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# United Kingdom nationwide study of avascular necrosis of the jaws including bisphosphonate-related necrosis☆

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**Abstract**

We aimed to record all new patients who presented to departments of oral surgery, oral medicine, and oral and maxillofacial surgery, and to dental hospitals in the UK, with avascular necrosis of the jaws including bisphosphonate-related necrosis (BRONJ) over a 2-year period (1 June 2009–31 May 2011). They were eligible irrespective of age, cause, or coexisting conditions. Data on incidence, clinical characteristics, risk factors, and coexisting conditions were collected. A total of 383 cases were registered: 369 were described as BRONJ, 5 as avascular necrosis, and 9 were unknown. Bisphosphonates had been given orally in 207 (56%), intravenously in 125 (34%), both orally and intravenously in 27 (7%), and was unknown in 9 (2%); one had been given denosumab. The main risk factor was dental extraction, and the mandible was commonly affected. The median duration of administration until onset of BRONJ was 3 years in those treated intravenously and 4 years in those treated orally. Levels of engagement with the study varied between regions, and extrapolation from the 2 most involved (Merseyside and Northern Ireland) found around 8.2–12.8 cases/million/year, which is 508–793 patients/year across the UK. To our knowledge this is one of the first studies to estimate national rates of BRONJ. It confirms that the risk and incidence are low. With changes in trends for antiresorptive bone medication, and increasing numbers of elderly people, it would be useful to repeat the registration in the future.


*Keywords:* Bisphosphonates; Jaw necrosis; Pharmacovigilance; Cancer; Osteoporosis; National incidence

## Introduction

Bisphosphonates are used in the management of osteoporosis (treatment and prophylaxis), Paget's disease, malignancies involving bone such as myeloma, breast cancer, and prostate cancer, and tumour-induced hypercalcaemia.[1] Their efficacy in the treatment and prevention of the skeletal complications associated with these conditions has made a considerable difference to patients and is responsible for their widespread use. However, bisphosphonate-related osteonecrosis of the jaw (BRONJ) has emerged as a serious complication in a small number of patients with the first cases being reported in 2003.[2] Various terms have been used to describe the condition, the most recent of which is antiresorptive osteonecrosis of the jaw (ARONJ), but as BRONJ was the term used from the outset of this study, it will be used in this paper.

The paucity of data from well-designed studies does not allow precise estimation of the number of patients exposed

☆ Details of 327 cases were submitted to the Pharmacovigilance division of the Medicines and Healthcare products Regulatory Agency (MHRA), the UK medicines regulator, for assessment as part of their role ensuring the safety, quality and efficacy of medicines.

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to bisphosphonates,[3] and most of those published are either cohort studies or case series based at single centres. Many early reports of BRONJ concerned patients with cancer who were given the aminobisphosphonates, zoledronic acid and disodium pamidronate intravenously.[4–6] However, the number of cases of BRONJ in patients who take bisphosphonates orally (mainly to treat and prevent postmenopausal osteoporosis) is increasing.[7–9] Osteoporosis affects around 3 million postmenopausal women in the UK, and in over one million of them the diagnosis is confirmed.[10] It is estimated that drugs are used in 10%–20% of cases.[11]

The mean incidence of osteonecrosis of the jaw has been calculated as 7% (range 0%–27.5%) for bisphosphonates given intravenously, and 0.12% (range 0%–4.3%) for those taken orally.[12] Events that seem to precipitate BRONJ include a history of trauma (extractions), dental surgery, or dental infection,[13] and the extent and duration of exposure to bisphosphonates given intravenously seem to correlate with the risk of developing the condition.[14] The cumulative risk from long-term oral use is unknown. Systemic risk factors seem to include underlying malignant disease (breast or prostate cancer, multiple myeloma), and coexisting conditions such as rheumatoid arthritis and diabetes. They also include medications such as steroids, and immunosuppressive (such as methotrexate) and antiangiogenic drugs.[15]

Apart from nationwide, retrospective, questionnaire-based studies in Japan,[16] Sweden,[17] Canada,[18] and the USA,[19] and cases reported to medical agencies in the 4 Nordic countries,[20] we know of no published studies that adequately report the incidence of avascular necrosis, specifically BRONJ, in a general population. Although risk factors have been proposed, previous work has been limited to selected groups, and recommendations have been based on them.[21,22] A UK nationwide study would provide a better understanding of incidence, risk factors, and case management.

We aimed to identify and describe the characteristics of all new referrals with avascular necrosis of the jaw, including BRONJ, to departments of oral surgery, oral medicine, oral and maxillofacial surgery, and to dental hospitals in England, Wales, Scotland, and Northern Ireland, over a 2-year period from 1 June 2009 to 31 May 2011. We also aimed to estimate the national incidence.

## Methods

All patients who first presented with avascular necrosis of any cause, including BRONJ, between 1 June 2009 and 31 May 2011 were eligible irrespective of age or coexisting conditions.

To distinguish avascular necrosis and BRONJ from other conditions of delayed healing, we adapted the working definition of BRONJ from that used by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[15]: "Patients may be considered to have avascular ONJ if the first two characteristics are present: (1) exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and (2) no history of radiation therapy to the jaws, and if there is (3) current or previous treatment with a bisphosphonate, then the patient is considered as having BRONJ".

The project team worked with the Faculty of General Dental Practice of the Royal College of Surgeons of England, the British Association of Oral and Maxillofacial Surgeons (BAOMS), the British Society of Oral Medicine Faculty of Dental Surgery, the British Association of Oral Surgeons, and the Association of British Academic Oral and Maxillofacial Surgeons. All departments of oral and maxillofacial surgery in England, Wales, Scotland, and Northern Ireland were approached, and designated clinical leads were identified at each site. Oral and maxillofacial departments were asked to link with university-based departments of oral medicine and oral surgery to identify cases. Awareness of the project was raised through the BAOMS and the Faculty of General Dental Practice, the Royal College of Surgeons of England, and through national meetings, local audits, journals, and newsletters.

This was a longitudinal case series study the cases for which were collected prospectively over a 2-year period. Data included age, sex, date first seen, details of the condition that indicated prescription of bisphosphonate, the one prescribed and the route of administration, and prescribing and past medical history. Coexisting conditions and medication, alcohol and smoking status, the initiating event, site of BRONJ, and oral health, were also included. Details were collected at a local level and data entry was facilitated by a dedicated web-tool (SNAP).[23] Initially, patients could be registered with minimum data on a paper-based form. A paper-based pilot was run in the Merseyside region in autumn 2008, and the web-based registration and data collection system was piloted in spring 2009.

### *Statistical method*

SPSS Statistics for Windows (version 19.0, IBM Corp, Armonk, USA) was used for data cleaning and analysis. Uniformity of case ascertainment over time was tested with chi square goodness of fit. Fisher's exact test was used to compare age groups (under and over 65 years) regarding the oral-only route. The Mann–Whitney test was used to compare intravenous and oral routes by age and area affected.

We used population estimates for 2009 to calculate incidence.[24] The first, which were based on the catchment of strategic health authorities (SHA) in England, were calculated from admissions from 2006/07 to 2008/09, and 2009 mid-year population estimates from the Office for National Statistics, using the proportional flow method. The second, which were mid-year population estimates for 2009 based on residents within local government boundaries of the UK, enabled the resident population for the "Merseyside" patch to be compiled. We computed 95% (exact Poisson) confidence