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REVIEW ARTICLE

Dental management of patients at risk of osteochemonecrosis of the jaws: a critical review

S Fedele[1], N Kumar[2], R Davies[2], J Fiske[3], S Greening[4], S Porter[1]

[1]*Oral Medicine and Special Care Dentistry Unit, UCL Eastman Dental Institute, London, UK;* [2]*Special Care Dentistry, UCLH Eastman Dental Hospital, London, UK;* [3]*Department of Sedation and Special Care Dentistry, King's College London Dental Institute, London, UK;* [4]*Wales DCDP Kings, Gwent Healthcare NHS Trust, Newport, UK*

Osteonecrosis of the jaw bones is a complication of bisphosphonate (BP) drug usage characterised by transmucosal exposure of necrotic bone, often followed by infection and pain. Osteonecrosis is observed in cancer patients on high-potency intravenous BP more frequently than in osteoporotic individuals using low-potency oral BP. The management of osteonecrosis caused by BP is often unsatisfactory and control of risk factors is considered the most effective means of prevention. Surgical manipulation and dental infection of the jawbone are the major risk factors, hence it is suggested that careful management of oral health and relevant dental procedures may decrease the risk of osteonecrosis in individuals on BP. Recommendations for dentists and oral surgeons have been suggested by different groups of clinicians but they are often controversial and there is no clear evidence for their efficacy in reducing the likelihood of osteonecrosis development. This report critically reviews current dental recommendations for individuals using BP with the aim of helping the reader to transfer them into practice as part of pragmatic and non-detrimental clinical decisions making.
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Introduction

Osteonecrosis of the jawbones is a complication of bisphosphonates (BP) therapy characterised by transmucosal exposure of necrotic bone, often followed by infection and pain (Fleisch, 1998; Russell *et al*, 1999; Lipton *et al*, 2000; Berenson *et al*, 2001; Green, 2004; Marx *et al*, 2005; Leite *et al*, 2006; Liberman, 2006; Migliorati *et al*, 2006; Woo *et al*, 2006; Keating and Scott, 2007; Dannemann *et al*, 2007; Hewitt and Farah, 2007; Ruggiero and Drew, 2007; Merck & Co., 2008; Sachs, 2008). Although there remains no definitive consensus on diagnostic criteria, most authors define BP-associated osteonecrosis of the jaws (BOJ) as an area of exposed bone in the maxillofacial region that does not heal within 6–8 weeks after identification in a patient who is receiving or has been exposed to BP and has not had radiotherapy to the head and neck region. Additional signs can include pain, swelling, paraesthesia, suppuration, sinus tracts and non-specific radiological abnormalities (Khosla *et al*, 2007; Silverman and Landesberg, 2009).

Recent long-term prospective studies have highlighted the fact that BOJ could occur in up to 28% of cancer patients on high-potency intravenous BP (Durie *et al*, 2005; Bamias *et al*, 2005; McLeod *et al*, 2007; Hasmim *et al*, 2007; Allegra *et al*, 2007; Boonyapakorn *et al*, 2008), while the prevalence of osteonecrosis related to oral BP may account for less than 0.3% of individuals (McLeod *et al*, 2007). The majority of patients with BOJ have a history of bone surgery and postsurgical delayed wound healing (Marx *et al*, 2005; Durie *et al*, 2005; Bamias *et al*, 2005; Migliorati *et al*, 2006; Woo *et al*, 2006; Dannemann *et al*, 2007; Hewitt and Farah, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Boonyapakorn *et al*, 2008), although other risk factors have been reported (see Table 1) (Marx *et al*, 2005; Migliorati *et al*, 2006; Woo *et al*, 2006; Campisi *et al*, 2007; Dannemann *et al*, 2007; Hewitt and Farah, 2007; Marx *et al*, 2007; Ruggiero and Drew, 2007). As management of BOJ is often unsatisfactory, there is general agreement that major efforts should be spent on prevention and control of risk factors (Marx *et al*, 2005; Durie *et al*, 2005; Bamias *et al*, 2005; Migliorati *et al*, 2006; Woo *et al*, 2006; Dannemann *et al*, 2007; Hewitt and Farah, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Boonyapakorn *et al*, 2008). Of these, dento-alveolar surgery and infection are the most easily controlled factor. Nevertheless, no clear guidance for clinicians

Correspondence: S Fedele, Oral Medicine and Special Care Dentistry Unit, UCL Eastman Dental Institute, 256 Gray's Inn Road, WC1X 8LD, London, UK. Tel: 0044 (0)20 7915 1004, Fax: 0044 (0)20 7915 1005, E-mail: s.fedele@eastman.ucl.ac.uk
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Table 1 Reported risk factors for bisphosphonate (BP) drug usage-associated osteonecrosis of the jaws (BOJ)

Factor	*Comment*
Potency of BP	More potent BP are associated with a greater risk
Route of administration of BP	Intravenous BP are associated with a greater risk than oral BP
Length of BP therapy	Longer treatment regimens are associated with a greater risk
Total dosage of BP therapy	Higher dosage is associated with a greater risk
Concomitant/previous therapies	Chronic corticosteroid therapy Chemotherapy Oestrogenic therapy
Underlying disease	Individuals with cancer are at higher risk than those with osteoporosis Among different cancer types, the risk is higher for multiple myeloma, followed by breast, prostate and other solid cancers
Dental surgery (any surgical trauma to the jawbones)	In 33–86% of reported cases, oral surgery preceded the diagnosis of bone necrosis and the areas affected were coincident with the surgical site
Dental infections	This includes dental infection that affects the alveolar bone such as periodontitis, periodontal abscess, apical periodontitis, etc.

exists. Although dental recommendations have been published, they merely reflect expert opinion, are not evidence-based and are often controversial. The aim of this article is to review critically available recommendations regarding the dental management of patients on or who are scheduled for BP therapy.

Risk of BP-related osteonecrosis: two distinctive groups of patients

Current data indicate that intravenous high-potency BP are much more frequently associated with BOJ than is oral low-potency BP (Marx *et al*, 2005; Durie *et al*, 2005; Bamias *et al*, 2005; Migliorati *et al*, 2006; Woo *et al*, 2006; Dannemann *et al*, 2007; Hewitt and Farah, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Boonyapakorn *et al*, 2008). Such a significant difference in terms of prevalence and risk of BOJ has led to the classification of two distinctive groups of patients on the basis of the route of administration and relative potency of the medication. The first group is those people on oral or low-potency BP and the second is those people in receipt of intravenous or high-potency BP. Different dental considerations apply to these two groups of patients (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; Marx *et al*, 2007; Pickett, 2006; Weitzman *et al*, 2007) and to respective subgroups comprising individuals due to start and subjects who are already on BP therapy.

Patients due to commence oral BP therapy

Although some few authors recommend no additional dental examination/procedure other than regular reviews and treatment as required (Khosla *et al*, 2007), the general advice is that on-going dental infection and asymptomatic or quiescent dental disease should be promptly managed and any surgical/invasive dental treatment should be undertaken before the start of BP therapy (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). This recommendation applies also to elective bone surgery (e.g. implants), and suggests a period of at least 4–8 weeks between completion of bone manipulation (e.g. surgery) and commencement of BP therapy to allow sufficient time for complete bone healing (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). The majority of published recommendations highlight that it is essential that patients are fully informed of the potential oral risks of BP and that they are placed on a rigorous preventive programme including effective plaque control, dietary advice, and antibacterial and/or fluoride mouthwash. In addition, dentures should be carefully and regularly reviewed to avoid any mucosal ulceration that might be caused by sharp denture borders or metal clasps, especially at sites prone to trauma e.g. mandibular tori and mylohyoid ridge (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). Critical evaluation of these recommendations is difficult as currently there is no evidence based on rigorous clinical trials that these preventive measures significantly reduce the risk of BOJ development. However, it is generally accepted that sensible practical recommendations may be considered clinically relevant when high-quality research evidence is unavailable (Altman and Bland, 1995; Craig and Smyth, 2002; Edwards *et al*, 2008). Accordingly Table 2 provides critical comments on the above reported recommendations detailing the level of evidence and safety/risk of different dental procedures. Overall, it can be concluded that all dental procedures are reasonably safe

Table 2 Oral BP therapy and critical review of dental recommendations

Dental treatment to provide	*Individuals due to start oral BP*		*Individuals receiving oral BP*	
	Recommendation/comment	*Level of evidence*	*Recommendation/comment*	*Level of evidence*
Restorative	Safe Consider surgical alternatives for teeth with poor-prognosis It may help preventing BOJ *via* prevention of bone infection	Low But recommendation is clinically sensible	Safe Consider non-restorative alternatives for teeth with poor prognosis. It may help reducing the risk of BOJ via prevention of bone infection	Low But recommendation is clinically sensible
Endodontic (non-surgical)	Safe Consider surgical alternatives for teeth with poor prognosis It may help preventing BOJ *via* prevention of bone infection	Low But recommendation is clinically sensible	Likely safe Insufficient evidence to suggest that root canal treatment may trigger BOJ It may help reducing the risk of BOJ *via* prevention of bone infection	Low But recommendation is clinically sensible
Surgery (including endodontic surgery and implants)	Safe Time for completing physiological bone healing process before the start of BP therapy (e.g. 4–8 weeks) should be left if possible. It may help preventing BOJ *via* prevention of bone infection	Low But recommendation is clinically sensible	Relatively safe It may help reducing the risk of BOJ *via* prevention of bone infection but may trigger BOJ itself The small risk of BOJ does not contraindicate surgical procedure	Low But recommendation is clinically sensible No evidence to support any of the suggested risk-reduction strategies (see Table 3)
Periodontology	Safe In case of periodontal surgery, enough time for completing physiological bone healing process before the start of BP therapy (e.g. 4–8 weeks) should be left if possible. It may help preventing BOJ *via* prevention of bone infection	Low But recommendation is clinically sensible	Relatively safe It may help reducing the risk of BOJ *via* prevention of bone infection but periodontal bone surgery may trigger BOJ itself The small risk of BOJ does not contraindicate periodontal surgery	Low But recommendation is clinically sensible. No evidence to support any of the suggested risk-reduction strategies (see Table 3)
Prosthodontic	Safe Mucosal trauma should be avoided where possible	Low But recommendation is clinically sensible	Likely safe Mucosal trauma should be avoided where possible	Low But recommendation is clinically sensible
Orthodontics	Safe Enough time for completing physiologic bone healing process before the start of BP therapy (e.g. 4–8 weeks) should be left if possible	Low But recommendation is clinically sensible	Likely safe Some studies reported slow/impaired tooth movements No evidence to support the theory that increased turnover can cause further accumulation of BP into the alveolar bones and trigger osteonecrosis	Low But recommendation is clinically sensible

BOJ, bisphosphonate (BP) drug usage-associated osteonecrosis of the jaws.

in individuals due to start oral BP and available recommendations stating so can be considered clinically sensible. In some instances, they might also contribute to prevent BOJ *via* avoiding that dental infections occur when the patient has already started oral BP.

Patients receiving oral BP

For individuals already on oral BP therapy, current recommendations refer to two different scenarios, namely whether they have ongoing dental disease or not.

Patients receiving oral BP without dental diseases. For those individuals without dental disease, it is advised that the focus should be on prevention to avoid future dental infections and the need for invasive dental procedures (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*,

2008). Appropriate measures may include caries prevention, regular oral hygiene instruction and denture review. These recommendations can be viewed as sensible clinical advice, even though there is no supportive evidence from controlled clinical trials of their effectiveness.

Patients receiving oral BP with dental diseases. Dental infections have the potential to trigger the development of BOJ, hence the majority of recommendations suggest to provide appropriate oral care before this can occur (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). However, the dilemma is that some of these dental interventions (e.g. extractions and periodontal surgery) are invasive and may in themselves trigger the osteonecrotic process.

Non-invasive dental treatments do seem to be safe as they do not involve bone manipulation and only few cases of BOJ have been reported after non-surgical endodontic procedures (Sarathy *et al*, 2005; Fugazzotto and Lightfoot, 2006). However, when critically analysed, these reports are controversial as a spontaneous osteonecrotic process may be present before treatment and may possibly cause painful symptoms that, together with non-specific radiological findings, could be misdiagnosed as apical periodontitis.

Orthodontic tooth movements have been reported to be potentially impaired in patients on oral BP but they have not been related to development of BOJ (Keim, 2006; Rinchuse *et al*, 2007; Zahrowski, 2007).

Invasive procedures are theoretically more of a risk than non-invasive ones as they have been reported to trigger up to 50–70% of cases of oral BP-associated osteonecrosis (Marx *et al*, 2005, 2007). However, the majority of recommendations suggest that there is no invasive dental procedure that is absolutely contraindicated (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). Available recommendations state that urgent invasive procedures should be performed promptly as they are aimed at treating/preventing alveolar bone infection, which is itself a risk factor of BOJ (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). It has been suggested that elective surgical procedures, such as endo-osseus implant placement, are not contraindicated either (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). Most authors have suggested that, if surgery is not urgent or aimed at treating bone infection, a clear explanation of the benefit, alternatives and risks of the procedure should be provided to the patient, so they can take an informed decision (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; Edwards *et al*, 2008). Adequate information should include that associated risk factors (e.g. corticosteroid therapy and diabetes) have the potential to increase the risk of BOJ. Duration of oral BP therapy has been suggested to be important in evaluating the risk of BOJ, with 3 years being the proposed threshold to differentiate individuals at low and high risk (Marx *et al*, 2007).

Critical evaluation of these recommendations is difficult because of lack of prospective studies. Table 2 details the relevant level of evidence and the safety/risk of available recommendations. As guidance regarding safety of elective surgery (e.g. endo-osseus implant placement) has caused significant concern among clinicians, further critical analysis is worthwhile. Four recent unrelated studies have shown no significant association between dental implants and osteonecrosis in patients on oral BP. However their results should be read with caution as the majority of studied patients, where reported, received surgical procedures in the first months or years of therapy (Jeffcoat, 2006; Fugazzotto *et al* 2007; Bell and Bell, 2008; Grant *et al* 2008) when the cumulative dosage of oral BP and the relative risk of BOJ are considered to be low.

Moreover, the recommendations of considering surgical interventions safe if provided during the first 3 years of oral BP therapy is questionable as BOJ has been reported to occur in the first 2 years of treatment with oral BP (Pazianas *et al*, 2007; Yarom *et al*, 2007) and a recent review of literature reported no clear time dependency (Pazianas *et al*, 2007).

Invasive dental procedures in patients on oral BP and risk-reduction strategies. Some researchers have attempted to introduce strategies to reduce the risk of BOJ associated with oral surgery (and other invasive procedures) for individuals on oral BP. These are summarised in Table 3. It has been suggested that a threshold of length of exposure to oral BP, which identifies a higher risk of osteonecrosis, exists and that this can help to categorise individuals into appropriate risk groups. Marx *et al* (2007) suggested that patients with a history of fewer than 3 years of exposure to oral BP are at extremely low risk of BOJ and can safely receive surgical procedures (Marx *et al*, 2007). They also suggested that in individuals with a history of >3 years of oral BP use (or <3 years with concomitant corticosteroid or chemotherapy use), the evaluation of degree of bone turnover

Table 3 Strategies to identify/reduce the risk of osteonecrosis in patients on oral bisphosphonate (BP) drug usage scheduled for oral surgery

Strategy	*Description*	*Comment*
Evaluation of CTX levels and potential discontinuation of BP	CTX > 150 pg ml^{-1}: low risk, surgery safe CTX < 150 pg ml^{-1}: high risk. Defer surgery, plan drug holiday and wait for CTX to rise	Not supported by any evidence
Discontinuation of oral BP	Discontinuation of oral BP for 1–3 months before surgery ±3 months after	Not supported by any evidence
Sextant-by-sextant approach	Applies to cases where surgery is planned in multiple quadrants. Treat one quadrant first, and wait for 2 months. In case of normal healing and no osteonecrosis, multiple-quadrant treatments can be provided safely at once	Not supported by any evidence but non-harmful and clinically sensible
Conservative surgical techniques	e.g. Primary tissue closure	Not supported by any evidence but non-harmful and clinically sensible
Topical antimicrobials	Chlorhexidine before, during and up to 2 months after surgery	Not supported by any evidence but non-harmful and clinically sensible
Systemic antibiotics	In case of extensive surgical manipulation of the bone, use of prophylactic systemic antibiotics may be considered by the clinician, also depending on the presence of concomitant factors (abscess, acute infection, other therapies, etc.). A regimen of amoxicillin ± metronidazole or clindamycin for 2 days before and 14 days after surgery has been suggested	Not supported by any evidence. Potentially harmful because of the risk of antibiotic resistance and potential allergic reactions
Alternative extraction techniques	Elastic-induced gradual orthodontic tooth exfoliation. An elastic (orthodontic) band is placed around the cervical part of the tooth to induce extrusive movement in 1–3 months (mean 6 weeks). Separation of the roots, endodontic therapy and regular grounding of the crown is required	Potentially effective but data are from one case s eries without controls. Time consuming and inadequate in case of acute infection

CTX, C-terminal telopeptide.

inhibition [*via* serum C-terminal telopeptide (CTX) levels] could help in identifying subgroups of patients at different degrees of risk (Marx *et al*, 2007). They recommended deferring the surgery in patients with CTX level lower than 150 pg ml^{-1} (this indicates that bone turnover is highly impaired and the risk of ostenecrosis is greater) and planning, together with the prescribing physician, discontinuation of oral BP for 6–9 months (described as a 'drug holiday') to allow the CTX value to rise and surgery to be safely performed (Marx *et al*, 2007). Other researchers have suggested that the discontinuation of oral BP for 1–3 months could help in any case (regardless of the length of exposure and evaluation of bone turnover markers) as the anti-angiogenic effect of BP would be reduced and, consequently, wound healing after surgery would be improved, thus potentially reducing the risk of osteonecrosis (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Campisi *et al*, 2007).

The American Dental Association expert panel suggested that dentists should be 'sensibly cautious' in performing surgical procedures in individuals on oral BP (American Dental Association Council on Scientific Affairs, 2006; Edwards *et al*, 2008). In cases where planned surgery involves multiple quadrants, they recommend commencing with one quadrant, waiting for 2 months, and if no complication occurs, considering it is safe to treat the remaining quadrants at one time (American Dental Association Council on Scientific Affairs, 2006; Edwards *et al*, 2008). Other strategies such as conservative surgical technique, use of chlorhexidine, prophylaxis with systemic antibiotics and elastic-induced gradual orthodontic tooth exfoliation have also been suggested (see Table 3) (Migliorati *et al*, 2005; American Dental Association Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Marx *et al*, 2007; American Society for Bone and Mineral Research Task Force on Osteonecrosis of the Jaw *et al*, 2008; Edwards *et al*, 2008; Regev *et al*, 2008).

When critically reviewed (see Tables 2 and 3), all the above-reported risk-reduction strategies are found to derive from expert opinion or small non-controlled case series and have in common the absence of significant supportive evidence. Reviews performed by other authors on single aspects of these recommendations confirm the current lack of evidence (Baim and Miller, 2009; Don-Wauchope and Cole, 2009).

Patients due to commence intravenous BP therapy

Most authors recommend, whenever possible, undertaking all necessary and all elective dental treatment, including surgery, prior to starting intravenous BP therapy (see Table 4). The rationale for this is to prevent bone infection and the need for invasive treatments at a stage when the patient is on intravenous BP (Migliorati

Table 4 Intravenous bisphosphonate (BP) drug usage therapy and critical review of dental recommendations

Dental treatment to provide	*Individuals due to start i.v. BP*		*Individuals receiving i.v. BP*	
	Recommendation/comment	*Level of evidence*	*Recommendation/comment*	*Level of evidence*
Restorative	Safe Consider surgical alternatives for teeth with poor prognosis It may help preventing BOJ *via* prevention of bone infection	Low, but recommendation is clinically sensible	Safe Consider non-restorative alternatives for teeth with poor prognosis It may help reducing the risk of BOJ via prevention of bone infection	Low But recommendation is clinically sensible
Endodontic (non-surgical)	Safe Consider surgical alternatives for teeth with poor prognosis It may help preventing BOJ *via* prevention of bone infection	Low, but recommendation is clinically sensible	Likely safe Insufficient evidence to suggest that root canal treatment may trigger BOJ It may help reducing the risk of BOJ *via* prevention of bone infection	Low But recommendation is clinically sensible
Surgery (including endodontic surgery and implants)	Safe Time for completing physiological bone healing process before the start of BP therapy (e.g. 4–8 weeks) should be left if possible It may help preventing BOJ *via* prevention of bone infection	Low, but recommendation is clinically sensible	Contraindicated. When surgery cannot be avoided, there are risk-reduction strategies and alternative techniques to consider (see Table 5)	Significant evidence that oral surgery is contraindicated
Periodontology	Safe In case of periodontal surgery, enough time for completing physiological bone healing process before the start of BP therapy (e.g. 4–8 weeks) should be left if possible It may help preventing BOJ *via* prevention of bone infection	Low, but recommendation is clinically sensible	Non-surgical therapy is likely to be safe. It may help reducing the risk of BOJ *via* prevention of bone infection Surgical therapy is contraindicated	Significant evidence that periodontal surgery is contraindicated
Prosthodontic	Safe Mucosal trauma should be avoided where possible	Low, but recommendation is clinically sensible	Likely safe Mucosal trauma should be avoided where possible	Low But recommendation is clinically sensible
Orthodontics	Safe Enough time for completing physiological bone healing process before the start of BP therapy (e.g. 4–8 weeks) should be left if possible	Low, but recommendation is clinically sensible	Likely safe Some studies reported slow/impaired tooth movements No evidence to support the theory that increased turnover can cause further accumulation of BP into the alveolar bones and trigger osteonecrosis	Low But recommendation is clinically sensible

et al, 2005; Hellstein and Marek, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Weitzman *et al*, 2007). It has been suggested that all necessary dento-alveolar surgery and oral surgical procedures should be carried out at least 4–6 weeks prior to the first BP infusion to ensure adequate bone healing. The objective of management is to achieve optimal oral health that can be maintained during BP therapy, thus reducing the likelihood of osteonecrosis development. Moreover, it is usually recommended that implant surgery is not contraindicated at this stage, provided there is sufficient time for osseo-integration to occur.

Critical evaluation of these recommendations is difficult as no substantial clinical trial has demonstrated that provision of surgery/restorative dentistry before starting intravenous BP therapy is effective in reducing occurrence of BOJ compared with controls (individuals on intravenous BP who are not provided the same intervention). However, two very recent independent studies found that the provision of preventive dental screening and treatment reduces significantly the risk and incidence of BOJ with respect to controls (6.7% *vs* 26.3% and 3.2–1.3%) (Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008). Even though better planned and larger studies are required to confirm these data, the general advice of providing preventive dental treatment is easy to follow in daily practice and unlikely to expose the patient to any harm.

The applicability of them, however, is questionable. BP therapy cannot be delayed in patients with malignancy because of severe bone pain and risk of fracture or life-threatening hypercalcemia, and regrettably, patients are not always warned about potential dental complications of BP treatment (Barker *et al*, 2007). A recent survey among UK healthcare professionals who manage patients with multiple myeloma found that less than half of the 263 responders asked patients to see their dentists before starting intravenous BP treatment (Barker *et al*, 2007).

Patients receiving intravenous BP

To discuss available recommendations, it is useful to classify individuals on intravenous BP into two groups: those with and those without ongoing dental disease.

Individuals receiving intravenous BP without dental disease. It has been recommended that in this group, major efforts should be made to maintain a healthy oral status (Durie *et al*, 2005; Migliorati *et al*, 2005; Hellstein and Marek, 2006; Pickett, 2006; Weitzman *et al*, 2007; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Barker *et al*, 2007; Campisi *et al*, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008). Robust preventive regimes and regular oral health check-ups should be provided to minimise the likelihood of future oral infections, need for surgical/invasive dental procedures and occurrence of denture-induced mucosal trauma. These recommendations are not supported by clinical trials but are clinically sensible, realistic, do not represent a burden for the patients and can be considered clinically relevant until stronger evidence is available (Craig and Smyth, 2002).

Individuals receiving intravenous BP with dental disease. Patients with ongoing dental disease are considered at high risk of developing BOJ resulting from dental infection and/or invasive procedures. There is general agreement that in the case of caries and mild-to-moderate periodontitis, restorative and non-surgical periodontal therapies can be safely provided as they do not generally involve any bone manipulation (Bamias *et al*, 2005; Durie *et al*, 2005; Marx *et al*, 2005; Migliorati *et al*, 2005; Hellstein and Marek, 2006; Migliorati *et al*, 2006; Pickett, 2006; Woo *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Barker *et al*, 2007; Campisi *et al*, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Weitzman *et al*, 2007; Boonyapakorn *et al*, 2008; Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008). These procedures are not considered to be triggers of BOJ. It is advocated that non-restorable teeth are treated by decoronation and endodontic treatment of the remaining roots, thus avoiding extraction (Bamias *et al*, 2005; Durie *et al*, 2005; Marx *et al*, 2005; Migliorati *et al*, 2005; Hellstein and Marek, 2006; Migliorati *et al*, 2006; Pickett, 2006; Woo *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Barker *et al*, 2007; Campisi *et al*, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Weitzman *et al*, 2007; Boonyapakorn *et al*, 2008; Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008). However, endodontics remains an area of controversy. While there are few reported cases of BOJ associated with endodontic therapy (Sarathy *et al*, 2005; Fugazzotto and Lightfoot, 2006), it cannot be excluded that a spontaneous osteonecrotic process was already present before treatment (causing painful symptoms, and radiological findings that could have been misdiagnosed as apical periodontitis).

Caution has been recommended regarding orthodontic therapy as tooth movements have been reported to be potentially impaired in animals and humans using BP because of the inhibition of osteoclasts. However, there remain no reports of BOJ in these patients (Zahrowski, 2007; Keim, 2006; Rinchuse *et al*, 2007).

Little information is available regarding the safety and feasibility of prosthetic dental procedures in patients on intravenous BP. Most authors have recommended minimising denture-associated mucosal trauma and avoiding extensive fixed prosthodontic work (Bamias *et al*, 2005; Durie *et al*, 2005; Marx *et al*, 2005; Migliorati *et al*, 2005; Hellstein and Marek, 2006; Migliorati *et al*, 2006; Pickett, 2006; Woo *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Barker *et al*, 2007; Campisi *et al*, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Weitzman *et al*, 2007; Boonyapakorn *et al*, 2008; Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008). The rationale behind the latter recommendation was not explained: however, it could be relevant to the long-term prognosis of crowned teeth (Valderhaug *et al*, 1997) that may increase the risk of dental/bone infection. Where removable prostheses are considered, the recommendation of reducing the risk of mucosal trauma especially upon lingual/palatal tori, bony exostoses and mylohyoid ridge (Migliorati *et al*, 2005) using soft lining materials, and preferring tooth-borne rather than mucosa-supported partial dentures (Bamias *et al*, 2005; Durie *et al*, 2005; Marx *et al*, 2005; Migliorati *et al*, 2005; Hellstein and Marek, 2006; Migliorati *et al*, 2006; Pickett, 2006; Woo *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Barker *et al*, 2007; Campisi *et al*, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Weitzman *et al*, 2007; Boonyapakorn *et al*, 2008; Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008) seems to be clinically sensible and realistic.

The majority of recommendations regarding invasive dental procedures state that unnecessary surgery, such as dental implantology, is contraindicated in this group of patients (Bamias *et al*, 2005; Durie *et al*, 2005; Marx *et al*, 2005; Migliorati *et al*, 2005; Hellstein and Marek, 2006; Migliorati *et al*, 2006; Pickett, 2006; Woo *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Barker *et al*, 2007; Campisi *et al*, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007; Ruggiero and Drew, 2007; Weitzman *et al*, 2007; Boonyapakorn *et al*, 2008; Dimopoulos *et al*, 2008; Ripamonti *et al*, 2008). Table 4 shows the safety and level of evidence of available recommendations.

Invasive dental procedures in patients on intravenous BP and risk-reduction strategies. In instances where surgical treatment cannot be avoided, risk reduction measures have been proposed (see Table 5). It has been suggested that a threshold of length of exposure to intravenous BP, which identifies a higher risk of osteonecrosis, exists and that this can help to categorise individuals into appropriate risk groups. Although 3 months of BP therapy is suggested as a safe period with no significant risk of triggering BOJ (Migliorati *et al*, 2005; Woo *et al*, 2006), this is not supported by any evidence. Even if the risk is lower, it still exists (Marx *et al*, 2005; Weitzman *et al*, 2007; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Landis *et al*, 2007; McLeod *et al*, 2007). The evaluation of degree of bone turnover inhibition, as indicated by serum CTX levels, was found to be not relevant in estimating the risk of BOJ in patients on intravenous BP by two separate studies (Bagan *et al*, 2008; Marx *et al*, 2007). Other researchers have recommended the discontinuation of oral BP for 1–3 months to allow osteoclast recovery (Van den Wyngaert *et al*, 2007) and reduce the anti-angiogenic effect of BP (Campisi *et al*, 2007). They suggested that this would improve wound healing after surgery, thus potentially reducing the risk of osteonecrosis (Campisi *et al*, 2007; Van den Wyngaert *et al*, 2007). This is not supported by clinical data and is based on the unproven theory that BOJ pathogenesis is associated with the inability of bone and epithelial cells to complete a normal wound healing process after trauma (Migliorati *et al*, 2005; Hellstein and Marek, 2006; Leite *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Ruggiero and Drew, 2007). Other strategies such as conservative surgical technique (e.g. primary tissue closure), use of chlorhexidine mouthwash, prophylaxis with systemic antibiotics and use of local anaesthetic agents without vasoconstrictors have also been suggested to reduce the risk of BOJ (Table 5) (Valderhaug *et al*, 1997; Sarathy *et al*, 2005; Fugazzotto and Lightfoot, 2006; Marx *et al*, 2007; Mavrokokki *et al*, 2007; Rinchuse *et al*, 2007; Bagan *et al*, 2008).

Some of these recommendations, although not based on significant evidence, are clinically sensible and unlikely to cause any significant harm or adverse side effect. Others, however, suggest long-term use of medications that might expose the patients to side effects and long-term complications (e.g. bacterial resistance to antibiotic or allergic reactions) and should be considered with caution.

Antibiotic prophylaxis before and after surgery has been recommended by some authors in all cases where alveolar surgery is involved and by others only when additional risk factors for severe bone infection are

Table 5 Strategies to identify/reduce the risk of osteonecrosis in patients on intravenous BP scheduled for oral surgery

Strategy	*Description*	*Comment*
Evaluation of CTX levels	Evaluation of degree of bone turnover inhibition (via CTX levels) to identify subgroups of patients at different degrees of risk	Studies showed negative results
Discontinuation of i.v. BP	Discontinuation of i.v. BP for 1–3 months	Not supported by any evidence
Interventions within 3 months of exposure to i.v. BP	Surgical procedures can be safely performed during the first 3 months of therapy with i.v. BP	Not supported by any evidence. Risk during the first months is low but still present
Conservative surgical techniques	e.g. Primary tissue closure	Not supported by any evidence but non-harmful and clinically sensible
Topical antimicrobials	Chlorhexidine before, during and after surgery	Not supported by any evidence but non-harmful and clinically sensible. It may be stopped when the wound healing process is completed
Systemic antibiotics	(i) Antibiotic prophylaxis to be always prescribed (ii) Antibiotic prophylaxis to be prescribed only in case of extensive surgical manipulation of the bone, and presence of concomitant factors (abscess, acute infection, other therapies, etc.). A regimen of amoxicillin ± metronidazole or clindamycin for 2 days before and 14 days after surgery has been suggested	Not supported by any evidence. Potentially harmful because of the risk of antibiotic resistance and potential allergic reactions
Alternative extraction techniques	Elastic-induced gradual orthodontic tooth exfoliation. An elastic (orthodontic) band is placed around the cervical part of the tooth to induce extrusive movement in 1–3 months (mean 6 weeks). Separation of the roots, endodontic therapy and regular grounding of the crown is required	Potentially effective but data are from one case series without controls. Time consuming and inadequate in case of acute infection
Local anaesthetic without vasoconstrictor	Vasoconstrictor may alter the process of wound healing after surgery and may increase the risk of osteonecrosis	Not supported by any evidence or any case report

present and/or when treatment involves significant manipulation of the alveolar bone (Marx *et al*, 2005; Migliorati *et al*, 2005; Campisi *et al*, 2007; McLeod *et al*, 2007; Montefusco *et al*, 2008; Van den Wyngaert *et al*, 2007). Again, none of these recommendations has been validated in case–control prospective studies and it remains unknown if antibiotic prophylaxis effectively reduces the risk of BOJ. In consideration of the lack of evidence, potential adverse effects, cost and other possible complications of antibiotic prophylaxis (e.g. bacterial resistance), it would be sensible to conclude that the use of antibiotics can only be justified when there is evidence of on-going infection or clinically significant risk of infection caused by local or systemic factors (e.g. chemotherapy). An alternative extraction technique consisting of elastic-induced gradual orthodontic tooth exfoliation has been proposed (Regev *et al*, 2008) but is not feasible in individuals with acute dental infection.

Conclusions

Available recommendations on dental management of individuals using or scheduled for BP therapy are hindered by controversy and lack of evidence. A critical analysis of reported guidance can help clinicians to transfer it into practice as part of pragmatic and non-detrimental clinical decisions making.

The recommendation of providing, when possible, restorative and surgical dental treatment before the commencement of both oral and intravenous BP therapy, together with instigation of a long-term regimen of preventive dentistry and regular check-ups, is not evidence-based and supported by only two studies. However, it is reasonable, clinically sensible and non-harmful for the patients.

For patients already on BP, restorative and non-surgical treatments appear to be safe as they have not yet been reported to trigger BOJ. Moreover, they have the potential to reduce the risk of future bone infection and need for surgery, hence theoretically reducing the risk of BOJ development.

With regard to invasive surgical procedures, different considerations apply. There seems to be no contraindicated surgical procedures in individuals on oral BP, although caution is recommended in assessing individuals with concomitant risk factors. Regarding individuals on intravenous BP, there is convincing evidence to suggest that elective surgical procedures are contraindicated in all cases; when alveolar surgery cannot be avoided, the risk of BOJ development is significant. For both oral and intravenous BP, none of the suggested risk-reduction strategies has been demonstrated effective and therefore only sensible and practical precautions to reduce bone trauma and to minimise the risk of infection can be recommended. Most importantly, there is need to ensure that patients taking BP are well informed of the oral risks and triggers for BOJ, so they can make informed decisions about undergoing any dental procedures. The need for research to support or refute current thinking is urgent.

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Conflict of interest statement

All authors of the present study disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organisations within that could inappropriately influence (bias) their work.

Author contributions

Stefano Fedele had the original idea, performed literature review, analyzed the data, wrote the manuscript draft and developed the tables. Navdeep Kumar and Roger Davies contribute to data interpretation and manuscript writing. Janet Fiske reviewed and edited the data and advised on manuscript structure. Sue Greening and Stephen Porter revised and finalized the manuscript.

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