>Statement of Objectives

After reading this lesson you will be able to:

1. Routinely discuss and make recommendations about management of factors associated with increased risk for osteopenia and osteoporosis.
2. Discuss the pathophysiology associated with progression of bone mineral density decrease.
3. Recommend non-pharmacological and pharmacological management strategies for managing osteoporosis

>Instructions

1. After carefully reading this lesson, study each question and select the one answer you believe to be correct. Circle the appropriate letter on the attached reply card.
2. Complete the card and mail, or fax to (416) 764-3937.
3. Your reply card will be marked and you will be advised of your results in a letter from Rogers Publishing.
4. To pass this lesson, a grade of 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies).
(Note: some provinces require individual pharmacists to notify them.)

>Disclosure

The author, expert reviewers and *Pharmacy Practice* magazine have each declared that there is no real or potential conflict of interest with the sponsor of this lesson.

CEP 1 CEU

Approved for 1 CE unit by the Canadian Council on Continuing Education in Pharmacy.

File # 323-1005

OSTEOPOROSIS — A PHARMACIST'S ACTION GUIDE FOR PREVENTION AND MANAGEMENT

by Tom Smiley, BScPhm, Pharm D

Carol, a married 52-year-old woman with two daughters in their early 20's, approaches you at the pharmacy counter. She is in good health and is asking for a refill of her levothyroxine 0.1 mg tablets that she has been taking for 10 years. Carol only sees her doctor once a year for a check-up. Carol tells you that someone told her she should start taking calcium supplements after the age of 50. She wants to know if this is true.

INTRODUCTION

Osteoporosis has been defined by the World Health Organization (WHO) as a "skeletal disease characterized by low bone mass and a micro-architectural deterioration of bone tissue with a resultant increase in fragility and risk of fracture."[1] The prevalence of osteoporosis increases with age. Carol is one of many who have discovered too late in life that calcium and vitamin D intake should be evaluated throughout life. By age 50, an estimated one in four women and one in eight men already have osteoporosis.[1] Table 3 outlines the Osteoporosis Society of Canada (OSC) recommendations for calcium and vitamin D intake according to age.

As our Canadian population ages, the prevalence of osteoporosis is expected to rise well above the current level of approximately 1.4 million cases.[1] Hip fractures associated with osteoporosis result in mortality within the first year in over 20% of cases.[2] Most women would be surprised to realize that the risk of death due to hip fracture in their lifetime exceeds risk of death resulting from breast cancer. In addition, people with osteoporosis may suffer reduced quality of life as a result of reduction or loss of mobility, lower self-esteem, decreased independence and disfigurement.[2] Pharmacists can make an impact on the morbidity and mortality associated with osteoporosis by proactively promoting osteoporosis prevention strategies that can be implemented throughout life, and by raising awareness about osteoporosis and its debilitating consequences. Offering recommendations for effective management of documented osteoporosis is also an important role for the pharmacist.

BONE REMODELLING AND EFFECTS ON BONE MINERAL DENSITY (BMD)

Bone tissue is constantly in a state of breaking down and rebuilding, a process known as "remodelling." Cells that absorb bone tissue are known as osteoclasts, while bone builders are known as osteoblasts. In childhood, bone formation exceeds bone absorption. This process allows growth to occur. During teenage years, increased hormone production stimulates new bone formation. After approximately age 35, bone mass peaks, with bone resorption beginning to exceed bone formation.[3] This causes a decline in bone mass at a rate of 0.3 to 0.5% per year in both men and women. A higher BMD at its peak (i.e., approximately age 35) therefore affords a head-start in the quest to maintain strong bones throughout life. With the onset of menopause, a decline in 17β-estradiol concentrations accelerates cortical bone (dense bone forming outer shell of skeleton) loss by 2 to 3% per year in women. The loss grad-

ually decreases over the next 8 to 10 years. Cancellous (also known as trabecular) bone (porous bone forming interior structures of bone) loss begins between the ages of 30 and 35. Over their lifetime, women may lose 50% of cancellous and 30% of cortical bone, whereas men may lose only 30% and 20% respectively.[3]

As suggested above by the WHO definition of osteoporosis, the risk for fragility fracture is a function of both bone density and bone architecture. Therefore, although a diagnosis of osteoporosis is made based on bone density measurements, one must keep in mind that it does not tell the whole story in terms of a patient's risk of fracture.[2] Fragility fracture refers to a fracture caused by injury that would not be sufficient to fracture normal bone (e.g., falling from standing height or less). Bone quality and relative fracture risk has been defined by WHO (and adopted by OSC) through BMD levels that are indicated by "T-scores." The T-score indicates the number of standard deviations that a BMD is above or below the mean for a normal young adult population of the same sex and race.[2] It is estimated that relative risk for fracture approximately doubles for each standard deviation of bone density below baseline.[4] Table 1 outlines definitions of bone quality and relative fracture risk according to T-scores.

TABLE 1 **Bone quality terminology according to relative risk of fragility fracture**

Normal BMD	T-score between 2.5 and -1.0
Osteopenia* (low BMD)	T-score between -1.0 and -2.5
Osteoporosis	T-score less than -2.5
Severe Osteoporosis	T-score lower than -2.5 and evidence of fragility fracture

**Radiologists often use the term "osteopenia" to describe bone that appears depleted of mineral content on plain X-ray film.*

WHO IS AT RISK FOR OSTEOPOROSIS?

You can think of a number of questions to ask Carol so that she may better understand her particular risk factors for osteoporosis and take preventive measures. You begin by telling her that the key predictors of fracture due to osteoporosis are low BMD, having a bone fracture before age 40 and increasing age. In order to help her better, you present Table 2 outlining major and minor risk factors and ask her to tick the ones that apply to her while you are getting her prescription ready.

Based on Table 2, the 2002 OSC Guidelines recommend that postmenopausal women and men over age 50 with at least one major or two minor risk factors should undergo BMD testing, as well as those with a personal history of fragility fracture after age 40 or nontraumatic vertebral compression deformities.[2] All people over the age of 65 should have a BMD test. People taking chronic oral glucocorticoid therapy (prednisone 7.5 mg daily or equivalent for more than 3 months) should usually be started on bisphosphonate therapy with BMD measurement and follow-up.[2]

Recent clinical studies associated with the use medroxyprogesterone injectable suspension for birth control and treatment of endometriosis indicate that the drug causes significant BMD decline that is related to duration of use. This information should be part of the risk-benefit assessment for any woman considering treatment with this agent.

Bone Mineral Density Measurement Options

Measurement of BMD with Dual energy X-ray absorptiometry (DXA) at the spine and hips is the gold standard for risk assessment at these most common sites for osteoporotic fractures.[5] DXA is a very accurate tool for diagnosing osteoporosis, and also for following up response to therapy after one or two years of treatment.

If DXA is not available for risk assessment, then quantitative ultrasound (QUS) is an alternative. This technique is not precise enough to be used for follow-up. Calcaneal ultrasound (at the heel) can be used to predict risk of fracture at the wrist and spine, but is not as reliable as direct measurement, such as DXA, for assessing relative risk of fracture at the hip.[5] When used on patient clinic days, this form of risk assessment should be used only to identify those patients who would benefit from further follow-up from their physician.

Biochemical markers allow for evaluation of bone turnover rates over time. With further study, they could have an important role in the future for monitoring response to antiresorptive therapy. Bone formation markers include serum osteocalcin, bone-specific alkaline phosphatase and procollagen I carboxyterminal propeptide. Markers of bone resorption include urinary hydroxyproline, urinary pyridonoline, urinary deoxypyridinoline, and collagen Type I cross-linked N telopeptide and collagen Type I cross-linked C telopeptide.

LIFESTYLE MANAGEMENT FOR PREVENTION OF OSTEOPOROSIS

Calcium and Vitamin D

Carol's prescription is ready and she hands you the questionnaire (see Table 2) with only one box ticked. Carol admits that she does not consume much milk, cheese or yogurt. Upon further discussion, and with

FACULTY OSTEOPOROSIS — A PHARMACIST'S ACTION GUIDE FOR PREVENTION AND MANAGEMENT

ABOUT THE AUTHOR

Tom Smiley is a pharmacist consultant with Pharmavision Health Consulting who remains active in community practice at Dell Pharmacy in Brantford, Ont. In addition to his clinical experience with patients over the past 25 years, Tom has developed and presented many CE lessons and workshops for pharmacists in the area of women's health and osteoporosis. He has also written many patient brochures and website postings on these topics. Tom currently sits on the executive committee of the Ontario Pharmacists Association board of directors and was recently appointed to the Family Health Team Action Group by the Ontario Ministry of Health.

REVIEWERS

All lessons are reviewed by pharmacists for accuracy, currency and relevance to current pharmacy practice.

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ROGERS

TABLE 2 Risk factors for osteoporosis indicating need for assessment

Please put a checkmark in the appropriate box if the following statements apply to you

Major Risk Factors	Minor Risk Factors
❒ I am older than 65 years ❒ I have a compression fracture in a vertebrae or have had one in the past ❒ I had a bone fracture caused by a minor injury after age 40 ❒ One or both of my parents broke a bone after a minor bump or fall ❒ I have taken oral steroid medications (e.g., prednisone) for more than 3 months ❒ I have trouble absorbing minerals and vitamins such as calcium and vitamin D (as a result of a condition such as celiac disease or Crohn's disease) ❒ I have primary hyperparathyroidism (a condition of the parathyroid glands) ❒ I fall easily ❒ I have been diagnosed with low bone mineral density (known as osteopenia) by a radiologist who took an X-ray. ❒ I am a man and have a condition called hypogonadism (low testosterone levels) ❒ I am a woman and had an early menopause (before age 45)	❒ I have rheumatoid arthritis ❒ I have a past history of overactive thyroid (known as hyperthyroidism) ❒ I use medications to prevent seizures (known as anticonvulsants) ❒ I don't eat many foods with calcium in them (e.g., milk, cheese) ❒ I am a smoker ❒ I consume more than 2 drinks of alcohol daily. If yes, how many? _____ ❒ I drink more than 4 cups of coffee daily. If yes, how many? _____ ❒ I weigh less than 57 kg (125 pounds) ❒ I have lost more than 3 cm in height since age 25. ❒ I use chronic heparin treatment

TABLE 3 Recommended intake of calcium and vitamin D according to 2002 OSC guidelines[2]

Population Group	Age	Recommended daily calcium intake	Recommended daily vitamin D intake
Prepubertal children	4-8 yrs	800 mg	N/A
Adolescents	9-18 yrs	1,300 mg	N/A
Women	19-50 yrs or Pregnant or lactating (≥18 yrs)	1,000 mg	400 IU
	Post menopausal or >50 yrs	1,500 mg	800 IU
Men	19-50 yrs	1,000 mg	400 IU
	>50 years	1,500 mg	800 IU

the aid of the calcium calculator found on the Osteoporosis Society of Canada website (www.osteoporosis.ca), you determine that Carol consumes approximately 500 mg elemental calcium daily. Carol mentions that both her daughters consume approximately the same amount of calcium daily. Should they be taking supplements?

Carol is a typical concerned mother, thinking of her family before herself. In fact, the OSC recommends that women between 19 and 50 years of age consume 1,000 mg of elemental calcium daily along with 400 IU vitamin D, while women over 50 years of age (or postmenopausal) should consume 1,500 mg calcium daily with 800 IU vitamin D (see Table 3). We would first suggest that Carol and her daughters increase their intake of calcium and vitamin D through foods. If this cannot be achieved, then calcium and vitamin D supplementation should be suggested.

As per Table 3, Carol should take 1,500 mg supplemental calcium and 800 IU vitamin D while her daughters should take 1,000 mg supplemental calcium and 400 IU vitamin D.

It is important to note that patients taking cyclical etidronate therapy packaged with one elemental calcium 500 mg tablet often are not aware that they should ingest a total of 1,500 mg elemental calcium from all sources, every day.

Pharmacists need to ensure that patients understand the importance of obtaining the recommended amounts of elemental calcium and vitamin D through diet and supplement (if necessary). The choice of calcium supplements needs to be based only on the amount of elemental calcium supplied as there is no evidence to support the benefit of adding magnesium, or obtaining the calcium from particular sources (e.g., coral).

Additional Lifestyle Prevention Recommendations

The following are additional modifiable lifestyle recommendations for preserving bone mass and preventing fractures:[2]

- Reduce excessive caffeine intake. (Less than 4 cups of coffee per day.)
- Quit smoking - Female smokers reach menopause at an earlier age, on average, than non-smokers (due to increased metabolism of estrogen).[6]
- Limit alcohol intake to one to two standard drinks daily. Risk of falls and fractures rises as alcohol intake increases.
- Maintain adequate protein intake.
- Avoid excess dietary sodium (i.e. consume less than 2,100 mg or 90 mmol daily). Processed foods are the most common source of excess sodium.
- Chronic exercise (especially impact exercises) leads to an improvement in BMD in boys and girls as well as men and premenopausal women. In postmenopausal women, impact exercise may reduce rate of bone loss or lead to some bone gain in the short term.
- Excess physical activity (e.g., long-distance running) may be detrimental to BMD.
- Exercise programs individually tailored and including muscle strengthening, balance training and walking over one year are effective in reducing falls and injuries that can lead to fragility fracture (general group exercise programs have not been shown to be effective in reducing falls).
- Fall prevention strategies include removing clutter and obstacles from living area, having regular vision tests, use of walking aids and protectors where appropriate, assessment of drugs such as benzodiazepines, narcotics or anticholinergics that may increase risk for falls (including those that may cause orthostatic hypotension).

PHARMACOLOGICAL TREATMENTS FOR PREVENTION AND MANAGEMENT OF OSTEOPOROSIS

UNTIL THE INTRODUCTION OF TERIPARATIDE TO the Canadian market, all available pharmacologic agents used for prevention and management of osteoporosis were antiresorptive in nature. These agents reduce fracture risk by slowing down bone loss through inhibition of osteoclast activity, while evidence suggests that teriparatide may have an impact on laying down of bone through stimulation of osteoblasts.

Table 4 outlines the role of currently available therapies in the treatment of osteoporosis according to the 2002 OSC guidelines.

Table 5 overviews recommended doses and available dosage forms for treatments recommended for prevention and management of osteoporosis.

Bisphosphonates

Bisphosphonates are non-hormonal and have been shown through clinical trial to improve BMD and reduce risk for fragility fracture.

- Three different bisphosphonates available in Canada (etidronate, alendronate and risedronate) differ with respect to potency, toxicity and dosing regimen.
- Etidronate is non-nitrogen-containing, while alendronate and risedronate are nitrogen-containing and more potent. No head-to-head trials currently exist to compare alendronate and risedronate in terms of fracture risk reduction. However, alendronate and risedronate are the only two bisphosphonates with clinical trial data supporting significant risk reduction for hip fractures.
- Bisphosphonates are poorly absorbed (1 to 5%) and must be taken on an empty stomach (see Table 5 for dosing regimens).
- Bisphosphonates should not be taken within one to two hours of any products high in calcium or mineral supplements such as iron or magnesium.
- Once-weekly bisphosphonates (i.e., alendronate and risedronate) have been shown to be as effective as their once-daily counterparts in improving BMD at the spine and hip. It is assumed that they are, therefore, also as beneficial in reducing fracture risk.
- Bisphosphonates should not be used by pregnant or lactating women, as safety has not been established.
- Women of child-bearing potential should use good birth control methods. If pregnancy is considered, the bisphosphonate should be discontinued and lifestyle modifications (e.g., calcium intake, physical activity) discussed.
- The most common side effects with bisphosphonates are gastrointestinal in nature and are usually self-limiting.
- INR should be monitored in any patient using warfarin and adding or withdrawing bisphosphonate therapy as increases in prothrombin time have been reported with etidronate.
- Bisphosphonates should not be used in patients with severe kidney disease (creatinine clearance <35 mL/minute)

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene is currently the only selective estrogen receptor modulator (SERM) available in Canada. The following are some important points to consider when assessing appropriateness of recommending this therapy:

- Demonstrates estrogen-agonist effects in some tissues and estrogen-antagonistic effects in others.
- Positive effects on BMD and lipid metabolism without risks of HRT on the breast and uterus.
- Vasodilation and leg cramps are common side effects. Raloxifene may promote or aggravate hot flushes associated with perimenopause and menopause.
- Increases risk for thromboembolic

TABLE 4 **Osteoporosis prevention and management recommendations (Adapted from 2002 OSC guidelines)**

Patient Circumstances and Indication for Treatment	Treatment
Postmenopausal women with low bone density (i.e., preventative therapy)	***First-Choice*** Alendronate Etidronate Raloxifene Risedronate HRT (in women with vasomotor symptoms - always evaluate risk vs. benefit) ***Second-Choice*** Ipriflavone
Treatment for post-menopausal women with osteoporosis	***First-Choice (with or without fragility fracture and no vasomotor symptoms)*** Alendronate Raloxifene Risedronate ***Second-Choice (with or without fragility fracture and no vasomotor symptoms)*** HRT (always evaluate for risk-benefit) Nasal calcitonin (in women at least 5 years postmenopausal) ***First-Choice (without fragility fracture and with vasomotor symptoms)*** HRT (always evaluate risk-benefit) ***Second-Choice (without fragility fracture and with vasomotor symptoms)*** Alendronate Risedronate Raloxifene Nasal calcitonin (in women at least 5 years postmenopausal)
Preventive therapy in women who experience menopause before age 45.	***First-Choice*** HRT (always evaluate for risk-benefit)
Non-pregnant premenopausal women with osteoporosis	Nasal calcitonin may be considered
Prevention or treatment of glucocorticoid-induced osteoporosis in men and women requiring prolonged glucocorticoid therapy (>3 months with prednisone 7.5 mg or greater or equivalent)	Alendronate Risedronate Etidronate
Treatment for men with low bone mass or osteoporosis	***First-Choice*** Alendronate Etidronate ***Second-Line*** Nasal calcitonin
Pain associated with acute vertebral fractures in men or women	***First-Choice*** Nasal or parenteral calcitonin

**Note - Parathyroid hormone derivative (teriparatide) was not available at time of publication of 2002 OSC Guidelines. It is indicated for use in postmenopausal women with severe osteoporosis or in men with primary or hypogonadal severe osteoporosis who are at high risk of fracture or who have failed or are intolerant to previous osteoporosis therapy.*

TABLE 5 *Overview of pharmacologic interventions in prevention and treatment of osteoporosis*

Drug	Dosage	Additional Information
Bisphosphonates		
Etidronate/calcium carbonate	400 mg etidronate daily for 2 weeks, then 500 mg calcium daily	Dose taken in 3-month cycles. Etidronate: take on empty stomach. (Supplemental calcium required to meet daily calcium requirements)
Alendronate	5 mg daily for prevention 10 mg daily or 70 mg weekly for treatment	Alendronate: take on empty stomach before first food or drink of day, with a full glass of water and remain upright for at least 30 minutes.
Risedronate	5 mg daily or 35 mg weekly for prevention or treatment	Risedronate: take on empty stomach at least 30 minutes from food or drink and remain upright for at least 30 minutes.
Hormone Replacement Therapy—Estrogen Products*		
Oral conjugated estrogens	0.3, 0.625, 0.9, 1.25 mg available; recommended dose 0.625 mg daily.	HRT is 1st line for prevention and 2nd line for treatment in women with vasomotor symptoms only (always evaluate risk-benefit)
Oral estropipate	0.625, 1.25, 2.5 mg available (0.625 mg ~ 0.625 mg conjugated estrogen)	Natural estrogen, less potent than estradiol. Cyclical therapy.
Oral micronized estradiol-17β	0.5, 1, 2 mg available (1 mg ~ 0.625 mg conjugated estrogen)	Micronization reduces first pass in liver
Transdermal 17β estradiol	Available in 25, 37.5, 50, 75, 100 mcg strengths depending on brand (applied twice weekly) (50 mcg ~ 0.625 mg oral conjugated estrogen daily. Matrix patch (Climara®) for once weekly application available in 50 or 100 mcg strength	50 mcg = 0.625 mg oral conjugated estrogen. Transdermal products bypass the liver. Choice in liver/gallbladder disease, triglyceridemia, history of thromboembolism.
Topical estrogen gel Estrogen vaginal ring	Not indicated for osteoporosis	
Hormone Replacement Therapy—Progestin products*		
Medroxyprogesterone acetate	2.5 to 5 mg daily continuously or 5 to 10 mg daily for 10 to 14 days of each cycle.	Methyl group reduces first-pass metabolism.
Micronized progesterone	100 to 300 mg daily , usually for last 14 days of estrogen treatment per cycle	Contains peanut oil. Do not use if peanut allergy present.
Hormone Replacement Therapy—Combination estrogen-progestin products		
Estradiol-norethindrone patch	Estradiol 50 - 2 patches/week for 2 weeks, followed by norethindrone 140 or 250/estradiol 50 combined in the same patch - 2 patches/ week for 2 weeks. Or continuous therapy with norethindrone 140 or 250/estradiol 50 patches (1 patch twice weekly)	This product provides continuous estrogen and sequential progestin therapy for women with intact uterus.
Ethinyl estradiol - norethindrone acetate oral tablets	Ethinyl estradiol 5 mg plus norethindrone acetate 1 mg/tablet taken on daily basis	For women with intact uterus.
Selective Estrogen Receptor Modulators (SERMs)		
Raloxifene	60 mg daily without regard to food.	Agonist at bone and lipids. Antagonist at breast and uterus.
Calcitonin		
Calcitonin salmon nasal spray	200 IU intranasally daily	Alternate nostrils daily. Indicated for women at least 5 years postmenopausal with low bone mass relative to healthy premenopausal females.
Parathyroid Hormone Derivative		
Teriparatide subcutaneous injection	20 mcg daily, subcutaneous injection	Available in prefilled pen device. Pen delivers 20 mcg teriparatide per dose and must be discarded after 28 days.

Note: At the time of writing of this CE module, a new once-monthly bisphosphonate (ibandronate) was available in the U.S. but not in Canada.

events by about 3 times (similar to estrogen).[7] In one large study, approximately 1% of treated patients suffered a thromboembolic event. Raloxifene should be discontinued 72 hours prior to surgery, and during prolonged immobilization (e.g., after surgery).
- Should not be used in premenopausal and pregnant or lactating women.
- Absorption is significantly reduced by co-administration of cholestyramine.
- INR should be monitored in patients using warfarin when raloxifene is added or withdrawn as increased prothrombin times have been noted with raloxifene use.
- Research suggests that raloxifene protects against breast cancer and cardiovascular disease.[8,9]

Hormone Replacement Therapy (HRT)

The Women's Health Initiative was the first study to show through a randomized controlled trial that HRT significantly reduces risk for fragility fracture in postmenopausal women with osteoporosis.[10]
- The Women's Health Initiative (WHI) results for women with intact uterus suggested that compared to placebo, the group of women taking HRT (conjugated estrogens 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily) for more than 4 years experienced (for each 10,000 women per year):[10]
  - 8 more cases of breast cancer
  - 7 more cases of coronary heart disease
  - 8 more cases of stroke
  - 6 fewer cases of colorectal cancer
  - 5 fewer cases of hip fracture
- In the arm of the WHI trial for women without intact uterus it was found that conjugated estrogens 0.625 mg daily did non affect coronary heart disease rates, but did increase risk of stroke in older women (12 more cases per 10,000 women per year). Risk of hip fracture was decreased by 6 cases per 10,000 women per year.[11]
- Therefore, taking into account evidence from the two arms of the WHI trial, HRT is indicated for treatment only for those women who are postmenopausal and experiencing moderate to severe vasomotor symptoms, and as prevention for women who have had early menopause (before age 45). (See Table 4.)
- It is recommended that reassessment of use of HRT be undertaken once yearly and especially after 4 years of use and discussion with patient about overall risks versus benefits take place.[12]
- For women with intact uterus, combination HRT used on a continuous basis avoids withdrawal bleeding. Breakthrough bleeding occurs in approximately 40% of users during first 3 to 6 months of treatment. After one year, 75 to 87% are amenorrheic.[13]
- Cyclic estrogen and progestin - most well studied is estrogen taken days 1 to 25 and progestin days 15 to 25.
- Continuous estrogen with progestin taken days 1 to 12 or 1 to 14 is another regimen used. Maximum protection against endometrial hyperplasia or cancer is afforded by using progestin 12 to 14 days each month.[13]
- Currently available dosage forms for estrogen include oral conjugated estrogen, estrogen gel 2.5 mg (1.5 mg estradiol 17β daily) and transdermal estradiol 50 mcg twice weekly. Dosage form considerations include:[13]
  - Topical therapy avoids first pass through liver and may reduce risk for liver and gallbladder disease.
  - Topical preparations increase levels of triglycerides only marginally compared to oral estrogen.
  - Oral estrogen has a more positive effect on LDL and HDL profiles compared to topical preparations.
  - Nausea is more common with oral therapy while skin allergy is possible with transdermal patch.
  - Adherence to medication regimen may be improved for some patients with use of twice-weekly or once weekly patch.
- Contraindications to estrogen include:[13]
  - Unexplained vaginal bleeding prior to use
  - Acute liver disease
  - Active thromboembolic disease
  - Known or suspected carcinoma of the breast.
- Side effects (most are temporary) occur in about 10% of women taking estrogen and include nausea, vomiting, loss of appetite, bloating, headache and mastalgia (breast tenderness). Reduction in dose may help in some cases. Starting with lower dose of estrogen and increasing to targeted dose may help prevent side effects.[13]
- Contraindications to use of progestins include:[13]
  - Known or suspected carcinoma of the breast
  - Undiagnosed vaginal bleeding
  - Pregnancy
- Side effects of progestin may include mastalgia, alterations in mood and bloating. If side effects occur with a cyclic progestin regimen, switching to a continuous combined regimen may resolve the issue.

Calcitonin

Calcitonin is a naturally-occurring peptide hormone that inhibits bone resorption through its effect on osteoclasts. Salmon calcitonin is found in pharmaceutical products as it is more potent than human calcitonin.
- Calcitonin in the treatment of osteoporosis is only officially indicated for women who are more than 5 years postmenopausal (only age group for which evidence exists).[14]
- Salmon calcitonin nasal spray is associated with fewer side effects than injectable calcitonin and is the preferred dosage form for administration of this drug.
- Recommended dose of salmon calcitonin nasal spray is 200 IU (one spray) in one nostril per day, alternating nostrils with each dose. Patients should be instructed to prime the nasal pump before using it for the first time.
- Unopened bottles of calcitonin nasal spray should be refrigerated. Once opened the spray is stable at room temperature for 4 weeks.
- Although not an official indication, the 2002 OSC guidelines suggest that nasal calcitonin may be considered for treatment of osteoporosis in nonpregnant premenopausal women, and in men with osteoporosis.[2]
- Injectable calcitonin is not officially indicated for osteoporosis management, but is commonly used for pain (as is nasal calcitonin) associated with vertebral fractures due to its efficacy in these circumstances. It is available in 1 mL dosage units of 200 IU/mL, and 100 IU/mL.
  - Most studies have used injectable calcitonin 100 IU units once daily for pain due to vertebral fractures.
  - One head-to-head study suggested equivalence of injectable calcitonin 100 IU once daily and intranasal calcitonin 200 IU once daily for relief of pain due to vertebral fracture.

Teriparatide

Teriparatide is derived from parathyroid hormone (PTH) and consists of the first 34 of 84 amino acids of PTH, which is the biologically active portion of the molecule.[15] It is the first medication that appears to stimulate osteoblasts (instead of inhibiting osteoclasts) to encourage bone formation.
- Teriparatide is approved for treatment of postmenopausal women with severe osteoporosis who are at high risk for fracture or who have failed or are intolerant to other therapies. It is also indicated for increasing bone mass in men with primary or hypogonadal severe osteoporosis who have failed or who are intolerant to other treatments.[15]
- Teriparatide has been found in clinical trials to reduce the incidence of new vertebral fractures by 65% relative to placebo and new non-vertebral fractures by 55%.[15]
- Significant reductions in height loss and incidence of new or worsening back pain were noted in the teriparatide treatment groups.[15]
- Teriparatide is generally well-tolerated with most common side effects being nausea, dizziness and leg cramps. Allergic reactions have infrequently

been experienced shortly after injection. Symptoms include acute dyspnea, orofacial edema, generalized urticaria and chest pain. Local injection site reactions may also occur. Rare reports of orthostatic hypotension have also been reported. These events usually occur within the first 4 hours of dosing and resolve within a few minutes to a few hours.[15]

- Contraindications to use of teriparatide include severe renal impairment, primary hyperparathyroidism, pre-existing hypercalcemia, Paget's disease, unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy involving the skeleton and bone metastases, or a history of skeletal malignancies.[15]
- Due to a concern over incidence of osteosarcoma found in rats (but not in humans to date) with use of teriparatide, the current recommended maximum lifetime exposure for the drug is 18 months.
- Teriparatide is available as a 28-day pre-filled subcutaneous injection pen. The recommended dose is 20 mcg daily. The pen should be discarded after 28 days regardless of whether there is still solution in the pen.[15]

Ipriflavone

Ipriflavone is available without a prescription and is recognized as a second-line alternative for prevention of osteoporosis by the 2002 OSC guidelines. (See Table 4.) There are currently no good quality studies comparing ipriflavone to other osteoporosis therapies. The following points originate from the 2002 OSC guidelines:[2]

- Ipriflavone 200 mg 3 times daily has been found effective in maintaining BMD in the spine in postmenopausal women, but evidence does not exist to suggest that it prevents fractures in postmenopausal women with osteoporosis.
- Patients taking this medication should be monitored closely as long-term effects are uncertain. In one study, 29 of 238 women taking the medication exhibited severe lymphopenia.
- Ipriflavone is a cytchrome P450 2C9 inhibitor and may interact with theophylline, phenytoin, warfarin, nifedipine and caffeine.

PHARMACISTS AND OSTEOPOROSIS INTERVENTION

THERE ARE MANY OPPORTUNITIES FOR pharmacists to intervene with patients at risk for osteoporosis or requiring osteoporosis management.

- Create awareness about the need for appropriate calcium and vitamin D exposure throughout life and inquire about intake at all ages. Post the daily requirements according to age to stimulate questions and discussion with your patients.
- Refer patients who meet indications for BMD assessment to their doctor. Write a note to the physician outlining the risk factors that qualify the patient for the assessment. You may want to create a risk factor table similar to Table 2 and check off the appropriate boxes.
- Recommend healthy lifestyles to promote stronger bones.
- Help your patients make informed choices about osteoporosis prevention and management by referring to 2002 OSC guidelines and recommended resources. These guidelines are available online at www.osteoporosis.ca
- Consider holding "bone health" clinics with scheduled appointments to discuss individual risks for osteoporosis. Be sure to have ample literature available on recommendations for lifestyle (including calcium and vitamin D intake as well as physical activity). Heel ultrasound tests are popular for these types of clinics. Ensure that clients understand that these tests are not diagnostic, but will give them a better sense of whether they should visit their doctor about this issue.
- Monitor patients who are using medications for osteoporosis. Assess tolerance to medications, appropriate dosing and potential drug interactions. Ensure patients know exactly how to take their medications and why they are important. Ensure patients understand the ongoing role of calcium and vitamin D in strong bone health and when to take these medications in relation to bisphosphonates (for example).

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QUESTIONS

Case #1: *Judy is a healthy 30-year-old mother of one. She is active and takes a multiple vitamin that includes 200 mg elemental calcium and 400 IU vitamin D daily. Using the calcium calculator, you estimate she gets 300 mg elemental calcium through her diet.*

1. Why should Judy be concerned about calcium and vitamin D intake at this time of her life?

a) Approximately one in four women have osteoporosis by age 35.
b) Bone mass usually starts to decline at age 25.
c) Judy does not need to be concerned because osteoporosis is not an issue until the menopausal years.
d) A higher BMD early in life may afford protection in later years.

2. Which is the most appropriate recommendation for Judy (according to 2002 OSC guidelines) in her present circumstance?

a) Add 1,000 mg calcium and 400 IU vitamin D through diet or as supplements.
b) Add 500 mg calcium daily through diet or as a supplement.
c) Add 400 IU vitamin D daily through diet or as a supplement.
d) Judy does not require a supplement as long as she remains active.

3. Judy tells you her 80-year-old grandmother has osteoporosis and had a hip fracture recently. In what percentage of

cases do hip fractures result in mortality?
a) 10% mortality within the first 5 years after fracture
b) 20% mortality within the first year of fracture
c) 30% mortality within the first 6 months of fracture
d) 30% mortality within the first year of fracture

4. If Judy is diagnosed at age 40 (pre-menopausal) with osteoporosis, which is the most appropriate recommendation for therapy?
a) Alendronate
b) Raloxifene
c) HRT
d) Nasal calcitonin

Case #2: *Bessie is a 70-year-old woman who smokes 10 cigarettes daily and has had a recent compression fracture in one of her vertebrae that she thinks was due to a minor bump. Bessie does not suffer from vasomotor symptoms. She hands you a prescription and you notice that the doctor has written T-score = -2.7. Bessie is currently taking hydrochlorothiazide 25 mg daily for blood pressure, diltiazem 240 mg CD for blood pressure and atrial fibrillation control, and warfarin for clot prevention secondary to atrial fibrillation.*

5. Which term best defines Bessie's present condition?
a) Mild osteoporosis
b) Postmenopausal osteoporosis
c) Osteoporosis
d) Severe osteoporosis

6. What is a major risk factor for osteoporosis in Bessie's case?
a) Smoking
b) Older than 65 years
c) Compression fracture in vertebrae
d) b and c

7. How quickly does cortical bone loss decline with onset of menopause in women?
a) 0.3-0.5% per year
b) 1-2% per year
c) 2-3% per year
d) 3-4% per year

8. Bessie had not been sent for a BMD test before this incident. Which circumstance should have prompted a referral for this test (according to 2002 OSC guidelines)?
a) Age 45, premenopausal, and consuming 3 standard drinks of alcohol or 4 cups of coffee daily.
b) 55 years old, postmenopausal and falls easily
c) 60 years old and smokes
d) 62 years old and low calcium intake

9. Which BMD measurement tools would be appropriate for BMD measurement intended to diagnose osteoporosis status?
a) Dual energy X-ray absorptiometry or biochemical markers
b) Biochemical markers or quantitative ultrasound
c) Dual energy X-ray absorptiometry only
d) Quantitative ultrasound only

10. How much total elemental calcium intake and vitamin D (from all sources) should Bessie be receiving?
a) 1,500 mg calcium and 800 IU vitamin D
b) 1,200 mg calcium and 400 IU vitamin D
c) 1,000 mg calcium and 800 IU vitamin D
d) 1,000 mg calcium and 400 IU vitamin D

11. What effects could smoking have on Bessie's BMD?
a) Toxic chemicals of smoke break down bone.
b) Nicotine reduces calcium absorption.
c) Smoking may cause increased metabolism of estrogen.
d) Smoking inhibits calcium absorption.

12. Which medication is NOT a first-choice recommendation for Bessie in her current circumstance?
a) Alendronate
b) Risedronate
c) Etidronate
d) Raloxifene

13. Which class of drugs would warrant closer INR monitoring for Bessie if prescribed?
a) Supplemental calcium
b) Calcitonin
c) Parathyroid hormone derivative
d) Bisphosphonates

14. Under what circumstances would teriparatide be indicated?
a) Any woman with severe osteoporosis.
b) Any woman with severe osteoporosis who has failed other therapies.
c) Any woman with severe osteoporosis who does not want to take raloxifene.
d) b or c

Case #3: *Rebecca is a 51-year-old female executive who has not had a menstrual period for one year and suffers from moderate to severe vasomotor symptoms (e.g., hot sweats). She has never had a fragility fracture. She currently takes amlodipine 5 mg daily for blood pressure control. A recent BMD indicates a T-score of -2.7.*

15. Which medication would be indicated as second-line treatment of osteoporosis in Rebecca's circumstance?
a) Risedronate
b) Ipriflavone
c) Nasal calcitonin
d) Etidronate

16. If Rebecca decides HRT is a good choice for her, which combination of estrogen and progestin would afford greatest protection against endometrial hyperplasia?
a) Continuous estrogen with progestin taken days 1-12.
b) Continuous estrogen with continuous progestin.
c) Cyclic estrogen on days 1-25 and progestin days 15-25.
d) All regimens have been found equally effective in protecting against endometrial hyperplasia.

17. In explaining risk of breast cancer with HRT use to Rebecca, how might you put it into perspective?
a) There is approximately a 10% chance per year that breast cancer will occur with use of HRT.
b) There are approximately 8 extra cases of breast cancer per 10,000 women per year after 4 years of HRT use compared to placebo.
c) There is approximately a 5% chance per year the breast cancer will occur with use of HRT.
d) There are approximately 15 extra cases of breast cancer per 10,000 women per year after 4 years of HRT use compared to placebo.

18. What is the advantage of using topical estrogen therapy compared to oral therapy?
a) Topical therapy avoids first pass to the liver and may reduce risk for liver and gallbladder disease.
b) Topical therapy has a more positive effect on HDL and LDL profiles.
c) Topical therapy does not require progestin combination in women with intact uterus.
d) a and c

19. Which osteoporosis medication would be most likely to cause worsening of Rebecca's vasomotor symptoms?
a) Nasal calcitonin
b) Raloxifene
c) Alendronate
d) Calcium plus vitamin D

20. Which therapy would be most appropriate for osteoporosis prevention in a woman taking prednisone 10 mg daily chronically for asthma treatment?
a) Bisphosphonate
b) Teriparatide
c) Raloxifene
d) HRT

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Feedback on this CE lesson
1. Do you now better understand how to care for patients with osteoporosis? ❑ Yes ❑ No
2. Was the information in this lesson relevant to your practice? ❑ Yes ❑ No
3. Will you be able to incorporate the information from this lesson into your practice? ❑ Yes ❑ No
4. Was the information in this lesson... ❑ Too basic ❑ Appropriate ❑ Too Difficult
5. Do you feel this lesson met its stated learning objectives? ❑ Yes ❑ No
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