# Medication-related osteonecrosis of the jaw (MRONJ): New insights on ethically responsible risk preventive strategies.
# Part 2: Risk factors, triggers, modifiers, and ethical considerations

Johan Hartshorne[1] and Hugo Johan Kotzé[2]

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## Executive summary

### Clinical significance

- Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious adverse effect commonly seen in patients taking anti-resorptive (AR) and/or anti-angiogenic agents (AA) for metastatic cancer or osteoporosis.
- Dentists play a significant role in identifying patients at risk, preventing MRONJ, and early detection of MRONJ.
- The purpose of Part 2 of this series is to equip dental practitioners with a comprehensive understanding of the risk factors, triggers, and modifiers associated with MRONJ: outline the principles of risk classification, and provide an ethical framework for clinical decision-making related to risk assessment and treatment planning aimed at the prevention of MRONJ.

### Key points

- AR and AA medications remain the most common causes of MRONJ.
- Patient medical history and clinical examination remain the most sensitive diagnostic tools for MRONJ risk assessment and prevention.
- Concurrent use of AR and AA agents increases the risk of MRONJ.
- The risk of MRONJ is higher in cancer patients compared to osteoporosis patients.
- Prolonged therapy (>3 years) with AR/AA medications is associated with a higher risk of MRONJ.
- High-dose recipients of ARs are at greater risk of MRONJ.
- Concurrent systemic disease increases the risk of MRONJ.
- Simultaneous use of corticosteroids with AR/AA increases the risk of MRONJ.
- Active smoking more than doubles the risk of MRONJ development.
- Coincident dental infection, bacterial infection, and inflammation are potential modifiable risk factors of MRONJ.

[1] Johan Hartshorne
B.Sc., B.Ch.D., M.Ch.D., M.P.A., Ph.D. (Stell), FFPH.RCP (UK)
General Dental Practitioner
Intercare Medical and Dental Centre, Tyger Valley, Bellville, South Africa, 7530
Email: johan.laptop@intercare.co.za

[2] Hugo Johan Kotzé
BDS (UWC)
General Dental Practitioner
Intercare Medical and Dental Centre, Tygervalley, Bellville, South Africa, 7530
Email: hugokotze17@gmail.com

- Ill-fitting dentures are a potential modifiable risk factor for MRONJ.
- Tooth extraction is the most common local trigger for MRONJ in patients receiving AR/AA therapy.

## Practice implications

- Dental practitioners play a critical role in early detection of patients at risk, classifying a patient's risk level, providing preventive dental care, and comprehensive management to reduce MRONJ risk.
- Encouraging patients to maintain good oral hygiene and attend regular dental check-ups is another essential ethical responsibility.
- Prompt diagnosis and treatment of local dental and periodontal infections are critical in minimising MRONJ risk.
- Recognising risk factors and using tailored preventive measures for individual patients remains the most effective way to prevent MRONJ.
- The early identification of risk factors and prevention of MRONJ in patients receiving treatment for osteoporosis or metastatic bone malignancies is not only a clinical matter, but also a deeply ethical responsibility.

## Background

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious (adverse condition) complication in patients receiving AA and/or AA therapy for bone metastatic cancers or osteoporosis. It causes progressive bone destruction in the maxillofacial region.[1-7] MRONJ may develop spontaneously or following invasive dental procedures, such as tooth extraction, periodontal treatment, implant placement, or ill-fitting dentures. Among these, tooth extraction remains the most common triggering event.[1,3,4]

MRONJ has emerged as a significant comorbidity in cancer patients treated with AA or high doses of AR medications such as bisphosphonates (BPs) or denosumab.[7] In osteoporosis management, AR medications such as BP and denosumab are widely prescribed. In contrast, patients with osteolytic bone diseases, such as bone metastasis from solid tumours (e.g., breast, prostate, and lung cancer), are often treated with a combination of AR and AA medications.[8] These medications are essential for managing disease progression as well as the skeletal consequences from osteoporosis or bone metastases, which otherwise can lead to increased pain, mortality rates, and reduced quality of life.[9,10] While the benefit of these medications on managing the primary disease is well established, their potential to induce MRONJ underscores the critical importance of prevention.[6]

Dentists play a vital role in identifying patients at risk and detecting MRONJ in its early stages.[11] However, assessing, preventing, and managing MRONJ can be very challenging, with significant implications for patients and clinicians.[2,6,8,12] Therefore, preventive interventions should be implemented before, during, and after AR or AA therapy to minimise the risk of MRONJ." [13-19]

### • *Purpose*

This narrative review is intended for dentists who manage patients receiving AR or AA medications prescribed to prevent and treat a wide variety of medical conditions.

Part 2 of this series will discuss Risk factors, triggers, and modifiers, as well as ethical considerations, to inform dental practitioners about the risk factors associated with MRONJ and the classification of a patient's risk level. It will also define the ethical principles guiding clinical decision-making for the prevention of MRONJ.

## Risk factors, triggers, and modifiers for MRONJ

Patient medical history and clinical examination remain the most reliable tools for assessing and preventing MRONJ.[20] Although it is impossible to identify who will develop MRONJ, current evidence suggests that the following key risk factors contribute to the development of MRONJ. They must be considered when estimating and mitigating the risk of MRONJ. (**Table 1**) [1,6,13,21-30]

### • *Medication-related risk factors*

#### *(i) Type of medication*

The classes of AR and AA medications used for treating bone metastatic cancers and osteoporosis are outlined in **Table 2**.[1,2,13,31]

#### *Antiresorptive medications – Bisphosphonates and Denosumab*

Bisphosphonates (BPs) have a high affinity for mineralised bone, particularly the alveolar bone in the mandible, where there is a high rate of bone remodelling.[32] BPs have a poor absorption rate and limited bioavailability (1%) when taken orally. In contrast, approximately 50% of IV-administered BPs are readily bioavailable to bind to bone target cells. This corresponds with clinical observations that MRONJ occurs most frequently in individuals who receive intravenous BPs. Bisphosphonates (BPs) (**Table 1**) are antiresorptive

**Table 1:** Critical risk factors associated with MRONJ

| | | |
|---|---|---|
| **Medication-related** | Type of Medication<br>-Antiresorptive medications (AR)<br>-Antiangiogenic medications (AA)<br>-Immunosuppressants<br>-Targeted medications | -Therapeutic indication<br>-High dose and frequency<br>-Prolonged use of AR (duration) (>3 years)<br>-Concurrent use of AR and AA<br>-History of long-term use of immunosuppressant medications (e.g., corticosteroids, chemotherapy) |
| **Systemic factors (Co-morbidity)** | -Gender<br>-Age<br>-Primary disease:<br><br><br>-Other systemic diseases:<br><br><br>-Other treatments<br><br>-Poor lifestyle: | Female<br>>65<br>Breast, prostate, renal, lung cancer, multiple myeloma, osteoporosis, Paget's disease<br><br>Cancer, Diabetes mellitus, hyperparathyroidism, chronic kidney disease, vitamin D deficiency<br><br>Chemotherapy, corticosteroids<br><br>Smoking, obesity |
| **Oral-related local factors** | -Dento-alveolar surgery<br><br>-Odontogenic infection<br><br>-Periodontal disease<br>-Poor oral hygiene<br><br>-Dental trauma | Tooth extraction, dental implant, periodontal surgery<br><br>Tooth abscess<br><br>Infection & Inflammation<br><br>Defective or ill-fitting prosthesis |

medications used to prevent vertebral and nonvertebral fractures in patients with osteoporosis and osteopenia. They are also effective in managing cancer-related conditions, including skeletal-related events associated with bone metastases such as breast, prostate, and lung cancer, and multiple myeloma. BPs are also prescribed for other metabolic bone diseases such as Paget's disease of bone and osteogenesis imperfecta.[1]

Denosumab is a fully humanised monoclonal antibody directed against receptor activator of nuclear factor-kB ligand (RANKL), It is an antiresorptive agent than inhibits osteoclast function and its associated bone resorption process.[1,33] (**Table 2**) For cancer -related indications (i.e., solid cancer metastases to bone, giant cell tumour of bone, and hypercalcemia of malignancy), denosumab is marketed under the trade name Xgeva®, it is administered at doses of 120mg subcutaneously every four weeks. For osteoporosis, it is sold as Prolia® and administered at a lower dose of 60 mg subcutaneously every six months. (**Table 1**)

### *Antiangiogenic medications*

Antiangiogenic (AA) medications, also known as angiogenesis inhibitors, include drug classes such as human monoclonal antibodies, vascular endothelial growth factor (VEGF) inhibitors, mTOR inhibitors, and tyrosine kinase inhibitors. These agents inhibit the formation of new blood vessels by binding to molecules that are involved in the angiogenesis cascade.[34] (**Table 2**)

Angiogenesis, or the development of new blood vessels, is a key factor in the growth and metastasis of certain solid tumours (Breast, prostate, lung).[1] These tumours secrete pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), to stimulate new vessel development through downstream signalling pathways.[35,36]

Among bisphosphonates (BP) (e.g., Zoledronic acid, Alendronic acid, Ibandronic acid), RANKL inhibitors (e.g., Denosumab), and radiotherapy drugs (Radium-223 dichloride) exhibited the highest risk of MRONJ.[31] The risk of MRONJ is significantly higher with denosumab than with zoledronic acid.[37,38] (**Table 2**)

A recent study in the adult Finnish population reported that denosumab users had a fivefold higher risk of developing MRONJ compared with bisphosphonate users, regardless of dosage level.[39] Concurrent use of corticosteroids further

**Table 2:** Classification of medications most commonly associated with MRONJ

| Type / Category (Indication/Use) | Chemical name (Brand) | Route/ Frequency/ Dosage | Mechanism | Risk level |
|---|---|---|---|---|
| **Antiresorptive agents (AR)** | | | | |
| Oral Bisphosphonates (Osteoporosis) | Alendronate (**Fosamax®**)<br>Risedronate (**Actonel®**) | Oral / Daily | Inhibits bone resorption | Low risk |
| Parenteral BPs (osteoporosis, Bone metastasis, Multiple myeloma, Hypercalcemia, Skeletal dysplasia, Paget's disease) | Ibandronate (**Boniva®**)<br>Zolendronate (**Aclasta®**) (**Zometa®**)<br>Pamidronate (**Aredia®**) | V/Q3M<br>Annual | Inhibits bone resorption | High risk – long-term intake |
| **Receptor activator of nuclear factor kappa-B Ligand (RANKL) inhibitor (Monoclonal antibody against RANKL)** | | | | |
| (Osteoporosis)<br><br>(Cancer-related, bone-metastatic disease, Hypercalcemia) | Denosumab (**Prolia®**)<br><br>Denosumab (**Xgeva®**) | 60mg Subcutaneously Every 6 months<br>120mg SC Every 4 weeks | Inhibits osteoclast function and bone resorption | Low risk Low dose<br><br>High risk – High dose, long-term intake |
| **Selective estrogen receptor modulators (SERMs)** | | | | |
| | Raloxifene (**Evista®**) | Oral / Daily | | |
| **Duel effect (Antiresorptive and Anabolic)** | | | | |
| Monoclonal antibody (Targeted receptors) | Romosumab (**Evinity®**) | Subcutaneously Monthly for 1 yr | Reduces bone resorption, promotes bone formation | High risk Long-term intake |
| **Antiangiogenic medications (non-antiresorptive medications)** | | | | |
| Tyrosine kinase inhibitors (TKIs) (Prostate, Breast, Kidney cancer) | Sunitinib (**Sutent®**)<br>Sorafenib (**Nexavar®**)<br>Erlotinib (**Torceva®**) | Oral | Anti-VEGFR Multiple targets Blocks angiogenesis | High risk long-term intake and sequential use with AR |
| Mammalian target of rapamycin (mTOR) inhibitors (Kidney, prostate, breast cancer) | Verolimis (**Affinitor®**)<br>Temsirolimis (**Torisel®**) | Oral<br>IV | Anti-mTOR Inhibits angiogenesis Immunosuppressant) | High risk long-term intake and sequential use with AR |
| **Immunosupression / Immunomodulatory medication** | | | | |
| (Malignancy, Autoimmune diseases) | Corticosteroids<br>Methotrexate<br>Thalidomide | Variable | Immune modulation | High risk with concurrent use with AR/AA |
| **Chemotherapeutic / Oncology agents/Targeted cytostatic agents** | | | | |
| (Malignancy) | Methotrexate (**Abitrexate**)<br>Erlotinib (**Ercyta®**) | Variable IV/Oral | Immune suppression | High risk with concurrent use with AR/AA |
| Radio-therapy agent (Prostate cancer) | Radium-223 dichloride (**Xofigo®** ) | Variable | Variable | High risk with concurrent use with AR/AA |

**Table 3:** Estimated risk of developing MRONJ by therapeutic indication

| Medication | Osteoporosis patients Avg 0,05% | Cancer patients Avg <5% |
|---|---|---|
| Alendronate **(Fosamax®)** (BP-Oral) | 0,05% | <5% |
| Zolendronate (**Aclasta®**) BP parenteral (IV) | 0,02% (<2 per 10,000) | 0-18% |
| Ibandronate (**Boniva®**) BP (parenteral (IV) | <0,05% (<5 per 10,000) | |
| Denosumab (**Prolia®**) Subcutaneously | <0,3% | 0-6.9%<5% |
| Romosumab (**Evinity®**) Subcutaneously | 0,03-0,05% | |

increases the risk of developing MRONJ.[39] Patients with long-term corticosteroid use, malignancy, or chemotherapy may experience immune suppression, which leads to an imbalance in bone turnover and reduced bone remodelling, and, ultimately, increases the risk of MRONJ.[39]

Recent research suggests that an increasing number of new drug classes and novel medications are being reported that are associated with MRONJ.[31] Although the main etiological factors for MRONJ are AR and AA medications, new research indicates that additional drugs that are not typically associated with the condition may also play a role in its development. For instance, MRONJ has been documented in patients receiving secukinumab for psoriasis,[40] intravenous tocilizumab for rheumatoid arthritis,[41]and long-term simvastatin for hypercholesterolemia.[42] The dental community needs to be aware of new medications associated with MRONJ that are being reported every day. [43]

### *(ii)Therapeutic indication for treatment*

The risk of MRONJ is significantly higher in cancer patients (<5%) than in osteoporosis patients (<0,05%).1 (**Table 3**)

Osteoporosis patients treated with AR medications (e.g., BPs or denosumab or <3yrs) with no concurrent use of immunosuppressive drugs are generally considered low risk for MRONJ.

In contrast, osteoporosis patients with long-term treatment of Zolendronate (IV BPs), long-term Denosumab intake, or those concurrently taking immunosuppressive medications (e.g., steroids) are considered a high risk for MRONJ.[8]

Patients with metastatic cancers or immunocompromised conditions (e.g., multiple myeloma) who are treated with high-dose IV BPs (Zolendronate) or Denosumab (Xgeva®), and in combination with AA agents (e.g., Bevacizumab, Sunitinib) or chemotherapeutic agents (e.g., immunosuppressants (corticosteroids), selective oestrogen receptor modulators (SERMs) (Raloxifene), monoclonal antibodies (Romosozumab), and radiopharmaceuticals and antiangiogenics are generally considered high risk for MRONJ.[8]

### *(iii) Duration of medication*

The risk of MRONJ is associated with cumulative exposure to AR/AA medications.[44] Prolonged use of BPs is associated with a higher risk of MRONJ, particularly when taken for over four years.[39,45,46]

A systematic review and meta-analysis reported that the incidence of MRONJ increased with prolonged use of denosumab: 0.5-2.1% after 1 year, 1.1-3.0% after 2 years, and 1.3-3.2% after 3 years of treatment.[37] "A longer mean duration of AR medications before MRONJ onset was observed in patients affected by osteoporosis, whereas a shorter mean duration was observed in all metastatic bone cancer patients,

**Table 4:** Effect of duration of AR medication on risk of MRONJ[1]

| Duration | Zolendronate (BP) (IV) | Denosumab (Subcutaneous) |
|---|---|---|
| 1yr | 0,5% | 0,8% |
| 2yr | 1,0% | 1,8% |
| 3yr | 1,3% | 1,8% |

and in particular in those affected by prostate cancer with bone metastases or multiple myeloma."[47] While duration may be a risk factor, the overall risk remains low. (**Table 4**)

### *(iv) Medication dosing frequency and route of administration*

In a recent study of an adult Finnish population, Kujanpää and co-workers found that the incidence of MRONJ was 0,3% in low-dose and 9% in high-dose AR therapy recipients. [39]

Similarly, Yokoo and co-workers found that in breast cancer patients with bone metastasis, receiving 32 or more denosumab doses significantly increased the likelihood of MRONJ. [3]

The route of administration – whether IV versus PO - of AR/AA is no longer considered a risk factor for MRONJ.[48]

### • *Systemic factors*

Several systemic factors have been implicated in the development of MRONJ. Uncontrolled diabetes mellitus, cancer, chemotherapy, smoking, and long-term glucocorticoid use have been identified as potential risk factors for MRONJ due to their impact on bone metabolism and wound healing.[1,6,44,49] Studies have consistently demonstrated that active smokers have more than double the risk of MRONJ, compared to non-smokers or former smokers, emphasizing the importance of smoking cessation.[4,50,51]

Demographics – In general, there is a higher incidence of MRONJ in females, with a mean reported age of 67 years.[31] However, a recent study in the Finnish adult population found that males receiving high-dose AR therapy had a higher risk of MRONJ (54,5%) compared to females (45.5%).[39]

### • *Oral-related local risk factors*

Oral-related local risk factors are important contributors to the development of MRONJ. In general, MRONJ is more likely to appear in the mandible (75%) than the maxilla (25%).[2]

### *(i)Odontogenic infection and periodontal disease*

Several studies have implicated coincident dental disease, inflammation, or bacterial infection as potential risk factors for MRONJ.[1,44,52]

Patients with concomitant inflammatory dental and oral disease and infections – such as periodontitis and periapical infections - are predisposed to a heightened risk of developing MRONJ.[53] The degree of severity of underlying infection/inflammation may increase the risk of MRONJ.[1,4]

Untreated periodontal disease and poor dental health (apical infections and dental abscesses), and ill-fitting dentures, are considered as potential modifiable risk factors for MRONJ.[44]

### *(ii) Dento-alveolar interventions*

Dentoalveolar intervention was the most frequently reported local trigger for MRONJ (386 cases, 71.9 %). Among the 386 dentoalveolar interventions, 382 were tooth extractions, while in 4 patients the placement of a dental implant preceded MRONJ."[47] Performing invasive dental procedures in cancer patients receiving zoledronic acid increased the risk of developing MRONJ by 4.7 times.[4]

The risk of MRONJ increased significantly when tooth extraction was performed in patients with existing periodontal disease; therefore, periodontal diseases should be proactively managed in patients taking bisphosphonates.[54] Overall, tooth extraction remains the most common precipitating event for MRONJ.[1,3,4]

### *(iii) Removable prostheses*

Denture use, especially ill-fitting dentures, increases the risk of MRONJ in cancer patients.[4]

### • *Risk-based preventive dental screening*

It is essential to evaluate whether a patient taking AR or AA medications is at a low or higher risk of developing complications based on their medical condition, type,

**Table 5:** Checklist for patient risk level

| Risk factor | Patient risk level Low risk | Patient risk level High risk |
|---|---|---|
| Medical condition diagnosed or receiving therapy: | ☐ Osteoporosis | ☐ Cancer |
| Medical history: Current, past, future use of AR/AA | ☐ None | ☐ Yes |
| Type of medication – AR, AA, | ☐ Bisphosphonates | ☐ Denosumab, AA |
| Dosage | ☐ Low | ☐ High |
| Duration | ☐ < 4 years | ☐ 4> years |
| Concurrent Immunomodulators or suppressants | ☐ None | ☐ Corticosteroids |
| Co-morbidities | ☐ None | ☐ Diabetes |
| Complicating factors | ☐ None | ☐ Smoking |
| | | ☐ Poor oral hygiene |

dosage, and duration of medication therapy, as well as any other co-morbidities and potential complication factors.[44] (**Tables 1 & 5**)

When taking or confirming a patient's medical history, ask about past, current, or potential future use of AR or AA medications, as well as the medical condition for which they were prescribed.

Assign a level of risk (Low or higher) based on the patient's medical history (**Table 5**) and ensure that the assigned risk level is recorded in the patient's clinical record.

Any low-risk patient who continues to take BP medications after their 5-year dental check-up should be reclassified as higher risk.[55]

Patients who have received AA medications in combination with AR medications should be allocated to a risk group based on their medical history of AR medication use.[55] (**Table 5**).

It is suggested that risk-based preventive dental screening protocols should consider the patient's risk of developing MRONJ and life expectancy to maximize the benefits and limit the potential burden of dental interventions.[44,55]

## Ethical considerations and prevention of MRONJ

Prevention of MRONJ in patients receiving treatment for osteoporosis or metastatic bone malignancies is not only a clinical responsibility but an ethical one.

The key ethical principles in preventing MRONJ are:

1. Non-maleficence - avoiding risks and minimising harms;
2. Beneficence - maximising benefits and acting in the patient's best interest;
3. Autonomy - ensuring informed consent and shared decision-making;
4. Justice - fairness and equitable access to preventive care specialist referral pathways;
5. Veracity - truthful communication; and
6. Professional responsibility - collaboration and competence.

These principles are well-established in clinical ethics and dental ethics frameworks, including the Health Professions Council of South Africa (HPCSA), the FDI, and the National Dental and Medical Councils.

- ***Principle of Beneficence ("Do good")***

The principle of beneficence emphasises maximising patient benefit and acting in the patient's best interests by controlling infection and pain while preserving systemic skeletal health.

- **Acting in the patient's best interest** means that the clinician should prioritize the patient's overall health, not just the dental outcome. Sometimes, extraction is the most beneficial treatment option to eliminate infection, despite the risk of MRONJ.
- **Preventive Dental Care / Optimization of oral health:** Before initiating AR/AA therapy, a proactive dental assessment and treatment planning should be carried out to remove potential future sources of infection. It is ethically required to reduce the likelihood of later extractions. Carers should also be included in discussions.
- **Interceptive dental care:** A comprehensive examination, periodontal management, caries control, extraction of

hopeless teeth, and definitive restorations before therapy starts. This reduces the need for invasive procedures and aligns with both non-maleficence and beneficence.

- ***Principle of Non-Maleficence ("Do No Harm")***

The principle of non-maleficence underlines the ethical duty to avoid risk and minimise harm through careful planning and the use of minimally traumatic techniques, exploring non-surgical alternatives when possible, and appropriate timing of interventions. Medications prescribed for dental and medical conditions have potential adverse effects that warrant a risk-benefit consideration.[1]

Tooth extraction is often necessary to resolve infection or pain, yet it carries a risk of triggering MRONJ.

Ethical risk–benefit analysis and balance should therefore explicitly weigh:

1. Current dental disease burden and prognosis,
2. MRONJ/poor-healing risk modifiers (drug, dose, duration, route; comorbidities; local infection), and
3. The potential systemic harms of interrupting effective antiresorptive therapy (e.g., fracture risk with delayed denosumab).

This framework supports conservative care where feasible and underscores the importance of documenting patient-centred decisions. Tooth extraction is often necessary to resolve infection or pain, yet it carries a risk of triggering MRONJ. Clinicians must minimize avoidable harm through careful treatment planning and exploring evidence-based non-surgical alternatives when possible.

In clinical treatment decisions where complications are readily corrected, treatment decisions are implemented straightforwardly. However, where complications are significant, deciding to treat becomes more challenging.[1] Before commencement of AR or AA therapy, or as soon as possible thereafter, patients should be rendered as dentally fit as feasible, prioritising preventive care.

Higher-risk cancer patients should preferably undergo a comprehensive dental assessment, with remedial dental treatment where required, before commencement of therapy.[55]

- **Timing and Drug Holidays:** Ethically, it may be necessary to consider treatment timing relative to AR therapy, in consultation with the patient's physician/oncologist, while recognizing uncertainties in evidence for "drug holidays."
- **Surgical Technique:** Using atraumatic techniques, primary closure, and antibiotics when indicated is ethically obligatory to minimize the risk of necrosis.

- ***Principle of Autonomy ("Respect patients' right to self-determination")***

Autonomy is based on the patient's right to informed consent and shared decision-making. Communicating the risks of MRONJ to patients is essential for ensuring appropriate medical and dental management of the primary disease, as well as for preventing and managing potential adverse effects.[1] Respect for autonomy requires transparent discussion of material risks (MRONJ, delayed healing), reasonable alternatives to extractions (endodontic therapy, root retention/coronal amputation), uncertainties (e.g., benefits of drug holidays), and potential outcomes (e.g., pain, infection, reduced oral function, and impact on quality of life.[56]

Critical elements of autonomy include:

- **Informed Consent:** Patients must be given clear, understandable information about the potential risk of MRONJ, alternatives to treatment, expected outcomes, and the importance of prioritising and maintaining optimal oral health.
- **Shared Decision-Making:** Respecting autonomy requires a collaborative approach — patients should be empowered to weigh the risks and benefits in the context of their values, preferences, and prognosis.
- **Material risk of MRONJ:** Patients should be informed that due to the medication they are taking, there may be a risk of developing MRONJ, but ensure that they understand that the risk is small. A patient mustn't be discouraged from taking their AR or AA medication or from undergoing dental treatment. The discussion and advice provided should be clearly documented in the patient's clinical record.[55]

- ***Principle of Justice***

The principle of justice requires fairness and equitable access to preventive care specialist referral and collaborative pathways where required.

- **Equitable Access:** Patients should have equal access to preventive dental evaluation before starting AR/AA therapy, regardless of socioeconomic status. Unfortunately, many patients are only seen after treatment has begun.
- **Resource Allocation:** Preventive dental care reduces long-term costs and suffering; ethically, health systems should invest in early intervention strategies.
- **Vulnerable Groups:** The elderly, cancer patients in palliative care, or individuals with limited health literacy

deserve special consideration to ensure they are not disadvantaged in risk prevention or decision-making. Ensure that patients with limited resources receive preventive counselling and timely referral; leverage publicly available guidance to standardize care.

Dental practitioners and medical aid policymakers must ensure that patients have access to high-quality, timely, and affordable dental care to prevent avoidable cases of MRONJ.[44]

- ***Principle of Veracity (Truthfulness and Transparency)***
  - **Honesty:** Clinicians must be honest about the uncertainties in MRONJ prevention, including areas of drug holidays and variability in reported risk percentages.
  - **Transparent communication**: Both overemphasizing and underemphasizing risks is ethically problematic. Balanced, evidence-based communication is essential.

- ***Principle of Professional Responsibility***
  - **Interdisciplinary Collaboration and medical liaison:** Dentists, oral surgeons, oncologists, and general practitioners must coordinate care — preventing MRONJ is a shared responsibility. Communicate timing and plan with the prescriber for denosumab users and for patients with significant comorbidities.
  - **Up-to-Date Knowledge:** Clinicians have an ethical obligation to remain current with evolving guidelines and adapt their practices accordingly.
  - **Documentation:** Thorough record-keeping of risk discussions, informed consent, and clinical decisions protects both patient and practitioner ethically and legally. Provide written information outlining risks, alternatives, expected recovery, and what to report post-op.
  - **Audit and quality improvement:** Clinicians should track outcomes, healing times, and any suspected MRONJ cases to refine local protocols.

## Conclusion

Medication-related osteonecrosis of the jaw (MRONJ) represents a complex, multifactorial condition that lies at the intersection of pharmacology, oral pathology, and clinical ethics. Its occurrence reflects an interplay of risk factors, biological modifiers, and procedural or systemic triggers that challenge both diagnostic precision and preventive responsibility in dental practice. Although potent AR and AA medications are central to managing osteoporosis and metastatic bone disease, their therapeutic benefits are counterbalanced by the potential for severe oral complications, particularly when invasive dental procedures, such as tooth extractions, are performed. Thus, an ethically grounded understanding of MRONJ requires more than clinical awareness—it demands an integrative approach that balances medical benefit, patient autonomy, and professional duty of care.

From a risk perspective, MRONJ is influenced by both intrinsic and extrinsic determinants. Patient-related factors such as age, cancer, systemic health, immune competence, and concurrent therapies modify susceptibility, while medication-related variables— medication class, dose, duration, and mechanism of action—further shape the likelihood of MRONJ risk. Local triggers such as tooth extraction, periodontal infection, ill-fitting prostheses, and poor oral hygiene remain critical precipitating events. Importantly, these risk and trigger interactions are dynamic, often amplified by systemic conditions like diabetes, corticosteroid use, or cancer therapies. Recognising this multifactorial landscape enables clinicians to move beyond simplistic cause-and-effect assumptions toward a nuanced model of prevention and management.

Ethically, MRONJ prevention and treatment invoke the principles of beneficence, non-maleficence, autonomy, and justice. Beneficence obliges dental practitioners to act in the patient's best interest by promoting oral health and minimizing treatment-related harm. Non-maleficence reinforces the moral imperative to avoid or reduce unnecessary surgical trauma in at-risk patients through conservative, evidence-based care. Respect for patient autonomy requires full disclosure of risks and benefits, ensuring informed consent and shared decision-making before dental procedures. The principle of justice extends to equitable access to preventive dental care and timely medical-dental collaboration, particularly for vulnerable populations receiving long-term AR or AA therapy.

In clinical practice, ethically responsible management of MRONJ risk involves proactive communication, individualized care planning, and interprofessional collaboration and liaison. Dental practitioners must maintain vigilance through comprehensive medical history assessments, pre-therapy dental screening, optimisation of oral health, routine monitoring of high-risk patients, and prompt treatment of dental or periodontal infections. Ethical decision-making further requires transparent dialogue with prescribing physicians and oncologists to coordinate treatment timing and mitigate modifiable risk factors. When

MRONJ does occur, clinicians are ethically bound to provide compassionate, evidence-based management that prioritizes pain control, infection management, and quality of life.

Although MRONJ remains a relatively uncommon complication, its clinical implications warrant increased awareness among dental practitioners, particularly those involved in the dental management of cancer and osteoporotic patients.

Ultimately, the prevention and management of MRONJ should not be viewed solely as a procedural challenge but as an ethical commitment to patient-centered care. By integrating scientific understanding with ethical discernment, dental practitioners uphold the integrity of their profession and the well-being of their patients. A reflective, preventive, and ethically guided approach—anchored in collaboration, empathy, and clinical excellence—remains the cornerstone of reducing MRONJ incidence and ensuring that therapeutic progress in medicine does not come at the cost of oral health and human dignity.

Ongoing research is required to elucidate the fundamental factors and modifiers of MRONJ, including patient- and treatment-specific risk factors, severity, progression, and healing factors. This will inform clinical decision-making and guide ethically sound, patient-centred management strategies.

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