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Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review)

Rollason V, Laverrière A, MacDonald LCI, Walsh T, Tramèr MR, Vogt-Ferrier NB

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[Intervention Review]

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ)

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ABSTRACT

Background

Bisphosphonate drugs can be used to prevent and treat osteoporosis and to reduce symptoms and complications of metastatic bone disease; however, they are associated with a rare but serious adverse event: osteonecrosis of the maxillary and mandibular bones. This condition is called bisphosphonate-related osteonecrosis of the jaw or BRONJ. BRONJ is diagnosed when people who are taking, or have previously taken, bisphosphonates have exposed bone in the jaw area for more than eight weeks in the absence of radiation treatment. There is currently no "gold standard" of treatment for BRONJ. The three broad categories of intervention are conservative approaches (e.g. mouth rinse, antibiotics), surgical interventions and adjuvant non-surgical strategies (e.g. hyperbaric oxygen therapy, platelet-rich plasma), which can be used in combination.

Objectives

To determine the efficacy and safety of any intervention aimed at treating BRONJ.

Search methods

We searched the following databases to 15 December 2015: the Cochrane Oral Health Group Trials Register, the Cochrane Breast Cancer Group Trials Register (20 September 2011), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Ovid, EMBASE via Ovid, CancerLit via PubMed, CINAHL via EBSCO and AMED via Ovid. We scanned the references cited in retrieved articles and contacted experts in the field, the first authors of included papers, study sponsors, other bisphosphonates investigators and pharmaceutical companies. We searched for ongoing trials through contact with trialists and by searching the US National Institutes of Health Trials Register (clinicaltrials.gov) and the World Health Organization Clinical Trials Registry Platform. We also conducted a grey literature search to September 2015.

Selection criteria

Randomised controlled trials (RCTs) comparing the effects of any treatment for BRONJ with another treatment or placebo.

Data collection and analysis

Two review authors independently screened the search results, assessed the risk of bias in the included trials and extracted data. When in dispute, we consulted a third review author.

Main results

One small trial at high risk of bias met the inclusion criteria. The trial randomised 49 participants, most of whom had cancer. It compared standard care (defined as surgery, antibiotics and oral rinses at the discretion of the oral-maxillofacial surgeon) to standard care plus hyperbaric oxygen therapy (2 atmospheres twice a day for 40 treatments). The trial measured the percentage of participants who improved or healed at three, six, 12 and 18 months and last contact. It also measured mean weekly pain scores.

At three months, the study found that the participants in intervention group were more likely to have an improvement in their osteonecrosis than the standard care group participants (risk ratio (RR) 1.94, 95% confidence interval (CI) 1.01 to 3.74). There was no clear difference between the groups for the outcome 'healed' at three months (RR 3.60, 95% CI 0.87 to 14.82). There was no clear difference between the groups for improvement or healing when they were evaluated at six, 12 and 18 months and last contact.

The study did not give any information on adverse events.

Although the findings suggest adjunctive hyperbaric oxygen improved BRONJ, the quality of the evidence is very low since the only study was underpowered and was at high risk of bias due to lack of blinding, cross-over of participants between groups and very high attrition (50% at 12 months and 80% at 18 months in this study, which was designed for an intended follow-up of 24 months).

Authors' conclusions

There is a lack of evidence from randomised controlled trials to guide treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ). One small trial at high risk of bias evaluated hyperbaric oxygen therapy (HBO) as an adjunct to "standard" care and could not confirm or refute the effectiveness of HBO. There are two ongoing trials of teriparatide treatment for BRONJ. We found no randomised controlled trials of any other BRONJ treatments. High quality randomised controlled trials are needed. We provide recommendations for their focus and design.

PLAIN LANGUAGE SUMMARY

Interventions for treating osteonecrosis of the jaw bones associated with bisphosphonate drugs

Review question

How well do treatments for bisphosphonate-related osteonecrosis of the jaw bones, or 'BRONJ', work and how safe are they?

Background

Bisphosphonates are drugs very similar to pyrophosphate (a normal substance found in bone). They are used to lessen symptoms and complications due to the spread of cancer to the bones, and to prevent and treat fragile bones in osteoporosis (a condition where tiny holes in the bones makes them brittle). These drugs can cause a rare but serious condition called bisphosphonate-related osteonecrosis of the jaw or 'BRONJ'. BRONJ affects the healing of bone damage by interrupting the process of removing dead bone and laying down new bone. When this happens, parts or all of the jaw bone becomes friable (a bit like chalk), and eventually this dead bone can be exposed. This makes it difficult for people to eat, speak or brush their teeth, and it often causes severe pain.

Many different treatments are currently used for BRONJ. They can be categorised as non-invasive treatments (such as antibiotics and mouth rinses), surgical approaches or "add-on" treatments used to enhance usual care (for example, ozone therapy or use of blood plasma that has been enriched with platelets). Different treatments may be combined.

Study characteristics

Review authors, working with the [Cochrane Oral Health Group](#), carried out a thorough search up to 15 December 2015 for studies that randomly allocated participants to different treatments for BRONJ (or to a 'placebo' condition that has no active treatment). This type of study design is known as a 'randomised controlled trial'. We only found one relevant completed study and two ongoing studies. The completed study compared people with BRONJ being treated with surgery, antibiotics and mouth rinses to people receiving the same 'standard care' with an add-on treatment called hyperbaric oxygen therapy, which is thought to increase bone renewal. There were 49 participants, most of whom had cancer.

Key results

The study found that the participants in intervention group were more likely than the standard care group participants to have an improvement in their osteonecrosis at three months, but there was no clear difference between the groups when they were evaluated at six, 12 and 18 months and last contact. There was no clear difference between the groups at any time point for complete healing. These results are not reliable as the quality of the evidence is very low. The study did not assess whether there were any side effects of the treatment.

Quality of the evidence

The study had several important flaws: for example, there was a very small number of participants, some participants changed groups during the study and there was a loss of participants during the study.

Authors' conclusions

There is insufficient evidence to conclude whether hyperbaric oxygen therapy is a useful add-on to standard care in the treatment of BRONJ. There are two ongoing trials of teriparatide, a hormonal treatment for BRONJ. We found no randomised controlled trials of any other treatments for BRONJ. As there is a lack of good quality scientific evidence to decide how best to treat BRONJ, high quality trials are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Adjunctive hyperbaric oxygen therapy compared with standard care for BRONJ

Adjunctive hyperbaric oxygen therapy compared with standard care for BRONJ

Patient or population: people with bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Settings: hospital

Intervention: hyperbaric oxygen therapy in addition to surgery, antibiotics and oral rinse

Comparison: surgery, antibiotics and oral rinse

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk ¹	Corresponding risk				
	Standard care	Hyperbaric oxygen therapy				
Healing of osteonecrosis (dichotomous outcome ('healed' vs. 'improved', 'unchanged' and 'worse') measured at 3 months)	100 per 1000	360 per 1000 (87 to 1000)	RR 3.60 (0.87 to 14.82)	45 (1)	very low ² ⊕○○○	Only 45 of the study's original 49 participants were assessed
Improvement in osteonecrosis (dichotomous outcome ('healed' and 'improved' vs. 'unchanged' and 'worse') measured at 3 months)	350 per 1000	680 per 1000 (354 to 1000)	RR 1.94 (1.01 to 3.74)	45 (1)	very low ² ⊕○○○	Only 45 of the study's original 49 participants were assessed
Adverse effects	The included study did not measure adverse effects					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1. Risk in the control group.

2. Quality of the evidence was downgraded by one level for imprecision and two levels for high risk of bias.

BACKGROUND

Description of the condition

Bisphosphonates are synthetic analogues of the endogenous substance pyrophosphate (a normal constituent of the bone matrix), which inhibit bone resorption and thus have a hypocalcaemic effect. They are an extremely effective treatment for reducing symptoms and complications of metastatic bone disease and for preventing and treating osteoporosis (Stevenson 2005; Wells 2008a; Wells 2008b; Wells 2008c). Bisphosphonate analogues differ in activity, potency and adverse effect profiles. Bisphosphonates are associated with a serious adverse event: osteonecrosis of the maxillary and mandibular bones. In this condition, the affected bone becomes friable, non-viable and eventually exposed. The oral complications can have negative impact on quality of life by affecting eating, speaking and maintenance of oral hygiene.

The first clinical descriptions of bisphosphonate-related osteonecrosis of the jaw (BRONJ) are attributed to Marx and Ruggiero. In 2003, Marx described 36 cases of exposed necrotic jaw bone detected in people who had been treated with intravenous bisphosphonates as part of cancer therapy (Marx 2003). In June 2004, Ruggiero reported 63 additional cases of osteonecrosis of the jaw identified by retrospective chart review of people with the diagnosis of refractory osteomyelitis and a history of chronic bisphosphonate therapy (Ruggiero 2004).

According to the American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw: "Patients may be considered to have BRONJ if all of the following three characteristics are present: 1) current or previous treatment with a bisphosphonate; 2) exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and 3) no history of radiation therapy to the jaws. It is important to understand that patients at risk for BRONJ or with established BRONJ can also present with other common clinical conditions not to be confused with BRONJ. Commonly misdiagnosed conditions may include, but are not limited to, alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint disorders" (Ruggiero 2009). BRONJ may be asymptomatic or present with pain, swelling, loose teeth and altered sensation (Ruggeiro 2007).

Intravenous bisphosphonate treatment seems to pose a greater risk of BRONJ than oral administration, though oral treatment longer than three years may increase the risk (Ruggiero 2009). Dentoalveolar surgery is often a precipitating factor for BRONJ symptoms so preventive measures include maintaining good oral hygiene and undertaking any necessary dental treatment before beginning a course of intravenous bisphosphonate treatment. Some clinical guidelines recommend that people at risk of BRONJ should take a three-month break from oral bisphosphonates before and after dental treatment (Ruggiero 2009); however, other guidelines state there is no evidence that this reduces the risk of BRONJ (SDCEP 2011). Greater drug strength, longer duration of use, older age and a history of inflammatory dental disease are associated with a higher risk of BRONJ (Ruggiero 2009).

The true incidence of BRONJ is unknown. Reported rates range from 0.028% (Solomon 2013) to 18.6% (Walter 2008), depending on indication for treatment, study population and sample size.

Our review focused specifically on the treatment of BRONJ, although other medications (denosumab, bevacizumab, cabozantinib, sunitinib) have also been associated with jaw osteonecrosis, the condition then being called medication-related osteonecrosis of the jaw (MRONJ) (AAOMS 2014).

Description of the intervention

There is currently no 'gold standard' of treatment for BRONJ. Interventions used to treat this complication are diverse, controversial and largely empirical. Three broad categories of interventions have been described: classical 'wound-healing' conservative treatment, diverse surgical techniques and different "add-on" treatments. These three approaches are often used in combination, either at the same time or in succession (AAOMS 2014; Ruggiero 2009).

- Conservative treatment:
 - * disinfectant mouth rinses (saline, chlorhexidine, chlorine, peroxide);
 - * antibiotic therapy (local, systemic, or both);
 - * antifungal therapy.
- Surgical techniques:
 - * surgical debridement, sequester removal, surgical sinus drainage procedures (antroostomy);
 - * extraction of teeth within osteonecrotic bone, management of implants;
 - * bone resection;
 - * surgical wound closure, reconstructive surgery, grafts;
 - * laser-assisted surgery;
 - * fluorescence-assisted surgery.
- Adjuvant non-surgical treatment strategies:
 - * hyperbaric oxygen therapy;
 - * pentoxifylline and tocopherol (vitamin E);
 - * ozone therapy;
 - * low level laser therapy (LLLT) for biostimulation, pain relief, anti-inflammatory treatment (erbium-doped yttrium aluminium garnet (Er:YAG); neodymium-doped yttrium aluminium garnet (Nd:YAG), sodium-doped yttrium aluminium perovskite (Nd:YAP), etc.);
 - * platelet-rich plasma;
 - * parathyroid hormone and teriparatide;
 - * bone morphogenetic protein (BMP).

How the intervention might work

Treatments are empirical with different modes of action hypothesised for each modality.

Conservative management, with no or minimal surgical intervention, aims to provide optimal local conditions for wound healing and, in particular, to fight super-infection and remove necrotic soft tissues as well as allowing spontaneous extrusion of bone sequestra.

Surgical techniques aim to remove dead bone and accelerate wound closure. In severe cases, removing parts of the jaw makes it possible to insert synthetic jaw prostheses.

Hyperbaric oxygen therapy is thought to increase bone turnover by stimulating osteoclast differentiation, activity and viability and thus to represent a useful adjunctive treatment (Freiberger 2012).

Pentoxifylline and tocopherol have been used concurrently in radiation-induced tissue necrosis. In BRONJ treatment trials, they are also administered together. Pentoxifylline reduces blood viscosity and improves erythrocyte flexibility, microcirculatory flow and tissue oxygen concentrations. It also has an anti-tumour necrosis factor effect and may inhibit inflammatory reactions and decrease fibrosis. It most likely has an effect in decreasing pain and accelerating healing in radiation-induced tissue necrosis (Delanian 1999). Tocopherol is an antioxidant; its effect could influence platelet aggregation. It also impairs tissue fibrosis.

Ozone (O₃) gas has strong oxidation and antimicrobial effects (bactericidal, viricidal and fungicidal). It has immuno-stimulating and analgesic properties and acts on blood cells (erythrocytes, leukocytes, platelets and endothelial cells), thus affecting the microcirculation and vascular system (Azarpazhooh 2008; Bocci 2004; Saini 2011). Some researchers believe that ozone stimulates tissue healing through its oxidant, antimicrobial and fibro-inducing effects and thus can be useful in treating BRONJ (Ripamonti 2012).

LLLT consists of applying a beam of light generated by lasers (an abbreviated term for 'light amplification by stimulated emission of radiation') or light-emitting diodes on the surface of wounded tissue sites so as to deliver energy in the depth of the tissues. Contrary to high-power lasers used in surgery, LLLT is thought to modify cell function favourably by reducing pro-inflammatory cytokines and by increasing anti-inflammatory growth factors and cytokines. Dosage, wavelength, site and duration of treatment all contribute to the variability of LLLT effects (Neiburger 1999; Page 2014). Several different types of crystals are used to focalise and amplify the light energy. In BRONJ, the materials used for LLLT have included Er:YAG, Nd:YAG and Nd:YAP.

Platelet-rich plasma is produced by concentrating platelets from whole blood. It contains growth factors that are thought to be useful for tissue healing by increasing tissue vascularisation (Lai 2015; Longo 2014).

Parathyroid hormone mediates bone remodelling. Teriparatide is a recombinant human parathyroid hormone. Effects are dose dependant with intermittent low doses stimulating bone formation through osteoblast activation. (Dayisoylu 2013).

BMP belongs to a group of growth factor cytokines. It induces the differentiation of mesenchymal cells into mature bone and has been used as adjunctive therapy in different oral and mandibular reconstruction surgeries to promote bone remodelling. BMPs for clinical use are produced using recombinant deoxyribonucleic acid (DNA) technology (recombinant human BMPs; rhBMPs) (Moghadam 2001; Wikesjö 2009).

Why it is important to do this review

Although the first case series of BRONJ was described in 2003, our bibliographic search in 2010 indicated that data for the treatment of BRONJ was essentially empirical. Before 2010, several major

narrative reviews had been published (Capsoni 2006; Migliorati 2006; Woo 2006), and numerous professional associations offered advice as to how the condition could be prevented and how to manage established disease (Khan 2008; MRHA 2006; Pazianas 2007; Ruggiero 2009). These recommendations were largely based on experience and opinion. Some were issued by the pharmaceutical producers of bisphosphonates themselves or by other industry-sponsored associations. These findings prompted our systematic review. We applied stringent criteria to trial design retaining only randomised controlled trials (RCTs). Our conclusions offer guidance for future research.

The Cochrane Oral Health Group undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain on *The Cochrane Library* (Worthington 2015). This review was identified as a priority title by the oral and maxillofacial surgery expert panel (Cochrane OHG priority review portfolio).

OBJECTIVES

To determine the efficacy and safety of any intervention aimed at treating BRONJ.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs (published or unpublished). We planned to exclude split-mouth studies of treatments that could contaminate other sites in the mouth.

Types of participants

Study participants could be people of any age and either sex, in any setting, with BRONJ. Exposure to bisphosphonates could be past or current. We included people with cancer receiving chemotherapy, corticosteroids or hormonal therapies, as well as people with osteoporosis. The diagnosis of BRONJ could be clinical (AAOMS 2014; Ruggiero 2009), but preferably should have been confirmed with radiological and histological data.

We also excluded studies of people with osteonecrosis from occupational hazards (fluoride or phosphate exposure), people with radiotherapy-induced osteonecrosis of the jaw and people with other causes of avascular necrosis of the bone (sickle cell disease or other primarily ischaemic diseases).

Types of interventions

We included studies describing the outcome of surgical or non-surgical management of BRONJ.

Definitions

- By non-surgical management, we mean use of topical or systemic interventions.
- By surgical management, we mean surgical debridement, including necrotic bone resection, sequestrum removal or dental extraction within osteonecrotic bone, as well as more extensive resections of the affected bone and reconstructive surgery, including use of allografts or xenografts.

We considered the following comparisons for this review:

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review)

- any experimental intervention (surgical or non-surgical) versus none (placebo; no treatment);
- any experimental intervention (surgical or non-surgical) versus an active control (surgical or non-surgical);
- any combined intervention (e.g. surgical debridement plus antibiotics plus antiseptic mouthwash) versus none (placebo; no treatment);
- any combined intervention (e.g. surgical debridement plus antibiotics plus antiseptic mouthwash) versus an active control (surgical or non-surgical or a combined intervention).

We considered any length of treatment and, for drug therapy, all administration routes.

Types of outcome measures

Primary outcome

- Healing of the osteonecrosis as indicated by one or more of the following six indicators.
- Improvement in the clinical grade of the lesions according to the American Academy of Oral and Maxillofacial Surgeons staging of BRONJ ([AAOMS 2014](#); [Ruggiero 2009](#)).

Stage*	Description*
At risk	No apparent exposed/necrotic bone in people treated with oral or intravenous bisphosphonates
0	No clinical evidence of necrotic bone but non-specific clinical findings and symptoms
1	Exposed/necrotic bone in people who were asymptomatic and had no evidence of infection
2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
3	Exposed/necrotic bone in people with pain, infection and 1 of the following: pathological fracture, extraoral fistula or osteolysis extending to the inferior border

- Wound healing (yes or no).
- Improvement in exposed bone quality (judged clinically on inspection of the mouth by a dentist or a dental/oral surgeon as exposed bone that is less friable, less devitalised, less necrotic).
- Halt in bone disease progression as per imaging techniques such as: X-ray examination (improvement of sclerotic changes, mottling and bone fragmentation, improvement of formed sequestrum or persistent extraction sockets), computed tomography (CT) scan, magnetic resonance imaging (MRI) (surface area of the bone disease, localisation, evidence of bone marrow disease), positron emission tomography (PET)/CT imaging (decreased abnormal focal uptake) ([Raje 2008](#)).
- Halt in bone disease progression as visualised with doxycycline viable bone fluorescence (surface area of the bone disease, localisation, evidence of bone marrow disease) ([Pautke 2009](#)).
- Healing of sinus tract or deep periodontal pockets.

- Improvement in nutritional intake or in the ability of eating different types of food (normal diet, blended or pureed foods, liquid diets).
- Quality of life.
- Health economic measures, such as effect on healthcare consumption, number or length of hospitalisations, health resource use.

Adverse events

- Any effect not listed as an outcome and reported as an adverse effect by the authors or deemed as such by us.
- New or worsening signs of infection, intraoperative bleeding, medication adverse effects.

We decided to classify the time points for outcome measurement as: immediate (less than 24 hours after intervention); early (one to eight days after intervention) and long term (more than eight days after intervention).

Search methods for identification of studies

We developed detailed search strategies for each database. These were based on the search strategy developed for MEDLINE but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. The initial searches were performed without an RCT filter, but subsequent top-up searches combined the subject search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (as published in Box 6.4.c in the *Cochrane Handbook for Systematic Reviews of Interventions*) ([Higgins 2011](#)) ([Appendix 1](#)). The search strategy was applied without an RCT filter up to March 2013 and with the RCT filter from April 2013 to December 2015.

Secondary outcomes

- Mortality rate and cause of death.
- Pain: presence and level of pain, use of analgesia during the first two weeks after intervention, use of analgesics, duration of pain, per cent pain relief.
- Improvement of pre-existing accompanying symptoms other than pain, such as mucosal oedema, super-infection, purulent discharges, fistulae to skin, or inflammatory reactions including fever.

Electronic searches

We searched the following databases:

- the Cochrane Oral Health Group Trials Register (to 15 December 2015) (see [Appendix 2](#));
- the Cochrane Breast Cancer Group Trials Register (to 20 September 2011) (see [Appendix 2](#));
- the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 1) (see [Appendix 3](#));
- MEDLINE via Ovid (1946 to 15 December 2015) (see [Appendix 1](#));
- EMBASE via Ovid (1980 to 15 December 2015) (see [Appendix 4](#));
- CancerLit via PubMed (1950 to 15 December 2015) (see [Appendix 5](#));
- CINAHL via EBSCO (1937 to 15 December 2015) (see [Appendix 6](#));
- AMED via Ovid (1985 to 15 December 2015) (see [Appendix 7](#));
- the Database of Randomised Controlled Trials in Hyperbaric Medicine (1966 to 15 December 2015) (see [Appendix 8](#)).

Language

The search attempted to identify all relevant studies irrespective of language or alphabet. We translated papers in alphabets other than latin.

Searching other resources

Two review authors (NV, VR) searched the following databases for ongoing trials (see [Appendix 9](#) for the search terms used):

- US National Institutes of Health Trials Register (clinicaltrials.gov) (to 15 December 2015);
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/default.aspx) (to 15 December 2015).

We conducted a cited reference search through Web of Science and Scopus to see where our included and excluded studies had been cited, to attempt to identify further clinical trials. We retrieved the articles citing the single identified RCT from Web of Science and Scopus and 12 non-randomised comparative studies (see [Characteristics of excluded studies](#) table) previously identified from MEDLINE via Ovid and evaluated them for inclusion.

Two review authors (NV, VR) sought grey literature to 15 September 2015 in the following (see [Appendix 10](#) for the search terms):

- the Grey Literature Report in Public Health of The New York Academy of Medicine (www.greylit.org);
- GreyNet International (www.greynet.org);
- Grey Literature for Dentistry (guides.library.utoronto.ca/dentistrygreylit);
- Grey Literature in the Health Sciences (guides.library.upenn.edu/healthgreylit?hs=a);
- Open Grey (www.opengrey.eu);
- National Technical Information Service (www.ntis.gov).

To identify additional studies and results, two review authors (NV, VR) scanned the references cited in the retrieved grey literature (mainly doctorate theses), but did not find any additional experimental trials on BRONJ treatment.

Using email addresses on abstracts and articles, we contacted:

- experts in the field;
- the first author of the included RCT;
- study sponsors;
- other bisphosphonates investigators;
- pharmaceutical companies.

As BRONJ has only recently been more widely recognised, we found that much of the medical literature focused on incidence, risk factors and other epidemiological data and that trials reporting on BRONJ treatment are still in their infancy (March 2015).

Data collection and analysis

Selection of studies

Two review authors (NV, VR) sorted the identified publications by type (primary versus secondary literature) on the basis of article title and abstract if available. We further classified primary literature reports according to design and applied inclusion/exclusion criteria to select articles describing the effects of interventions designed to treat BRONJ. The review authors were unblinded regarding the study author(s), their institutional affiliations and the site of publication of reports. We obtained the full article for all studies appearing to meet the inclusion criteria or in instances where there was insufficient information from the title, keywords and abstract to make a decision. Two review authors independently assessed all studies for eligibility. We referred instances of uncertainty in the study selection process to the other members of the review team and ultimately resolved disagreements by mutual discussion.

At the preliminary stage triage, the exclusion criteria were:

- not a primary study (e.g. guidelines, reviews, expert opinions);
- not the population of interest (e.g. cellular or animal studies, not on BRONJ and not on people with BRONJ but on their doctors);
- other (e.g. not on BRONJ treatment).

This left us with interventional observations including case reports, case series (separating studies with individual patient data and studies in which results had been pooled), non-randomised clinical trials and RCTs.

For this publication, we included RCTs only.

Data extraction and management

Two review authors (from NV, VR, LM, TW) selected the studies and extracted data independently. We resolved differences in data extraction coding by discussion. We used Review Manager software ([RevMan 2014](#)).

We recorded the following data if available.

- General characteristics - year of publication, language of publication, country of origin and source of study funding.
- Trial design - sample size, method of allocation, blinding and comparative group characteristics.
- Details of the participants including demographic characteristics, age, any orodental disease diagnoses, radiograph examinations, edentulous or not, presence of other

stated medical conditions, medications and smoking habits. We accounted for drop-outs whenever possible.

- Details of exposure to bisphosphonates: ever, current or past. Dose, route of administration.
- Details on the type of intervention (see [Types of interventions](#)).
- Details of the outcomes reported (see [Types of outcome measures](#)), including method of assessment (where measurement scales were used, we recorded whether or not they were validated), and time intervals.
- Reported results of the interventions.

Assessment of risk of bias in included studies

Two review authors (NV, VR) appraised the risk of bias in the included study with the tool recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* as appropriate for RCTs ([Higgins 2011](#), Chapter 8.5). We referred instances of disagreement in risk of bias assessments to one of the other members of the review team (MT) and resolved them by discussion.

Measures of treatment effect

We analysed the data using standard Cochrane systematic review methods as outlined in [Higgins 2011](#). For dichotomous outcomes, we expressed the estimate of effect as risk ratio (RR); for continuous outcomes, we expressed the estimate of effect as the mean difference (MD) if studies reported an outcome using the same scales, or standardised mean difference (SMD) if studies reported an outcome using different scales. We calculated the 95% confidence interval (CI) alongside the effect estimate. Where insufficient information was reported to enable these effect measures to be calculated, we provided a narrative report of the summary measures.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We planned to contact study authors when necessary for clarification of data or to obtain missing data.

Assessment of heterogeneity

We planned to assess clinical heterogeneity on the basis of the participants and the interventions in the included studies. We planned to undertake a meta-analysis when there were studies with sufficient similarities in the participants, interventions and outcomes. We would have assessed statistical heterogeneity using the χ^2 test for heterogeneity (P value < 0.1) and the I^2 statistic. The I^2 values range from 0% (may not be important) to 100% (considerable heterogeneity). The importance of the observed value of the I^2 statistic depends on: magnitude and direction of effects and strength of evidence for heterogeneity (e.g. P value from the χ^2 test) ([Higgins 2011](#)).

Assessment of reporting biases

If there had been more than 10 studies for meta-analysis, we would have assessed possible publication bias by visually inspecting a funnel plot for asymmetry. If detected, we would have carried out further investigation using the methods described by [Egger 1997](#) for continuous outcomes and [Rücker 2008](#) for dichotomous outcomes.

We planned to assess time lag bias by comparing the dates of publication of studies showing a particular intervention being effective against the dates of publication of those studies showing no or insignificant effect. We would also have considered multiple publication bias and location bias and contacted study authors for further details where these were suspected.

We planned to verify whether effect size of the interventions was related to publication in English language journals, MEDLINE accessibility, impact factor size, or a combination of these, but this was not necessary (only one RCT identified).

We planned to check for citation bias by looking at the number of times a study has been cited (Web of Science, Scopus) and whether this number was influenced by the nature and direction of the results.

Data synthesis

We planned to carry out a meta-analysis when pooling of the data was clinically and statistically appropriate. We would have used random-effects or fixed-effect meta-analyses as appropriate to combine quantitative data. For comparisons where a meta-analysis could not be carried out, we provided a narrative reporting of the summary measures and treatment effects.

Subgroup analysis and investigation of heterogeneity

We planned to assess clinical heterogeneity by considering the types of bisphosphonate, participants and interventions in each study. Such sources of heterogeneity may include, but are not limited to:

- type and indication of the bisphosphonate therapy (people with cancer versus people with osteoporosis), route of administration (oral versus parenteral), duration of therapy;
- participant characteristics (age, socioeconomic status, setting, ethnicity, general health status, smoking);
- orodental co-morbidities (prior interventions, edentulous, periodontal status - type and severity of disease);
- location of the osteonecrosis (maxilla, mandible, palate, unilateral, bilateral);
- type, duration and intensity of interventions (extent of surgical excisions, length of therapy, type and route of drug administration, alterations in ambient pressures and length of exposure for hyperbaric oxygen therapy, etc.).

If we had identified other important sources of heterogeneity during the course of the review, we would have explored and identified them as post-hoc analyses.

Sensitivity analysis

If there had been sufficient RCTs, we planned to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment and incomplete follow-up.

Summarising results and assessing the quality of the evidence

We created a 'Summary of findings' table for each comparison and presented summary information for the main outcomes: healing and adverse events. Two review authors (LM, TW) assessed the quality of the evidence as high, moderate, low or very low in

accordance with GRADE criteria for study design, consistency, precision and directness of results, and publication bias (GRADE 2004; Higgins 2011).

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#) tables.

Results of the search

Our broad search strategy retrieved 3224 articles. Two review authors (NV, VR) excluded those that were not primary studies, not the population, disease or intervention of interest, or where there was no intervention or no reported outcome of the intervention. We identified two ongoing clinical trials ([ACTRN12612000950864](#);

[UMIN000009132](#); see [Characteristics of ongoing studies](#) table). The 403 remaining articles were classified by study design. Of these, we gave detailed consideration to 13 studies with comparison groups that were potentially eligible for inclusion, but after inspection of the full papers, we excluded 12 of them because they were not randomised (see [Characteristics of excluded studies](#) table).

One study met the pre-specified inclusion criteria of this review. This study was an unblinded, RCT on the effect of standard care defined as surgery, antibiotics and oral rinses at the discretion of the oral-maxillofacial surgeon (control group) compared to the same treatment and hyperbaric oxygen as an adjunct. We found no RCTs on the therapies (conservative and surgical approaches) recommended in the guidelines issued by most professional associations.

[Figure 1](#) shows the study flow diagram.

Figure 1. Study flow diagram.

Included studies

Only one study was eligible for inclusion in this review. The study had 49 randomised participants (45 participants contributed data for first analysis at three months and 18 contributed data at 18 months' follow-up). Novartis funded the study. See [Characteristics of included studies](#) table for study details. Briefly, it was an

interventional, unblinded, RCT. The enrolment period was July 2006 to December 2010. The trial screened 133 participants for eligibility, 49 of whom were included in the trial.

Participants were randomised into two groups.

- Control group: standard care defined as surgery, antibiotics and oral rinses at discretion of oral-maxillofacial surgeon.
- Hyperbaric oxygen therapy group: standard care plus hyperbaric oxygen therapy (2 atmospheres twice a day for 40 treatments).

There were 27 participants in the control group and 22 in the hyperbaric oxygen therapy plus standard care group. The participants were outpatients (Duke referral area of central North Carolina and participants recruited through the internet) that had BRONJ as described by the Task Force of the American Society for Bone and Mineral Research (Khosla 2007). They had been treated with bisphosphonates for multiple myeloma (39.6% of total sample), breast cancer (25% of total sample), osteoporosis (14.6% of total sample) or another indication (20.4% of total sample). The mean age was 66.3 years in the control group and 66.1 years in the standard care plus hyperbaric oxygen therapy group. At baseline, 15/27 (56%) people in the control group were women, and 13/22 (60%) people in the hyperbaric oxygen therapy group were women.

The RCT reported four outcomes for a follow-up duration of up to 24 months:

- change from baseline in oral lesion size and number (translated into a binary outcome variable, i.e. healed or improved versus unchanged or worse);
- time to improvement;
- pain;
- quality of life.

The trial authors reported that two outcomes would be reported in a separate publication:

- serum measurements of bone turnover;
- bone turnover signalling.

Time points for collection of the oral lesion data were baseline, three, six, 12, 18 and 24 months (or at last contact). Pain was assessed weekly. Quality of life was assessed at baseline and six months. There was some cross-over of participants from their allocated treatment arm to the alternative trial arm. For this reason, the authors presented the data based on the treatment that was received rather than treatment allocated.

Ongoing trials

We identified two ongoing trials:

- [ACTRN12612000950864](#) is a randomised, double-blind, placebo-controlled trial comparing subcutaneous teriparatide injections (20 µg/day) plus calcium (600 mg/day tablet) plus vitamin D (1000 IU/day tablet) supplementation to placebo saline injections plus calcium (600 mg/day tablet) plus vitamin D (1000 IU/day tablet) supplementation for eight weeks in people treated with bisphosphonates or denosumab. The trial is being conducted in Australia. The target sample is 68 participants and follow-up will be one year. Primary outcomes are clinical staging of osteonecrosis of the jaw and radiological staging of osteonecrosis of the jaw. Secondary outcomes are bone formation and resorption markers (PINP, beta-CTX), jaw osteoblast activity, as measured by 18F-sodium fluoride (NaF)-PET imaging and quality of life, as measured by Oral Health Impact Profile 14 questionnaire.

- [UMIN000009132](#) is a parallel, open, active RCT comparing two different commercialised teriparatide preparations (Forteo® versus Teribone®) for efficacy and safety outcomes. The trial is being conducted in Japan. It will include females only and has a target sample size of 15.

Excluded studies

We considered 13 abstracts to be potentially eligible for inclusion, but after inspection of the full papers, we excluded 12 of them because they were not RCTs. See [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Allocation

The generation of the randomisation sequence was not reported. Concealment of allocation was done using opaque envelopes. Selection bias may be present, so we judged the level of risk to be unclear.

Blinding

We assessed the risk of performance and detection bias as high. Study personnel were not blinded to therapy. In regards to change from baseline in oral lesions size and number, the oral-maxillofacial surgeon was not told the participants' assignments before the initial staging examination. On subsequent assessments, the evaluators were not blinded to treatment group. The participants were not blinded to therapy.

Incomplete outcome data

We assessed the risk of attrition bias as high. The last contact was intended to be 24 months after consent; however, if a person died, was unable to return to the investigation site or was lost to follow-up, lesion scores were based on the notes of the last contact or on reports from physicians in the person's home town. The attrition rate was very high. At the 12-month evaluation, 50% of participants were lost to follow-up and at 18 months, only approximately 20% of participants were available for analysis. Thirteen out of 49 participants did not complete all follow-up visits. At the end of the study, 15/49 participants had died (three early deaths). The missing outcome data were not balanced between the intervention groups (at the end of the follow-up period, there were six participants left in the standard care group and 12 in the hyperbaric oxygen therapy plus standard care group).

Selective reporting

All clinical data mentioned in [ClinicalTrials.gov](#) were reported in the trial publication. However, some laboratory results (serum measurements of bone turnover and bone turnover signalling) were withheld. As these were not primary outcomes and the trial authors stated that they would be reported in a separate publication, we assessed the risk of reporting bias as low.

Other potential sources of bias

Five participants crossed over from the standard care group to the hyperbaric oxygen therapy plus standard care group (especially three late cross-overs) and one participants crossed over from the hyperbaric oxygen therapy plus standard care group to the standard care group. Analysis of data was done by treatment

group and not by intention-to-treat. We assessed the risk of other potential sources of bias as high.

Effects of interventions

See: [Summary of findings for the main comparison Adjunctive hyperbaric oxygen therapy compared with standard care for BRONJ](#)

We identified only one eligible study with a single comparison (hyperbaric oxygen as an adjunct to standard care (surgery and antibiotics)) ([Freiberger 2012](#)), and presented this data at multiple time points as an additional table ([Table 1](#)). The study was at high risk of bias.

Our primary outcome, healing of the osteonecrosis, was reported as a change from baseline in oral lesion size and number (translated into a binary outcome variable, i.e. healed (gingival coverage with no exposed bone) or otherwise and healed or improved (decrease in size or number of baseline lesions) or otherwise). Scores were based on direct observation by the study's oral-maxillofacial surgeon. However, if a participant died, was unable to return to Duke University Medical Center or was lost to follow-up, lesion scores were based on the notes of the last scheduled or unscheduled Duke University Medical Center contact or on reports from local or referring physicians in the person's home town. The study investigators assessed only two of our secondary outcomes of interest, pain and quality of life. Pain was self assessed using a 0- to 10-point Likert scale. Quality of life was self assessed using the Duke Health Profile, a 17-question instrument with six health domains (physical, mental, social, general, perceived health and self esteem) and four dysfunction measurements (anxiety, depression, pain and disability).

Outcomes based on the change in lesion scores were measured at each time point. Visits were scheduled at baseline, three, six, 12 and 18 months. Pain was measured weekly and quality of life was measured at baseline and six months.

Except for one participant in the standard care group who continued bisphosphonate administration for one month after the initial evaluation, all participants discontinued bisphosphonates before or at the time of consent.

Primary outcome

Healing of the osteonecrosis

The RCT reported healing of osteonecrosis as change from baseline in oral lesion size and number, and clinical severity ([Freiberger 2012](#)).

Possible outcomes were:

- healed (gingival coverage with no exposed bone);
- improved (decrease in size or number of baseline lesions);
- unchanged (no change in size or number of baseline lesions);
- worse (increase in size or number of baseline lesions compared with their condition at the time of consent).

There was some evidence of a beneficial effect of hyperbaric oxygen therapy for 'improvement' ('healed' plus 'improved' versus 'unchanged' and 'worse') at the first time point evaluated (three months: RR 1.94, 95% CI 1.01 to 3.74), but this was not demonstrated at any other time points. For the outcome

'healed' ('healed' versus 'improved', 'unchanged' and 'worse'), the range of effects contained within the CIs included both no effect of the intervention and some effect of the intervention for all time points. [Table 1](#) details the effect estimates and 95% CIs.

Secondary outcomes

Pain

The study authors recorded pain scores weekly using a 0- to 10-point Likert scale (0 = no pain) and calculated the change referenced to the initial value ([Freiberger 2012](#)). Sixteen of the 42 participants evaluated for pain did not report any pain at baseline. There was no difference in baseline pain scores between the two treatment groups before hyperbaric oxygen therapy. This outcome was incompletely reported, presented as figures and a narrative only; it reported no numerical summary statistics for pain, meaning that we could not carry out a re-analysis for this outcome. The authors of the study reported that "subjects with pain who received hyperbaric oxygen therapy exhibited a rapid decrease in pain within the first three weeks of therapy. Pain scores decreased from baseline for 2 groups over the course of the study" and "the change in average weekly pain score in the hyperbaric oxygen therapy and control groups differ ($P < 0.01$, linear regression) from week 1 to week 16 (P not significant at >16 weeks)".

Quality of life

The study investigators measured self reported quality of life at baseline and six months' follow-up using the generic Duke Health Profile ([Freiberger 2012](#)). They reported only within-group comparisons for each of the domains. As summary statistics were not reported, we were unable to present or re-analyse the data to provide between-group comparisons.

Other secondary outcomes

The trialists did not measure our other secondary outcomes (mortality rate and cause of death, improvement of pre-existing accompanying symptoms other than pain, improvement in nutritional intake or in the ability of eating different types of food, health economic measures) ([Freiberger 2012](#)).

Adverse events

The study reported no information on adverse events ([Freiberger 2012](#)).

DISCUSSION

Summary of main results

Classical 'wound-healing' conservative treatments and surgery are the two treatments most frequently used for BRONJ. These treatments are employed empirically, drawing on the many case-series reports, as they have not been investigated in RCTs. The only completed RCT of BRONJ treatment investigated an adjunctive therapy, hyperbaric oxygen therapy. Two RCTs evaluating teriparatide are ongoing.

Overall completeness and applicability of evidence

The only eligible RCT was an evaluation of adjunctive therapy (hyperbaric oxygen) for people undergoing surgery ([Freiberger 2012](#)). It was unblinded and loss to follow-up was substantial. We could draw no definitive conclusions as to the efficacy of

hyperbaric oxygen therapy. There are only two ongoing RCTs, one evaluating teriparatide treatment for BRONJ versus placebo and the other comparing two types of teriparatide treatment. There is no blinded RCT on any other treatment applied at present to people with BRONJ, although we know that there are thousands of these iatrogenic cases treated worldwide.

Quality of the evidence

Extensive review of the literature on BRONJ treatment identified only one completed RCT, which constitutes the body of evidence of this review. Overall evidence from this trial of hyperbaric oxygen adjunctive therapy for people undergoing surgery is undermined by its unblinded design, low number of participants and high attrition rate. A serious concern is the underpowered nature of the study (they did not meet the required sample size of 70 participants and the proportion of cross-over). Therefore, we downgraded the quality of the evidence to very low. We could draw no definite conclusions regarding the effectiveness of hyperbaric oxygen therapy as an add-on therapy for BRONJ treatments. No other treatment modalities can be reported upon.

Potential biases in the review process

Finding only one RCT raises the question of potential selection bias. Since the initial publication of the protocol for this review in 2010 (Vogt-Ferrier 2010), the review process has been extensive and systematic. The Cochrane Oral Health Group Trials Search Co-ordinator (Anne Littlewood) performed all searches in the databases, apart from those for grey literature and the hyperbaric oxygen therapy database (carried out by NV and VR) and the search strategy was intentionally very wide. We applied no language restriction. Alexandra Laverrière contacted about 200 experts and authors in hopes of getting additional data. We believe that selection bias was avoided.

Agreements and disagreements with other studies or reviews

Recently, there have been several other systematic and literature reviews of treatments for BRONJ (Fliefel 2015; Khan 2015; Rupel 2014; Silva 2016; Spanou 2015). These reviews included all types of trial designs while our review focused on RCTs. Our literature search was more comprehensive with 12 different databases searched, a wide time span, a thorough grey literature search, contact with authors and experts, identification of ongoing trials and no language restriction. All reviews agree that management of BRONJ remains controversial and that there is no definitive standard of care for this disease. All conclude that controlled studies should be performed.

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence from randomised controlled trials to guide treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Treatment should be determined for each individual situation based on clinical judgement and patient preference.

Implications for research

The Freiburger 2012 randomised controlled trial on hyperbaric oxygen therapy as an adjunct to standard surgical care involved a small number of participants and was at high risk of performance,

detection and attrition bias. Therefore, it cannot be used to support or refute a benefit for adjunctive hyperbaric oxygen therapy in treating BRONJ. Two trials are currently underway to evaluate teriparatide treatment for BRONJ. This systematic review has identified the need for well-designed, adequately powered randomised controlled trials to assess the benefits of all proposed treatments for BRONJ.

The implications for further research arising from this review fall into two categories: improving the conduct and reporting of future research, and specifying important research questions.

Improving the conduct and reporting of future research

Most treatment centres offer multimodal treatments combining conservative treatment with surgical techniques and sometimes more innovative non-surgical treatments. Therefore, it has been impossible to establish the efficacy of individual treatment options.

In general, for all BRONJ treatment research protocols, either single or combined modalities, the following rules should be applied (Higgins 2011).

- Diagnosis and staging of the disease should be assessed with standardised reproducible scales. Included participants should be registered in a centralised pharmacovigilance database, such as the World Health Organization Vigibase or Eudravigilance and the worldwide unique number available to identify participants included in several treatment trials.
- Randomisation should be carried out and described in sufficient detail to allow an assessment of whether it produced comparable groups. The participant should be the unit of randomisation and analysis, rather than individual BRONJ sites (Jull 2015).
- Allocation concealment should be carried out and described in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
- Blinding of participants or personnel (preferably both) should be done. While it may be very difficult to blind participants and medical professionals with regard to surgical interventions, as well as to certain aspects of minimally invasive conservative management (such as wound exudate removal, or necrotic tissue debridement), it is possible to blind outcome assessors, or to use photography and computer programmes to measure wound size. The methods used for blinding the outcome assessors should be described providing information to whether the proposed blinding was effective.
- Common, quantifiable and clinically relevant endpoints (time to complete wound healing, pain, treatment acceptability and participant satisfaction), including objective measurements if possible, should always be used. When continuous or categorical data are synthesised in binary outcomes, the procedure should be clearly described and justified.
- Research must adopt a survival approach for the analysis of time-to-event data, such as time to healing.
- A sufficiently long follow-up period of at least six months is essential if treatment effects on indolent, often long-standing BRONJ sites are to be detected. This can be difficult in people with cancer with short life expectancy.
- When working with people with cancer, attrition bias can weaken treatment protocols. The completeness of outcome

data for each main outcome, including attrition and exclusions from the analysis must be fully described.

- A systematic collecting and thorough reporting of adverse events is required. Structured questionnaires should be designed with a standardised terminology such as MedDRA (Medical Dictionary for Regulatory Activities).
- An estimation of costs should complete the clinical evaluation of treatments.

Apart from the above general recommendations, the following recommendations are specific for multimodal treatment modalities.

- Studies should be clearly presented as being multimodal that is multicomponent and multilevel interventions. The putative underlying mechanisms of action of combined interventions, the elements identified as the "active" intervention of this combined healthcare programme, and the factors that mediate and moderate its effectiveness should be described as precisely as possible. The following two examples illustrate this general principal and were weaknesses we found in actual studies on BRONJ treatment: in a study on the distinctive role of teriparatide on intractable BRONJ, all participants received "conventional care with or without sequestrectomies" but no description of this management (e.g. which antibiotics were given, at which dose and duration) and which participants underwent surgery was available. Another example could be when a multicentric study offers a certain treatment to all participants but follow-up is entrusted to different local healthcare settings to avoid long-distance travelling to sick participants, the effect of the setting (in which the follow-up care is given), as a contextual factor, should also be explored and described.
- Investigators planning complex interventions should include a graphical description of the important elements and relationships between the different components of the management strategy.
- A means to bypass the problems associated with multimodal intervention studies, especially when exploring the efficacy of new treatment modalities, could be to standardise the conservative care and the surgery in order to show the efficacy of the added intervention only.
- Multimodal studies should be built as to include multiple treatment arms, with stratification by BRONJ staging and participant co-morbidities.

Such research can only be accomplished by multicentric collaboration or referral to a single designated specialised centre with a very large geographic recruitment. In these conditions, randomised controlled trials exploring single modalities are more simple to design and could bring clearer answers but are farther from the (complex) clinical reality ([Petticrew 2013](#)).

Important research questions

There is currently no 'gold standard' of treatment for BRONJ. Three broad categories of interventions have been described: classical conservative wound healing management, surgery and "add-on" adjuvant treatments.

Conservative treatment

Classical 'wound-healing' conservative management mainly implies minimising environmental factors that are known to impair tissue healing and fighting infection. In BRONJ treatment, this includes promoting oral hygiene, using topical treatments ('mouth rinses', disinfectant or not) and systemic anti-infective therapy. Many aspects of these conservative treatments would be interesting to research.

We have found few data on which antibiotics are given, at what dose, by which route, for how long and to which participants. Comparisons of the effectiveness of various antibiotics and their risks are mostly lacking.

How important is stopping bisphosphonates once BRONJ is present in view of the long "half-life" of these drugs?

No-one appears to have made an inventory of the various mouth rinses used throughout the world and how they are applied under such commonly used terms as 'good oral hygiene' or 'standard conservative management' ([Fernandez 2012](#)). We do not know whether disinfectant mouth rinses are better than saline mouthwashes or just frequent rinses with tap water for improving the oral status of the mouth. Regardless of the liquid solution used, is the volume or temperature of the mouth rinse important? We do not know how often people use them at home. Should it be done daily? Less or more?

As for antifungal treatments, are they formulated simply as mouth rinses? Are they swallowed? Which ones are prescribed? How do they compare? When should they be prescribed? For how long?

Is nutritional state an important factor to promote healing of BRONJ? Many people have cancer or are elderly, or both, and the mouth lesion can in itself impair adequate feeding either because of the pain, or the dysguesia or through loss of appetite. How do well-nourished people with BRONJ compare to malnourished people with BRONJ?

Moreover, does immunosuppression state make a difference to the BRONJ healing outcome?

Surgical techniques

Surgery has been defined as a medical speciality that uses operative manual and instrumental techniques. Timing, type of participants, type of procedure, degree of invasiveness and instruments used are all differentiating features of surgical operations. Most publications do not give sufficient detail on the procedures used for other surgeons to reproduce the technique.

Very broadly, answers to such basic questions as the following could be useful.

- Is it better to operate early or later? Should surgery be reserved for cases failing conservative management?
- Do people who receive preoperative anti-infective preparation do better than those who do not?
- Does the type of anaesthesia or analgesia affect outcome?
- When is debridement sufficient? How long should one wait for spontaneous extrusion of the diseased bone (sequestrum)?
- As in other types of resective oral surgery, do nerves and other tissue parts need particular care? ([Coulthard 2014](#)).

- Should surgeons endeavour to remove only BRONJ-affected bone or can more extensive removal of bone facilitate prosthetic reconstruction of the jaw and healing?
- What instruments should be used? Does laser-assisted or fluorescent-assisted surgery improve the outcome? If so, what protocols are effective?
- Does perioperative drainage, placement of drains or delayed closure affect the incidence of bleeding, swelling, pain or infection?
- How to best close the surgical site (flaps, types of sutures)?
- What is the best treatment for fistulae or other complications (sinus drainage)?

Innovative non-surgical adjuvant treatments

The following treatments have been used as adjuvant treatments in people with BRONJ:

- hyperbaric oxygen therapy;
- pentoxifylline and tocopherol (vitamin E);
- ozone therapy;
- low level laser therapy for biostimulation, pain relief, anti-inflammatory treatment (erbium-doped yttrium aluminium garnet (Er:YAG); neodymium-doped yttrium aluminium garnet (Nd:YAG), natrium-doped yttrium aluminium perovskite (Nd:YAP), etc.);
- platelet-rich plasma;
- parathyroid hormone and teriparatide;
- bone morphogenetic protein.

Researchers designing trials for adjuvant treatments should follow the recommendations for multimodal treatments as described above.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Freiberger 2012

Methods	Interventional, prospective, unblinded, randomised controlled trial
Participants	<p>133 participants assessed; 49 consented (84 excluded or declined to participate); 27 control (standard care), 22 experimental (HBO and standard care)</p> <p>Outpatients (Duke referral area of central North Carolina and participants recruited through internet)/university medical centre; USA</p> <p>Mean age: control group 66.3 years/HBO group 66.1 years</p> <p>Sex: control group 55.6% female/HBO group 59.1% female</p> <p>Condition treated with bisphosphonates: multiple myeloma (39.6% of total sample), breast cancer (25% of total sample), osteoporosis (14.6% of total sample), other indication (20.4% of total sample)</p>
Interventions	<p>Group 1: standard care defined as surgery, antibiotics and oral rinses as needed at discretion of oral-maxillofacial surgeon</p> <p>Group 2: standard care + HBO (2.0 atmospheres for 2 hours twice a day for 40 treatments)</p>
Outcomes	<p>4 outcomes reported:</p> <ul style="list-style-type: none"> change from baseline in oral lesion size and number (translated into a binary outcome variable, i.e. healed or improved vs. unchanged or worse) time to improvement pain quality of life <p>2 to be reported in a separate publication:</p> <ul style="list-style-type: none"> serum measurements of bone turnover bone turnover signalling <p>Time points for main outcome of healing were at 0, 3, 6, 12, 18 and 24 months (or at last contact)</p> <p>Pain levels were assessed weekly through telephone or email contact from study co-ordinator</p> <p>Quality of life was assessed at baseline and 6 months</p>

Freiberger 2012 (Continued)

Notes Participants were enrolled from July 2006 to December 2010. Study duration was not mentioned but participants were followed-up for 2 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of randomisation sequence not reported
Allocation concealment (selection bias)	Low risk	Concealment of allocation using opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and staff not blinded to therapy
Blinding of outcome assessment (detection bias) All outcomes	High risk	In regards to change from baseline in oral lesion size and number, the oral-maxillofacial surgeon was not told the participants' assignments before the initial staging examination. On subsequent assessments, the evaluators were not blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	The attrition rate was very high. At the 12-month evaluation, 50% of participants were lost to follow-up and at 18 months, only about 20% of participants were available for analysis. 13/49 participants did not complete all follow-up visits. At the end of the study, 15/49 participants had died (3 early deaths). The missing outcome data were not balanced between the intervention groups (at the end of the follow-up period, there were 6 participants in the standard care group and 12 participants in the standard care + HBO group)
Selective reporting (reporting bias)	Low risk	All collected clinical data mentioned in ClinicalTrials.gov were reported in the publication. However, some laboratory results (serum measurements of bone turnover and bone turnover signalling) were withheld. These were not primary outcomes and the authors clearly stated that they would be reported in a separate publication
Other bias	High risk	5 cross-overs from standard care group to standard care + HBO group (especially 3 late cross-overs) and 2 cross-over from standard care + HBO to standard care group. Analysis of data was done by treatment group and not by intention-to-treat

HBO: hyperbaric oxygen therapy.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Atalay 2011	Not an RCT
Gasparini 2010	Not an RCT
Graziani 2012	Not an RCT
	Duplicated subject-per-report bias

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review)

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Study	Reason for exclusion
Kim 2014	Not an RCT
Lee 2014	Not an RCT
Manfredi 2011	Not an RCT Duplicated subject-per-report bias
Pelaz 2014	Not an RCT
Vescovi 2007	Not an RCT Duplicated subject-per-report bias
Vescovi 2010	Not an RCT Duplicated subject-per-report bias
Vescovi 2012a	Not an RCT Duplicated subject-per-report bias
Vescovi 2012b	Not an RCT Duplicated subject-per-report bias
Vescovi 2014	Not an RCT Duplicated subject-per-report bias

RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

[ACTRN12612000950864](#)

Trial name or title	Does Teriparatide Reverse Osteonecrosis of the Jaw in Patients Treated with Either Bisphosphonates or Denosumab? A Randomised, Controlled Trial
Methods	Prospective, randomised, double-blind, placebo-controlled study
Participants	Men and women 18 years or older. Target sample size = 68 Exclusion criteria: <ul style="list-style-type: none"> • previous craniofacial radiotherapy • pregnancy • hypercalcaemia or pre-existing primary hyperparathyroidism • severe renal impairment (eGFR < 30) • Known metabolic bone disease, excluding osteoporosis or metastatic bone disease • Growth hormone deficiency • Secondary hyperparathyroidism with parathyroid hormone greater than 2-fold above upper limit of reference range
Interventions	Group 1: subcutaneous teriparatide injections (20 µg/day) + calcium (600 mg/day tablet) + vitamin D (1000 IU/day tablet) supplementation

ACTRN12612000950864 (Continued)

Group 2: placebo saline injections + calcium (600 mg/day tablet) + vitamin D (1000 IU/day tablet) supplementation for 8 weeks

Outcomes	<p>Primary outcomes: clinical staging of osteonecrosis of the jaw and radiological staging of osteonecrosis of the jaw, as assessed by cone beam CT</p> <p>Secondary outcomes: bone formation and resorption markers (P1NP, beta-CTX), jaw osteoblast activity, as measured by NaF-PET imaging and quality of life, as measured by Oral Health Impact Profile 14 questionnaire</p> <p>1-year follow-up</p>
Starting date	11 September 2012
Contact information	peterre@unimelb.edu.au
Notes	<p>We contacted the trial author (Peter Ebeling) and he responded to let us know that the trial will be completed in April 2016 and the data submitted for publication in second half of 2016</p> <p>Conducted in University of Melbourne, Australia</p>

UMIN000009132

Trial name or title	Study to the Effect of Teriparatide Formulation Forteo versus Teribon on Bisphosphonate-Related Osteonecrosis of the Jaw in Osteoporosis Patients
Methods	Parallel, randomised, open study
Participants	<p>Women, aged ≥ 20 years; target sample size = 15</p> <p>Inclusion criteria: female outpatients with bisphosphonate-related osteonecrosis of the jaw who require continued treatment for osteoporosis and whose stage of bisphosphonate-related osteonecrosis of the jaw is ≥ 2. Signed informed consent forms must be obtained</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • hypercalcaemic disorders • potential risk of osteosarcoma • people with Paget's disease of bone • unexplained elevations of alkaline phosphatase • young adults with open epiphyses • people with prior external beam or implant radiation involving the skeleton • people with bone metastases, history of skeletal malignancies • metabolic bone diseases other than osteoporosis • pregnancy or women with suspected pregnancy • people with hypersensitivity to teriparatide or to any of its excipients • serious cardiac disease, serious hepatic disorder, renal disease • use of active vitamin D3 or digoxin • no informed consent • unsuitability for the trial based on clinical judgement
Interventions	Teriparatide as Forteo® vs. teriparatide as Teribone®
Outcomes	Efficacy and safety (pain and bone formation)

UMIN000009132 (Continued)

Starting date	28 August 2012
Contact information	yumiko@med.kagawa-u.ac.jp
Notes	We contacted the trial author (Yumiko Ohbayashi) who confirmed that the study still has another 1-2 years to run Conducted in Kagawa university in Japan

CT: computed tomography; eGFR: estimated glomerular filtration rate; NaF-PET: 18F-sodium fluoride positron emission tomography.

ADDITIONAL TABLES

Table 1. Effects of interventions - healing

Time point	Improved HBO	Total HBO	Improved standard care	Total standard care	RR (95% CI)
3 months	17	25	7	20	1.94 (1.01 to 3.74)
6 months	16	23	9	17	1.31 (0.78 to 2.22)
12 months	11	15	4	9	1.65 (0.75 to 3.64)
18 months	7	12	2	6	1.75 (0.51 to 5.98)
Last contact	17	25	8	21	1.78 (0.97 to 3.28)
Time point	Healed HBO	Total HBO	Healed standard care	Total standard care	RR (95% CI)
3 months	9	25	2	20	3.60 (0.87 to 14.82)
6 months	9	23	7	17	0.95 (0.44 to 2.04)
12 months	6	15	3	9	1.20 (0.39 to 3.65)
18 months	4	12	2	6	1.00 (0.25 to 4.00)
Last contact	13	25	7	21	1.56 (0.77 to 3.18)

CI: confidence interval; HBO: hyperbaric oxygen therapy; RR: risk ratio.

APPENDICES

Appendix 1. MEDLINE via Ovid search strategy

1. Osteonecrosis/
2. (osteonecro\$ or "bone necrosis").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. osteochemonecro\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. or/1-3
5. exp Jaw/
6. Jaw Diseases/ci [Chemically Induced]

7. Alveolar Bone Loss/ci [Chemically Induced]
8. (jaw\$ or jawbone\$ or mandib\$ or maxill\$ or (alveolar adj4 bone)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9. or/5-8
- 10.4 and 9
- 11.exp Diphosphonates/
- 12.(diphosphonate\$ or bisphosphonate\$ or aminobisphosphonate\$ or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 13.("etidronate disodium" or didronel or "clodronate disodium" or Bonefos or "Tiludronate disodium" or Skelid or Fosamax or Aredia or Actonel or Zometa or Boniva).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 14.or/11-13
- 15.10 and 14

The searches were done without an RCT filter up to April 2013, a top-up search was performed with the RCT filter below in January 2015.

The Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011].

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 2. The Cochrane Oral Health Group Trials Register/the Cochrane Breast Cancer Group Trials Register search strategy

(osteonecros* or "bone necrosis" or osteochemonecros*)

Appendix 3. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

- #1 MeSH descriptor Osteonecrosis this term only
- #2 (osteonecro* in All Text or "bone necrosis" in All Text)
- #3 osteochemonecro* in All Text
- #4 (#1 or #2 or #3)
- #5 MeSH descriptor Jaw explode all trees
- #6 MeSH descriptor Jaw Diseases this term only
- #7 MeSH descriptor Alveolar Bone Loss this term only
- #8 (alveolar in All Text near/4 bone* in All Text)
- #9 (jaw* in All Text or mandibl* in All Text or maxill* in All Text)
- #10 (#5 or #6 or #7 or #8 or #9)
- #11 (#4 and #10)
- #12 MeSH descriptor Diphosphonates explode all trees
- #13 (diphosphonate* in All Text or bisphosphonate* in All Text or aminobisphosphonate* in All Text or alendronate in All Text or risedronate in All Text or pamidronate in All Text or "zoledronic acid" in All Text or ibandronate in All Text)
- #14 ("etidronate disodium" in All Text or didronel in All Text or "clodronate disodium" in All Text or Bonefos in All Text or "Tiludronate disodium" in All Text or Skelid in All Text or Fosamax in All Text or Aredia in All Text or Actonel in All Text or Zometa in All Text or Boniva in All Text)
- #15 (#12 or #13 or #14)
- #16 (#11 and #15)

Appendix 4. EMBASE (Ovid) search strategy

1. Osteonecrosis/

2. (osteonecro\$ or "bone necrosis").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. osteochemonecro\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. or/1-3
5. exp Jaw/
6. Jaw Diseases/
7. Alveolar Bone Loss/
8. (jaw\$ or jawbone\$ or mandib\$ or maxill\$ or (alveolar adj4 bone)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9. or/5-8
- 10.4 and 9
- 11.exp Diphosphonates/
- 12.(diphosphonate\$ or bisphosphonate\$ or aminobisphosphonate\$ or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 13.("etidronate disodium" or didronel or "clodronate disodium" or Bonefos or "Tiludronate disodium" or Skelid or Fosamax or Aredia or Actonel or Zometa or Boniva).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 14.or/11-13
- 15.10 and 14

The searches were done without an RCT filter up to April 2013, a top-up search was performed with the RCT filter below in January 2015.

1. random\$.ti,ab.
2. factorial\$.ti,ab.
3. (crossover\$ or cross over\$ or cross-over\$).ti,ab.
4. placebo\$.ti,ab.
5. (doubl\$ adj blind\$).ti,ab.
6. (singl\$ adj blind\$).ti,ab.
7. assign\$.ti,ab.
8. allocat\$.ti,ab.
9. volunteer\$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15

Appendix 5. CancerLit (PubMed) search strategy

- #1 Search Osteonecrosis [mh:noexp]
- #2 Search osteonecro* or "bone necrosis"
- #3 Search osteochemonecro*
- #4 Search #1 or #2 or #3
- #5 Search Jaw [mh:exp]
- #6 Search Jaw Diseases [mh:noexp]
- #7 Search Alveolar Bone Loss [mh:noexp]
- #8 Search jaw* or jawbone* or mandib* or maxill*
- #9 Search "alveolar bone"
- #10 Search #5 or #6 or #7 or #8 or #9
- #11 Search Diphosphonates [mh:exp]
- #12 Search diphosphonate* or bisphosphonate* or aminobisphosphonate* or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate
- #13 Search "etidronate disodium" or didronel or "clodronate disodium" or Bonefos or "Tiludronate disodium" or Skelid or Fosamax or Aredia or Actonel or Zometa or Boniva
- #14 Search #11 or #12 or #13
- #15 Search #4 and #10
- #16 Search #14 and #15

The searches were done without an RCT filter up to April 2013, a top-up search was performed with the RCT filter below in January 2015. The Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2009

revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.a of *The Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0.2 [updated September 2009]:

```
#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 drug therapy [sh]
#6 randomly [tiab]
#7 trial [tiab]
#8 groups [tiab]
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 animals [mh] not humans [mh]
#11 #9 NOT #10
```

Appendix 6. CINAHL (EBSCO) search strategy

```
S1 MH "Osteonecrosis"
S2 osteonecro* or "bone necrosis"
S3 osteochemonecro*
S4 S1 or S2 or S3
S5 MH "Jaw+"
S6 MH "Jaw Diseases"
S7 jaw* or jawbone* or mandib* or maxill*
S8 alveolar N4 bone
S9 S5 or S6 or S7 or S8
S10 S4 and S9
S11 MH "Diphosphonates+"
S12 diphosphonate* or bisphosphonate* or aminobisphosphonate* or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate
S13 "etidronate disodium" or didronel or "clodronate disodium" or Bonefos or "Tiludronate disodium" or Skelid or Fosamax or Aredia or Actonel or Zometa or Boniva
S14 S11 or S12 or S13
S15 S10 AND S14
```

The searches were done without an RCT filter up to April 2013, a top-up search was performed with the addition of the Cochrane Oral Health Group filter for identifying RCTs in CINAHL via EBSCO in January 2015:

```
S1 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH Crossover design or MH Factorial Design
S2 TI ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or AB ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or SU ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study")
S3 TI random* or AB random*
S4 AB "latin square" or TI "latin square"
S5 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)
S6 MH Placebos
S7 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)
S8 TI blind* or AB mask* or AB blind* or TI mask*
S9 S7 and S8
S10 TI Placebo* or AB Placebo* or SU Placebo*
S11 MH Clinical Trials
S12 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)
S13 S1 or S2 or S3 or S4 or S5 or S6 or S9 or S10 or S11 or S12
```

Appendix 7. AMED (Ovid) search strategy

```
1. Osteonecrosis/
2. (osteonecro$ or "bone necrosis").mp.
3. osteochemonecro$.mp.
4. or/1-3
5. exp Jaw/
6. Jaw Diseases/
```

7. Alveolar Bone Loss/
8. (jaw\$ or jawbone\$ or mandib\$ or maxill\$ or (alveolar adj4 bone)).mp.
9. or/5-8
- 10.4 and 9
- 11.(diphosphonate\$ or bisphosphonate\$ or aminobisphosphonate\$ or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate).mp.
- 12.("etidronate disodium" or didronel or "clodronate disodium" or Bonefos or "Tiludronate disodium" or Skelid or Fosamax or Aredia or Actonel or Zometa or Boniva).mp.
- 13.11 or 12
- 14.10 and 13

Appendix 8. Database of Randomised Controlled Trials in Hyperbaric Medicine

osteonecrosis OR bisphosphonates

Appendix 9. US National Institutes of Health Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform search strategy

osteonecrosis AND jaw AND bisphosphonates

Appendix 10. Grey literature searches

osteonecrosis OR osteoporosis OR bisphosphonates

WHAT'S NEW

Date	Event	Description
29 February 2016	Amended	Minor edit to Summary of findings table

HISTORY

Protocol first published: Issue 4, 2010

Review first published: Issue 2, 2016

Date	Event	Description
13 April 2010	Amended	Minor edits to protocol.

CONTRIBUTIONS OF AUTHORS

Co-ordinated the review: Nicole Vogt (NV).

Developed the protocol: NV, Victoria Rollason (VR), Martin Tramèr (MT).

Wrote the protocol: NV, VR.

Developed the search strategy: NV, VR (with Anne Littlewood (ALi) of the Oral Health Group).

Searched for trials: NV, VR, ALi.

Selected the trials: NV, VR, MT, Laura MacDonald (LM), Tanya Walsh (TW).

Assessed trial for risk of bias: NV, VR, MT.

Assessed quality of the evidence: LM, TW.

Co-ordinated contact with BRONJ experts: Alexandra Laverrière (AL).

Contacted authors of ongoing RCTs: LM

Extracted trial data: NV, VR, MT, AL, LM, TW.

Analysed and interpreted the data: NV, VR, MT, LM, TW.

Wrote Results and Discussion: NV, VR, AL, LM, TW.

Produced 'Summary of findings' table: LM, TW.

Provided clinical perspective, expert advice: MT.

DECLARATIONS OF INTEREST

Victoria Rollason: none known.
Alexandra Laverrière: none known.
Laura MacDonald: none known.
Tanya Walsh: none known.
Martin Tramèr: none known.
Nicole B Vogt-Ferrier: none known.

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- Cochrane Oral Health Group Global Alliance, Other.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review from *Interventions for treating osteonecrosis of the jaw associated with bisphosphonates* (Vogt-Ferrier 2010) to *Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ)*.

We edited the Background to describe the intervention more thoroughly, particularly current practice and how the intervention might work.

We decided not to include studies other than randomised controlled trials in the review. We modified the sections that referred to non-randomised studies (objectives, types of studies and assessment of risk of bias) accordingly. We modified the search strategy, adding an "RCT only" filter from April 2013 to December 2015.

We added quality of life as a secondary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

*Standard of Care; Anti-Bacterial Agents [therapeutic use]; Bisphosphonate-Associated Osteonecrosis of the Jaw [surgery] [*therapy]; Combined Modality Therapy [methods]; Hyperbaric Oxygenation [*methods]; Mouthwashes [therapeutic use]; Pain Measurement; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans