The role of the pharmacist in the prevention of Medication-Related Osteonecrosis of the Jaw (MRONJ).

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Abstract:

Medication Related Osteonecrosis of the Jaw (MRONJ) is a rare adverse effect of a number of anti-resorptive and anti-angiogenic drugs that typically presents following a dental extraction. MRONJ is difficult to treat and can have a significant negative effect on quality of life, therefore the implementation of preventive measures is recommended. The multidisciplinary healthcare team should work to educate patients on the need for good oral hygiene and ensure that patients undergo remedial dental work prior to the initiation of implicated medications.

As the medication experts in the multidisciplinary team, a key element of the pharmacist's role is to educate both patients and other healthcare professionals on the safe and effective use of medications. This therefore represents an opportunity for pharmacists working in all settings to contribute to the prevention of MRONJ.

This article provides a summary of the key background information in relation to the prevention of MRONJ and discusses the potential role of pharmacists working in community pharmacy, secondary care and in general practice.

Keywords: Community Pharmacy, Interprofessional Working, Medication Related Osteonecrosis of the Jaw, MRONJ, Medication Safety, Prevention, Primary Care, Oral Health, Secondary Care

Key Points

- Medication Related Osteonecrosis of the Jaw (MRONJ) is a rare complication that typically presents following a dental extraction in some patients prescribed anti-resorptive or anti-angiogenic drugs;
- MRONJ is challenging to treat and can have a significant negative effect of quality of life;
- Patients should undergo remedial dental work prior to the initiation of implicated medicines and maintain good oral hygiene throughout treatment;
- A multidisciplinary approach to the prevention of MRONJ is recommended, with pharmacists playing a key role in the education of patients on appropriate preventive measures;
- Improved communication and interprofessional collaboration with medical and dental colleagues could improve patient outcomes.

Oral health promotion has traditionally been the preserve of dental health professionals, but with the increasing recognition of the link between oral and general health, there is an increased importance in other health professionals promoting oral health. Wilson and Soni, the former and current president of the British Dental Association and Royal Pharmaceutical Society respectively, recently published an opinion piece in the British Dental Journal; emphasising the opportunities for pharmacy and dentistry to spearhead a new era of interprofessional healthcare, integrate dentistry into general healthcare provision and for example, collaborate to improve oral cancer screening, the management of diabetes and the oral health of patients in residential care homes[1].

A key area of overlap between the two professions relates to the adverse effects of medication; there are a number of established adverse effects of medications which can impact negatively on patients' oral health. These include xerostomia (dry mouth), taste disturbances, increased salivation, gingival overgrowth and osteonecrosis of the jaw[2-4].

Case reports of osteonecrosis of the jaw linked to bisphosphonate therapy began to emerge in the early 2000s. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) is now well documented in the literature and has been subject to a number of Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA) prescribing safety alerts[4-6]. Although oral bisphosphonates remain the most commonly prescribed implicated agents, a number of other drugs which are used in the management of osteoporosis, Paget's disease or in the treatment of cancer have subsequently been attributed to the potential development of osteonecrosis of the jaw (Table 1). This has led to a change in the terminology used to describe the condition which is now referred to as medication-related osteonecrosis of the jaw (MRONJ)[7].

Table 1. Drugs with MHRA Safety Updates for MRONJ at April 2017

Bisphosphonates		
Drug Name	Trade name (s)	Indication
alendronic acid	Binosto® (Internis Pharmaceuticals Ltd) Fosamax® (MSD) Fosavance® (MSD)	Osteoporosis
sodium risedronate	Actonel® (Warner Chilcott UK) Actonel Combi® (Warner Chilcott UK)	Osteoporosis Paget's Disease
zolendronic acid	Aclasta® (Novartis) Zometa® (Novartis)	Osteoporosis Paget's Disease Cancer
ibandronic acid	Bondronat® (Atnahs Pharma UK) Bonviva® (Atnahs Pharma UK) Iasibon® Quodixor®	Osteoporosis Cancer
sodium pamidronate	Aredia®	Paget's Disease Bone pain Cancer
sodium clodronate	Bonefoc® Clasteon® (Beacon Pharmaceuticals) Loron® (Intrapharm Laboratories)	Bone pain Cancer
RANKL Inhibitors		
Drug Name	Trade name (s)	Indication
denosumab	Prolia® (Amgen) Xgeva® (Amgen)	Osteoporosis Cancer
Anti-angiogenic Drugs		
Drug Name	Trade name (s)	Indication
bevacizumab	Avastin® (Roche)	Cancer
sunitinib	Sutent® (Pfizer)	Cancer
aflibercept	Zaltrap® (Sanofi)	Cancer

Reproduced, (with permission) from the Scottish Dental Clinical Effectiveness Programme[8].

MRONJ is a complex phenomenon, and the official definition provided by the American Association of Oral and Maxillofacial Surgeons is as follows:

“Exposed bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region that has persisted for more than eight weeks in patients with a history of treatment with anti-resorptive or anti-angiogenic drugs, and where there has been no history of radiation therapy to the jaw or no obvious metastatic disease to the jaws”[(7)]. Figure.1 shows the intra-oral appearance of a patient with MRONJ.

Insert Figure 1 about here

Legend - Exposed necrotic bone is evident in the lower right region of the mandible, following extraction of the posterior teeth. Image courtesy of Dr F. Graziani and Dr Nisi

The occurrence of MRONJ is thought to be related to the unique nature of the blood supply, structure and function of the jaw bones, and the microbiology of oral plaque biofilm in contributing to lesion development. The jaw bones (maxilla and mandible) have a high blood supply which may result in an increased concentration of implicated medicines in this area. Furthermore, alveolar bone (that part of the jaw bone which supports the teeth) remodelling occurs at a much higher rate than elsewhere in the skeleton (likely as a result of forces related to chewing and the presence of teeth) and thus there is a higher uptake of implicated medications in the alveolar bone compared with elsewhere in the body[(9)].

It is difficult to provide precise prevalence rates for MRONJ, with varying reports published in the existing literature[(8)]. The current consensus is that the estimated incidence of MRONJ in cancer patients treated with anti-resorptive or anti-angiogenic drugs is 1% and in osteoporosis patients treated with anti-resorptive drugs is 0.01-0.1%[(8)].

With an ageing population and a specific focus on the prevention of skeletal related events (SREs), the prescribing of oral bisphosphonates has increased considerably

over recent years; in England prescribing data reveal 6,007,071 individual supplies of alendronic acid 70mg in 2018 compared with 2,841,358 in 2006[10,11]. SREs, such as bone fractures, resulting from cancer that has metastasised to the bone are associated with significant morbidity and reductions in quality of life. Intravenous bisphosphonates, such as zoledronic acid and the monoclonal antibody denosumab are licenced for the prevention of SREs in osteoporosis and in patients with bone metastases.

Prescribing rates of other drugs implicated in the development of MRONJ have also risen significantly in recent years and are expected to rise further. Prescribing of denosumab has increased with 52,210 individual supplies in England during 2018 compared with 43,063 in 2017[10,11]. The introduction of intravenous bisphosphonates in the treatment of early breast cancer has also been described as a risk for MRONJ development and approximates to a further 20,000 patients being prescribed bisphosphonates annually in the UK[12]. The overall increase in prescribing of implicated medications is therefore likely to result in more patients becoming at risk of developing osteonecrosis of the jaw, making this rare condition a greater issue of concern in the context of clinical practice.

Invasive dentoalveolar surgery, which includes commonly performed procedures such as tooth extractions, is the major risk factor in the development of MRONJ, with studies reporting that approximately 50-60% of patients with MRONJ identified tooth extraction as a specific precipitating event[7]. The evidence supporting other risk factors is limited but these include concomitant corticosteroid use, poor oral hygiene, ill-fitting dentures, tobacco use and co-morbid conditions such as diabetes and anaemia[7].

Diagnosis of MRONJ can be challenging, particularly for non-specialists and at-risk patients should be referred for general dental assessment and specific diagnosis and treatment intervention where necessary, as specified in the Summary of Product Characteristics for the major implicated drugs. The key signs and symptoms of MRONJ include: pain; exposed necrotic bone in the oral cavity; signs of infection such as fistula, swelling, cellulitis and pus exudation, tingling and numbness / pins and needles (hypoesthesia or paraesthesia) in the chin or lower lip, loosening of teeth (mobility) and bad breath (halitosis)[13].

MRONJ is difficult to treat and can cause significant morbidity. A small study of 34 patients with MRONJ utilising the Oral Health Impact Profile (OHIP-14), a validated and widely used oral health related quality of life indicator, found that the condition significantly ($p<0.001$) affects quality of life[14]. Our previous qualitative study of patients diagnosed with MRONJ highlighted significant quality of life implications, particularly the physical, psychological and social impacts associated with the condition[15]. This includes significant pain, regular use of analgesic medication and antibiotics, the need for invasive surgery, and the social anxiety of eating awkwardly in public.

Due to the significant morbidity associated with MRONJ and the limited treatment options available, the elimination or stabilisation of oral disease before initiating antiresorptive agents is recommended as a preventive strategy for MRONJ in clinical guidelines[8]. Therefore, it is important that patients are fully informed about the risk, the appropriate preventive strategies and signposted to dental services, preferably before these drugs are commenced. Studies have identified that dental screening and preventive strategies reduce the risk of osteonecrosis of the jaw. A study by Dimopoulous et al (2009), reported a statistically significant reduction in the incidence

of MRONJ amongst multiple myeloma patients prescribed zoledronic acid following the implementation of preventive measures; the incidence rate before the implementation of preventive measures was 0.671/100 person-months and 0.230/100 person-months afterwards [IR ratio 2.92, P = 0.029, 95% confidence interval 1.06-8.03][16]. Vandone et al (2012) also reported a 50% reduction in the incidence rate with screening and pre-treatment preventive dental care in patients with bone metastases from solid tumors prescribed iv bisphosphonates; osteonecrosis of the jaw was observed in 5.5% of patients (n= 11/200) not receiving preventive dental measures and 2.8% (n= 6/211) in those receiving preventive dental care before and during treatment with bisphosphonates[17].

This represents an important opportunity for pharmacists in different settings to provide information to patients and healthcare professionals on the risk of and prevention of MRONJ. Evidence to support the current role of pharmacists in this regard is limited; a questionnaire of healthcare professionals in North Wales identified that only 11.8% of medical general practitioners (GPs) (n=120) and 9.7% of pharmacists (n=60) advised patients to alert their dentist to their use of bisphosphonates[18]. A second small study (n=55) found that the majority of patients acquired knowledge about the drug they were prescribed from the patient information leaflets that are supplied with the medication (62%) with few patients (13%) receiving this information directly from their GP. When asked to identify side effects of bisphosphonate therapy, only 32% of patients receiving intravenous and 17% of patients receiving oral, bisphosphonates were aware of the potential risk of developing MRONJ[19].

In our previous qualitative study of patients diagnosed with MRONJ participants described a perceived hierarchy in relation to the management of their health; they

expected prescribers to utilise professional judgment on the suitability of the medication for them, and to provide information related to the adverse effects of medications. However, participants highlighted the importance of the pharmacist in reinforcing advice and were positive towards the pharmacist's role in providing information on medications and conducting medication reviews[15].

However, our previous qualitative study of GPs and pharmacists in North East England indicated that both professional groups had limited knowledge of both MRONJ and awareness of the recommended preventive strategies. Participants described the often complex medical histories of patients prescribed implicated medicines and that other aspects of patient care are frequently prioritised, overlooking the advice related to the risk and prevention of MRONJ[20].

Our findings therefore suggest that patient safety continues to be compromised as patients' are not receiving appropriate oral health advice and required preventive dental treatment before taking these implicated medications.

There is however a significant challenge in effectively engaging patients in recognising the need for dental care; the most recent Adult Dental Health Survey (2009) identified that 23% of dentate adults do not attend the dentist at least every 2 years[21]. Our previous qualitative study with patients also identified a number of barriers to dental care; including low priority of oral health care, patient's phobia of dental treatment and the financial implications of dental care[15].

There is, of course, significant literature supporting the role of the pharmacist in relation to the appropriate use of medicines and in multidisciplinary working[22]. However, the literature is limited in relation to the role of the pharmacist in the delivery of oral health advice and in particular working interprofessionally with dental

healthcare professionals. The prevention of MRONJ necessitates effective multidisciplinary working and represents an excellent opportunity for pharmacists in all settings to provide integrated, patient centred care. As the medication experts in the multidisciplinary team, a key component of the clinical pharmacists' role should include education of other healthcare professionals on the safe and effective use of medicines and the risks of MRONJ; this includes the education and provision of clinical and medication advice to dentists, whom receive limited pharmacology and medication safety related education compared to pharmacists. This role not only relates to the prevention of MRONJ, but to the management of other new or established medications which can impact on oral health or the safe provision of dental treatment. It is important that adverse drug reactions are reported and this is another key role of pharmacists in all settings, particularly now that MRONJ is associated with medications other than bisphosphonates.

Table 2 summarises the evidence base and the implications for clinical practice.

Table 2. Summary of Evidence Base and Implications for Practice

Evidence Base	Implications for Practice
MRONJ is a rare adverse effect of certain medications. Affecting approx. 1% of cancer patients prescribed anti-resorptive and anti-angiogenic medication and 0.1% of patients prescribed anti-resorptive medication for osteoporosis[8].	Pharmacists should be aware of the implicated medicines and therefore be in a position to provide appropriate preventive advice where appropriate.
MRONJ is difficult to treat, therefore patients should undergo remedial dental treatment prior to initiating implicated medications[7-8].	Patient newly prescribed implicated medicines should be referred to the dentist on prescribing. This advice should be supported by the interprofessional team, during prescribing and with subsequent supply of the medication
Patients are at highest risk of developing MRONJ following a dental extraction[7-8].	Patients should be advised to inform their dentist that they take implicated medications. Access to Summary Care

	Records should be considered for dental teams.
Implicated medicines, such as bisphosphonates, have a number of complicated and important counselling points[26].	Consideration should be made to the complexity of information and advice required when patients are prescribed these medications. More detailed counselling and time to discuss issues should be provided during consultations and inclusion of bisphosphonates in the NMS/MUR should be considered.

The community pharmacist

Community pharmacies are generally regarded as being easily accessible and, in many cases, provide the most frequent opportunity for patients to access a healthcare professional. Pharmacists in community settings have demonstrated an acceptance that oral healthcare can be part of their professional role and that the simple educational interventions can influence positive intentions in relation to the oral health habits of patients[23-24].

Community pharmacists are unlikely to work with the implicated IV medications regularly, however, across the country, they dispense millions of prescriptions for oral bisphosphonates. The NMS is an advanced service within the NHS Community Pharmacy Contractual Framework, that supports patients newly prescribed medicines for long-term conditions; however the service specification does not currently include bisphosphonates[25]. This is a missed opportunity; leaving the issue of MRONJ aside, this group of drugs has a number of issues that it would potentially benefit patients to be counselled about through an extended discussion and follow up with their pharmacist. The list of counselling points listed in the Summary of Product Characteristics (SPC) for alendronic acid is extensive and includes the following[26]; *take once per week; take on an empty stomach; a full glass of water (plain water); 30 minutes before food, drink or medicine; avoid coffee, mineral water or juice; swallow*

whole; do not crush or chew; stay upright; do not lie down until you have eaten a meal; when to take your calcium supplements; oesophageal adverse effects; and finally if you haven't forgotten everything else, look after your teeth and *use in caution with poor dental health, gum disease or if requiring a dental extraction.*

The NMS would provide the pharmacist and the patient time to have a thorough discussion related to the administration instructions of the drug, but also facilitate an important discussion on the need to maintain good oral hygiene and oral health, and to visit the dentist before initiation. This represents an important opportunity to ensure that patients are signposted appropriately and that they are empowered to make informed decisions in relation to their treatment and lifestyle management.

Like the NMS, the Medication Use Review (MUR) service does not specifically include bisphosphonates in the service specification[27]. MURs are also part of the NHS Community Pharmacy Contractual Framework and provide patients with structured, adherence-centred, polypharmacy reviews. Although many patients prescribed bisphosphonates have complex needs and may be eligible for an MUR due to polypharmacy considerations, this is again a potential lost opportunity to reinforce preventive advice to patients.

The clinical pharmacist in general practice

The growth of the pharmacist's role in general practice represents a significant opportunity to utilise the extensive knowledge base and skill set in relation to the safe and effective management of medications and long-term conditions. The Primary Care Pharmacy Association's Clinical Pharmacist in General Practice Job Description details examples of duties and responsibility for pharmacists in this setting[28]; this includes managing long-term conditions, performing medication use reviews,

implementing medication safety guidance, supporting public health campaigns and signposting to appropriate healthcare professionals.

Patients prescribed medications implicated in the development of MRONJ fall into many of these categories; pharmacists in this role have access to full medical records, often co-ordinate discharges from secondary care and the transfer of information between healthcare settings. Clinical pharmacists are experienced at taking accurate medication histories and have a key role in ensuring accurate documentation of all the medications that patients both historically and currently take. Medication may also be initiated by pharmacist independent prescribers and patients may have their medication reviewed as part of a chronic disease management clinic or be specifically identified as part of a targeted intervention.

The evaluation of clinical pharmacists in general practice pilot studies by the University of Nottingham found that patients benefited from increased lifestyle advice and the provision of advice that improves medicines adherence, and reduces the adverse effects of medication[29]. However, the delivery of oral health care education in this setting has not been particularly explored; pharmacists, commissioners, and researchers should be encouraged to be innovative and incorporate oral health advice as an integral part of their current roles. Practitioners should be aware of oral health issues and integrate these into their current practices where appropriate; for example, as part of the lifestyle advice that already forms part of medication reviews and chronic disease management clinics.

Secondary care

Many of the more recent medications to be implicated in the development of MRONJ are prescribed, dispensed and administered in secondary care settings[30]. A referral

service for dental screening from haematology and oncology clinics in Wales was established with over 90% of the patients referred for screening reporting satisfaction with the service[31]. Such referral pathways could, and should, naturally incorporate specialist pharmacists involved in the care of higher risk oncology patients or those prescribed IV bisphosphonates or denosumab.

Other roles in an acute setting include the management of patients after falls and fractures, medication reviews and discharge planning, and deprescribing medicines in line with clinical guidelines to reduce adverse drug effects, Long term therapy with bisphosphonates is associated with an increased risk of MRONJ and therefore represents a potential target for intervention. An interesting finding from our qualitative studies was that many patients were unclear on the duration of treatment with bisphosphonates with some patients having taken these medicines for many years[15].

Other collaborative opportunities

The prevention of MRONJ represents just a small proportion of the potential collaborative opportunities for pharmacists and dental care professionals. We know that 23% of the population do not attend for regular dental appointments and the ease of access to pharmacies represents a significant opportunity to engage this group of patients and work collaboratively with dentists as discussed by Wilson and Soni[1,21]. Pharmacists already play a key role in the prevention of the oral adverse effects of inhaled medication, such as oral candidiasis and in the provision of smoking cessation services.

A pilot oral health promotion intervention in County Durham showed that patients are receptive to oral health advice when provided by pharmacists; the pilot found that a brief intervention can result in positive intentions to change oral health behaviours[24].

There is increasing evidence of a two-way relationship between periodontitis (gum disease) and diabetes; periodontitis is a chronic inflammatory disease caused by bacterial infection of the supporting tissues surrounding the teeth, which is usually painless and often goes unnoticed and untreated until it reaches an advanced stage[32]. The Cochrane Collaboration published a review in 2015, highlighting that randomised controlled trials have demonstrated that periodontal therapy is associated with approximately a 3-4 mmol/mol (0.3-0.4%) reduction in HbA1c levels after 3 months[33]; this is a clinical impact equivalent to adding a second drug to a pharmacological regimen[34]. Pharmacists, in all settings, see patients with diabetes regularly, and this represents an opportunity to target patients who can benefit significantly from oral health education.

Cancer of the ‘mouth’ or oral cavity and ‘throat’ oropharyngeal cancer rank as the seventh most common cancers globally, with the highest incidence rates in males over the age of 60 years and patients living in deprived areas[35-36]. A recent study of oral cancer in Scotland found that in the majority of diagnosed cases no contact had been made with a dentist in the 2 years preceding the diagnosis; the study concluded that early detection strategies in alternative settings should be explored[37] representing another opportunity to involve pharmacists.

Conclusion

In summary, MRONJ is a rare complication that typically presents following a dental extraction in some patients prescribed anti-resorptive or anti-angiogenic drugs; it is difficult to treat and can result in significant negative effects on quality of life. Pharmacists should be aware of this risk and the recommended preventive advice, which could be incorporated into current roles across the pharmacy sectors. Further exploration of the pharmacist's' role and interprofessional collaboration with medical and dental colleagues may also provide significant benefits to other patient groups, in which oral heath advice or interventions could potentially improve patient outcomes.

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