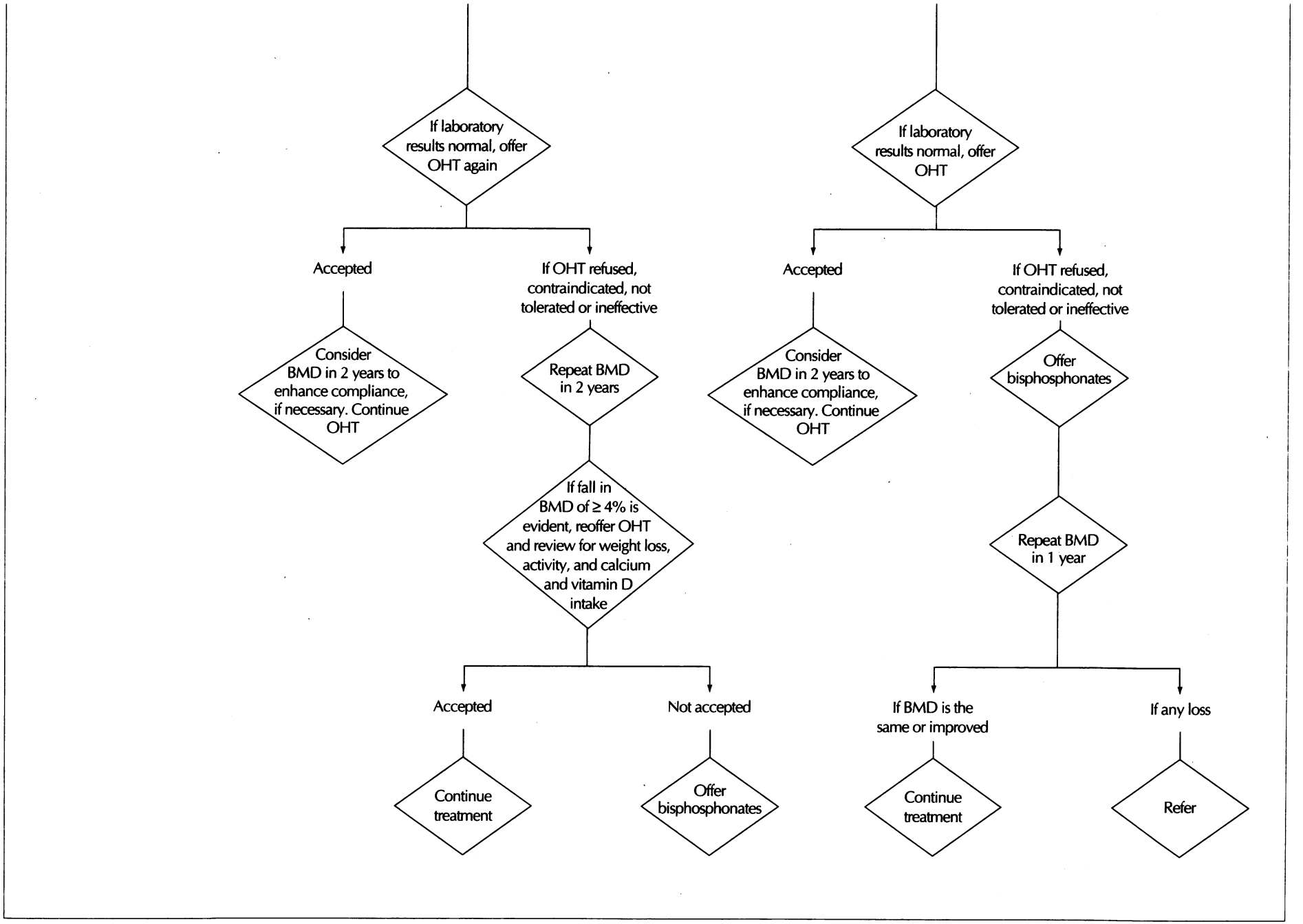


Fig. 2: Algorithm for managing osteoporosis when bone densitometry is available.

mined largely by the maximum amount of bone accumulated during growth (peak bone mass is usually achieved in the second to fourth decade)[17–19] and the rate and duration of accelerated postmenopausal and age-associated bone loss. The lower the peak bone mass or the greater the rate of bone loss, the greater the risk of osteoporosis. With each decline in bone mass of one standard deviation from the young adult mean fracture risk doubles.[20]

Men and women naturally begin losing bone around age 35, at a rate of 0.5% to 1% per year.[1] Women lose bone at an accelerated rate after menopause: 3% to 5% per year, lasting an average of 10 years.[1] A man will probably lose two thirds as much bone mass as a woman.[21]

Menopause and the associated decline in levels of estrogen and progesterone are estimated to account for one third to half of the bone loss experienced by women.[22] Men lose bone at an accelerated rate after about age 65, which may be associated with an age-related decline in gonadal function that occurs in some men.[23]

Risk factor assessment

Osteoporosis is usually asymptomatic until a fracture occurs. As a result, osteoporosis in most patients is diagnosed after a fracture. Older men and women who present with a fracture (typically of the spine, wrist or femur) should be investigated for osteoporosis, as should anyone with recurrent fractures.

Certain conditions predispose to loss of bone and increased risk for osteoporotic fractures. The diagnosis can be made before a fracture occurs, and treatment can be initiated to reduce further bone loss and, in fact, to increase bone mass. Patients to target for investigation include the following.

- Women who have had an early menopause (ages 40 to 45), premature menopause (before age 40) or bilateral oophorectomy before normal menopause (ages 45 to 55).[24,25]
- Younger women who have amenorrhea or oligomenorrhea due to ovarian hormone deficiency states (e.g., eating disorders, stress, excessive or competitive exercise, hyperprolactinemia).[26,27]
- Women not receiving OHT for at least 5 years after menopause. These women are thought to be at increased risk of osteoporotic fracture as a result of the accelerated rate of bone loss that occurs postmenopausally.
- Patients expected to undergo prolonged treatment (i.e., more than 3 months) with oral glucocorticosteroids.[28]
- Patients with primary hyperparathyroidism.[29,30]
- Patients with a strong family history of osteoporosis.[31–33]
- Post-chemotherapy patients (especially those with breast cancer and hematologic cancer).[34]
- Men who have hypogonadism for any reason.[35,36]

Unfortunately, our understanding of these factors is still insufficiently sensitive and specific to predict an individual person's overall risk of fracture. At best, risk factors can predict only about one third of variability in bone mass.[37] Nevertheless, the presence of one or more risk factors is not insignificant. In one recent study, the most important predictors of osteoporosis were increased age, low body weight, poor muscle strength and estrogen deficiency.[38]

Concomitant drug therapy and iatrogenic drug problems

The risk of osteoporotic fractures can be increased by medications that promote loss of bone mineral density or reduce neuromuscular functioning and thus increase the risk of falling.

Several drugs have been associated with decreased bone mass and increased risk of osteoporotic fractures. These include glucocorticosteroids, anticonvulsants, heparin (prolonged administration), excessive doses of thyroxine and antineoplastic drugs (e.g., high-dose methotrexate) used to treat certain cancers.

It is essential to titrate medications and dosages to maintain disease control while minimizing the adverse effect on bone. Thyroxine replacement therapy should maintain a normal serum thyroid-stimulating hormone level. All older patients, especially those who require oral glucocorticosteroid or anticonvulsant therapy, should maintain an adequate intake of calcium (1000 to 1500 mg/d) and vitamin D (400 to 800 IU/d); in some cases, other osteoporosis therapies may be required to prevent bone loss.

Sedative medications and hypnotics are frequently prescribed for elderly osteoporotic patients. Even short-acting agents at bedtime may be dangerous to the elderly patient. Long-acting drugs can impair neuromuscular control and greatly increase the risk of falling. These drugs should be avoided if possible.

Clinical evaluation of osteoporosis

The following points should be covered when investigating patients who are at high risk for or have been diagnosed with osteoporosis.

- Decrease in height (accurate measurements of height should be made yearly starting at age 35).
- Thoracic kyphosis and abdominal protrusion.
- Acute or chronic back pain from thoracic to lumbar region.
- Gynecologic disorders, including early bilateral oophorectomy, menstrual dysfunction including amenorrhea and oligomenorrhea and age at menopause.[24–27]
- Medications (including oral glucocorticoids,[28,39] anticonvulsants,[31,40] excessive doses of thyroid medication, sedatives[31,41] and antineoplastics).

- Previous fractures.[31,42]
- Family history of osteoporosis.[31–33]
- Gastrointestinal disorders (especially those resulting in gastrectomy) and chronic liver diseases.[29,43,44]
- Renal diseases.[29,45]
- Endocrine diseases (e.g., hypogonadism in men,[35] hyperparathyroidism,[29,46] hyperthyroidism[31,47,48] and Cushing's syndrome).[29,49]
- Diet, especially lifetime calcium intake;[33,50] use of vitamin supplements including vitamin D; lactose intolerance.
- Level of activity and any occurrence of prolonged sedentary periods (e.g., prolonged bed rest).[33,51]
- Regular smoking or alcohol abuse.[31,33,52,53]

Measurement of bone mineral density

Measurement of bone mineral density (BMD), or bone densitometry, is the best available method to confirm or rule out a diagnosis of osteoporosis.[20,54–57] However, the decision to measure BMD must be made rationally. BMD measurements are not recommended as a mass screening tool.[58,59]

If a physician and a menopausal patient have clearly made the decision to begin and continue long-term OHT (for 10 years), there is no reason to measure bone density routinely. However, if a patient at risk for osteoporosis requires support in making a decision to begin OHT, and the physician is reasonably assured that concrete evidence of osteopenia or osteoporosis would be of value, densitometry may be recommended.[60] The use of densitometry to make decisions regarding OHT has been shown to be cost effective.[61]

Currently, the OSC supports the following clinical indications for densitometry.[4,58]

- Menopause in women in whom information on bone density is considered essential to decision-making about OHT, as well as hypogonadism in adult men and women of any age: to diagnose significantly low bone mass in order to decide about ovarian or testicular hormone therapy.
- Vertebral fractures or radiologic evidence of osteopenia: to diagnose osteoporosis in the spine in order to decide about further diagnostic evaluation and therapy.
- Long-term oral glucocorticoid therapy: to diagnose low bone mass in order to adjust therapy.
- Primary hyperparathyroidism: to diagnose low bone mass in order to identify those at risk for severe skeletal disease who may be candidates for surgical intervention.
- A strong family history of osteoporosis, or the presence of other risk factors for osteoporosis: to decide about OHT.
- Ongoing therapy for osteoporosis: to monitor the efficacy of therapy.

Currently the best available means of BMD measurement is dual-energy x-ray absorptiometry (DXA).[62] DXA measures bone mass in the spine, the hip and total body by scanning and filtering x-rays from a stable source.[63] DXA scans are accurate (error rate of 4% to 8%), precise (error rate of 1% to 3%), fast (3 to 10 minutes) and result in low radiation exposure (10 to 30 μSv).

An imperfect correlation exists between measurements of the lumbar spine and femur in approximately 20% to 25% of cases, and measurement at each site is best for predicting fracture risk at that site.[31,42,54] Unless some specific indication exists to examine a single or alternative site (e.g., metal rods in the spine or a prosthetic hip replacement), the examination of patients to diagnose osteopenia should include measurements of both the lumbar spine and femoral neck. The cost of such an examination (spine plus hip) in Canada in 1995 ranged from $75 to $200.

Recent evidence indicates that measurement of only one site may be sufficient to diagnose osteopenia in women over age 65 and that the femoral neck may be the best site.[64] The lumbar spine is usually measured to assess treatment response; it can be measured with more precision than can the femoral neck, and changes there are more readily detected. In younger patients, analysis of a single site, such as the spine, may also be considered.

Dual-photon absorptiometry (DPA) is a less accurate and precise indicator of bone density than is DXA, but in some areas of Canada DPA may be the only available method. If DPA is the only available method it may be used for detection of low axial bone density.

Ultrasound densitometry is promising, though unproven, for assessing skeletal mass and other bone characteristics.[65] Potential advantages are an absence of ionizing radiation, ability to measure structural strength of bone (DXA measures only bone density), a relatively brief procedure time and portability.[66–70] Thus far, only peripheral sites can be measured by USD, and some researchers have concluded that measurements of the hip or spine are unlikely to become possible in the near future.[65]

The vital information derived from bone densitometry is the measured bone density, and an interpretation of its implications for increased risk of fragility fractures. The report received from the laboratory should include a comment about the increase in fracture risk, by site of measurement. This is indicated by the number of SDs below the mean reference range for young, healthy adults.

The following are the recommended WHO diagnostic categories for BMD readings taken at the lumbar spine and femoral neck for adult women. Results (T scores) are compared with the mean for young adults.[1,20]

- *Normal:* a value for BMD not more than 1 SD below the mean for young adults.
- *Osteopenia:* a value for BMD between 1 and 2.5 SDs below the mean for young adults.
- *Osteoporosis:* a value for BMD more than 2.5 SDs below the mean for young adults.

- *Severe osteoporosis:* a value for BMD more than 2.5 SDs below the mean for young adults, in the presence of one or more fragility fractures.

Osteopenia carries a 2-fold increase in risk for fracture compared with normal, and osteoporosis (without fracture) carries a 4- to 5-fold increase in risk for fracture. The presence of pre-existing fractures in an osteoporotic person increases the risk of further fractures 20-fold.[42,71,72]

Densitometry measures calcium in bone. Falsely elevated levels (in the whole spine or selected vertebrae) may result from the presence of nonstructural calcification due to, for example, confluent aortic calcification, discogenic vertebral sclerosis and degenerative arthritis. Therefore, radiographs may be required to complement densitometry, particularly in people more than 60 years old.[73]

Radiography

Plain x-ray radiographic diagnosis of osteopenia is insensitive and unreliable. Losses of less than 25% to 30% of bone mass are not observable by this method.[1,74,75] Nevertheless, x-ray radiography assessment of fractures has a role in osteoporosis management.

If a patient presents with back pain, or a reduction in height is noted as part of the clinical evaluation, radiographic studies of the spine may be required. Single lateral views of the thoracic and lumbar spine will establish the presence of vertebral fractures. In addition, a single anteroposterior view of the pelvis may provide useful information concerning abnormalities of the hip joints, the femoral necks and the pelvis.

Radiographs are useful in distinguishing osteoporotic fractures from the most common causes of back pain: degenerative disc disease, metastatic bone cancer, multiple myeloma, osteoarthritis of the posterior intervertebral facet joints, sacroiliac disease and osteoarthritis of the hip joints.

Laboratory investigations

The laboratory investigations shown in Table 1 should be used to exclude secondary causes of osteoporosis.

Management of acute back pain due to osteoporotic fractures

Osteoporotic fractures may be painless, and gradual compression of several vertebrae may lead to progressive dorsal kyphosis. Nevertheless, an acute, severe vertebral compression may be devastating and disabling. Sometimes the pain occurs with no apparent cause or with rolling over in bed. Because the commonly used analgesics (e.g., acetaminophen with codeine) and nonsteroidal anti-inflammatory drugs (NSAIDs) are often not helpful in this type of back pain, the following approaches to managing osteoporotic patients with pain are suggested.

- The pain may be so disabling that the patient is unable to care for herself or himself independently, or even with visiting nursing services. Hospital admission may be indicated then, with the expectation of a 10- to 14-day stay. It is often helpful to consult the anesthesiology or pain service for assistance with pain management.
- It may be necessary to use narcotics in the acute phase of pain; slow-release morphine (30 mg) once or twice daily (depending on when the pain is most disabling) can be useful.
- If there is severe muscle spasm or if pain persists despite full analgesic coverage, other measures may be needed. Calcitonin is recommended in this instance as an initial treatment for acute, severe, unrelenting back pain secondary to fracture, as it also has analgesic properties. A trial of epidural injections of local anesthetics or glucocorticosteroids may also be help-

Table 1: Laboratory investigations used to exclude secondary causes of osteoporosis*

Investigation	Expected result in patients with osteoporosis	Comments
Complete blood count	Normal	Full investigation
Serum calcium measurement	Normal	If elevated, consider primary hyperparathyroidism, metastatic cancer, multiple myeloma or other cause of nonstructured calcification; if low, consider osteomalacia
Alkaline phosphatase measurement	Normal, but level will increase transiently with fracture	If persistently elevated in absence of fracture, consider other bone disease or liver disease
Serum creatinine measurement	Normal	If elevated, evaluate for renal impairment
Serum protein electrophoresis	Normal	If monoclonal band is present, consider multiple myeloma

*Clinical suspicion of other secondary causes will determine the need for further investigations.

ful in breaking the pain cycle. If no relief follows three such treatments, it is not worth persevering with this approach, but if there is relief, the treatment can be used as necessary.

- More than half of these acute or semi-acute episodes resolve with very little residual pain over 6 to 12 weeks. However, the disability may last longer than this, and a few patients will have chronic pain syndrome, which can be quite intractable and produces long-term reductions in the ability to perform daily household tasks. For these patients particularly, a structured exercise program is recommended for pain management. Although there are very few tailor-made osteoporosis exercise programs in Canada, many community centres, particularly the YMCA/YWCA, are developing back-care programs. Patients should be introduced to them. Physiotherapists can also play a useful role.
- Chronic back pain in elderly patients may be due to many causes other than compression fractures. Degenerative disc disease and degenerative changes in the posterior intervertebral facet joints are common. A set of x-rays of the spine should be obtained so that the extent of these other (often coexisting) conditions can be assessed.
- Other efforts to control pain require some imagination. It is worth trying acupuncture, transcutaneous nerve stimulation and anti-inflammatory drugs as well as the usual analgesics and NSAIDs. Patients should always be given instructions to do back-extension strengthening exercises regardless of whether a local exercise program is available.

Fall avoidance

Preventing falls in the osteoporotic patient will reduce injury and improve quality of life. Thirty percent of elderly people fall yearly, and 5% to 10% of these falls result in fracture.[76] Risk factors for falling include advanced age; certain chronic neurological conditions (e.g., stroke and Parkinson's disease); impaired cognition and balance; slow gait; poor vision; foot problems or inappropriate footwear; and the use of certain drugs (e.g., long-acting sedatives).[76-78]

An assessment of the functional balance and gait speed can be easily done in an office with the timed "Up and Go" test.[79] With the patient sitting in a standard chair with arms, the physician asks her or him to stand, walk to a wall 3 m away at a safe pace, turn around and return to a seated position. With usual ambulation the task is completed within 10 seconds. Those needing longer than 20 seconds should be targeted for balance and general exercise programs, which will decrease the risk for falls.[79] Inactivity also appears to increase the risk of falling; thus, moderate physical activity should be encouraged in all adults if possible.

Some hazards such as scatter rugs, electrical wires and poor lighting are implicated in one third to half of falls.[80] Efforts should be made to eliminate these indoor environmental hazards.

Identification of risk factors for falling coupled with a management plan to deal with identified problems (e.g., postural hypotension, medication use, physical inactivity, environmental hazards) decreases the likelihood of falling. Patients who do fall require a thorough evaluation incorporating a history, physical examination and environmental assessment to identify remedial problems. Referral of these patients to a physiotherapist or a specific exercise program can be helpful.

Caution should be exercised in the use of sedative medications or drugs with sedative effects, which can slow reflexes and decrease coordination.[31]

Physical activity

The primary purpose of physical activity in people with osteoporosis is to reduce the risk of falls and fractures. Exercise programs for patients at risk for or with osteoporosis should be aimed at increasing strength, coordination, balance and flexibility.[81] Improved physical fitness can also improve posture in the osteoporotic elderly person and lessen the pain associated with daily activities.

Immobilization should be avoided if possible. Bone homeostasis depends on both chemical and mechanical factors. Prolonged bed rest or immobilization can result in increased calcium excretion and bone loss.[82] For some patients, the combined effects of chronic pain, recurrent fractures and gradual deformation of the spine may result in decreased mobility, functional disability and social isolation. These problems, in turn, result in decreased strength and coordination, making the patient even more susceptible to falls and fractures.

Physical activity positively affects bone mass. Exercise can help maintain bone mass in menopausal women whether or not they have osteoporosis.[83,84] Exercise has also been shown to slow accelerated postmenopausal bone loss,[85] increase functional ability[86] and reduce chronic pain.[87,88]

Patients with osteoporosis may be physically deconditioned and may have other medical problems such as cardiorespiratory disease. Therefore, a physician must consider both the risks and benefits of physical activity. Exercises must be safe and beneficial. In patients with osteoporosis, exercise should not cause pain (either in the back or the joints), chest symptoms or shortness of breath. Elderly patients should be assessed for risk for falls to identify those in greatest need of exercise programs.

Exercise programs for patients with osteoporosis

The optimal type of osteogenic activity provides relatively high levels of strain.[89] Given that muscular contrac-

tions exert strain on the bone, muscle-strengthening exercises for the upper and lower body and axial skeleton are beneficial. However, prescribing high loads in anyone with osteoporosis, especially in older patients, must be done with caution. The strengthening program should be submaximal, incorporate the major muscle groups and be performed as tolerated by the individual patient.

Postural retraining is a key goal. Education on proper posture during standing and sitting is important. In addition, patients should be taught effective ways of doing activities of daily living (e.g., bending and getting up from lying down) that will not threaten further fractures. Back exercises, including the pelvic tilt, isometric abdominal strengthening exercises and gentle back-extension exercises, should be performed regularly. People with a history of vertebral compression fractures or a diagnosis of osteoporosis determined by DXA should avoid flexion exercises.

To promote endurance and improve cardiovascular fitness, low-impact forms of aerobic exercise are suggested. Cardiovascular exercise may include walking, bicycling, swimming, dance routine or low-impact aerobics.

Exercises aimed specifically at balance, such as Tai Chi[90] and Tinetti's progressive balance exercises,[91] have been shown to prevent falls.[81]

Most important in an exercise program for patients with osteoporosis is making physical activity a regular part of their daily routine. The benefits of regular exercise will encourage compliance. Even those with coexistent problems such as arthritis, heart disease or frailty should be encouraged to be physically active and, whenever possible, to join community group-exercise programs, provided the program begins gradually and the activity stays within moderate intensities.

Patients in exercise programs should obtain proper nutrition to prevent excessive weight loss and the impaired immune function that results from inadequate protein, vitamin and mineral intake.

The positive effects of exercise are an adjunct to other therapies. Exercise (with or without calcium supplementation) should not be thought of as a replacement for OHT in postmenopausal patients with osteoporosis.

Table 2: Recommended daily nutritional intake of calcium

Age, yr	Sex	Recommended daily intake, mg
7–9	Both	700
10–12	Male	900
	Female*	1200–1400
13–16	Both	1200–1400
17–18	Both	1200
19–49	Both	1000
≥ 50	Both	1000–1500†

*Girls go through their adolescent growth spurt 2 years earlier than boys on average.
†A minimum of 1000 mg is recommended, but a higher intake may be advisable if the risk of osteoporosis is high.

Nutritional supplementation

Calcium

The OSC currently recommends that adults obtain 1000 mg to 1500 mg of elemental calcium per day for optimal bone health[92] (Tables 2 and 3). If this cannot be achieved by diet alone (for most, three or more servings of dairy products), then calcium supplementation should be recommended. An important consideration in calcium supplementation is its bioavailability. Name brands of carbonate or citrate preparations are preferred.[92] At the above amounts, calcium is virtually free of side effects. It is best given in divided doses, with meals. Magnesium is not required to enhance calcium absorption. Patients should understand that adequate calcium intake by diet or supplements (alone or in combination with physical activity) can reduce but will not prevent accelerated bone loss associated with ovarian hormone deficiency.[93]

Vitamin D

Vitamin D increases calcium absorption in the gastrointestinal tract. Vitamin D deficiency may lead to secondary hyperparathyroidism and increased bone resorption, therefore causing or aggravating osteoporosis.[45,94,95] Vitamin D deficiency is most prevalent among institutionalized elderly patients in winter, but studies have shown that homebound Canadians in general may experience significant vitamin D deficiency, especially in winter,[94,96] and in those who use sunscreens continually.[97]

The current recommended nutritional intake for vitamin D is 200 IU in adults aged 50 and older. The OSC

Table 3: Foods considered excellent sources of calcium

Food	Serving	Calcium, mg
Almonds	125 mL	200
Baked beans	250 mL	163
Buttermilk	250 mL	301
Cheese, firm (e.g., Brick, Cheddar, Colby, Edam and Gouda)	50 g	350
Milk (whole, 2%, 1% and skim)	250 mL	315
Mozzarella cheese, partly skimmed	50 g	366
Salmon, pink, canned, with bones	½ of 213-g can	225
Salmon, sockeye, canned, with bones	½ of 213-g can	242
Sardines, canned, with bones	55 g (11 small)	210
Swiss cheese	50 g	480
Yogurt, plain	175 g	292
White beans, cooked	250 mL	170

recommends that people over 65 or those with osteoporosis have a dietary intake of 400 to 800 IU per day.[88,92,95,98,99] The use of much higher doses of vitamin D (e.g., 50 000 IU per week) is not usually needed for the treatment of osteoporosis but may be required in individual circumstances.

Although the importance of adequate vitamin D nutrition is well established, the efficacy of any of the vitamin D-derived compounds in the treatment of osteoporosis has not been conclusively demonstrated. Possible side effects of vitamin D analogs and metabolites are hypercalcemia, hypercalciuria, renal calcification and renal stones. More research is needed into their potential benefits and risks. At present, prescription of the vitamin D metabolite calcitriol for the treatment of osteoporosis should be reserved for physicians with a special interest in the treatment of metabolic bone disease.

Drug therapies for prevention and treatment of osteoporosis

Ovarian hormone therapy

The OSC considers "ovarian hormone therapy" to be a more appropriate term for what is commonly referred to as estrogen or hormone replacement therapy, and the term should not be interpreted as referring to oral contraceptives.

Benefits

OHT is the front-line pharmaceutical therapy for the prevention and treatment of osteoporosis in postmenopausal women (see the decision aid in Appendix 1 for recommendations for prescribing OHT). Physicians agree that postmenopausal estrogen therapy (with or without concurrent progesterone therapy) prevents the accelerated bone loss that normally occurs with menopause.[25,100–116] Conjugated equine estrogen (CEE) therapy, given at a minimal effective dose, increases or preserves bone density in all areas of the skeleton that have been studied. Overall fracture risk is reduced by more than 50% in women who start OHT early in their menopause and continue with it for 6 to 9 years.[104,105,111–116] At this time, no other therapy (including calcium supplementation) has comparable efficacy. Thus, all women at high risk for osteoporosis should be offered OHT unless there are specific contraindications (see "Risks").

OHT given to women many years past menopause also appears to have a beneficial effect on bone.[116,117] It appears to have a protective effect against coronary artery disease.[118–121] We now have encouraging results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial,[122] and we await the results of the Women's Health Initiative.

When OHT is used in the prevention and treatment of osteoporosis, the purpose is not to replicate the premenopausal cycle of estrogen and progesterone but, rather, to provide the lowest and safest level of ovarian hormone dosage that will protect against osteoporotic fracture.[104]

Risks

If OHT is being used in the prevention or treatment of osteoporosis, women should be carefully monitored and evaluated for possible adverse events.

Concern exists about the possible risk of breast cancer in women treated with estrogen.[123–128] Although many studies have failed to disclose an increased incidence of breast cancer,[127] some have shown a small increase with prolonged therapy (10 years or longer).[128] Further studies are being undertaken to clarify this issue.

The use of estrogen alone (without progestin) significantly increases the risk of endometrial cancer. This risk increases with dose and duration of use. With 5 or more years of use, there is at least a 5-fold increase in risk of endometrial cancer.[129] (For estrogen and progestin regimens see "Regimens.") The best available evidence shows that cyclic progestin prevents the development of endometrial hyperplasia and endometrial carcinoma. More evidence is required to evaluate whether alternative progestin regimens, such as those utilizing lower-dose cyclic progestin or continuous combined estrogen–progestin, are equally effective in preventing endometrial cancer.[130–137]

Counselling patients

Women at risk for osteoporosis or with osteoporotic fractures should be considered for OHT. However, routine counselling of patients about OHT is not current practice in Canada or the United States.[138] It is important for physicians to keep abreast of developments in knowledge and practice in this area.

Women who experience premature menopause (before 40 years of age) for any cause, including those who undergo premenopausal bilateral oophorectomy, and have not received OHT are at high risk for osteoporosis. Such women should be offered OHT as a preventive measure, unless contraindicated.

Physicians and patients should discuss the use of OHT during perimenopause, especially if the patient has risk factors for osteoporosis and significant osteopenia as measured by DXA. A low-dose oral contraceptive may be considered in at-risk younger women (less than age 40) or for perimenopausal women at low risk for complications from oral contraceptives (i.e., nonsmoker, normal weight, no family history of cardiovascular disease, normotensive).[139,140] Women considered at risk for oral contraceptive complications because of weight, fam-

ily history of cardiovascular disease or high blood pressure may be given an oral contraceptive if other factors weigh favourably in a benefit–risk assessment.

In counselling about OHT, the physician should carefully review the patient's risk–benefit status and ensure that she has the appropriate information to make an informed choice. The woman's total health history must be carefully reviewed, and a physical examination should be carried out. The OSC does not recommend the use of OHT in all postmenopausal women. An individualized approach with continuing dialogue is necessary, including careful follow-up with regular gynecologic and breast examinations and mammography.

Regimens

All forms of estrogen (including transdermal, equine and synthetic estrogens) are effective in preventing bone loss. Estrogen therapy given alone (without progestin) should be considered only in women who have had a hysterectomy. A recent trial indicated that progesterone may have important bone effects;[27] however, further study is required.

The minimum effective daily doses of estrogen for the prevention and treatment of osteoporosis are:

- Conjugated equine estrogen, 0.625 mg.
- Estrone sulfate — estropipate, 0.625 mg.
- Estradiol-17β, 1 to 2 mg.
- Estradiol, transdermal, 50 to 100 mcg.

Progestins are given along with estrogen therapy to prevent the development of endometrial hyperplasia and carcinoma. Progestin preparations available in Canada for OHT and their doses for use in osteoporosis are:

- Medroxyprogesterone acetate (MPA), 2.5, 5 and 10 mg.
- Micronised oral progesterone, 100, 200 and 300 mg.
- Norethindrone, 0.35 and 0.7 mg.

Possible estrogen–progestin regimens for osteoporosis are:[141,142]

- Continuous (daily) estrogen–cyclic progestin (MPA or equivalent, 5 to 10 mg/d, taken from day 1 through 10 to 14 of each calendar month).
- Continuous (daily) combined estrogen–progestin (2.5 mg of MPA per day, together with 0.625 mg of conjugated equine estrogen per day).
- Cyclic estrogen–progestin (pill-free interval) (e.g., 0.625 mg of conjugated equine estrogen per day from day 1 to 25, and MPA from day 12 or 14 to 25).

It is the responsibility of the physician who prescribes OHT to be fully knowledgeable about the options, regimens, side effects, and absolute and relative contraindications (Appendix 1). Inappropriate or unscheduled bleeding requires appropriate endometrial surveillance.

A small proportion of women do not respond to OHT and continue to lose bone. Therefore, appropriate monitoring of those at high risk for osteoporosis should be carried out during therapy. In a woman at risk for osteoporotic fracture or with established osteoporosis who is unwilling to try OHT or is intolerate or unresponsive, bisphosphonates are the next treatment of choice (see "Bisphosphonates").

Duration of treatment

For the skeletal benefits to accrue, long-term OHT may be needed. Data suggest that the positive effects of this therapy last only as long as the therapy is continued. An increased rate of bone loss resumes once therapy is stopped.[103] Therapy should be continued for a minimum of 10 years beyond menopause for maximum bone protection.[143]

Contraindications

Physicians and their patients should take into account the absolute and relative contraindications to OHT. Absolute contraindications to estrogen are:[100]

- History of unexplained vaginal bleeding.
- Active liver disease.
- Breast cancer.
- Active vascular thrombosis.

In addition, caution is warranted and low initial dosages of estrogen are preferred (specific monitoring may be necessary) in the following conditions:[100]

- Migraine.
- History of thromboembolism.
- Familial hypertriglyceridemia.
- Uterine leiomyomas (fibroids).
- Endometriosis.
- Uterine cancer.
- Gall bladder disease.
- Strong family history of breast cancer.
- Chronic hepatic dysfunction.

Low-dose OHT may not cause recrudescence of headaches, fibroids or endometriosis because circulatory blood levels of OHT are much lower than premenopausal endogenous levels.

Compliance

In women over 65, lower estrogen doses should be used at the beginning of OHT therapy because re-establishing estrogen stimulation, especially to the breast and uterus, can result in side effects (uterine bleeding, mastalgia) that lead women to reject the treatment.

The addition of cyclic progestin to an estrogen regimen will result in regular withdrawal bleeding in 50% to 80% of women. Bleeding becomes less prevalent as the length of treatment increases.[131] Withdrawal bleeding is a major reason for noncompliance.. Therefore, continuous, combined progestin regimens, which do not promote withdrawal bleeding, should be considered for this group.

Although more than 40% of women receiving OHT experience irregular breakthrough bleeding for the first 3 to 6 months of therapy, the endometrium is usually then rendered atrophic and most patients become amenorrheic after 12 months.[144] This regimen often is most acceptable to women who are well past menopause and do not wish to resume cyclic menstrual bleeding.

Mastalgia may be decreased with a brief estrogen-free interval, although some bone benefits may be lost.

The goal of OHT should be to attain the minimum effective dosage for preventing future bone loss. Nevertheless, some patients tolerate only a suboptimal dose. Here, the physician may achieve a good result by increasing calcium supplementation (1500 mg/d), increasing the progestin to 10 mg of medroxyprogesterone daily or, possibly, adding a bisphosphonate.

Bisphosphonates

Bisphosphonates, forming a newer class of drugs used in the treatment of established osteoporosis, are a useful alternative to OHT in postmenopausal women with osteoporosis and may be useful in men and in patients with corticosteroid-induced osteoporosis.[145–149]

All bisphosphonates act on bone similarly; they bind permanently to mineralized bone surfaces and, by inhibiting osteoclastic activity, reduce the amount of bone degraded during the remodelling cycle. Thus, their main effect is the inhibition of bone resorption. Typically, bone mass increases most rapidly during the first year of treatment, probably because the temporary effect of bisphosphonates is to acutely slow down bone turnover. In the longer term, bone turnover appears to return to normal, but there is a continuing but slow increase in bone mass because the bone remodelling unit remains in positive balance.

Two bisphosphonates, etidronate and alendronate, have received regulatory approval in Canada for the treatment of patients with established osteoporosis: those with pre-existing fragility fractures and those who meet bone-density criteria for osteoporosis. Although the terms of the Health Protection Branch bone-density indications for the two drugs differ, the OSC Scientific Advisory Board recommends use of the WHO bone-density criteria for osteoporosis (a T score of –2.5 or lower) until more definitive studies are done. (See preceding section "Bone mineral density" and Fig. 2 for the management of osteoporosis when bone densitometry is accessible.) Bisphosphonates should not be given to younger, perimenopausal women with a low BMD measurement as long-term prophylaxis against osteoporosis.

Etidronate

Treatment with cyclical etidronate has produced significant increases (5%) in spinal bone density and a significant reduction in vertebral fracture rates among postmenopausal women with osteoporosis.[150–152] The patients enrolled in North American and European clinical trials of etidronate have now been followed up for as long as 7 years; the average increase in BMD over the lumbar spine approached 8%,[153] and fracture rates in the spine were reduced.[150,151] In the long term, small increases in BMD (about 3%) over the femoral neck were seen, but the studies were not of sufficient power to detect a reduction in hip fracture rates.

The regimen for treating osteoporosis with etidronate is to give 400 mg/d for 14 days every 3 months. Calcium supplementation, exclusive of dietary calcium, is not recommended during the 2-week cycle of etidronate but is given during the rest of the 3-month cycle. Etidronate is given cyclically because it may cause abnormalities of bone mineralization when used continuously. To avoid potential errors in taking cyclical etidronate, it has been packaged commercially as a blister pack of tablets containing one full 14-day cycle of etidronate followed by 76 days of a calcium supplement (500 mg of calcium carbonate), at an annual cost of approximately $150. Its intermittent dosage and relatively low cost make cyclical etidronate an acceptable treatment for many patients.

Alendronate

In a 2-year dose-finding study involving postmenopausal osteopenic women, 10 mg/d of alendronate increased the lumbar spine BMD by 7% and the femoral neck BMD by 5%.[154] In a 3-year controlled study of alendronate the rate of new vertebral fractures was 48% lower in the treatment group than in the placebo group.[155] Treatment with 10 mg of alendronate daily produced a progressive total increase in the BMD of about 9% in the spine and about 6% in the femoral neck.[154,155] At the World Congress of Osteoporosis in Amsterdam, May 17 to 20, 1996, preliminary data analysis was presented from the Fracture Intervention Trial, a randomized placebo-controlled study of alendronate involving over 2000 patients. A significant reduction in both the hip and vertebral fracture rates was reported in the treatment group. A full report of the study is expected to be published in the near future.

The effects of alendronate on bone mass and fracture reduction may occur somewhat more rapidly than those of cyclical etidronate, which is in keeping with the known differences in potency between the two drugs. Unlike etidronate, but in common with all other bisphosphonates so far evaluated, alendronate has no known propensity to inhibit mineralization in bone; therefore, it can safely be used daily.

Alendronate is prescribed at a continuous dose of 10 mg/d. The drug must be taken with a full glass of water at least 30 minutes before breakfast. This regimen costs

about $640 annually. Daily supplemental calcium is recommended[92] but should not be taken at the same time of day as alendronate. Generic calcium carbonate supplying 500 mg elemental calcium per day can be obtained for about $40 annually depending on the brand used.

Duration of treatment

About 80% to 85% of patients will maintain or increase their bone mass with bisphosphonate treatment. Therapy is continued for 5 to 7 years. Ongoing clinical trials will determine the appropriate duration of therapy. It is unclear whether all patients with low bone mass but no fractures should receive prolonged bisphosphonate therapy to prevent future fractures. Such patients who are over 70 years of age may be treated more conservatively with calcium and vitamin D supplements. Bisphosphonates may be considered for use in those who continue to lose bone mass or develop fractures.

Side effects

Side effects of bisphosphonates are minimal and include gastrointestinal symptoms, transient altered taste and, rarely, hypersensitivity leading to rashes. Apart from periodic monitoring of BMD to detect the occasional nonresponder, more intrusive monitoring seems unnecessary.

All bisphosphonates are poorly absorbed and must be taken on an empty stomach with no liquid other than water.

Other bisphosphonates

Other potent bisphosphonates (risedronate, tiludronate, clodronate, pamidronate and ibandronate) are currently undergoing clinical trials in osteoporosis.[156–158] Although it seems to be proven that bisphosphonates reduce the incidence of new vertebral fractures in postmenopausal women with established osteoporosis, information is needed on their ability to prevent hip fractures, which are the most serious medical, physical and social consequence of osteoporosis.

Other drugs not yet approved by the Health Protection Branch

The following drugs are being used by some physicians for the treatment of osteoporosis:

- Salmon calcitonin by subcutaneous injection in a dose of 50 to 100 MRC units daily: a nasal spray preparation has recently been approved in the United States.[159,160]
- Enteric-coated sodium fluoride, 20 to 40 mg/d orally.[161,162]
- Calcitriol (1,25-$(OH)_2$-vitamin D), 0.25 to 0.50 μg/d orally.[163–165]
- Cyclical clodronate, 400 mg/d for 1 month, followed by 2 months off: this cycle is then repeated.[156]

Each of these agents has been shown in some clinical trials to improve bone mass, but their efficacy in preventing fractures is not firmly established.

The use of these agents should be restricted to patients who fail to respond to conventional therapy. They should be prescribed only by physicians familiar with their associated toxic effects.

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Appendix 1: Recommendations for prescribing ovarian hormone therapy

Counselling guidelines for hormone replacement therapy (HRT)

1. **Educate the woman considering HRT**
   Women should have the opportunity to learn about the benefits and risks of HRT, consider the personal importance of these risks and benefits and participate with their practitioner in decision making.[1] Decision aids are useful[2] in preparing women for informed decision-making; from them women learn about osteoporosis, heart disease, risk factors, prevention strategies, and HRT benefits and risks. Decision aids also help women to weigh their own personal benefits and risks, for example, by completing a personal worksheet[3] on:
   (a) personal risks of osteoporosis, heart disease and breast cancer, hormonal history, other health problems;
   (b) personal values or importance attached to benefits and risks;
   (c) current health practices to promote healthy bones, heart and breasts;
   (d) questions for the practitioner;
   (e) preferences for decision participation; and
   (f) initial predisposition to taking long-term preventive HRT.

   The format can be self-administered via computer, video or audiotape and booklet, or practitioner-administered via a decision board.
2. **Facilitate decision-making at a follow-up visit**
   (a) *Assess potential benefits, risks and contraindications to HRT.* Verify risk for osteoporosis, coronary artery disease and breast cancer. Reinforce the woman's correct interpretations of her risk and re-align misconceptions or unrealistic expectations. Answer questions.
   (b) *Clarify the woman's personal value of the benefits and risks.* Ask the woman to state the importance she attaches to the benefits and risks. Acknowledge the woman's personal values.
   (c) *Choose an alternative.* Assist the woman to identify the factors that make the decision difficult. Consider the woman's potential benefits and risks, personal values and preferences for decision participation. Facilitate her decision to accept or decline HRT or to delay the decision and to consider other health promotion practices.

   For value-laden choices such as HRT, a decision is considered "effective" when it is informed, consistent with personal values, and carried out.[2]
   (d) *Plan decision implementation.* If the woman *declines* HRT, have her discuss plans regarding alternative health promotion practices.

   If the woman *accepts* HRT, identify the appropriate regimen tailored to the woman's health needs using the following prescription algorithm. *Because of the high dropout rate with HRT, it is essential that the woman is aware of potential side effects and management strategies of the selected regimen.* The woman may also discuss complementary health promotion practices.

   If the woman *delays* the decision, plan appropriate follow-up testing and discuss other health promotion practices.

Hormone replacement therapy prescription algorithm

1. **Screen for:**
   (a) *Absolute contraindications:*[4] active liver disease, breast cancer, active vascular thrombosis, history of unexplained vaginal bleeding.
   (b) *Pre-existing conditions requiring careful management:*[4] gall bladder or chronic liver disease; history of endometriosis, fibroids, history of uterine or ovarian cancer, fibrocystic breast disease; hypertension, hypertriglyceridemia, migraine, transient ischemic attacks, history of thromboembolism.
2. **Assess baseline parameters:**
   Weight; blood pressure; breast examination and mammogram; pelvic examination; fasting lipid levels; bone mineral density if at risk of bone loss[5] (family history, early surgical or natural menopause before age 40 to 45 years, history of amenorrhea or oligomenorrhea from hormone deficiency states, long-term use of glucocorticosteroids, high-dose thyroid replacement therapy, chemotherapy or heparin, primary hyperparathyroidism) or if decision about HRT would be affected by knowing bone density; endometrial surveillance if at high risk for endometrial cancer[4] (obesity, upper-body fat pattern, chronic anovulation or dysfunctional uterine bleeding, chronic liver disease).

Prescription algorithm developed by Elaine Jolly, MD, FRCSC, as part of the HRT Decision Aid. Counselling guidelines developed by the University of Ottawa HRT Decision Aid Group: Annette M. O'Connor, RN, PhD; Elaine Jolly, MD, FRCSC; Peter Tugwell, MD, MSc, FRCPC; Thomas J. Elmslie, MSc, MD, CCFP, FRCPC; George A. Wells, PhD; Ruth McPherson, PhD, MD, FRCPC; Andreas Laupacis, MD, FRCPC, MSc; Ian Graham, MA, PhD; Helen Bunn, RN, PhD

The Osteoporosis Society of Canada considers "ovarian hormone therapy" to be a more appropriate term than "hormone replacement therapy" (HRT); however, this appendix retains the term used by the Ottawa group.

Copies of the University of Ottawa HRT Decision Aid can be obtained from Annette M. O'Connor or Peter Tugwell, Ottawa Health Decision Centre, Clinical Epidemiology Unit, Ottawa Civic Hospital Loeb Research Institute, 1053 Carling Ave., Ottawa ON K1Y 4E9; tel 613 798-5555, ext. 6183, fax 613 761-5492.

3. **Prescribe according to uterine status:**
   (a) *Intact uterus*: use combination estrogen and progestin. Estrogen alone (unopposed) is *not recommended* because of increase in risk of endometrial cancer. If unopposed estrogen is used, there *must* be yearly endometrial monitoring (vaginal ultrasound and endometrial sampling) and follow-up of unscheduled vaginal bleeding.
   (b) *Hysterectomy*: use estrogen alone (unopposed).

ESTROGEN CHOICES

Drug	Suggested starting dose (2–3 mo)	Protective dose[4,5] (for osteoporosis and ?coronary artery disease)	Degree of trial evaluation	Lipid effects[4]	Estimated cost for 3-mo prescription*
ORAL					
Conjugated equine estrogen (Premarin)	0.3 mg	0.625 mg	++++ ++++	Raises HDL, lowers LDL, raises triglycerides	$12.03
Micronized estradiol-17ß (Estrace)	0.5 mg (½ tablet)	1–2 mg	+	As above	$21.44
Estrone sulfate (Ogen)	0.3 mg (½ tablet)	0.625 mg	+	As above	$17.20
Conjugated estrone sulfate (CES)		0.625 mg	Generic equivalent (no trials)	Assumed as above	$7.65
TRANSDERMAL					
Estradiol (Estraderm)	25 µg	50–100 µg	++	HDL neutral or elevated; lowers LDL and triglycerides	$65.01
VAGINAL†					
Conjugated equine estrogen (Premarin Vaginal Cream)		0.625 mg/g			$16.10
Estrone sulfate (Ortho Dienestrol Cream)		1.0 mg/g			$9.09
Estradiol-17ß (Estring)		2 mg (releases 7.5 µg/24 h)			$72.60

*April 1996 representative Ottawa pharmacy price, in Canadian dollars, at a protective dose for 90-day prescription; excludes dispensing fees, which range from $4 to $12 per drug refill.
†Vaginal preparations are not designed for systemic use but can be used locally for urogenital symptoms. However, with regular use of vaginal creams, there is some systemic absorption, and regular use will stimulate the endometrium. To protect the endometrium, add progestin at least once every 3 months. The silastic vaginal ring (Estring) does not require progestin because systemic absorption occurs only for a few hours after initial insertion. The ring remains in the upper portion of the vagina and is changed by the patient every 3 months.

Estrogen recommendations*

Drug Conjugated equine estrogen (Premarin) has been evaluated most and is affordable.
Synthetic estrogens (Estrace, Ogen, CES) are better tolerated, especially for women prone to headaches or allergies.
The transdermal patch (Estraderm) is recommended for women with upper gastrointestinal or liver disease, clotting problems or high triglyceride levels.[4]

Dose Use low starting dose for 2 to 3 months and titrate up to minimum protective dose; women with severe menopausal symptoms may be titrated faster up to levels that control symptoms; women who have been postmenopausal for more than 10 years may take longer to titrate to protective dose.

Timing Daily. However, if the woman has night sweats or nausea, try at bedtime; if she has pronounced menopausal symptoms, try twice daily, in divided doses.

Regimen Continuous estrogen; if mastalgia persists beyond 3 months, try cyclic regimen with pill-free interval of 4 to 5 days.

*Personal communication, Dr. Elaine Jolly.

PROGESTIN CHOICES

Drug	Daily dosage[6] (12–14 days/mo), mg*	Degree of trial evaluation	Lipid effects[4,7] (dose dependent)	Tolerance	Estimated cost for 3-mo prescription†
Medroxyprogesterone acetate (Provera)	2.5, 5, 10	++++	Lowers HDL, raises LDL, lowers triglycerides	++	$11.75
Micronized progesterone (Prometrium)	100, 200, 300, at bedtime	++	No effect on HDL or LDL, lowers triglycerides	++++, but causes somnolence	$39.44
Norethindrone (Micronor)	0.35, 0.70	+	Lowers HDL, raises LDL, lowers triglycerides	++	$20.15

*Halve dose if taken daily for 30 days.
†April 1996 representative Ottawa pharmacy price, in Canadian dollars, at protective dose for 90-day prescription; excludes dispensing fees, which range from $4 to $12 per drug refill.

Progestin recommendations*

Drug Medroxyprogesterone acetate (Provera) has been evaluated most in clinical trials and is more affordable.

Micronized progesterone (Prometrium) is a natural progesterone, is often better tolerated and has more beneficial lipid effects.[7]

Norethindrone (Micronor) may produce less bleeding and breast stimulation.

Dose Start with 10 mg of medroxyprogesterone or equivalent for women 0 to 3 years postmenopause, 5 mg or equivalent for women 4 to 10 years postmenopause and 2.5 mg or equivalent for women more than 10 years postmenopause. Then titrate down to dose that produces appropriate bleeding pattern; higher-dose estrogen requires higher-dose progestin.

Regimen Women up to 5 years postmenopause and obese older women are at higher risk for bleeding problems with HRT. A progesterone challenge for 10 to 14 days sheds the endometrium and decreases bleeding problems.[8] If a woman 1 year or more postmenopause has withdrawal bleeding from challenge, sample endometrium. Five days after completing progesterone challenge, start HRT regimen according to how recently menopause occurred: if menopause began 6 to 12 months previously use cyclic sequential (estrogen daily and progestin on days 1 to 12); if menopause began more than 1 year previously use continuous combined estrogen and progestin daily.

*Personal communication, Dr. Elaine Jolly.

Transdermal combination estrogen and progestin

Estracomb contains: Estraderm (estradiol, 50 µg/patch), 4 patches over first 2 weeks, and Estraderm (estradiol, 50 µg/patch) plus Neta (norethindrone, 0.25 µg/patch), 4 patches over last 2 weeks. The cost for 1 month is $68.15 (April 1996 Canadian dollars), excluding dispensing fee.

4. **Conduct follow-up surveillance**
   (a) Evaluate tolerance to HRT every 3 months until stable. Use menstrual calendar to monitor bleeding pattern and timing of HRT side effects. See "Troubleshooting" (next page) for strategies to manage side effects.
   (b) Conduct vaginal ultrasound for unscheduled bleeding (endometrial thickness of 4 mm or less is acceptable;[9] 5 to 8 mm needs repeat ultrasound and probable endometrial sample; more than 8 mm needs endometrial sample).
   (c) Arrange annual pelvic exam; mammogram every 1 to 2 years; annual breast exam; monthly breast self-exam; monitor changes in blood pressure, lipid levels and weight. Repeat bone densitometry in 2 years if baseline bone mineral density is low and to assess adequacy of osteoporosis treatment.[5]

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TROUBLESHOOTING[4]

Pre-existing conditions requiring careful management

History of endometriosis	If uterus is intact and pain is a problem, continuous low-dose progestin, with or without low-dose estrogen, theoretically may reduce the risk of recurrence.
Fibroids	Premenopausally, estrogen stimulates growth of fibroids; postmenopausally, the natural decline of estrogen shrinks fibroids. The use of postmenopausal estrogen is not contraindicated. If rapid growth occurs with estrogen, thorough investigation is needed. Submucosal fibroids may also be a cause of abnormal bleeding in women taking HRT and may require follow-up. Hysteroscopy is useful in diagnosing and treating submucous lesions.
Gall bladder disease	Estrogen is associated with 2-fold increase in risk of disease. Consider transdermal estrogen to avoid first pass through the liver if there is a history of gall bladder disease.
Gastrointestinal problems, nausea	Decrease dosage. Use transdermal route.
Hypertriglyceridemia	Oral estrogens increase triglyceride levels. Transdermal estrogen and all progestins lower triglyceride levels.
Hypertension	Trials show decreased hypertension with HRT.[4] The 1% to 2% of patients exhibiting increased blood pressure with oral estrogen tend to be those with excessive weight gain. If hypertension occurs with HRT, try transdermal route.
Chronic liver disease	Oral estrogen may not be metabolized well with liver dysfunction. Use transdermal route if liver function test results are stable.
Migraine headaches	Use low-dose and continuous regimens. Try synthetics (Estrace, Ogen, CES). Try transdermal route.
History of ovarian cancer	HRT use does not increase risk of ovarian cancer. After treatment of stage I cancer, HRT can be offered. The effect of HRT on rare nonepithelial ovarian cancer is unknown.
History of thromboembolism	No increased risk has been reported in trials.[4] Stop HRT if disease is active. For those with history of thromboembolism associated with pregnancy or oral contraceptives, try transdermal route, which theoretically poses less risk because hepatic clotting factors are not affected.
Transient ischemic attacks (TIAs)	Limited data are available. If there is a remote history, transdermal HRT is theoretically preferable to oral therapy. If the TIA is current or ongoing, HRT should be withheld.
History of uterine cancer	If the cancer was stage 1, grade 1, and there was no recurrence, estrogen can be used. There is no consensus on HRT if grade or stage of cancer was higher or if nonsurgical treatment was used.

HRT side effects*

Bleeding	Shedding the endometrium with a progesterone challenge test before starting HRT decreases troublesome bleeding.[4] Withdrawal bleeding associated with HRT use decreases with time. Unscheduled bleeding that persists for more than 6 months or new bleeding requires surveillance and sampling of endometrial tissue.
Depression	Progestin may be a contributing factor. Try lowering dose or switching to oral micronized progesterone (Prometrium). If depression persists after 12 weeks of HRT, use appropriate depression therapy and consider discontinuing HRT.
Headache	Headaches may be due to estrogen or progestin withdrawal. If so, try a continuous regimen. Headaches may also be due to either estrogen or progestin. Try lowering dose of either. Try a synthetic estrogen (Estrace, Ogen, CES). Try transdermal estrogen.
Mastalgia	Use lowest possible dose of estrogen and progestin. Cycle estrogen with pill-free interval of 4 to 5 days. Try norethindrone (Micronor) or oral micronized progestin (Prometrium).
Premenstrual syndrome (PMS)	PMS is associated with bleeding on cyclic therapy. Change to continuous therapy. Reduce progestin dose. Switch to oral micronized progestin (Prometrium). During progestin use, women should reduce salt, caffeine and refined carbohydrate intake and increase exercise.[10]
Skin irritation	Wave patch in the air to let alcohol dry before applying. Apply mild hydrocortisone cream (0.5%) to site of last patch application. If severe, change to oral route. A new matrix patch (Vivelle) is less irritating and is now available (37.5, 50, 75, 100 µg/patch).
Weight gain	Trials show as much weight gain in placebo groups as in those receiving HRT.[7]

*Use of a menstrual calendar to monitor bleeding patterns and side effects aids management.