**Critically Appraised Topic (CAT)**

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| **Project Team:**  |
| **Camila Negron**  |
| **Project Team Participants:**  |
| **Tim Semon****Camila Negron****Nicholas Politis****Theran Semrad** |
| **Clinical Question:** |
| **How can the risk of osteonecrosis be reduced in patients requiring extractions after bisphosphonate use?** |
| **PICO Format:** |
| **P:** |
| **Patient with gross decay on tooth taking bisphosphonates** |
| **I:** |
| **Extraction of tooth with delayed treatment** |
| **C:** |
| **versus extraction of tooth during treatment** |
| **O:** |
| **decreases the likelihood of osteonecrosis** |
| **PICO Formatted Question:** |
| **In patients with previous bisphosphonate use, will the delayed treatment increase the prognosis vs. continued treatment while proceeding with extraction?** |
| **Clinical Bottom Line:** |
| **Patient needs to have non-restorable #18 treated while being treated with Denosumab (Prolia) injections, and previous bisphosphonate use.**  |
| **Date(s) of Search:**  |
| **10/20/2020** |
| **Database(s) Used:** |
| **PubMed** |
| **Search Strategy/Keywords:** |
| **Bisphosphonates, dental extractions, osteonecrosis, denosumab** |
| **MESH terms used:** |
| **Osteonecrosis/chemically induced, Osteonecrosis/ prevention & control, Bisphosphonate-Associated Osteonecrosis of the Jaw, drug holiday, Denosumab, Dental Extractions** |
| **Article(s) Cited:** |
| 1. **Ruggiero S, Et. Al , American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw, J Oral Maxillofac Surg, 2014, Volume: 72, Page Numbers: 1938-1956**
2. **S. Aljohani et al., Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series, Journal of Cranio-Maxillo-Facial Surgery, 2018, Volume: 46 Page Numbers: 1515-1525**
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| **Study Design(s):** |
| 1. Expert Opinion/Position Paper
2. Case Series
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| **Reason for Article Selection:** |
| 1. This is the most recent position paper from the AAOMS that can be used to guide a provider, along with their own clinical judgement on how to manage MRONJ
2. This article is specific to denosumab, and treatment outcomes can be predicted based on this case study.
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| **Article(s) Synopsis:** |
| 1. The concept of a drug holiday in patients receiving oral BPs or denosumab who require tooth extractions has been an ongoing area of controversy, with sparse data to support current recommendations. The AAOMS Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw, revised in 2009, recommended discontinuing oral BPs for 3 months before and 3 months after invasive dental surgery—systemic conditions permitting. However, there is currently no evidence that interrupting BP therapy alters the risk of ONJ in patients after tooth extraction. As a fully humanized antibody, denosumab blocks the receptor-mediated activation of osteoclasts and has no binding affinity for bone matrix. Therefore, unlike BPs, the antiresorptive effects of denosumab should be mostly dissipated within 6 months of stopping the drug. However, there are no studies to support or refute the strategy of stopping denosumab therapy in the prevention or treatment of MRONJ.

PATIENTS RECEIVING ANTIRESORPTIVE THERAPY FOR OSTEOPOROSIS:1. For patients who have taken an oral BP for less than 4 years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary. This includes any and all procedures common to oral and maxillofacial surgeons, periodontists, and other dental providers.
2. For those patients who have taken an oral BP for less than 4 years and have taken corticosteroids or antiangiogenic medications concomitantly, the prescribing provider should be contacted to consider discontinuation of the oral BP (drug holiday) for at least 2 months before oral surgery, if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred.
3. For those patients who have taken an oral BP for longer than 4 years with or without any concomitant medical therapy, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for 2 months before oral surgery, if systemic conditions permit. The BP should not be restarted until osseous healing has occurred
4. The risk of DRONJ in osteoporosis patients treated with denosumab is estimated to be from 0.01% to 0.03%, and in cancer patients treated with denosumab to be from 1% to 2% (Aljohani et al., 2017). This incidence is comparable to that of BRONJ. In a combined analysis of three phase III trials in patients with metastatic bone disease receiving antiresorptive therapies, incidence of ONJ was higher in denosumab group in comparison to the bisphosphonates group, 1.8% and 1.3% respectively A retrospective medical chart review was carried out at two German institutions: the Department of Oral and Maxillofacial Surgery, Ludwig-Maximilians-University, Munich, and the Department of Oral and Maxillofacial Surgery and University Medical Center Hamburg-Eppendorf, Hamburg. All patients diagnosed and treated for DRONJ between July 2011 and April 2017 were identified. This study included all patients diagnosed with DRONJ based on the following criteria: 1) MRONJ diagnosis based on AAOMS criteria in patients receiving denosumab with or without history of bisphosphonates intake; and 2) a minimum period of 3 months between the last administration of bisphosphonates and DRONJ onset. The exclusion criteria were: a history of head and neck radiation, obvious metastasis to jaw bones and a history of bisphosphonates within the 3 months preceding the onset of DRONJ. A total of 63 patients were identified and fulfilled the entry criteria. Out of those 63 patients, 55% had DRONJ following a dental extraction. The mandible was affected in 40 cases (63.5%), MRONJ was located in the molar area in 20 patients (31.7%). There were three different treatment strategies observed. Surgical treatment was performed in 66 lesions in 60 patients, of them 27 lesions underwent fluorescence-guided surgery, 38 lesions were treated with conventional surgery (57.5%), and one patient underwent extraction and curettage. A total of 53 lesions treated surgically were followed up. Surgical treatment has led to healing in 38 lesions (71.7%), non-healing in 9 cases (17%), and partial healing in 6 sites (11.3%). A total of 22 lesions treated with fluorescence-guided bone resection were followed up. Complete mucosal healing was obtained in 77.3% of the patients treated by fluorescence-guided bone surgery (17/22) (Fig. 2feg). One lesion had partial healing (4.5%), and 4 lesions (18.2%) did not heal. In all, 31 lesions managed with conventional surgery were followed up. Complete mucosal healing was obtained in 67.7% of the patients treated with this surgical technique (21/31). Five lesion (16.1%) failed to heal, while 5 (16.1%) healed partially. The lesion treated with extraction and curettage of the bony socket healed completely. A total of 34 lesions in 31 patients with previous bisphosphonates were detected. No significant difference in the demographics, clinical characteristics and DRONJ stage of bisphosphonate-naïve patients (n ¼ 32, 50.8%) and those who had had bisphosphonates before (n ¼ 31, 49.2%). Moreover, statistical significance between prior bisphosphonate therapy and outcomes of treatment was not observed. we did not see an association between a denosumab holiday and DRONJ healing. However, a positive effect of denosumab cessation on DRONJ can be assumed, given its short half-life. It is very important to know that pausing denosumab even for short intervals can result in remarkable rebound in bone remodeling and bone mineral density (BMD) and might lead to increased fracture risk.
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| **Levels of Evidence:** (For Therapy/Prevention, Etiology/Harm) See <http://www.cebm.net/index.aspx?o=1025>[ ]  **1a** – Clinical Practice Guideline, Meta-Analysis, Systematic Review of Randomized Control Trials (RCTs)[ ]  **1b** – Individual RCT[ ]  **2a** – Systematic Review of Cohort Studies[ ]  **2b** – Individual Cohort Study[ ]  **3** – Cross-sectional Studies, Ecologic Studies, “Outcomes” Research[ ]  **4a** – Systematic Review of Case Control Studies[ ]  **4b** – Individual Case Control Study[x]  **5** – Case Series, Case Reports[x]  **6** – Expert Opinion without explicit critical appraisal, Narrative Review[ ]  **7** – Animal Research[ ]  **8** – In Vitro Research |
| **Strength of Recommendation Taxonomy (SORT) For Guidelines and Systematic Reviews**See article **J Evid Base Dent Pract 2007;147-150**[ ]  **A** – Consistent, good quality patient oriented evidence[ ]  **B** – Inconsistent or limited quality patient oriented evidence[x]  **C** – Consensus, disease oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening |
| **Conclusion(s):** |
| 1. This patient receives corticosteroid injections in the hip and shoulder 2-3x a year, in addition to having been on an oral bisphosphonate (Fosamax). Because of this, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for at least 2 months before oral surgery and not restarted until osseous healing has occurred.
2. Within the limitations of this retrospective study, characteristics of DRONJ were investigated. DRONJ tends to develop after administration of 16.4 doses. The previous use of bisphosphonates does not appear to affect DRONJ severity or treatment response. Based on the findings, we recommend surgical treatment, particularly fluorescence-guided surgery, to allow complete removal of necrotic bone and to prevent ONJ progression.
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