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

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

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Abstract

Osteonecrosis of the jaw bones is a complication of bisphosphonate drug usage (BP), characterized by trans-mucosal 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 due to 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 lessen 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.

Introduction

Osteonecrosis of the jawbones is a complication of bisphosphonates (BP) therapy characterized by trans-mucosal 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, 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 Landsberg, 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 A et al, 2007; Boonyapakorn et al, 2008), whilst 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 post-surgical 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

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3 Farah, 2007; McLeod et al, 2007 ; Ruggiero and Drew, 2007; Boonyapakorn et
4 al, 2008), although other risk factors have been reported (see table 1) (Marx et al,
5
6 al, 2008), although other risk factors have been reported (see table 1) (Marx et al,
7
8 2005; Migliorati et al, 2006; Woo et al, 2006; Campisi et al, 2007; Dannemann et
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10 al, 2007, Hewitt and Farah, 2007; Marx et al, 2007; Ruggiero and Drew, 2007).
11
12 As management of BOJ is often unsatisfactory, there is general agreement that
13
14 major efforts should be spent on prevention and control of risk factors (Marx et al,
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16 2005; Durie et al, 2005; Bamias et al, 2005 ; Migliorati et al, 2006; Woo et al,
17
18 2006; Dannemann et al, 2007, Hewitt and Farah, 2007; McLeod et al, 2007;
19
20 Ruggiero and Drew, 2007; Boonyapakorn et al, 2008). Of these, dento-alveolar
21
22 surgery and infection is the most easily controlled factor. Nevertheless, no clear
23
24 guidance for clinicians exists. Although dental recommendations have been
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26 published, they merely reflect expert opinion, are not evidence-based, and are
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28 often controversial. The aim of this paper is to critically review available
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30 recommendations regarding the dental management of patients on or who are
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32 scheduled for BP therapy.
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41 **Risk of BP-related osteonecrosis: two distinctive groups of patients**

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43 Current data indicate that intravenous high-potency BP are much more frequently
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45 associated with BOJ than is oral low-potency BP (Marx et al, 2005; Durie et al,
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47 2005; Bamias et al, 2005 ; Migliorati et al, 2006; Woo et al, 2006; Dannemann et
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49 al, 2007, Hewitt and Farah, 2007; McLeod et al, 2007 ; Ruggiero and Drew,
50
51 2007; Boonyapakorn et al, 2008). Such a significant difference in terms of
52
53 prevalence and risk of BOJ has led to the classification of two distinctive groups
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3 of patients on the basis of the route of administration and relative potency of the
4 medication. The first group is those people on oral or low potency BP and the
5
6 second is those people in receipt of intravenous or high potency BP. Different
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8 dental considerations apply to these two groups of patients (Migliorati et al, 2005;
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10 American Dental Association Council on Scientific Affairs, 2006; Hellstein and
11
12 Marek, 2006; Advisory Task Force on Bisphosphonate-Related Osteonecrosis
13
14 of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007;
15
16 Khosla et al, 2007; Landis et al, 2007; Marx et al, 2007; Pickett, 2006; Weitzman
17
18 et al, 2007) and to respective sub-groups comprising individuals due to start and
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20 subjects who are already on BP therapy.
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30 ***(1) Patients due to commence oral BP therapy***

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32 Although some few authors recommend no additional dental
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34 examination/procedure other than regular reviews and treatment as required
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36 (Khosla et al, 2007), the general advice is that on-going dental infection and
37
38 asymptomatic or quiescent dental disease should be promptly managed and any
39
40 surgical/invasive dental treatment should be undertaken before the start of BP
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42 therapy (Migliorati et al, 2005; American Dental Association Council on Scientific
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44 Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on
45
46 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
47
48 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et al, 2007;
49
50 Edwards et al, 2008). This recommendation applies also to elective bone surgery
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52 (e.g. implants), and suggests a period of at least 4 to 8 weeks between
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3 completion of bone manipulation (e.g. surgery) and commencement of BP
4 therapy to allow sufficient time for complete bone healing (Migliorati et al, 2005;
5 American Dental Association Council on Scientific Affairs, 2006; Hellstein and
6 Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related
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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 Osteonecrosis 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 in order to avoid any mucosal ulceration that might be caused by sharp denture borders or metal clasps, especially in sites prone to trauma e.g. mandibular tori, 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 Osteonecrosis 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 (Craig and Smyth, 2002; Edwards et al, 2008). Accordingly table 2 provides critical comments on the

1
2
3 above reported recommendations detailing the level of evidence and safety/risk
4 of different dental procedures. Overall, it can be concluded that all dental
5
6 of different dental procedures. Overall, it can be concluded that all dental
7
8 procedures are reasonably safe in individuals due to start oral BP and available
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10 recommendations stating so can be considered clinically sensible. In some
11
12 instances they might also contribute to prevent BOJ *via* preventing that dental
13
14 infections occur when the patient has already started oral BP.
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20 **(2) Patients receiving oral BP**

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22 For individuals already on oral BP therapy, current recommendations refer to two
23
24 different scenarios, namely whether they have ongoing dental disease or not.
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27 *(2a) Patients receiving oral BP without dental diseases*

28
29 For those individuals without dental disease, it is advised that the focus should be
30
31 on prevention in order to avoid future dental infections and the need for invasive
32
33 dental procedures (Migliorati et al, 2005; American Dental Association Council on
34
35 Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task
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37 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
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39 Association of Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx e
40
41 t al, 2007; Edwards et al, 2008). Appropriate measures may include caries
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43 prevention, regular oral hygiene instruction, and denture review. These
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45 recommendations can be viewed as sensible clinical advice, even though there is
46
47 no supportive evidence from controlled clinical trials of their effectiveness.
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52 *(2b) Patients receiving oral BP with dental diseases*

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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 Osteonecrosis 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, 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 analyzed, 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; Marx et al, 2007). However, the majority of recommendations suggest that there is no invasive dental procedure that is

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3 absolutely contraindicated (Migliorati et al, 2005; American Dental Association
4 Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006;
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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 Osteonecrosis 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 Osteonecrosis 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-osseous 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 Osteonecrosis 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 Osteonecrosis of the Jaws, American

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3 Association of Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et
4 al, 2007; Edwards et al, 2008). Adequate information should include that
5
6 associated risk factors (e.g. corticosteroid therapy, diabetes) have the potential to
7
8 increase the risk of BOJ. Duration of oral BP therapy has been suggested to be
9
10 important in evaluating the risk of BOJ, with 3 years being the proposed threshold
11
12 to differentiate individuals at low and high risk (Marx et al, 2007).
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17 Critical evaluation of these recommendations is difficult due to lack of prospective
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19 studies. Table 2 details the relevant level of evidence and the safety/risk of
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21 available recommendations. As guidance regarding safety of elective surgery
22
23 (e.g. endo-osseus implant placement) has caused significant concern among
24
25 clinicians, further critical analysis is worthwhile. Two recent retrospective studies
26
27 have shown no significant association between dental implants and
28
29 osteonecrosis in patients on oral BP. However their results should be read with
30
31 caution as the majority of studied patients, where reported, received surgical
32
33 procedures in the first months or years of therapy (Jeffcoat, 2006; Bell and Bell,
34
35 2008) when the cumulative dosage of oral BP and the relative risk of BOJ is
36
37 considered to be low.
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42 Also the recommendations of considering surgical interventions safe if provided
43
44 during the first 3 years of oral BP therapy is questionable as BOJ has been
45
46 reported to occur in the first 2 years of treatment with oral BP (Pazianas et al,
47
48 2007, Yarom et al, 2007) and a recent review of literature reported no clear time
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50 dependency (Pazianas et al, 2007).
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3 (2c) *Invasive dental procedures in patients on oral BP and risk-reduction*
4
5 *strategies*
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8 Some researchers have attempted to introduce strategies to reduce the risk of
9 BOJ associated with oral surgery (and other invasive procedures) for individuals
10 on oral BP. These are summarized in Table 3. It has been suggested that a
11 threshold of length of exposure to oral BP which identifies a higher risk of
12 osteonecrosis exists and that this can help to categorize individuals into
13 appropriate risk groups. Marx and coworkers suggested that patients with a
14 history of fewer than 3 years of exposure to oral BP are at extremely low risk of
15 BOJ and can safely receive surgical procedures (Marx et al, 2007). They also
16 suggested that in individuals with a history of greater than 3 years of oral BP use
17 (or less than 3 years with concomitant corticosteroid or chemotherapy use) the
18 evaluation of degree of bone turnover inhibition (*via* serum C-terminal telopeptide
19 [CTX] levels) could help in identifying subgroups of patients at different degrees
20 of risk (Marx et al, 2007). They recommended deferring the surgery in patients
21 with CTX level lower than 150 pg/mL (this indicates that bone turnover is highly
22 impaired and the risk of osteonecrosis is greater) and planning, together with the
23 prescribing physician, discontinuation of oral BP for 6-9 months (described as a
24 “drug holiday”) to allow the CTX value to rise and surgery to be safely performed
25 (Marx et al, 2007). Other researchers have suggested that the discontinuation of
26 oral BP for 1-3 months could help in any case (regardless of the length of
27 exposure and evaluation of bone turnover markers) as the anti-angiogenic effect
28 of BP would be reduced and, consequently, wound healing after surgery would
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3 be improved, thus potentially reducing the risk of osteonecrosis (Advisory Task
4 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
5 Association of Oral and Maxillofacial Surgeons, 2007; Campisi et al, 2007).
6
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9
10 The American Dental Association expert panel suggested dentists should be
11 '*sensibly cautious*' in performing surgical procedures in individuals on oral BP
12 (American Dental Association Council on Scientific Affairs, 2006; Edwards et al,
13 2008). In cases where planned surgery involves multiple quadrants, they
14 recommend commencing with one quadrant, waiting for 2 months, and if no
15 complication occurs, considering it is safe to treat the remaining quadrants at one
16 time (American Dental Association Council on Scientific Affairs, 2006; Edwards et
17 al, 2008). Other strategies such as conservative surgical technique, use of
18 chlorhexidine, prophylaxis with systemic antibiotics, and elastic-induced gradual
19 orthodontic tooth exfoliation have also been suggested (see Table 3) (Migliorati
20 et al, 2005; American Dental Association Council on Scientific Affairs, 2006;
21 Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on
22 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
23 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et al, 2007;
24 American Society for Bone and Mineral Research Task Force on Osteonecrosis
25 of the Jaw, 2008; Edwards et al, 2008; Regev et al, 2008).
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48 When critically reviewed (see tables 2 and 3), all the above-reported risk-
49 reduction strategies are found to derive from expert opinion or small non-
50 controlled case series and have in common the absence of significant supportive
51 evidence. Reviews performed by other authors on single aspects of these
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3 recommendations confirm the current lack of evidence (Baim and Miller, 2009;
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5 Don-Wauchope and Cole, 2009).
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8 9 **(3) Patients due to commence intravenous BP therapy**

10
11 Most authors recommend, whenever possible, undertaking all necessary and all
12
13 elective dental treatment, including surgery, prior to starting intravenous BP
14
15 therapy (see table 4). The rationale for this is to prevent bone infection and the
16
17 need for invasive treatments at a stage when the patient is on intravenous BP
18
19 (Migliorati et al, 2005; Hellstein and Marek, 2006; Advisory Task Force on
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21 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
22
23 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Landis et al, 2007;
24
25 McLeod et al, 2007; Weitzman et al, 2007). It has been suggested that all
26
27 necessary dento-alveolar surgery and oral surgical procedures should be carried
28
29 out at least 4-6 weeks prior to the first BP infusion in order to ensure adequate
30
31 bone healing. The objective of management is to achieve optimal oral health that
32
33 can be maintained during BP therapy, thus reducing the likelihood of
34
35 osteonecrosis development. Moreover, it is usually recommended that implant
36
37 surgery is not contraindicated at this stage, provided there is sufficient time for
38
39 osseo-integration to occur.
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47 Critical evaluation of these recommendations is difficult as no substantial clinical
48
49 trial has demonstrated that provision of surgery/restorative dentistry before
50
51 starting intravenous BP therapy is effective in reducing occurrence of BOJ
52
53 compared to controls (individuals on intravenous BP who are not provided the
54
55 same intervention). However two very recent independent studies found that the
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4 provision of preventive dental screening and treatment reduces significantly the
5 risk and incidence of BOJ with respect to controls (6.7% versus 26.3% and 3.2%
6 to 1.3%) (Dimopoulos et al, 2008; Ripamonti et al, 2008). Even though better
7
8 planned and larger studies are required to confirm these data, the general advice
9
10 of providing preventive dental treatment is easy to follow in daily practice and
11
12 unlikely to expose the patient to any harm.
13
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16
17 The applicability of them however is questionable. BP therapy can not be delayed
18
19 in patients with malignancy due to severe bone pain and risk of fracture or life-
20
21 threatening hypercalcemia and, regrettably, patients are not always warned
22
23 about potential dental complications of BP treatment (Barker et al, 2007). A
24
25 recent survey among UK healthcare professionals who manage patients with
26
27 multiple myeloma found that less than half of the 263 responders asked patients
28
29 to see their dentists before starting intravenous BP treatment (Barker et al, 2007).
30
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32

33 34 ***(4) Patients receiving intravenous BP***

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36 To discuss available recommendations, it is useful to classify individuals on
37
38 intravenous BP into two groups: those with and those without ongoing dental
39
40 disease.
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43 44 *(4a) Individuals receiving intravenous BP without dental disease*

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46 It has been recommended that in this group major efforts should be made to
47
48 maintain a healthy oral status (Durie et al, 2005; Migliorati et al, 2005; Hellstein
49
50 and Marek, 2006; Pickett, 2006; Weitzman et al, 2006; Advisory Task Force on
51
52 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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54 Oral and Maxillofacial Surgeons, 2007; Barker et al, 2007; Campisi et al, 2007;
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3 Khosla et al, 2007 ; Landis et al, 2007; McLeod et al, 2007; Dimopoulos et al,
4
5 2008; Ripamonti et al, 2008). Robust preventive regimes and regular oral health
6
7 check-ups should be provided to minimise the likelihood of future oral infections,
8
9 need for surgical/invasive dental procedures, and occurrence of denture-induced
10
11 mucosal trauma. These recommendations are not supported by clinical trials but
12
13 are clinically sensible, realistic, do not represent a burden for the patients, and
14
15 can be considered clinically relevant until stronger evidence is available. (Craig
16
17 and Smyth, 2002)

21
22 *(4a) Individuals receiving intravenous BP with dental disease*

23
24 Patients with ongoing dental disease are considered at high risk of developing
25
26 BOJ due to dental infection and/or invasive procedures. There is general
27
28 agreement that in the case of caries and mild-to-moderate periodontitis,
29
30 restorative and non-surgical periodontal therapies can be safely provided as they
31
32 do not generally involve any bone manipulation (Bamias et al, 2005; Durie et al,
33
34 2005; Marx et al, 2005; Migliorati et la, 2005; Hellstein and Marek, 2006;
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36 Migliorati et al, 2006; Pickett, 2006; Woo et al, 2006; Advisory Task Force on
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38 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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40 Oral and Maxillofacial Surgeons, 2007; Barker et al, 2007; Campisi et al, 2007 ;
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42 Khosla et al, 2007; Landis et al, 2007 ; McLeod et la, 2007; Ruggiero and Drew,
43
44 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 2008;
45
46 Ripamonti et al, 2008). These procedures are not considered to be triggers of
47
48 BOJ. It is advocated that non-restorable teeth are treated by decoronation and
49
50 endodontic treatment of the remaining roots, thus avoiding extraction (Bamias et
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3 al, 2005; Durie et al, 2005; Marx et al, 2005; Migliorati et la, 2005; Hellstein and
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5 Marek, 2006; Migliorati et al, 2006; Pickett, 2006; Woo et al, 2006; Advisory Task
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7 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
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9 Association of Oral and Maxillofacial Surgeons, 2007; Barker et al, 2007; Campisi
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11 et al, 2007 ; Khosla et al, 2007; Landis et al, 2007 ; McLeod et la, 2007;
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13 Ruggiero and Drew, 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ;
14
15 Dimopoulos et la, 2008; Ripamonti et al, 2008). Endodontics however remains an
16
17 area of controversy. Whilst there are few reported cases of BOJ associated with
18
19 endodontic therapy (Sarathy et al, 2005 ; Fugazzotto and Lightfoot 2006) it
20
21 cannot be excluded that a spontaneous osteonecrotic process was already
22
23 present before treatment (causing painful symptoms, and radiological findings
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25 that could have been misdiagnosed as apical periodontitis).
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32 Caution has bee recommended regarding orthodontic therapy as tooth
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34 movements have been reported to be potentially impaired in animals and
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36 humans using BP because of the inhibition of osteoclasts. There remain however
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38 no reports of BOJ in these patients (Zahrowsk, 2007; Keim, 2006, Rinchuse et al,
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40 2007).
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44 Little information is available regarding the safety and feasibility of prosthetic
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46 dental procedures in patients on intravenous BP. Most authors have
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48 recommended minimising denture-associated mucosal trauma and avoiding
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50 extensive fixed prosthodontic work (Bamias et al, 2005; Durie et al, 2005; Marx et
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52 al, 2005; Migliorati et la, 2005; Hellstein and Marek, 2006; Migliorati et al, 2006;
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54 Pickett, 2006; Woo et al, 2006; Advisory Task Force on Bisphosphonate-Related
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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 la, 2007; Ruggiero and Drew, 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 2008; Ripamonti et al, 2008). The rationale behind the latter recommendation was not been 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) by 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 la, 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 la, 2007; Ruggiero and Drew, 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 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 la, 2005; Hellstein and Marek, 2006; Migliorati et al, 2006; Pickett,

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2006; Woo et al, 2006; Advisory Task Force on Bisphosphonate-Related
Osteonecrosis 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 la, 2007; Ruggiero and Drew, 2007; Weitzman et
al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 2008; Ripamonti et al,
2008). Table 4 summarizes the safety and level of evidence of available
recommendations.

*(4c) 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 categorize 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, 2006 ; Advisory Task Force on
Bisphosphonate-Related Osteonecrosis 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 C-terminal telopeptide [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

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2
3 recommended the discontinuation of oral BP for 1-3 months in order to allow
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5 osteoclast recovery (Van den Wyngaert et al, 2007) and reduce the anti-
6
7 angiogenic effect of BP (Campisi et al, 2007). They suggested that this would
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9 improve wound healing after surgery, thus potentially reducing the risk of
10
11 osteonecrosis (Campisi et al, 2007; Van den Wyngaert et al, 2007). This is not
12
13 supported by clinical data and is based on the unproven theory that BOJ
14
15 pathogenesis is associated with the inability of bone and epithelial cells to
16
17 complete a normal wound healing process after trauma (Migliorati et al, 2005;
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19 Hellstein et al, 2006; Leite et al, 2006; Advisory Task Force on Bisphosphonate-
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21 Related Osteonecrosis of the Jaws, American Association of Oral and
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23 Maxillofacial Surgeons, 2007; Khosla et al, 2007; Ruggiero and Drew, 2007).
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25 Other strategies such as conservative surgical technique (e.g. primary tissue
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27 closure), use of chlorhexidine mouthwash, prophylaxis with systemic antibiotics,
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29 and use of local anaesthetic agents without vasoconstrictors have also been
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31 suggested to reduce the risk of BOJ (table 5) (Valderhaug et al, 1997; Sarathy et
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33 al, 2005 ; Fugazzotto and Lightfoot 2006; Marx et al, 2007; Mavrokokki et al,
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35 2007 ; Rinchuse et al, 2007 ; Bagan et al, 2008).

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37 Some of these recommendations, although not based on significant evidence,
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39 are clinically sensible and unlikely to cause any significant harm or adverse side
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41 effect. Others however suggest long-term use of medications that might expose
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43 the patients to side effects and long-term complications (e.g. bacterial resistance
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45 to antibiotic or allergic reactions) and should be considered with caution.
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3 Antibiotic prophylaxis before and after surgery has been recommended by some
4 authors in all cases where alveolar surgery is involved and by others only when
5 additional risk factors for severe bone infection are present and/or when
6 treatment involves significant manipulation of the alveolar bone (Marx et al, 2005;
7 Migliorati et al, 2005; Campisi et al, 2007; McLeod et al, 2007 ; Montefusco et al,
8 2007; Van den Wyngaert et al, 2007). Again, none of these recommendations
9 has been validated in case-control prospective studies and it is not known if
10 antibiotic prophylaxis effectively reduces the risk of BOJ. In consideration of the
11 lack of evidence, potential adverse effects, cost, and other possible complications
12 of antibiotic prophylaxis (e.g. bacterial resistance) it would be sensible to
13 conclude that the use of antibiotics can only be justified when there is evidence of
14 on-going infection or clinically significant risk of infection due to local or systemic
15 factors (e.g. chemotherapy). An alternative extraction technique consisting of
16 elastic-induced gradual orthodontic tooth exfoliation has been proposed (Regev
17 et al, 2008) but is not feasible in individuals with acute dental infection.
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41 **Conclusions**

42 Available recommendations on dental management of individuals using or
43 scheduled for BP therapy are hindered by controversy and lack of evidence. A
44 critical analysis of reported guidance can help clinicians to transfer it into practice
45 as part of pragmatic and non-detrimental clinical decisions making.
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51 The recommendation of providing, when possible, restorative and surgical dental
52 treatment before the commencement of both oral and intravenous BP therapy,
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3 together with instigation of a long-term regimen of preventive dentistry and
4 regular check-ups, is not evidence-based and supported by only two studies. It is
5
6 however reasonable, clinically sensible and non-harmful for the patients.
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10 For patients already on BP, restorative and non-surgical treatments appear to be
11 safe as they have not yet been reported to trigger BOJ. Moreover, they have the
12 potential to reduce the risk of future bone infection and need for surgery, hence
13 theoretically reducing the risk of BOJ development.
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17 With regards to invasive surgical procedures different considerations apply.
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19 There seems to be no contraindicated surgical procedures in individuals on oral
20 BP, although caution is recommended in assessing individuals with concomitant
21 risk factors. Regarding individuals on intravenous BP, there is convincing
22 evidence to suggest that elective surgical procedures are contraindicated in all
23 cases; when alveolar surgery cannot be avoided, the risk of BOJ development is
24 significant. For both oral and intravenous BP, none of the suggested risk-
25 reduction strategies have been demonstrated effective and therefore only
26 sensible and practical precautions to reduce bone trauma and to minimize the
27 risk of infection can be recommended. Most importantly, there is need to ensure
28 that patients taking BP are well informed of the oral risks and triggers for BOJ, so
29 they can make informed decisions about undergoing any dental procedures. The
30 need for research to support or refute current thinking is urgent.
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54 **Conflict of Interest statement**

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3 All authors of the present manuscript disclose any actual or potential conflict of
4 interest including any financial, personal or other relationships with other people
5 or organizations within that could inappropriately influence (bias) their work
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Table 1: Reported risk factors for 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	<ul style="list-style-type: none"> - Chronic corticosteroid therapy - Chemotherapy - Estrogenic therapy
Underlying disease	<ul style="list-style-type: none"> - 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 co-incident with the surgical site.
Dental infections	This includes dental infection that affects the alveolar bone such as periodontitis, periodontal abscess, apical periodontitis etc.

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 <i>via</i> 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 <i>via</i> 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 <i>via</i> 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 <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.
Surgery (including endodontic surgery and implants)	Safe. Time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Relatively safe. It may help reducing the risk of BOJ <i>via</i> 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 physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Relatively safe. It may help reducing the risk of BOJ <i>via</i> 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).
Prosthetic	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.

Table 3: strategies to identify/reduce the risk of osteonecrosis in patients on oral BP scheduled for oral surgery

Strategy	Description	Comment
Evaluation of CTX levels and potential discontinuation of BP	CTX > 150 pg/mL: low risk, surgery safe	Not supported by any evidence
	CTX < 150 pg/mL: high risk. Defer surgery, plan drug holiday and wait for CTX to rise.	
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 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 due to 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.

Table 4: Intravenous BP therapy and critical review of dental recommendations

Dental treatment to provide	Individuals due to start iv BP		Individuals receiving iv 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 physiologic 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 can not 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 physiologic 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.
Prosthetic	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.

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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 iv BP	Discontinuation of iv BP for 1-3 months	Not supported by any evidence
Interventions within 3 months of exposure to iv BP	Surgical procedures can be safely performed during the first 3 months of therapy with iv BP.	Not supported by any. 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 due to 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	Potentially effective but data are from one case series without controls. Time-consuming and inadequate in case of

	regular grounding of the crown is required.	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.

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

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Abstract

Osteonecrosis of the jaw bones is a complication of bisphosphonate drug (BP) usage, characterized by trans-mucosal 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 due to 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 lessen 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.

Introduction

Osteonecrosis of the jawbones is a complication of bisphosphonates (BP) therapy characterized by trans-mucosal 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, 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 Landsberg, 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 A et al, 2007; Boonyapakorn et al, 2008), whilst 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 post-surgical 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

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3 Farah, 2007; McLeod et al, 2007 ; Ruggiero and Drew, 2007; Boonyapakorn et
4 al, 2008), although other risk factors have been reported (see table 1) (Marx et al,
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6 al, 2008), although other risk factors have been reported (see table 1) (Marx et al,
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8 2005; Migliorati et al, 2006; Woo et al, 2006; Campisi et al, 2007; Dannemann et
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10 al, 2007, Hewitt and Farah, 2007; Marx et al, 2007; Ruggiero and Drew, 2007).
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12 As management of BOJ is often unsatisfactory, there is general agreement that
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14 major efforts should be spent on prevention and control of risk factors (Marx et al,
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16 2005; Durie et al, 2005; Bamias et al, 2005 ; Migliorati et al, 2006; Woo et al,
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18 2006; Dannemann et al, 2007, Hewitt and Farah, 2007; McLeod et al, 2007;
19
20 Ruggiero and Drew, 2007; Boonyapakorn et al, 2008). Of these, dento-alveolar
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22 surgery and infection is the most easily controlled factor. Nevertheless, no clear
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24 guidance for clinicians exists. Although dental recommendations have been
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26 published, they merely reflect expert opinion, are not evidence-based, and are
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28 often controversial. The aim of this paper is to critically review available
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30 recommendations regarding the dental management of patients on or who are
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32 scheduled for BP therapy.
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41 **Risk of BP-related osteonecrosis: two distinctive groups of patients**

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43 Current data indicate that intravenous high-potency BP are much more frequently
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45 associated with BOJ than is oral low-potency BP (Marx et al, 2005; Durie et al,
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47 2005; Bamias et al, 2005 ; Migliorati et al, 2006; Woo et al, 2006; Dannemann et
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49 al, 2007, Hewitt and Farah, 2007; McLeod et al, 2007 ; Ruggiero and Drew,
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51 2007; Boonyapakorn et al, 2008). Such a significant difference in terms of
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53 prevalence and risk of BOJ has led to the classification of two distinctive groups
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3 of patients on the basis of the route of administration and relative potency of the
4 medication. The first group is those people on oral or low potency BP and the
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6 second is those people in receipt of intravenous or high potency BP. Different
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8 dental considerations apply to these two groups of patients (Migliorati et al, 2005;
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10 American Dental Association Council on Scientific Affairs, 2006; Hellstein and
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12 Marek, 2006; Advisory Task Force on Bisphosphonate-Related Osteonecrosis
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14 of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007;
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16 Khosla et al, 2007; Landis et al, 2007; Marx et al, 2007; Pickett, 2006; Weitzman
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18 et al, 2007) and to respective sub-groups comprising individuals due to start and
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20 subjects who are already on BP therapy.
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30 ***(1) Patients due to commence oral BP therapy***

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32 Although some few authors recommend no additional dental
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34 examination/procedure other than regular reviews and treatment as required
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36 (Khosla et al, 2007), the general advice is that on-going dental infection and
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38 asymptomatic or quiescent dental disease should be promptly managed and any
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40 surgical/invasive dental treatment should be undertaken before the start of BP
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42 therapy (Migliorati et al, 2005; American Dental Association Council on Scientific
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44 Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on
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46 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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48 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et al, 2007;
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50 Edwards et al, 2008). This recommendation applies also to elective bone surgery
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52 (e.g. implants), and suggests a period of at least 4 to 8 weeks between
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3 completion of bone manipulation (e.g. surgery) and commencement of BP
4 therapy to allow sufficient time for complete bone healing (Migliorati et al, 2005;
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6 American Dental Association Council on Scientific Affairs, 2006; Hellstein and
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8 Marek, 2006; Pickett, 2006; Advisory Task Force on Bisphosphonate-Related
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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 Osteonecrosis 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 in order to avoid any mucosal ulceration that might be caused by sharp denture borders or metal clasps, especially in sites prone to trauma e.g. mandibular tori, 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 Osteonecrosis 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 to suggest 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 (Craig and Smyth, 2002; Edwards et al, 2008). Accordingly table 2 provides critical

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3 comments on the above reported recommendations detailing the level of
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5 evidence and safety/risk of different dental procedures. Overall, it can be
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7 concluded that all dental procedures are reasonably safe in individuals due to
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9 start oral BP and available recommendations stating so can be considered
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11 clinically sensible. In some instances they might also contribute to prevent BOJ
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13 via preventing that dental infections occur when the patient has already started
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15 oral BP.
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22 ***(2) Patients receiving oral BP***

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24 For individuals already on oral BP therapy, current recommendations refer to two
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26 different scenarios, namely whether they have ongoing dental disease or not.
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29 *(2a) Patients receiving oral BP without dental diseases*

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31 For those individuals without dental disease, it is advised that the focus should be
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33 on prevention in order to avoid future dental infections and the need for invasive
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35 dental procedures (Migliorati et al, 2005; American Dental Association Council on
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37 Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task
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39 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
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41 Association of Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx e
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43 t al, 2007; Edwards et al, 2008). Appropriate measures may include caries
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45 prevention, regular oral hygiene instruction, and denture review. These
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47 recommendations can be viewed as sensible clinical advice, even though there is
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49 no supportive evidence from controlled clinical trials of their effectiveness.
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54 *(2b) Patients receiving oral BP with dental diseases*

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3 Dental infections have the potential to trigger the development of BOJ, hence the
4 majority of recommendations suggest to provide appropriate oral care before this
5 can occur (Migliorati et al, 2005; American Dental Association Council on
6 Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task
7 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
8 Association of Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx e
9 t al, 2007; Edwards et al, 2008). However, the dilemma is that some of these
10 dental interventions (e.g. extractions, periodontal surgery) are invasive and may
11 in themselves trigger the osteonecrotic process.
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24 Non-invasive dental treatments do seem to be safe as they do not involve bone
25 manipulation and only few cases of BOJ have been reported after non-surgical
26 endodontic procedures (Sarathy et al, 2005; Fugazzotto and Lightfoot, 2006).
27 However, when critically analyzed, these reports are controversial as a
28 spontaneous osteonecrotic process may be present before treatment and may
29 possibly cause painful symptoms that, together with non-specific radiological
30 findings, could be misdiagnosed as apical periodontitis.
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41 Orthodontic tooth movements have been reported to be potentially impaired in
42 patients on oral BP but they have not been related to development of BOJ (Keim,
43 2006; Rinchuse et al, 2007; Zahrowski 2007).
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48 Invasive procedures are theoretically more of a risk than non-invasive ones as
49 they have been reported to trigger up to 50-70% of cases of oral-BP-associated
50 osteonecrosis (Marx et al, 2005; Marx et al, 2007). However, the majority of
51 recommendations suggest that there is no invasive dental procedure that is
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3 absolutely contraindicated (Migliorati et al, 2005; American Dental Association
4 Council on Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006;
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8 Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws,
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10 American Association of Oral and Maxillofacial Surgeons, 2007; Khosla et al,
11
12 2007; Marx et al, 2007; Edwards et al, 2008). Available recommendations state
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14 that urgent invasive procedures should be performed promptly as they are aimed
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16 at treating/preventing alveolar bone infection, which is itself a risk factor of BOJ
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18 (Migliorati et al, 2005; American Dental Association Council on Scientific Affairs,
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20 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on
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22 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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24 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx e t al, 2007;
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26 Edwards et al, 2008). It has been suggested that elective surgical procedures,
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28 such as endo-osseus implant placement, are not contraindicated either (Migliorati
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30 et al, 2005; American Dental Association Council on Scientific Affairs, 2006;
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32 Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on
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34 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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36 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et al, 2007;
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38 Edwards et al, 2008). Most authors have suggested that, if surgery is not urgent
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40 or aimed at treating bone infection, a clear explanation of the benefit, alternatives
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42 and risks of the procedure should be provided to the patient, so they can take an
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44 informed decision (Migliorati et al, 2005; American Dental Association Council on
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46 Scientific Affairs, 2006; Hellstein and Marek, 2006; Pickett, 2006; Advisory Task
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48 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
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3 Association of Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et
4 al, 2007; Edwards et al, 2008). Adequate information should include that
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6 associated risk factors (e.g. corticosteroid therapy, diabetes) have the potential to
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8 increase the risk of BOJ. Duration of oral BP therapy has been suggested to be
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10 important in evaluating the risk of BOJ, with 3 years being the proposed threshold
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12 to differentiate individuals at low and high risk (Marx et al, 2007).
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17 Critical evaluation of these recommendations is difficult due to lack of prospective
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19 studies. Table 2 details the relevant level of evidence and the safety/risk of
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21 available recommendations. With regards to elective surgery (e.g. endo-osseus
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23 implant placement), two recent retrospective studies have shown no significant
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25 association between dental implants and osteonecrosis in patients on oral BP.
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27 However their results should be read with caution as the majority of studied
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29 patients, where reported, received surgical procedures in the first months or
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31 years of therapy (Jeffcoat, 2006; Bell and Bell, 2008) when the cumulative
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33 dosage of oral BP and the relative risk of BOJ is considered to be low.
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38 Also the recommendation of considering surgical interventions safe if provided
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40 during the first 3 years of oral BP therapy is questionable, as BOJ has been
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42 reported to occur in the first 2 years of treatment with oral BP (Pazianas et al,
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44 2007, Yarom et al, 2007) and a recent review of literature reported no clear time
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46 dependency (Pazianas et al, 2007).
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50 *(2c) Invasive dental procedures in patients on oral BP and risk-reduction*
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52 *strategies*
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3 Some researchers have attempted to introduce strategies to reduce the risk of
4 BOJ associated with oral surgery (and other invasive procedures) for individuals
5 on oral BP. These are summarized in Table 3. It has been suggested that a
6 threshold of length of exposure to oral BP which identifies a higher risk of
7 osteonecrosis exists and that this can help to categorize individuals into
8 appropriate risk groups. Marx and coworkers suggested that patients with a
9 history of fewer than 3 years of exposure to oral BP are at extremely low risk of
10 BOJ and can safely receive surgical procedures (Marx et al, 2007). They also
11 suggested that in individuals with a history of greater than 3 years of oral BP use
12 (or less than 3 years with concomitant corticosteroid or chemotherapy use) the
13 evaluation of degree of bone turnover inhibition (*via* serum C-terminal telopeptide
14 [CTX] levels) could help in identifying subgroups of patients at different degrees
15 of risk (Marx et al, 2007). They recommended deferring the surgery in patients
16 with CTX level lower than 150 pg/mL (this indicates that bone turnover is highly
17 impaired and the risk of osteonecrosis is greater) and planning, together with the
18 prescribing physician, discontinuation of oral BP for 6-9 months (described as a
19 “drug holiday”) to allow the CTX value to rise and surgery to be safely performed
20 (Marx et al, 2007). Other researchers have suggested that the discontinuation of
21 oral BP for 1-3 months could help in any case (regardless of the length of
22 exposure and evaluation of bone turnover markers) as the anti-angiogenic effect
23 of BP would be reduced and, consequently, wound healing after surgery would
24 be improved, thus potentially reducing the risk of osteonecrosis (Advisory Task
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3 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
4 Association of Oral and Maxillofacial Surgeons, 2007; Campisi et al, 2007).

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7
8 The American Dental Association expert panel suggested dentists should be
9
10 '*sensibly cautious*' in performing surgical procedures in individuals on oral BP
11
12 (American Dental Association Council on Scientific Affairs, 2006; Edwards et al,
13
14 2008). In cases where planned surgery involves multiple quadrants, they
15
16 recommend commencing with one quadrant, waiting for 2 months, and if no
17
18 complication occurs, considering it is safe to treat the remaining quadrants at one
19
20 time (American Dental Association Council on Scientific Affairs, 2006; Edwards et
21
22 al, 2008). Other strategies such as conservative surgical technique, use of
23
24 chlorhexidine, prophylaxis with systemic antibiotics, and elastic-induced gradual
25
26 orthodontic tooth exfoliation have also been suggested (see Table 3) (Migliorati
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28 et al, 2005; American Dental Association Council on Scientific Affairs, 2006;
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30 Hellstein and Marek, 2006; Pickett, 2006; Advisory Task Force on
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32 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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34 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Marx et al, 2007;
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36 American Society for Bone and Mineral Research Task Force on Osteonecrosis
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38 of the Jaw, 2008; Edwards et al, 2008; Regev et al, 2008).

39
40
41 When critically reviewed (see tables 2 and 3), all the above-reported risk-
42
43 reduction strategies are found to derive from expert opinion or small non-
44
45 controlled case series and have in common the absence of significant supportive
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47 evidence. Reviews performed by other authors on single aspects of these
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3 recommendations confirm the current lack of evidence (Baim and Miller, 2009;
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5 Don-Wauchope and Cole, 2009).
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8 9 **(3) Patients due to commence intravenous BP therapy**

10
11 Most authors recommend, whenever possible, undertaking all necessary and all
12
13 elective dental treatment, including surgery, prior to starting intravenous BP
14
15 therapy (see table 4). The rationale for this is to prevent bone infection and the
16
17 need for invasive treatments at a stage when the patient is on intravenous BP
18
19 (Migliorati et al, 2005; Hellstein and Marek, 2006; Advisory Task Force on
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21 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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23 Oral and Maxillofacial Surgeons, 2007; Khosla et al, 2007; Landis et al, 2007;
24
25 McLeod et al, 2007; Weitzman et al, 2007). It has been suggested that all
26
27 necessary dento-alveolar surgery and oral surgical procedures should be carried
28
29 out at least 4-6 weeks prior to the first BP infusion in order to ensure adequate
30
31 bone healing. The objective of management is to achieve optimal oral health that
32
33 can be maintained during BP therapy, thus reducing the likelihood of
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35 osteonecrosis development. Moreover, it is usually recommended that implant
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37 surgery is not contraindicated at this stage, provided there is sufficient time for
38
39 osseo-integration to occur.
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47 Critical evaluation of these recommendations is difficult as no substantial clinical
48
49 trial has demonstrated that provision of surgery/restorative dentistry before
50
51 starting intravenous BP therapy is effective in reducing occurrence of BOJ
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53 compared to controls (individuals on intravenous BP who are not provided the
54
55 same intervention). However two very recent independent studies found that the
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3 provision of preventive dental screening and treatment reduces significantly the
4 risk and incidence of BOJ with respect to controls (6.7% versus 26.3% and 3.2%
5 versus 1.3%) (Dimopoulos et al, 2008; Ripamonti et al, 2008). Even though better
6 planned and larger studies are required to confirm these data, the general advice
7 of providing preventive dental treatment is easy to follow in daily practice and
8 unlikely to expose the patient to any harm.
9

10
11 The applicability of them however is questionable. BP therapy can not be delayed
12 in patients with malignancy due to severe bone pain and risk of fracture or life-
13 threatening hypercalcemia and, regrettably, patients are not always warned
14 about potential dental complications of BP treatment (Barker et al, 2007). A
15 recent survey among UK healthcare professionals who manage patients with
16 multiple myeloma found that less than half of the 263 responders asked patients
17 to see their dentists before starting intravenous BP treatment (Barker et al, 2007).
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20 21 22 **(4) Patients receiving intravenous BP**

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24 To discuss available recommendations, it is useful to classify individuals on
25 intravenous BP into two groups: those with and those without ongoing dental
26 disease.
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28 29 *(4a) Individuals receiving intravenous BP without dental disease*

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31 It has been recommended that in this group major efforts should be made to
32 maintain a healthy oral status (Durie et al, 2005; Migliorati et al, 2005; Hellstein
33 and Marek, 2006; Pickett, 2006; Weitzman et al, 2006; Advisory Task Force on
34 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
35 Oral and Maxillofacial Surgeons, 2007; Barker et al, 2007; Campisi et al, 2007;
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3 Khosla et al, 2007 ; Landis et al, 2007; McLeod et al, 2007; Dimopoulos et al,
4
5 2008; Ripamonti et al, 2008). Robust preventive regimes and regular oral health
6
7 check-ups should be provided to minimise the likelihood of future oral infections,
8
9 need for surgical/invasive dental procedures, and occurrence of denture-induced
10
11 mucosal trauma. These recommendations are not supported by clinical trials but
12
13 are clinically sensible, realistic, do not represent a burden for the patients, and
14
15 can be considered clinically relevant until stronger evidence is available. (Craig
16
17 and Smyth, 2002)

21
22 *(4a) Individuals receiving intravenous BP with dental disease*

23
24 Patients with ongoing dental disease are considered at high risk of developing
25
26 BOJ due to dental infection and/or invasive procedures. There is general
27
28 agreement that in the case of caries and mild-to-moderate periodontitis,
29
30 restorative and non-surgical periodontal therapies can be safely provided as they
31
32 do not generally involve any bone manipulation (Bamias et al, 2005; Durie et al,
33
34 2005; Marx et al, 2005; Migliorati et la, 2005; Hellstein and Marek, 2006;
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36 Migliorati et al, 2006; Pickett, 2006; Woo et al, 2006; Advisory Task Force on
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38 Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of
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40 Oral and Maxillofacial Surgeons, 2007; Barker et al, 2007; Campisi et al, 2007 ;
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42 Khosla et al, 2007; Landis et al, 2007 ; McLeod et la, 2007; Ruggiero and Drew,
43
44 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 2008;
45
46 Ripamonti et al, 2008). These procedures are not considered to be triggers of
47
48 BOJ. It is advocated that non-restorable teeth are treated by decoronation and
49
50 endodontic treatment of the remaining roots, thus avoiding extraction (Bamias et
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3 al, 2005; Durie et al, 2005; Marx et al, 2005; Migliorati et la, 2005; Hellstein and
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5 Marek, 2006; Migliorati et al, 2006; Pickett, 2006; Woo et al, 2006; Advisory Task
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7 Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American
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9 Association of Oral and Maxillofacial Surgeons, 2007; Barker et al, 2007; Campisi
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11 et al, 2007 ; Khosla et al, 2007; Landis et al, 2007 ; McLeod et la, 2007;
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13 Ruggiero and Drew, 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ;
14
15 Dimopoulos et la, 2008; Ripamonti et al, 2008). Endodontics however remains an
16
17 area of controversy. Whilst there are few reported cases of BOJ associated with
18
19 endodontic therapy (Sarathy et al, 2005 ; Fugazzotto and Lightfoot 2006) it
20
21 cannot be excluded that a spontaneous osteonecrotic process was already
22
23 present before treatment (causing painful symptoms, and radiological findings
24
25 that could have been misdiagnosed as apical periodontitis).
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32 Caution has bee recommended regarding orthodontic therapy as tooth
33
34 movements have been reported to be potentially impaired in animals and
35
36 humans using BP because of the inhibition of osteoclasts. There remain however
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38 no reports of BOJ in these patients (Zahrowsk, 2007; Keim, 2006, Rinchuse et al,
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40 2007).
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44 Little information is available regarding the safety and feasibility of prosthetic
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46 dental procedures in patients on intravenous BP. Most authors have
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48 recommended minimising denture-associated mucosal trauma and avoiding
49
50 extensive fixed prosthodontic work (Bamias et al, 2005; Durie et al, 2005; Marx et
51
52 al, 2005; Migliorati et la, 2005; Hellstein and Marek, 2006; Migliorati et al, 2006;
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54 Pickett, 2006; Woo et al, 2006; Advisory Task Force on Bisphosphonate-Related
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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 la, 2007; Ruggiero and Drew, 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 2008; Ripamonti et al, 2008). The rationale behind the latter recommendation was not been 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) by 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 la, 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 la, 2007; Ruggiero and Drew, 2007; Weitzman et al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 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 la, 2005; Hellstein and Marek, 2006; Migliorati et al, 2006; Pickett,

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3 2006; Woo et al, 2006; Advisory Task Force on Bisphosphonate-Related
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2006; Woo et al, 2006; Advisory Task Force on Bisphosphonate-Related
Osteonecrosis 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 la, 2007; Ruggiero and Drew, 2007; Weitzman et
al, 2007 ; Boonyapakorn et al, 2008 ; Dimopoulos et la, 2008; Ripamonti et al,
2008). Table 4 summarizes the safety and level of evidence of available
recommendations.

*(4c) 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 categorize 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, 2006 ; Advisory Task Force on
Bisphosphonate-Related Osteonecrosis 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 C-terminal telopeptide [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 in order 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 et al, 2006; Leite et al, 2006; Advisory Task Force on Bisphosphonate-Related Osteonecrosis 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.

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3 Antibiotic prophylaxis before and after surgery has been recommended by some
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5 authors in all cases where alveolar surgery is involved and by others only when
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7 additional risk factors for severe bone infection are present and/or when
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9 treatment involves significant manipulation of the alveolar bone (Marx et al, 2005;
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11 Migliorati et al, 2005; Campisi et al, 2007; McLeod et al, 2007 ; Montefusco et al,
12
13 2007; Van den Wyngaert et al, 2007). Again, none of these recommendations
14
15 has been validated in case-control prospective studies and it is not known if
16
17 antibiotic prophylaxis effectively reduces the risk of BOJ. In consideration of the
18
19 lack of evidence, potential adverse effects, cost, and other possible complications
20
21 of antibiotic prophylaxis (e.g. bacterial resistance) it would be sensible to
22
23 conclude that the use of antibiotics can only be justified when there is evidence of
24
25 on-going infection or clinically significant risk of infection due to local or systemic
26
27 factors (e.g. chemotherapy). An alternative extraction technique consisting of
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29 elastic-induced gradual orthodontic tooth exfoliation has been proposed (Regev
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31 et al, 2008) but is not feasible in individuals with acute dental infection.
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41 **Conclusions**

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43 Available recommendations on dental management of individuals using or
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45 scheduled for BP therapy are hindered by controversy and lack of evidence. A
46
47 critical analysis of reported guidance can help clinicians to transfer it into practice
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49 as part of pragmatic and non-detrimental clinical decisions making.
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53 The recommendation of providing, when possible, restorative and surgical dental
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55 treatment before the commencement of both oral and intravenous BP therapy,
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3 together with instigation of a long-term regimen of preventive dentistry and
4 regular check-ups, is not evidence-based and supported by only two studies. It is
5 however reasonable, clinically sensible and non-harmful for the patients.
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10 For patients already on BP, restorative and non-surgical treatments appear to be
11 safe as they have not yet been reported to trigger BOJ. Moreover, they have the
12 potential to reduce the risk of future bone infection and need for surgery, hence
13 theoretically reducing the risk of BOJ development.
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16
17 With regards to invasive surgical procedures different considerations apply.
18
19 There seems to be no contraindicated surgical procedures in individuals on oral
20 BP, although caution is recommended in assessing individuals with concomitant
21 risk factors. Regarding individuals on intravenous BP, there is convincing
22 evidence to suggest that elective surgical procedures are contraindicated in all
23 cases; when alveolar surgery cannot be avoided, the risk of BOJ development is
24 significant. For both oral and intravenous BP, none of the suggested risk-
25 reduction strategies have been demonstrated effective and therefore only
26 sensible and practical precautions to reduce bone trauma and to minimize the
27 risk of infection can be recommended. Most importantly, there is need to ensure
28 that patients taking BP are well informed of the oral risks and triggers for BOJ, so
29 they can make informed decisions about undergoing any dental procedures. The
30 need for research to support or refute current thinking is urgent.
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54 **Conflict of Interest statement**

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

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Table 1: Reported risk factors for BOJ

Risk Factors	Comments
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	<ul style="list-style-type: none"> - Chronic corticosteroid therapy - Chemotherapy - Estrogenic therapy
Underlying disease	<ul style="list-style-type: none"> - 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 co-incident with the surgical site.
Dental infections	This includes dental infection that affects the alveolar bone such as periodontitis, periodontal abscess, apical periodontitis etc.

Table 2: Critical review of dental recommendations with respect to oral BP therapy

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 <i>via</i> 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 <i>via</i> 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 <i>via</i> 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 <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.
Surgery (including endodontic surgery and implants)	Safe. Time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Relatively safe. It may help reducing the risk of BOJ <i>via</i> 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 physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Relatively safe. It may help reducing the risk of BOJ <i>via</i> 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).
Prosthetic	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.

Table 3: strategies to identify/reduce the risk of osteonecrosis in patients on oral BP undergoing oral surgery

Strategy	Description	Comment
Evaluation of CTX levels and potential discontinuation of BP	CTX > 150 pg/mL: low risk, surgery safe	Not supported by any evidence
	CTX < 150 pg/mL: high risk. Defer surgery, plan drug holiday and wait for CTX to rise.	
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 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 due to 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.

Table 4: Critical review of dental recommendations with respect to intravenous BP therapy

Dental treatment to provide	Individuals due to start iv BP		Individuals receiving iv 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 physiologic 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 can not 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 physiologic 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.
Prosthetic	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.

Table 5: strategies to identify/reduce the risk of osteonecrosis in patients on intravenous BP undergoing 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 iv BP	Discontinuation of iv BP for 1-3 months	Not supported by any evidence
Interventions within 3 months of exposure to iv BP	Surgical procedures can be safely performed during the first 3 months of therapy with iv BP.	Not supported by any. 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 due to 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	Potentially effective but data are from one case series without controls.

	movement in 1-3 months (mean 6 weeks). Separation of the roots, endodontic therapy and regular grounding of the crown is required.	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.