

The role of dental care providers in the management of patients prescribed bisphosphonates: brief clinical guidance

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Dental care providers are likely to see patients who take bisphosphonates for various medical conditions, including osteoporosis, bony metastatic tumors, multiple myeloma, breast cancer, and prostate cancer. Bisphosphonates accumulate in areas of high bone turnover, leading to suppression of bone turnover and the aging of keratocytes. These adverse effects predispose the maxillary and mandibular bone to development of medication-related osteonecrosis of the jaw (MRONJ), specifically among oncology patients treated with intravenous bisphosphonate therapy. Studies have shown that stopping bisphosphonate therapy, temporarily (drug holiday) or permanently, is not significantly effective. The effectiveness of a drug holiday is likely limited due to the pharmacologic activity of bisphosphonates and their persistent, long-term effect on bone. Therefore, patients should not be discouraged from taking bisphosphonates for an existing medical condition. A dental health assessment by an oral surgeon, a dental specialist, or a well-trained general dental practitioner is highly recommended prior to treatment with bisphosphonate. The evaluating clinician must attempt to eliminate or mitigate risk factors to prevent the development of MRONJ. It is crucial for dental care providers to recognize the clinical signs and symptoms of MRONJ, including its radiographic appearance. In cases of any suspicious oral lesion, early referral to an oral surgeon is crucial. It is better to avoid dental extractions during the active period of treatment and to treat the tooth carefully with nonsurgical root canal treatment instead. This review provides brief clinical guidance for dental care providers regarding management of patients prescribed bisphosphonates and ways to help minimize patients' risk of developing MRONJ.

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Bisphosphonates are one of the most widely used bone-modifying agents.¹ They are a nonmetabolized analog of pyrophosphate, consisting of 2 groups of phosphate with 2 chains (designated R_1 and R_2) bound together by a carbon atom.^{2,3} There are 2 classes of bisphosphonates, defined by the presence or absence of a nitrogen atom, that have different modes of action.^{4,5} For example, the nitrogen group is extremely bone selective and has a high affinity for calcium ions.^{6,7} Therefore, it is attracted strongly to the bone.

During the bone resorption process, bisphosphonate is released from the bone surface, where it is taken up by osteoclasts.⁸ This inhibits farnesyl pyrophosphate synthase and targets protein prenylation (reversed by a substrate for protein prenylation, geranylgeraniol), leading to reduction of the function and activity of osteoclasts, thus enhancing their apoptosis and stimulating osteoclast inhibitor factors, which in turn induce the downregulation of matrix metalloproteinases and bone formation.^{1,7-9}

Unfortunately, bisphosphonates accumulate in areas of high bone turnover—such as the mandible and maxilla—leading to suppression of bone turnover and the aging of keratocytes, resulting in defective reepithelization in the oral cavity and delayed wound healing.^{5,10,11} Bisphosphonates also have antiangiogenesis effects, reducing the blood supply to tissues (Chart).¹² These unwanted effects predispose the maxillary and mandibular bone to development of medication-related osteonecrosis of the jaw (MRONJ). MRONJ is defined as an unhealed, exposed area of bone that is present for more than 8 weeks in a nonirradiated maxilla or mandible of a patient treated with bisphosphonates and/or certain other antiresorptive (denosumab) and antiangiogenic therapies.^{13,14} The conventional appearance of MRONJ on a periapical dental radiograph is a thickening of the lamina dura, moderate bony sclerosis, and osteolysis in the socket, which might extend into the inferior alveolar nerve canal, causing a narrowing of the canal and resulting in painful neuropathy (Figure).¹⁵⁻¹⁷

The original term used to describe this condition was *bisphosphonate-related osteonecrosis of the jaw* (BRONJ), but it recently has been replaced with the broader term *MRONJ*, as other forms of antiresorptive therapy in addition to bisphosphonates have been found to cause osteonecrosis involving the mandible and maxilla.^{18,19} The term *MRONJ* will be used in the present review, which provides brief clinical guidance for dental care providers regarding management of patients prescribed bisphosphonates and ways to help minimize patients' risk of developing MRONJ.

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Chart. Pathophysiology of medication-related osteonecrosis of the jaw.

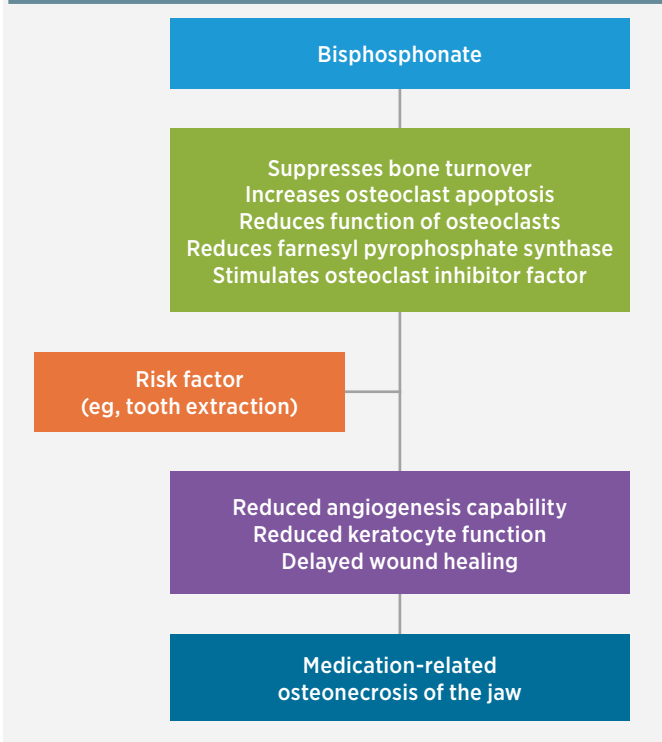


Figure. Conventional periapical dental radiographic appearance of medication-related osteonecrosis of the jaw for a patient treated with intravenous bisphosphonate. Note the thickening of the lamina dura, moderate bony sclerosis, and osteolysis in the socket.

Medical conditions treated with bisphosphonates

Use of bisphosphonates can help to prevent bone resorption and fracture, reducing the risk of morbidity and mortality.² Bisphosphonates are used to treat women with postmenopausal osteoporosis.²⁰ They are also used in the treatment of other nonmalignant medical conditions, such as osteogenesis imperfecta, fibrous dysplasia, Paget disease, and primary hyperparathyroidism.²⁰⁻²⁵

Bisphosphonates are also prescribed for treatment of several malignant conditions, including bone tumors associated with metastatic cancer, hypercalcemia of malignancy, multiple myeloma, and bone cancers such as Ewing sarcoma (the second most common bone cancer in young adolescents).^{2,26-29} Additionally, as they have an antitumor effect, bisphosphonates can be used in the treatment of breast and prostate cancers.³⁰⁻³²

Incidence and prevalence of MRONJ

The exact incidence of MRONJ is still unknown.³³ However, studies have shown that the risk of developing MRONJ in patients prescribed an oral bisphosphonate differs substantially from the risk in patients prescribed intravenous therapy.³³⁻³⁶ Furthermore, the incidence of MRONJ differs depending on the reason the patient takes the drug; underlying medical conditions; and duration of exposure to the drug. For instance, some medical reports have estimated the incidence of MRONJ to be 1% (1 case per 100) in cancer patients treated with antiresorptive or antiangiogenic drugs and 0.01%-0.10% (1-10 cases per

10,000) in osteoporosis patients treated with antiresorptive drugs.³⁵

In their systematic review, Khan et al found the greatest incidence of osteonecrosis of the jaw (1%-15%) among oncology patients, who receive these medications in high doses at frequent intervals.³⁶ They estimated the incidence of osteonecrosis of the jaw among osteoporosis patients to be 0.001%-0.01%, a rate only slightly higher than the reported incidence among the general population (less than 0.001%).³⁶

Lo et al found obvious differences in the prevalence of MRONJ in different areas of the world.³⁷ They discovered that the prevalence of MRONJ in the United States was 1 in 1537 of the entire cohort study (8572 patients received oral bisphosphonates), which represents 28/100,000 per person-years of exposure.³⁷ Conversely, a retrospective study in Saudi Arabia reported no cases of MRONJ in 88 patients undergoing bisphosphonate therapy (79 patients [89.8%] received oral bisphosphonates and 9 patients [10.2%] received intravenous bisphosphonates).³⁸ A 3-year, international, multicenter, randomized, double-blind, placebo-controlled clinical trial study of 7714 patients with postmenopausal osteoporosis (3862 patients in the zoledronic acid group and 3852 patients in the placebo group) reported only 2 MRONJ cases (1 participant in each group).³⁹ Furthermore, a Swedish retrospective study of 64 patients with osteogenesis imperfecta who received monthly intravenous infusion of bisphosphonates did not report any MRONJ cases.⁴⁰ In the United Kingdom, a study recording new cases of avascular necrosis of the jaws

Table 1. Reported use of bisphosphonates and development of MRONJ in patients with different medical conditions.

Study		Patients		Bisphosphonate therapy			Cases of MRONJ
Author (year)	Type	No.	Age (y)	Reasons	Route	Duration (y)	
Alzoman (2011) ³⁸	Retrospective cohort	88	30-80	Bone diseases in 76 patients; cancer in 8 patients; unreported in 4 patients	79 Oral 9 IV	1.0-9.0	No cases reported
Lo et al (2010) ³⁷	Retrospective cohort	8572	76-82	Any medical condition except dementia or HIV; patients taking IV bisphosphonates were excluded	Oral	2.5-4.7	9
Walter et al (2009) ⁵⁵	Retrospective cohort	75	30-92	Metastatic breast cancer	Oral or IV every 3 or 4 wk	6.0-9.3	4
Vahtsevanos et al (2009) ²⁸	Longitudinal cohort	1621	41-92	Multiple myeloma, breast cancer, or prostate cancer	IV	> 0.5	80
Grbic et al (2008) ³⁹	3-Year, international, multicenter, randomized, double-blind, placebo-controlled clinical trial	7714 (3862 in zoledronic acid group and 3852 in placebo group)	65-89	Postmenopausal osteoporosis	IV	3.0	2 (1 in each group)
Malmgren et al (2008) ⁴⁰	Retrospective cohort	64	0.25-20.90	Osteogenesis imperfecta	Monthly IV infusion for all 64 patients; 10 continued with oral therapy	0.5-12.5	No cases reported

Abbreviations: HIV, human immunodeficiency virus; IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw.

over a 2-year period documented 369 cases of MRONJ.⁴¹ The authors reported:

A total of 383 cases [of avascular necrosis of the jaws] were registered: 369 were described as BRONJ, 5 as avascular necrosis, and 9 were unknown. Bisphosphonates had been given orally in 207 (56%), intravenously in 125 (34%), both orally and intravenously in 27 (7%), and was unknown in 9 (2%); one had been given denosumab.⁴¹

Risk factors and prevention

The differences in reported incidence rates may reflect the unclear clinical guidance on preventing the development of MRONJ. Current guidance is mainly based on expert opinions as well as case and clinical series reports. A randomized, controlled, prospective experimental study recommended that

bisphosphonate therapy be stopped temporarily or permanently at the time of a dental procedure to help reduce the risk of developing MRONJ.⁴² However, another study has shown that there was no statistically significant difference in the development of MRONJ when a patient submits to a preoperative drug holiday.⁴³ Additionally, a drug holiday is not justified in patients who are at risk for spinal fracture.⁴⁴ For osteoporosis patients who are at risk of fracture, the benefits of continuing the drug outweigh the risk of rare adverse events in the early phases of bisphosphonate therapy.⁴⁵ Therefore, a drug holiday is still considered to be controversial, as randomized clinical trial studies based on risk and benefit assessments are not yet available for the selection of candidates.⁴⁶ If a drug holiday is considered, its duration and length should be individualized for each patient based on fracture history and the patient's other underlying medical conditions; it should not be standard for every patient.^{45,47}

Table 2. Staging and treatment strategies for medication-related osteonecrosis of the jaws suggested by the American Association of Oral and Maxillofacial Surgeons.^{13,14}

Stage	Oral manifestations	Recommendations
0	<ul style="list-style-type: none"> • Unexposed necrotic bone with nonspecific symptoms such as odontalgia, jaw pain, sinusitis, and neurosensory dysfunction • Clinical investigation showing loosening of teeth with periapical pathosis not related to odontogenic infection • Radiographic appearance of bone loss, change of trabecular pattern, osteosclerosis, and thickening of the lamina dura 	<ul style="list-style-type: none"> • Systemic approaches, including prescribed analgesics for chronic pain and antimicrobial medications to control infection • Close follow-up to detect progression to a higher stage of disease • Patient education about the possible risk factors
1	<ul style="list-style-type: none"> • Asymptomatic exposed necrotic bone with no evidence of infection • Radiographic appearance similar to the findings in stage 0 	<ul style="list-style-type: none"> • Antimicrobial mouthrinse • Close monitoring every 3 months • Patient education about the possible risk factors
2	<ul style="list-style-type: none"> • Symptomatic, exposed necrotic bone; pain and redness in the affected region; and evidence of infection, with or without purulent discharge 	<ul style="list-style-type: none"> • Systemic antibiotics, antimicrobial mouthrinse, and analgesics • Debridement and gentle irrigation to help reduce infection and irritation
3	<ul style="list-style-type: none"> • Findings similar to those in stage 2 but extending to the inferior border of the mandible, maxillary sinus, and zygoma • Pathologic fracture and extraoral fistula 	<ul style="list-style-type: none"> • Conservative approaches with antimicrobial medication and analgesics • Antimicrobial mouthrinse • Surgical debridement or resection

General recommendations:

- An oral surgeon should be consulted at all stages.
- Most microbes isolated from exposed bone are sensitive to the penicillin category of antimicrobial medications. However, for patients who are allergic to penicillin, other antimicrobial agents could be used (eg, clindamycin, metronidazole, or erythromycin).
- Microbial culture sensitivity testing is recommended.

Generally, bisphosphonates are well tolerated and rarely cause clinically significant side effects.¹¹ As noted, however, MRONJ has been reported in some patients under treatment with bisphosphonates, more specifically those treated with intravenous injections.⁴⁹⁻⁵⁰ The greater incidence associated with intravenous bisphosphonates may reflect the fact that they are taken at higher doses over shorter intervals than oral bisphosphonates.⁵¹ For example, intravenous pamidronate and/or zoledronic acid have been associated with most cases of MRONJ.^{52,53} A cohort study by Vahtsevanos et al reported the incidence of MRONJ in 1621 oncology patients who received monthly intravenous doses of bisphosphonates.²⁸ The reported incidences were 3.1%, 4.9%, and 8.5% for breast cancer, prostate cancer, and multiple myeloma, respectively. The study clearly showed that oncology patients undergoing intravenous bisphosphonates are at a high risk of developing MRONJ.²⁸ In contrast, some researchers consider the association between oral bisphosphonates and osteonecrosis of the jaw to be insignificant.⁵⁴ Table 1 shows studies investigating different medical conditions treated with bisphosphonates as well as the route and duration of administration and any associated development of MRONJ.^{28,37-40,55}

Because of the lack of consensus on risks, the guidelines for patients treated with bisphosphonates and undergoing dental

procedures (such as oral surgery or dental implant placement) are often vague and lack supporting evidence.⁵⁴ However, the rarity of these cases does not justify dental neglect of these patients, and dental care providers have to assess any patient treated with these drugs, either orally or intravenously. Table 2 shows a summary of the staging and treatment strategies for MRONJ suggested by the American Association of Oral and Maxillofacial Surgeons.^{13,14}

Some studies have identified other contributing factors that might increase the risk of developing MRONJ. As noted previously, an increased risk is particularly associated with intravenous administration of bisphosphonate.⁵⁶ Other risk factors include intraoral trauma, oral surgery, concurrent anticancer treatment, dental extractions, poorly fitted dental appliances, concurrent use of glucocorticoids (possibly resulting in corticosteroid-related osteoporosis), smoking, alcohol abuse, periodontal diseases, and dental diseases.^{12,56-62} Dental care providers must attempt to eliminate or mitigate risk factors to prevent the development of MRONJ.

Differential diagnosis

Dental care providers have to differentiate any lesion suspected of being MRONJ from other conditions, such as sinusitis, mucositis,

periapical pathosis, osteoradionecrosis, periodontitis, gingivitis, and osteomyelitis.⁶³ The patient's medical and dental histories and a preliminary clinical examination are the key factors for diagnosis of MRONJ. Once MRONJ has been identified in a patient, it is necessary to consult with an oral surgeon or refer the patient to an osteonecrosis center, if one is available, as early treatment will help to slow the progression of the disease.

Dental management of patients treated with bisphosphonate therapy

Dental treatment prior to bisphosphonate therapy

Prior to starting bisphosphonate therapy, the patient should be assessed by an oral surgeon, a dental specialist, or a well-trained general dental practitioner. The clinician should strive to improve the patient's oral health by removing any foci of infection through extraction of nonrestorable or infected teeth and perform follow-up examinations to determine the success of the healing process.^{38,64} Additionally, simple restorations, scaling, polishing, and the adjustment of poorly fitting dentures should be performed before bisphosphonate therapy begins.

The dental team should always give general advice to the patient to help reduce the risk of MRONJ and prevent oral disease.³⁴ This includes advice on the patient's oral hygiene regimen, smoking cessation, and diet (especially reduction of sugar intake) and recommendations for regular dental follow-up. The dental team must discuss the signs and symptoms of MRONJ with the patient so he or she can detect the condition in the early stages and seek assistance.⁶⁵ Patients need to report newly developed oral lesions, loose teeth, swelling, pain, and chronic unhealed lesions to their general dental practitioners. The use of dental alert cards for patients at risk of MRONJ (eg, oncology patients) is recommended.⁶⁶ These cards provide valuable information immediately to any dental professional treating the patient.

Dental treatment during and after bisphosphonate therapy

Patients undergoing bisphosphonate therapy should not be subjected to any procedures that have an impact on bone, such as dental extractions, implants, complex restorations, periodontal debridement, and root surface debridement.³⁵ However, patients can undergo routine treatments, such as scaling, polishing, simple restorations, and radiographic examinations.³⁵ Additionally, it is important for the dental team to inform the patient about both the possibility and rarity of MRONJ verbally and in writing.

A recent systematic review showed that there was no scientific evidence of the efficacy of the MRONJ prevention guidelines in patients subjected to tooth extraction.⁶⁷ A laboratory-based study on mice exposed to antiresorptive medications showed that extraction of diseased teeth led to poor healing, including mucosal defects and osteonecrosis; in contrast, when healthy teeth were extracted, mucosal healing was normal in 90% of mice.⁶⁸ The results suggest that the presence of dental disease is an important factor in the development of MRONJ. This is especially true in patients treated with intravenous bisphosphonates. In such cases, dental care providers have to assess the situation and consult with an oral surgeon about proper management of diseased teeth.

Root canal treatment has shown effective results in relieving pain and avoiding dental extractions that might precipitate MRONJ.⁶⁹⁻⁷¹ Although nonsurgical endodontic treatment appears safe, care should be taken during rubber dam and clamp adjustment.^{72,73}

As noted, the management of patients treated with bisphosphonate therapy is controversial. However, a prospective 6-year study concluded that initiation of a preventive dental care protocol prior to bisphosphonate therapy and regular follow-up dental care at 3-month intervals during therapy will significantly reduce the risk that patients will develop MRONJ.⁷⁴

Conclusion

Dental care providers have to consider the possibility that MRONJ may develop in any patients treated with bisphosphonates in the past. Additionally, dentists must carefully assess any patients who are currently prescribed bisphosphonates, particularly those treated intravenously. It is preferable if oral pathoses and dental disease can be eliminated or mitigated before bisphosphonate therapy is initiated. The inclusion of dentistry in the care pathway for these patients is the key factor to avoid possible future complications.

There is no absolute evidence to support the idea that the risk of MRONJ is reduced by stopping the medication temporarily or permanently. The effectiveness of drug holidays is likely limited due to the pharmacologic activity of bisphosphonates and their persistent, long-term effect on bone. In cases of any suspicious oral lesion, early referral to an oral surgeon is crucial. It is better to avoid dental extractions during the active period of treatment and to treat the tooth carefully with nonsurgical root canal treatment instead.

There is a substantial lack of evidence and consistency in the reported incidences of MRONJ in different countries. The reported incidences of MRONJ should be interpreted with caution based on each country's guidelines, if they are available. Further clinical trials in conjunction with regular follow-up examinations are required to determine the factors involved in the development of MRONJ and their relative importance, which will help in the establishment of consistent preventive guidelines.

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