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Khan, Ishfaq

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REVIEW

WILEY

Medication-related osteonecrosis of the external auditory canal – A rapid review of the literature and relevance to special care dentists

Ishfaq Khan BDS, MFDS (RCPS), DSCD (RCSEd)[1,2]

[1]School of Dentistry, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[2]Midlands Partnership University NHS Foundation Trust, Dental Services, St George's Hospital, Staffordshire, UK

Correspondence
Midlands Partnership University NHS Foundation Trust, Dental Services, St George's Hospital, Staffordshire, ST16 3SR, UK.
Email: dental.research@mpft.nhs.uk

Abstract

Aims: There is growing evidence that anti-resorptive and anti-angiogenic medications can cause medication-related osteonecrosis of the external auditory canal (MROEAC). It is possible that patients taking risk medications may also suffer from concomitant medication -related osteonecrosis of the jaw (MRONJ) or temporomandibular joint (TMJ) involvement. The aim of this paper is to conduct a rapid review of the literature on MROEAC, and, its relevance to special care dentists.

Methods and Results: A rapid review of the literature was carried out using PubMed, Science Direct and Google Scholar to identify papers relating to MROEAC. The grey literature and non-English papers were also consulted. Overall, 19 papers were identified from 2005 until December 2022.

Conclusions: Patients at risk of MRONJ may also be at risk of MROEAC and present to special care dentists. Dental/orofacial disease may cause signs and symptoms suggestive of MROEAC. It should be considered as a potential cause of orofacial pain in special care patients. MROEAC can have a significant impact on a patient's dental treatment, including access, the provision of sedation, communication difficulties, and consent issues.

KEYWORDS

medication-related osteonecrosis of the external auditory canal, medication-related osteonecrosis of the jaw, orofacial pain, special care dentistry

1 | INTRODUCTION

Anti-resorptive and anti-angiogenic medications have several indications, including the management of osteoporosis, bone metastases, osteogenesis imperfecta, and cancer. Bisphosphonates may be used specifically in Ear, Nose and Throat (ENT) surgery, for example, in the management of sensorineural hearing loss due to otosclerosis.[1]

It is acknowledged that patients taking anti-resorptive or anti-angiogenic medications may suffer from potential medication-related osteonecrosis of the jaw (MRONJ), especially following invasive dental surgery such as dental extractions, but this complication may also occur spontaneously.[2] Such patients are recommended to have a dental screening prior to the commencement of risk medications in order to prevent MRONJ. Guidance has

been produced for dental surgeons, oncologists, and other healthcare professionals on how to manage patients at risk of MRONJ.[3,4]

The risk of MRONJ is thought to be higher in patients being treated for cancer, concurrently taking systemic steroids, previously diagnosed with MRONJ, or if they have taken risk medications for more than 5 years.[3] The list of medications associated with MRONJ continues to increase[4] with several case reports published in the literature.[5]

However, bisphosphonates may potentially affect any bone within the human body, one case report described bisphosphonate associated osteonecrosis of the thumb, many years after discontinuation of the bisphosphonates,[6] and another case described osteonecrosis of the calvarial bone associated with bisphosphonates.[7] Other specific bisphosphonate complications include gastrointestinal complications (dysphagia, discomfort, and oesophageal irritation) and nephrotoxicity,[8] and atypical femoral fractures which may increase the risk of falls.[9] In addition, complications of anti-angiogenic medications include fatigue, delayed healing, bleeding, hypertension, pruritus, thrombosis, and myocardial infarction.[10] These medications, therefore, have a significant impact on a patient's oral and general health.

Medication-related osteonecrosis of the external auditory canal (MROEAC) is another lesser- known complication of these medications, which if untreated can also lead to a significant loss of quality of life.[11] The Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom has recognised this complication in relation to bisphosphonates and denosumab since 2017,[12] but there is still very little awareness or knowledge about MROEAC among healthcare professionals.[11] Some of the signs and symptoms associated with MROEAC may present as dental/orofacial disease in special care patients; therefore, it is important for dental surgeons (especially special care) to be aware of its potential clinical presentation and management, and refer potential cases for assessment.

1.1 | Rationale for a rapid review

The author was only able to identify one previous systematic review into MROEAC.[13] Several other papers also used review in their titles, but this was not a systematic review of the literature (see 3.1 Characteristics of the selected studies). Box 1 demonstrates the characteristics of the only systematic review.

Rapid reviews have the advantage of a more timely systematic assessment of the literature (with certain limitations such as the number of databases searched), allowing answers to clinical questions to be more rapidly achieved than traditional systematic reviews. Rapid reviews can also be completed by single authors and do not require large teams to complete, often finished in 1 week to 6 months once the protocol has been approved.[14]

This paper aims to be the first rapid review of the literature with a focus on concomitant dental presentations in patients diagnosed with MROEAC, and also its importance to special care dentists. A rapid review of the literature is required due to the increasing incidence of MROEAC and its potential presentation in special care patients.

Box 1-Characteristics of the only previous systematic review into MROEAC.[13]

Systematic review	Characteristics
Lopez-Simon, E., Corriols-Noval, P., Castillo-Ledesma, N., & Morales-Angulo, C. Osteonecrosis de conducto auditivo externo secundaria a bifosfonatos. Revisión sistemática. Revista. ORL 2019; 10 (4): 295–303.	– The systematic review looked at patients aged 18 years and older. – Authors used the PubMed database for the systematic review – Search was limited to papers ranging from 2003–2019 but grey literature was excluded – Authors only looked for bisphosphonate-associated osteonecrosis (BPECO) of the external auditory canal. – There was no active search for concomitant MRONJ/dental disease related to MROEAC.

2 | MATERIALS AND METHOD

2.1 | Searching method

A rapid review was carried out using the principles outlined by Cochrane rapid reviews interim guidance[14] up until December 2022, although there are no universal guidelines for rapid reviews, and a single author was used to complete the rapid review.

Electronic searches were carried out using PubMed, and Google Scholar using the terms: (medication-related OR bisphosphonate* OR diphosphonate*) AND (osteonecrosis) AND (ear canal OR auditory canal). A further electronic search was carried out using Science Direct (which does not support wildcards) using the terms: (medication-related OR bisphosphonate OR diphosphonate) AND

(osteonecrosis) AND (ear canal OR auditory canal). In addition, grey literature (such as government websites, internet free search, and Open Grey), and papers not in English were also considered to reduce language and publication bias. The search was also complemented with Medical Subject Headings (MeSH) and free words related to MROEAC. The title and abstract of each paper were assessed for suitability for the rapid review. The references of obtained papers were also assessed to find other suitable literature for inclusion.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were clinical articles including case reports and case series, previous reviews, English and non-English papers. Papers from 2005 to December 2022 were assessed, as the first reported case in the literature was in 2005.[15]

The exclusion criteria were: veterinary medicine articles, papers directly focused on MRONJ, conference papers and textbooks. Conference papers and textbooks were excluded due to the information normally being outdated, less peer reviewed and also it is uncommon for new cases or knowledge to be initially reported in conference abstracts or textbooks.

The risk of bias was reduced by including adult and child studies, all clinical settings and study designs, non-English and international papers, grey literature and using three different databases to identify papers for inclusion. This differs from most other rapid reviews, which may be limited to one search database and exclude grey literature and non-English publications.[16] The Joanna Briggs Institute (JBI) critical appraisal tools for case series and case reports were used to evaluate the risk of bias of individual studies.

2.3 | Selection of studies

The title and abstracts were initially screened for relevance against the inclusion and exclusion criteria and then the full texts were obtained if deemed suitable for inclusion. Studies were identified to answer the following questions:

1. What was the primary diagnosis of the patient who suffered MROEAC?
2. Which medication was associated with MROEAC and how long was the patient taking the risk medication for?
3. Which sex is most commonly affected by MROEAC?
4. How many patients also suffered from concomitant MRONJ/TMJ involvement or other dental disease?

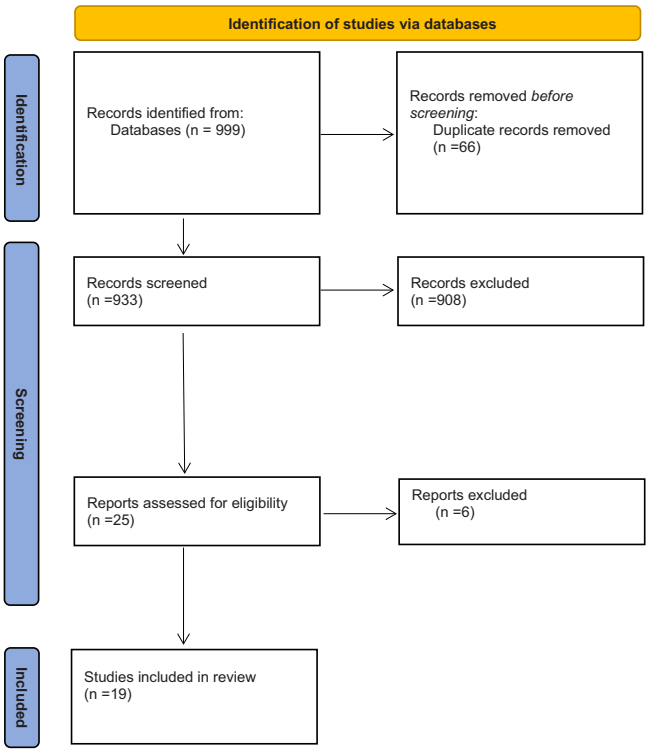

FIGURE 1 Flow diagram for rapid review into MROEAC. MROEAC, medication-related osteonecrosis of the external auditory canal.

2.4 | Data collection

All articles found for review were entered into a data form and the full text of the articles identified as suitable were assessed to identify relevant information. Papers not in English were translated using two different neural machine translation tools (Google Translate and DeepL) to ensure accuracy; in certain cases the English translation was already available. Each paper was assessed for: number of cases, risk medication, diagnosis, age and sex of the patient, whether there was unilateral or bilateral involvement, duration of treatment and whether there was concomitant MRONJ/ TMJ involvement or other dental disease.

3 | RESULTS OF A RAPID REVIEW INTO MROEAC

In total 999 search results were obtained (Google Scholar = 680, PubMed = 19 and Science Direct = 300), of which 66 were duplicates (Figure 1). Overall 19 papers were identified as suitable for inclusion making it the most productive and comprehensive review in comparison to previous reviews into MROEAC.

3.1 | Characteristics of the selected studies

A variety of articles were identified during this rapid review, including, correspondence to the editor, (non-systematic) reviews, case reports/series and one previous systematic review (Table 1)[11,13,15,17–33]. Six papers were excluded from the review following inspection of the full text (Table 2).[34–39] Most papers were in English, followed by Japanese and other languages included German and Spanish. Another case report in Japanese described a case of MRONJ and bilateral ear canal osteonecrosis, but the author was not able to access the paper despite contacting the journal.[29] In addition, information was also obtained from government websites on the incidence and management of MROEAC.[12,40]

4 | DISCUSSION

4.1 | General MROEAC considerations

MROEAC is a very rare complication, and it is considered less common than MRONJ (the MHRA in December 2015, suggested the risk of bisphosphonate-associated osteonecrosis of the external auditory canal as fewer than 1 in 10,000 patients[40]). In 2015, 29 potential cases of MROEAC associated with bisphosphonates were reported worldwide, including 11 cases in the literature.[40]

In total, the author was able to identify 30 cases in the literature up until December 2022.[11,15,17–33] However, Peřina et al. 2021 also reported one unpublished case of a 67–year– old female who they treated for rheumatoid arthritis with zoledronate and denosumab, who also presented with MRONJ in addition to MROEAC, but unfortunately the patient died due to cardiac comorbidity before they could publish the case.[11] A further potential case considered was a 79-year-old female treated for osteoporosis with alendronate and presenting with a peritonsillar abscess with otorrhea,[26] and in addition five more cases of patients presenting with exposed bone in the external auditory canal following long term bisphosphonate therapy may have also satisfied the criteria for MROEAC.[41]

Due to the limited knowledge and awareness of MROEAC among ENT surgeons, it may be misdiagnosed as cholesteatoma, malignant external otitis or temporal bone malignancy,[24] meaning the actual number of cases may be higher than reported in the literature.

Similar to MRONJ, the condition was assumed to be only associated with bisphosphonates, but because subsequent case reports described similar clinical findings associated with denosumab,[11,30,31] sorafenib,[28] and sunitinib,[32] some authors have now referred to the condition as medication-related ear canal osteonecrosis (MRECO).[11] MRECO may be defined as 'bone of the ear canal exposed for 8 weeks in patients using risk medication (bisphosphonates, denosumab, bevacizumab, temsirolimus, and sunitinib), in the absence of previous radiotherapy in the temporal area, exclusion of metastases, and cholesteatoma'.[42]

The possible aetiology of MROEAC is believed to be similar to MRONJ: the reduced ability of bone to respond to physiological demands, reduced osseous remodelling and blood flow associated with anti-resorptive and anti-angiogenic medications predispose to osteonecrosis.[15] The external auditory canal has a very thin layer separating it from bone and a highly colonised bacterial environment, similar to the oral cavity[17] and the tympanic ring also has a poor vascular supply.[43]

Risk factors include steroids and chemotherapy, with or without local risk factors such as infection or trauma[40] (such as from cotton swabs or fingers) and wax plug with wound formation.[19] There is no current evidence of spontaneous MROEAC, but it is important to note that benign idiopathic osteonecrosis of the external auditory canal can occur in the absence of risk medication, for example, following trauma.[40]

Clinical presentation varies, but most commonly there is ulceration and bone exposure affecting the floor of the external auditory canal. Signs and symptoms include otalgia, otitis, otorrhea, and in advanced stages facial paresis, hearing loss and potential mastoid and TMJ involvement may occur. Early treatment may help to prevent complications.[11] In certain cases, the patient maybe asymptomatic.[27] Bisphosphonates are also known to increase the risk of ear canal cholesteatoma, a common differential diagnosis of MROEAC.[41,42] Other differential diagnoses include otitis externa, radio-osteonecrosis, temporal bone pathology, and malignancy.[24]

Special investigations include otoscopy, microbiological sampling, histological exam/biopsy, bloods,[24] MRI[24] audiogram (for hearing loss),[28] gallium- labelled white cell scanning (to confirm area of necrotic bone),[15] and computed tomography. Some authors suggest technetium 99 radioisotope scintigraphy to detect early preclinical ischaemic osteonecrosis.[28] Dental assessment should also be considered as many dental causes may cause symptoms suggestive of otologic disease and to rule out concomitant MRONJ/TMJ involvement (see 4.3 Dental relevance and management of patients with suspected MROEAC).

Treatment in the literature mirrors the management of MRONJ. Initial treatment includes potential discontinuation of the risk medication, conservative management, oral and intravenous antibiotics, topical corticosteroids, local debridement, and removal of the bony sequestrum. In advanced cases, surgical treatment and reconstruction are required, but with the risk of recurrence.[27] There is

TABLE 1 Papers included in rapid review into MROEAC.

Number	Article	Type of article	Language	Considerations
1	Polizzotto et al. 2005;[15]	Correspondence/ case report	English	The first case of MROEAC reported in the literature involved a 64-year-old male who suffered from immunoglobulin G kappa multiple myeloma. The patient was treated initially with pamidronate and then, after 5 years, with zoledronate. The patient was also prescribed dexamethasone. The patient developed mobility of the upper right second molar and lower right second molar, which were subsequently extracted, and the patient was later diagnosed with MRONJ.
2	Froelich et al. 2011;[17]	Retrospective study	English	This paper looks retrospectively at 13 patients who developed osteonecrosis of the external auditory canal between 2005 and 2009, and patient histories were reviewed for possible previous or current bisphosphonate therapy. Three patients with osteonecrosis of the external ear canal and long-term bisphosphonate therapy were identified. They had been treated either for breast cancer or multiple myeloma.
3	Bast et al. 2012[18]	Case report	German/ English	This paper presents the case of a patient who developed bilateral BPECO after receiving long-term bisphosphonate therapy. The patient also developed osteonecrosis of the maxilla, which was successfully treated by the long-term administration of antibiotics and surgical rehabilitation. The authors recommend that ENT surgeons consider BPECO as a differential diagnosis and rule out radio-osteonecrosis, malignant external otitis, and external ear carcinoma in patients presenting with symptoms similar to BPECO.
4	Salzman et al. 2013;[19]	Case report	English	Case report of a 79-year-old female who suffered from BPECO with temporomandibular joint involvement following treatment for osteoporosis with alendronate for 10 years. The authors noted that the patient was a habitual cotton bud user for aural toilet.
5	Kharazmi et al. 2013;[20] And Kharazmi et al. 2013[21]	Correspondence to the editor/Short communication	English	Two different journals (Journal of Craniofacial Surgery and the British Journal of Oral and Maxillofacial Surgery) report the same three cases of BPECO. The cases are based on reports from the Swedish national database of adverse drug reactions (SWEDIS) received from Swedish dentists and physicians from 1965 up to and including 2012.
6	Wickham et al. 2013[22]	Case report	English	This paper published two case reports on BPECO. Firstly, a 64-year-old male with a history of immunoglobulin G kappa multiple myeloma developed a right external auditory canal ulcer six years after treatment with clodronate. The second case report describes a 72-year-old female taking alendronate for osteoporosis who was initially diagnosed and treated for right-sided otitis externa. She was later found to have underlying exposed bone in the right external auditory canal, and a computed tomography scan confirmed destruction of the temporal bone.
7	Thorsteinsson et al. 2015[23]	Case report	English	This paper represents a case report of a 76-year-old female who presented with bilateral BPECO following long-term treatment with oral and intravenous bisphosphonates for osteoporosis.
8	Takahashi et al. 2017[24]	Case report	English	Represents the case of a 71-year-old female who was taking alendronate for osteoporosis and was initially diagnosed with left-sided otitis externa. The authors identified destruction of the temporal bone following a computed tomography scan; malignancy was ruled out by biopsy, and the patient was diagnosed with BPECO. Surgical debridement and the cessation of the alendronate helped to improve the patient's symptoms rapidly.

(Continues)

TABLE 1 (Continued)

Number	Article	Type of article	Language	Considerations
9	Koide and Hokari, 2017[25]	Case report	Japanese/ English (abstract)	Describes a case of BPECO in an 88-year-old female treated for osteoporosis; the diagnosis was confirmed with a computed tomography scan, and the patient was treated with aluminium acetate liquid ointment, and linear polarised infra-red ray phototherapy.
10	Kataoka et al. 2018[26]	Case report	Japanese/ English (abstract)	Reports a case of an 80-year-old female diagnosed with osteoporosis and rheumatoid arthritis who had been taking alendronate and later developed bilateral BPECO and a concomitant right-sided external auditory canal-temporomandibular joint fistula.
11	McCadden et al. 2018[27]	Review (not systematic)/case reports	English	The authors carried out a review (not systematic) of existing cases of BPECO in the literature and then reported six cases of BPECO from their own experience. Treatment included cessation of bisphosphonates, topical treatment, and surgical debridement.
12	Canzano et al. 2019[28]	Case report	English	First case report in the literature of osteonecrosis of the external auditory canal associated with sorafenib treatment. A 58-year-old male with right-sided otorrhea and otalgia was treated for otitis externa for 1 month with no resolution. Previous medical history included treatment with sorafenib for metastatic renal cell cancer. Computed tomography of the temporal bone showed a large right external auditory canal bony erosion with involvement of the tympanic bone and bony sequestra extending to the mastoid cells and temporomandibular joint. A biopsy ruled out temporal bone malignancy. Treatment included a right subtotal petrosectomy with obliteration of the surgical cavity with abdominal fat.
13	Yamaguchi, 2019[29]	The title of the paper suggests it is a case report of a patient who presented with MRONJ and bilateral MROEAC. The exact medication and duration of treatment is not identifiable.	Japanese	The Author and Journal of the paper did not reply to request for access to the article. Abstract or full text could not be accessed.
14	Lopez-Simon et al. 2019[13]	Systematic review	Spanish/English	The first systematic review of BPECO from September 2003 until February 2019. Seven articles were identified, including a total of 17 patients with MROEAC. 76% were women and 24% men, between the ages of 51 and 89. The duration of time elapsed until complications appeared ranged from 15 months to 20 years, and the most common presentation was a unilateral ulceration with bone exposure in 41% of cases. The floor of the external auditory canal was the initial place of presentation in 100% of cases.

(Continues)

TABLE 1 (Continued)

Number	Article	Type of article	Language	Considerations
15	True et al. 2021[30]	Case report	English	A case report of a 79-year-old female with severe osteoporosis and destructive osteoarthritis who received more than 10 years of once-weekly bisphosphonate therapy before commencing denosumab. Four months following denosumab treatment, the patient presented with bilateral hearing loss and right-sided otalgia. Necrotising otitis externa, cholesteatoma, and malignancy were ruled out, and bilateral osteonecrosis of the external auditory canal was diagnosed. Treatment included regular aural toilet, Terra-Cortril ointment, and bismuth-iodine-paraffin paste packing. At 1-year follow-up, bilateral external auditory canals were completely re-epithelialised with no pain or affected hearing.
16	Takeda et al. 2021[31]	Case report	English	The authors report a case of denosumab-induced osteonecrosis of the left external auditory canal in an 81-year-old female treated for osteoporosis. Treatment included a left radical mastoidectomy due to a poor response to conservative treatment. Denosumab was discontinued, and there was no recurrence.
17	Peřina et al. 2021[11]	Case report	English	The authors report a case of a 68-year-old female treated for breast cancer with denosumab who developed osteonecrosis of the jaw and external auditory canal. Successful early treatment included resection of the necrotic bone with primary wound closure.
18	Eguia et al. 2022[32]	Case report	English	A case report of an 80-year-old male with metastatic renal cell carcinoma treated with zoledronate and sunitinib who went on to develop unilateral MROEAC.
19	Abelardo and Jaramillo, 2022[33]	Case report	English	This paper describes three cases of MROEAC in older patients associated with alendronate. The patients had a diagnosis of osteopenia, osteoporosis, fragility fractures, and polymyalgia rheumatica. The patients were receiving regular microsuctioning and the application of topical antibiotics with steroids, but due to the COVID-19 pandemic, this was not possible, and following review in 4-5 months, the ear pathology had significantly improved with healthy re-epithelialisation. The authors conclude that in bisphosphonate-induced osteonecrosis of the external ear canal, excessive and repeated microsuctioning can delay re-epithelialisation, and gradually increasing the intervals between microsuctioning could aid in the overall resolution of the disease.

Abbreviations: BPECO, bisphosphonate-associated osteonecrosis of the external auditory canal; MROEAC, medication-related osteonecrosis of the external auditory canal; MRONJ, medication -related osteonecrosis of the jaw.

no consensus on a drug holiday for the management of MROEAC.[13]

Due to the rarity of the condition, prevention may be inefficacious[11]; the benefits of anti-resorptive or anti-angiogenic medications outweigh the risk of MROEAC.[22] One paper suggested a revision to non-nitrogen containing forms of bisphosphonates (which may be less likely to cause MROEAC) before complete cessation of bisphosphonate treatment in patients diagnosed with MROEAC.[33] Other authors have advised that elective auditory canal surgery should be completed prior to a patient starting risk medication, that patients should be instructed in proper self-cleaning of the external auditory canal and that hearing devices should be well fitting to avoid trauma.[20]

Patients with several risk factors for external otitis should potentially be assessed by ENT surgeons prior to the commencement of risk medications.[23] Risk factors for external otitis would include patients susceptible

TABLE 2 Excluded papers and rationale for exclusion.

Number	Article	Reason for exclusion
1	Froelich, 2011[34]	The journal 'Reactions' reports on the retrospective study Froelich et al., 2011. There are no additional cases of MROEAC reported.
2	Brookler, 2015[35]	This was a letter to the editor disputing the Salzman et al. 2013 paper and his diagnosis of BPECO.
3	Salzman et al., 2015[36]	This was a letter to the editor replying to Brookler, 2015. In this letter Salzman et al. state why they believe their case report fits the criteria for BPECO.
4	Prescrire Int, 2016[37]	This paper reported the adverse effects of bisphosphonates, specifically the adverse effect of osteonecrosis of the external auditory canal.
5	Chitra, 2020[38]	Conference paper which addresses the prevention and management of BPECO.
6	True et al., 2022[39]	Republished case report from 2021 in the Journal *Drug and Therapeutics Bulletin (BMJ).*

Abbreviations: BPECO, bisphosphonate-associated osteonecrosis of the external auditory canal; MROEAC, medication-related osteonecrosis of the external auditory canal.

to infections, swimmers, patients with hearing impairment (and requiring hearing aids), diabetics, patients with skin disorders affecting the ear, patients with Down's syndrome, and older adults. It is advisable that before starting patients on risk medications, they are informed of the rare complication of MROEAC in order to gain informed consent.

4.2 | Emerging clinical considerations for special care dentists

The exact mechanism, clinical picture, risk factors, special investigations, and treatment for MROEAC are yet to be definitively determined due to the rarity of the condition.[13] However, some trends can be drawn from the case reports published in the literature (see Table 3).

4.3 | Primary diagnosis treated by risk medications associated with MROEAC

The majority of MROEAC cases appear to occur in older patients, and none have been reported in children; who are less likely to be taking bisphosphonates or other risk medications. Most cases have been in patients treated for osteoporosis.[19–27,29–31,33] Other cases involve patients being treated for multiple myeloma[15,17,18,22] breast cancer[11,17,23] rheumatoid arthritis,[11] metastatic renal cell carcinoma,[28,32] osteopenia and polymyalgia rheumatica[33] all conditions more common in the older population.

4.4 | Associated medications and length of use

Most MROEAC cases in the literature occurred in patients taking medications for more than 2 years, although two cases had been taking risk medications for less than 2 years.[27,31] Most cases have been attributed to bisphosphonates (in particular alendronate), likely due to bisphosphonates being more commonly prescribed compared to other risk medications currently associated with MROEAC. In numerical values: Alendronate = 16, Zoledronate = 6 (+1 including the unpublished case), Pamidronate = 4, Denosumab = 3 (+1 including the unpublished case), Risedronate = 2, Clodronate = 1, Ibandronate = 1, Sunitinib = 1 and Sorafenib = 1. In certain cases, the patient had been on two different (drug class) risk medications.[30,32] The most common route associated with MROEAC was orally; however, this may reflect the more common form of drug delivery.

4.5 | Sex most commonly affected by MROEAC

Females have a higher incidence of MROEAC compared to males. This may be because osteoporosis is more common in females due to menopausal changes later in life[25]; breast cancer, rheumatoid arthritis, osteopenia, and polymyalgia rheumatica are also more common in females. Of the 31 cases (including the unpublished case), at least 23 cases (74%) were female.

4.6 | Incidence of concomitant MRONJ/TMJ involvement or other dental disease

At least eight cases (26%) (including one unpublished case) of MROEAC were associated with MRONJ or TMJ involvement.[11,15,18,19,26,28,29] This would suggest that patients at risk of MRONJ are also at risk of MROEAC or TMJ issues, no other dental pathology was identified from the literature. This number may also be under-represented

TABLE 3 Emerging clinical considerations from a rapid review of the cases associated with MROEAC KEY: * Author unable to access article despite request to journal (data taken from title of paper). # The age range reported for MROEAC patients was from 69 to 89 years.

Reference	Number of cases	Risk medication	Diagnosis	Age	Sex	Unilateral/ Bilateral involvement	Duration of treatment (in complete years)	MRONJ/TMJ involvement
Polizzotto et al. 2005[15]	1	Pamidronate Zoledronate	Multiple myeloma	64	Male	Unilateral	9	MRONJ
Froelich et al. 2011[17]	3	Zoledronate	Breast cancer	51	Female	Bilateral	5	No
		Pamidronate Zoledronate	Breast cancer	70	Female	Unilateral	11	No
		Pamidronate	Multiple myeloma	64	Female	Unilateral	6	No
Bast et al. 2012[18]	1	Pamidronate Zoledronate	Multiple myeloma	68	Male	Bilateral	>9	MRONJ
Salzman et al. 2013[19]	1	Alendronate	Osteoporosis	79	Female	Unilateral	10	TMJ involvement
Kharazmi et al. 2013[20,21]	3	Alendronate	Osteoporosis	74	Female	Bilateral	N/A	No
		Alendronate	Osteoporosis	67	Female	Unilateral	> 2	No
		Alendronate	Osteoporosis	88	Female	Unilateral	Several years	No
Wickham et al. 2013[22]	2	Clodronate	Multiple myeloma	64	Male	Unilateral	6	No
		Alendronate	Osteoporosis	72	Female	Unilateral	4	No
Thorsteinsson et al. 2015[23]	1	Alendronate Ibandronate Zoledronate	Breast cancer Osteoporosis	76	Female	Bilateral	Alendronate-8 Ibandronate-3 Zoledronate-3	No
Takahashi et al. 2017[24]	1	Alendronate	Osteoporosis	71	Female	Unilateral	11	No
Koide and Hokari, 2017[25]	1	Alendronate Risedronate	Osteoporosis	88	Female	Unilateral	5	No
Kataoka et al. 2018[26]	1	Alendronate	Osteoporosis	80	Female	Bilateral	5	TMJ involvement
McCadden et al. 2018[# 27]	6	Alendronate	Osteoporosis	80	Female	Bilateral	1 (20 months)	No
		Risedronate	Osteoporosis	80	Female	Unilateral	15	No
		Alendronate	Osteoporosis	86	Female	Unilateral	6	No
		Alendronate +2 further cases reported.	Osteoporosis	89	Male +2 Females	Unilateral	10	No

(Continues)

TABLE 3 (Continued)

Reference	Number of cases	Risk medication	Diagnosis	Age	Sex	Unilateral/ Bilateral involvement	Duration of treatment (in complete years)	MRONJ/TMJ involvement
Canzano et al. 2019[28]	1	Sorafenib	Metastatic renal cell carcinoma	58	Male	Unilateral	2	TMJ involvement
Yamaguchi., 2019*[29]	1	–	Osteoporosis	–	–	Bilateral	–	MRONJ
True et al. 2021[30]	1	Alendronate Denosumab	Osteoporosis	79	Female	Biilateral	Alendronate > 10 Denosumab (4 months)	No
Takeda et al. 2021[31]	1	Denosumab	Osteoporosis	81	Female	Unilateral	1 (1.5 years reported)	No
Peřina et al. 2021[11]	1	Denosumab	Breast cancer	68	Female	Unilateral	3	MRONJ
Eguia et al. 2022[32]	1	Sunitinib Zoledronate	Metastatic renal cell carcinoma	80	Male	Unilateral	14	No
Abelardo and Jaramillo, 2022[33]	3	Alendronate	Osteopenia	71	Female	Bilateral	>5	No
		Alendronate	Fragility fractures, polymyalgia rheumatica	76	Male	Unilateral	4	No
		Alendronate	Osteoporosis	83	Female	Bilateral	> 5	No

Abbreviation: MRONJ/TMJ, medication -related osteonecrosis of the jaw/temporomandibular joint.

as ENT surgeons may not have actively looked for the diagnosis of MRONJ or TMJ involvement or may not feel comfortable diagnosing dental pathology. Special care dentists should therefore be aware of this complication[44] and ENT surgeons should consider referral to special care dentists to rule out concomitant MRONJ or other dental disease. It is not yet known if patients previously diagnosed with MROEAC have a higher risk of developing MRONJ or if it is the case the other way.

Thirteen cases of temporal bone osteonecrosis following bisphosphonate therapy have also been reported in the literature, with potentially life threatening complications.[43] Temporal bone, like the mandible, is dense with a poor vascular supply, predisposing it to medication-related osteonecrosis.[45] There is one reported case of temporal bone osteonecrosis with concomitant MRONJ in a 57–year–old female treated for osteoporosis with alendronate, this patient presented with otalgia and facial nerve palsy.[43]

4.7 | Dental relevance and management of patients with suspected MROEAC

The management of orofacial pain is within the remit of special care dentistry and special care patients may have conditions which predispose them to otologic disease. These patients may also be taking risk medications for MROEAC (Box 2).

Patients with Paget's disease, osteoporosis, multiple myeloma, multiple sclerosis, rheumatoid arthritis, and cerebral palsy may fall into this category. In addition, special care dentists will treat patients who have breast cancer, renal cell carcinoma, and other oncological diseases who may be taking risk medications.

Dental surgeons share their surgical space with ENT surgeons; many conditions presenting in the mouth may cause referred symptoms affecting the ear due to their common embryonic origin and neural innervation. It is important to consider the differential diagnosis of MROEAC in patients taking risk medications and complaining of otologic issues.

A full medical and pharmacological history is very important in the diagnosis of MROEAC; by definition, patients must be taking a risk medication for the diagnosis of MROEAC. Several medications are also potentially associated with ototoxicity (leading to otologic issues such as potential hearing loss), such as aminoglycoside antibiotics, macrolides, metronidazole, salicylates/NSAIDs, diuretics, chemotherapy drugs (e.g., vinca-alkaloids, platinum compounds, and bleomycin), and anti-malarials, which need to be ruled out.[8]

The patient should be questioned about any history of ENT surgery, ENT disease (e.g., sensorineural hearing loss due to otosclerosis treated with risk medication), aural habits (e.g., use of cotton swabs), and if they have suffered from otological trauma or complaints such as otalgia, otorrhea, or hearing loss.

Patients with otalgia may present to special care dentists for assessment. Several dental diseases may present as secondary causes of otalgia. This can include dental pain or infection (from caries or periodontal disease), sinusitis, impacted third molars, temporomandibular joint dysfunction (TMJD), or orofacial pain such as trigeminal neuralgia and temporal arteritis (which may be linked to polymyalgia rheumatica). Salivary gland diseases such as sialadenitis and sialolithiasis may also cause secondary otalgia; other late presentations of MROEAC may include facial paresis, and conductive hearing loss.

Special care dentists should also consider referral for MRI and computed tomography. Orthopantomography

Box 2-Dental Relevance of MROEAC for special care dentists

Dental relevance of medication-related osteonecrosis of the external auditory canal for special care dentists.

1. Patients with MRONJ may also present with medication-related osteonecrosis of the external auditory canal.
2. Dental and orofacial pain may cause symptoms similar to medication-related osteonecrosis of the external auditory canal such as otalgia and TMJD.
3. Many special care patient groups are susceptible to otologic disease and likely taking risk medications.
4. Complications of medication-related osteonecrosis of the external auditory canal include hearing impairment and facial paresis, which may affect dental management.
5. Inhalational sedation with nitrous oxide may be contraindicated in certain patients (e.g., patients who have had recent ear surgery).
6. Certain special care patient groups (e.g., patients with hearing impairment, older adults, Down's syndrome, or diabetics) who are at higher risk of external otitis may benefit from referral to ENT prior to commencing risk medications, as they may have a higher risk of MROEAC.
7. Patients presenting with signs indicative of potential medication-related osteonecrosis of the external auditory canal and taking risk medications should be referred to ENT and dental/orofacial disease (including MRONJ) should be ruled out.

(and other dental imaging that shows the external auditory canal, such as lateral cephalograms) may be useful in advanced cases (e.g., patients with a potential diagnosis of MROEAC and presenting with late features such as facial paresis or TMJ involvement), as it may show pathology (e.g., osteonecrosis) of the external auditory canal or TMJ. Patients presenting with otalgia, otorrhea, otitis externa, or symptoms suggestive of cholesteatoma such as conductive hearing loss, tinnitus, dizziness, or facial weakness on one side and who are taking risk medications should be referred to ENT for assessment.[40,44] The author further advocates routinely asking patients taking risk medications about signs of MRONJ and MROEAC to ensure timely diagnosis and referral, as patients may themselves not be aware of the risk of MROEAC due to the limited awareness among ENT surgeons. At-risk patients should be encouraged to report any otologic symptoms to their medical doctor.[11] Long term review following cessation of the risk medication in patients diagnosed with MROEAC is advised.[31]

Depending on the complications and subsequent treatment for MROEAC, dental care may also be affected. Patients may not be suitable for treatment under inhalational sedation with nitrous oxide (e.g., if there has been recent ear surgery), and inhalational sedation with nitrous oxide may also rarely be associated with otalgia.[46] Other considerations for patients who may develop hearing impairments may include: access, dental anxiety, communication difficulties, consent or capacity issues, and avoiding medications associated with ototoxicity.

Dental implications for patients who may suffer from facial paresis may include difficulty with home care, communication issues, increased risk of angular cheilitis, microstomia/trismus resulting in reduced intraoral access, hyperacusis or deafness, xerostomia (and therefore increased risk of intraoral disease such as caries and oral infections), and ageusia.

5 | LIMITATIONS OF THE RAPID REVIEW

The limitations of this rapid review include a single author, however, for rapid reviews, this is acceptable[16] and the author was able to yield more results than previous reviews (including the only existing systematic review) into MROEAC. Other limitations include the number of databases searched, however, the risk of bias was reduced by the inclusion of non- English papers, grey literature, and JBI critical appraisal tools.[47] The use of neural machine translation tools in comparison to human translation have inherent limitations, which include difficulty interpreting verbs, rare words, long sentences, and context, plus word alignment may be an issue.[48]

6 | CONCLUSIONS

Special care patients at risk of MRONJ are also at risk of the rare complication of MROEAC, and this may affect their dental management. Dental/orofacial disease may cause symptoms similar to MROEAC, such as otalgia or temporomandibular joint dysfunction. At-risk patients should be asked about any otological complaints and, if appropriate, referred to ENT surgeons for further assessment. It is likely that more medications will be associated with MROEAC as awareness of the condition improves. Closer collaboration between ENT surgeons and special care dentists is required to ensure safer, comprehensive care for patients being treated with risk medications.

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