Oral Health Management of Patients Prescribed Bisphosphonates

This guidance aims to help minimise the risk of bisphosphonate related osteonecrosis of the jaw (BRONJ) developing in patients who are taking bisphosphonate medications and is based on guidance provided by the Scottish Dental Clinical Effectiveness Programme (April 2011) and Mr Simon Hodder (Consultant in Oral and Maxillofacial Surgery, ABMU Health Board). It does not override the clinician's right, and duty, to make decisions appropriate to each patient, with their informed consent. It is advised that departures from this guidance, and the reasons for this, are fully documented in the patient's clinical record.

What is BRONJ?

BRONJ is defined as exposed, necrotic bone in the maxilla or mandible that has persisted for more than eight weeks in patients taking bisphosphonates and where there has been no history of radiation therapy to the jaw. Symptoms include delayed healing following a dental extraction or other oral surgery, pain, soft tissue infection and swelling, numbness, paraesthesia or exposed bone.

Bisphosphonates and how they work

Bisphosphonates (*see Table 1 on page 2*) are drugs that inhibit bone resorption and decrease bone turnover, as assessed by biochemical markers, by hindering the formation, recruitment and function of osteoclasts. Bisphosphonates are internalized by osteoclasts, causing disruption of osteoclast-mediated bone resorption due to inhibition of osteoclastic activity and apoptosis of osteoclasts. This results in the production of dense bone by osteoblasts and the loss of normal bone physiology.

Table 1: Bisphosphonate Drugs Prescribed in the United Kingdom

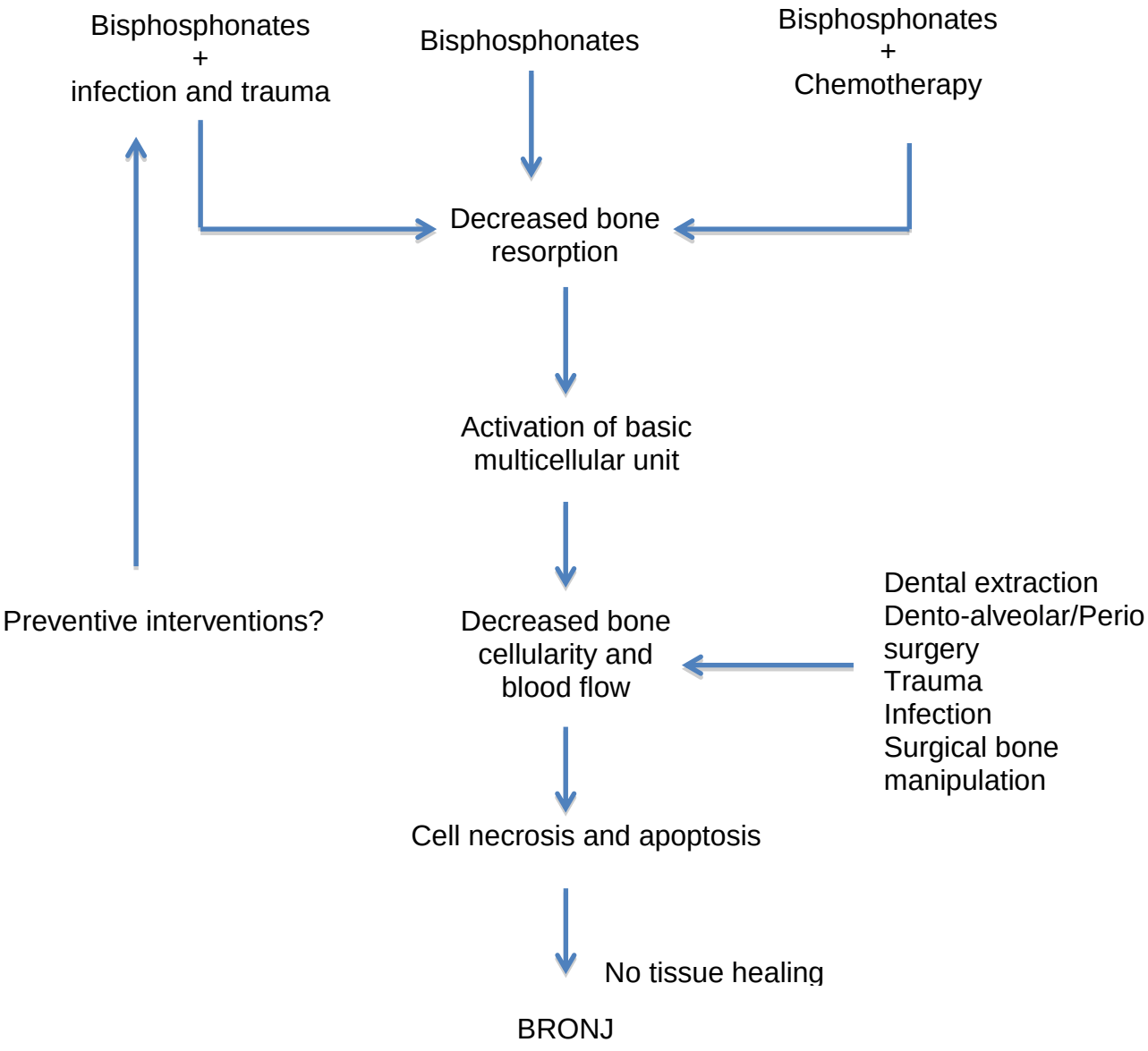
Drug Name	Trade Name	Primary Indication
Alendronic acid	Fosamax Fosavance	Osteoporosis
Risendronate sodium	Actonel	Osteoporosis. Paget's disease
Zolendronic acid	Aclasta Zometa Reclast	Paget's disease. Skeletal events associated with bone metastases. Hypercalcaemia
Etidronate disodium	Didronel	Osteoporosis. Paget's disease
Tiludronic acid	Skelid	Paget's disease
Ibandronic acid	Bondronat Bonviva	Osteoporosis. Bone metastases. Hypercalcaemia
Pamidroniate disodium	Aredia	Paget's disease. Bone pain. Skeletal events associated with bone metastases. Hypercalcaemia
Sodium clodronate	Bonefos Loron	Bone pain. Skeletal events associated with bone metastases. Hypercalcaemia

Bisphosphonates are not metabolized and high concentrations are maintained within bone for long periods of time. They accumulate at sites of high bone turnover making the jaws particularly susceptible as the high alveolar bone turn over in the maxilla and mandible (10 times that of long bones and 5 times that of basal mandibular bone) leads to greater accumulation of the drug here. These areas are easily traumatised by dental procedures, dentures or during eating allowing infection to enter and the reduced bone turnover and bone blood supply can lead to death of the bone or osteonecrosis and BRONJ (*see page 3*). The mandible is a favoured site for occurrence of BRONJ.

Bisphosphonates are used most commonly in the management of osteoporosis but are also used in the management of many other non-malignant and malignant conditions.

Table 2: Conditions that may be treated with bisphosphonates

Non-malignant	Malignant
Osteoporosis	Multiple myeloma
Paget's disease	Breast cancer
Osteogenesis imperfecta	Prostate cancer
Fibrous dysplasia	Bony metastatic lesions
Primary hyperparathyroidism	Hypercalcaemia of malignancy
Cystic fibrosis	



BRONJ Risk

Whilst there are some factors that may increase the risk of BRONJ it should be acknowledged that this is an extremely rare condition and it is very important that patients are not discouraged from taking bisphosphonate drugs or from undergoing dental treatment.

Potency of drugs

- Etidronate = 1
- Alendronate = 1,000
- Zoledronate = 10,000
- Alendronate (Fosamax) half life 10 years plus
- The only difference between oral and IV drug administration is that it takes longer to build up in bones with the oral route (5years till risk) than the IV route (1 year).

Low risk

A patient is at low risk of developing BRONJ if they are about to start bisphosphonate therapy for any condition or are taking a bisphosphonate to prevent or manage osteoporosis without any of the higher risk factors below.

Higher risk

A patient is at higher risk of developing BRONJ if any of the following factors are present:

- A previous diagnosis of BRONJ
- The patient is taking bisphosphonates to manage a malignant condition
- Another non-malignant systemic condition affecting bone (e.g. Paget's disease) has been diagnosed
- The patient is undergoing treatment for a rare medical condition (e.g. osteogenesis imperfecta)
- The patient is also taking systemic corticosteroids or other immunosuppressants
- The patient is also undergoing coagulopathy, chemotherapy or radiotherapy.

Management

All Patients

Ask about past, current or possible future use of bisphosphonates when taking a medical history.

Dentists should be aware that patients may not know that their medication is a bisphosphonate but if they have one of the conditions listed in Table 2 then in the United Kingdom they are likely to be prescribed a bisphosphonate drug.

Patients prescribed bisphosphonates

Try to get the patient as dentally fit as possible before commencement of bisphosphonate therapy or as soon as possible.

It may be helpful to use an information leaflet on bisphosphonates as a basis for further discussion.[1]

Prioritise care that will reduce mucosal trauma, avoid subsequent extractions or any oral surgery or procedure that may impact on bone.

1. Carry out any remedial dental work and try to reduce any periodontal/dental infection or disease
2. Adjust or replace poorly fitting dentures to minimise future mucosal trauma
3. Give preventive advice, emphasizing the importance of:
    - maintaining good oral hygiene
    - a healthy diet and reducing sugary snacks and drinks
    - smoking cessation and limiting alcohol intake
    - regular dental checks and reporting any symptoms such as loose teeth, pain, or swelling, as soon as possible
4. Patients should have routine treatment for scale and polish, simple restorations, regular recall and radiological review
5. Orthodontic tooth movement during bisphosphonate therapy is possible but unpredictable, especially in low-risk patients. Bisphosphonate use is associated with longer orthodontic treatment times among extraction patients, increased odds of poor space closure, and increased odds of poor root parallelism

6. If a patient has spontaneous or chronic bone exposure, refer to an oral surgery/oral and maxillofacial surgery (OS/OMFS) specialist
7. Avoid extractions or any oral surgery or procedures which may impact on bone (i.e. dento-alveolar or periodontal surgery, deep root planing, complex restorations, implants) if there is an alternative treatment option
8. An exception is to consider removal of teeth of poor prognosis if this will avoid extractions or other bone impacting treatments later during the patient's bisphosphonate therapy.

In these circumstances, follow the risk assessment and management recommendations below.

If any extraction or any oral surgery or procedure which may impact on bone is necessary

Advise the patient that there may be a risk of BRONJ to enable informed consent to be obtained but ensure that they understand that BRONJ is an extremely rare condition so that they are not discouraged from taking their medication or undergoing treatment.

Record that this advice has been given.

Allocate the patient to a risk group and follow the recommended management strategy.

Low risk

Straightforward extractions and other bone impacting treatments can and should be carried out in primary care.

Consider periodontal surgery in lower risk cases to eliminate disease but non-surgical periodontal treatment only should be considered in higher risk cases.

New dentures should be reviewed in at risk patients to confirm comfort and stability and soft linings can be considered in higher risk patients.

The circumstances for seeking advice from an (OS/OMFS) specialist are the same as for a patient who is not on a bisphosphonate.

Perform extractions/oral surgery/procedures that may impact on bone in primary care as atraumatically as possible, avoid raising flaps and achieve good haemostasis.

Review healing at 4 weeks after carrying out any invasive treatment.

If surgery sites fail to heal within 4 to 6 weeks, refer to an OS/OMFS specialist.

Higher risk

Seek advice from an OS/OMFS specialist preferably by letter, about whether to treat the patient in primary care for any extraction, oral surgery or procedure which may impact on bone or whether to refer.

Recalls

Regular dental recalls are essential and their frequency should be determined according to oral health status.

Important

There is no supporting evidence that BRONJ risk will be reduced if the patient temporarily, or even permanently, stops taking bisphosphonates prior to invasive dental procedures since the drugs may persist in the skeletal tissue for years.

If a patient has taken bisphosphonates in the past but is no longer taking them for whatever reason (i.e. completed or discontinued the course, taking a drug holiday), allocate them to a risk group as if they are still taking them.

Patients taking any bisphosphonate drug are at some, albeit unknown risk of developing BRONJ spontaneously.

Investigations

OPT and periapical radiographs (dense lamina dura), CT Scans 3D, SPECT scans (Osteomyelitis).

There is a phase called the latent phase when the bone is not yet exposed and necrotic but the effects of bisphosphonates are slowly affecting the jaws. At such a stage it may be possible to see sclerotic bone and widened lamina dura of teeth which could indicate a predisposal for BRONJ.

Currently newer investigations such as CTX markers C, terminal cross linking telopeptide markers, are a great value for risk assessment of patients on bisphosphonates. However once the damage is done to the bone then surgery or a conservative mode of treatment is the only option

Classification of Oral Necrosis (Marx)

- Stage 1a - Bisphosphonate induced osteonecrosis of the jaw, largest area of which measures less than 1cms
- Stage 1b - If the largest area of exposed bone measures more than 1cms
- Stage 2a - If the single area of exposed bone is less than 2cms and is accompanied by pain or clinical infection or both
- Stage 2b - When area of exposure is greater than 2cms and accompanied by pain or clinical infection
- Stage 3a - Those with multiple areas of exposure greater than 3cms without any significant osteolysis or pathological fractures or orocutaneous fistulae
- Stage 3b - Those with multiple areas of exposure greater than 3 cms and showing signs of significant osteolysis, fistula or pathological fracture

Treatment

Class 1a/1b - Conservative management.

Class 2a/2b – Antibiotics.

Class 2a/2b - Surgical management. Debridement and closure of the necrotic area local flaps with minimal periosteal stripping.

Class 3a/3b - Block resection of the jaw. Reconstruction with reconstruction plate, load baring plate, fixed in non-infected area and good soft tissue coverage. Reconstruction with free flaps is not a primary option and can lead to further problems. If infection occurs it may be needed to remove all metal work and go for external pin fixation.

Other treatment options include Ozone and PTH treatment.

Dental treatment when on Biphosphonates for more than 6 months IV

Extractions should be as atraumatic as possible.

If tooth fracture is likely then a surgical approach with a small local flap is needed.

Antibiotic cover is not proven but carried out by many treating these cases.
Routine restorations are not contraindicated nor are superficial scaling and polishing.
Deep subgingival scaling should be avoided.
Endodontic treatment to retain teeth instead of extraction is indicated.

Antibiotics

Ekinella, Moraxella, Actinomyces are the most common organisms seen in infections of exposed necrotic bone in BRONJ and Penicillin V is of great value.
The other drug of value is Levofloxacin (Flucloxacillin).
Augmentin is also used.
Clindamycin is not used due to resistance of some Actinomyces and other bacteria found in the chronic infected cases.
Antibiotic therapy for 6 weeks to 3 months may be required.

Conclusion

BRONJ has become increasingly prevalent in those patients taking 2nd and 3rd generation nitrogen-containing Biphosphonates.
These lesions are slow to heal and have the potential to become infected chronically.
The mandible is a favoured site for occurrence.
Dental practitioners need to be aware of this condition and the need for early recognition.
Patients must be warned about the side effect of these drugs when they are prescribed.

DHJ Davies
Clinical Service Manager/Senior Dental Officer - Community Dental Service
Specialist in Special Care Dentistry
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Treatment Protocol for Dental Practitioners

Lower risk

1. Oral bisphosphonates taken for less than 1 year
2. Do not stop the bisphosphonates

Simple extraction

- Atraumatic technique
- No infection present
    - No pre or post-operative antibiotics
    - Post-operative Chlorhexidine mouthwash
- Infection present
    - Post-operative antibiotics for 1 week
    - Post-operative Chlorhexidine mouthwash

Surgical extraction

Minimal soft tissue elevation and bone exposure

- No infection present
    - No pre or post-operative antibiotics
    - Post-operative Chlorhexidine mouthwash for 2 weeks
- Infection present
    - Post-operative antibiotics for 1 week
    - Post-operative Chlorhexidine mouthwash for 2 weeks

Higher risk

1. Intravenous bisphosphonates and oral bisphosphonates taken for more than 1 year
2. Do not stop the bisphosphonates

Simple and surgical extractions

Atraumatic technique

Minimal soft tissue elevation and bone exposure

- No infection present
    - Post-operative antibiotics for 1 week
    - Post-operative Chlorhexidine mouthwash for 2 weeks
- Infection present
    - Pre-operative antibiotics for 1 week
    - Pre-operative Chlorhexidine mouthwash for 1 week
    - Post-operative antibiotics for 2 weeks
    - Post-operative Chlorhexidine mouthwash for 2 weeks

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