

Osteoporosis

Pharmacological Options and Considerations
for Prevention and Management



Table of Contents

■ Osteoporosis Management Summary	2
■ Fracture Risk Assessment	8
■ Nonpharmacologic Choices	14
■ Calcium and Vitamin D	18
■ Pharmacological Options	24
Bisphosphonates	28
Hormone Therapy	37
Raloxifene	49
Denosumab	51
Teriparatide	54
■ References	56
■ CE Questions	60
■ Notes	66

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Disclosure: The author has no conflict of interest to disclose. One of the expert reviewers wishes to disclose that he has been a paid speaker, member of an advisory board, and received funds from a commercial entity other than this one.

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Osteoporosis Management Summary

Osteoporosis Management Summary

Learning Objectives:

After consulting this counselling guide, pharmacists will be better able to:

1. Assess osteoporosis risk of patients.
2. Individualize prevention and treatment for osteoporosis according to calculated risk and patient assessment.
3. Recommend vitamin D and calcium sources and amounts needed for prevention and treatment of osteoporosis.
4. Educate patients about differences between drugs and classes of drugs used to prevent and treat osteoporosis.
5. Counsel patients on potential adverse events and precautions associated with medication(s) used to prevent and treat osteoporosis.

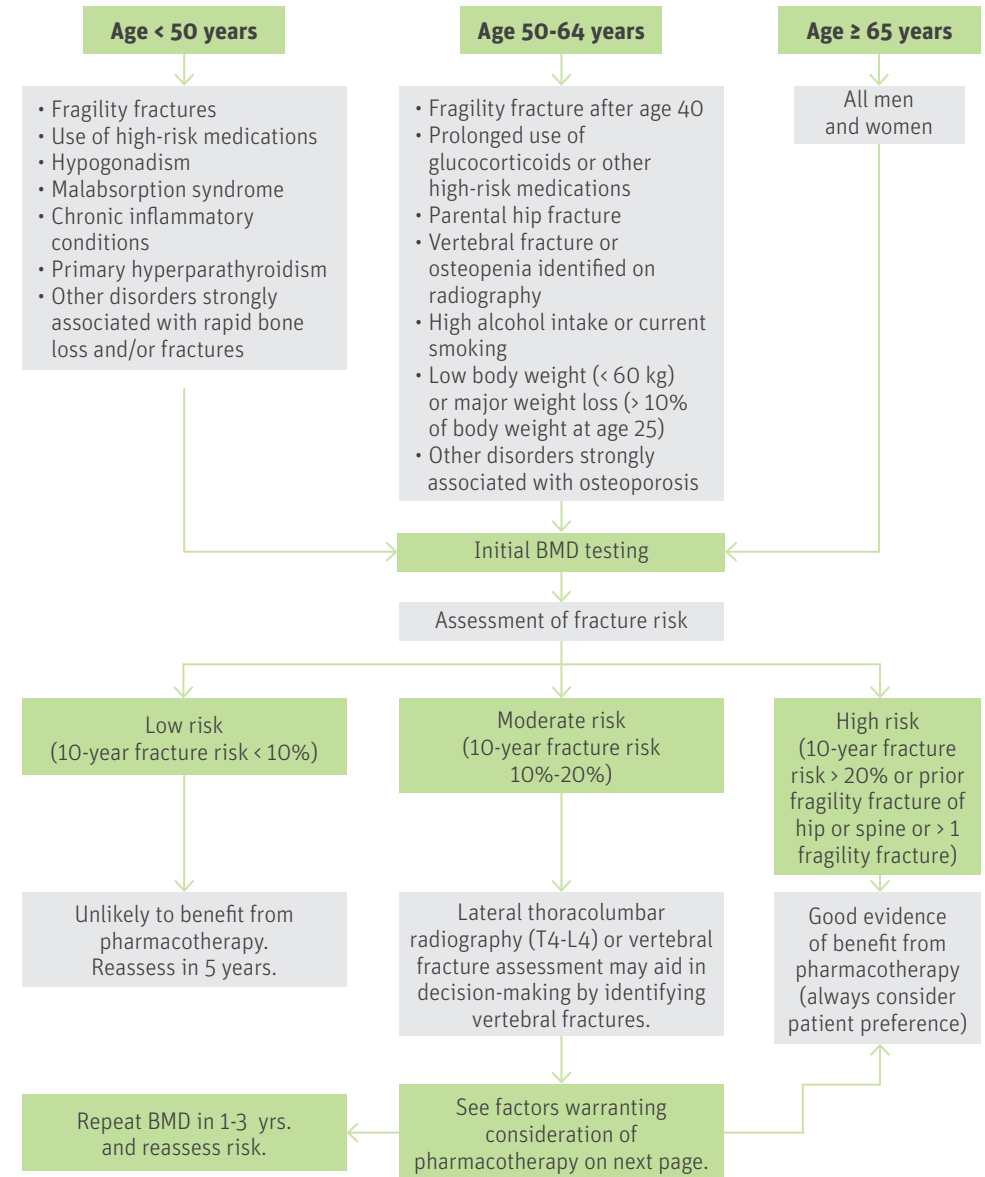
The Pharmacist's Role in Recommending Treatment for the Prevention and Treatment of Osteoporosis

There are many issues that must be taken into consideration when recommending treatment and counselling patients about the role of medicines in the prevention and management of osteoporosis. Following is a brief step-by-step summary:

- Assess need for bone mineral density measurement based on clinical risk factors.¹
- Assess ten-year major osteoporotic fracture risk for your patient using Canadian version of the World Health Organization FRAX® tool or the tool of the Canadian Association of Radiologists and Osteoporosis Canada (CAROC).¹
- Recommend treatment for patients according to patient's absolute risk of osteoporosis-related fractures in collaboration with patient and physician.¹
- Advise patients of the reason for recommending treatment and the differences in options between drug classes and within each drug class being recommended.
- Advise patients of adverse effects, risks, and need for monitoring for each drug being recommended.
- Ensure the patient understands the exact dose of the drug to be taken, exactly when to take the drug, side effects to expect, and those side effects that should be reported to a health professional.
- Address patient concerns that may arise when receiving a generic version of their previous medication by using simple language to explain processes in place to ensure quality of the generic version. The quality standards for brand name drugs and generic drugs are the same, as the ingredients, manufacturing processes and facilities for all drugs must meet the federal guidelines for Good Manufacturing Practices. In order to be deemed bioequivalent, the generic drug manufacturer must show that the generic drug delivers the same amount of medicinal ingredient at the same rate as the brand name drug in each healthy individual who uses both versions of the drug through studies known as "comparative bioavailability" studies. Nonmedicinal ingredients, like fillers and ingredients that colour the drug, may be different from those of the brand name product. The generic manufacturer must provide studies showing that the different nonmedicinal ingredients have not changed the quality, safety or effectiveness of the generic drug.

Management of Osteoporosis: Canadian Guidelines Algorithm¹

Encourage basic bone health for all individuals over age 50—including regular active weight bearing exercise, calcium and vitamin D (diet and supplements) and fall prevention strategies.



↳ Indicates that evidence for benefit from pharmacotherapy is not as strong in this instance as for other recommendations

Osteoporosis Management Summary

Osteoporosis Definitions

The World Health Organization (WHO) defines osteoporosis as a BMD of 2.5 or more standard deviations below that of a normal young adult (i.e., T-score \leq -2.5) for postmenopausal women and men over age 50 years as measured by central dual energy x-ray absorptiometry (DEXA).¹ Osteopenia is defined as a BMD between 1 and 2.5 standard deviations below the young adult mean. A person who has a T-score of \leq -2.5 and already has one or more fractures is said to have severe or established osteoporosis.¹

Factors beyond High Ten-Year Fracture Risk Warranting Consideration of Pharmacological Therapy in Moderate Risk Patients:¹

- Additional vertebral fracture(s) by vertebral fracture assessment or lateral spine radiograph
- Previous wrist fracture in individuals aged $>$ 65 and those with T-score \leq -2.5
- Lumbar spine T-score \ll femoral neck T-score
- Rapid bone loss
- Men undergoing androgen-deprivation therapy for prostate cancer
- Women undergoing aromatase inhibitor therapy for breast cancer
- Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
- Recurrent falls (\geq 2 in the past 12 months)
- Other disorders strongly associated with osteoporosis, rapid bone loss, or fractures

Fracture Risk Assessment

Fracture Risk Assessment

Assess Major Osteoporotic Fracture Risk for Your Patient


- Assess risk factors for major osteoporotic fracture in each patient
- Bone mineral density should be conducted for those indicated (see Table 1) 
- Before dispensing medications for osteoporosis prevention or management, issues such as indications, contraindications, and potential adverse effects should be assessed and discussed with the patient.

Table 1: Indications for Measuring Bone Mineral Density¹

Older Adults (age ≥ 50 years)	Younger Adults (age < 50 years)
<input type="checkbox"/> Age ≥ 65 (both women and men)	<input type="checkbox"/> Fragility fracture
<input type="checkbox"/> Clinical risk factors for fracture (menopausal women, men 50-64 yrs.)	<input type="checkbox"/> Prolonged use of glucocorticoid therapy*
<input type="checkbox"/> Vertebral fracture or osteopenia identified on radiography	<input type="checkbox"/> Use of other high-risk medications*
<input type="checkbox"/> Fragility fracture after the age of 40	<input type="checkbox"/> Hypogonadism or premature menopause (age < 45 yrs.)
<input type="checkbox"/> Parental history of hip fracture	<input type="checkbox"/> Malabsorption syndrome
<input type="checkbox"/> Prolonged use of glucocorticoid therapy*	<input type="checkbox"/> Primary hyperparathyroidism
<input type="checkbox"/> Use of other high-risk medications*	<input type="checkbox"/> Other disorders strongly associated with rapid bone loss and/or fracture
<input type="checkbox"/> High alcohol intake	
<input type="checkbox"/> Current smoking	
<input type="checkbox"/> Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25 yrs.)	
<input type="checkbox"/> Other disorders strongly associated with osteoporosis	
<input type="checkbox"/> Rheumatoid arthritis	

* ≥ 7.5 mg daily prednisone-equivalent dose for at least 3 months cumulative therapy in the previous year
 † For example, aromatase inhibitors or androgen deprivation therapy

Identify Medications that May Be Contributing to Low BMD and/or Risk of Fracture and Inform Patient and Physician

Table 2: Medications that May Increase Risk for Osteoporosis³

Aluminum-containing antacids	Synthetic glucocorticoids (e.g., prednisone)	Proton pump inhibitors
Some antiseizure medications (e.g., phenytoin, carbamazepine)	Androgen deprivation therapy	Mood-altering drugs (e.g., antidepressants, benzodiazepines, some antipsychotic medications)
Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole)	Heparin	Alpha adrenergic blockers (e.g., tamsulosin)
Some cancer chemotherapeutic agents	Diuretics	Thiazolidinediones (pioglitazone and rosiglitazone)
Cyclosporine and tacrolimus	Medroxyprogesterone acetate injection for contraception	Thyroid hormones in excess

Determine Your Patient's 10-Year Major Osteoporotic Fracture Risk

The Osteoporosis Canada guidelines recommend two different, but closely related, tools for estimating the ten-year risk of a major osteoporotic fracture (i.e., fracture of the hip, vertebra [clinical], forearm, or proximal humerus).¹ The tools are:

1. The fracture risk assessment tool (FRAX[®]) of the World Health Organization (WHO) that is specific to Canada
2. The updated tool of the Canadian Association of Radiologists and Osteoporosis Canada (CAROC)

Both of these tools utilize the BMD (T-score) for the femoral neck only. The tools have been calibrated and directly validated for Canadians. The FRAX tool and CAROC tools are valid for use in individuals 50 years and older.¹

BMD (bone mineral density) may be used but is not required for assessment of ten-year major osteoporotic fracture risk via the FRAX tool. An option exists to use body mass index (BMI), gender, and age along with consideration of many other clinical risk factors (see next page) to assess ten-year risk of a major osteoporotic fracture.¹ Fracture discrimination using the FRAX tool with BMD is better than the FRAX tool without BMD.

Although the T-score for the femoral neck is most often not accessible to the community pharmacist, information about the other clinical risk factors needed to assess ten-year major osteoporotic risk via the FRAX tool BMI calculation are available through patient assessment. Point-of-care risk assessment is therefore possible at the pharmacy, and may be of benefit when BMD assessment has not been conducted in the recent past and is not scheduled in the near future.

The WHO Fracture Risk Assessment Tool (FRAX)

The FRAX tool specific for Canada uses gender, age, body mass index, prior fracture, parental hip fracture, prolonged glucocorticoid use (at doses of prednisolone 5 mg daily [or equivalent] or higher for more than 3 months), rheumatoid arthritis (or secondary causes of osteoporosis), current smoking, alcohol intake (three or more standard drinks daily), and (optionally) BMD of the femoral neck.¹ This risk assessment is especially useful when BMD assessment is not available, as the patient's body mass index (BMI) may be used to assess risk as an alternative. However, fracture discrimination using the FRAX tool with BMD is better than the FRAX tool without BMD.

The FRAX tool requires access to software, website, or paper charts. The FRAX tool can be accessed online at <http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19>. Risk of major osteoporotic fracture over the next ten years may be calculated via the software program after input of patient data.⁴

Paper charts can be used to assess major osteoporotic fracture risk in the next 10 years for individuals of various ages.

Paper charts for women of various ages are available online at http://www.sheffield.ac.uk/FRAX/charts/Chart_CA_ost_wom_bmi.pdf.

For men, the paper charts are available online at http://www.sheffield.ac.uk/FRAX/charts/Chart_CA_ost_men_bmi.pdf.

On the following page is an example of a paper-based chart for probability of a major osteoporotic fracture in a 50-year-old woman whose BMI is known.

Probability of a Major Osteoporotic Fracture in the Next Ten Years in a 50-Year-Old Woman According to BMI^{4,5}

Number of CRFs	BMI (kg/m ²)						
	15	20	25	30	35	40	45
0	3.3	3.1	3.0	2.6	2.3	2.0	1.8
1	5.3 (3.6-7.7)	4.9 (3.3-6.8)	4.7 (3.2-6.4)	4.1 (2.8-5.6)	3.6 (2.4-4.9)	3.2 (2.1-4.3)	2.8 (1.9-3.7)
2	8.4 (4.6-14)	7.6 (4.1-13)	7.2 (3.8-12)	6.3 (3.3-11)	5.5 (2.9-9.6)	4.8 (2.5-8.4)	4.2 (2.2-7.4)
3	13 (6.5-22)	12 (5.6-21)	11 (5.2-20)	9.4 (4.5-17)	8.3 (3.9-15)	7.3 (3.4-13)	6.4 (3.0-12)
4	20 (11-30)	17 (9.5-27)	16 (8.5-26)	14 (7.4-23)	12 (6.5-20)	11 (5.6-18)	9.4 (4.9-16)
5	29 (19-37)	25 (17-33)	23 (16-30)	20 (14-27)	18 (12-24)	16 (11-21)	14 (9.5-19)
6	42	36	32	29	25	22	20
Age = 50 years CRF = Clinical Risk Factor							

For example, based on the FRAX chart above, a 50-year-old woman with two clinical risk factors (e.g., current smoking, rheumatoid arthritis) and a body mass index of 30 kg/m² would have a mean estimated ten-year fracture risk of 6.3% (range of 3.3% to 11%).

Nonpharmacologic Choices

Nonpharmacologic Choices

Nonpharmacologic Choices for Fracture Risk Reduction⁶

- Regular exercise (especially impact type).
- Reduce risk of falling such as minimize hazards for falling in the house and assess drugs implicated in falls (e.g., benzodiazepines, psychotropics).
- Facilitate smoking cessation.
- Dietary measures:
 - Adequate protein, calcium and vitamin D intake.
 - Avoid excessive alcohol (> 2 drinks per day) and caffeine (> 4 cups of coffee per day or equivalent).

Calcium and Vitamin D

Calcium and Vitamin D

Assess Calcium and Vitamin D Intake

Calcium intake: how much do patients need?

Adequate calcium and vitamin D intake is necessary to attain and maintain normal bone quantity and quality and thus achieve optimal bone strength and reduce risk for osteoporosis.⁷ Table 3 outlines recommended calcium intake from all sources as recommended by the updated Dietary Reference Intakes (DRIs) published by Health Canada.⁸

Age Group	Recommended Dietary Allowance (RDA) per Day
Children 4-8 years	1000 mg
Adolescents 9-18 years	1300 mg
Women 19-50 years	1000 mg
Men 19-50 years	1000 mg
Women 51-70 years	1200 mg
Men 51-70 years	1000 mg
Adults > 70 years	1200 mg
Pregnant or lactating women 19-50 years	1000 mg

Note: Recommendations for calcium and vitamin D intake for patients in long-term care can be found online at <http://www.cmaj.ca/content/early/2015/09/14/cmaj.141331>

Calcium Supplementation

Where it is not possible to attain recommended daily intake of calcium through diet alone, supplemental calcium is indicated. Table 4 outlines calcium salts available and elemental calcium available from each salt.⁹

Calcium Salt	Elemental Calcium (%)
Calcium carbonate	40.0
Calcium phosphate (tribasic)	40.0
Calcium citrate	21.0
Calcium lactate	13.0
Calcium gluconate	9.0

Patients should be educated to look for the amount of elemental calcium in each product and/or speak to the pharmacist before purchasing supplemental calcium. For example, 1250 mg calcium carbonate contains 500 mg elemental calcium.

Calcium Supplement Counselling Tips

- The absorption of calcium salts other than calcium citrate is impaired in fasted individuals and is best taken with meals when gastric acid release is stimulated.⁹
- Calcium should be taken in single doses of elemental calcium not exceeding 500 mg, as these doses are absorbed more easily and more completely than larger doses.⁹
- Calcium may interfere with the absorption of other medications. Examples of medications that may be more poorly absorbed when taken with calcium include acid-lowering agents (H₂-receptor antagonists, proton pump inhibitors), aluminum hydroxide, bisphosphonates, calcium channel blockers, digoxin, iron supplements, levothyroxine, phenytoin, quinolones, tetracyclines, and thiazide diuretics.⁹
- Calcium salts are contraindicated in people with hypercalcemia and hypercalciuria (e.g., in hyperparathyroidism, vitamin D overdosage, bone metastases), severe cardiac disease, ventricular fibrillation, and calcium loss due to immobilization.⁹
- Studies have shown conflicting results with respect to the effect of calcium on cardiovascular (CV) disease.⁸ Until further safety information is available, high doses of calcium supplements should not be used in those who do not need extra calcium. Those requiring extra calcium should first consider increasing dietary intake before taking supplements. Health Canada recommends that patients not exceed 1500 mg/day from supplements alone. Other experts have recommended a lower maximum of 500 mg/day from supplements alone.⁹

Vitamin D Recommendations

According to a large survey conducted between August 2009 and November 2011 by Statistics Canada, approximately 32% of Canadians have blood concentrations of vitamin D that are below a level considered sufficient for healthy bones for most people (< 50 nmol/L).¹⁰

Calcium and Vitamin D

Vitamin D intake recommendations from Health Canada are presented in Table 5:

Age Group	Recommended Dietary Allowance (RDA) per Day
Infants 0-6 months	400 IU (10 mcg)*
Infants 7-12 months	400 IU (10 mcg) *
Children 1-3 years	600 IU (15 mcg)
Children 4-8 years	600 IU (15 mcg)
Children and Adults 9-70 years	600 IU (15 mcg)
Adults > 70 years	800 IU (20 mcg)
Pregnancy & Lactation	600 IU (15 mcg)
*Adequate Intake rather than Recommended Dietary Allowance.	
Note: Recommendations for calcium and vitamin D intake for patients in Long-Term Care can be found online at http://www.cmaj.ca/content/early/2015/09/14/cmaj.141331	

To achieve optimal vitamin D levels, supplementation with greater than 1000 IU may be necessary.¹ The Tolerable Upper Intake Levels of Vitamin D according to age and as published by Health Canada are presented in Table 6.

Age Group	Tolerable Upper Intake Level (UL) per Day
Infants 0-6 months	1000 IU (25 mcg)
Infants 7-12 months	1500 IU (38 mcg)
Children 1-3 years	2500 IU (63 mcg)
Children 4-8 years	3000 IU (75 mcg)
Children and Adults 9-70 years	4000 IU (100 mcg)
Adults > 70 years	4000 IU (100 mcg)
Pregnancy & Lactation	4000 IU (100 mcg)
Note: Osteoporosis Canada recommends 800–2000 IU vitamin D per day for individuals who are age 50 and older and at risk for osteoporosis. ¹	

An optimal serum level of 25-hydroxyvitamin D is 75 nmol/L or greater.¹ If an individual is receiving pharmacologic therapy for osteoporosis, measurement of 25-hydroxyvitamin D should be conducted three to four months after adequate supplementation. Repeat of the test is required only if vitamin D levels are not found to be optimal.¹

Determination of Calcium and Vitamin D Supplementation Needs

Determination of Calcium and Vitamin D Supplementation Needs

Calcium

Daily Elemental Calcium Needs (A) _____

Estimation of Daily Elemental Calcium Intake* (B) _____

Daily Elemental Calcium required from supplement (A – B) _____

*Estimation of the calcium content of common foods can be found on the Dietitians of Canada website at <http://www.dietitians.ca/Your-Health/Nutrition-A-Z/Calcium/Food-Sources-of-Calcium.aspx> as well as on the Osteoporosis Canada website at <http://www.osteoporosis.ca/osteoporosis-canada-calcium-calculator/>

Vitamin D

Supplementation recommendation based on age _____

Pharmacist recommendation for product(s) which will supply recommended amounts of calcium and/or vitamin D

An app entitled “Get Enough Helper” is available online at <https://www.dairygoodness.ca/getenough/app>. It helps users to track servings of various food groups, including milk and alternatives consumed during the day.

Pharmacological Options

Review of Available Prevention and Treatment Options

In Canada, the choice of medication for prevention and treatment of osteoporosis is aided by the recommendations of the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada,¹ and should take into account the prescriber's clinical judgment and the preferences of the patient. Before prescribing pharmacological therapy, a thorough pretreatment assessment, which includes a comprehensive personal and family history, a physical examination, diagnostic imaging, BMD measurements and appropriate laboratory investigations should take place. Current evidence suggests that many patients with fractures do not undergo appropriate assessment or treatment.¹ Pharmacists are in an ideal position to narrow the care gap that exists for these high-risk patients through enhanced knowledge and application of osteoporosis prevention and treatment strategies.

Pharmacological Options in Canada for Prevention and Management of Osteoporosis Include:

Bisphosphonates

- Alendronate, etidronate, risedronate, zoledronic acid

Hormone therapy

- Estrogen +/- progestogens

Selective estrogen receptor modulator

- Raloxifene

RANK ligand inhibitor

- Denosumab

Bone-forming agent

- Teriparatide

Choose the Most Appropriate Therapy for Your Patient

Pharmacologic therapy should be offered to patients at high absolute risk (> 20% probability for major osteoporotic fracture over ten years) as well as individuals over age 50 who have had a fragility fracture of the hip or vertebra or those who have had more than one fragility fracture.¹ Please see page 6 for additional factors warranting consideration of pharmacological treatment (e.g., for those at moderate fracture risk).

Following are evidence-based recommendations for treatment choices as published in the 2010 Osteoporosis Canada guidelines:¹

1. For menopausal women requiring treatment of osteoporosis, alendronate, risedronate, zoledronic acid and denosumab can be used as therapies for prevention of hip, nonvertebral and vertebral fractures.
2. For menopausal women requiring treatment of osteoporosis, raloxifene can be used as first-line therapy for prevention of vertebral fractures.
3. For menopausal women requiring treatment of osteoporosis in combination with treatment for vasomotor symptoms, hormone therapy can be used as first-line therapy for prevention of hip, nonvertebral and vertebral fractures.
4. For menopausal women intolerant of first-line therapies, etidronate can be considered for prevention of vertebral fractures.
5. For men requiring treatment of osteoporosis, alendronate, risedronate, and zoledronic acid can be used as therapies for prevention of fractures.
6. Testosterone is not recommended for the treatment of osteoporosis in men.

Appropriate Therapy for Special Groups¹

- For individuals over age 50 who are on long-term glucocorticoid therapy (≥ 3 months cumulative therapy during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily), a bisphosphonate (alendronate, risedronate, zoledronic acid) should be initiated at the outset and should be continued for at least the duration of the glucocorticoid therapy.
- Teriparatide should be considered for those at high risk for fracture who are taking glucocorticoids (≥ 3 months cumulative therapy during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily).
- For long-term glucocorticoid users who are intolerant of first-line therapies, etidronate may be considered for preventing loss of bone mineral density.
- Women who are taking aromatase inhibitors and men who are undergoing androgen-deprivation therapy should be assessed for fracture risk, and osteoporosis therapy to prevent fractures should be considered.

Ensure that therapy is right for your patient.

Please see Table 7 for indications and associated doses for each of the bisphosphonate therapies.

Contraindications

- Alendronate is contraindicated in patients with abnormalities of the esophagus that delay emptying, such as stricture or achalasia (a condition in which the muscles of the lower part of the esophagus fail to relax, preventing food from passing into the stomach), in patients who cannot stand or sit upright for at least 30 minutes, in patients with hypocalcemia, and in those with renal insufficiency (creatinine clearance < 35 ml/min).¹¹
- Etidronate is contraindicated in patients with clinically overt osteomalacia, until appropriate treatment has been initiated for it.¹²
- Risedronate is contraindicated in patients with hypocalcemia.¹³
- Zoledronic acid is contraindicated in patients with severe renal impairment (creatinine clearance < 35 ml/min), in those with evidence of acute renal impairment, in pregnancy, during breastfeeding, and in those with non-corrected hypocalcemia at time of infusion.¹⁴
- All bisphosphonates are contraindicated in patients with severe renal impairment.
- All bisphosphonates are contraindicated in patients with hypersensitivity to any bisphosphonate.
- All bisphosphonates are not intended for use in pregnancy and lactation.

Inform patients about possible warnings and precautions associated with bisphosphonate therapy.

Alendronate

Advise patients to speak with their doctor before starting **alendronate** therapy if they:¹¹

- have cancer, gum disease, poor oral hygiene, or diabetes. If they are receiving chemotherapy, radiotherapy, corticosteroids, or immunosuppressive drugs. If they have been a smoker, or are a heavy alcohol user. Any of these conditions should prompt a dental examination before starting alendronate.
- have had any medical problems, including known kidney disease
- have or have had any dental problems
- have any allergies
- have any swallowing or digestive problems

Alendronate is not indicated for use in children under 18 years of age. There have been side effects reported with alendronate that may affect the patient's ability to drive or operate machinery. Individual responses to alendronate may vary.

Etidronate and Calcium Carbonate

Advise patients to speak with their doctor before starting **etidronate and calcium carbonate** therapy if they:¹²

- have unresolved osteomalacia
- have a history of kidney stone formation or problems with their kidneys
- are pregnant or nursing
- are allergic to any of the components of the medication
- are taking warfarin
- are taking tetracycline
- have a gastrointestinal disorder which makes them prone to diarrhea (e.g., Crohn's disease, colitis, irritable bowel syndrome, food poisoning)
- have one of the following risk factors: cancer, chemotherapy, radiotherapy of the head or neck, treatment with corticosteroids, or dental problems or dental infections. If so, a dental examination and any necessary dental procedures should be considered before starting treatment with etidronate plus calcium.

Risedronate

Advise patients to speak with their doctor before starting **risedronate** therapy if they:¹³

- have had problems or disease in their kidneys, esophagus, stomach or intestines
- cannot carry out dosing instructions (see Table 7)
- are pregnant or nursing
- have one of the following risk factors: cancer, chemotherapy, radiotherapy of the head or neck, treatment with corticosteroids or dental problems or dental infections. If so, a dental examination and any necessary dental procedures should be considered before starting treatment with risedronate.

Zoledronic Acid (5 mg/100 ml)

Advise patients to speak with their doctor before starting **zoledronic acid (5 mg/100 ml)** therapy if they:¹⁴

- are being treated with any other bisphosphonate or another brand of zoledronic acid
- are unable to take daily calcium and/or vitamin D supplements
- are pregnant or plan to become pregnant

- are breastfeeding
- have kidney problems. Worsening of kidney function, including kidney failure, may happen when taking zoledronic acid
- had some or all of their parathyroid glands or thyroid gland surgically removed.
- had sections of their intestine removed
- need any dental procedures such as a root canal or tooth extraction (this does not include regular dental cleaning). Dental examination with any necessary preventive dentistry should be carried out prior to treatment with zoledronic acid. The patient should continue with regular dental cleanings and practice good oral hygiene
- have a rapid and irregular heartbeat
- have a sudden headache, numbness in their face or limbs, particularly down one side of the body. If they experience confusion and have trouble talking or understanding what is being said. If they have vision problems, and trouble walking or keeping their balance
- have asthma from taking acetylsalicylic acid
- have any pain in their hip, groin, or thigh. Zoledronic acid can cause unusual fractures in the thigh bone

Zoledronic acid is not recommended for patients under 18 years of age.

Zoledronic acid is to be given by intravenous infusion in no less than 15 minutes.

Inform patients about possible interactions with bisphosphonates.

Advise patients to let their healthcare professionals know of ALL medications that are being taken (including prescription, non-prescription and natural health products). In particular, the following products may interact with the particular bisphosphonate listed as indicated:

- This is not a complete list of drug interactions. Please consult individual product monographs for the full list of medications that may interact with bisphosphonates.

Alendronate ¹¹	Risedronate ¹³
<ul style="list-style-type: none"> • calcium supplements • antacids • other multivalent cations • other oral medications <p>The medications above will interfere with the absorption of alendronate if they are taken at the same time. Patients should wait at least one-half hour after taking alendronate before taking any other oral medication, as other oral medications will interfere with the absorption of alendronate.</p>	<ul style="list-style-type: none"> • vitamins • mineral supplements • antacids • other medications <p>Risedronate should be taken on an empty stomach. Medications which may contain substances such as calcium, magnesium, aluminum, and iron should be taken at a different time of day than risedronate.</p> <p>Risedronate delayed-release (DR) tablets should be taken with food. Medicines which reduce stomach acid (e.g., proton pump inhibitors and H₂ blockers) can affect the absorption of risedronate DR.</p>
Etidronate plus Calcium Carbonate ¹²	Zoledronic Acid (5 mg/ 100 ml) ¹⁴
<ul style="list-style-type: none"> • warfarin • tetracycline <p>The following foods and medicines should not be taken within 2 hours of taking etidronate:</p> <ul style="list-style-type: none"> • antacids • vitamins with mineral supplements such as iron, calcium supplements, laxatives containing magnesium, and foods, especially foods high in calcium, such as milk or milk products • other medications 	<ul style="list-style-type: none"> • any medicines known to be harmful to kidneys (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) • diuretics • aminoglycoside antibiotics • other medications

Inform patients about side effects associated with bisphosphonates.*

*This is not a complete list of side effects.

Alendronate

The following side effects with **alendronate** have been reported:¹¹

- Digestive disturbances – nausea, vomiting or black and/or bloody stools.
- Some digestive disturbances may be severe including irritation or ulceration of the esophagus which can cause chest pain, heartburn or difficulty or pain upon swallowing. These reactions may occur especially if patients do not drink the recommended amount of water with alendronate and/or if they lie down in less than 30 minutes or before their first food of the day. Esophageal reactions may worsen if patients continue to take alendronate after developing symptoms suggesting irritation of the esophagus. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Bone, muscle and/or joint pain – these symptoms are rarely severe. Patients who develop severe bone, joint and/or muscle pain should contact their physician. Most patients experience relief after stopping the drug.
- Rarely, patients may also experience joint swelling or swelling in their hands or legs.
- Transient flu-like symptoms (rarely with fever), typically at the start of treatment, have occurred.
- In rare cases patients taking alendronate may get itching or eye pain, or a rash that may be made worse by sunlight. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Hair loss has been reported.
- Rarely, severe skin reactions may occur. Allergic reactions such as hives or, rarely, swelling of the face, lips, tongue and/or throat, which may cause difficulty in breathing or swallowing, may occur. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Patients may experience dizziness, vertigo, or a changed sense of taste.
- Rarely, symptoms of low blood calcium may occur (e.g., numbness or tingling around the mouth or in the hands or feet; muscle spasms in the face, hands, or feet). The patient should be advised to stop taking the drug and seek immediate medical attention.
- Rarely, stomach or other peptic ulcers (some severe) have occurred. Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.
- Rarely, patients have had jaw problems associated with delayed healing and infection (osteonecrosis of the jaw), often following tooth extraction. The patient should be advised to stop taking the drug and seek immediate medical attention.

- Very rarely, patients have experienced fracture in a specific part of the thigh bone. Patients should be told to seek medical attention if new or unusual pain in the hip or thigh occurs.

Etidronate and Calcium Carbonate

The following side effects with **etidronate plus calcium carbonate** have been reported:¹²

- Nausea and diarrhea (most common)
- Headache
- Inflammation of the stomach
- Leg cramps
- Joint pain

Uncommon side effects include (less than 1 in 100):

- Allergic reactions such as: hives, skin rash and itching. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Painful or inflamed eyes, sensitivity to light and decreased vision. The patient should be advised to stop taking the drug and seek immediate medical attention.

Rarely reported side effects include (less than 1 in 1000):

- Confusion
- Burning sensation of the tongue including pain and swelling of the tongue or esophagus. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Hair loss
- Sensation of numbness
- Prickling or tingling
- Worsening of asthma. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Blood disorders with symptoms of bleeding, bruising and increased infection.

Very rarely reported side effects include (less than 1 in 10,000):

- Non-healing jaw wounds (osteonecrosis of the jaw). Patients should be told to consult their doctor if they experience persistent pain in their mouth, teeth or jaw, or if their gums or mouth heal poorly.
- Unusual fractures in the thigh bone. A doctor should be consulted if a patient experiences new or unusual pain in their hip, groin, or thigh. The patient should be advised to stop taking the drug and seek immediate medical attention.

- Worsening of stomach and intestinal ulcers. The patient should be advised to stop taking the drug and seek immediate medical attention.

Risedronate

The following side effects with **risedronate** have been reported:¹³

- Drugs like risedronate may cause problems in the esophagus, stomach and intestines, including ulcers. Patients should be informed to stop taking risedronate and call their doctor right away if they have trouble or pain upon swallowing, heartburn, chest pain and black or bloody stools (applies to risedronate and risedronate DR)
- Abdominal pain, heartburn and nausea (most common)
- Pain in bones, joints or muscles, rarely severe. Pain may start as soon as one day or up to several months after starting risedronate.
- Monthly dose risedronate may cause short-lasting, mild flu-like symptoms. These symptoms usually decrease after subsequent doses.
- Rarely patients have reported non-healing jaw wounds (osteonecrosis of the jaw) while receiving risedronate or other bisphosphonates. Patients should be told to consult their doctor if they experience persistent pain in their mouth, teeth or jaw, or if their gums or mouth heal poorly.
- Very rarely patients have reported unusual fractures in their thigh bone while receiving bisphosphonates. A doctor should be consulted if a patient experiences new or unusual pain in their hip, groin, or thigh.
- Eye pain, redness or inflammation; sensitivity to light, decreased vision. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Painful tongue
- Allergic and skin reactions such as: hives; rash (with or without blisters); swelling of face, lips, tongue, or throat; difficult or painful swallowing; trouble breathing. The patient should be advised to stop taking the drug and seek immediate medical attention.
- Symptoms of low blood calcium level such as numbness, tingling and muscle spasms.

Risedronate DR

The following side effects with **risedronate DR** have been reported:¹³

- Abdominal pain, heartburn, nausea (most common)
- Other common side effects include pain in bones, joints, or muscles, rarely severe. The pain may start as soon as one day or up to several months after starting risedronate DR.
- Additional common side effects include diarrhea, constipation, inflammation of the pharynx and/or nose, and upper respiratory tract infection.

- Rarely patients have reported non-healing jaw wounds (osteonecrosis of the jaw). Patients should be told to consult their doctor if they experience persistent pain in their mouth, teeth or jaw, or if their gums or mouth heal poorly.
- Very rarely patients have reported unusual fractures in their thigh bone while receiving bisphosphonates. A doctor should be consulted if a patient experiences new or unusual pain in their hip, groin, or thigh.

Zoledronic Acid

The following side effects with **zoledronic acid** have been reported:¹⁴

Common side effects that should be discussed with a healthcare professional only if severe include:

- Post-dose symptoms: fever, chills, fatigue, pain, malaise
- Headache
- Nausea, vomiting, diarrhea, abdominal pain
- Dizziness
- Excessive sweating
- Rash

Common side effects that should be discussed with a healthcare professional in all cases include:

- Bone, joint, and/or muscle pain or stiffness
- Shortness of breath

Uncommon side effects that should be discussed with a healthcare professional only if severe include:

- Tiredness, weakness, lethargy
- Skin reactions (redness, swelling and/or pain) at the infusion site

Uncommon side effects that should be discussed with a health professional in all cases include:

- Hypocalcemia: numbness, tingling sensation (especially in the area around the mouth), muscle spasms.
- Rapid and irregular heartbeat, palpitations

Pharmacological Options: **Bisphosphonates**

(Alendronate, Etidronate and Calcium Carbonate, Risedronate, Zoledronic Acid 5 mg/100 ml)

- A sudden headache, numbness in the face or limbs, particularly down one side of the body; patient experiences confusion and has trouble talking or understanding what is being said; patient has vision problems, and trouble walking or keeping their balance.
- Kidney failure (weakness, tiredness, loss of appetite, puffy eyes, hands and feet, changes in urine colour or absence of urine production, changes in kidney function laboratory tests).
- Eye disorder (eye pain, light sensitivity, eye redness, decreased vision, eye inflammation).

Rare side effects that should be discussed with a health professional in all cases include:

- Osteonecrosis of the jaw: (numbness or feeling of heaviness in the jaw, poor healing of the gums especially after dental work, loose teeth, exposed bone in mouth, pain in the mouth, teeth or jaw, swelling or gum infection, bad breath).

Very rare side effects that should be discussed with a healthcare professional in all cases include:

- Difficulty breathing with wheezing or coughing in asthma patients who are allergic to ASA
- Avascular necrosis (osteonecrosis) of the hip or knee: poor blood supply to an area of bone leading to bone death; bone pain, joint pain, muscle spasms, joint stiffness
- Failure of broken bone to heal (non-union) or broken bone taking longer than usual to heal (delayed union): persistent pain at the fracture site, no or slow progress in bone healing on imaging tests.
- Thigh or groin pain
- Severe allergic reactions (dizziness, difficulty breathing, loss of consciousness due to shock [dangerously low blood pressure])

This is not a complete list of side effects. For any unexpected effects while taking bisphosphonate therapy, patients should be informed to contact their doctor or pharmacist.

Pharmacological Options: **Hormone Therapy**

Hormone (Estrogen +/- Progestogen) Therapy (HT)

Ensure that therapy is right for your patient.

Please see Table 7 for indications and associated doses for estrogen/progestin therapies.

Contraindications

Estrogens and estrogen/progestin combinations are contraindicated in patients with any of the following disorders:¹⁵⁻¹⁹

- Patients who are hypersensitive to the drug(s) or to any ingredients in the formulation
- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g., endometrial cancer), unless the progestin component is being used as a treatment for endometrial or breast cancer
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer unless the progestin component is being used as a treatment for breast cancer in postmenopausal women
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision (or diplopia) due to ophthalmic vascular disease
- Classical migraine
- Lactation
- From estradiol-17 β transdermal product monograph: porphyria
- From estradiol hemihydrate transdermal system product monograph: presence or history of liver tumours (benign or malignant)

Inform the patient about warnings and precautions associated with hormone therapy.¹⁵⁻¹⁹

Serious Warnings and Precautions¹⁵⁻¹⁹

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined estrogen plus progestin therapy and oral estrogen-alone therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined estrogen plus progestin.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral estrogen-alone.

Therefore, the following should be highly considered:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.

Estrogens with or without progestins should be used at **the lowest effective dose** and for **the shortest period of time** possible. Regular medical follow-up is advised.

BREAST CANCER

The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult their doctor before starting HRT (hormone replacement therapy). Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor. Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. Women should review technique for breast self-examination with their doctor.

ENDOMETRIAL HYPERPLASIA

The use of estrogen-alone therapy by postmenopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

The purpose of adding a progestin medication to estrogen therapy is to reduce the risk of endometrial hyperplasia. Patients should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with their physician. They should also report any unexpected or unusual vaginal bleeding to their doctor. If a patient has her uterus removed, she is not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

OVARIAN CANCER

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

HEART DISEASE AND STROKE

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo. The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

ABNORMAL BLOOD CLOTTING

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in postmenopausal women taking combined estrogen plus progestin compared to women taking placebo. The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in postmenopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo. The risk of blood clots also increases with age, if the patient or a family member has had blood clots, if the patient smokes or if she is severely overweight. The risk of blood clots is also temporarily increased if the patient is immobilized for long periods of time and following major surgery. Patients should discuss risk factors for blood clots with their doctor since blood clots can be life-threatening or cause serious disability.

GALLBLADDER DISEASE

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

DEMENTIA

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined estrogen plus progestin compared to women taking placebo. The WHIMS indicated no difference in the risk of dementia in postmenopausal women age 65 and over with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

SKIN SENSITIVITY *(from estradiol hemihydrate transdermal system product monograph only)*

Contact sensitization (extreme sensitivity of the skin) has been known to occur with the use of topical applications. Although it is extremely rare, patients who develop contact sensitization to any component of the patch may have a severe hypersensitivity reaction with continued use of the patch.

TUMOURS ON THE LIVER *(from estradiol hemihydrate transdermal system product monograph only)*

Benign tumours on the liver have been associated with the use of combined estrogen and progestin oral contraceptives. Although benign and rare, these tumours may rupture and cause death from bleeding in the abdominal cavity. Such tumours have not yet been reported in association with other estrogen or progestin preparations, but they should be considered if abdominal pain and tenderness occurs, or if there is a large abdominal mass, or if sudden and significant drop in blood pressure occurs as a result of the bleeding. Liver cancer has also been reported in women taking estrogen-containing oral contraceptives, however it is not known if this occurred as a result of taking these drugs.

Oral or Transdermal Estrogen

Advise patients to speak with their doctor before starting **oral or transdermal estrogen** therapy if they (listed precautions are included in all product monographs that include indication for oral or transdermal estrogen for prevention and/or treatment of osteoporosis, unless otherwise noted):¹⁶⁻¹⁹

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, liver tumours, or jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy

- have been told that they have a condition called hereditary angioedema or if they have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract
- have been diagnosed with lupus
- have been diagnosed with hearing loss due to otosclerosis
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- are breastfeeding
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have had recent surgery, or are scheduled for future surgery or need long bedrest (from conjugated estrogens oral tablets, 17 β -estradiol oral tablets, estradiol hemihydrate transdermal system and estradiol-17 β transdermal patch product monographs)
- have systemic lupus erythematosus (from estradiol hemihydrate transdermal system and estradiol-17 β transdermal patch product monographs)
- have been told that they have a condition called hereditary hemangioma, or if they have had episodes of rapid swelling of the hands, feet, lips, eyes, tongue, throat (airway blockage) or digestive tract (from estradiol hemihydrate transdermal system and estradiol-17 β transdermal patch product monographs)
- have a history of depression (from conjugated estrogens oral tablets, estradiol hemihydrate transdermal system and estradiol-17 β transdermal patch product monographs)
- have problems with their thyroid (from conjugated estrogens oral tablets and estradiol-17 β transdermal patch product monographs)
- have phlebitis (inflamed varicose veins) (from estradiol-17 β transdermal patch product monograph)

- have had several miscarriages (from estradiol-17 β transdermal patch product monograph)
- have gallbladder disease (from conjugated estrogens oral tablets and estradiol-17 β transdermal patch product monographs)
- have or have had chloasma (yellow-brown patches on the skin) (from estradiol hemihydrate transdermal system product monograph)
- have or have had chorea minor (illness with unusual movements) (from estradiol hemihydrate transdermal system product monograph)

Oral medroxyprogesterone

Advise patients to speak with their doctor before starting **oral medroxyprogesterone** therapy if they:¹⁵

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- smoke

Inform about possible interactions with hormone therapy.

From oral conjugated estrogens product monograph¹⁶

Patients should tell their doctor or pharmacist if they are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products (such as St. John's wort). Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain relief, and tuberculosis) may affect how C.E.S.[®] works. C.E.S.[®] may also affect how other medicines work.

From 17 β -estradiol oral tablets product monograph¹⁷

Drugs that may interact with 17 β -estradiol oral tablets include certain drugs used to prevent blood clots, control diabetes, control high blood pressure, prevent inflammation (containing phenylbutazone), control epilepsy (e.g., phenobarbital, phenytoin, or carbamazepine), control anxiety (e.g., meprobamate), and treat bacterial infection such as antibiotics containing rifampicin. Grapefruit juice and some herbal products available over the counter may also interact with medications containing 17 β -estradiol.

From estradiol hemihydrate transdermal system product monograph¹⁸

Patients should tell their doctor or pharmacist if they are taking any other medications, including prescription and non-prescription medications, over-the-counter medications, vitamins or herbal products (such as St. John's wort), or drink grapefruit juice. There are some medicines that may interfere with the effects of estradiol hemihydrate transdermal system and the estradiol hemihydrate transdermal system may interfere with the effects of other medicines.

From transdermal estradiol-17 β product monograph¹⁹

Patients should tell their doctor or pharmacist if they have taken, or recently taken, any other medications. This particularly includes the following:¹⁹

- anti-anxiety medicines (e.g., barbiturates, meprobamate)
- anti-epileptic medicines (e.g., phenobarbital, phenytoin or carbamazepine)
- phenylbutazone
- antibiotics and other anti-infective medicines (e.g., rifampicin, ketoconazole, erythromycin, rifabutin, nevirapine, efavirenz)
- herbal medicines (e.g., St John's wort).

The following interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens (like hormone therapy):²⁰ acetaminophen, vitamin C, aminoglutethimide with medroxyprogesterone acetate (MPA), atorvastatin, clofibrac acid, cyclosporine, morphine, prednisolone, salicylic acid, temazepam, theophylline.

These medicines may be affected by transdermal ethinyl estradiol or, conversely, they may affect how well transdermal ethinyl estradiol works. The patient's doctor may need to adjust the treatment dosage.

From oral medroxyprogesterone product monograph¹⁵

Drugs that may interact with medroxyprogesterone include:

- Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampin)
- Aminoglutethimide
- Some herbal (e.g., St. John's wort) and natural products that are bought without a prescription.

Inform about side effects associated with hormone therapy.

From oral conjugated estrogens product monograph¹⁶

All medicines can have side effects. Patients should check with their doctor as soon as possible if any of the following occur:

- abdominal discomfort, indigestion, sleep disturbance, irritability, anxiety, unusual fatigue, cold sweat, swelling of the ankles, fingers or abdomen due to fluid retention (edema) persisting for more than 6 weeks; change in weight; change in sex drive; change in vaginal discharge (may be a sign that too much estrogen is taken); hair loss; excessive hairiness; spotty darkening of the skin particularly on the face or abdomen (chloasma); rash; itching; acne; dryness or discoloration of the skin; purple skin patches; contact lens discomfort.

The following are serious side effects that have been associated with conjugated estrogens:

- **Common (talk with doctor or pharmacist in all cases):** breast lump; unexpected vaginal bleeding; painful and/or heavy periods; vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge)

- **Common (stop taking drug and call your doctor or pharmacist):** pain or swelling in the leg
- **Uncommon (talk with your doctor or pharmacist in all cases):** abdominal pain, nausea or vomiting
- **Uncommon (stop taking drug and call your doctor or pharmacist):** persistent sad mood; decline of memory or mental ability
- **Rare (stop taking drug and call your doctor or pharmacist):** sudden severe headache or worsening of headache; vomiting; dizziness; fainting; disturbance of vision or speech or weakness or numbness in an arm or leg; crushing chest pain or chest heaviness; sharp pain in the chest, coughing blood, or sudden shortness of breath; intolerable breast tenderness
- **Very Rare (stop taking drug and call your doctor or pharmacist):** sudden partial or complete loss of vision; jaundice

From 17 β -estradiol oral tablets product monograph¹⁷

Women rarely have severe side effects from taking estrogens. However, if patients have any of the symptoms listed below, they should speak with their doctor immediately:

- **Common (should talk with doctor or pharmacist in all cases):** Abdominal pain, nausea or vomiting
- **Uncommon (should stop taking drug and call doctor or pharmacist):** Lumps or discharge from the breast (depending on symptoms, may not need to stop drug); crushing chest pain or chest heaviness; pain or swelling in the legs or feet; persistent sad mood; sharp pain in the chest; coughing blood or sudden shortness of breath; sudden partial or complete loss of vision; sudden severe headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg; sudden loss of coordination; jaundice
- **Uncommon (should talk with doctor or pharmacist in all cases):** pain in groin; unexpected vaginal bleeding

The following side effects go away during treatment as the body adjusts to them. However, patients should check with their doctor if they continue or become bothersome:

- Bloating, stomach cramps, headaches (mild), dizziness (mild).
- Many women who are taking estrogens with a progestin will start having monthly vaginal bleeding, similar to menstrual periods again. This effect will continue for as long as the medicine is taken. However, monthly bleeding should not occur in women who have had a hysterectomy.

Other possible side effects include breast pain and swelling; irregular vaginal bleeding or spotting; vaginal itching/discharge or pain; depression, nervousness, and/or irritability; allergic reaction and rash; hair loss or abnormal hair growth; increased blood sugar levels; changes in blood pressure; acne; change in cholesterol and/or triglyceride levels; change in weight.

From estradiol hemihydrate transdermal system product monograph:¹⁸

The following side effects generally do not require medical attention, and will usually go away as the body adjusts to the medication:

- **Common:** breast pain, breast tenderness, bloating, dizziness, localized darkening of the skin, mood swings, redness or mild irritation under or around the patch
- **Uncommon:** muscle cramps, breast enlargement

The patient should be informed to tell their doctor if they think they are reacting poorly to the medication or are having other problems.

The following are serious side effects that have been associated with estradiol hemihydrate transdermal system:

- **Common (should talk with doctor or pharmacist in all cases):** abdominal pain, nausea or vomiting; unexpected vaginal bleeding
- **Common (should talk with doctor or pharmacist only if severe):** changes in body weight; heavy periods; migraine headaches; persistent skin irritation; retention of fluid
- **Uncommon (should stop taking drug and call doctor or pharmacist):** change in speech, crushing chest pain or chest heaviness; pain or swelling in the leg; persistent sad mood; sharp pain in the chest, coughing blood or sudden shortness of breath; sudden partial or complete loss of vision; sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg
- **Uncommon (should talk with doctor or pharmacist in all cases):** breast lump; change in vision; easy bruising, excessive nose bleeds, excessive heavy periods; first migraine headache; fluid retention or bloating persisting for more than 6 weeks; high blood pressure; rapid pulse or dizziness; skin redness, warmth, swelling, tenderness, pain or hardening of tissue around a vein; vomiting

From transdermal estradiol-17 β product monograph¹⁹

All medicines can have side effects. Patients should check with their doctor as soon as possible if any of the following occur:

- **Most common adverse drug reactions ($\geq 1\%$):** swelling of the lower legs, ankles, fingers or abdomen due to edema; change in weight; vaginal bleeding or spotting and changes in vaginal discharge; headache; depression; migraine; dizziness; nausea; abdominal pain and swelling; tender breasts and breast enlargement; persistent or severe skin irritation, redness, rash or itching of the skin after the patch has been removed.
- **Less common adverse drug reactions ($< 1\%$):** change in sex drive; hair loss; excessive hairiness; vomiting; lump or mass in breast; fibroids; vaginal thrush
- **Adverse drug reactions with unknown frequency:** easy bruising; excessive nose bleeds; spotty darkening of the skin, particularly on the face or abdomen (chloasma); purple skin patches; acne; decline of memory or mental ability; rapid mood changes; contact lens discomfort; dry eyes; gallbladder disease (tendency to form gallstones); nervousness; back pain and pain in extremity; signs or symptoms that blood clots may have formed in body (pains in the calves, thighs or chest, sudden shortness of breath, coughing blood or dizziness); increase in blood pressure; yellowing of the eyes or skin; diarrhea; signs of an allergic reaction (sudden troubled breathing, tightness of the chest, general rash or itching); uncontrollable jerky movements (chorea); skin inflammation and rash (rash with painful red lumps, pain in joints and muscle swelling, blistering of lips, eyes, skin peeling); breast pain, irregular heavy vaginal bleeding or constant spotting (possible signs of endometrial hyperplasia); menstrual cramps; breast discharge; lumps in the breast (non-cancerous); hives; worsening of porphyria (a condition affecting the liver); varicose veins.

From oral medroxyprogesterone acetate product monograph¹⁵

The following side effects have been reported with the use of medroxyprogesterone:

- Breast tenderness; breast milk secretion; breakthrough bleeding, spotting (minor vaginal bleeding); irregular menstrual periods; amenorrhea; vaginal secretions; headaches; nervousness; dizziness; insomnia; sleepiness; fatigue; premenstrual syndrome-like symptoms; itching, hives, skin rash; acne; hair loss; hair growth; abdominal discomfort; nausea; bloating; fever; increase in weight; swelling; moon-shaped face.

Pharmacological Options: *Hormone Therapy*

Hormone (Estrogen +/- Progestogen) Therapy (HT)

The following serious side effects have been reported with the use of medroxyprogesterone acetate (unknown frequency in all cases):

- ***Should talk with doctor or pharmacist in all cases:*** abdominal pain; nausea or vomiting; breast lump; unexpected vaginal bleeding
- ***Should stop taking drug and call doctor or pharmacist:*** persistent sad mood; pain or swelling in the leg/inflamed vein; sharp pain in the chest, coughing blood or sudden shortness of breath; sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg; sudden partial or complete loss of vision; yellowing of the skin or eyes (jaundice); crushing chest pain or chest heaviness

This is not a complete list of side effects. For any unexpected effects while taking hormone therapy medications, patients should be informed to contact their doctor or pharmacist.

Pharmacological Options: *Raloxifene*

Ensure that therapy is right for your patient.

Please see Table 7 for indications and associated doses for raloxifene therapy.

Contraindications²⁰

- Women of childbearing potential.
- Women who are breastfeeding.
- Women with present or past history of thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.

Inform the patient about warnings and precautions associated with raloxifene therapy.

Before starting raloxifene, the patient should tell their doctor if they:²⁰

- are pregnant, breastfeeding, still have menstrual bleeds, or have had a menstrual bleed in the last year, as raloxifene is only for postmenopausal women.
- have had an allergic reaction to any medicine they have taken.
- have or ever had liver problems.
- have or ever had blood clots in the veins. If the patient takes warfarin or other coumarin derivatives, raloxifene may not be suitable. Raloxifene is contraindicated in women with an active or past history of blood clots in the veins. If the patient is taking the blood thinners for other reasons their doctor may need to check their prothrombin time and adjust the dose of medication when the patient begins taking raloxifene.
- are currently on any other medications, prescription or non-prescription.
- have had a stroke or have a history of other significant risk factors for stroke, such as a “mini-stroke” (transient ischemic attack [TIA]), or a type of irregular heartbeat (atrial fibrillation).

If while taking raloxifene, the patient plans to be immobile, such as staying in bed after surgery or taking a long plane trip, she should stop taking raloxifene at least 3 days before, to reduce her risk of blood clots in the veins. Raloxifene can be reintroduced once the patient is on her feet.

Inform about possible interactions with raloxifene.²⁰

- The effect of raloxifene is significantly reduced if taken with cholestyramine. Therefore, patients should not take cholestyramine while taking raloxifene.
- The combination of raloxifene with hormone therapy is not recommended.
- Patients should check with their doctor before taking any other medication with raloxifene.

Inform about side effects associated with raloxifene.²⁰

During clinical trials, some women did have mild side effects, however most women did not find these side effects serious enough to stop taking raloxifene. The most common side effects of raloxifene are hot flashes and leg cramps. Another common side effect is flu-like symptoms.

Similar to estrogen replacements, raloxifene may increase the risk of blood clots in the veins. Although this is an uncommon side effect, patients should be told to contact their doctor immediately if they experience any of the following unusual symptoms:²¹

- Redness, swelling, heat or pain in the calves and legs
- Sudden chest pain or shortness of breath
- A sudden change in vision

The following serious side effects have been reported with the use of raloxifene:

- **Uncommon (patient should stop taking drug and call doctor or pharmacist in all cases):** Blood clots in the veins (symptoms of redness, swelling, heat or pain in the calves and legs)
- **Rare (patient should stop taking drug and call doctor or pharmacist in all cases):** Blood clots in the lungs (symptoms of sudden chest pain or shortness of breath)
- **Rare:** Stroke fatality – women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene.

This is not a complete list of side effects. For any unexpected effects while taking raloxifene, patients should be informed to contact their doctor or pharmacist.

Ensure that therapy is right for your patient.

Please see Table 7 for indications and associated doses for denosumab therapy.

Contraindications²¹

- Patients who are hypersensitive to the drug or any component of the product; anaphylactic reactions have been reported
- Hypocalcemia
- Indicated only for postmenopausal women and not recommended for women who could become pregnant

Inform the patient about warnings and precautions associated with denosumab.²¹

- Prolia® (denosumab) contains the same medicine as Xgeva® (denosumab), which is used to reduce the risk of developing cancer-related complications. Prolia®, which is given at a lower dose than Xgeva® once every 6 months, should not be used to treat this condition.
- There is an increased risk of skin infection (cellulitis) with denosumab therapy, most commonly on the leg. Patients should see a doctor urgently if they develop swollen, red, hot or painful skin, with or without fever.
- Patients should take calcium and vitamin D supplements as recommended by their healthcare professional.
- Denosumab is recommended for women after menopause (more than one year after last period).

Before patients use denosumab, they should talk to their doctor or pharmacist if they:²¹

- Have low blood calcium
- Cannot take daily calcium and vitamin D
- Had parathyroid or thyroid surgery (glands located in the neck)
- Have been told they have trouble absorbing minerals in their stomach or intestines (malabsorption syndrome)
- Have kidney problems or are on kidney dialysis
- Have ever had an allergic reaction to denosumab
- Plan to have dental surgery or teeth removed
- Have a history of cancer
- Could become pregnant
- Are allergic to rubber or latex

Pharmacological Options: Denosumab

Additional warnings and precautions associated with denosumab use include the following:²¹

- The needle cover on the single use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons allergic to it.
- Denosumab may interfere with normal bone and tooth development in fetuses, nursing babies, and children under 18 years of age.
- Children under 18 years of age should not take denosumab.
- Women who are pregnant or could become pregnant should not take denosumab. Patients should tell their doctor right away if they become pregnant while taking denosumab.
- Nursing mothers should not take denosumab. It may also interfere with breastfeeding.
- Denosumab may lower levels of calcium in the blood. Low blood calcium should be treated before receiving denosumab. Symptoms of low blood calcium may include muscle spasms, twitches, cramps, numbness or tingling in hands, feet or around the mouth, and weakness. Some patients may not have any symptoms of low calcium.

Patients should tell their doctor right away if they have symptoms of infection, including fever or chills, skin that looks red, swollen, hot or tender to touch, severe abdominal pain, frequent or urgent need to urinate or burning feeling when urinating.²¹

Patients should tell their doctor if they have any of the following symptoms of skin problems that do not go away or get worse: redness, itching, rash, dry or leathery skin, open, crusted or peeling skin, blisters.

After patients start taking denosumab, they should:²¹

- Take good care of their teeth and gums, and see their dentist regularly
- See their dentist if they have a history of dental problems (such as poorly fitting dentures or gum disease)
- Tell their dentist that they are taking denosumab, especially if they are having dental work
A dental condition called osteonecrosis of the jaw which can cause tooth and jawbone loss has been reported in patients treated with denosumab. Patients should tell their doctor and dentist immediately about any dental symptoms, including pain or unusual feeling in their teeth or gums, or any dental infections.²¹

Some people have developed unusual fractures in their thigh bone. Patients should contact their doctor if they experience new or unusual pain in their hip, groin, or thigh.²¹

Inform about possible interactions with denosumab.²¹

Patients should discuss with their doctor and pharmacist any medications, vitamins, or herbal products they are taking before using denosumab.

Inform about side effects associated with denosumab.²¹

Like all medications, denosumab can cause side effects. Possible side effects include:

- Pain in muscles, arms, legs or back. These side effects were also very common in patients taking placebo.
- Hypocalcemia (symptoms of low blood calcium may include muscle spasms, twitches, cramps, numbness or tingling in fingers, toes or around the mouth) (Rare).
- Allergic reactions (e.g., rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing).
- Skin condition with itching, redness and/or dryness (eczema) (Common).
- Injection site reactions (Uncommon).
- Skin infection with swollen, red area of skin, that feels hot and tender and may be accompanied by fever (cellulitis) (Uncommon).
- Common cold (runny nose or sore throat).

The following serious side effects have been reported with the use of denosumab:

- **Common ($\geq 1\%$, in 1% to 10% of patients) (Talk with doctor or pharmacist only if severe.):** skin condition with itching, redness and/or dryness (eczema).
- **Uncommon ($\geq 0.1\%$, $< 1\%$) (Talk with doctor or pharmacist in all cases.):** skin infection (mainly cellulitis) leading to hospitalization, erysipelas (serious and rapid skin infection commonly on the face or legs).
- **Rare ($\geq 0.01\%$, $< 0.1\%$) (Talk with doctor or pharmacist in all cases.):** low calcium levels in the blood.
- **Rare ($\geq 0.01\%$, $< 0.1\%$) (Talk with doctor or pharmacist in all cases, Stop taking drug if circumstances warrant.):** endocarditis (inflammation of the inner lining of the heart); sore in mouth involving gums or jawbones (osteonecrosis of the jaw); allergic reaction (feeling faint, trouble breathing/wheezing, throat tightness, swelling of face, lips or tongue, rash, hives).
- **Very Rare ($\leq 0.01\%$) (Talk with doctor or pharmacist in all cases.):** unusual thigh bone fractures.

This is not a complete list of side effects. For any unexpected effects while taking denosumab, patients should be informed to contact their doctor or pharmacist.

Ensure that therapy is right for your patient.

Please see Table 7 for indications and associated doses for teriparatide therapy.

Contraindications²²

- Hypersensitivity to teriparatide or any of its excipients
- Pre-existing hypercalcemia
- Severe renal impairment
- Metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone)
- Unexplained elevations of alkaline phosphatase
- Prior external beam or implant radiation therapy involving the skeleton
- Bone metastases or a history of skeletal malignancies
- Pregnancy and nursing mothers
- Paediatric patients or young adults with open epiphysis

Inform the patient about warnings and precautions associated with teriparatide.

Serious Warnings and Precautions²²

As part of drug testing, teriparatide was given to rats for a significant part of their lifetime. In these studies, teriparatide caused some rats to develop osteosarcoma, a bone cancer. The potential to cause osteosarcoma in rats was increased with higher doses and longer periods of treatment. Osteosarcoma in humans is a serious but very rare cancer. Osteosarcoma occurs in about 4 out of every million people each year. None of the patients in the clinical trials or post-treatment follow-up developed osteosarcomas. Osteosarcoma has been reported rarely in people who took prescription teriparatide. It is not known if people who take teriparatide have a higher chance of getting osteosarcoma. Patients should discuss any safety concerns they have about the use of teriparatide with their doctor.

Inform about possible interactions with teriparatide.²²

Patients should tell their healthcare provider and pharmacist about all the medicines they are taking when they start taking teriparatide, and if they start taking a new medicine after they start teriparatide treatment. Healthcare providers should be informed about all medicines that patients get with prescriptions and without prescriptions, as well as herbal or natural remedies.

Inform about side effects associated with teriparatide.²²

Most of the side effects of teriparatide are mild. The most common side effects of teriparatide are dizziness, nausea, pain in and around joints, and leg cramps. If a patient becomes dizzy, they should not drive or operate machinery; they should sit or lie down until the symptoms go away. If symptoms continue or get worse, they should call a doctor before continuing treatment. Patients should be advised to contact healthcare provider if they have continuing nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs that there is too much calcium in blood.

This is not a complete list of side effects. For any unexpected effects while taking teriparatide, patients should be informed to contact their doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at **1-866-234-2345**
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to **1-866-678-6789**, or
 - Mail to: **Canada Vigilance Program**
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

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CE Questions

Submitting Answers to the CE Questions

1. Create an account at www.healthlearning.ca if you do not already have one.
2. Log in to your Pear Health eLearning account and click CE COURSES.
3. Select “Osteoporosis: Pharmacological Options and Considerations for Prevention and Management Guide,” then click ENROL NOW.
4. Follow the onscreen prompts to complete the order.
5. Click MY ACCOUNT/ENROLLED COURSES.
6. Enter the CE and select the answers to the CE Test, then click SUBMIT.

Note:

You must correctly answer seven out of ten (70%) in order to obtain 1.0 CE unit. You may make two attempts to achieve a passing grade.

If you achieve 70% or more on your first attempt, your test results and Letter of Completion will be emailed to you for your personal records. You can access this document under MY ACCOUNT/COMPLETED COURSES.

Case 1: Jill is a 51-year-old woman who has been generally healthy for most of her life. She was diagnosed with hypertension two years earlier and currently takes perindopril 4 mg daily for blood pressure control. She has osteoarthritis in her hands and takes acetaminophen 1 g QID prn for pain. Her normal intake of acetaminophen is 1 to 2 g daily. Jill has never smoked and she drinks alcohol only on occasion. Her weight is 58 kg and her body mass index (BMI) is 20 kg/m².

1. Jill has just had a check-up at her doctor’s office and was told that she should have a bone mineral density test done. Which of the following is the primary reason for this?
 - a. She has osteoarthritis
 - b. She is 45 years of age or older
 - c. Her weight is below 60 kg
 - d. Answers a and c are both correct
2. Which of the following best corresponds to Jill’s 10-year risk of a major osteoporotic fracture according to FRAX® assessment if she has one clinical risk factor?
 - a. 3.3%
 - b. 4.9%
 - c. 7.6%
 - d. 12.0%
3. Jill tells you that she gets about 600 mg elemental calcium daily from her diet. Which of the following supplements would be your best recommendation?
 - a. 1000 mg calcium citrate daily
 - b. 1500 mg calcium lactate daily
 - c. 2000 mg calcium gluconate daily
 - d. 1500 mg calcium carbonate daily
4. Jill informs you that her doctor has recommended that she take 2000 IU vitamin D based on the results of a 25-hydroxyvitamin D laboratory test. What would your response be to this?
 - a. That is far too high as the dietary reference intake for a woman your age is only 600 IU daily
 - b. Since there is no tolerable upper intake level of women over 50, the dose should be fine
 - c. The dose is well within the tolerable upper intake level for an individual your age
 - d. You must be at high risk for osteoporosis if your doctor recommended a dose of vitamin D as high as that

CE Questions

Case 2: Mary is a 64-year-old woman who has been found to have a 10-year estimated risk for major osteoporotic fracture of 24%. Subsequently, Mary had a BMD test that revealed she has osteopenia. Her doctor would like to start her on bisphosphonate therapy for primary prevention of osteoporosis.

5. Which of the following is first-line therapy for prevention of vertebral fractures only?
 - a. Raloxifene
 - b. Denosumab
 - c. Alendronate
 - d. Zoledronic acid
6. Mary has been prescribed risedronate 35 mg delayed-release tablet. Which one of the following statements about this medication is TRUE?
 - a. It should be taken once a month to prevent osteoporosis
 - b. It should be taken in the morning, with breakfast
 - c. It is indicated for treatment of glucocorticoid-induced osteoporosis
 - d. All of the above statements are TRUE
7. Mary tells you that the bisphosphonate she is taking is upsetting her stomach and that she has heard there is an injectable drug that might help to prevent this. You let her know that she is thinking of zoledronic acid and that it could be an option for her. What dose would you recommend?
 - a. One dose only and monitor
 - b. One dose yearly
 - c. One dose twice a year
 - d. One dose each month
8. She asks about additional injectable medications for osteoporosis management and you ask if she might be thinking about denosumab or teriparatide. Which of the following statements about denosumab and teriparatide is TRUE?
 - a. Both are administered on a daily basis
 - b. Denosumab is indicated for all women with osteoporosis
 - c. Teriparatide may be used for as long as it is deemed effective
 - d. Denosumab may reduce blood calcium levels
9. Mary tells you that one of her friends is taking a drug for osteoporosis and that she needs to be sure to observe good dental hygiene. You tell her that she is probably referring to a side effect called osteonecrosis of the jaw, which is a rare but important side effect. Which of the following drugs would Mary's friend most likely to have been taking?
 - a. Alendronate
 - b. Raloxifene
 - c. Denosumab
 - d. Answers a and c are both possibilities
10. Which of the following statements about risks associated with use of hormone therapy for management of osteoporosis is TRUE ?
 - a. The WHI trial results suggest that dementia risk is reduced in all women using hormone therapy
 - b. The WHI trial results suggest an increased risk of blood clots in the large veins of all women taking hormone therapy
 - c. The WHI trial results suggest that oral hormone therapy plus progestin but not transdermal hormone plus progestin therapy increases risk of breast cancer
 - d. The WHI trial results suggest increased risk of stroke and coronary heart disease in women who have had a hysterectomy taking estrogen therapy



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