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Bisphosphonate Agents for the Management of Pain Secondary to Bone Metastases: A Systematic Review of Effectiveness and Safety

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Bisphosphonate Agents for the Management of Pain Secondary to Bone Metastases: A Systematic Review of Effectiveness and Safety

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Authorship

Rebecca Wong was the author of the Cochrane review published on this topic. She was responsible for the conduct of protocol drafting; article selection; data collection; interpretation of the results; and drafting and finalizing the report.

Vijay Shukla co-authored the protocol; performed article selection; performed data extraction with Dr. Wong; participated in the interpretation of results; and participated in drafting and finalizing the report.

Phil Wiffen was the co-author of the Cochrane review published on this topic. He contributed to protocol drafting; article selection; interpretation of results; and drafting and finalizing the report.

Shaila Mensinkai was responsible for the design and execution of the literature search strategies, for writing the methods section and associated appendix for literature searching and for verifying and formatting bibliographic references.

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Conflicts of Interest

R. Wong, V. Shukla, S. Mensinkai and P. Wiffen reported no conflicts of interest.

REPORT *IN BRIEF*

January 2004

Bisphosphonate drugs to manage pain secondary to bone metastases

Technology Name
The bisphosphonates etidronate, clodronate, pamidronate, zoledronate and ibandronate are examined.

Disease/Condition
Primary cancers such as breast, prostate and multiple myeloma can metastasize into the bone. The most common symptom is pain, which may be difficult to control.

Technology Description
Bisphosphonates inhibit the activity of bone-destroying cells called osteoclasts. Different bisphosphonates inhibit bone resorption initiated by osteoclasts with different intensity. The loss of bone can lead to pain and other complications such as fractures or compression of the spinal cord. Some bisphosphonates are available orally and others intravenously, affecting the clinical setting where they can be used. Three generations of bisphosphonates have received Health Canada's approval for different clinical indications.

The Issue
Although no bisphosphonate is approved in Canada for pain relief in cancer patients with bone metastases, they are being used to treat patients with bone pain. The extent that bisphosphonates are used to relieve bone pain and the cost involved are unknown.

Assessment Objectives
To determine the effectiveness and safety of specific bisphosphonates in the management of pain for patients with bone metastases, compared to placebo or other analgesic alternatives.

Methodology
An extensive literature search identified randomized controlled trials of patients with bone metastases, where the use of bisphosphonates were compared to placebo, no treatment, other bisphosphonates or other treatments. The main outcome measure was the proportion of patients with pain relief in the short term (within 12 weeks). Ultimately, 50 articles were found including studies of mixed quality.

Conclusions
- Bisphosphonates modestly reduce pain in patients with bone metastases within 12 weeks of treatment.
- There is no evidence that can be used to determine the most efficacious dosage regimen or the type of bisphosphonate agent to use.
- Bisphosphonates are generally well tolerated, nausea and vomiting being the most common adverse effects.
- The circumstances under which bisphosphonates should be used remain unclear. This review supports the current practice of using bisphosphonates for pain relief in palliative care or in pain clinics, when other treatments are ineffective. The widespread use of bisphosphonates in patients with mild or localized pain, however, may be inappropriate.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Wong R, Shukla VK, Mensinkai S, Wiffen P. **Bisphosphonate agents for the management of pain secondary to bone metastases: a systematic review of effectiveness and safety.**

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EXECUTIVE SUMMARY

The Issue

The skeleton is a common site for metastatic involvement due to primary cancers such as multiple myeloma and those of the breast and prostate. Pain, which is a common and disabling symptom, is not always easy to control. To manage this pain, there is increasing interest in the use of drugs known as bisphosphonates. The members of the drug group assessed were etidronate, clodronate, pamidronate, zoledronate and ibandronate.

Objectives

This assessment examined the effectiveness and safety of specific bisphosphonate agents, compared with placebo and other analgesics, to manage the pain of bone metastases.

The use of bisphosphonates to prevent skeletal complications is a related but different objective and will not be assessed. Similarly, the duration of treatment is not the objective of the current review.

Methods

An extensive literature search was conducted on MEDLINE®, EMBASE®, Cancerlit, BIOSIS Previews® and Current Contents.® There were no language, publication or date restrictions. Randomized controlled studies were included if they evaluated pain outcome with bisphosphonate treatment compared to placebo, no treatment or active controls. The primary outcome of interest was pain relief. Secondary outcomes included reductions in analgesic use, mean pain scores, mean analgesic scores and adverse effects. Six secondary analyses investigated the impact of different variables on the primary outcome. Data were pooled to provide summary statistics where possible. Odds ratios (ORs) were used for categorical variables and standardized mean scores were used for continuous variables as summary statistics.

Results

The review identified 51 trials, with more than 9,000 patients meeting pre-set selection criteria. The available data (nine trials, N=1,289) showed that at 12 weeks, bisphosphonates provided pain relief in patients with bone metastases, with an odds ratio (OR) 1.87 [95% confidence interval (CI) 1.23 to 2.86].

Secondary analyses of the data found the beneficial effect was preserved even when studies were restricted to those with blinded controls, only patients with pain were admitted to the trials and pain evaluation was restricted to patient-expressed pain scores. Secondary endpoints also support this conclusion, with patients on bisphosphonate regimens requiring significantly fewer analgesics (three trials, N=192) OR 2.37 [95% CI 1.1 to 5.12].

Qualitatively, there was a reduction in mean pain scores and morphine consumption with bisphosphonates. A quantitative measure was impossible since data from standardized pain scores and morphine equivalent consumption could not be pooled. The complexity of measuring pain was a factor that limited the interpretation of results.

There was no observable difference between lower and higher doses of the various bisphosphonates, nor was there any observable difference when pamidronate was compared to clodronate. Zoledronate was not significantly different than pamidronate, although there is a trend to suggest that it is more effective.

Differences in effect for various primary cancer sites or different bisphosphonates could not be identified through subgroup analyses because of the small number of trials. There were also insufficient trials to directly compare bisphosphonates with other therapies. Bisphosphonates were generally well tolerated, with nausea and vomiting being the most commonly reported adverse effect.

None of the bisphosphonates are approved specifically for pain management of bone metastases. Our review makes the assumption that all bisphosphonates are pharmacologically similar in their pain-relieving effect and it is clinically appropriate to pool together results from individual drugs.

Pain is a subjective outcome. Furthermore, the methodology used to define pain relief can vary significantly between studies, thereby affecting trial outcome. While secondary analyses addressed some of these factors, they may have limited statistical power. The clinical relevance of statistically significant differences is discussed by the authors.

There are limited data on the newer bisphosphonates. Data will be incorporated into review updates as part of the collaboration between the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and the Cochrane Collaboration.

Conclusions

- Bisphosphonates were found to be moderately effective in relieving painful bone metastases compared with placebo when patients were assessed at 12 weeks. Prescribers and candidates for this therapy should have realistic expectations of the moderate effect.
- No one drug regimen was found to be superior to another and the effect was not limited to any specific cancer pathology.
- There were no studies with adequate outcomes to allow comparisons of bisphosphonates with therapies such as other analgesic regimens, palliative radiotherapy and palliative chemotherapy.
- The delayed effect (benefit at 12 weeks) and adverse effects should be considered when making treatment choices.

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1 INTRODUCTION

1.1 Background

1.1.1 Disease condition and patient group

The skeleton is a common site for metastatic involvement due to primary cancers such as multiple myeloma, breast cancer and prostate cancer. Other cancers can also lead to skeletal metastases. Pain, which is the most common symptom, can be accompanied by other skeletal complications, including fractures and spinal cord compressions. These complications affect the quality of life of patients with cancer.

The use of bisphosphonate drugs for pain relief is increasingly popular. Studies suggest that pain is reduced for patients receiving bisphosphonates.[1,2] Bisphosphonate drugs may be used to provide pain relief for patients with bone metastases and to prevent skeletal complications. This report focuses on the use of bisphosphonates to provide pain relief. To be beneficial, this effect must be realized in the short term. When bisphosphonates are used to prevent skeletal complications, patients may not have pain and may not have bone metastases. The outcome of interest is the prevention, reduction or delay of skeletal complications (including bone pain).

Bisphosphonates are structural analogues of pyrophosphonates, which are natural components of bone crystal deposition. Side-chain modifications of the pyrophosphonate structure give rise to the different generations of bisphosphonates. With each successive generation, there is increasing potency in the inhibition of osteoclast-mediated bone resorption. Bisphosphonates exert their effects through multiple modes of action. Cancer cells initiate a humoral activity, resulting in an imbalance between osteoclast and osteoblast activities. Bisphosphonates provide physicochemical protection for underlying bone mainly through an affinity to bone. The pain-relieving effect of bisphosphonates in the short term is likely to be mediated by cytokines, while long-term pain reduction may be due to reductions in skeletal events and complications. These mechanisms are poorly understood.

1.1.2 Current clinical practice in Canada

Pain due to metastatic disease is often a symptom that requires careful management for patients with cancer. Analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs and opioids have been indispensable in the management of cancer pain and bone pain. Pain can also be reduced through the use of antineoplastic therapies. Despite the use of increasingly versatile and potent analgesics and palliative antineoplastic therapies such as radiotherapy and chemotherapy, the achievement of adequate pain control may be limited in some situations.

Bisphosphonates have an established role in cancer therapy as the treatment of choice for the management of hypercalcemia.[3] They provide an accepted benefit in the delay of skeletal events for patients with breast cancer [4,5] and multiple myeloma[6] and are part of standard therapy in these situations. Recently, they have been approved for a similar role in patients with prostate cancer. In these clinical contexts, bisphosphonates are used to provide "maintenance therapy" for months.

No bisphosphonate has yet been approved by Health Canada specifically for the management of pain in cancer patients. In Canada, however, the use of bisphosphonates specifically for pain relief occurs in clinical practice for patients with bone pain, typically in oncology centres or home palliative care environments.

1.1.3 Variation in services in Canada

There is no population-based information available to describe variations in the use of bisphosphonates in Canada. The variation in access to bisphosphonates for pain relief is subject to:

- approval by Health Canada for the indication
- clinicians' interpretation of drug effectiveness for the indication
- coverage by the provincial drug formulary
- coverage by the hospital or cancer clinic drug formulary
- coverage by third-party insurers
- unit cost and patients' willingness to pay out of pocket.

Table 1 outlines Health Canada's approved indications for specific bisphosphonates.[7] Ibandronate has not received Health Canada's approval for clinical use and is excluded in Tables 1 to 3.

Table 2 outlines the listings for bisphosphonates in provincial drug formularies.[8]

Table 3 lists the approximate unit cost and cost for a month of therapy, assuming that injections occur every three weeks (q3w) for pamidronate. The costs increase with each successive generation of bisphosphonates.

Table 1: Health Canada's approved indications for specific bisphosphonate agents

Drug	Route	Health Canada Approved Indications
Etidronate	Oral	• Established postmenopausal osteoporosis diagnosed using objective measuring techniques
Clodronate	Oral or intravenous	• Hypercalcemia of malignancy • Osteolysis resulting from bone metastases of malignant tumours (used as an adjunct in management)
Pamidronate	Intravenous	• Tumour-induced hypercalcemia • Conditions associated with increased osteoclastic activity: predominantly lytic bone metastases and multiple myeloma • Symptomatic Paget's disease of bone
Zoledronate	Intravenous	• Tumour-induced hypercalcemia • Complications from bone metastases due to prostate cancer (used with standard antineoplastic therapy)

- Of the indications listed in Table 1, none address the use of bisphosphonates for the management of pain. The interpretation of the indications "osteolysis resulting from bone metastases of malignant tumours" for clodronate, "conditions associated with increased osteoclastic activity" for pamidronate and "complications from bone metastases due to prostate cancer" for zoledronate have been interpreted to include pain relief for patients with bone metastases.
- On an out-patient basis, bisphosphonates can be taken orally (clodronate) or intravenously (IV) through home care or hospital infusion services (clondronate, pamidronate and zoledronate). Subcutaneous routes have been described[9,10] but they are rarely used in practice.

Table 2: Provincial drug formulary listing for bisphosphonate agents

	Etidronate	**Clodronate**	**Pamidronate**	**Zoledronate**
Newfoundland and Labrador				
Quebec				
Ontario (January 2003)	For treatment of Paget's disease For management of hypercalcemia of malignancy	For control and prophylaxis of hypercalcemia of malignancy For treatment of bone metastases in patients with breast cancer For prevention and treatment of osteolytic lesions in patients with multiple myeloma	Not in formulary	Not in formulary
Manitoba	Not in formulary	Not in formulary	Treatment of osteoporosis for patients unable to absorb oral medications Ankylosing spondylitis resistant to conventional treatment	Under review
Saskatchewan (October 2002 to July 2003)	For treatment of symptomatic Paget's disease of bone for six-month period (coverage can be renewed after drug holiday of at least 90 days) For treatment of heterotopic calcification For symptomatic management of bone pain due to cancer in palliative care For treatment of osteoporosis in patients who are intolerant of the calcium in Didrocal®	Not in formulary	For treatment of osteoporosis in patients unable to tolerate oral bisphosphonates	Not in formulary

	Etidronate	**Clodronate**	**Pamidronate**	**Zoledronate**
Alberta	For treatment of Paget's disease and maintenance therapy in treatment of hypercalcemia Requests for treatment of osteoporosis not considered	Not in formulary but cost listed	Not in formulary but cost listed	For treatment of tumour-induced hypercalcemia in patients with documented evidence of intolerance or lack of response to clodronate or pamidronate (special authorization granted for 24 months)
British Columbia	Covered by palliative drug program, but no criteria listed	Covered by palliative drug program, but no criteria listed	Pamidronate disodium will be available as restricted benefit for indication of osteolytic bone metastases Covered by palliative drug program, but no criteria listed	Not in formulary
New Brunswick (December 2002)	Etidronate 200 mg tablets listed as regular benefits, so they can be prescribed for any indication	Clodronate 400 mg tablets listed as regular benefits, so they can be prescribed for any indication	Not in formulary	Not in formulary
Nova Scotia	Listed as full benefit	Covered for bone pain	Approved on case by case basis for bone pain	
Prince Edward Island (June 2000)	Exceptional drug status coverage For treatment of symptomatic Paget's disease of bone for six-month period (coverage can be renewed after drug holiday of at least 90 days) Consideration for coverage given to individuals who have failed to respond to therapeutic trials such as hormone replacement or calcium therapy (for osteoporosis)	Not in formulary	Not in formulary	Not in formulary

Alendronate is generally not listed for use in cancer indications. Thus, it is excluded. Etidronate is listed for use in the management of hypercalcemia (Ontario), the symptomatic management of bone pain due to cancer in palliative care (Saskatchewan) and palliative care (British Columbia). Clodronate is approved for the management of hypercalcemia (Ontario) and in palliative use (British Columbia). Pamidronate is listed for palliative use in British Columbia. Zoledronate is listed for use in the treatment of tumour-induced hypercalcemia in patients with a documented intolerance of or lack of response to clodronate or pamidronate. The availability of bisphosphonates for individuals without provincial formulary coverage, hospital formulary coverage or third-party insurance coverage is a function of the cost of the drug. The information in Table 2 represents the availability of these drugs for most Canadians at the time that this report was written.

Table 3: Typical unit and average monthly costs (C$) for specific bisphosphonate agents

	Etidronate 200 mg/day	**Clodronate 400 mg x 4 daily**	**Pamidronate 90 mg IV q3w**	**Zoledronate 4 mg IV q3w**
Unit cost	1.31*	1.75 x 4*	299.93**	558.73**
Monthly cost	40	210	400	745

*Based on pricing from Ontario drug formulary 2002
**Based on pricing from Alberta drug formulary 2002

1.1.4 Economic impact in Canada

Upon confirmation of effectiveness and approval for the indication of pain relief for bone metastases, the number of patients who may be suitable candidates to take bisphosphonates would be a function of the selection criteria and the proportion of patients fulfilling the selection criteria.

There are alternative treatment options in standard practice (e.g. radiotherapy, analgesics) to manage pain secondary to painful bone metastases. Whether bisphosphonates are adopted for refractory cases only or as an alternative or an addition to other therapies would result in various economic impacts.

The proportion of patients who are prescribed bisphosphonates for the prevention of the complications of bone metastases will likely increase over time. It has recently increased in many provinces with the adoption of bisphosphonates for the management of patients with breast cancer and of those with multiple myeloma. Patients with prostate cancer will increasingly be treated with bisphosphonates, given the recent approval of zoledronate for the treatment of prostate cancer. Breast cancer and prostate cancer are two common cancers and both that are associated with a high incidence of bone metastases. If these patients receive early treatment with bisphosphonates, the economic impact of adopting bisphosphonates for pain relief is difficult to estimate.

The administration of these drugs has economic implications in terms of direct and indirect costs such as IV support through out-patient infusion programs or home infusion programs (typically funded by home care programs). Other indirect costs include health care team visits and laboratory support for routine blood tests (e.g. creatinine).

An economic evaluation[11] was reported as part of a randomized trial addressing the use of pamidronate in patients with advanced cancer and osteolytic bone disease and pain.[12] The trial was conducted in Switzerland at one institution (University of St. Gallen). All direct costs for in-patient and out-patient care were recorded. The authors concluded that treatment with pamidronate reduced pain and did not add to the costs. Similar Canadian studies are unavailable.

1.2 Technology Overview

There are three generations of bisphosphonate agents that have received Health Canada's approval for different clinical indications (Table 1). Approved indications include osteoporosis and Paget's disease. In patients with cancer, approved indications include hypercalcemia and osteolytic bone metastases. These drugs have not received approval specifically for pain relief in patients with bone metastases.

The drugs are used in a spectrum of clinical settings from family practice to tertiary hospitals. Drug use is a function of its availability and the route of administration. Oral bisphosphonates (e.g. clodronate) can be prescribed in out-patient settings. Bisphosphonates given via the IV route require infusion facilities; they are less convenient to use and are typically delivered in clinic or hospital environments, although home infusion pumps can be used.

For optimal therapy, the management of bone pain requires a multimodality and a multidisciplinary approach. Pharmacological alternatives include opioid analgesics (e.g. morphine) and non-opioid analgesics (e.g. non-steroidal anti-inflammatories, steroids, antidepressants). Antineoplastic therapies as alternatives include radiotherapy, chemotherapy and hormonal therapy. The choice depends on the setting (e.g. whether a patient's pain is diffuse or localized); local disease status (e.g. lytic versus sclerotic disease, pending pathological fractures); availability of therapies (e.g. radiotherapy versus bisphosphonates); convenience (e.g. taking the drug once a day versus once every three weeks) and side effects (e.g. gastrointestinal side effects from bisphosphonates).

2 OBJECTIVES

The objectives of this assessment are to examine the evidence related to the effectiveness and safety of specific bisphosphonate agents in the management of pain for patients with bone metastases as compared with placebo and as compared with available analgesic alternatives.

3 CLINICAL EFFECTIVENESS REVIEW

3.1 Methods

3.1.1 Literature search strategy

Published and unpublished records, including abstracts, were sought. Published literature and meeting abstracts were obtained from electronic databases by using a sensitive search strategy (Appendix 1). The electronic databases searched included MEDLINE®, EMBASE®, CANCERLIT®, BIOSIS Previews®, Current Contents® and the Cochrane library. The search strategy included MeSH headings, descriptors and keywords for the disease (bone metastases) and the drugs (bisphosphonates). Generic and trade names; and registry numbers for bisphosphonates were used. A clinical trial filter used to restrict retrieval to relevant studies was used. No language restrictions were imposed.

Documents in the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) library collection and on web sites of regulatory agencies, health technology assessment and related agencies (including specialized databases such as those of the University of York NHS Center for Reviews and Dissemination) were searched. The Google™ search engine was used to retrieve scientific proceedings and abstracts from professional associations.

The search was conducted in November 2001. Periodic updates were performed on the National Library of Medicine's PubMed database and the CD-ROM issues of the Cochrane Library to capture additional records. The last PubMed update was conducted in December 2002. DIALOG® alerts were established on MEDLINE®, EMBASE®, CANCERLIT® and BIOSIS Previews® databases until March 2003.

3.1.2 Selection criteria

For a study to be included in our review, all the following criteria had to be met:

- Study design was a randomized controlled trial (RCT), including parallel and crossover designs.
- Patient population included those with bone metastases.
- Patients either had or did not have bone pain at the time of trial enrolment, provided pain was measured as an outcome.
- One study arm included the use of bisphosphonate agents.
- One study arm included the use of placebo, no treatment, different types of bisphosphonate agents, different doses of the same bisphosphonates or other treatment modalities.
- The use of antineoplastic therapy or rescue pain medications was permitted provided that they were available uniformly to all trial participants (where such therapy was not part of the intervention being studied).
- Pain was measured as one of the outcomes.

3.1.3 Data extraction strategy

RW and VS independently reviewed citations and abstracts and discarded those not fulfilling the selection criteria. For the data extraction form, see Appendix 3. Duplicate studies were identified and excluded to ensure that each RCT was included only once. For a summary of duplicate reporting, see Appendix 4. Disagreement between the two reviewers was resolved by discussion. A third reviewer (PJW) was designated as the adjudicator in case of any persisting differences, but adjudication was unnecessary.

3.1.4 Quality assessment

The quality of the included RCTs was assessed using the Jadad scale, which assesses the appropriateness of randomization and double-blinding and the description of withdrawals and dropouts (Appendix 2). Trials are assessed on the scale, which has quantitatively a maximum high score of five. Information about allocation concealment was also collected from the trials. Two reviewers (RW and VS) assessed the quality of the RCTs independently. Any disagreement was resolved by discussion. A third reviewer (PJW) was designated as the adjudicator in case of any persisting differences, but adjudication was unnecessary.

3.1.5 Data analysis methods

Our review assumes that there is a class effect due to bisphosphonates and that it is clinically appropriate to pool the results from all bisphosphonate studies. The effects of individual bisphosphonates can also be examined (Figures 1, 6 and 7).

Data analysis was conducted using Cochrane Review Manager 4.1. For continuous outcomes, weighted mean differences; and for binary outcomes, a pooled odds ratio (OR) with a 95% confidence interval (CI)) were calculated. Intention-to-treat data (i.e. all patients randomized to the relevant treatment arm used as the denominator) were used where possible, but this was impossible with most continuous outcomes. Where it was impossible, end-point data as reported in the studies were used.

Data homogeneity was examined clinically and statistically using the chi square test. Homogeneous data were pooled, using the fixed effects model, to provide a summary statistic. Qualitative data were presented descriptively.

3.1.6 Choice of comparators and outcome measures

We were interested in the effectiveness of bisphosphonates for the provision of pain relief, so only short-term outcomes were relevant. Data pertaining to pain outcomes within 12 weeks were extracted to reveal:

- the proportion of patients with pain relief
- the mean or median pain scores measured through the use of pain scales
- other pain and analgesic outcome measures reported in the trials
- quality of life measurements

- adverse drug events, including the number of withdrawals due to adverse drug events.

The availability of appropriate endpoints was not universal across the included RCTs.

Pain relief can be expressed using several methods. There is no consensus on the methods of reporting, the minimum reporting standard and the minimal clinically important difference. From the perspective of informing individual patient choices, the proportion of patients with pain relief is more understandable than a difference in pain scores. From a methods perspective, the proportion of patients with pain relief (a dichotomous outcome) is more amenable to quantitative analysis. Mean and median pain scores require standardization and the appropriate confidence intervals and ranges to allow for the calculation of a summary statistic. As a result, we used the proportion of pain relief to compare results.

Other measures including mean pain score, proportion of patients with analgesic reduction and mean morphine equivalent consumption were used as secondary quantitative measures. Outcomes from placebo and open control studies were used.

Since the focus of our review was pain relief, it was reasonable to assume that if it was not achievable within a few weeks, it was unlikely to be clinically relevant. As a result, we limited the assessment of pain and analgesic outcomes to within 12 weeks.

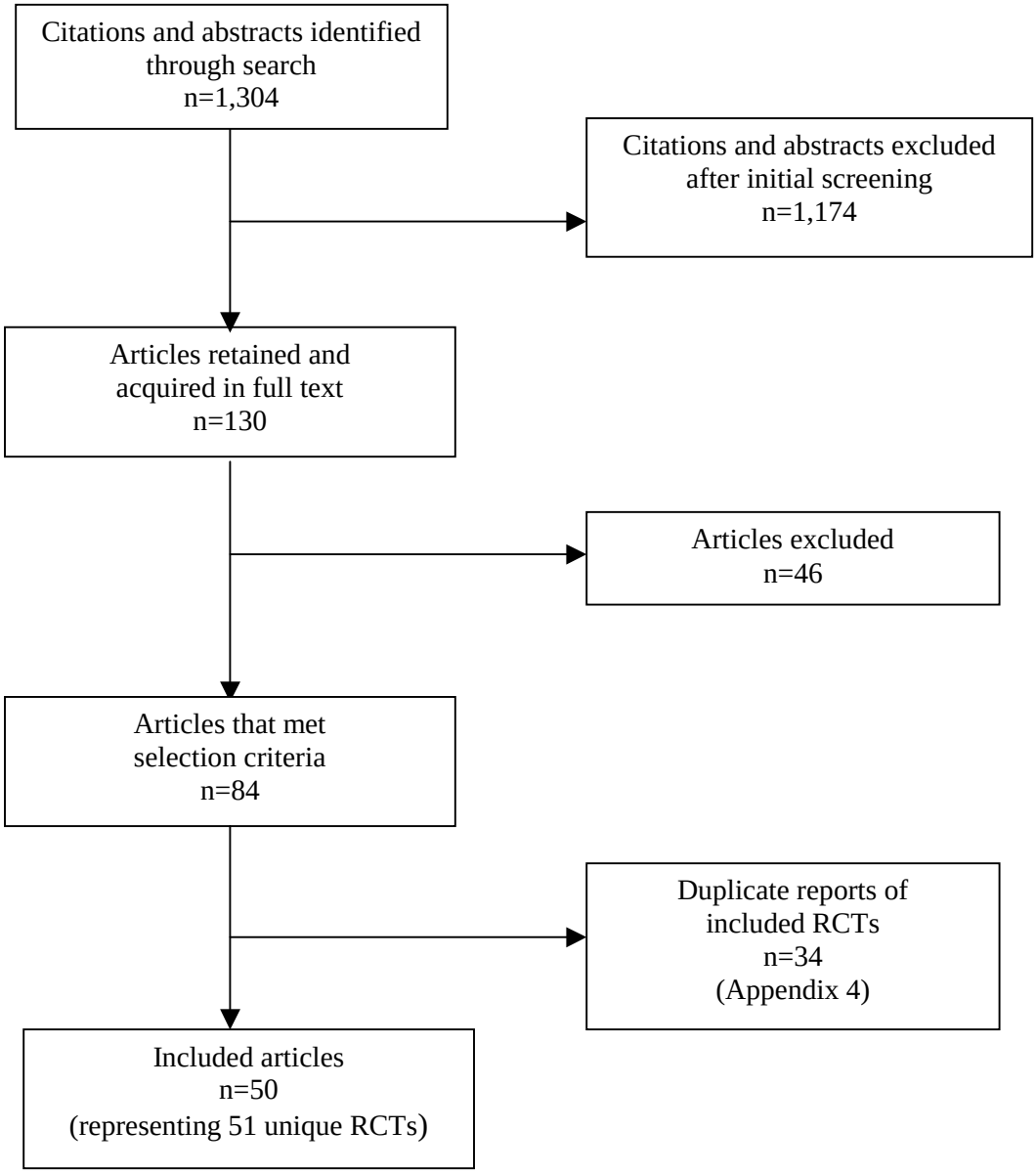
There was no attempt to impose formal criteria to distinguish clinical versus statistical significance in the reporting of results. The criteria used in the original studies to define response were used. Thus, they were consistent in but may vary across studies. The clinical significance of the analyses was discussed.

3.2 Results

3.2.1 Quantity of research available

The initial search was conducted in November 2001; 1,304 citations and abstracts were identified. After screening, 1,174 were excluded, leaving 130. Articles were obtained in full text and evaluated by RW and VS. Application of the selection criteria resulted in the inclusion of 84 articles. Of these, 34 were duplicate references for RCTs that were already included. Ultimately, 50 articles (representing 51 unique RCTs) fulfilled the selection criteria and were included.

Flow of selection process of citations and articles



3.2.2 Details of population studied

a) Primary sites (Table 3)

A total of 51 RCTs [12,1314-62] involving 9,425 randomized patients (range per RCT of 12 to 1,646 patients) formed the basis of this report [Adami (1989)[13] contained data from two trials].

Of the 51 RCTs, 12 included patients with bone metastases,[12,14,22,31,32,39,47,49-51,61,62] 18 included patients with breast cancer,[15,17,20,23,24,27-29,34,35,37,38,41,45,55,58-60] 10 included patients with multiple myeloma,[16,18,21,25,26,36,40,43,46,54] three included patients with breast cancer and patients with multiple myeloma [19,48,52] and eight included patients with prostate cancer only.[13,30,33,42,53,56,57]

The RCTs looking at bone metastases generally included patients with advanced disease where systemic antineoplastic therapies were unlikely to be effective. These trials were more likely to study, as their primary objective, the pain-relieving qualities of bisphosphonate agents. The trials that included patients with prostate cancer were described in recent publications and involved newer bisphosphonates.

b) Types of publications

Although unpublished reports were sought, none were obtained. No unpublished data were made available through direct communication with authors. Of the 51 RCTs selected, three were found only in protocol form [15,33,48] and four were published only as abstracts.[17,20,27,28] The remaining 44 RCTs were published in full.

With respect to the measurement of RCT quality, the three protocols were not assessed. The quality scores are shown in Table 4. The frequency distribution were 7, 13, 11, 10 and 7 for quality scores 1, 2, 3, 4 and 5 respectively (maximum score=5).

Table 4: RCT by primary disease site(s) and quality scores of these RCTs

References	Any Bone Metastases	Breast	Multiple Myeloma (MM)	Breast and MM	Prostate	RCT Quality Score (maximum score=5)
Arican 1999[14]	+					2
Cascinu 1998[22]	+					1
Ernst 1992[31]	+					5
Ernst 1997[32]	+					4
Jagdev 2001[39]	+					1
Koeberle 1999[12]	+					3
Moiseenko 1998[47]	+					2
O'Rourke 1995[49]	+					3
Piga 1998[50]	+					3
Robertson 1995[51]	+					4
Vinholes 1997a[61]	+					5
Zhang 1997[62]	+					2
Diel 1999a (Abs)[27]		+				3
Diel 1999b (Abs)[28]		+				2
Gomez-Postrana 1996[35]		+				2
Kristensen 1999[41]		+				3
Tubiana- Hulin 2001[59]		+				4
Ausili-Cefaro (protocol)[15]		+				Na
Coleman 1998[23]		+				2
Conte 1994[24]		+				1
Elomaa 1983[29]		+				2
Glover 1994[34]		+				2
Hortobagyi 1996a[37]		+				4
Hultborn 1999[38]		+				3
Martoni 1991[45]		+				2
Siris 1983[55]		+				5
Theriault 1999[58]		+				5
van Holten-Verzantzoort1993[60]		+				2
Bell 1995[17]		+				2
Body 1999[20]		+				2
Berenson 2001a[19]				+		4
Novartis 2001(protocol)[48]				+		Na
Rosen 2001[52]				+		5
Siris 1980[54]			+			5
Daragon 1993[25]			+			3
Delmas 1982a[26]			+			3
Heim 1995[36]			+			2
Kraj 2000a[40]			+			1
McCloskey 1998[46]			+			3
Belch 1991[16]			+			4
Berenson 1996a[18]			+			4
Brincker 1998[21]			+			4
Lahtinen 1992[43]			+			4
Adami 1989 trial 1[13]					+	1
Adami 1989 trial 2[13]					+	1
Elomaa 1992[30]					+	1
Kylmala 1997[42]					+	4
Smith 1989[56]					+	3
Strang 1997[57]					+	3
Faroqui 1996 (protocol)[33]					+	Na
Saad 2002[53]					+	5

Na=not applicable

c) Types of controls (Tables 5 to 10)

The type of control used as a comparator affects the power of inference of available data. RCTs can be classified depending on whether they compare bisphosphonate agents with placebo (n=32), with no treatment (n=7) or with active controls (n=12). Placebo controls minimize the risk of bias that stems from knowledge about whether an active drug is being taken. No treatment or open controls refers to studies where those in the control group are given no bisphosphonates, so that they act as a comparison to those in the arm that does not receive bisphosphonates. In some instances, patients were receiving antineoplastic therapies, the same as what was available to the control group. With active controls, all study arms receive bisphosphonates. In these studies, the objective is to evaluate whether there is a dose-response relationship or to compare the effectiveness of one drug versus another.

In addition to the 12 studies where all treatment arms received bisphosphonates (i.e. active controls), there are 12 studies that include comparisons between active arms. These studies are listed under the heading of "active controls" and identified with an asterisk in Tables 5 to 10). Of the included studies with active controls, 18 compare different dosage regimens of the same bisphosphonate, five compare different types of bisphosphonates[19,28,39,52,62] and one compares bisphosphonate and cisplatin in patients with prostate cancer.[33]

The effectiveness of each bisphosphonate agent is best studied through the examination of trials comparing the drug of interest with placebo. When compared with placebo, three studies examine etidronate,[16,25,56]18 clodronate,[13,26,29-32,35,42,43,45,46,49-51,54,55,57,59] seven pamidronate,[17,18,21,37,38,58,61] two zoledronate [48,53] and two ibandronate.[20,28]

The power of inference is weaker when studies include arms that involve no treatment. There are two studies with open controls examining clodronate [14,36] and three examining pamidronate.[24,40,60]

In RCTs comparing different doses of the same drug, there are data on relative effectiveness and an examination of the routes of administration. These RCTs include one trial of etidronate[64] (Table 5), five of clodronate[13,14,27,32,39,47,49] (Table 6), four of pamidronate[12,22,23,34] (Table 7), four of zoledronate [19,48,52,53] (Table 8) and two of ibandronate [20,28] (Table 9).

RCTs comparing different types of bisphosphonates provide data on their relative effectiveness (Table 10). Comparisons are made between pamidronate and clodronate (n=3),[28,39,62] pamidronate and zoledronate (n=2)[19,52] and pamidronate and cisplatin in patients with prostate cancer (n=1).[33]

Table 5: RCTs assessing etidronate by type of study arms

Etidronate	Placebo	5 mg/kg/d	10 mg/kg/d	7.5 mg/kg/d IV x 3 d, then 200 mg bid po	7.5 mg/kg/d IV x 3 d, then placebo	Placebo, then 200 mg bid po
Placebo control						
Belch 1991[16]	+	+				
Daragon 1993[25]	+		+			
Smith 1989[56]	+			+	+	+
Active controls (*studies have placebo or open controls and active arm comparisons, which are listed in this table)						
Smith 1989*[56]	+			+	+	+

Table 6: RCTs assessing clodronate by type of study arms

Clodronate			PO	PO					IV				IM	Other
	Placebo	Open	400 mg/ d po	800 mg/ d po	1,200 mg/ d po	1,600 mg/ d po	2,400 mg/ d po	3,200 mg/ d po	300 mg IV x 5 d	600 mg IV x 1 d	900 mg IV x 1 d	1,500 mg IV x 1 d	100 mg/d	
Placebo control														
Adami 1989 trial 1[13]	+								+					
Delmas 1982a[26]	+					+								
Elomaa 1983[29]	+													1.6 to 3.2 g/d
Elomaa 1992[30]	+													3.2 g/d po x 1 mo then 1.6 g/d po x 5 mo
Gomez-Postrana 1996[35]	+													300 mg/d IV x 5d, then 1,600 mg/d po x 6 mo
Kymala 1997[42]	+													300 mg/d IV x 5 d then 1,600 mg/d po x 12 mo
Lahtinen 1992[43]	+						+							

Martoni 1991[45]	+													300 mg/d IV x 7 d then 100 mg/d IM x 3 wk, then 100 mg alt d IM x 2 mo
McCloskey 1998[46]	+					+								
O'Rourke 1995[49]	+		+			+		+						
Piga 1998[50]	+					+								
Robertson 1995[51]	+					+								
Siris 1980[54]	+							+						
Siris 1983[55]	+							+						
Strang 1997[57]	+													300 mg IV/d x 3 d then 1,200 mg/ d po x 4 wk
Tubiana-Hulin 2001[59]	+					+								
Ernst 1992[31]	+									+				
Ernst 1997[32]	+									+		+		
Open control														
Heim 1995[36]		+				+								
Kristensen 1999[41]		+		+										
Arican 1999[14]		+		+		+								
Active controls (*studies have placebo or open controls and active arm comparisons, which are listed in this table)														
Moiseenko 1998[47]									+			+		
Adami 1989 trial 2[13]					+								+	
Jagdev 2001[39]						+								1,500 mg IV x 1 dose + 1,600 mg/ d po
Diel 1999a[27]							+				+			
Arican 1999*[14]		+		+		+								
Ernst 1997*[32]	+									+		+		
O'Rourke 1995*[49]	+		+			+		+						

d=day; IV=intravenous; bid=twice a day; po=per os ; mo=month; IM=intramuscular ; wk=week; alt=alternate

Table 7: Studies assessing pamidronate by type of study arm

Pamidronate										
			IV						**PO**	
	Placebo	**Open**	**30 mg IV**	**45 mg IV**	**60 mg IV**	**90 mg IV**	**120 mg IV, then placebo 4 wk later**	**Placebo, then 120 mg IV 4 wk later**	**150 mg/d po**	**300 mg/d po**
Placebo controls										
Bell 1995[17]	+				+					
Berenson 1996a[18]	+					+				
Brincker 1998[21]	+								+	
Hortobagyi 1996a[37]	+					+				
Hultborn 1999[38]	+				+					
Theriault 1999[58]	+					+				
Vinholes 1997a[61]							+	+		
Open controls										
Conte 1994[24]		+		+						
Van Holten-Verzantzoort 1993[60]		+								+
Kraj 2000a[40]		+			+					
Ausili-Cefaro 1999 (protocol)[15]		+				+				
Active comparisons										
Koeberle 1999[12]					+	+				
Cascinu 1998[22]				+	+	+				
Coleman 1998[23]									+	+
Glover 1994[34]			+		+	+				

IV=intravenous; wk=week; d=day; po=per os

Table 8: Studies assessing zoledronate by type of study arm

Zoledronate						
	Placebo	**0.4 mg**	**2 mg**	**4 mg**	**8/4 mg**	**Others**
Placebo controls						
Novartis[48]	+					Single dose versus double dose
Saad 2002[53]	+			+	+	
Active controls (*studies have placebo or open controls and active arm comparisons, which are listed in this table)						
Berenson 2001a[19]		+	+	+		
Rosen 2001[52]				+	+	
Saad 2002*[53]				+	+	
Novartis*[48]						Single dose versus double dose

Table 9: Studies assessing ibandronate by type of study arm

Ibandronate			
	Placebo	**2 mg IV**	**6 mg IV**
Placebo controls			
Diel 1999b[28]	+	+	+
Body 1999[20]	+	+	+
Active controls (*studies have placebo or open controls and active arm comparisons, which are listed in this table)			
Diel 1999b*[28]		+	+
Body 1999*[20]		+	+

IV=intravenous

Table 10: Studies assessing different types of bisphosphonates by type of study arm

	Clodronate			**Pamidronate**				**Zoledronate**				**Cisplatin**
Dose	**300 mg/d**	**1,600 mg/d**	**2,400 mg/d**	**Dose unknown**	**30 mg/d**	**60 mg/d**	**90 mg/d**	**0.4 mg**	**2 mg**	**4 mg**	**8/4 mg**	
Pamidronate versus cisplatin												
Faroqui 1996[33] (protocol)				+								+
Pamidronate versus clodronate (*studies have placebo or open controls and active arm comparisons, which are listed in Tables 5 to 9)												
Zhang 1997[62]	+				+							
Jagdev 2001*[39]		+					+					
Diel 1999a (abstract)*[27]			+			+						
Pamidronate versus zoledronate (*studies have placebo or open controls and active arm comparisons, which are listed in Tables 5 to 9)												
Berenson 2001a*[19]							+	+	+	+		
Rosen 2001*[52]							+			+	+	

d=day

3.2.3 Assessment of clinical effectiveness

a) Proportion of patients with pain relief

Of the 51 studies, 13 provided outcome data based on the proportion of patients with pain relief (Figure 1). Of these, nine studies compared bisphosphonates to open or placebo controls. Odds ratios (ORs) and confidence intervals (CIs) were calculated. Pooled data showed:

- week 4: OR 1.34 [95% CI 0.96 to 1.85]
- week 8: OR 2.52 [95% CI 0.71 to 8.93]
- week 12: OR 2.2 [95% CI 1.36 to 3.5].

An OR >1 favours the use of the intervention. A CI that excludes the value of one indicates that the effect is statistically significant, while a CI that includes the value of one indicates that effect is not significant.

The results show a trend toward pain relief at weeks 4 and 8, although this does not reach statistical significance. It does become statistically significant at week 12. Six [95% CI 4 to 11] patients must be treated for one to experience pain relief.

b) Mean or median pain scores

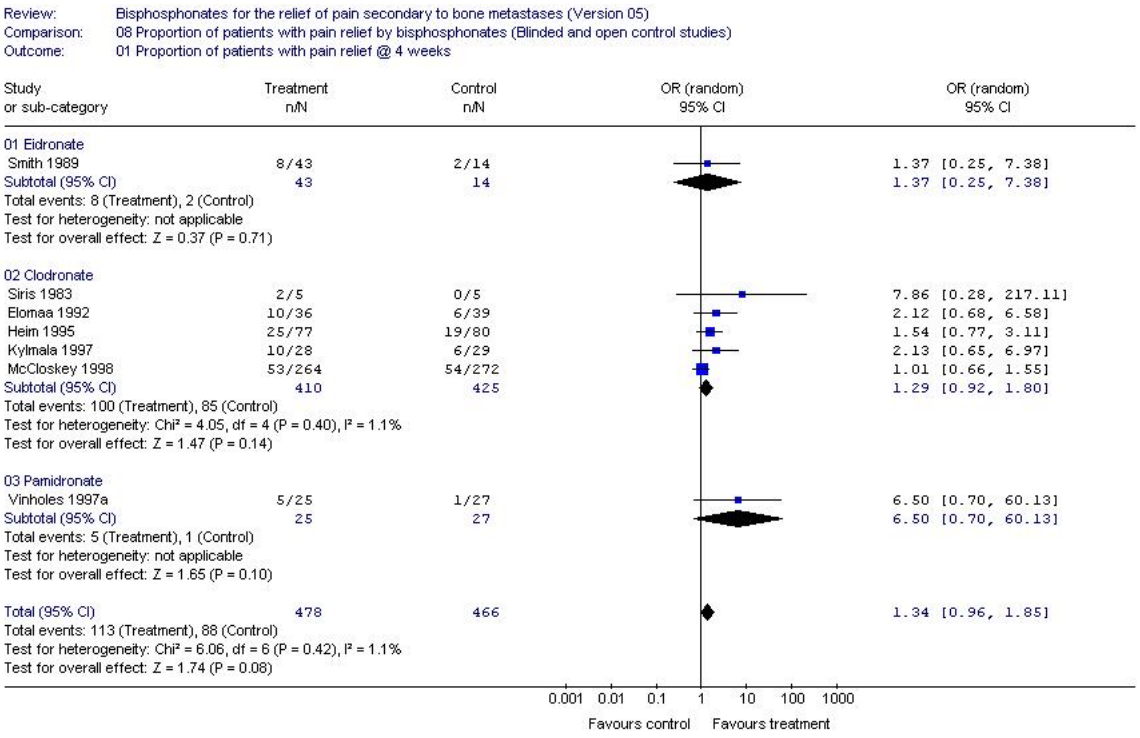
Of the 51 trials, seven reported pain scores outcomes beyond 12 weeks (Figure 2). Two[21,57] did not provide data but stated that there was no significant difference in the pain experienced by patients in the biphosphonate arms versus the control arms. One[59] stated that there was a difference in mean pain score between the treatment arms (p value=0.01). Outcome data for mean or median pain relief were found for 23 trials. Of these, 15 compared bisphosphonates to open or placebo controls.

We intended to provide standardized means with standard deviations for a quantitative summary, but standard deviations were unavailable for many trials. For qualitative inspection, the data were tabulated as presented in the trials for qualitative inspection.

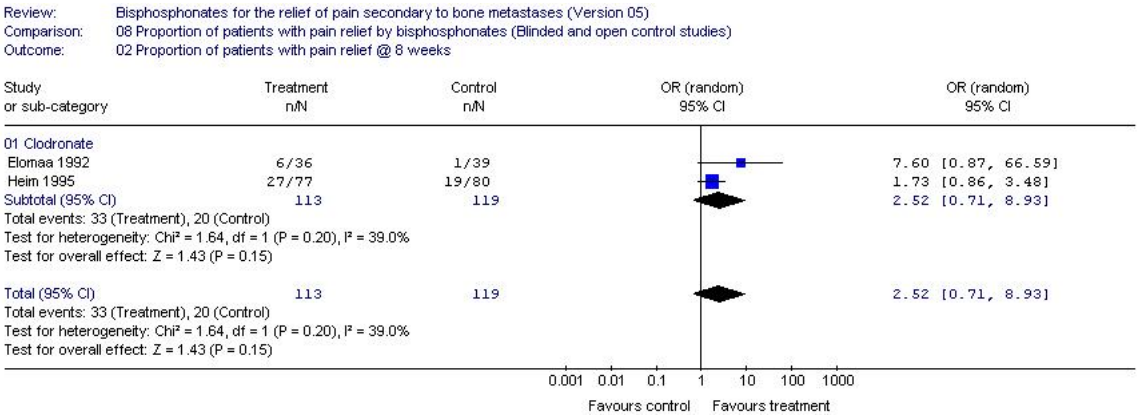
The pain scores for the treatment groups were generally lower than those found for the control groups, although the difference is modest. Most of the pain scores were based on a 10-point scale. At four weeks, there was a reduction in the mean pain score of 0.65 [95% CI -2.77 to -1.46]. At 12 weeks, the corresponding reduction in mean pain score was 0.35 [95% CI -0.39 to -0.31].

Figure 1: Proportion of patients with pain relief

Proportion of patients with pain relief at four 4 weeks



Proportion of patients with pain relief at eight weeks



Proportion of patients with pain relief at 12 weeks

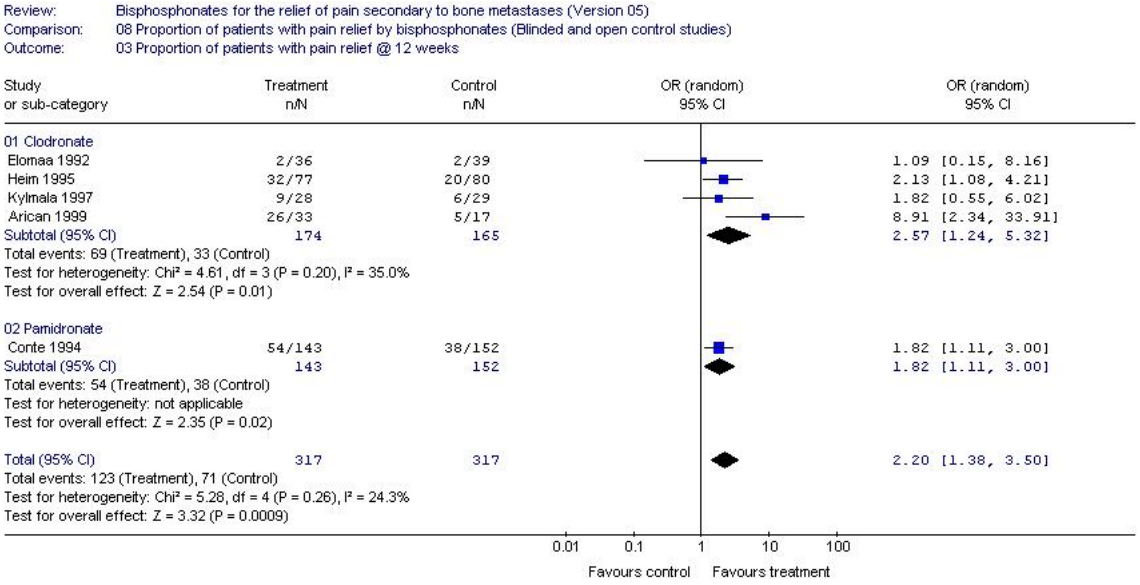
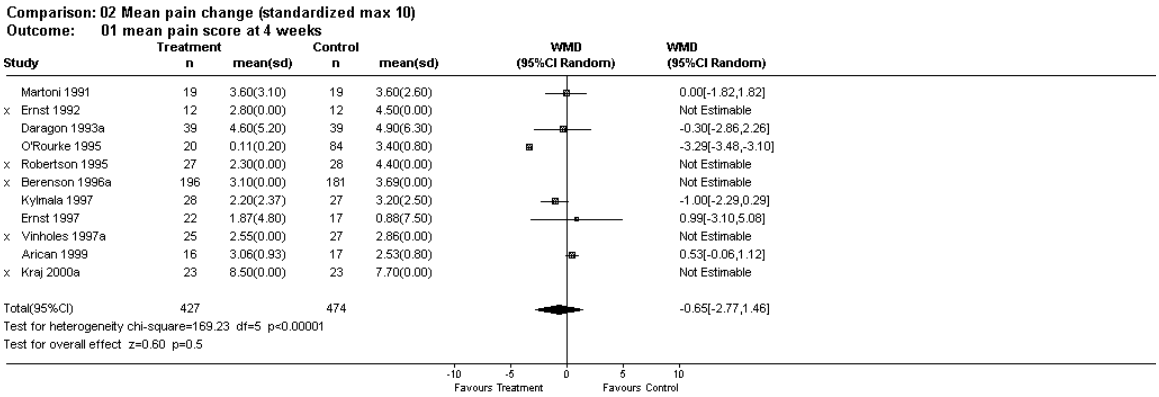
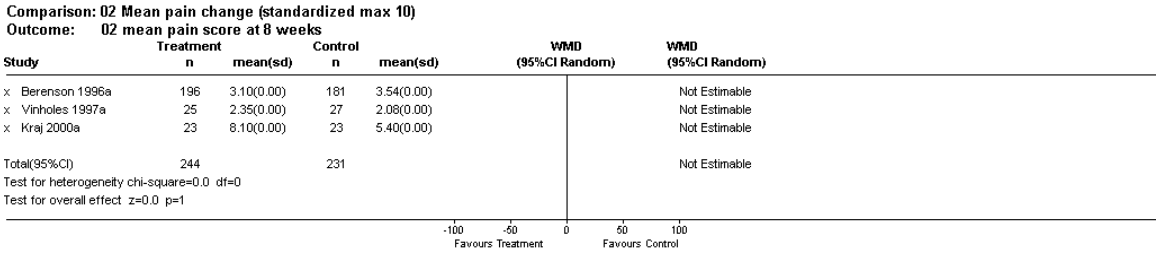


Figure 2: Mean pain scores

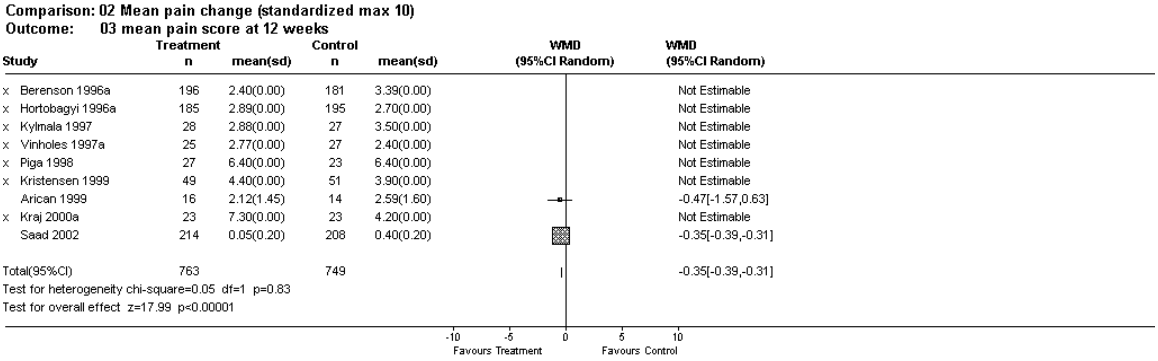
Mean pain score at week 4



Mean pain score at week 8



Mean pain score at week 12



c) Proportion of patients with reduction in analgesic use

Of the 51 trials, three reported outcomes related to the use of analgesics, but not within the 12-week time frame (Figure 3). Four did not provide data[21,38,49,53] and stated that there were no differences between the intervention and control arms. One trial stated patients took less analgesia in the study arm than in the control arm. Five trials [13,31,32,41] provided data for morphine equivalents and 11[12,14,22,25,29,30,36,42,45,50,51] provided data on proportional reductions in analgesic intake.

Of the 12 trials providing data using proportions, the proportions of patients with reductions in analgesic use were available in five studies.[30,32,42,45,50] Three trials had results at week 4 and three trials had results at week 12. One trial provided data at eight weeks.[30] Pooled results produced ORs in favour of the treatment groups:

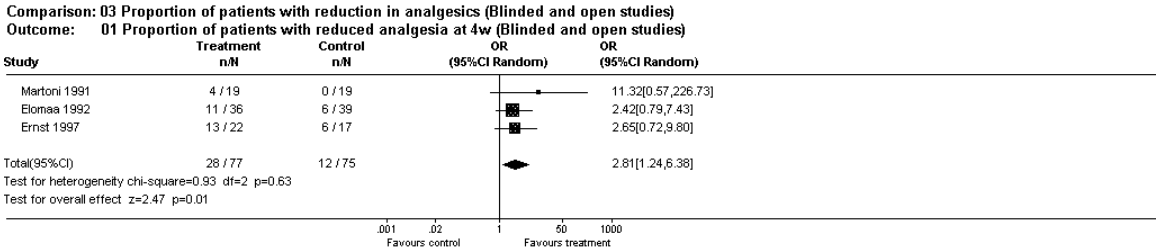
- week 4: OR 2.81 [95% CI 1.24 to 6.38]
- week 12: OR 2.37 [95% CI 1.1 to 5.12].

These results indicated that there were significantly more patients with reduced analgesic consumption in the bisphosphonate arms when compared with no treatment at weeks 4 and 12.

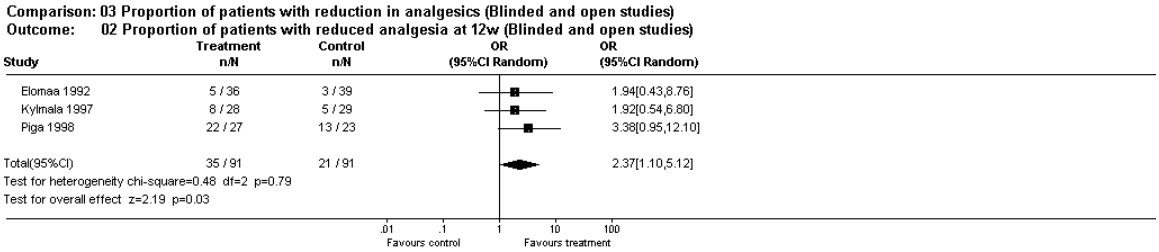
Other proportions used included the proportion of patients using no analgesics [21,30,36,42] and the proportion of patients with increased use of analgesics.[51] These were not analyzed, as they were not the endpoints of interest and were reported by a small subset of trials.

Figure 3: Proportion of patients with reduction in analgesics (morphine equivalent)

Proportion of patients with reduction in analgesics at week 4



Proportion of patients with reduction in analgesics at week 12



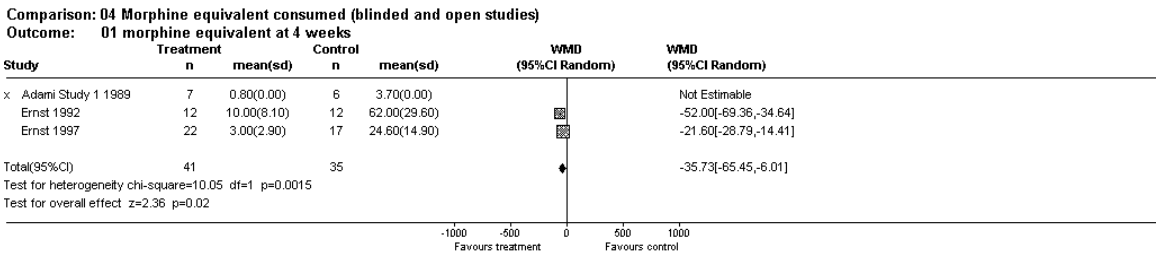
d) Reductions in use of analgesics

Patients often take different types of analgesics. Each of these differs in its effectiveness to provide pain relief. To consider this quantitatively, researchers often use the concept of "morphine equivalent." The amount of oral morphine that would provide the equivalent analgesic value to what is being taking by the patient is calculated using a standard conversion factor. While there are several sets of conversion factors commonly used, these are usually consistently applied in individual studies.

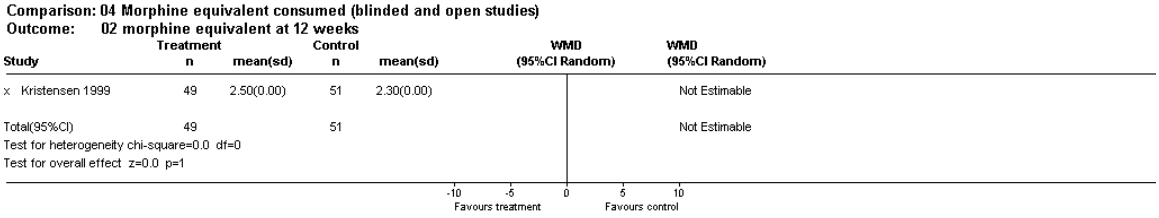
Of the five trials providing data for the morphine equivalent, one was a dose comparison,[13] two compared the intervention to placebo[31,32] and one was compared to no treatment.[41] The data were not amenable to quantitative analysis. The available data (Figure 4) supported the use of lower amounts of analgesic agent in the intervention arms.

Figure 4: Morphine equivalent consumed

Morphine equivalent consumed at week 4



Morphine equivalent consumed at week 12



e) Adverse effects

Only trials comparing the intervention with a placebo or open controls were used in looking at toxicity. Of the 51 trials, 39 had either a placebo or an open control arm. Data from these 39 trials were included in Figure 5. No adverse effects were described in 17 trials (listed as "no toxicity reporting" in Figure 5). Three trials described the use of a toxicity grading system with World Health Organization (WHO) criteria. For trials comparing the intervention with open or placebo control, 46 symptom categories were used (Figure 5). In general, more recent trials reported more symptom categories, while older trials reported fewer categories. Adverse effects could not be separated into those reported during the period of interest (12 weeks) versus those experienced over the course of the trial. Any adverse effects reported were tabulated. The reporting of adverse effects in comparisons of bisphosphonate agents with open or placebo control was presented for each drug under the categories used in the primary trials.

For etidronate, two toxicities were described (abdominal pain and allergic reactions). No significant differences were found between the bisphosphonate and control arms.

For clodronate, 22 categories of adverse effects were identified. Ten trials did not present any adverse effects and one trial stated that there were no adverse effects.[29] Of the adverse effects described, only "diarrhea or constipation" was significantly different between patients taking bisphosphonate agents and those taking controls OR 3.67 [95% CI 1.12 to 12.06].

For pamidronate, 22 categories of adverse effects were identified. No toxicity was reported from two trials.[17,40] Of the adverse effects described, three were significantly different between the pamidronate and control arms. Hypocalcemia was documented in 4% of patients receiving pamidronate versus 2% receiving placebo or no treatment. The definition of hypocalcemia was biochemical, <2 mmol/L (Conte 1994), <1.9 mmol/L,[18] <1.8 mmol/L and symptomatic,[37] while no definition was provided in one study.[58] The OR was 2.5 [95% CI 1.27 to 4.93]. A local reaction occurred in 7% versus 3% of patients. The OR was 2.67 [95% CI 1.25 to 5.7]. Discontinuation of the drug occurred in 6% versus 2% of patients. The OR was 2.8 [95% CI 1.62 to 4.84]. Musculoskeletal pain occurred in more patients who did not receive pamidronate than in those who did.

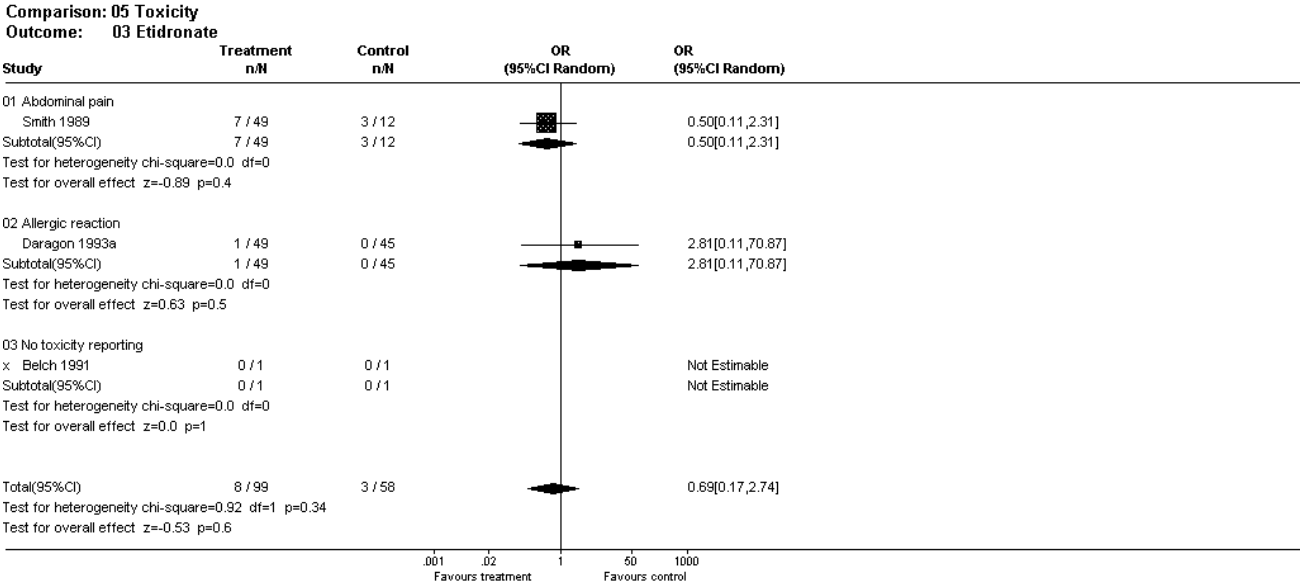
For zoledronate, adverse effects were reported in a trial that compared the drug to a control; 14 categories were identified.[53] Data were available from Saad *et al.*,[53] who reported that significantly more events of anemia, limb edema and fever occurred in the

zoledronate arm when compared with the control arm. The incidence of anemia was 27% versus 18% OR 1.7 [95% CI 1.12 to 2.57]. For limb edema, the incidence was 20% versus 13% OR 1.72 [95% CI 1.08 to 2.75]. For fever, it was 21% versus 13% OR 1.77 [95% CI 1.11 to 2.83]. Elevations in serum creatinine (grade 3) were compared: the incidence was 4% for zoledronate-treated patients and 1% for patients on placebo OR 4.7 [95% CI 1.09 to 20.39]. Similarly, deterioration in renal function differed: 18% zoledronate-treated patients versus 12% for patients on placebo OR 1.7 [95% CI 1.04 to 2.78].

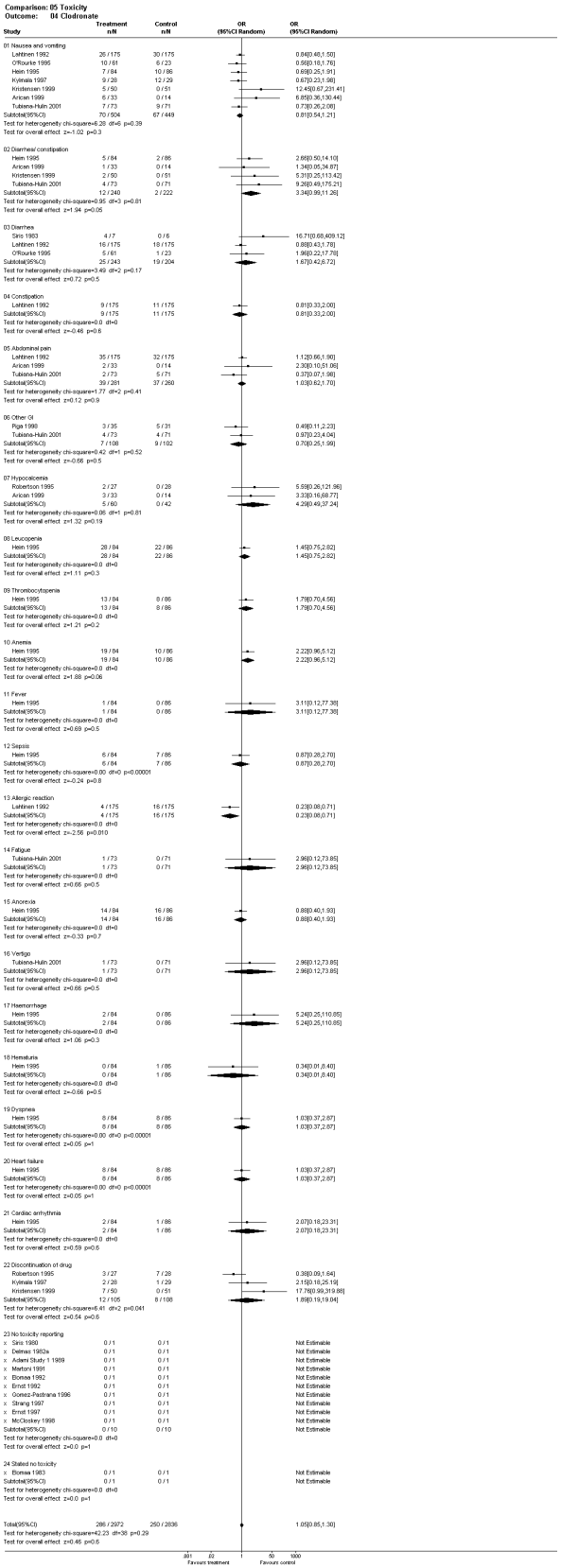
Bisphosphonates were generally well tolerated. Apart from clodronate, where a difference in diarrhea and constipation was noted, no gastrointestinal adverse effects were found to be significantly different between the study and control arms. Similarly, there were no data describing significant ophthalmic toxicities. Of the studies providing data on adverse effects, discontinuation of therapy and nausea and vomiting were the most commonly reported. Other adverse events described included abdominal discomfort, allergic reactions, hypocalcemia, myalgia and fever.

Figure 5: Adverse effects

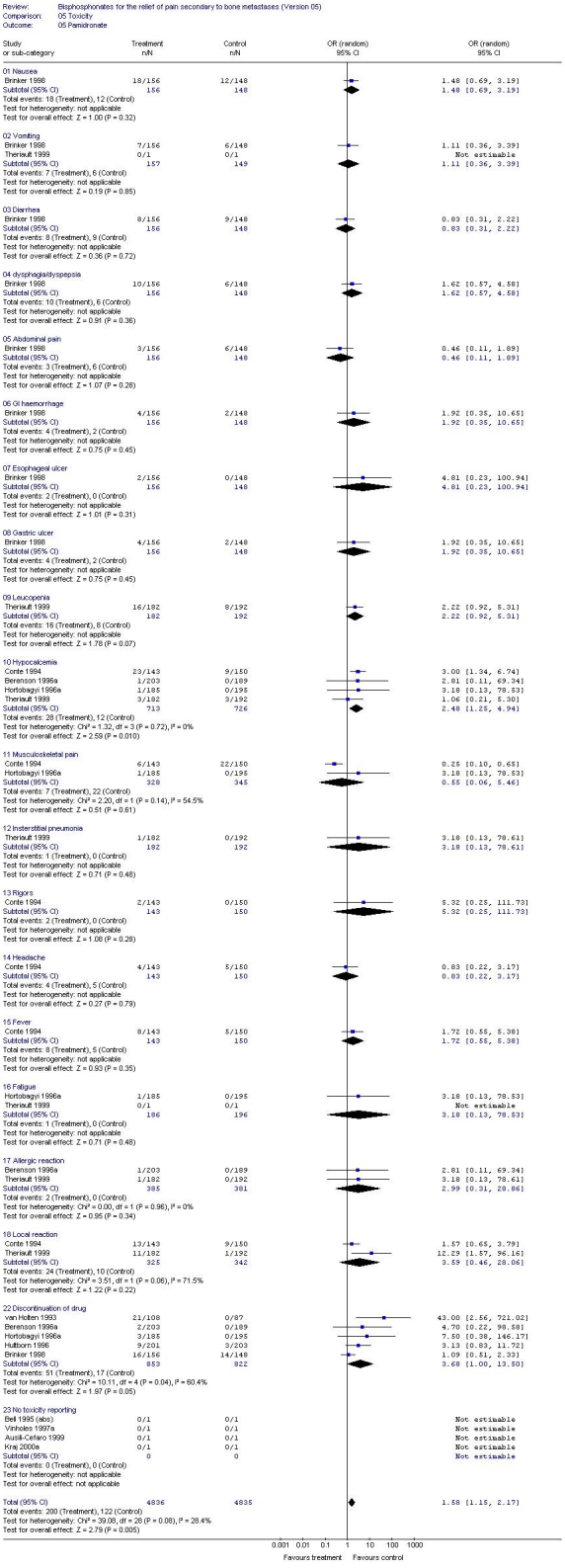
Adverse effects: etidronate



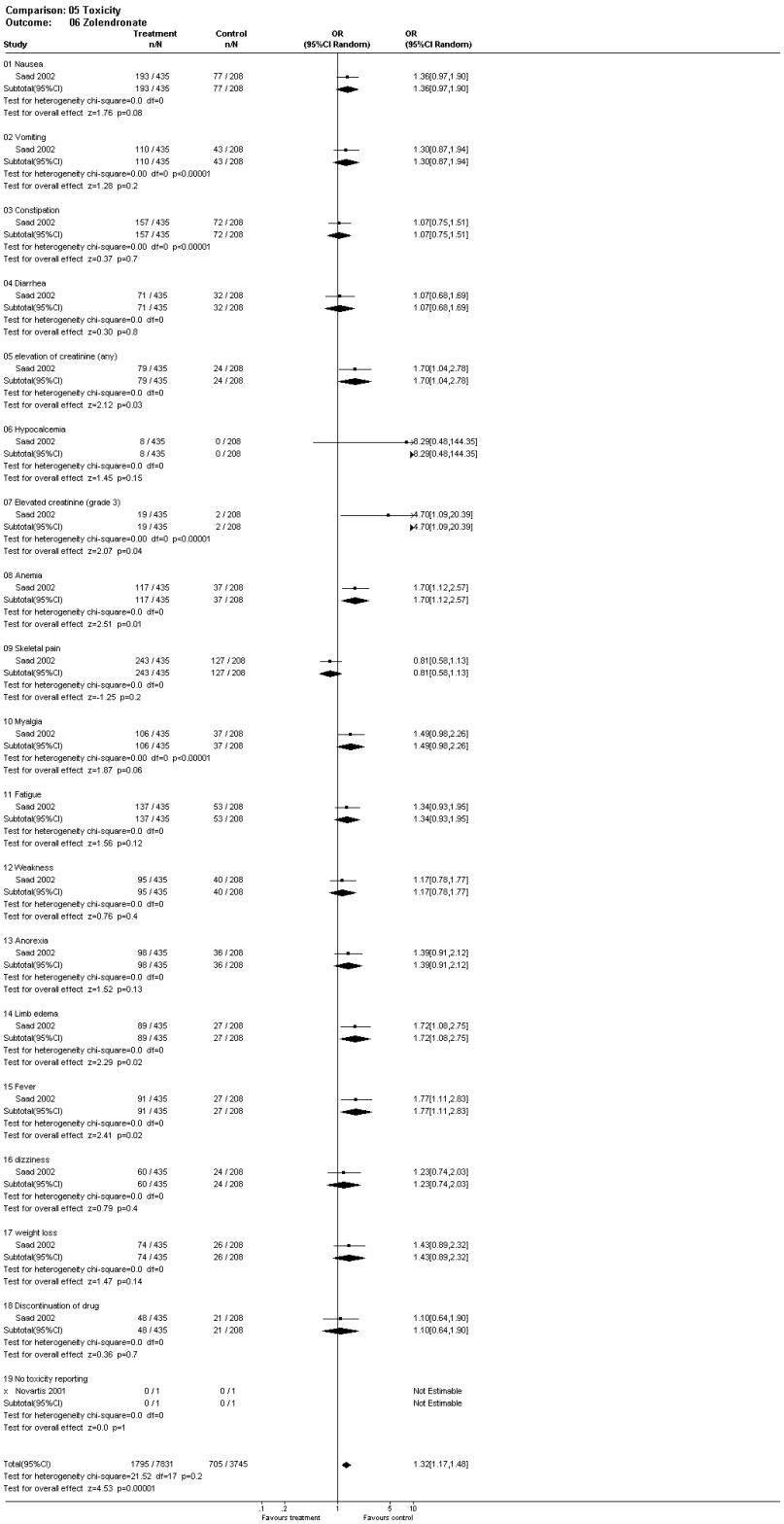
Adverse effects: clodronate



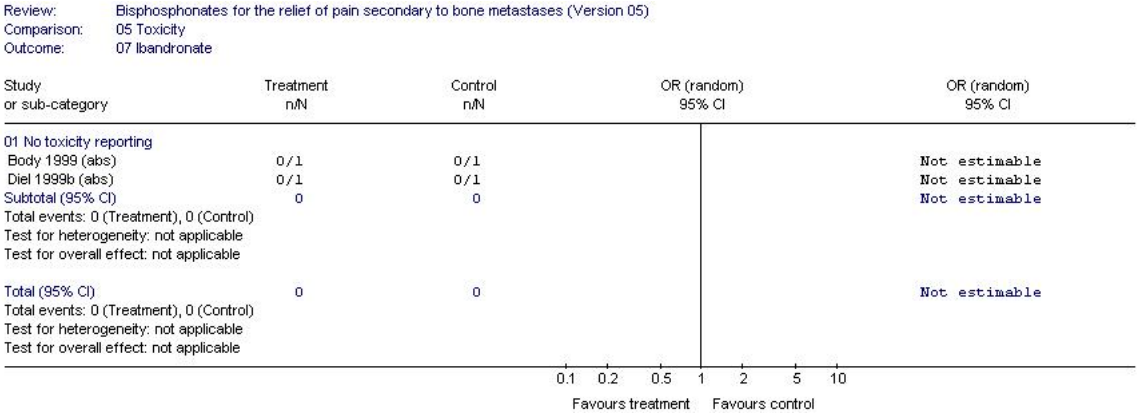
Adverse effects: pamidronate



Adverse effects: zoledronate



Adverse effects: ibandronate



f) Quality of life

Quality of life comparisons were presented in eight studies.[18,20,28,37,41,53,61,66] Of these, seven presented comparisons at a point beyond our time frame of interest (three months). Berenson *et al.*[18] reported no difference in quality of life at baseline and at nine months. Body *et al.*[20] described a significant increase in quality of life as measured by European Organization for Research and Treatment in Cancer quality of life core module (30 items) EORTC QLQ30 in the 6 mg dose ibandronate. The time frame of reporting was not described, although the study duration was two years. Diel *et al.*[28] described a significant improvement in patients treated with 6 mg ibandronate compared with placebo. Kristensen[41] described no significant difference between baseline and three to six months for patients receiving clodronate versus placebo. Harvey[66] reported that, at nine months, quality of life had decreased significantly less with bisphosphonates than with placebo. Hortobagyi[37] stated that fewer patients in the pamidronate group than in the placebo group had decreased in quality of life scores at the last measurement (this study involved a treatment period of 12 months).

One study, Vinholes *et al.*,[61] provided a quality of life comparison in the time frame of interest. This study described a small but non-significant improvement in quality of life compared with baseline in the pamidronate arm at four weeks; quality of life worsened in the placebo arm.

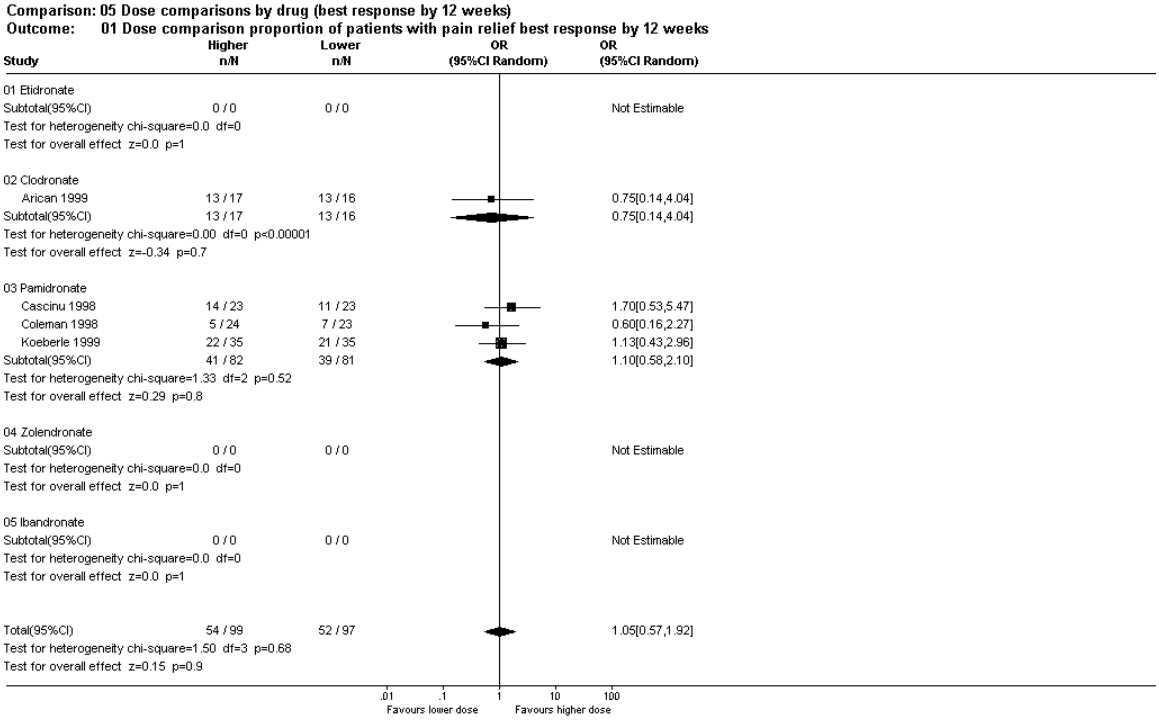
3.2.4 Dose regimen

a) Dose regimen comparison

There were 18 trials with different dose and route comparisons for the same bisphosphonate agent: etidronate (n=1), clodronate (n=7), pamidronate (n=4), zoledronate (n=4) and ibandronate (n=2) (Figure 6).

Four trials measured the proportion of patients with pain improvement within 12 weeks. Data comparing the highest and lowest doses were tabulated where more than two doses were compared. The best response within 12 weeks was used. All trials were presented in the same Metaview table. Pooling of the data displayed a trend (not statistically significant) in support of a dose to response relationship. Insufficient data were available to permit the comparisons of mean pain scores or changes in analgesic use.

Figure 6: Comparison of different bipshosphonates



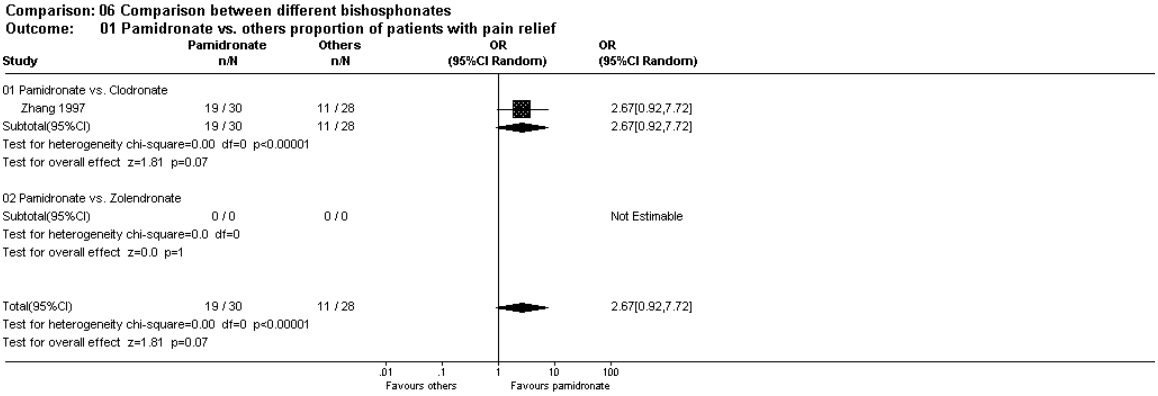
b) Different bisphosphonate comparisons

Figure 7 shows six trials that compared pamidronate with alternative drugs, including other bisphosphonates. One trial,[33] presented as a protocol only, was designed to compare the drug with cisplatin, three[27,39,62] compared it with clodronate and two[19,52] compared it with zoledronate.

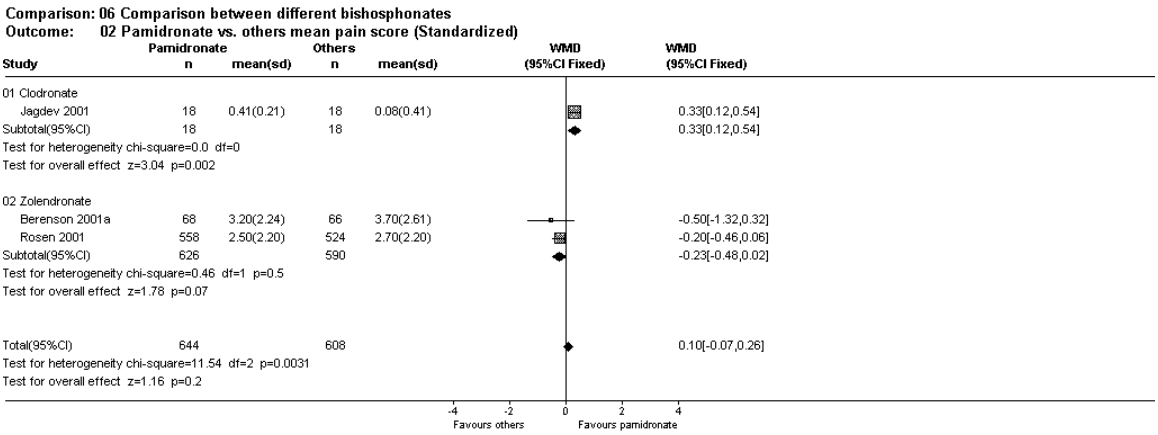
To examine the proportion of patients with pain relief, data were available for one trial.[62] In this trial, pamidronate 30 mg/day was compared to clodronate 300 mg/day for five days. There was a trend toward greater benefit from pamidronate. Using standardized mean pain scores (maximum score=10), pamidronate showed an advantage over clodronate in one trial.[39] The weighted mean difference between the two study arms was 0.33 [95% CI 0.12 to 0.54]. There was a non-statistically significant benefit due to the use of zoledronate versus pamidronate in two studies [19,52] with a mean difference of 0.23 [95% CI 0.02 to 0.48].

Figure 7: Comparison of different types of bisphosphonates

Comparison of different types of bisphosphonates for proportion of patients with pain relief



Comparison of different types of bisphosphonates for mean pain score



3.2.5 Secondary analyses

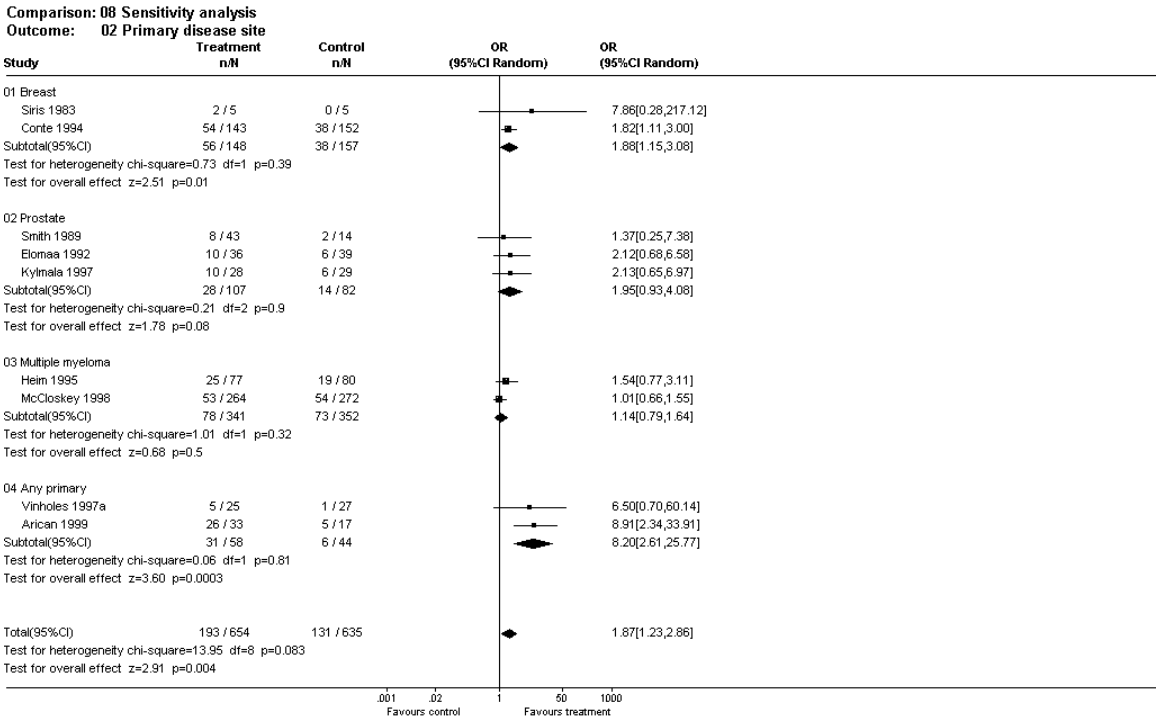
Secondary analyses were conducted using the proportion of patients with pain relief (Figure 8). A small subset of trials provided data for each time point of interest (seven, two and five studies for four, eight and 12 weeks respectively). To maximize the number of trials in the sensitivity analysis, the parameter “best response by 12 weeks” was used. Data points representing the best response by week 12 were used. The summary statistic for “proportion of patients with pain relief, best response by 12 weeks” was OR 1.87 [95% CI 1.23 to 2.86].

Sensitivity analyses were conducted for several variables, hypothesized *a priori*, including:

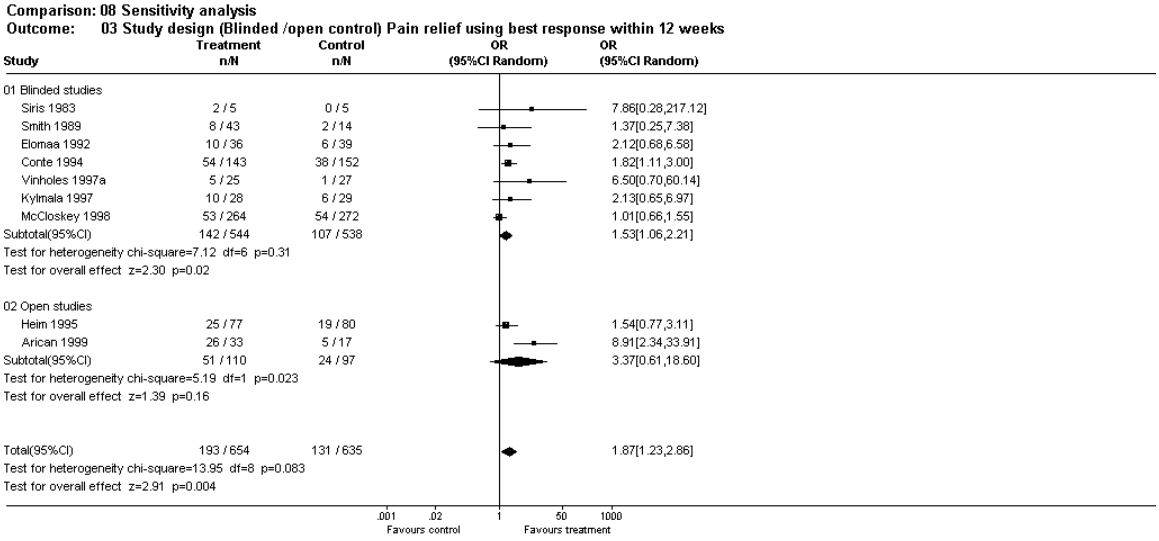
- primary disease site
- control arm blinded versus open
- pain as an entry criteria
- pain reported by patient
- stringent study design
- trial quality.

Figure 8: Secondary analyses

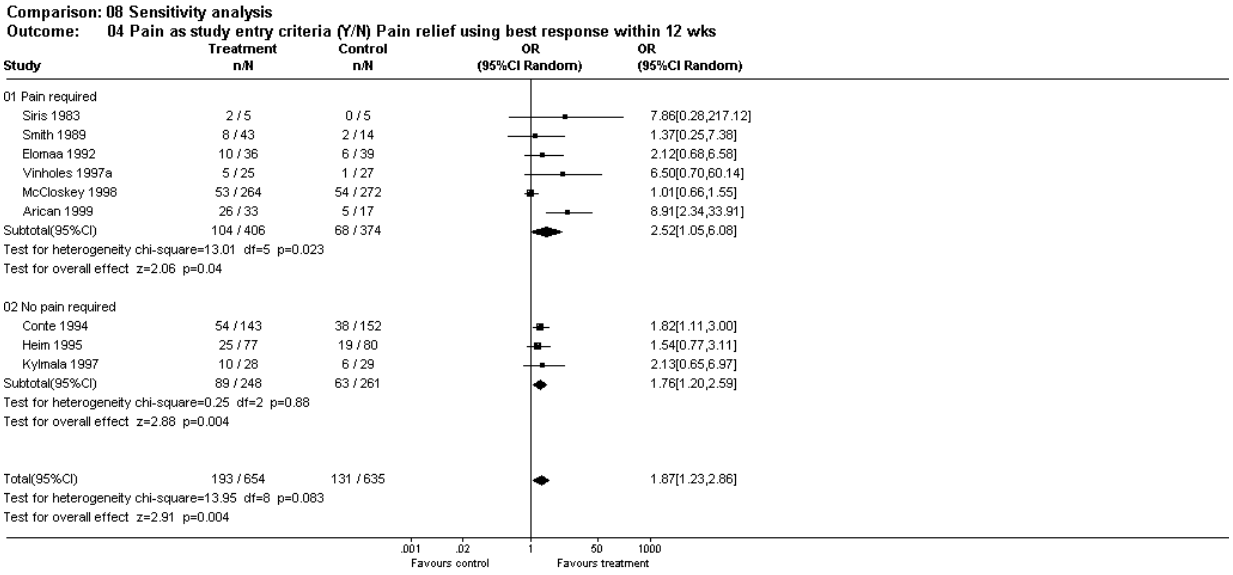
Secondary analysis by primary disease site



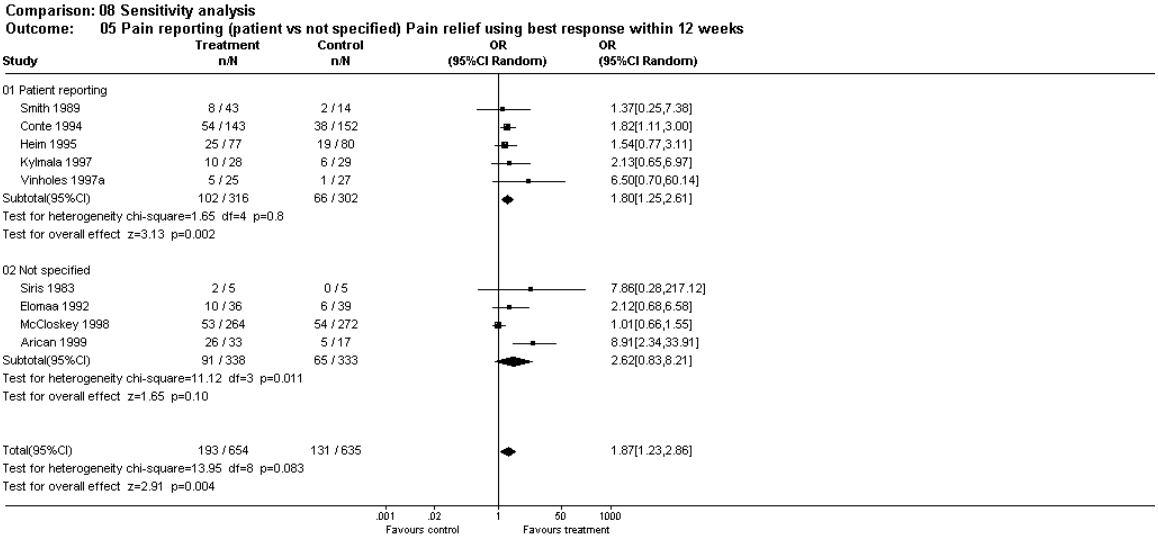
Secondary analysis by type of control (blinded versus open control)



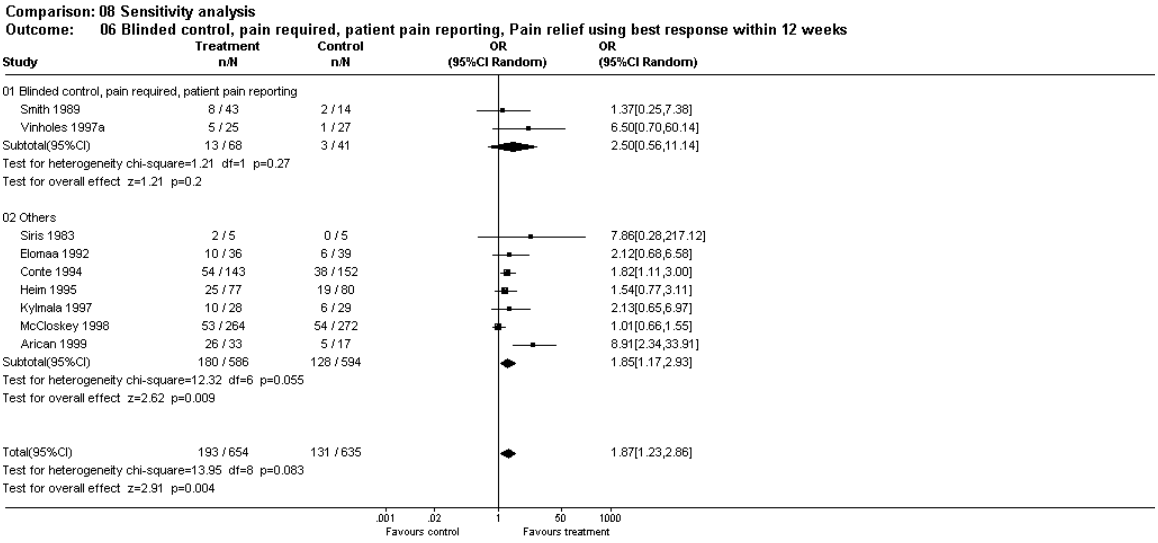
Secondary analysis: pain as study entry criteria or not



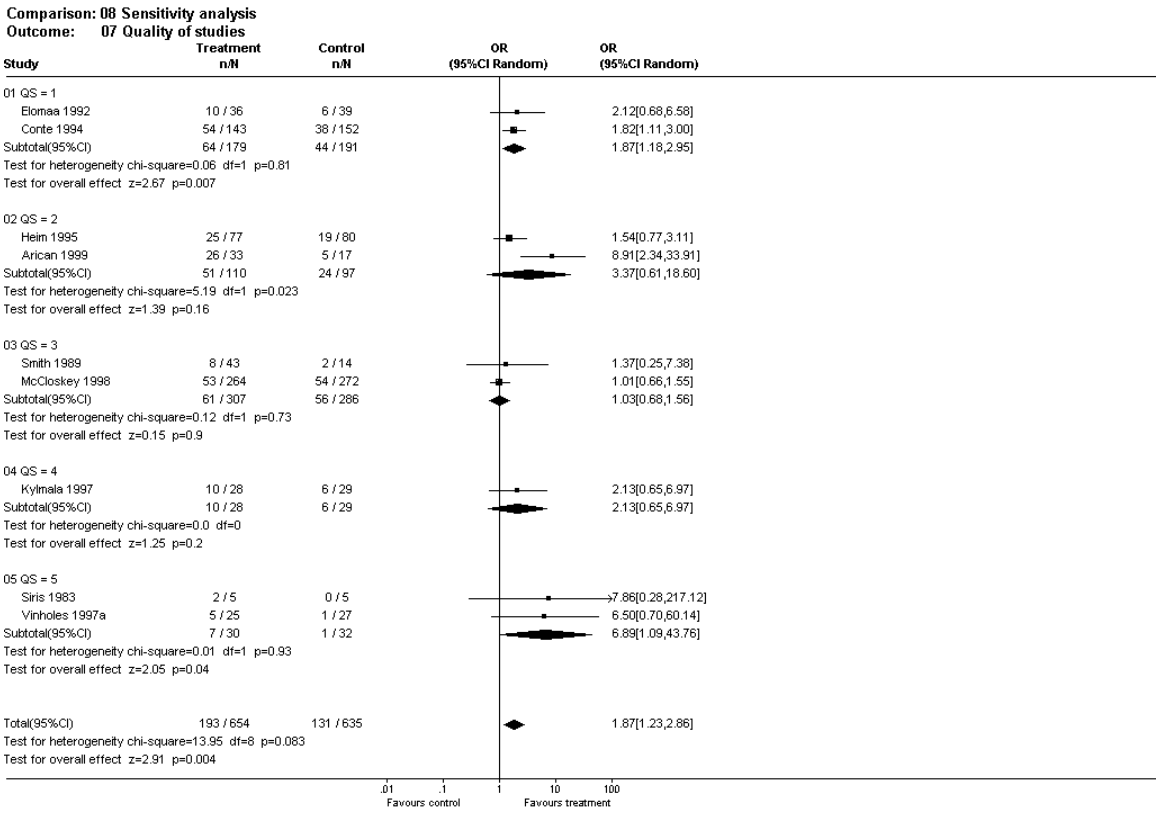
Secondary analysis: pain specified as patient reported or not



Secondary analysis for combined “best” design criteria (blinded, patient reported pain and all patients had pain at study entry) versus others



Secondary analysis for study quality



a) Effect due to primary site of a cancer

For this variable, too few trials contained adequate data to allow the performance of sensitivity analyses (Figure 8). Of the nine available trials, two involved patients with breast cancer (N=305), three involved prostate cancer (N=189), two involved multiple myeloma (N=693) and two involved patients with any histopathology (N=102). Among the trials examining patients with breast cancer and bone metastases, the effect remained statistically significant. For prostate cancer and multiple myeloma, there was a non-significant trend. For the group with the greatest primary effect, the OR was 8.2 [95% CI 2.61 to 25.77].

b) Effect due to control arm blinding

When only trials using blinded controls were included in the analysis, the magnitude of benefit was smaller, but still statistically significant OR 1.53 [95% CI 1.06 to 2.21] (Figure 8).

c) Effect due to whether pain was a required trial entry criterion

Some trials only recruited patients who had pain at the time of randomization. When these trials were compared with those that did not require pain at trial entry, the effect was preserved; OR 2.52 [95% CI 1.05 to 6.08] (Figure 8).

d) Effect due to whether pain was specified as "patient-expressed"

Some trials stated that pain was documented as expressed by the patient. When these trials were contrasted with those that did not document pain in this way, the effect was confined to the former group of trials OR 1.8 [95% CI 1.25 to 2.61] (Figure 8).

e) Effect due to "stringent trial design" (restriction to trials with blinded controls, patient-expressed pain and pain required at trial entry)

If our review had started with the most stringent trial selection criteria in terms of pain study, two trials would have provided data on the proportion of patients with pain relief (Figure 8). There was a non-significant trend in support of benefit.

f) Effect by trial quality

Out of a maximum score of five, the quality of the trials ranged from one to five (Figure 8). There was no consistent effect from trial quality.

3.2.6 Summary of clinical effectiveness

- Of the 51 trials (N=9,467) that fulfilled the selection criteria for our review, nine (N=1,289) provided data on the proportion of patients with pain relief within 12 weeks of trial entry. The data supported the effectiveness of pain relief OR 1.87 [95% CI 1.23 to 2.86].
- Secondary analyses using the proportion of patients with pain relief (best response) as a primary endpoint demonstrated that this effect was preserved when the requirements were restricted to blinded controls, pain at trial entry and pain scores restricted to those that were patient-expressed.
- The secondary endpoints supported this conclusion. The number of patients able to reduce their analgesic intake was significantly higher in the bisphosphonate groups (three studies, N=192) OR 2.37 [95% CI 1.1 to 5.12].
- Standardized pain scores and morphine equivalent consumption were not amenable to data pooling due to the limited availability of CI figures. Qualitative inspection of available data supported a modest reduction in mean pain score and morphine consumption with the use of bisphosphonates.
- No effect was observed in the data comparing lower versus higher doses of bisphosphonate agents.
- There was no statistically significant difference when pamidronate was compared to clodronate or zoledronate.
- Analyses by primary site and type of bisphosphonate were limited due to the small number of trials available. Significant differences between primary sites or between bisphosphonates were not observed.
- Bisphosphonates were generally well tolerated. Nausea and vomiting were the most commonly reported adverse effects.
- There were no trials with adequate data to allow direct comparisons between bisphosphonates and other therapies such as analgesics alone, palliative radiotherapy or palliative chemotherapy.

4 DISCUSSION

This report updated a 2001 Cochrane review,[67] which included 30 RCTs. In our review, 21 RCTs were added. The additional trials were recent RCTs and protocols that included patients with prostate cancer and trials examining the drugs zoledronate and ibandronate.

The data support a statistically significant effect of bisphosphonates on pain relief within 12 weeks. The amount of pain is reduced in the order of <1 out of a 10-point scale, based on qualitative observation of available data.

Pamidronate 60 and 90 mg q3 to 4 weeks and clodronate 1,600 mg/day orally are the most commonly studied regimens. No evidence-based conclusions can be drawn in terms of the most efficacious dosage or type of bisphosphonate agent.

The evidence available on adverse effects indicates that there is no increase in toxicities with the use of bisphosphonates. For etidronate, there is no significant difference in toxicity. There is an increase in "diarrhea or constipation" for patients receiving clodronate. For pamidronate, there are increases in serum hypocalcemia, drug discontinuation and local reactions. For zoledronate, grade 3 elevation of creatinine, anemia, fever and limb edema are significantly increased in patients. The toxicity profiles highlighted in these studies do not confirm some of the more common toxicities of bisphosphonates such as those of the gastrointestinal tract (flu-like illness;[68]nausea and vomiting;[69] esophagitis[70-72]). Other toxicities such as fever,[69] phlebitis,[70] creatinine elevation,[69] hypocalcemia [73] and rare but potentially serious complications such as uveitis[70,74] and scleritis[70] are not observed.

Report Limitations

- To include pain data that may be available as secondary endpoints, broad RCT selection criteria are used. As a result, many of the included trials do not have the required outcomes to allow their inclusion. Pain relief is not the primary endpoint in many of the trials and thus, it is not reported in enough detail to allow the extraction of endpoints for analysis.
- Pain is a subjective outcome. There are many methodological issues in its reporting that can affect trial outcomes. While our review tries to account for some of the factors (e.g. use of patient-expressed pain data), others (type of pain, average versus worse pain) cannot be considered. There are many ways in which pain outcomes can be reported; there is no consensus on which outcomes are the most important. Positive pain outcomes in trials may be preferentially highlighted, while negative ones are not reported.
- Many trials do not present standard deviations for continuous variables (morphine equivalent, pain scores). This limits the quantitative analyses of data.
- Quality of life, especially in trials designed to address the effect on short-term pain relief, is seldom reported.

- Adverse effects reporting is a secondary endpoint. Adverse effects are reported in more detail for more recent trials. This reporting does not always distinguish between what is treatment-related or not, is not confined to the 12-week time frame of interest and includes small numbers of patients for rare adverse effects.

Despite these limitations, our review collates information from trials that study the role of bisphosphonates in patients with cancer and involve over 9,000 patients. This represents the most comprehensive collection of data available to examine the effectiveness of bisphosphonates for the relief of pain due to bone metastases. Among these studies, colorectal cancer, lung cancer and less common malignancies are sparsely represented. Despite the wide spectrum of patients and study designs, the data are sufficiently homogeneous to permit quantitative analyses in some cases. Thus, it may be reasonable to generalize the findings to patients with pain due to bone metastases.

We found no similar reviews that addressed the use of bisphosphonates in short-term pain relief for a range of cancers. Several disease-specific systematic reviews have been conducted to address the role of bisphosphonates in the management of multiple myeloma [6,75] and breast cancer.[5] The Cancer Care Ontario Practice Guideline Initiative updated their guideline in December 2002 on the use of bisphosphonates in women with breast cancer. One key recommendation was: "[i] in patients with bone metastases and pain, treatment with pamidronate or clodronate may be a useful adjunct to conventional measures for pain control."[76] Berenson *et al.*[75] published the 2002 ASCO (American Society of Clinical Oncology) clinical practice guidelines for bisphosphonates in multiple myeloma. They concluded that "intravenous pamidronate or zoledronic acid are recommended for patients with pain due to osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures or impending fractures" (level II evidence, grade B recommendation). Our findings are consistent with these recommendations and provide more details on the limitations of available data.

In practice, bisphosphonates are used for pain relief, especially in palliative care and pain clinics. In these settings, they serve as one treatment option available for the management of patients, particularly where more common modalities, such as analgesics and radiotherapy, are less effective than they need to be. In this regard, our review supports current practice.

What remain unclear are the circumstances under which bisphosphonates should be used. The favourable toxicity profile and ease of administration (oral) may make it easy for physicians to prescribe some forms of this medication in the ambulatory setting. The widespread use of bisphosphonates, however, in patients with mild localized pain, when less costly and equally effective modalities are available, may be inappropriate. Similarly, the use of bisphosphonates for skeletal complications, such as pending pathological fractures and early cord compression may not be the best choice. The modest pain relief and the availability of treatment alternatives must be taken into account when considering bisphosphonates as therapy for pain control.

With the increasing use of bisphosphonates as “adjunctive therapy” for patients with multiple myeloma, breast cancer and prostate cancer, examination of the effectiveness of bisphosphonates in patients who have failed other therapies is beyond the scope of this review.

To assess the use of bisphosphonates in the management of pain secondary to bone metastases, areas for consideration include route of administration, economic impact and effectiveness in comparison with alternative therapies.

To permit evaluations and comprehensive comparisons, future research must incorporate standard methods of reporting pain outcomes, including measurement of the proportion of patients achieving pain relief. Also desirable is the use of standard deviations when reporting continuous variables such as pain score and morphine equivalent.

5 CONCLUSIONS

Bisphosphonates are moderately effective in relieving pain for patients with bone metastases when this is assessed within 12 weeks. No drug regimen is superior and the effect is not limited to any cancer pathology. There are no studies with adequate outcomes to allow comparisons of bisphosphonates with therapies such as other analgesic regimens, palliative radiotherapy and palliative chemotherapy. Prescribers and patients should have realistic expectations in terms of its modest effect. The delayed effect (benefit at 12 weeks) and adverse effects should be considered when making treatment choices.

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Appendix 1: Literature Search Strategies

Guide to Search Syntax (Ovid, DIALOG®, Cochrane Library)

Exp	Explode the search term. Retrieve the search concept plus all narrower terms.
$	Truncation symbol. Retrieve plural and variant endings of search terms.
Adj	Proximity operator. Words must be adjacent.
adj#	Proximity operator. Words must be adjacent each other within the specified number.
/	Descriptor i.e., subject heading (a controlled, thesaurus term).
ti	Search in titles.
mp	Major headings including title, keywords, subject headings, abstract, heading word, registry number.
!	Explode the search term. Retrieve the search concept plus all narrower terms.
?	Truncation symbol, single character. Retrieve plural and variant endings of search terms.
*	Truncation symbol, any number of characters.
(w)	Proximity operator. Words must be adjacent.
()	Proximity operator. Words must be adjacent.
(n)	Proximity operator. Words must be near each other in any order.
de	Descriptor i.e., subject heading (a controlled, thesaurus terms).
ME	Medical subject heading.
tw	Text Word (includes words from titles, abstracts and keywords).
ab	Search in article abstract.
" "	Search phrases.
rn	Registry number (i.e. CAS).

Databases/Dates	Limits	Subject Headings/Keywords
Ovid Technologies Inc. Ovid Multiple Database Search MEDLINE® (1966 to October Week 5 2001) EMBASE® (1980 to 2001 Week 46) BIOSIS Previews® (1970 to 2001 Week 47) CANCERLIT® (1975 to October 2001) Current Contents® /All Editions (1993 Week 26 to 2001 Week 49)	Human	bone neoplasms/ OR bone neoplasm/ OR multiple myeloma/ OR neoplasm metastasis/ OR neoplasms/ OR ((bon$ adj metastas$s) OR (metastastic adj carcinoma)).mp,tw. OR (neoplasm$ OR cancer$).mp,tw. **AND** alendronate/ OR diphosphonate/ OR etidronic acid/ OR etidronate/ OR didronel/ OR pamidronate/ OR zolendronate/ OR diphosphonates.mp. OR (alendronate adj (sodium OR disodium)).mp,tw. OR (etidronate adj (sodium OR disodium)). mp,tw. OR (bisphosphonate$ OR diphosphonate$ OR etidronate).mp,tw. OR (didronel OR osteodidronel OR diphos OR difosfen OR osteum OR etidron OR didronate OR didrocal OR didro-kit OR didronel pmo OR bonefos OR ostac OR dichloromethylene adj bisphosphonate).mp,tw.

Databases/Dates	Limits	Subject Headings/Keywords
		(pamidronate OR aredia OR actonel OR alend OR bifosa OR eucalen OR fosalan OR fosamax OR indrol OR mavil OR neobon OR osteovan).mp,tw. OR ((risedronate adj sodium) OR (risedronate adj sodium adj hemi-pentahydrate)).mp,tw. OR (ibandronic adj acid).mp,tw. OR (sodium adj ibandronate).mp,tw. OR (bondronat OR ibandronat OR skelid OR clodronate OR zometa OR zolendronate OR tiludronate).mp,tw. OR (clodronic adj acid).mp,tw. OR (bisphosphonate$ adj (agent$ OR derivative$)).mp,tw. OR (66376-36-1 OR 2809-21-4 OR 10596-23-3).rn, rw.

Databases/Dates	Limits	Subject Headings/Keywords
		AND exp clinical trials/ OR exp clinical trial/ OR exp meta analysis/ OR exp controlled clinical trial/ OR exp controlled clinical trials OR exp evaluation studies/ OR exp evidence-based medicine/ OR exp randomized controlled trials/ OR exp randomized controlled trial/ OR follow-up studies/ OR follow-up study/ OR prospective study/ OR major clinical study/ OR controlled study/ OR random allocation/ OR double-blind method/ OR single-blind method/ OR placebos/ OR placebo/ OR research design/ OR comparative study/ OR crossover procedure/ OR [randomized controlled trial OR controlled clinical trial OR clinical trial].pt. OR (random$ OR randomi$ed OR RCT OR control$ OR prospectiv$ OR placebo$ OR double-blind$ OR single-blind$).mp,tw. OR ((singl$ OR doubl$ OR trebl$ OR tripl$) adj5 (blind$ OR mask$ OR dumm$)).mp,tw. OR ((meta adj analys$s) OR metaanaly$ OR (meta adj analy$)).mp,tw. OR ((random adj allocation) OR (clinical adj trial$)).mp,tw. OR

Databases/Databases	Limits	Subject Headings/Keywords
		(research adj (integration OR overview)).mp,tw. OR (integrative adj research).mp,tw. OR ((research OR quantitative OR methodologic OR systematic OR collaborative) AND (review$ OR overview$ OR synthes$s OR integration)).mp,tw. OR (multicenter stud$ OR multi-cent$r$ stud$ OR multicent$ stud$).mp,tw. *Total hits 1304 references* *EMBASE® 408 references* *BIOSIS Previews® 34 references* *MEDLINE® 757 references* *Current Contents® 105 references* *Search performed on 22 November 2001*
DIALOG® Alerts MEDLINE® CANCERLIT®		bone neoplasms/de OR multiple myeloma/de OR neoplasm metastasis/de OR neoplasms/de OR bon?()metastas?s/ti,ab OR metastastic()carcinoma/ti,ab OR neoplasm?/ti,ab OR cancer?/ti,ab OR tumo?r/ti,ab OR metastastic()disease?/ti,ab AND diphosphonates!/de OR alendronate/de OR etidronic acid/de OR etidronate/de OR didronel/de OR pamidronate/de OR /de OR bisphosphonate?/ti,ab OR diphosphonate?/ti,ab OR didronel/ti,ab OR osteodidronel/ti,ab OR diphos/ti,ab OR difosfen/ti,ab OR osteum/ti,ab OR

Databases	Limits	Subject Headings/Keywords
		etidron/ti,ab OR didronate/ti,ab OR didrocal/ti,ab OR didro-kit/ti,ab OR didronel()pmo/ti,ab OR pamidronate/ti,ab OR aredia/ti,ab OR actonel/ti,ab OR pamidronate/ti,ab OR aredia/ti,ab OR actonel/ti,ab OR alend/ti,ab OR bifosa/ti,ab OR eucalen/ti,ab OR fosalan/ti,ab OR fosamax/ti,ab OR indrol/ti,ab OR mavil/ti,ab OR neobon/ti,ab OR osteovan/ti,ab OR risedronate/ti,ab OR risedronate()sodium/ti,ab OR ibandronic()acid/ti,ab OR bondronat/ti,ab OR ibandronat/ti,ab OR skelid/ti,ab OR clodronate/ti,ab OR zometa/ti,ab OR zoledronate /ti,ab OR tiludronate/ti,ab OR clodronic acid/ti,ab OR bisphosphonate()agent?/ti,ab OR bisphosphonate()derivative?/ti,ab OR bonefos/ti,ab OR ostac/ti,ab OR dichloromethylene()bisphosphonate/ti,ab **AND** double-blind method/de OR meta-analysis/de OR random allocation/de OR dt=meta analysis OR dt=randomized controlled trial OR dt=controlled clinical trial OR [(random? OR double(w)blind? OR double(w)dumm? OR double(w)mask? OR triple(w)blind? OR triple(w)dumm? OR triple(w)mask? OR treble(w)blind? OR treble(w)mask? OR treble(w)dumm? OR placebo? OR meta(w)analy? OR metaanaly? OR quantitative(w)review? OR quantitative(w)overview? OR methodologic?(w)review? OR methodologic?(w)overview? OR control?(w)stud? OR control?(w)trial? OR RCT? ? OR control?(w)clinical(w)trial? OR control?(w)clinical(w)stud?)]ti,ab

Databases/Dates	Limits	Subject Headings/Keywords
DIALOG® Alerts EMBASE®		*Same keywords as Medline*
DIALOG® Alerts BIOSIS Previews®		alendronate/de OR bisphosphonates/de OR clodronate/de OR pamidronate/de OR ibandronate/de OR etidronate/ OR zoledronate/de OR *Same keywords as Medline* **AND** neoplasm/de OR multiple myeloma/de **AND** randomized controlled trial/de OR randomized clinical trial/de OR comparative study/de OR prospective study/de OR clinical trial/de OR *Same keywords as Medline*
National Library of Medicine PubMed Updates	Human	MeSH headings and keywords to mirror DIALOG® Medline search *Last update December 2002*
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library 2001, Issues 2, 3; 2002, Issues 1, 2, 3; 2003.		Bone-Neoplasms*:ME OR Multiple-Myeloma*:ME OR Neoplasm-Metastasis*:ME OR [(Bon* near Metastas*) OR (Metastastic near Carcinoma) OR ((Cancer* OR Neoplasm*) OR tumo*) OR (Metastastic near Disease*)] Textwords **AND** Diphosphonates*:ME OR Alendronate*:ME OR Etidronate-Disodium*:ME

Databases/Dates	Limits	Subject Headings/Keywords
		OR [(Etidronate OR Didronel OR Pamidronate OR Zolendronate OR Bisphosphonate* ORDiphosphonate* OR Osteodidronel OR Diphos OR Difosfen OR Osteum OR Etidron OR Didronate OR Didrocal OR Pamidronate OR Aredia OR Actonel OR Alend OR Fosamax OR Bifosa OR Eucalen OR Fosalan OR Indrol OR Mavil OR Neobon OR Osteovan OR Risedronate OR Bondronat OR Ibandronat OR Skelid OR Clodronate OR Zometa OR Zolendronate OR Tiludronate OR Bisphosphonate* OR Bonefos OR Ostac)] Textwords *The Cochrane Datebase of Systematic Reviews = 7 reviews; Database of Reviews and Effectiveness = 2 references;* *The Cochrane Controlled Trials Register = 263 references; NHS and other healthcare agencies = 11 abstracts*
Websites of Health Technology Assessment (HTA) and related agencies; clinical trial registeries; other databases		NICE; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD Databases; ASCO etc.

Appendix 2: Quality Assessment Instruments

RM number _____ Reviewer _____

A. Study Quality

1. Randomization: Total points: ☐ 0 ☐ 1 ☐ 2
A trial reporting that it is "randomized" receives one point. Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. If the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers), a point is deducted.

2. Double-blinding: Total points: ☐ 0 ☐ 1 ☐ 2
A trial reporting that it is "double-blind" receives one point. Trials that describe an appropriate method of double-blinding (identical placebo, active placebo) receive an additional point. If the report describes the trial as double-blind and uses an inappropriate method (e.g. comparison of tablets versus injection with no double dummy), a point is deducted.

3. Withdrawals and dropouts: Total points: ☐ 0 ☐ 1
A trial reporting the number and reason for withdrawals receives one point. If there is no statement, no point is given.

Total score ☐ low (0 to 2 points) ☐ moderate (3 to 4 points) ☐ high (5 points)

B. Allocation concealment

Adequate: central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes

Inadequate: alternation, reference to case record number or date of birth

Unclear: allocation concealment approach is not reported or fits neither of the above categories.

Allocation: ☐ adequate ☐ inadequate ☐ unclear

Appendix 3: Data Collection Sheet

Record number:		Lead author: Date:	

Patients: Number:	Age:	Condition:
Design, study duration and follow-up:		
Dosage regimen:		
Outcome measures:		
Analgesic outcome results:		
Withdrawals and adverse effects:		

Quality score:

Reviewer	Randomized?	Double-blind?	Withdrawals and dropouts?	Overall quality score
1				
2				
3				

Appendix 4: Primary Trials and Corresponding Duplicate References

Primary trials	**Duplicate references**
Berenson 1996a[18]	77-81
Berenson 2001a[19]	82
Coleman 1998[23]	83
Conte 1994[24]	84
Daragon 1993a[25]	85
Elomaa 1983[29]	86,87
Elomaa 1992[30]	88,89
Ernst 1997[32]	90,91
Glover 1994[34]	92
Heim 1995[36]	93
Hortobagyi 1998[94]	94-98
Jagdev 2001[39]	99
Koeberle 1999[12]	65
Kraj 2000a[40]	100
Smith 1989[56]	101
Theriault 1999[58]	97,98,102,103
van Holten Verzantvoort 1993 [60]	104-107
Vinholes 1997a[61]	63,108,109