Research paper

MEDICATION-RELATED OSTEONECROSIS OF JAWS: A SCOPING REVIEW OF CONTEMPORARY EVIDENCE

Dr. V Selva Sigamani[1], Dr. M Surenthar[2], Dr S K Kamaladharani[3]

[1]Postgraduate Resident, Department of Oral Medicine, Radiology and Special Care Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India
Email: selvarev52@gmail.com

[2]Assistant Professor, Department of Oral Medicine, Radiology and Special Care Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India
Email: surentharm.sdc@saveetha.com

[3]Postgraduate Resident, Department of Oral Medicine, Radiology and Special Care Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India
Email: 152510002.sdc@saveetha.com

Corresponding Author:
Dr. M Surenthar
Department of Oral Medicine, Radiology and Special Care Dentistry,
Saveetha Dental College and Hospitals,
Saveetha Institute of Medical and Technical Sciences (SIMATS),
Saveetha University,
Chennai-600077, Tamil Nadu, India
Email: surentharm.sdc@saveetha.com

ABSTRACT

Medication-related osteonecrosis of the jaws (MRONJ), previously termed bisphosphonate-related osteonecrosis of the jaws (BRONJ), represents a debilitating condition characterized by exposed necrotic bone in the maxillofacial region persisting for over eight weeks in patients exposed to antiresorptive or antiangiogenic agents, without a history of jaw radiation. Initially described by Marx in 2003 as osteochemonecrosis in patients receiving bisphosphonates for multiple myeloma and metastatic cancers, its incidence has risen with the ageing population and increased use of these drugs for osteoporosis, bone metastases from breast, prostate, and lung cancers, and other skeletal-related events. Aim of the review was to evaluate the prevalence of MRONJ associated with bisphosphonates, denosumab, and other antiresorptive drugs, and synthesize current evidence on its etiology, clinical outcomes, and preventive strategies by searching PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar from January 2014 to January 2026. Inclusion criteria encompassed original research (RCTs, observational studies) on MRONJ induced by bisphosphonates, denosumab, RANK-L inhibitors, VEGF inhibitors, in patients treated for both primary and secondary cancer or osteoporosis. Exclusions were case reports, case series, in vitro studies, and conference proceedings. Following duplicate removal, two reviewers independently screened titles/abstracts/full texts using Covidence software, with any discrepancies resolved by a third reviewer. Data relating to study design, population, interventions, and key outcomes (prevalence, pain, and functional status) were extracted. Risk of bias was evaluated using RevMan 5.2.0 for randomized controlled trials and ROBINS-I for non-randomized studies. Owing to substantial heterogeneity among studies, meta-analysis was precluded, and findings were synthesized narratively. From 7242 articles, 4 studies (6,761 participants) were included, primarily involving bisphosphonates (n=108) for breast cancer, multiple myeloma, and osteoporosis, and denosumab (n=6653). Bisphosphonates showed higher MRONJ incidence than other agents, with mandibular predominance, elderly females most affected, and elevated risk from intravenous administration. Denosumab exhibited higher MRONJ rates than zoledronic acid (3.2% vs. 2.3% over 3 years). Histopathological examination revealed osteoclast hyperactivity and increased multinucleation. Tooth extractions were found to act as precipitating factors in the onset of cases. According to a recent AAOMS position paper from 2022, it is advised to observe a drug holiday for three months prior to the dental procedure. Therefore, before starting anti-resorptive therapy, clinicians should be aware of risk factors and encourage preventive measures like thorough oral examinations with appropriate radiographs, oral hygiene instructions, and completion of necessary dental treatments. Low-moderate bias prevailed. Bisphosphonates pose the greatest MRONJ risk among antiresorptives, especially intravenously; prevention demands pre-treatment dental evaluation, drug holidays, and multidisciplinary care. Enhanced clinician awareness is crucial to mitigate this underrated entity.

Keywords: Bisphosphonate-Associated Osteonecrosis of the Jaw; Denosumab; Drug holiday; Osteonecrosis of the jaws.
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INTRODUCTION:

In its simplest etymological form, osteonecrosis can be considered as: osteo = bone, necrosis = becoming dead. Osteonecrosis is defined by Dorland's J. Hellstein as ‘‘necrosis of bone due to obstruction of its blood supply. Osteonecrosis of the jaw (ONJ) is a well-documented phenomenon, defined as osteonecrosis affecting the mandible or maxilla, most commonly due to ischemia and infection (1). The term osteonecrosis of the jaw (ONJ) was introduced in 2003 by Robert E. Marx, following the identification of jaw necrosis in patients with multiple myeloma and metastatic cancers receiving bisphosphonate therapy (2).

As the population ages and the prevalence of debilitating conditions increases, the use of medications for the prevention and treatment of metabolic bone diseases has also risen (1). The most common site of metastases is the bone, which is usually associated with breast (73%), prostate (68%), multiple myeloma (44%) and malignant tumours of the lung (36%). Skeletal-related events (SREs) brought on by bone metastases, such as pain, pathological fractures, hypercalcemia, and spinal cord compression, may require radiation therapy and surgery. They are also linked to an overall increase in mortality (3).

In 2009, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved denosumab for the treatment and prevention of bone metastases (4). The term "Bisphosphonate-Related Osteonecrosis of the Jaws" (BRONJ) was changed to "Medication-Related Osteonecrosis of the Jaws" (MRONJ) by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014. This was required because tyrosine kinase inhibitors (TKI), monoclonal antibodies (MABs), rapamycin inhibitors (mTORi), selective oestrogen receptor modulators (SERMs), immunosuppressants, and other antiresorptive and antiangiogenic drugs also cause the illness (5).

MRONJ can result in severe masticatory and functional abnormalities that significantly affect a patient's quality of life and can even be lethal (6). To this day, the cause of MRONJ is unknown. It is believed to be multifactorial because of a reduction in physiological bone remodelling, inflammation, infection, angiogenesis suppression, and a malfunctioning innate or acquired immunity (7). However, two new theories regarding the etiology of MRONJ are starting to surface. The first, referred to as "inside outside," works by preventing osteoclastic activity, which lowers bone turnover. The second, referred to as “Angiogenesis inhibition” due to the reduction of blood supply, causes osteonecrosis of the jaws.

To treat diseases like multiple myeloma and Paget's disease, which both have unfavorably high rates of bone resorption, a class of drugs called bisphosphonates was created in the late 1960s. Compared to earlier theories, the infectious component of bisphosphonate-induced osteonecrosis (ONJ) is now thought to be more important. For this kind of osteonecrosis, we believe that antimicrobial therapy is the most crucial treatment. Bisphosphonates attach to calcium ions in regions with high bone resorption and become integrated into the bone for up to ten years (9). They are partially internalized by phagocytosis or pinocytosis in cells such as

osteoclasts and osteoclast precursors, as well as in cells such as macrophages, osteoblasts, and chondroblasts. After being absorbed, they affect a variety of biochemical processes that result in apoptosis or even the reduction of osteoclasts' ability to reabsorb bone (10). Additionally, there have been reports of antiangiogenetic effects and direct interactions with tumor cells.

A potentially painful drug-induced complication of the jaw bones can be prevented in these patients if the proper medical history is obtained and the treatment protocol is followed (11). Although very effective in preventing bone resorption, a complication arising from these groups of drugs is the development of osteomyelitis of the jaw. This medication-related osteonecrosis occurs only in the jawbones (1)(12).

While intravenous pamidronate or zoledronic acid administration is the standard of care for treating tumor-induced hypercalcemia and bone metastases, bisphosphonate medication can be administered orally or intravenously (12). Alendronate is administered orally as part of the osteoporosis treatment protocol. A small number of cases of osteoporotic osteonecrosis of the jaws have been reported following long-term oral administration of alendronate (Fosamax®); however, intravenous therapy accounted for the majority of cases (13). The study aims to determine the prevalence of MRONJ (BRONJ/ARONJ) in dental practice. The objective is to explore the complications and the current level of evidence for the management of osteonecrosis of the jaws.

MATERIALS AND METHODS:

Materials and Methods

The review focused on patients with medication-related osteonecrosis of the jaw (MRONJ). The intervention/exposure of interest included bisphosphonates, while other antiangiogenic medications served as the comparison. The primary outcome assessed was the treatment outcome of osteonecrosis of the jaws.

Eligibility Criteria

Original research articles evaluating osteonecrosis of the jaw associated with the use of bisphosphonates, denosumab, RANK-L inhibitors, pamidronate, and zoledronate were included in the review. Studies involving patients receiving these medications for conditions such as osteoporosis, multiple myeloma, and breast cancer were considered eligible. Randomized controlled trials, prospective studies, retrospective studies, cohort studies, and case–control studies were included.

Case reports, case series, conference abstracts, conference presentations, and in vitro and in vivo animal studies were excluded from the review.

Search Strategy

A comprehensive literature search was performed using five electronic databases: MEDLINE, PubMed, Scopus, Web of Science, and Google Scholar. The search covered studies published between January 2014 and January 2026. In addition, the reference lists of the included articles were manually screened to identify any additional relevant studies that may have been missed during the electronic database search.

Study Selection

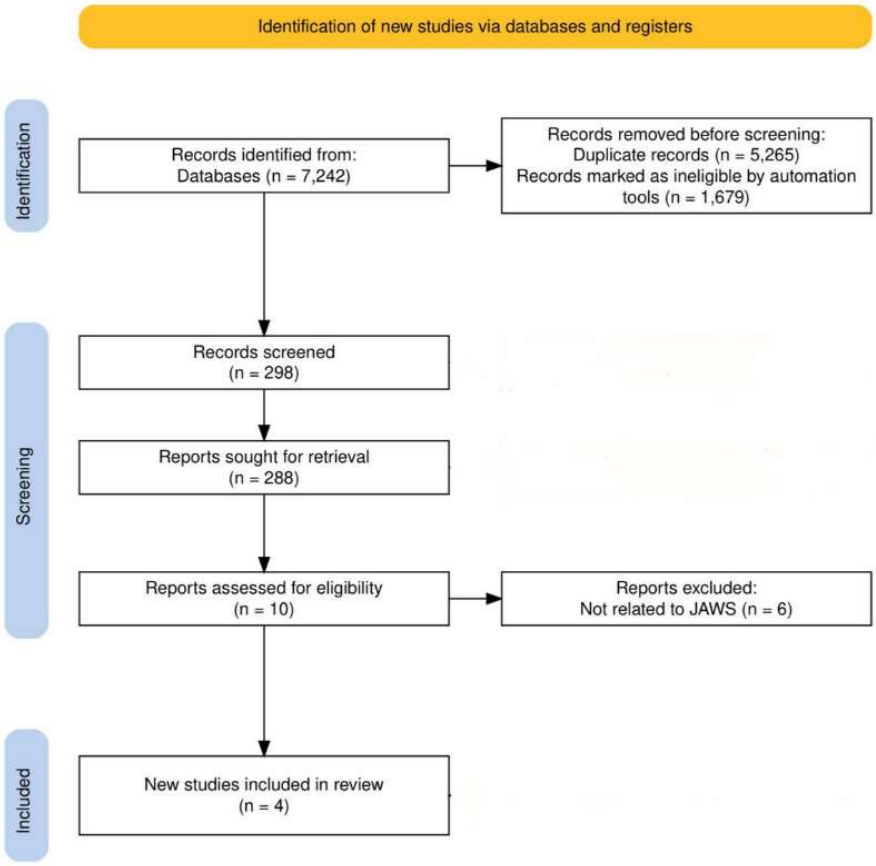

Fig 1: PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only

Following the removal of duplicates, all identified articles were imported into Covidence software for screening and management. The study selection process was conducted independently by two reviewers. Titles and abstracts were initially screened to identify potentially eligible studies, followed by full-text assessment for final inclusion. Each study was evaluated independently by at least two reviewers at every stage of screening. Any disagreements were resolved through discussion, and a third reviewer was consulted when consensus could not be reached. The study selection process is presented in the PRISMA flow diagram (Fig. 1).

Data Extraction

Data extraction was carried out using a standardized extraction form (Table 1). Extracted information included the author and year of publication, study title, study design, study population, intervention, comparison, outcomes, results, and conclusions. The primary outcome of interest was the prevalence of MRONJ associated with medications affecting bone resorption. Secondary outcomes included pain severity and functional outcomes.

Data Synthesis

Heterogeneity among the included studies was assessed by comparing study design, patient population, medications administered, and reported outcomes. Due to considerable

variability across studies, a meta-analysis was not performed. Instead, a narrative synthesis was conducted. Studies were grouped according to the medications evaluated, patient characteristics, safety and efficacy outcomes, functional outcomes, and other relevant study variables. The extracted data from the included studies are summarized in Table 1.

AUTHOR & YEAR	TITLE	STUDY DESIGN	POPULATION	INTERVENTION	COMPARISON	OUTCOME	RESULTS	CONCLUSION
Christian Gross et al., 2017	Medication-related osteonecrosis of the jaw secondary to bisphosphonate therapy: a comparison with osteoradionecrosis and osteomyelitis	Randomized controlled trial	Patients with osteonecrosis and osteomyelitis	Bisphosphonates	Anti-angiogenic drugs	Development of osteonecrosis and osteomyelitis	Osteoclast multinucleation was significantly higher in BRONJ compared to osteomyelitis, osteoradionecrosis, and controls, with presence of giant hypernucleated osteoclasts	MRONJ is characterized by increased osteoclast activity and enhanced cell fusion
Camilla Ottesen et al., 2022	Tooth extractions in patients with cancer receiving high-dose antiresorptive medication	Randomized controlled trial	Cancer patients at risk of osteonecrosis of the jaw	Antiresorptive drugs (bisphosphonates)	Anti-angiogenic drugs	Development of osteonecrosis following extraction	Osteonecrosis of the jaw developed in a subset of patients, including those receiving denosumab after tooth extraction	High-dose antiresorptive therapy does not eliminate the risk of osteonecrosis, with a predominance observed in bisphosphonate-treated patients
Stopeck et al., 2016	Safety of long term denosumab therapy: results from the open-label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer	Randomized controlled trial (extension phase)	Patients with metastatic breast and prostate cancer	Denosumab	Zoledronic acid	Incidence of osteonecrosis of the jaw	Exposure-adjusted ONJ incidence was higher in the denosumab group (1.9%) compared to zoledronic acid (1.2%), with additional cases observed after switching therapies	Long-term denosumab use demonstrates a consistent safety profile with no new safety signals; hypocalcemia rates were comparable
Noopur Raje et al., 2018	Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma	Double-blind, double-dummy, randomized controlled phase 3 trial	Newly diagnosed multiple myeloma patients with bone disease	Denosumab	Zoledronic acid	Time to first skeletal-related event, overall survival, progression-free survival, adverse events	Denosumab was non-inferior to zoledronic acid in delaying skeletal-related events, with similar osteonecrosis risk and fewer renal adverse effects	Denosumab is an effective alternative to zoledronic acid with comparable efficacy and improved renal safety

TABLE-1 showing study characteristics

RESULTS:

From 7242 articles, 4 studies (13,515 participants) were included, primarily involving bisphosphonates for breast cancer, multiple myeloma, and osteoporosis, and denosumab.

Bisphosphonates:

A total of two studies, involving 108 patients taking bisphosphonates for the treatment of breast cancer, multiple myeloma, and osteoporosis, support the use of bisphosphonates. According to Camilia Ottesan et al., temporary discontinuation (drug holiday) of high-dose antiresorptive therapy did not show a clear reduction in the risk of medication-related osteonecrosis of the jaw following tooth extraction (14).

Denosumab:

In total, two studies involving 6653 patients receiving denosumab for the treatment of osteoporosis support the idea that the drug causes osteonecrosis of the jaws. According to the current study's findings, using denosumab rather than Zoledronic acid is substantially linked to an increased risk of developing MRONJ.

DISCUSSION:

This scoping review aims to determine the prognosis of bisphosphates and other medications that cause osteonecrosis of the jaws, as well as the prevalence of MRONJ caused by antiangiogenic medications and bisphosphates (15). Marx initially observed osteochemonecrosis in patients receiving bisphosphates as a chemotherapeutic agent in 2003.

Due to reduced vascularity, continuous functional loading, and frequent exposure to invasive dental procedures such as tooth extractions and periodontal surgery, the jaws particularly the mandible are highly susceptible to the effects of anti-resorptive drugs, chronic infections, and related factors (16). RANK L inhibitors, mTOR inhibitors, anti-angiogenic medications, and bisphosphates are the four classes of anti-resorptive medications that cause MRONJ. Compared to the oral route of administration, which accounts for 0.14% of cases, the intravenous route of administration exhibits a higher incidence of MRONJ, with nearly 80% of affected patients (17).

Christian Gross et al. (2017) found that in MRONJ, particularly in Bisphosphonate specimens, there are variations in the number and morphology of multinucleated giant cells with hypernucleated osteoclasts. The profile value shows that osteoclast inactivation and a high cell fusion rate are characteristics of

MRONJ's osteoclast profile. In MRONJ and ORN specimens, Christian Gross et al. found a DC-STAMP (Dendritic Cell–Specific Transmembrane Protein) expression pattern (18).

Bisphosphonate therapy has been strongly associated with an increased risk of medication-related osteonecrosis of the jaw (MRONJ). In a study by Camilla Ottesen et al., involving 100 patients undergoing tooth extraction, approximately 60–70% were receiving bisphosphonates for the management of bone resorption (19). Bisphosphonates remain the most commonly implicated agents in MRONJ. However, higher doses and prolonged exposure to anti-resorptive medications are recognized risk factors and do not confer protection against the development of osteonecrosis.

According to the 2014 position paper by the American Association of Oral and Maxillofacial Surgeons, a diagnosis of medication-related osteonecrosis of the jaw (MRONJ) can be established when a patient presents with all of the following criteria: (1) current or previous treatment with antiresorptive or antiangiogenic medications; (2) exposed bone, or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, persisting for more than eight weeks; and (3) no history of radiation therapy to the jaws or evidence of metastatic disease involving the jaws.

The pathophysiology of MRONJ is multifactorial and includes mechanisms such as chronic inflammation and infection, inhibition of angiogenesis, and suppression of osteoclastic bone resorption and remodelling. Cancer patients enrolled in clinical trials and placed in placebo groups have a risk of ONJ that ranges from 0% to 0.019% (0-1.9 cases per 10,000 cancer patients). Compared to cancer patients receiving a placebo, cancer patients exposed to zolendronate have a 50–100 times higher risk of ONJ (21). The risk in cancer patients is similar to the risk of ONJ in patients exposed to zoledronate and denosumab. Patients receiving either zoledronate or denosumab had an ONJ risk of 0.17 to 0.04 per cent, which is comparable to the risk of patients receiving placebo (0% to 0.02%). The risk of ONJ is approximately 100 times lower for patients with osteoporosis exposed to antiresorptive drugs than for cancer patients receiving antiresorptive treatment (21).

The position paper (2022) states that AAOMS considers the Stage 0 category for MRONJ to be conceptually similar and does take into consideration the broad range of radiographic manifestations of MRONJ that occur before overt bone exposure. As a result, AAOMS has chosen to keep the current classification scheme exactly as it is. The MRONJ stages are as follows: Stage 0: asymptomatic with clinical and radiographic changes; Stage 1: bone exposure without pain; Stage 2: association with pain; Stage 3: association with pain and findings of pathologic fractures; Oro antral fistula; and radiographic findings of osteolysis extending from the inferior border of the mandible among cancer patients. Pain or discomfort, swelling, pus discharge, and fistula formation are clinical findings. Drug-associated risk factors that affect the development of MRONJ include the type of drug, the length of drug therapy, and the method of administration. MRONJ is more likely to occur in patients receiving nitrogen-containing Bisphosphonates, IV-administered Bisphosphonates or non-Bisphosphonates, and prolonged drug exposure (3). Osteosclerosis, osteolysis, and bony sequestrum are all visible on radiographs. The treatment includes adjuvant surgical techniques, antibiotic therapy, and sequestrum debridement. Because osteonecrosis of the jaws is a common side effect of taking bisphosphates, anti-angiogenic medications, mTOR inhibitors, and RANK-L inhibitors, patients are asked to report for follow-up every six months. A drug

holiday is a proposed strategy to lower the risk of MRONJ that involves the pause, cessation, or temporary discontinuation of anti-resorptive medications. According to a recent AAOMS position paper from 2022, it is advised to observe a drug holiday for three months before the dental procedure. Therefore, before starting anti-resorptive therapy, clinicians should be aware of risk factors and encourage preventive measures like thorough oral examinations with appropriate radiographs, oral hygiene instructions, and completion of necessary dental treatments (22).

The comparison of bisphosphates and anti-angiogenic medications, the inclusion of different tumor types, the normalization of follow-up periods that produced estimated values, and the inclusion of randomized control trials, retrospective studies, and case control studies are some of the study's limitations. Strict inclusion and exclusion criteria, which were used in both homogeneous studies, are among the study's strengths. The sample sizes allow for extremely statistically significant analyses, and the caliber of evidence provided by the selected articles provides a low risk of bias in the individual studies.

CONCLUSION:

In order to prevent the negative effects of the chemotherapeutic agents, a thorough medical examination and investigation are necessary. Apart from anti-angiogenic drugs, mTOR inhibitors, and RANK-L inhibitors, our study indicates that bisphosphates and denosumab are the most prevalent class of drugs that cause MRONJ among the four drug groups. When administered intravenously as opposed to orally, there is a greater chance of developing MRONJ. A multidisciplinary team comprising oncologists, oral physicians, gynecologists, and oral surgeons may be required. Even though ONJ is a recognized entity, there might be gaps in clinical practice and the medical literature regarding its diagnosis, treatment, and recognition. Increased awareness among healthcare professionals, improved risk factor characterisation, better diagnostic techniques, and improved cooperation between various specialities involved in the treatment of patients at risk for or impacted by ONJ are all necessary to close these gaps.

REFERENCES:

1. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol. 2012 May;23(5):1341–7.
2. Saad F, Gleason DM, Murray R. Zoledronic acid prostate cancer study G. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94.
3. Rosen LS, Gordon D, Tchekmedyian S. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial-the zoledronic acid lung cancer and other solid tumors study group. J Clin Oncol. 2003;21.
4. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med. 1996 Dec 12;335(24):1785–91.
5. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Efficacy of pamidronate in reducing skeletal

events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med. 1996 Feb 22;334(8):488–93.
6. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol. 1998 Feb;16(2):593–602.
7. Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC, et al. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol. 2002 Sep 1;20(17):3719–36.
8. Stopeck A, Brufsky A, Kennedy L, Bhatta S, Bhowmik D, Buchanan J, et al. Cost-effectiveness of denosumab for the prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. J Med Econ. 2020 Jan;23(1):37–47.
9. Jeon HL, Oh IS, Baek YH, Yang H, Park J, Hong S, et al. Zoledronic acid and skeletal-related events in patients with bone metastatic cancer or multiple myeloma. J Bone Miner Metab. 2020 Mar;38(2):254–63.
10. Muthukrishnan A, Bijai Kumar L, Ramalingam G. Medication-related osteonecrosis of the jaw: a dentist's nightmare. BMJ Case Rep. 2016 Apr 6;2016: bcr2016214626.
11. Muthukrishnan, Arvind, Laliytha Bijai Kumar, and Gomathi Ramalingam. 2016. "Medication-Related Osteonecrosis of the Jaw: A Dentist's Nightmare." BMJ Case Reports 2016 (April). https://doi.org/10.1136/bcr-2016-214626.
12. Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. Hematology Am Soc Hematol Educ Program. 2006;2006(1):356–60, 515.
13. Delmas PD. The use of bisphosphonates in the treatment of osteoporosis. Curr Opin Intern Med. 2005 Oct;4(5):512–6.
14. Ottesen C, Schiodt M, Jensen SS, Kofod T, Gotfredsen K. Tooth extractions in patients with cancer receiving high-dose antiresorptive medication: a randomized clinical feasibility trial of drug holiday versus drug continuation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Feb;133(2):165–73.
15. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Oct;102(4):433–41.
16. Baron R, Ferrari S, Russell RGG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone. 2011 Apr 1;48(4):677–92.
17. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. Bone. 1999 Jul;25(1):97–106.
18. Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Nat Rev Drug Discov. 2012 May;11(5):401–19.
19. Gross C, Weber M, Creutzburg K, Möbius P, Preidl R, Amann K, et al. Osteoclast profile of medication-related osteonecrosis of the jaw

secondary to bisphosphonate therapy: a comparison with osteoradionecrosis and osteomyelitis. J Transl Med [Internet]. 2017 Dec;15(1). Available from: http://dx.doi.org/10.1186/s12967-017-1230-8

20. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int. 2008 Jun;19(6):733–59.
21. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res. 2006 Oct 15;12(20 Pt 2):6222s – 6230s.
22. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012 Nov;48(16):3082–92.

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Conflict of interest

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