Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
Bobba *et al.* (2006)[112]	MEDLINE 1975 to 2006 14 studies in alendronate, eight studies in risedronate, ten studies in ibandronate and nine studies in zoledronate. RCTs and observational studies were included	Not reported	Alendronate, ibandronate, risedronate, zoledronate	Data not pooled	The authors concluded that the adverse events associated with alendronate, risedronate and oral ibandronate are minimal. However, zoledronate may be compromised by renal toxicity. Myalgias and arthralgias are evident in the acute phase following i.v. administration
Crandall (2001)[113]	MEDLINE 1996 to 2001 9 RCTs and 7 clinical trials	Postmenopausal osteoporosis, Paget's disease, participants with breast cancer and participants taking glucocorticoids	Risedronate	Data not pooled	Across six RCTs of risedronate for any condition, safety data indicated that risedronate is similar to placebo and does not include any notable upper GI adverse event rate.
Kherani, Papaioannou and Adachi (2002)[114]	Not reported Pivotal trials	Postmenopausal osteoporosis	Alendronate, risedronate	RR of discontinuing treatment with alendronate, 1.15 (95%CI 0.93 to 1.42) RR of discontinuing treatment with risedronate, 0.94 (95%CI 0.80 to 1.10)	Both alendronate and risedronate studies demonstrate similar adverse event rates between placebo and active treatment.

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Lloyd-Jones 2006[116]	(Medline, Embase, Cinahl, Biosis, Cochrane Central Register of Controlled Trials, Science Citation Index, Social Sciences Citation Index) to April 2006 34 studies	Not reported	Alendronate, risedronate	Data not pooled	UK prescription event monitoring studies suggest that therapy with daily alendronate or risedronate is associated with a high level of reporting of a number of conditions in the first month of therapy, particularly those affecting the upper gastrointestinal tract
Umland and Boyce (2001)[115]	MEDLINE 1966 to 2000 Clinical studies and review articles	Osteoporosis and Paget's disease	Risedronate	Data not pooled	Risedronate has been associated with a lower incidence of gastric ulcers than alendronate. However, that adverse events associated with risedronate are generally comparable to those observed with placebo in most clinical trials
Krueger *et al.* (2007)[117]	MEDLINE 1966 to 2007 11 case reports and 26 case series studies	Some studies in osteoporosis, others not reported	Mainly zoledronate	Data not pooled	Intravenous bisphosphonates, especially zoledronate, are more likely to predispose patients to osteonecrosis of the jaw. However, in addition to bisphosphonate use, there appear to be several other factors involved in the development of osteonecrosis of the jaw. Other risk factors noted from the included studies were dental extraction or trauma to the jaw exposing part of the

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					bone
Van den Wyngaert, Huizing and Vermorken (2006)[118]	MEDLINE 1966 to 2005 22 studies based on retrospective chart reviews without control,	Three studies included patients with osteoporosis	Zoledronate	Data not pooled	Across the studies, 69.3% of patients had undergone a dental extraction prior to the development of osteonecrosis. This would confirm the importance of trauma in the initiation of the disease.
Woo, Hellstein and Kalmar (2006)[119]	MEDLINE 1966 to 2006 29 case reports	85% of affected patients had multiple myeloma or metastatic breast cancer, and 4% had osteoporosis	Zoledronate, alendronate	Data not pooled	The prevalence of osteonecrosis in patients with cancer is 6% to 10% and the prevalence in those taking alendronate for osteoporosis is unknown. More than half of all cases (60%) occur after dentoalveolar surgery, and the remaining 40% are probably related to infection, denture trauma, or other physical trauma
Lee *et al.* (2014)[120]	MEDLINE, EMBASE to 2012 12 cohort and case-control studies	Non-cancer patients	Oral and i.v. administered bisphosphonates	Use of BPs was associated with a significantly increased risk of ONJ or ON of other sites [odds ratio (OR) 2.32; 95 % CI 1.38–3.91; I2=91 %]. The summary OR was 2.91 (95 % CI 1.62–5.22; I 2=85.9 %) for adjusted studies. Use	Bisphosphonates in non-cancer patients is associated with a substantial risk for jaw osteonecrosis and that patients receiving i.v. bisphosphonates are at highest risk

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				of BPs was associated with higher risk on ONJ (OR 2.57; 95 % CI 1.37–4.84; I 2=92.2 %) than ON of other sites (OR 1.79; 95 % CI 0.71–4.47; I 2=83.3 %). Meta-regression analysis did not find design characteristics or outcome definitions to be significant sources of heterogeneity	
Giusti, Hamdy and Papapoulos (2010)[121]	PubMed to 2012 27 case series or case reports	Women treated with a bisphosphonate at a dosing regimen used for the prevention or treatment of osteoporosis	In most cases, the bisphosphonate was alendronate,	Data not pooled	The analysis allowed the clinical identification of patients at risk of developing atypical fractures. However, that long-term bisphosphonate therapy is not a prerequisite for development of atypical fractures. Moreover, the use of glucocorticoids and proton pump inhibitors are important risk factors
Gedmintas, Solomon and Kim (2013)[122]	MEDLINE and EMBASE databases 1990 to 2012 Five case-control and six cohort studies	Mainly women	mainly alendronate but also ibandronate, risedronate, zoledronate	Bisphosphonate exposure was associated with an increased risk of subtrochanteric, femoral shaft, and	There is an increased risk of atypical fracture among bisphosphonate users. However, atypical fractures are rare events even in bisphosphonate users.

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
				AFF, with adjusted RR of 1.70 (95% confidence interval [CI], 1.22–2.37). studies examining at least 5 years of bisphosphonate use showed adjusted RR of 1.62 (95% CI, 1.29–2.04).	
Andrici, Tio and Eslick (2012)[123]	MEDLINE, PubMed, EMBASE to 2013 Seven cohort or case-control studies	Any who had filed a prescription for any antiresorptive drug	Any bisphosphonate	odds ratio of 1.74 (95%CI, 1.19 to2.55)	The results suggest a possible association between oral bisphosphonates and oesophageal cancer, which was increased with a longer exposure period. An increased risk was observed for Etidronate, but not Alendronate
Sun *et al.* (2013)[124]	Four cohort studies and three case control studies	Not reported	Alendronate was the main bisphosphonate	Pooled relative risk (RR) 1.23, 95 % CI 0.79–1.92] and case–control studies [pooled odds ratio (OR) 1.24, 95 % CI 0.98–1.57] secondary analysis, no significant increased risk of oesophageal cancer was found in alendronate users (pooled RR 1.08, 95 % CI 0.67–1.75 in	Bisphosphonate treatment was not significantly associated with excess risk of oesophageal cancer

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
				cohort studies; pooled OR 1.16, 95 % CI 0.82–1.63 in case–control studies)	
Loke, Jeevanantham and Singh (2009)[125]	MEDLINE to 2008 Eleven studies including nine RCTs	Patients with osteoporosis or fractures	Alendronate, risedronate, zoledronate	Bisphosphonates significantly increased risk of serious adverse events for atrial fibrillation compared to placebo (OR 1.47, 95% CI 1.01 to 2.14; nine RCTs). One case-control study found that patients with atrial fibrillation were more likely to have used bisphosphonates than control patients (adjusted OR 1.86, 95% CI 1.09 to 3.15, I =46%). The second case-control study found no association	Bisphosphonates were associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents precluded any definitive conclusions with respect to risk