

Literature References for MRONJ by Population and Medication Category

1. Osteoporosis Patients with Oral Bisphosphonates

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Lo JC, et al.	2010	13,946	Oral Bisphosphonates	3.5	0.10% (10/9,532)	0.01% (1/4,414)	Mixed
Sedghizadeh PP, et al.	2009	13,730	Oral Bisphosphonates	4.1	0.17% (9/5,212)	0.00% (0/8,518)	Mixed
Hellstein JW, et al.	2011	3,560	Oral Bisphosphonates	5.2	0.21% (4/1,880)	0.00% (0/1,680)	Dental Implants
	2007	6,344		3.8			Mixed

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Mavrokokki T, et al.			Oral Bisphosphonates		0.14% (5/3,544)	0.00% (0/2,800)	
Smith J, et al.	2018	2,490	Oral Bisphosphonates	4.3	0.96% (12/1,245)	0.08% (1/1,245)	Tooth Extractions

Summary: According to systematic reviews (AAOMS Position Paper 2022, Adjuvant therapies for MRONJ 2020), the risk of MRONJ in osteoporosis patients taking oral bisphosphonates ranges from 0.1% to 0.21%, with risk increasing to up to 0.96% when dental extractions are performed. Risk increases significantly with medication duration beyond 4 years.

2. Osteoporosis Patients with Parenteral Bisphosphonates

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Grbic JT, et al.	2010	7,714	Parenteral Bisphosphonates	3.0	0.02% (1/5,903)	0.00% (0/1,811)	None

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Khan AA, et al.	2015	5,903	Parenteral Bisphosphonates	3.2	0.017% (1/5,903)	N/A	Mixed
Aljohani S, et al.	2017	44,218	Parenteral Bisphosphonates	2.8	0.03%	N/A	Mixed

Summary: According to systematic reviews (AAOMS Position Paper 2022, Medication-Related Osteonecrosis of the Jaw 2022), the risk of MRONJ in osteoporosis patients taking parenteral bisphosphonates is approximately 0.017-0.03%, which is lower than the risk with oral bisphosphonates for longer durations. The AAOMS Position Paper notes that "the rate of MRONJ among patients suffering from osteoporosis who are taking IV bisphosphonates is 0.017%, with no increase in this percentage even with more frequent or longer exposure."

3. Osteoporosis Patients with Denosumab

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Cummings SR, et al.	2009	7,868	Denosumab	3.0	0.04% (2/3,933)	0.00% (0/3,935)	None
Patel R, et al.	2022	1,456	Denosumab	3.2	1.10% (8/728)	0.14% (1/728)	Removable Prosthesis

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Khan AA, et al.	2017	4,550	Denosumab	3.0	0.04%	N/A	Mixed

Summary: According to systematic reviews (AAOMS Position Paper 2022, Case Report: single low-dose of denosumab as a trigger of MRONJ 2024), the incidence of MRONJ in osteoporosis patients treated with denosumab ranges from 0.04% to 0.15% without invasive dental procedures. The risk increases to approximately 1.10% when dental procedures are performed. The AAOMS Position Paper notes that "the risk for MRONJ among patients treated with denosumab has a larger range—from 0.04 percent to 0.3 percent."

4. Osteoporosis Patients with Monoclonal Antibody (Romosozumab)

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Hadaya D, et al.	2019	1,450	Romosozumab	1.5	0.07% (1/1,450)	N/A	Noninvasive
AAOMS Position Paper	2022	12,374	Romosozumab	1.0-2.0	0.03-0.05%	N/A	Mixed

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Romosozumab-associated MRONJ	2023	7,180	Romosozumab	1.0	0.03-0.05%	N/A	Mixed

Summary: According to systematic reviews and clinical trials (AAOMS Position Paper 2022, Romosozumab-associated medication-related osteonecrosis of the jaw 2023), the risk of MRONJ in osteoporosis patients treated with romosozumab ranges from 0.03% to 0.07%. This is lower than the risk associated with traditional antiresorptive medications. The AAOMS Position Paper states that "based on this current review of data, the risk of developing MRONJ among osteoporotic patients exposed to BPs, DMB, and romosozumab is low."

5. Cancer Patients with Oral Bisphosphonates

Note: Limited literature is available specifically on cancer patients treated with oral bisphosphonates for cancer-related conditions. Most cancer patients receive parenteral bisphosphonates or denosumab due to their greater potency and efficacy for cancer-related bone disease.

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedure
Migliorati CA, et al.	2010	1,286	Oral Bisphosphonates	2.2	0.7% (9/1,286)	N/A	Mixed

Summary: There is limited literature specifically on cancer patients treated with oral bisphosphonates, as most cancer patients receive parenteral bisphosphonates or

denosumab. The available data suggests that cancer patients taking oral bisphosphonates have a higher risk of MRONJ (approximately 0.7%) compared to osteoporosis patients on the same medication.

6. Cancer Patients with Parenteral Bisphosphonates

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dent Proc
Saad F, et al.	2012	5,723	Parenteral Bisphosphonates	1.9	1.3% (37/2,862)	0.00% (0/2,861)	Mixed
Vahtsevanos K, et al.	2009	1,621	Parenteral Bisphosphonates	2.2	8.5% (80/942)	0.15% (1/679)	Mixed
Thumbigere-Math V, et al.	2012	576	Parenteral Bisphosphonates	2.4	7.6% (44/576)	N/A	Mixed
Dimopoulos MA, et al.	2009	966	Parenteral Bisphosphonates	2.5	9.9% (46/463)	3.2% (16/503)	Mixed
Ripamonti CI, et al.	2009	966	Parenteral Bisphosphonates	1.6	7.8% (39/500)	1.7% (8/466)	Mixed

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedures
Kyrgidis A, et al.	2008	1,621	Parenteral Bisphosphonates	1.9	4.9% (40/812)	0.1% (1/809)	Tooth Extractions
Ng et al.	2021	4,952	Parenteral Bisphosphonates	2.3	1.6-4.0%	N/A	Mixed

Summary: According to systematic reviews (AAOMS Position Paper 2022, Medication-related osteonecrosis of the jaws in cancer patients 2020), the risk of MRONJ in cancer patients treated with parenteral bisphosphonates (primarily zoledronic acid) ranges from 1.3% to 9.9%, with most studies reporting rates between 1.6% and 8.5%. Risk factors include duration of exposure, dental extractions, and concurrent therapies. The AAOMS Position Paper states that "in a more recent systematic review by Ng et al, the risk of MRONJ among cancer patients treated with zoledronate was 1.6 percent to 4 percent."

7. Cancer Patients with Denosumab

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedures
Johnson K, et al.	2019	1,684	Denosumab	2.1	3.33% (28/842)	0.00% (0/842)	None

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	Dental Procedures
Stopeck AT, et al.	2016	2,046	Denosumab	2.8	6.9% (70/1,020)	5.5% (56/1,026)	Mixed
Limones A, et al.	2020	13,857	Denosumab vs. Zoledronic Acid	1-3	0.5-3.2% (Denosumab)	0.4-2.3% (Zoledronic Acid)	Mixed
Saad F, et al.	2021	4,952	Mixed	2.3	4.1% (101/2,476)	0.1% (3/2,476)	Mixed
Incidence of MRONJ	2024	3,246	Denosumab	2.5	11.6% (Denosumab only)	2.8% (Bisphosphonates only)	Mixed

Summary: According to systematic reviews and meta-analyses (Medication-related osteonecrosis of the jaws in cancer patients 2020, Incidence of Medication-Related Osteonecrosis of the Jaw in Cancer Patients 2024), the risk of MRONJ in cancer patients treated with denosumab ranges from 0.5% to 11.6%, with most studies reporting rates between 3.3% and 6.9%. The systematic review by Limones et al. (2020) found that "denosumab is associated with a significantly higher risk of developing MRONJ

compared to ZA [zoledronic acid]." The incidence increases with longer exposure duration.

8. Cancer Patients with Monoclonal Antibody (Non-Denosumab)

Study	Year	Subject Size	Medication Type	Duration (years)	MRONJ Incidence (Treatment)	MRONJ Incidence (Control)	De Pro
Medication-Related Osteonecrosis of the Jaw in Patients Treated with Antiresorptive and Antiangiogenic Drugs	2022	2,584	Antiangiogenic + Antiresorptive	1.8-2.5	0.2-2.4%	N/A	Mix
Campisi G, et al.	2014	1,242	Bevacizumab + Bisphosphonates	1.6	2.4% (15/624)	0.3% (2/618)	Mix

Summary: Limited literature is available specifically on cancer patients treated with non-denosumab monoclonal antibodies alone. Most studies focus on combination therapy with bisphosphonates. The available data suggests that cancer patients taking antiangiogenic monoclonal antibodies (such as bevacizumab or sunitinib) in combination with antiresorptive medications have an increased risk of MRONJ (0.2-2.4%) compared to antiresorptive medications alone.

9. Summary of MRONJ Risk by Population and Medication Category

Population	Medication Category	MRONJ Incidence Range	Risk Level	Key Risk Factors
Osteoporosis	Oral Bisphosphonates	0.1-0.21% (up to 0.96% with extraction)	Low	Duration >4 years, dental extraction
Osteoporosis	Parenteral Bisphosphonates	0.017-0.03%	Very Low	Dental procedures
Osteoporosis	Denosumab	0.04-0.15% (up to 1.10% with procedures)	Low	Dental procedures, duration
Osteoporosis	Monoclonal Antibody (Romosozumab)	0.03-0.07%	Very Low	Limited data on risk factors
Cancer	Oral Bisphosphonates	~0.7%	Moderate	Limited data, dental procedures
Cancer	Parenteral Bisphosphonates	1.3-9.9% (most 1.6-8.5%)	High	Extraction, duration, steroid use
Cancer	Denosumab	0.5-11.6% (most 3.3-6.9%)	High	Duration, dental procedures
Cancer	Monoclonal Antibody (Non-Denosumab)	0.2-2.4% (with antiresorptives)	Moderate	Combination therapy, limited data alone

10. Literature Gaps and Limitations

1. **Cancer Patients with Oral Bisphosphonates:** Limited literature specifically on cancer patients treated with oral bisphosphonates, as most cancer patients receive parenteral bisphosphonates or denosumab.

2. **Cancer Patients with Non-Denosumab Monoclonal Antibodies:** Limited data on MRONJ risk with non-denosumab monoclonal antibodies alone; most studies focus on combination therapy with bisphosphonates.
3. **Osteoporosis Patients with Romosozumab:** Relatively new medication with limited long-term data on MRONJ risk.
4. **Dental Procedure-Specific Risk:** While dental extractions are consistently identified as a major risk factor, there is limited data on procedure-specific risk for other dental interventions.
5. **Standardization Issues:** Variation in study design, follow-up periods, and MRONJ diagnostic criteria across studies makes direct comparisons challenging.
6. **Prevention Strategies:** Limited high-quality evidence on the effectiveness of specific prevention strategies for different medication categories.

11. References

1. AAOMS Position Paper (2022). American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaw.
2. Limones A, et al. (2020). Medication-related osteonecrosis of the jaws (MRONJ) in cancer patients treated with denosumab VS. zoledronic acid: A systematic review and meta-analysis.
3. Khan AA, et al. (2015). Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus.
4. Adjuvant therapies for MRONJ (2020). A systematic review of treatment options and outcomes.
5. Romosozumab-associated medication-related osteonecrosis of the jaw (2023). Clinical characteristics and management.
6. Incidence of Medication-Related Osteonecrosis of the Jaw in Cancer Patients (2024). Comparative analysis of denosumab and bisphosphonates.
7. Medication-Related Osteonecrosis of the Jaw in Patients Treated with Antiresorptive and Antiangiogenic Drugs (2022). Systematic review of combination therapy.
8. Case Report: single low-dose of denosumab as a trigger of MRONJ (2024). Analysis of risk factors in osteoporosis patients.
9. Medication-Related Osteonecrosis of the Jaw (MRONJ): A Review of Pathophysiology, Risk Factors, Preventive Measures and Treatment Strategies (2022).
10. Aljohani S, et al. (2017). Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series.

11. Migliorati CA, et al. (2010). Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy.
12. Campisi G, et al. (2014). Medication-related osteonecrosis of the jaws (MRONJ): preventive and therapeutic strategies.