Treating Osteoporosis

WITH BISPHOSPHONATES

sigma
Canadian Menopause Society
Société canadienne de la ménopause

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Who is SIGMA?

SIGMA is the Canadian Menopause Society. We are professionals specialized in different areas of post-menopausal women's health care, including family practitioners, endocrinologists, gynecologists, rheumatologists, geriatricians, nurse-educators, and others. We seek to improve the care of our patients through educational initiatives directed to health care providers and patients. Please visit us at www.sigmamenopause.com.

Our information brochure on intravenous bisphosphonates is directed to patients considering osteoporosis therapy or those on therapy with questions regarding the medications. This information has been developed with the assistance of SIGMA osteoporosis experts across the country. We have answered commonly-asked questions in a way that is direct, clear and easy-to-understand. The information provided is general and not a substitute for your personal physician's advice.

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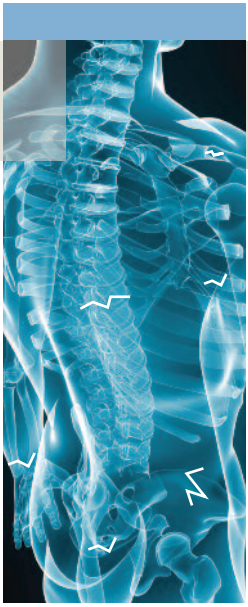
The Frequently Asked Questions We Will Address:



What is osteoporosis and why should I take medications for osteoporosis?

Osteoporosis is defined as a loss of bone strength leading to increased risk of "fragility fractures". These are fractures occurring without great trauma during non-vigorous day-to-day activities or after a fall from standing height. Fragility fractures occur most frequently in the spine, hip, wrist, pelvis, shoulder, and ribs. These fractures are important as often they are painful, may result in permanent deformity, and may result in loss of independence as we get older.

Your physician can evaluate your fracture risk (as a postmenopausal woman or a man over age 50) by asking questions regarding risks for osteoporosis, looking for signs of osteoporosis, and doing a bone density test (DXA test).

Fragility fractures are important as often they are painful, may result in permanent deformity, and may result in loss of independence as we get older.

If the bone density score (called a T-score) at the hip or spine is -2.5 or less, the lifetime risk of fracture is increased to a level where medications are generally advisable. This is in addition to calcium, vitamin D and lifestyle advice. A diagnosis of osteoporosis can also be made in a patient who has experienced a fragility fracture. In this case, medications should be started regardless of the bone density result since we know that such patients are at the highest risk of future fracture. Sometimes patients who are not on treatment have DXA results in the low bone density (or osteopenia) range. In such cases, the decision to use medications can be aided by calculating a 10-year risk of fragility fracture, using tools such as the World Health Organization (WHO) Fracture Assessment Tool (http://www.sheffield.ac.uk/FRAX/).

The 2010 North American Menopause Society guidelines (http://www.menopause.org/PSosteo10.pdf) would recommend medications be prescribed to postmenopausal women and men over age 50 with:

- a prior hip or spine fracture;
- T-score hip, spine or wrist less than or equal to -2.5;
- T-score between -1 and -2.5 and FRAX score for 10 year risk of osteoporotic fracture greater than 20% or hip fracture FRAX greater than 3%.

What are bisphosphonates and what are they used for?

Bisphosphonates are a class of medications used to treat a variety of bone conditions. These include high blood calcium, Paget's disease of bone, cancer which has spread to bone, and osteoporosis. Since their first approval for use in humans in 1977, these drugs have benefited many millions of women and men.

As a class, these medications are extremely safe and well-tolerated. The common features of drugs in this class include strong attachment to the surface of bone and the ability to slow the removal of old bone. Etidronate (Didrocal), was the earliest medication in this class to be introduced. There are now several available bisphosphonate medications, which can be dosed orally or intravenously.

Generic name	Route	Frequency of dosing for osteoporosis	Trade name	Paget's disease	High blood calcium	Bone cancer	Osteoporosis prevention	Osteoporosis treatment
Alendronate	Oral	Daily Weekly	Fosamax/ Fosavance	X			X	X
Clodronate	Oral/ intravenous	Daily/ cyclic	Bonefos	X	X			
Etidronate	Oral/ intravenous	Cyclic	Didrocal	X				X
Pamidronate	Intravenous	Monthly	Aredia	X	X	X		
Risedronate	Oral	Daily Weekly Monthly	Actonel	X			X	X
Zoledronic acid	Intravenous	Annually	Aclasta	X	X	X	X	X

Why are some bisphosphonates approved for cancer treatment, others for osteoporosis treatment and some for both?

Health Canada approvals for medications depend on the trials which have been performed. Some bisphosphonates have clinical trials showing effectiveness for osteoporosis, some for cancer, and some for both. Only intravenous bisphosphonate therapy has proven effectiveness for the prevention and treatment of cancer that has spread to bone. Bisphosphonate for bone cancer is given intravenously every 2 to 4 weeks; the same medications for osteoporosis can be given at intervals as long as every 1 to 2 years.

Bisphosphonates are also effective in preventing the bone loss associated with some cancer chemotherapy. Bisphosphonate side-effects are different in patients treated for cancer than for patients treated for osteoporosis. This is due to the higher bisphosphonate dosage in cancer patients as well as the other cancer treatments given at the same time such as chemotherapy and radiotherapy.

What are the differences between the different bisphosphonate drugs?

Bisphosphonate medications differ in chemical structure. This results in different binding to bone and different potency in slowing the removal of old bone. They also differ by dosing schedule (cyclic, daily, weekly, monthly, annually) and route of administration (oral, intravenous). The specific medications used are detailed on page 5. Bisphosphonates given by an intravenous infusion can ensure absorption of the medication with effectiveness lasting 1 year or longer. Etidronate can weaken bone if given continuously and must be given in cycles to allow the bone to recover. All other bisphosphonates do not have this effect and can be given continuously. Alendronate, risedronate and zoledronic acid have been shown to reduce spine, hip and non-spine fractures. Different bisphosphonate therapies have different approvals by Health Canada as a result of the trials which have been performed. Direct fracture comparison of one agent against another has not been performed and so we cannot answer whether one bisphosphonate is better than another at preventing fracture.

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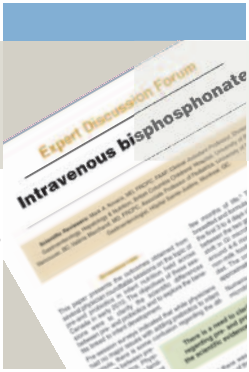
Can you help me understand the risks and benefits of these medications?



Physicians prescribe medications to benefit bone health and to reduce fragility fractures. They will consider all of the risks and benefits when choosing the right drug for the right patient at the right time in the patient's life. Usually, this information is from medical journals where the results of clinical trials testing a medication against a "dummy pill" (called a placebo) are published.

In patients with osteoporosis, we know that the benefits of bisphosphonate therapy in preventing fractures are great. A 65-year-old woman with a bone density T-score of -2.5 has a 10-year FRAX fracture risk of 20% and could anticipate a fracture risk reduction to about 10% (reduction of risk by 50%) by taking an osteoporosis medication.

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This reduction in risk is in addition to the benefits of calcium, vitamin D, and a healthy life style. In contrast, the risk of having a delay in dental bone healing after a tooth extraction on bisphosphonate (ONJ or osteonecrosis of the jaw) has been estimated to be less than 1 in 100,000.

How do I know that bisphosphonates are safe for me?

All treatments have risks and benefits. These risks and benefits of treatment must be first understood from the clinical trials where the drug is tested against a placebo, or an inactive dummy pill. Such trials in osteoporosis have involved 2,000 to 10,000 patients followed for 3 to 5 years. These trials have led to medication approvals from government agencies such as Health Canada and the FDA.

It is possible for rare side effects to occur which have not been seen in clinical trials. In such cases, "post-marketing surveillance" programs are put in place. We understand, however, that patients treated with osteoporosis medications will still have some fractures, since such treatments are not 100% effective in preventing fracture. A fracture occurring while someone is on treatment does not mean that the medication has failed or caused the fracture. It rather indicates that our treatments are effective in preventing some but not all fragility fractures.

Risks and Benefits of Osteoporosis

Mrs. T
- 65 years old
- T-score of -2.5
- Prior wrist fracture
- Family history: mother had hip fracture

Risk of subsequent fracture: 20% over 10 years
(*e.g.*, 20 out of 100 women over 10 years)

The benefit of treating with anti-osteoporosis therapy

Dramatically reduced risk of future fracture
(~50% reduction in fracture risk over 10 years)
e.g., 10 fractures prevented among 100 women over 10 years

Risks of treating with anti-osteoporosis therapy

Negligible increased risk of brittle bones or osteonecrosis of the jaw (ONJ)
e.g., for ONJ: less than 1 case / 100,000 patient-years with bisphosphonate

What the doctor might say:
"Mrs. T, if you take anti-osteoporosis therapy, your chances of having another fragility fracture in the next 10 years is cut in half, to about a one-in-ten chance. There is a very remote possibility of serious side effects. Your chances of having one of these serious side effects is less than one in 100,000.
Fragility fractures are a very significant problem that can seriously impact on your quality of life.
Bisphosphonate treatment can considerably reduce the risk of fragility fracture and is very safe in the vast majority of people who take it."

The benefits of anti-osteoporosis therapy outweigh the risks

How do the bisphosphonates work and why can dosing be daily, weekly, monthly or yearly?

After entering the blood stream, bisphosphonate medications bind rapidly to bone. Drug not bound to bone rapidly passes out of the body through the kidney. The bisphosphonate medication remains stuck on the bone surface for a long time where it decreases the functioning of bone removing cells (osteoclasts). With reduced removal of old bone, the healthy balance of bone removal and bone formation can be re-established. Because the bisphosphonate medication remains on the surface of bone for a long time, daily dosing is not required. The interval between doses depends on the amount of bisphosphonate sticking to the bone, the length of time the bisphosphonate stays stuck on the bone, and the strength of the particular bisphosphonate in slowing the removal of bone by osteoclasts. Because the usual reason for post-menopausal osteoporosis is over-activity of osteoclasts (which removes bone), treatment with bisphosphonate restores bone removal to a level similar to that of a younger person thereby decreasing the risk of fracture.

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What are the similarities between intravenous and oral bisphosphonates?

All bisphosphonates go to the surface of bone where they stick tightly. They are then available to slow the removal of bone by bone-removing cells called osteoclasts. They have no direct effects on the cells which form bone (osteoblasts). Intravenous bisphosphonates are directly given into the circulation making absorption more reliable than tablets. Both are able to stick to the surface of bone and remain for a long time. Both oral and intravenous bisphosphonates can prevent fractures from osteoporosis. Both forms of bisphosphonate will either increase or stabilize bone density over time.

What are the differences between intravenous and oral bisphosphonates?

The major difference in bisphosphonates is in the way in which they are given (into the vein or oral) and the interval between doses. Different bisphosphonate medications may have different abilities to prevent fractures and may have different side-effects. Intravenous bisphosphonates are 100% absorbed. Oral bisphosphonates are poorly absorbed with at best 1-3% of the tablet dose being absorbed. Dosing must be 30-60 minutes before breakfast, with just water and with delay of first food or drink until at least 30 minutes has passed. An important aspect of using medications for osteoporosis is whether the patient is willing to continue on long-term treatment. Many patients prefer taking their bisphosphonate at longer intervals. The longest interval dosing available is with zoledronic acid annual intravenous infusion.

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Why do oral bisphosphonates have such inconvenient dosing instructions?

Bisphosphonates are very poorly absorbed when given orally by tablet. Even if dosed properly, only 1% to 3% of the medication in the tablet is able to be absorbed and to enter the body. The remainder binds to stomach contents and does not get absorbed. It is for this reason that dosing must be 30-60 minutes before breakfast and with only plain water. The first food or drink of the day other than water must be delayed for at least 30 minutes in order to permit absorption. Other dosing schedules lower the effectiveness of the medications. You should drink at least 8 ounces of water when you take the tablet to be sure it goes into the stomach and that there is enough water to disperse the medication. After dosing, you should not lie down for 60 minutes to ensure that the medication does not wash back and cause heartburn symptoms.

What are the side effects of oral bisphosphonates?

The trials of tablet bisphosphonates show a low rate of stomach upset, not different in those treated as compared to those not treated. Nevertheless, there are people who do not tolerate bisphosphonate tablets due to stomach side effects. Often it is difficult to know whether stomach upset is from the osteoporosis tablet or from heartburn that might have occurred without the medication. Others with difficulty swallowing pills, unable to sit up after dosing, or with a disease interfering with absorption may not be suitable for tablet bisphosphonate therapy. In these cases, intravenous bisphosphonate offers the benefits of bisphosphonate therapy to patients without the possibility of stomach side-effects. In addition, patients taking many medications or diabetics unable to delay breakfast may also benefit from an intravenous bisphosphonate.

What are the side effects of intravenous bisphosphonate therapy?

With intravenous bisphosphonate therapy, there should be no stomach side effects as the medication is not passing through the stomach. Flu-like symptoms or "acute-phase reaction" may occur in the 3-4 days after the infusion (and occasionally with oral bisphosphonates). The muscle aches, mild fevers, and headaches are not the result of any virus infection and disappear within a few days, as soon after the medication has been cleared from the bloodstream. Symptoms may be prevented by taking sufficient fluids both before and after the infusion. This reaction occurs in up to 20% of patients on first infusion but in only about 3% of patients on second and subsequent infusions. Acetaminophen (Tylenol) taken before and after the infusion may be helpful. This side effect should last only a few days and if symptoms continue, you should consult with your physician.

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What would happen if I had an allergic reaction to intravenous or oral bisphosphonates?

Allergies to bisphosphonates are very rare. Should you have an allergic reaction to an oral or an intravenous therapy, your doctor could deal with this as with any other medical allergic reaction using medications such as adrenaline, antihistamine, and prednisone. Bisphosphonates do not remain in the blood circulation for very long and disappear rapidly by being deposited on the surface of bone or being removed through the kidneys. An allergic reaction would not be expected to last longer than the drug is circulating in the bloodstream, usually less than 48 hours. The medication that remains on the surface of bone would not cause an allergic reaction and would be similar whether you have taken this medication by mouth or by intravenous infusion. Allergic reactions are acute short-term problems different from other side effects of medications and are rarely described with the bisphosphonates.

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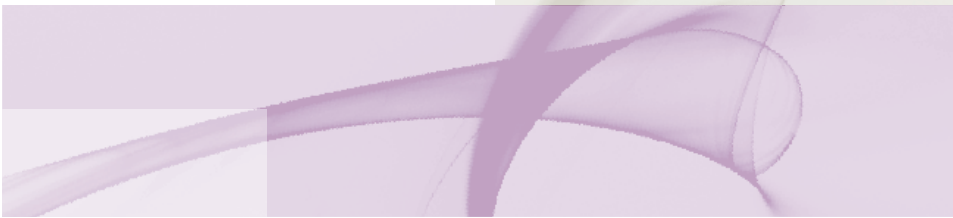
If I had a problem, how could the drug be removed from my body?

No medication can be easily removed from the body by other than natural mechanisms. In the case of bisphosphonates, the medication is cleared from the system by the kidneys or by depositing in bone. In the bone, it helps strengthen bone and reduces the risk for fractures. These medications cannot be immediately removed from the bone once given. If one does stop taking bisphosphonates, its effect will gradually disappear over the course of the following year. Whether taken daily, weekly, monthly, or yearly, the action of bisphosphonates is similar. The long action of some bisphosphonates (alendronate, zoledronic acid) would be seen in many instances to be an advantage of therapy, still providing bone protection up to one year after the medication has been discontinued.



What long-term information is available with bisphosphonate therapy? Should I take a drug holiday?

Long-term information is available for bisphosphonate therapy. These medications have been in use for over 40 years to treat various medical problems. Most medications are approved subsequent to clinical trials of only a few months' duration.

A drug holiday may seem attractive to some patients. We know, however, that if medication is stopped in a patient at risk of osteoporotic fracture, the fracture risk will return after a variable period of time.

Because osteoporosis therapies must be continued for many years, long-term information has been collected from clinical trials to a much greater extent than with other medicines. The main clinical trials with bisphosphonates must be for 3 years and involve thousands of patients. This long-term information is very reassuring. There is protection from fractures and safety from side effects over at least 10 years with alendronate therapy. Women who continue alendronate for 10 years have fewer fractures and better bone density than women on alendronate for just 5 years. A drug holiday may seem attractive to some patients. We know, however, that if medication is stopped in a patient at risk of osteoporotic fracture, the fracture risk will return after a variable period of time. There is no more reason to stop therapy and take a "drug holiday" from bisphosphonate (if you are at risk of fracture) than there is to stop blood pressure or cholesterol therapy.

The long-term osteoporosis data are for 10 years with alendronate, 7 years with risedronate, and 3 years with etidronate and zoledronic acid. With several of the bisphosphonates, there are studies in patients with other diseases (Paget's disease, high blood calcium, cancer) indicating their safety over the longer term.

What is osteonecrosis of the jaw and what is its link to bisphosphonates use?

Osteonecrosis of the jaw (ONJ) results in delayed healing for more than 8 weeks of mouth ulcers with exposed bone. This is usually after a tooth extraction or an oral surgery involving cutting the gums. It may also occur with radiation treatments for cancer. Other risks for poor healing include chemotherapy, prednisone, and poor oral hygiene. Slow healing in the mouth can also occur without any risk factors. In patients with cancer spread to the bones, high dose intravenous bisphosphonates (doses every 3 weeks) are given to prevent the cancer from invading bone. In such cancer patients on very high dose bisphosphonate therapy, a delay in dental healing of more than 8 weeks has been described in very few cases. In the controlled trials

of osteoporosis patients treated with any of the bisphosphonates, we have not seen any risk of ONJ. Therefore, the risk for osteoporosis patients must be extremely low, perhaps less than 1 in 100,000 persons treated.

You must also remember that persons not treated with bisphosphonates may also have a delay in dental healing often due to poor oral hygiene or infrequent dental care. Necessary dental surgery or dental implants should not be delayed or avoided because of bisphosphonate therapy. If desired, bisphosphonate therapy could be stopped 3 months before elective dental surgery and then restarted after everything has fully healed.

Will long-term treatment with bisphosphonates cause my bones to be brittle?

Bisphosphonates are effective in preventing fracture by slowing the removal of old bone. As bone ages, more calcium can deposit in the bone, making it stronger. This prevents fractures and there is no sign that fractures increase later in people who remain on therapy. Rather, women who continue bisphosphonate therapy such as alendronate for 10 years have fewer fractures and better bone density than women on alendronate for just 5 years. This ongoing fracture protection reassures us that bones do not become brittle. Recently, there have been reports of "chalk-stick fractures" of the thigh bone. These are rare fractures of the mid thigh bone, often occurring in patients with osteoporosis. In clinical trials of bisphosphonates, these fractures occur equally in those on bisphosphonate or not on bisphosphonate therapy.

Women who continue bisphosphonate therapy such as alendronate for 10 years have fewer fractures and better bone density than women on alendronate for just 5 years.

Although bisphosphonates reduce the risk of fracture by 40% to 70%, there will continue to be some osteoporosis patients on bisphosphonate treatment who will suffer a fracture. Overall, however, there is clearly effective fracture prevention with bisphosphonate use over at least 10 years.

Is there a risk of cancer with bisphosphonates?

There are no known cancer risks with bisphosphonate therapy. Indeed, intravenous bisphosphonates are used to treat patients with cancer, such as breast and prostate, which has spread to the bones. In such cases, they are given to reduce pain, decrease fractures and prolong life. Some trials suggest effectiveness of bisphosphonate therapy in preventing cancer recurrence or cancer spreading to the bones.

Is there a risk of heart rhythm problems on bisphosphonates?

Atrial fibrillation is a disturbance of the rhythm of the heart which is commonly seen in older individuals. Untreated, it can result in low energy, shortness of breath, and occasionally stroke. Most often it is due to hardening of the arteries and heart disease but not from medications. It often can be easily and effectively treated. The question of atrial fibrillation associated with bisphosphonate therapy arose when, in one trial, there was a small excess of serious atrial fibrillation associated with intravenous zoledronic acid therapy as compared to not taking this therapy. The numbers were small and further studies were undertaken. There were no heart rhythm problems seen in patients treated with other bisphosphonates, even in very elderly and frail patients or those taking very high doses of medication.

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Indeed, in frail elderly patients after hip fracture, annual intravenous zoledronic acid was seen to have reduced deaths by 28% as compared to only calcium and vitamin D. In this trial there was no difference in atrial fibrillation in patients on therapy. These reassuring data led the FDA and Health Canada to determine that the risk of atrial fibrillation should not be a decision-making factor for patients requiring osteoporosis therapy.

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For references and additional information, please visit www.sigmamenopause.com.

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