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Bisphosphonates for the relief of pain secondary to bone metastases.
Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD002068.
DOI: 10.1002/14651858.CD002068.

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TABLE OF CONTENTS

[Intervention Review]

Bisphosphonates for the relief of pain secondary to bone metastases

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 8, 2017.

Citation: Wong RKS, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD002068. DOI: 10.1002/14651858.CD002068.

ABSTRACT

Background

Bisphosphonates form part of standard therapy for hypercalcemia and the prevention of skeletal events in some cancers. However, the role of bisphosphonates in pain relief for bony metastases remains uncertain.

Objectives

To determine the effectiveness of bisphosphonates for the relief of pain from bone metastases.

Search methods

MEDLINE (1966 to 1999), EMBASE (1980 to 1999), CancerLit (1966 to 1999), *T he Cochrane L ibrary* (Issue 1, 2000) and the Oxford Pain Database were searched using the strategy devised by the Cochrane Pain, Palliative and Supportive Care Group with additional terms 'diphosphonate', 'bisphosphonate', 'multiple myeloma' and 'bone neoplasms'. (Last search: January 2000).

Selection criteria

Randomized trials of bisphosphonates compared with open, blinded, or different doses/types of bisphosphonates in cancer patients were included where pain and/or analgesic consumption were outcome measures. Studies where pain was reported only by observers were excluded.

Data collection and analysis

Article eligibility, quality assessment and data extraction were undertaken by both review authors. The proportions of patients with pain relief at 4, 8 and 12 weeks were assessed. The proportion of patients with analgesic reduction, the mean pain score, mean analgesic consumption, adverse drug reactions, and quality of life data were compared as secondary outcomes.

Main results

Thirty randomized controlled studies (21 blinded, four open and five active control) with a total of 3682 subjects were included. For each outcome, there were few studies with available data. For the proportion of patients with pain relief (eight studies) pooled data showed benefits for the treatment group, with an NNT at 4 weeks of 11[95% CI 6-36] and at 12 weeks of 7 [95% CI 5-12]. In terms of adverse drug reactions, the NNH was 16 [95% CI 12-27] for discontinuation of therapy. Nausea and vomiting were reported in 24 studies with a non-significant trend for greater risk in the treatment group. One study showed a small improvement in quality of life for the treatment group at 4 weeks. The small number of studies in each subgroup with relevant data limited our ability to explore the most effective bisphosphonates and their relative effectiveness for different primary neoplasms.

Authors' conclusions

There is evidence to support the effectiveness of bisphosphonates in providing some pain relief for bone metastases. There is insufficient evidence to recommend bisphosphonates for immediate effect; as first line therapy; to define the most effective bisphosphonates or their relative effectiveness for different primary neoplasms. Bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases.

PLAIN LANGUAGE SUMMARY

Bisphosphonates for the relief of pain secondary to bone metastases

Bisphosphonates give some relief from pain caused by cancer that has invaded bones. Patients with cancer that has spread to the bone frequently have pain. Pain control is an important part of cancer management. Bisphosphonates are medicines that affect the way bone develops, and are proving useful in treating patients with cancer that has invaded the bone (metastasis). This review looked at the effect of bisphosphonates on pain caused by bone metastases. Bisphosphonates do have some effect but are not as useful as either strong analgesics (such as morphine) or radiotherapy. However, where other methods of pain relief are inadequate, the addition of bisphosphonates can be beneficial. Bisphosphonates can cause nausea and vomiting.

BACKGROUND

Bisphosphonates are structural analogues of pyrophosphates, a naturally occurring component of bone crystal deposition. Different side chain modification of the basic pyrophosphate structure gives rise to the different generations of bisphosphonates, with different levels of activity. The mode of action of bisphosphonates are multiple. Predominantly, through strong affinity to bone, bisphosphonates provide physico-chemical protection by absorbing calcium phosphate, suppressing the normal functioning of mature osteoclasts, and prevent osteoclast precursors maturing.

Bisphosphonates have been shown to be effective in the management of patients with hypercalcemia (Body 1996), securing their place as standard therapy for this condition. More recently, bisphosphonates have been shown to be effective in decreasing morbidity related to bony metastasis in patients with breast cancer (Lipton 1997; CCOPGI 1999) and multiple myeloma (Bloomfield 1998). The available evidence has significantly changed the management of these patients in recent years, with the incorporation into standard clinical practice the use of bisphosphonates in breast cancer patients with early bone metastasis and newly diagnosed myeloma patients aimed to minimize the morbidity related to bony metastasis. In addition to the long-term effect of preventing tumor deposits into bone, bisphosphonates may also reduce pain arising from bone metastasis (Mannix 2000; Johnson 2001).

Pain is often a devastating symptom in the management of cancer patients. Analgesics have been indispensable in the management of cancer pain and are an integral part of cancer pain management. Despite the use of increasingly versatile and potent analgesics, co-analgesics, and other means such as radiotherapy, there remain situations where the achievement of adequate pain control is limited. In these situations the use of bisphosphonates in relieving pain from bone metastases is gaining popularity, although remains a subject of debate.

OBJECTIVES

The primary objective of this review is to determine the effectiveness of bisphosphonates for pain relief in patients with painful bony metastases.

METHODS

Criteria for considering studies for this review

Types of studies

Only studies using a randomized design published in full were included. (Abstracts were excluded). It was our intention to include all studies where the effect of bisphosphonate on cancer pain was assessed. We therefore interpreted this criterion broadly and accepted studies with any pain or analgesic outcome measures. Whether pain was an eligibility criterion or not would have an impact on the proportion of patients eligible to experience pain relief. Pain expressed by observers only (e.g., physicians) has well-documented discordance with patient reported pain scores (Cleeland 1989; Sutherland 1988; Van der Does 1989). Only studies with subject (patient) reported pain were included. Studies where the source of the pain scores was not specified were included.

Sensitivity analyses were used to assess the impact of:

- pain as an eligibility criterion in the primary studies
- pain specified as being patient-reported

Types of participants

Clinical trials including patients with bony metastases from any primary neoplasms were eligible for inclusion.

Types of interventions

Reports describing the use of bisphosphonates (oral or intravenous) were eligible for inclusion. The control arm could comprise placebo or open controls. Studies where different doses of bisphosphonates were compared (i.e., active controls) were also included but were analyzed separately. The use of antineoplastic therapy (chemotherapy, radiotherapy) did not constitute exclusion from the review provided these treatments were available uniformly to study participants in both treatment arms.

Types of outcome measures

The types of outcome measures compared between the study and control groups were:

Primary outcomes

- Proportion of patients with pain relief.

Secondary outcomes

- Mean or median pain score.
- Adverse drug reactions.
- Quality of life.
- Other pain and analgesic outcome measures reported in the trials.

Search methods for identification of studies

Studies for inclusion in this review were identified from:

Electronic databases

- MEDLINE (1966 to 1999)
- EMBASE (1980 to 1999)
- CancerLit (1966 to 1999)
- *The Cochrane Library* (CCTR) (2000)
- the Oxford Pain Database (1950 to 1994)

The search strategy devised by the Cochrane Pain, Palliative and Supportive Care Group for identifying randomized trials was used, with the addition of the following terms:

- diphosphonate*
- bisphosphonate*
- generic and trade names of bisphosphonates
- multiple myeloma
- bone neoplasms

The RCT filter developed by Dickersin et al (Dickersin 1994) was applied.

Reference lists

Reference lists from published trial reports and reviews were searched for potential studies for inclusion in the review.

No language restriction was applied to the search strategy.

Data collection and analysis

Article selection

Articles identified through the search strategy were assessed independently by both authors. Review authors were not blinded to the source or author of the document for article selection, data extraction or quality assessment.

Classification of trials by type of control arm

Studies with blinded placebo control arms produce less bias than over open controls (Schulz 1996). Studies employing active controls were included in order to explore whether a dose response relationship existed. If a dose response relationship was found, this would provide additional evidence of treatment effectiveness. Studies employing active controls were analyzed separately to address the dose response relationship. The effect of blinded versus open controls on the analysis was explored through sensitivity analysis.

Special considerations for interpreting selected outcomes of interest

1. Proportion of patients with pain relief

This was chosen as the primary outcome for this review as it was most suited for quantitative systematic review analysis and allowed the calculation of odds ratios, the pooling of data, and was amenable to analyses based on the intention-to-treat principle. In adopting this dichotomous outcome approach, it should be noted that it is sensitive to how the pain response was defined.

2. Mean or median pain score between study arms post treatment and mean analgesic consumption

This is a summary statistic that is commonly used in the reporting of pain trials but needs careful interpretation. In studies where the sample sizes are large, differences may be statistically significant without being clinically significant. The level of pain experienced by patients prior to the commencement of the intervention is rarely identical between study arms. This parameter is not amenable to an intention-to-treat analysis when the primary trialists did not use this approach in their reporting. Standard deviations are rarely reported, limiting the ability to use this as the summary statistic for quantitative analysis.

3. Analgesic endpoints

Analgesia is an unavoidable confounder in trials of this kind. As secondary outcomes, we chose to extract data regarding:

- the proportion of patients with analgesic reduction, and
- mean or median analgesic consumption.

The methodological considerations for the interpretation of these parameters are similar to those discussed above in relation to pain.

4. Adverse drug reactions

Reporting of adverse drug reactions was variable across the trials. Where available, similar descriptors were pooled. In general, the time frame in which adverse reactions were experienced was not specified.

5. Quality of life

Qualitative comparisons of available data were used.

6. Other endpoints

Clinical outcomes reported in addition to those selected as secondary outcomes for this review are tabulated and described in Table 1; Table 2; Table 3; Table 4.

Time frame of interest

To have significant clinical relevance, any pain relief intervention should have a measurable effect an immediate or intermediate time frame. We therefore selected our time frame of interest as within 12 weeks of the commencement of the intervention, and data were collected at 4 weeks, 8 weeks and 12 weeks.

Data extraction

Data extraction sheets were designed a priori and completed independently by the two authors. Where discrepancies arose, these were discussed and a consensus reached. Details of the information sought are given in Table 5.

Pooling of data

Homogeneity of outcome measures were assessed using Chi square statistics. Where results were considered homogeneous, data were pooled to provide a summary statistic. For dichotomous outcomes, odds ratios were used to compare pooled data. The number-needed-to-treat (NNT) for treatment effect was calculated where appropriate. For continuous data (e.g., standardized pain and analgesic scores) the weighted mean difference was used as the summary statistic.

In presenting the results in the MetaView tables, where more than two active arms are compared, the highest and lowest dose arms only are presented.

Sensitivity analysis/potential sources of heterogeneity

Sensitivity analyses were planned to examine the robustness of the primary conclusions in relation to the following parameters:
1. Nature of control arm (blinded versus open controls)
2. Pain as a study entry criterion (yes versus no)
3. Pain specified as patient reported (specified versus not specified)
4. Blinded controls, pain as study entry criterion and pain specified as patient reported
5. Route/type of bisphosphonates (first versus second versus third generation, intravenous versus oral route)
6. Primary disease site (prostate versus breast versus others)
7. Quality of study (Oxford Quality Scale) (Jadad 1996)

In order to conduct the sensitivity analyses, an outcome parameter that best represented the effectiveness of bisphosphonates in pain relief, and where the maximum number of studies were represented was desirable. We used, "the best response for the proportion of patients with pain relief within 12 weeks". This parameter was chosen retrospectively, due to the limited amount of data available at each time point of interest.

RESULTS

Description of studies

Search results

Eighty-five publications (full papers and abstracts) were identified, reporting on 51 randomized studies of the use of bisphosphonates in cancer. Twenty-one studies were excluded; the reasons for exclusion are described in the 'Characteristics of excluded studies' table. A total of 30 studies met the inclusion criteria for this review.

Twenty-one reports of placebo controlled double blind studies, four open control studies and five studies with active controls were eligible for inclusion (Table 1). These described 3582 participants, with 2096 receiving active treatments and 1586 placebo. In addition to the five studies with active controls, three of the blinded studies (Ernst 1997; O'Rourke 1995; Smith 1989), and one of the open control studies had more than one active arm (Arican 1999).

In summary, the results from 25 studies were available to address the primary objective of the review, and nine studies provided the basis to evaluate whether a dose response relationship existed. None of the active control studies compared different types of bisphosphonates.

Within the double-blind randomized studies, three were crossover studies (Siris 1983; Ernst 1992; Ernst 1997). Only results from the first randomization phase were included in our analyses since the washout periods were judged to be too short (two, two and zero weeks respectively).

Primary disease sites

The primary disease sites addressed were tabulated in Table 1. Nine studies addressed breast cancer, four prostate cancer, seven multiple myeloma, and ten studies included patients with any primary cancers. For studies which included patients with 'any primary site', the patients generally had more advanced disease.

Pain requirement as an entry criteria

Fourteen of the 30 studies required pain at entry into the study (Siris 1983; Smith 1989; Ernst 1992; Lahtinen 1992; Glover 1994; Robertson 1995; Ernst 1997; Strang 1997; Vinholes 1997a; Cascinu 1998; Coleman 1998; Moiseyenko 1998; Arican 1999).

Pain as the primary endpoint

Of the 30 included studies, only five studies were designed with pain relief as a primary endpoint (Conte 1994; Glover 1994; Koeberle 1999; Vinholes 1997a; Cascinu 1998). Of the remainder, seven studies were designed to describe differences in skeletal events, (Belch 1991; van Holten 1993; Berenson 1996; Hortobagyi 1996a; Hultborn 1996; Brinker 1998; Theriault 1999), two studies were designed to describe differences in radiological progression Lahtinen 1992; Coleman 1998), and one in urinary calcium excretion (O'Rourke 1995).

Types of biphosphonates studied

(Table 2, Table 3, Table 4)
Etidronate was used in three studies (Smith 1989; Belch 1991; Daragon 1993), pamidronate in 12 studies and clodronate in 15 studies.

Etidronate was administered orally in two studies (Belch 1991; Daragon 1993) and an initial intravenous route followed by oral maintenance in a study by Smith 1989. The dosing schedules used were as follows:

- 5 mg/kg/day for 28 days every other 28 days (Belch 1991)
- 10 mg/kg/day (Daragon 1993),
- Three dosing schedules were compared in one study:

- 7.5 mg/kg/day for 3 days, then 200 mg twice daily, orally, for one month;
- 7.5 mg/kg/day for 3 days then placebo;
- placebo for 3 days then 200 mg twice daily, orally, for one month; versus placebo (Smith 1989).

Clodronate was used in 15 trials, administered

- orally in nine studies,
- intravenously in three studies, and
- a mixture of intravenous, oral and intramuscular routes in three studies.

Pamidronate was used in 12 studies, administered:

- orally in three studies,
- intravenously in nine studies.

Additional details of the dose schedule are provided in Table 2; Table 3; Table 3.

Co-intervention

Co-interventions, either in the form of hormone therapy or chemotherapy, were administered in 22 of the 30 studies. Eight studies did not appear to use a co-intervention and, of these, seven recruited patients with any primary disease site, typically having failed systemic therapy (Arican 1999; Cascinu 1998; Ernst 1992; Ernst 1997; Koeberle 1999; Moiseyenko 1998; Piga 1998) and one recruited patients with prostate cancer (Strang 1997).

Life expectancy/performance status criteria

The studies included patients at different stages of their illness, ranging from early to late stages of metastatic disease. Twenty studies provided criteria to define the general condition of patients invited into the trials.

- 'Life expectancy' was used in 17 studies (time criteria ranging from more than one month to more than one year).
- performance status (WHO </ = 2, poor physical activity, Eastern Cooperative Oncology Group (ECOG) performance status </ = 2, ECOG </ = 3, >/ = 50%, Karnofsky performance status (KPS) 50-80) in six studies.
- Eleven studies did not provide any information.

Pain and analgesic measurement tools

A wide variety of pain measurement tools were used. Similarly, the reporting of analgesic intake varied between studies.

- One study integrated pain, analgesia and performance status to define treatment response (Vinholes 1997a).

- Six studies did not specify the pain measurement tools used (Siris 1983; Belch 1991; Elomaa 1992; van Holten 1993; Hortobagyi 1996a; Harvey 1996; Ernst 1997).
- The remaining 24 studies used the following:

1. Visual analogue scales (11 studies) (Ernst 1992; Smith 1989; Martoni 1991; Daragon 1993; O'Rourke 1995; Robertson 1995; Hultborn 1996; Strang 1997; Moiseyenko 1998; Piga 1998; Arican 1999)

2. Ordinal scales with:
- 0-3 point scale (Heim 1995),
- 0-4 point scale (Lahtinen 1992),
- 0-5 point scale (Brinker 1998; Conte 1994; Coleman 1998).

3. The Radiation Therapy Oncology Group (RTOG) pain scale (0-9 point scale based on the product of pain intensity (0-3) and severity (0-3)) was used in five studies (Delmas 1982a; Glover 1994; Berenson 1996; Vinholes 1997a; Theriault 1999).

4. Combination of pain measurement tools
Kylmala 1997 used both a visual analogue and a 0-4-point scale
Koeberle 1999 employed the visual analogue scale and present pain index.
Cascinu 1998 employed a quality of life questionnaire which focused on pain

Physician versus patient reporting

Subject/patient reported pain scores were specified in 18 studies. Of these 18 studies, physician reported scores were also collected in three studies (Delmas 1982a, Kylmala 1997, Smith 1989). A further thirteen studies did not specify whether pain was patient or physician reported.

Pain response criteria

The definition of pain response is important when interpreting 'proportion of patients with pain reduction' as an outcome measure.

Eight of the blinded or open control studies presented data on the proportion of patients with pain reduction. The criteria used included:

- proportion with no pain (Siris 1983;Elomaa 1992; Kylmala 1997)
- major pain reduction, not otherwise specified (Smith 1989)
- more than or equal to a 20% reduction in pain score (Vinholes 1997a)
- no pain or no need for treatments (Heim 1995)
- more than or equal to two category reductions in pain score over at least two consecutive reports (Conte 1994)
- definition not specified (Arican 1999).

For studies with active controls, the criteria used included
- more than 10 mm decrease in pain (Moiseyenko 1998)
- major response, not otherwise specified (Coleman 1998)
- did not provide a criterion although the pain scale used was an ordinal scale and it is reasonable to assume that any reduction of more than or equal to 1 point reduction was used (Cascinu 1998).
- definition not specified (Smith 1989; Arican 1999)
- provided a definition but no data on proportion of patients responding (Koeberle 1999)

Risk of bias in included studies

The quality of the 30 included studies was assessed using the Oxford Quality Scale (Jadad 1996). The Oxford Quality Scale scores achieved were not used to weight the results but used for sensitivity analyses to address the impact of quality on the primary conclusion.

Effects of interventions

No clinical or statistical heterogeneity was observed across the outcomes of interest permitting pooling of the data to provide summary statistics.

Proportion of patients with pain relief

(See Table of Comparisons: Comparison 01: 01-03)
Six placebo controlled trials (Siris 1983; Smith 1989; Elomaa 1992; Kylmala 1997; Vinholes 1997a; Arican 1999) and two open controlled studies (Conte 1994; Heim 1995) (i.e. eight of the 25 placebo or open control studies) provided data for this endpoint within the 12 -week time frame. Data were reported for different time points: five studies reported at four weeks, one study at eight weeks, and five studies at twelve weeks.

At week 4: OR 2.21 [95% CI 1.19 to 4.12], NNT 11 [95% CI 6 to 36]
At week 8: only one study provided these data so pooling for this time point was not meaningful
At week 12: OR 2.49 [95% CI 1.38 to 4.48], NNT 7 [95% CI 5 to 12]

Both week 4 and week 12 results showed a significant benefit for patients receiving bisphosphonates. Given the limited number of studies in which data were available, the results for 'best pain response within 12 weeks' were synthesized as follows:
OR 2.37 [95% CI 1.61 to 3.5] , NNT 6 [95% CI 5 to 11] in favor of the treatment group.
(This approach was adopted retrospectively, after the data extraction process revealed the limited data available).

Four of the remaining 17 studies with placebo or open controls (Martoni 1991; O'Rourke 1995; Strang 1997; Brinker 1998) did not provide usable data, but reported on the lack of difference between the pain response for treatment and control groups. A total of 619 patients were involved in these four studies, compared with 771 patients in the eight double blind and open control studies in which data for the proportion of patients with response were available (Siris 1983; Smith 1989; Elomaa 1992; Conte 1994; Heim 1995; Kylmala 1997; Vinholes 1997a; Arican 1999). Fourteen of the 26 placebo or open control studies had no data on the proportion of patients with pain relief during the time frame of interest.

The analyses also provided some insight into the time to, and durability of, the response. The responses observed between 4 and 12 weeks appear to be similar. The response pattern at less than 4 weeks could not be assessed due to the lack of data.

Mean/median pain score

(See Table of Comparisons: Comparison 02: 01-03)
Data were available from seven of the 25 studies (Daragon 1993; Robertson 1995; Berenson 1996; Hortobagyi 1996a; Kylmala 1997; Piga 1998; Arican 1999). However, a quantitative analysis was not possible because:

- in the majority of these studies there were differences in the baseline mean pain score,
- with the exception of two studies (Daragon 1993; Arican 1999), the standard deviations were not provided and therefore results could not be pooled.

In addition, an 'intention-to-treat analysis' could not be undertaken because the trialist did not use this approach.

Of the seven studies, five employed visual analogue scales (VAS) to assess pain levels (Daragon 1993; Robertson 1995; Kylmala 1997; Piga 1998; Arican 1999) and two studies used a 0-9 point scale (Berenson 1996; Hortobagyi 1996a). Standardization of the pain scores was not attempted. The mean pain scores for the study and control arms reported in the original papers are presented in the meta-analysis. Whilst there was a general trend showing the mean pain score was lower for the treatment arm, the magnitude of difference between the treatment and control arms ranged from -0.53 to 2.1 at week 4, and -0.37 to 1 at week 12.

This review serves to highlight the limitation of using mean or median pain scores as an endpoint to evaluate pain relief, especially when trying to interpret the results within a quantitative systematic review.

Proportion of patients with reduction in analgesics

(See Table of Comparisons: Comparison 03: 01-02)
Data for the proportion of patients with reduction of analgesics were available in five of the 26 trials (Martoni 1991; Elomaa 1992; Ernst 1997; Kylmala 1997; Piga 1998). Data were reported at different time frames (three trials had results at week 4 and three trials had results at week 12). Only one study provided data at 8 weeks (Elomaa 1992).

Pooled results gave an OR in favor of the treatment groups as follows:

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

Mean analgesic consumption

Three of the 25 studies reported on mean analgesic consumption (Ernst 1992; Robertson 1995; Ernst 1997). An additional three studies provided some description of the lack of difference in analgesic consumption (O'Rourke 1995; Hultborn 1996; Brinker 1998). There was insufficient information to allow a quantitative summary of the data.

Data from three studies that provided data were summarized here as reported from the original studies:
• Ernst 1997 describes an average change in morphine equivalent (mg) of -6.4 (standard error: S.E. 2.9) for the treatment arm and +24.6 (S.E. 14.9) for the placebo arm (P = 0.03)
• A similar study (Ernst 1992) reported an average change in morphine equivalent (mg) of + 10 (S.E. 8.1) for the treatment arm and + 62 (S.E. 29.6) for the placebo arm (P = 0.096)
• Robertson 1995 reported on the percentage increase in morphine equivalent (mg). At 4 weeks, this was 59% and 64% for treatment and control arm respectively.

These results should be interpreted in the context of the three studies that reported no difference in the analgesic use:

- Hultborn 1996 reports that the use of analgesics was insignificantly lower in the pamidronate group during follow up.
- Brinker 1998 compares the amount of analgesics taken during the trial, and reports no difference between the treatment and control arms (p=0.26).

For both of these studies, the time frames for analgesic comparison were not stated but, based on the study duration, it is likely that a longer time period than that of interest in this review (within 3 months) was allowed.

- O'Rourke 1995 reports that after 4 weeks' treatment, the overall analgesic requirement remained the same.

The problems relating to the interpretation of this endpoint are similar to those discussed for mean change in pain score.

Other analgesic endpoints reported

Four studies used other analgesic endpoints. The small number of studies that employed other endpoints limited the power of inference.

- Daragon 1993 reports on the number of patients taking codeine or morphine between the treatment arms
- Elomaa 1992 and Heim 1995 report on the proportion of patients with no analgesics
- Piga 1998 reports on the proportion of patients with no increase in analgesics

No analgesic information is provided for 12 of the 25 blinded, placebo controlled trials and two open control studies.

Implications from studies with active controls

(See Table of Comparisons: Comparison 04: 01)
Where more than two arms were available, the results for the highest and lowest dose arms only were presented in the MetaView tables. The results of these studies were best suited to address the effect of dose intensity. Within the context that the implications from the blinded placebo controlled trials support the effectiveness of the intervention, the presence of a dose response relationship would strengthen the primary conclusion that there was a treatment effect.

Of the nine studies with active controls, two studies cannot be used to assess dose response relationship. Moiseyenko 1998 examines the same total dose given on day one versus over five days; and Smith 1989 compares a regimen of 'loading and maintenance' with 'loading dose with placebo maintenance', and 'placebo loading with maintenance dose'.

Three studies present data on the proportion of patients with pain relief (Cascinu 1998; Coleman 1998); Arican 1999). However, the results are not statistically significant and no conclusions on a dose response can be drawn.

Four of the seven studies use other outcome measures, not amenable to quantitative analysis, including:

- the percentage reduction of pain score (Ernst 1997; Koeberle 1999)
- the median change in pain score (Glover 1994)
- an insignificant p-value (O'Rourke 1995)

Adverse drug reaction

(See Table of Comparisons: Comparison 05: 01-02)
Fourteen of 20 blinded studies, four of four open control studies, and five of six active control studies present information on adverse drug reactions. Of these, three studies employ the WHO toxicity classification criteria (WHO 1979), and four studies report on the number of patients where adverse drug reaction led to discontinuation of therapy. Details are provided in the 'Characteristics of Included Studies' Table. Nausea and vomiting is reported in 24 studies: OR 1.11 [95% CI 0.79 to 1.58] and indicates a non-significant trend for increased nausea and vomiting.

Discontinuation of therapy due to adverse effects (reported in three studies) - an outcome reflecting their severity - gave an OR of 8.53 [95% CI 1.25 to 58], NNH 16 [95% CI 12 to 27].

Other types of reactions are described, including abdominal pain, allergic reactions, and hypocalcemia. Insufficient data are provided to permit any conclusions to be drawn.

Quality of life

Quality of life comparisons are presented in four of the 26 studies (Berenson 1996; Harvey 1996; Hortobagyi 1996a; Vinholes 1997a). Of these, three presented quality of life comparisons at a time point beyond our time frame of interest (three months). Berenson 1996 reports no difference in quality of life at baseline and nine months. Harvey 1996 reports that, at nine months, quality of life had decreased significantly less with bisphosphonates than with placebo. Hortobagyi 1996a states that fewer patients in the pamidronate group than in the placebo group had a decrease in quality of life scores at last measurement (this study involved a treatment period of 12 months).

Only one study (Vinholes 1997a) provided a quality of life comparison within 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.

Sensitivity analysis

In interpreting our sensitivity analyses, the small number of studies with usable quantitative data should be noted, which limits the strength of the conclusions that can be drawn. We used the parameter, "proportion of patients with pain relief using best response within 12 weeks", to conduct our sensitivity analyses because this measure has some clinical significance for the primary objective of this review, and permits the inclusion of data from the greatest number of studies.

1. Type/and route of bisphosphonates

(See Table of Comparisons: Comparison 06: 01)
No formal sensitivity analysis was possible for etidronate since only one study addressed the outcome of interest (Smith 1989). Five studies provided data for oral clodronate and gave an OR of 3.26 [95% CI 1.8 to 5.89]. For intravenous pamidronate, two studies provided data (Conte 1994; Vinholes 1997a), and gave an OR of 2.35 [0.77 to 7.15].

The small numbers of studies meant conclusions could not be made regarding the relative effectiveness of bisphosphonates on patients with different dose preparations.

2. Primary disease site

(See Table of Comparisons: Comparison 06: 02)
Studies were grouped according to primary disease site using best response for proportion of patients with pain relief within 12 weeks. The results were as follows:

- breast cancer, OR 1.83 [95% CI 1.11 to 3.04]
- prostate cancer, OR 1.81 [95% CI 0.82 to 4.02]
- any primary cancer site, 8.47 [95% CI 2.69 to 27]
- one study included multiple myeloma patients with an OR of 3.51 [95% CI 1.08 to 11.4].

The small numbers of studies meant conclusions could not be made regarding the relative effectiveness of bisphosphonates on patients with different primary disease sites.

3. Nature of control: Blinded versus open

(See Table of Comparisons: Comparison 06: 03)
The exclusion of studies with open controls increased the homogeneity of the results from P = 0.28 for blinded and open studies to P = 0.62 for blinded studies only. The corresponding pooled estimates were 2.56 [95% CI: 1.57 to 4.18] and 1.92 [95% CI: 1.26 to 2.92] respectively, indicating that, while the pooled results remained statistically significant in favor of the use of bisphosphonates, the magnitude of the effect was smaller. The NNT was 6 for all studies and 8 for blinded studies only.

4. Pain as a study entry criteria

(See Table of Comparisons: Comparison 06: 04)
Exclusion of studies where pain was not an entry criterion gave an OR of 3.8 [95% CI 1.42 to 10.17] suggesting a stronger pain relief effect in studies where the presence of pain was an eligibility requirement.

5. Pain specified as patient reported

(See Table of Comparisons: Comparison 06: 05)
Five studies specified that pain outcomes were patient reported, and gave an OR of 2 [95% CI 1.31 to 3.06]. This supports the primary conclusion (proportion of patients with pain relief) although the magnitude was slightly smaller than when all studies are included.

6. Blinded studies; pain as eligibility requirement; and pain reported by patients

(See Table of Comparisons: Comparison 06: 06)
As discussed in the 'Types of studies' section, the most robust data upon which to evaluate our primary outcome would come from the inclusion of studies that fulfil all three criteria. However, only two studies meet these criteria (Vinholes 1997a; Smith 1989). In addition to the small number of studies eligible, the results were clinically heterogeneous making pooling of data illogical. The results are presented in the Table of Comparisons: Comparison 06: 04 for completeness only.

7. Quality of the studies

(See Table of Comparisons: Comparison 06: 07)
The quality of the studies is reported in the 'Characteristics of Included Studies' Table. The Oxford Quality Scale scores ranged from 1 to 5 with a median of 3. Sensitivity analysis based on the quality of studies using, 'the proportion of patients with best

response at 12 weeks', given the limitation of the small number of studies in each group, showed no quality effect.

DISCUSSION

It is unfortunate that, despite the identification of over 50 randomized studies in this topic area, with 21 of these being blinded placebo controlled trials, the data available to facilitate a meta-analysis of the effectiveness of bisphosphonate in providing pain relief are so limited that no robust conclusions can be reached. The multiple methods used by trialists, and lack of consensus on which pain endpoints should be included in the reporting of pain response, represent the major limiting factors. These are problems, not only within bisphosphonate trials, that are observed in other areas where pain measurement is a key outcome. Clinicians and researchers planning analgesic trials should seek advice at the planning stage from experts in pain trials.

The most important and clinically relevant endpoint for inclusion in quantitative reviews is the proportion of patients with pain relief, described for each arm of the trial. Even when no significant differences are observed, the relevant data must be reported to allow appraisal. Mean pain scores are not helpful in calculating effectiveness. Other endpoints, such as adverse effects (based on standardized toxicity classification criteria) and quality of life assessment would provide useful data and should be integrated into future trials.

The following conclusions regarding the effectiveness of bisphosphonates for pain relief should be interpreted with consideration for the small number of eligible studies.

- There is some evidence to suggest a significant benefit in favor of the use of bisphosphonates, OR 2.37 [95% CI: 1.61 to 3.5], NNT of 6 [95% CI 5 to 11] for the outcome, 'best response within 12 weeks';
- When the three most stringent criteria are applied (blinded control, pain as an eligibility criteria, and patient reported pain), only two studies can be included, precluding meaningful pooling of the results, and the amount of pain relief achieved from bisphosphonates appears to be small;
- In terms of the pattern of response over time, the magnitude of benefit from bisphosphonates at 4 weeks is similar to that observed at 12 weeks.

Despite the methodological limitations, the evidence suggests that bisphosphonates provide modest pain relief for patients with painful bony metastases.

- Adverse drug reactions were generally mild. We calculated a number needed to harm (NNH) of 16 [95% CI 12 to 27] for adverse drug reactions requiring discontinuation of therapy. There is a trend towards increased incidence of nausea and vomiting although this does not reach statistical significance.
- There were insufficient data to evaluate the impact of drug type; route of administration; and variation of response between different primary disease sites.

Analgesics have and will continue to be an important part of the management of painful bony metastases. In addition, where clinically appropriate, radiotherapy has been shown to be an important modality. In a review conducted by McQuay 1997, the NNT for the effectiveness of radiotherapy in pain relief was 3.6 [95% CI 3.2 to 3.9] for at least 50% pain relief, with a median duration of pain relief of 12 weeks.

For patients with diffuse, painful metastases, especially where analgesics, with or without radiotherapy, do not provide adequate pain relief, or are accompanied by unacceptable adverse drug reactions, the use of bisphosphonates for pain reduction is justifiable. Our review focused on answering the question whether patients in need of therapy for pain relief in the shorter term would benefit from bisphosphonate therapy, as in the example of patients with more advanced disease and limited life expectancies. The use of bisphosphonates with other longer term objectives such as reduction in skeletal event rates was not an objective of this review.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides an estimate of one patient benefiting with "some pain relief" for each six patients being treated. There are insufficient data to recommend its use to provide immediate effect, and the maximum response is likely to be observed by four weeks. Adverse drug reactions were severe enough to cause discontinuation of therapy in one out of every eleven patients treated.

Given these conclusions, there is insufficient evidence to recommend bisphosphonates for the management of painful bony metastases as first line therapy. Bisphosphonates should be considered in addition to analgesics and/or radiotherapy when these modalities alone are inadequate for the management of painful bony metastases. There is insufficient evidence to allow a recommendation to be made on the most effective bisphosphonates for this purpose. There is also insufficient evidence to recommend the selection of patients for this treatment strategy based on primary histologies.

Implications for research

This review shows that a significant body of research (30 studies) has failed to produce a clear answer, mainly because proven methods for assessing pain, and best practice in trial design, were not incorporated. This represents a terrible waste of research resources.

Future investigators should agree common criteria for the reporting of pain response in order to provide usable data in trials where pain as an outcome. The authors recommend the use of the proportion of patients with pain relief with predefined definitions for response. Ideally, this may involve an integrated pain and analgesic response criterion in order to take into account the potential confounding effect of other analgesics. The use of mean pain and/or analgesic scores as secondary endpoints is not recommended. If it is necessary to use this as an outcome, the inclusion of the standard deviation in the reporting of results is mandatory.

Studies focusing on subgroups who are most likely to benefit from bisphosphonates for pain relief, such as those with pain refractory to conventional analgesics, would be useful in order to better define the role of bisphosphonates for pain relief in patients with painful bony metastases.

ACKNOWLEDGEMENTS

The review authors would like to thank Dr Svetlana Rutter for her assistance in translating a Russian trial report.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arican 1999

Methods	2 active arms, 1 control Pain measurement tool: 10 cm VAS Definition of pain response: not specified Analgesic scale: 0: no narcotics, 1: 30 mg morphine, 2: 60 mg morphine, 3: 90 mg morphine Toxicity criteria: WHO classification
Participants	Any primary Bone metastases required Pain present Cointervention: none described Life expectancy > 3 months Other criteria: exclude bisphosphonates or radiotherapy within </ = 4 wks, hypercalcemia, renal dysfunction, Pagets disease, vitamin D deficiency
Interventions	Active arm 1: Clodronate Oral 800 mg/day x 3 months 16 pts Active arm 2: Clodronate Oral 1600 mg/day x 3 months 17 pts Control: No treatment 17 pts
Outcomes	Pain: a. Mean change b. Proportion of pts with pain reduction Analgesic: a. Proportion of pts. with analgesia reduction Others: a. Changes in urinary calcium, b. Urinary hydroxyproline, c. Serum ICTP (type 1 collagen degradation product). Withdrawals: Active arm 1: 0/16 Active arm 2: 0/17 Control: 3/17 Adverse effects: Active arm 1: Nausea and vomiting: 2/16 Abdominal pain: 1/16 Hypocalcemia:1/16 Active arm 2: Nausea and vomiting: 2/17 Diarrhea: 1/17 Abdominal pain: 1/17 Hypocalcemia: 2/17

Arican 1999 *(Continued)*

	Control arm: none described
Notes	QS = 2

Belch 1991

Methods	Active arm vs placebo control Pain measurement tool: not specified
Participants	Multiple myeloma 80% of patients has at least 1 lytic lesion, bony involvement not required Pain not required Co-intervention: melphalan and prednisone Performance status criteria: no specifications Other criteria: exclude serious concurrent illness, chronic renal failure
Interventions	1. Active arm: Etidronate Oral 5 mg/kg/day/ x28 days every other 28 days indefinitely 98 pts 2. Control arm: Placebo 78 pts All patients received melphalan and prednisone
Outcomes	Pain: a. P value shows no significant difference in pain Others: a. Episodes of hypercalcemia b. Pathological fractures c. Vertebral index Withdrawals: Active arm: 6/98 Control arm: 3/78 Adverse effects not reported
Notes	QS = 4 Study started with 3 arms with 2 active arms (an additional arm of etidronate 20 mg/kg/d). This arm was dropped because of reports of demineralization in another trial.

Berenson 1996

Methods	Active vs placebo control study, stratified by first or second line chemotherapy at study entry

Berenson 1996 *(Continued)*

	Pain measurement tool: 0-9 point scale [pain severity (0-3) x pain intensity (0-3)] Analgesic scale: 0-9 point scale
Participants	Multiple myeloma SIII with lytic lesions Pain not required Co-intervention: chemotherapy Performance status criteria: life expectancy: > 9 months Other criteria: exclude skeletal event within 2 wks of enrolment, renal dysfunction, liver dysfunction, abnormal ECG, previous bisphosphonates, calcitonin, corticosteroid
Interventions	1. Active arm: Pamidronate IV 90 mg/every 4 weeks Total of 36 weeks 203 pts 2. Control arm: Placebo 189 pts All patients received chemotherapy as was clinically indicated
Outcomes	Pain: a. Mean pain score in each group Analgesic: States no change, no details Others: a. Any skeletal events b. Performance status c. Quality of life d. Survival e. Radiological changes f. Serum paraproteins, beta 2 microglobulin, Urinary Bence Jones proteins Withdrawals: Active arm: 7/203 Control arm: 8/189 7. Adverse effects a. Active arm: Allergic reaction: 1/203 Hypocalcemia: 1/203 b. Control arm: none described
Notes	QS = 4

Brinker 1998

Methods	Active vs placebo control study, stratified by status on simultaneous study: on interferon, not on interferon trial, and not eligible for interferon trial Pain measurement tool: 6-point scale Pain score expressed by patient

Brinker 1998 *(Continued)*

	Analgesic scale: amount consumed in the last 24 hours
Participants	Multiple myeloma Lytic lesions not a requirement Pain not required Co-intervention: melphalan and prednisone+/- interferon Performance status criteria: life expectancy > 3 months Other criteria: exclude peptic ulcer, renal dysfunction
Interventions	1. Active arm: Pamidronate Oral 75 mg twice daily Indefinitely 152 pts 2. Control arm: Placebo 148 pts All pts receive melphalan and prednisone +/-interferon
Outcomes	1. Pain: Pamidronate 126/152 episodes severe pain Placebo 180/148 episodes severe pain Others: a. Skeletal related morbidity b. Survival c. Frequency of hypercalcemia Withdrawals a. Active arm: 16/152 b. Control arm: 14/148 Adverse effects a. Active arm: Nausea 18 Vomiting 7 Abdominal pain 3 Diarrhea 8 Dysphagia 10 GI hemorrhage 4 Esophageal ulcer 2 Gastric ulcer 4 b. Control arm: Nausea 12 Vomiting 6 Abdominal pain 6 Diarrhea 9 Dysphagia 6 GI hemorrhage 2 Esophageal ulcer 0 Gastric ulcer 2
Notes	QS = 4

Cascinu 1998

Methods	3 active arms Pain and mobility measurement tool: use QoL questionnaire with focus on pain and mobility. Patient reported Analgesic scale: total (mg) consumed in 24 hours
Participants	Any primary, failed hormones/ chemotherapy Bone metastases present Pain required Co-intervention: none described Performance status criteria: life expectancy >/ = 3 months Other criteria: exclude hypercalcemia, brain metastases, previous bisphosphonates, and ongoing chemotherapy
Interventions	Active arm 1: Pamidronate Intravenous 45 mg every 3 weeks for 12 weeks 23 pts Active arm 2: Pamidronate Intravenous 60 mg every 3 weeks for 12 weeks 24 pts Active arm 3: Pamidronate Intravenous 90 mg every 3 weeks for 12 weeks 23 pts
Outcomes	Pain: a. Proportion with pain and mobility reduction Analgesic: reduction seen in all three groups Withdrawal None 7. Adverse effects Active arm 1: Fever and myalgia: 1/23 Active arm 2: 0/24 Active arm 3: Fever and myalgia: 1/23
Notes	QS = 1

Coleman 1998

Methods	2 active arms Pain measurement tool: 6-point scale, and the Oswestry back pain questionnaire: patient reported Definition of pain response: any two of the following criteria: major response, any two of the lesser criteria in brackets: minor response a: reduction in pain by at least 2 category at 2 consecutive 4 weekly visits b: 20% (10%) improvement in the score of the pain and mobility questionnaire at two consecutive 4 weekly visits c: 50% (25%) reduction for at least 2 months in the dose of the most powerful analgesic taken Analgesic scale: 7-point analgesic scale based on total amount consumed in 24 hours
Participants	Breast cancer, failed at least 1 systemic therapy Bone metastases required (At least 2 lesions) Pain required Co-intervention: hormonal therapy that has been on going, no chemotherapy allowed Performance status criteria: life expectancy >/= 3 months, WHO performance status </=2 Other criteria: exclude peptic ulcer, bisphosphonates within last 6 months, hypercalcemia
Interventions	Active arm 1: Pamidronate Oral 150 mg twice a day indefinitely 24 pts Active arm 2: Pamidronate Oral 150 mg every morning and placebo every morning 23 pts
Outcomes	Pain: a. Proportion of patients with pain reduction Analgesic: Not an endpoint Others: Urinary calcium as a measure of bone resorption Adverse effects Active arm 1: 0/24 Active arm 2: (Grade 3) Nausea and vomiting: 3 Diarrhea: 2 Abdominal pain: 1
Notes	QS = 2

Conte 1994

Methods	Active vs control Pain measurement tool: 6-point scale. Patient reported

Conte 1994 *(Continued)*

	Definition of pain response: a. Some improvement: improvement by 1 point over 2 consecutive reports or by 2 points in 1 report b. Marked improvement: improvement by 2 points over at least 2 consecutive reports
Participants	Breast cancer, no previous chemotherapy Bone metastases required Pain not required. Co-intervention: chemotherapy Performance status criteria: no specifications Other criteria: none
Interventions	1. Active arm: Pamidronate Intravenous 45 mg every 3 weeks Indefinitely until toxicity or progressive bone disease 143 pts 2. Control arm: No additional intervention 152 pts All patients received chemotherapy, standardized for each participating institution
Outcomes	1. Pain: a. Proportion of patients with reduced pain No pain: 80/131 pamidronate 70/134 control Marked improvement: 54/131 pamidronate 38/134 control 2. Analgesic: stated is a secondary endpoint but no data /outcome reported Withdrawals Active arm: 6/143 Control arm: 6/152 Adverse reactions Active arm: Local reaction: 13 Fever: 8 Rigors: 2 Headache: 4 Musculoskeletal pain: 6 Hypocalcemia: 23 Control arm: Local reaction: 7 Fever 4 Rigors 0 Headache: 5 Musculoskeletal pain: 22 Hypocalcemia: 9
Notes	QS = 1

Daragon 1993

Methods	Active vs placebo control study, stratified by whether bone biopsy obtained Pain measurement tools: a. Visual analogue scale b. 3-point categorical scale Analgesic scale: analgesics consumed classified as: a. Paracetamol b. Codeine c. Morphine
Participants	Multiple myeloma (SII, III) Bone lesion not specified No pain requirement Co-intervention: chemotherapy Performance status criteria: poor physical activity Other criteria: exclude renal dysfunction, severe bone marrow insufficient, age >80, cardiac failure, diabetes, gastric or duodenal ulcer, prior chemotherapy, multiple myeloma diagnosed >3 months.
Interventions	1. Active arm: Etidronate Oral 10 mg/kg/day 4 months 49 pts 2. Control arm: Placebo 45 pts All patients receive cyclophosphamide and prednisone
Outcomes	1. Pain: a. Change in mean pain score of the group 2. Analgesic: a. Proportion of patients taking codeine/morphine Others: a. Karnofsky performance status change b. Incidence of new extraspinal mets c. Incidence of fractures d. Survival e. Change in Vertebral index f. Bone resorption as measured by urine hydroxyproline/ calcium/ creatinine levels Withdrawals Active arm: 10/49 Control arm: 6/45 Adverse effects Active arm: Skin allergy: 1 Control arm: Pancreatitis: 1
Notes	QS = 3

Delmas 1982a

Methods	Active vs placebo control Pain measurement tool: 0-9 point scale based on severity and duration Pain score expressed by: patient and physician
Participants	1. Multiple myeloma 2. Bone involvement not specified 3. Pain not required 4. Co-intervention: chemotherapy 5. Performance status criteria: no specifications 6. Other criteria: exclude patients previously treated with >10 cycles of chemotherapy, renal dysfunction
Interventions	1. Active arm: Clodronate Oral 800 mg twice a day for 2 years 7 pts 2. Control arm: Placebo 6 pts All patients received melphalan and prednisone
Outcomes	1. Pain: No pain data within 12 weeks of enrollment Others: a. Mean pain score change at 6 months b. Proportion with radiological progression at 1 year c. Comments on serum calcium, urinary calcium, phosphorus, alkaline phosphatase, and bone histomorphology for subgroup of patients. No withdrawals Adverse effects not reported
Notes	QS = 4

Elomaa 1992

Methods	Active vs placebo control Definition of pain response: proportion with no pain Analgesic response definition: proportion with no analgesic
Participants	Prostate cancer (failed 1 hormone) Bone metastases required Pain required Co-intervention: chemotherapy/hormonal therapy Performance status criteria: life expectancy >/=3 months

Elomaa 1992 *(Continued)*

	Other criteria: exclude radiotherapy within 2 weeks
Interventions	1. Active arm: Clodronate Oral 3.2 g per day for one month, then 1.6 g per day for 5 months For 6 months 36 pts 2. Control arm: Placebo 39 pts All patients received Estramustine
Outcomes	1. Pain: a. Proportion of patients with no pain 2. Analgesic: Analgesic consumption reduced in 15/17 Clodronate 3/17 placebo Others: a. Serum calcium b. Survival Evaluable data: 12 pts receiving Clodronate and 10 pts from the placebo group died within the first year of the study No adverse effects reported.
Notes	QS = 2

Ernst 1992

Methods	Active vs placebo Crossover study washout period: 2 weeks Pain measurement: 10 cm VAS, patient reported Analgesic scale: morphine equivalent for amount consumed in 24 hours
Participants	Any primary Bone metastases required Pain required Other criteria: exclude radiotherapy, or change in chemotherapy or hormonal therapy within 4 weeks, heart failure, and abnormal renal function tests
Interventions	1. Active arm: Clodronate Intravenous 600 mg x1 dose 2. Control arm: Placebo Crossover after 4 weeks 24 pts

Ernst 1992 *(Continued)*

Outcomes	1. Pain: a. Mean pain score change 2. Analgesic: a. Mean morphine equivalent change Others: a. Patient and physician preference b. Activity score Withdrawals: 3 for both arms, number excluded for each arm not described No adverse effects reported
Notes	QS = 5

Ernst 1997

Methods	2 active arms, 1 placebo control Crossover study: washout period: 2 weeks Pain measurement tool: 15 cm VAS, patient reported Analgesic scale: morphine equivalent for amount consumed in 24 hours
Participants	Any primary Bone metastases required Pain required Co-intervention: systemic therapy as part of standard practice Performance status criteria: no specifications Other criteria: exclude radiotherapy, chemotherapy within 4 weeks, cardiac failure, and renal failure.
Interventions	1. Active arm 1: Clodronate Intravenous 600mg x1 dose 2. Active arm 2: Clodronate Intravenous 1500 mg x1 dose 3. Control arm: Placebo Crossover after 2 weeks Patients on chemotherapy or hormonal therapy as part of standard care 60 pts
Outcomes	1. Pain:

Ernst 1997 *(Continued)*

	a. Mean change in pain score 2. Analgesic: a. Mean change in morphine equivalent Others: a. Patient preference 26/60 preferred pamidronate 12/60 preferred placebo 8/60 no preference No adverse effects reported Withdrawals: 9 pts
Notes	QS = 4

Glover 1994

Methods	4 active arms Pain measurement tool: a. 0-9 point scale [pain severity (0-3) x pain frequency (0-3)] severity: 0=none, 1 = mild, 2= moderate, 3= severe frequency: 0=none, 1 = occasionally, 2= >or =1/day, 3 = constant No relief: pain score >/= baseline Definition of pain response (Pain relief score): Complete relief: pain score of 0 Partial relief: pain score <4 Minimal relief: pain score less than baseline but >/=4 Analgesic scale: 0-9 point scale [type of medication (0-3) x frequency (0-3)] type: 0 = none, 1 = mild, 2 = mild narcotics, 3= strong narcotics frequency: 0= none, 1 = <daily, 2=once per day, 3= >1per day
Participants	Breast cancer Bone metastases required Pain required: Pain score >4 (i.e. at least moderate and intermittent) Co-intervention: May be on chemotherapy or hormonal therapy as part of standard clinical care Performance status criteria: life expectancy >3m Other criteria: exclude changes in chemotherapy/ hormones within 60 days, prior bisphosphonate, treatment for hypercalcemia within 90 days, radiotherapy within 2 weeks, history of hypercalcemia, pathological fractures, cord compression, renal, bone marrow dysfunction, ascites
Interventions	1. Active arm 1: Pamidronate Intravenous 30 mg every 2 weeks for 3 months 14 pts 2. Active arm 2: Pamidronate Intravenous 60 mg every 4 weeks

Glover 1994 *(Continued)*

	17 pts 3. Active arm 3: Pamidronate Intravenous 60 mg every 2 weeks 14 pts 4. Active arm 4: Pamidronate Intravenous 90 mg every 4 weeks 16 pts Chemo/hormonal therapy as part of standard clinical care unchanged at least 60 days
Outcomes	1. Pain: a. Change in mean pain score 2. Analgesic: a. Change in mean pain score Others: a. Urinary calcium/creatinine and hydroxyproline/creatinine ratios, serum osteocalcin and bone alkaline phosphatase b. Bone radiological response Withdrawals: Active arm 1: 5/14 Active arm 2: 2/17 Active arm 3: 1/14 Active arm 4: 2/16 Adverse effects (n = 51 evaluable) Described for all patients in study Fever: 6 Myalgia: 3 Increase pain: 5
Notes	QS = 2

Heim 1995

Methods	2 arm study, stratified by stage II vs III, bone involvement vs no bone involvement, high enrolment centers vs low enrolment centers 1 active arm, 1 open control Pain measurement tool: WHO criteria (0-3), patient reported Analgesic scale: analgesic consumed
Participants	Multiple myeloma (SII, SIII, and SI pretreated patients) No bone involvement required No pain requirement Co-intervention: chemotherapy Performance status criteria: life expectancy > 1 year, ECOG 0-2

Heim 1995 *(Continued)*

	Other criteria: exclude no bisphosphonates, no renal dysfunction
Interventions	1.Active arm: Clodronate Oral 1600 mg /day for 1 year 77 pts 2. Control arm: No treatment 80 pts All patients received melphalan and prednisone
Outcomes	1. Pain: at 3 months 85% no pain in Clodronate group 62% no pain in control group 2. Analgesic: a. Proportion with no analgesics Other: a. Bone response b. Incidence of hypercalcemia c. Bone resorption index d. Change in performance status e. Change in serum calcium levels f. Tumor response 13 pts withdrew from the study prior to treatment Adverse effects (WHO criteria) Grade 3-4 Active: Hemorrhage: 2 Fever: 1 Skin changes: 2 Anorexia: 14 Nausea: 7 Vomiting: 5 Dyspnea: 8 Infection: 6 Diarrhea: 3 Constipation: 2 Heart failure: 8 Cardiac arrhythmia: 2 Control: Hemorrhage: 3 Hematuria: 1 Skin changes: 1 Anorexia: 16 Nausea: 10 Vomiting: 1 Dyspnea: 8 Infection: 7 Diarrhea: 1 Constipation: 1 Allergy: 1 Heart failure: 8 Cardiac arrhythmia: 1

Heim 1995 *(Continued)*

Notes	QS = 2

Hortobagyi 1996a

Methods	Active vs placebo control stratified by ECOG PS 0,1 vs 2,3 Pain measurement tool: 0-9 point scale [pain severity (0-3) x pain intensity (0-3)] Analgesic scale: 0-9 point scale
Participants	Breast cancer Bone metastases required Pain required Co-intervention: chemotherapy as indicated clinically Performance status criteria: life expectancy > 9 months, ECOG PS </ = 3 Other criteria: exclude previous skeletal complications, hypercalcemia, ascites, renal, liver, cardiac dysfunction, bisphosphonate/radiotherapy within 60 days, calcitonin within 2 weeks.
Interventions	1. Active arm: Pamidronate Intravenous 90 mg monthly for 1 year 185 pts 2. Control arm: Placebo 197 pts Chemotherapy as is indicated clinically
Outcomes	1. Pain: a. Change in mean pain score 2. Analgesic: Not an endpoint Others: a. Time to first skeletal complication b. Proportion of patients with skeletal complication c. Performance status d. Change in Spitzer QoL score e. Radiological response f. Changes in urinary and serum markers for bone resorption e. CEA level Withdrawals: Active: 0/185 Control: 2/197 Adverse effects: Active: (withdrawn from study) Weakness: 1 Fatigue: 1 Hypocalcemia: 1

Hortobagyi 1996a *(Continued)*

	Control: None described
Notes	QS = 4 Update of these results in Hortobagyi 1998

Hultborn 1996

Methods	Active vs placebo, stratified by center Pain measurement tool: VAS, patient reported
Participants	Breast cancer Bone metastases required Pain not required Co-intervention: as clinically indicated Performance status criteria: life expectancy >3 months Other criteria: exclude previous bisphosphonates, hypercalcemia
Interventions	1. Active arm: Pamidronate Intravenous 60 mg every 4 weeks, up to 2 yrs 201 pts 2. Control arm: Placebo 203 pts
Outcomes	1. Pain: No significant difference between groups Others: a. Skeletal event free survival b. Cumulative incidence of skeletal events c. Hypercalcemia event free time d. Incidence of therapeutic activities for skeletal progression, change of antitumoral treatment e. Pain progression free survival f. Proportion of patients taking opioids Adverse effects (withdrawal from therapy) Active group: 9/201 Control group: 3/203
Notes	QS = 2

Koeberle 1999

Methods	2 active arms, stratified by diagnosis (breast vs myeloma), baseline pain intensity (</=40mm Vs >40 mm) Pain measurement tool:

Koeberle 1999 *(Continued)*

	a. 10 cm VAS b. PPA (0: no pain, 1: mild, 2: moderate, 3: severe, 4: intractable) (WHO definitions) Pain patient reported Definition of pain response: >/=20% reduction in pain intensity or PPA on 2 consecutive visits Analgesic scale: 0-5 point scale (WHO) 0: none, 1: mild analgesic, 2: non steroidal anti-inflammatory 3: opioids 4: opiates Analgesic response criteria: 1 point change in score in 2 consecutive visits or >/=2 point change
Participants	Any primary Bone metastases required Pain required (>/ = 2), and analgesic score >/ = 2 Co-intervention: none described Performance status criteria: no specification Other criteria: exclude prior bisphosphonates
Interventions	1. Active arm 1 : Pamidronate Intravenous 60 mg every 3 weeks x 6 doses over 18 weeks 35 pts 2. Active arm 2: Pamidronate Intravenous 90 mg every 3 weeks x6 doses over 18 weeks 35 pts
Outcomes	1. Pain: a. Change in mean pain score b. Duration of pain response 2. Analgesic: a. Proportion with improvement Others: a. Performance status b. Bone remineralization Adverse effects: (discontinuation of therapy) Active arm: 1/35 Control arm: 1/35
Notes	QS = 3

Kylmala 1997

Methods	Active vs placebo Pain measurement tool: 10 cm VAS, 0-4 ordinal scale Pain scores expressed by: patient (VAS) physician (ordinal scale)

Kylmala 1997 *(Continued)*

	Definition of pain response: not applicable Analgesic scale: 3 point scale (0: none, 1: non narcotics <x3/d, 2: non narcotic >x3/d, 3: narcotics)
Participants	Prostate cancer (hormonal therapy) Bone metastases required No pain required Co-intervention: hormonal/chemotherapy Performance status criteria: none Other exclusion radiotherapy within 2 weeks
Interventions	1. Active arm: Clodronate 300 mg/day IV x5 days, then 1.6 g/day oral x12 months 28 pts 2. Control arm: Placebo 29 pts All patients receive Estramustine
Outcomes	1. Pain: No significant difference in any pain score 2. Analgesic: a. Proportion of patients with reduced analgesic Others: a. Performance status change b. Clinical response i.e. better, same, or worse as scored by doctor c. Radiological response d. Biochemical markers of bone resorption, serum calcium, alkaline phosphatase. e. PSA levels Withdrawals: Active arm: 0/28 Control arm: 2/29 Adverse effects: Active arm: Nausea: 9 Control arm: Nausea: 11
Notes	QS = 4

Lahtinen 1992

Methods	Active vs placebo Pain measurement tool: 0-4 pain scale, patient reported Analgesic scale: Analgesic type used (narcotics Vs non-narcotics)
Participants	Multiple myeloma

Lahtinen 1992 *(Continued)*

	Bone lesion not required No pain requirement Co-intervention: chemotherapy Other: exclude patients who are asymptomatic, unable to tolerate chemotherapy, previous bisphosphonates
Interventions	1. Active arm: Clodronate Oral 2.4 g/day at 4 weeks post CT, then for 24 months 175 pts 2. Control arm: Placebo 175 pts 3. All patients received mephalan and prednisone
Outcomes	1. Pain: a. No pain data within 12 weeks b. No significant difference in pain at 12 months 2. Analgesic: b. No analgesic data within 12 weeks Withdrawals: Active arm: 7/175 Control arm: 7/175 Adverse effects Active arm: Nausea: 29 Diarrhea: 17 Abdominal pain: 18 Allergic reaction: 15 Control arm: Nausea: 25 Diarrhea: 15 Constipation: 8 Abdominal pain: 33 Allergic reaction: 3
Notes	QS = 4

Martoni 1991

Methods	Active vs placebo (stratified by type of bone lesion osteolytic vs blastic vs mix), type of anti-tumor therapy (chemotherapy and /or hormonal therapy) Pain measurement tool: VAS, patient reported Analgesic scale: analgesic consumed Analgesic response definition: Increase: no. of daily administration and or shift from the use of minor analgesics to morphine Decrease: reduction in the no of daily administration and /or shift from the use of morphine to minor analgesics

Martoni 1991 *(Continued)*

Participants	Breast cancer Bone metastases required No pain requirement Co-intervention: systemic therapy Performance status criteria: >/ = 50 Other: exclude abnormal calcium, renal dysfunction, and stable disease
Interventions	1. Active arm: clodronate 300 mg/day IV x7 days, +100mg/day IM x3 weeks, +100 mg IM alt days x2 months 19 pts 2. Control arm: Placebo 19 pts Patients also received chemotherapy/hormonal therapy as was clinically indicated
Outcomes	1. Pain: No significant difference in pain intensity 2. Analgesic: a. Proportion of patients with pain reduction Others: a. Urinary calcium/ hydroxyproline levels b. Incidence of hypercalcemia c. Incidence of pathological fractures d. Incidence of progressive bone disease No withdrawals Adverse effects: Described for all patients, none significant
Notes	QS = 3

Moiseyenko 1998

Methods	2 active arms Pain measurement tool: VAS 10 cm, patient reported Definition of pain response: >/=10 mm change
Participants	Any primary Bone metastases required Pain required Co-intervention: none described Performance status criteria: no specifications

Moiseyenko 1998 *(Continued)*

	Other criteria: none
Interventions	1. Active arm 1: Clodronate intravenous 300 mg x5 days 24 pts 2. Active arm 2: Clodronate Intravenous 1500 mg IV day 1 then placebo days 2-5 27 pts
Outcomes	1. Pain: a. Proportion with pain improvement 2. Analgesic: Not an endpoint Withdrawals: none Adverse effects: None reported
Notes	QS = 2 Russian article

O'Rourke 1995

Methods	3 active arms, 1 placebo arm (stratified by urinary calcium level: <0.35 vs >0.35 mmol/mmol creatinine) Pain assessment: 10 cm VAS, patient reported Toxicity criteria: WHO
Participants	Any primary Bone metastases required No pain requirement Co-intervention: unrestricted concomitant tumor therapy as clinically indicated Performance status criteria: life expectancy >1m Other criteria: exclude urinary calcium excretion <0.175mmol/mmol creatinine, radiotherapy within 1 month, chemotherapy/bisphosphonate within 3 months
Interventions	1. Active arm 1: Clodronate oral 400 mg /day x4 weeks 20 pts 2. Active arm 2: 1600mg 19 pts 3. Active arm 3: 3200mg 20 pts

O'Rourke 1995 *(Continued)*

	4. Placebo control: May receive hormone/systemic chemotherapy if unchanged in previous 3 months 21 pts
Outcomes	1. Pain: No change in bone pain 2. Analgesics: No change in analgesic requirements Withdrawals 4 for whole study Adverse effects: Active arm 1: Nausea or vomiting: 3 Diarrhea: 1 Active arm 2: Nausea or vomiting: 3 Diarrhea: 3 Active arm 3: Nausea or vomiting: 4 Diarrhea: 1 Control arm: Nausea or vomiting: 6 Diarrhea: 1
Notes	QS = 3

Piga 1998

Methods	Active vs placebo control Pain measurement tool: VAS Analgesic assessment: O: none, 1: NSAIDS 2: opiates Analgesic response definition: reduction in level
Participants	Any primary (poor prior response to chemotherapy) Bone metastases required No pain requirement Co-intervention: none described Performance status criteria: life expectancy >/=3m, PS >/=40 Other criteria: exclude hypercalcemia, renal dysfunction
Interventions	1. Active arm: Clodronate Oral 1600 mg/day x1 year 27 pts 2. Control

Piga 1998 *(Continued)*

	Placebo 23 pts
Outcomes	1. Pain: 10/22 worse on placebo 5/27 worse on Clodronate 2. Analgesic: a. Proportion of patients not requiring an increase Adverse effects: Active arm: GI discomfort: 3/27 Control arm: GI discomfort: 5/23
Notes	QS = 4

Robertson 1995

Methods	Active vs placebo (stratified for primary site: breast, lung vs others) Pain measurement tool: VAS. patient reported Analgesic scale: morphine equivalent Analgesic response definition: increase, static or reduced
Participants	1. Any primary (Resistant to first line chemotherapy) 2. Bone metastases required 3. Pain required 4. Co-intervention: hormonal/chemotherapy as clinically indicated 5. Performance status criteria: life expectancy: >2m 6. Other criteria: exclude renal dysfunction, use of bisphosphonates
Interventions	1.Active arm: Clodronate Oral 1600 mg/day Approx 170 days 27 pts 2. Control arm: Placebo 28 pts Patients can receive systemic therapy as was clinically indicated
Outcomes	1. Pain: a. Change of mean pain score 2. Analgesics: a. Proportion of patients with reduction Withdrawal: None reported Adverse effects Active arm: Hypocalcemia: 2/27 Control arm:

Robertson 1995 *(Continued)*

	Hypocalcemia: 0/28
Notes	QS = 5

Siris 1983

Methods	Active vs placebo Crossover study
Participants	Breast cancer with hypercalcemia/ hypercalciuria Bone metastases required Pain required Co-intervention: hormonal/ chemotherapy as clinically indicated
Interventions	1. Active arm: Clodronate Oral 3200 mg/day Total: 24 weeks 5 pts 2. Control arm: Placebo 5 pts Patients receiving chemotherapy/hormonal therapy as was clinically indicated
Outcomes	Withdrawals: 3 for whole group Adverse effects: Active arm: Diarrhea: 4/5 Control arm: Diarrhea: 0/5
Notes	QS = 5

Smith 1989

Methods	3 active arms, 1 placebo arm Pain measurement tool: VAS, patient and physician reported Definition of pain response: minor and major improvement, no criteria described Analgesic scale: assessment/criteria described
Participants	Prostate cancer (previous hormonal therapy) Bone metastases required Pain required Co-intervention: hormonal therapy as clinically indicated

Smith 1989 *(Continued)*

	Other criteria: exclude radiotherapy within 1 month, renal dysfunction
Interventions	1. Active arm 1: Etidronate Intravenous 7.5 mg/kg/day x3 days, then 200mg orally twice a day x1 month 13 pts 2. Active arm 2: Etidronate 7.5 mg/kg/day x3 days 12 pts 3. Active arm 3: Etidronte placebo x3, then 200mg orally twice a day x 1 month 14 pts 4. Active arm 4: Placebo only 12 pts Systemic therapy as clinically indicated
Outcomes	1. Pain: a. Proportion of patients with pain reduction 2. Analgesic: a. State no difference, no comparative data Toxicity: Yes Withdrawals: Active arm 1: 1/13 Active arm 2: 2/12 Active arm 3: 1/14 Placebo arm 4: 2/12 Adverse effects: No serious ADRs reported
Notes	QS = 3

Strang 1997

Methods	Active vs placebo Pain measurement tool: VAS, patient reported
Participants	Prostate cancer, hormone refractory Bone metastases required Pain required (> 20 mm on VAS) Co-intervention: none described Performance status criteria: life expectancy > 3 months Other criteria: exclude renal dysfunction, bisphosphonate within 1 month
Interventions	1. Active arm 1:

Strang 1997 *(Continued)*

	Clodronate Intravenous, 300 mg/day x3 days then oral 600 mg twice a day x4 weeks 25 pts 2. Active arm 2: Placebo 27 pts
Outcomes	1. Pain: P value only 2. Analgesic: Not a reported endpoint Adverse effects: not reported
Notes	QS = 3 study closed early due to lack of accrual

Theriault 1999

Methods	Active vs placebo (stratified by ECOG 0,1 vs 2, 3) Pain measurement tool: 0-9 point scale [pain severity (0-3) x pain intensity (0-3)] Analgesic scale: Type of medication x frequency
Participants	Breast cancer (on stable hormonal therapy within 3 months) Bone metastases required Pain not required Co-intervention: Hormonal/ chemotherapy as clinically indicated Performance status criteria: life expectancy >/=9 months Other criteria: exclude patients on chemotherapy, cord compression, calcitonin/ mitramycin within 14 days prior to enrolment, skeletal event within 2 weeks, renal cardiac, liver dysfunction
Interventions	1. Active arm: Pamidronate Intravenous 90 mg every 4 weeks x24 cycles 182 pts 2. Control arm: Placebo 192 pts Hormonal therapy / chemotherapy as was necessary
Outcomes	1 Pain: No data within 3 months of enrolment 2. Analgesic: No data within 3 months of enrolment Others: a. Skeletal morbidity rate b. Time to first skeletal event

Theriault 1999 *(Continued)*

	c. Survival d. Objective bone response rate e. Mean bone pain score at 1 year and at 12 cycles f. Mean analgesic requirement at 12 months and at 12 cycles g. Urine hydroxyproline/creatinine, calcium/creatinine ratios Adverse effects: Active arm: Allergic reaction: 1/182 Interstitial pneumonia: 1/182 Control arm: None
Notes	QS = 3

van Holten 1993

Methods	Active vs open control
Participants	Breast cancer Bone metastases required Pain required Co-intervention: unrestricted concomitant tumor therapy as clinically indicated Performance status criteria: life expectancy: </=6 months Other criteria: exclude hypercalcemia, upper gastrointestinal disease, and renal dysfunction
Interventions	1. Active arm: Pamidronate Oral 300 mg /day Indefinitely 79 pts 2. Control arm: No treatment 84 pts Unrestricted concomitant tumor therapy as clinically indicated
Outcomes	Others: a. Incidence of hypercalcemia b. Incidence of severe bone pain c. Incidence of symptomatic impending fractures d. Need for systemic treatment e. Need for radiotherapy f. Event free period for radiologic course of disease g. Survival Withdrawals: Active arm: 8/79 Control arm: 4/84 Toxicity: (Study discontinuation) Active: 19/79

van Holten 1993 *(Continued)*

	Control arm: None stated
Notes	QS= 2 Study started with pamidronate 600 mg, but due to severe GI side effects, dose reduced to 300 mg.

Vinholes 1997a

Methods	Active vs placebo Pain measurement tool: a. Overall pain score based on combination of pain (0-5), analgesic use (0-8), and Performance status (0-4) b. Pain intensity score: 0: none, 1: mild, 2: moderate, 3: severe, 4: very severe, 5: intolerable Patient reported pain Definition of pain response: >/=20% decrease in pain score on at least 2 consecutive measurements Analgesic scale and analgesic response definition part of overall pain score
Participants	Any primary Bone metastases required Pain required Co-intervention: stable hormonal therapy used prior to treatment Other criteria: exclude renal dysfunction, bisphosphonate </ = 3m prior to study
Interventions	1. Active arm: Pamidronate Intravenous 120 mg x1 dose 25 pts 2. Control arm: Placebo 27 pts All patients received pamidronate at 3 weeks after above (or earlier if symptoms) and continued as long as beneficial
Outcomes	1. Pain: Change in median % of baseline overall pain score Others: a. QoL b. Bone resorption markers, including NTx and Crosslaps, urine calcium pre and post treatment Withdrawals: Active: 3/25 Control: 1/27 Adverse effects: not reported
Notes	QS = 5

VAS: visual analogue scale
Pts: patients

N: number of evaluable patients
Withdrawal: number of patients withdrawal (N+ withdrawal= no. of patients randomized in the study)
ECOG PS : Eastern cooperative oncology Group performance status
vs: versus

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

Study	Reason for exclusion
Abildgaard 1998	Subgroup analysis of RCT From Brinker 1998
Ahmedzai 1997	Review article
Berenson 1994	Abstract only
Berenson 1997	RCT but duplicate. Primary study : Berenson 1996 (included studies)
Berenson 1998a	RCT but duplicate. Primary study :Berenson 1996 (included studies) no pain assessments
Berenson 1998b	Duplicate.Update of Berenson 1996 , no further evaluable data
Blomqvist 1996	Review article
Bloomfield 1998	Review article
Body 1993	Review article
Body 1996b	Review article
Body 1998	Review article
Chantraine 1984	RCT, no pain assessment
Chapuy 1980	RCT, no pain assessment
Clemens 1993	RCT, Primary study (Heim 1995) Interim report on subset of patients treated at one of the participating institution
Coleman 1994	RCT but duplicate; Primary study (Coleman 1998) included.
Coleman 1996	RCT but duplicate; primary study (Vinholes 1997b) included.
Coleman 1997b	RCT but duplicate; primary study (Vinholes 1997b) included.
Colleoni 1993	Not randomised
Conte 1996	RCT but duplicate; primary study (Conte 1994).
Costa 1993	Not randomised
Coukell 1998	Review article
Cresswell 1995	Not randomised
Crosby 1998	Not randomised
Delmas 1982b	RCT, no pain endpoints

Study	Reason for exclusion
Delmas 1991	Commentary
Delmas 1996	Editorial
Derrane 1998	Commentary
Diel 1997	RCT, no pain endpoint
Diel 1998	RCT but duplicate; primary study Diel 1997, excluded
Diener 1996	Clinical review
Dodwell 1990	Not randomised
Dooley 1999	Review
Dranitsaris 1999	Cost utility study
Dranitsaris 1999b	Cost utlity study
Elomaa 1983	RCT but duplicate; updates in Elomaa 1987,1988. No pain outcomes reported
Elomaa 1987	RCT but duplicate; primary study Elomaa 1983 , included. No pain outcomes reported
Elomaa 1988	RCT but duplicate; primary study Elomaa 1983, included. No pain outcomes reported
Engler 1998	No pain measures, randomisation not adequately described
Ernst 1993	RCT but duplicate; Primary study : Ernst 1997 included.
Ernst 1994	RCT but duplicate; Primary study: Ernst 1997 included.
Fitton 1991	Review
Fontana 1998	Abstract only
Francis 1995	Review
Fulfaro 1998	Review
Gucalp 1994	RCT, No pain assessment
Gurney 1993	Not randomised
Harvey 1996	Review article describing RCT (duplicate of Berenson 1996)
Hortobagyi 1996b	RCT but duplicate; primary study Hortobagyi 1996a, included
Hortobagyi 1997	RCT but duplicate; primary study Hortobagyi 1996a, included
Hortobagyi 1998	RCT but duplicate; primary study Hortobagyi 1996a, Duplicate of Hortobagyi 1996
Hulin 1994	RCT but duplicate; Primary study Tubiana 1995, excluded. Abstract only, no pain outcome
Iddon 1998	Review

Study	Reason for exclusion
Iveson 1994	RCT but duplicate; primary study Kanis 1996, excluded. No pain endpoint
Jung 1983	RCT, No pain assessment
Kanis 1991	Commentary
Kanis 1996	RCT, Inadequate pain outcome measures
Koberle 1997	RCT but duplicate; primary study Koberle 1999, included
Kristensen 1999	RCT, Physician reported pain
Kylmala 1993	RCT but duplicate; primary study Elomaa 1992 (included). Has more patients than Elomaa 1992, but no pain assessment
Laakso 1994	Economic analysis of study reported by Lahtinen 1992.
LaCivita 1996	Editorial
Lipton 1994a	RCT, interim results with no pain data. Same design as Glover 1994, (included study) although unclear whether it is the same study.Current study describe breast and prostate cancer, Glover breast only.
Lipton 1994b	Commentary
Lipton 1997b	RCT but duplicate; primary study Theriault 1999
Lipton 1998a	Review
Lipton 1998b	RCT, no pain assessment
Lipton 2000	RCT but duplicate; describe two studies. Primary studies Hortobagyi 1996 (included) Theriault 1999 (included)
Lortholary 1999	Review
Maolin 1998	Not randomised
Maxon 1991	RCT, evaluating Rhenium
McCloskey 1998	RCT, Physician reported pain only
Mercadante 1997	Review
Merlini 1990	Not randomised
Mundy 1999	Descriptive comment
Musto 1998	Review
Namer 1991	Commentary
Paterson 1991b	RCT but duplicate; primary study Paterson 1994. Comparing clodronate vs placebo. No pain measurement/outcome . Same study as Paterson 1993.

Study	Reason for exclusion
Paterson 1993a	RCT but duplicate; primary study Paterson 1994. No pain assessment
Paterson 1993b	RCT but duplicate; primary study Paterson 1994.
Paterson 1994	RCT, no pain assessment
Paterson 1997	Review
Paterson 1999	Commentary and opinion
Peest 1996	RCT. No clinical outcomes
Pelger 1998	Not randomised
Plosker 1994	Review article
Powles 1991	Commentary
Powles 1998	No pain assessment
Purohit 1994	RCT, no pain assessment
Radziwill 1993	Not randomised
Ravn 1996	RCT, No pain assessment
Riccardi 1994	Not randomised
Ripamonti 1998	Review article
Rose 1992	RCT, no pain assessment
Rotstein 1992	RCT, no pain assessment
Ryzen 1985	RCT, no pain assessment
Shucai 1999	RCT, Radiotherapy for control arm, excluded because of significant use of radiotherapy (the control intervention) in bisphosphonate arm.
Siris 1983b	RCT, no pain assessment
Strang 1996	Review article
Taube 1994	RCT, No pain assessment
Theriault 1996a	No pain outcomes
Theriault 1996b	RCT but duplicate; primary study Theriault 1999, included.
Thurlimann 1994a	Commentary
Thurlimann 1994b	Open study
Tubiana-Hulin 1995	RCT, abstract only, state pain reduction significant, p value only

Study	Reason for exclusion
Tyrrell 1994	Open study
Tyrrell 1995	Open study duplicat publication
van Holten 1991	earlier version of van Holten Verzantvoort 1993
van Holten 1994	RCT but duplicate; primary study 1993, included
van Holten 1996b	RCT but duplicate; primary study 1993, included.
Vinholes 1996a	Not randomised
Vinholes 1996b	RCT but duplicate; primary study Vinholes 1997b, Not full publication, abstract only
Vinholes 1997b	RCT, primary study ? No pain outcome measures
Vorreuther 1993	Not randomised
Walker 1997	Not randomised

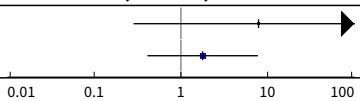
DATA AND ANALYSES

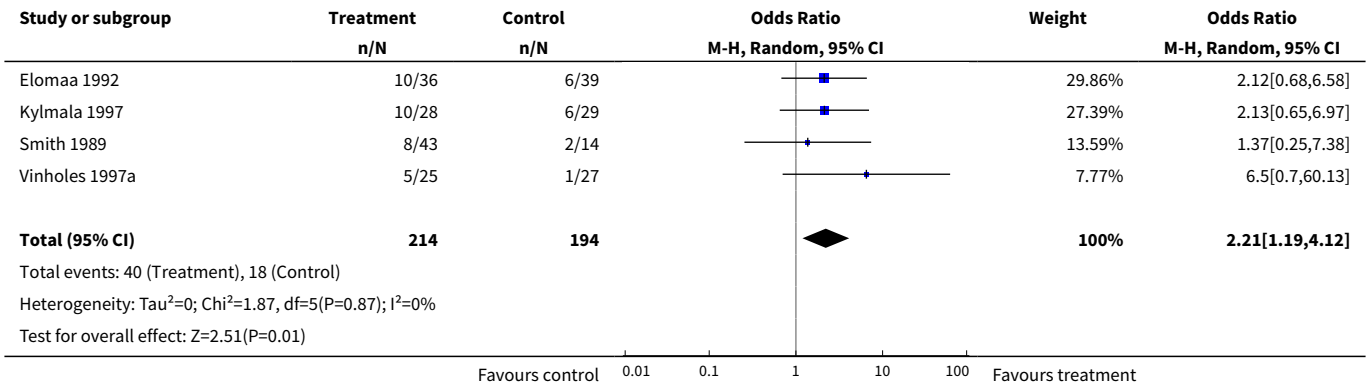
Comparison 1. Proportion of patients with pain relief (Blinded and open control studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with pain relief at 4 weeks (blinded and open studies)	6	408	Odds Ratio (M-H, Random, 95% CI)	2.21 [1.19, 4.12]
2 Proportion of patients with pain response at 8w (Blinded and open studies)	1	157	Odds Ratio (M-H, Random, 95% CI)	2.57 [0.64, 10.31]
3 Proportion of patients with pain relief at 12w (Blinded and open studies)	5	634	Odds Ratio (M-H, Random, 95% CI)	2.49 [1.38, 4.48]
4 Proportion of patients with pain relief with best response within 12 weeks (blinded and open studies)	8	723	Odds Ratio (M-H, Random, 95% CI)	2.37 [1.61, 3.50]

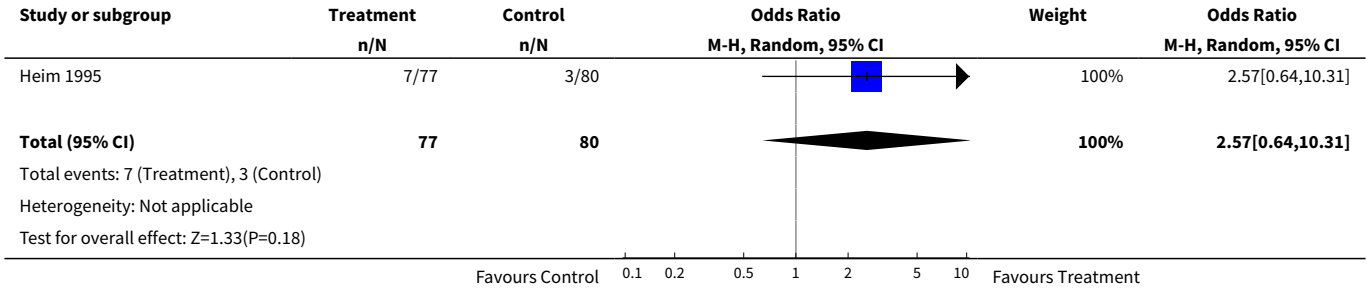
Analysis 1.1. Comparison 1 Proportion of patients with pain relief (Blinded and open control studies), Outcome 1 Proportion of patients with pain relief at 4 weeks (blinded and open studies).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Siris 1983	2/5	0/5		3.49%	7.86[0.28,217.11]
Heim 1995	5/77	3/80		17.88%	1.78[0.41,7.73]

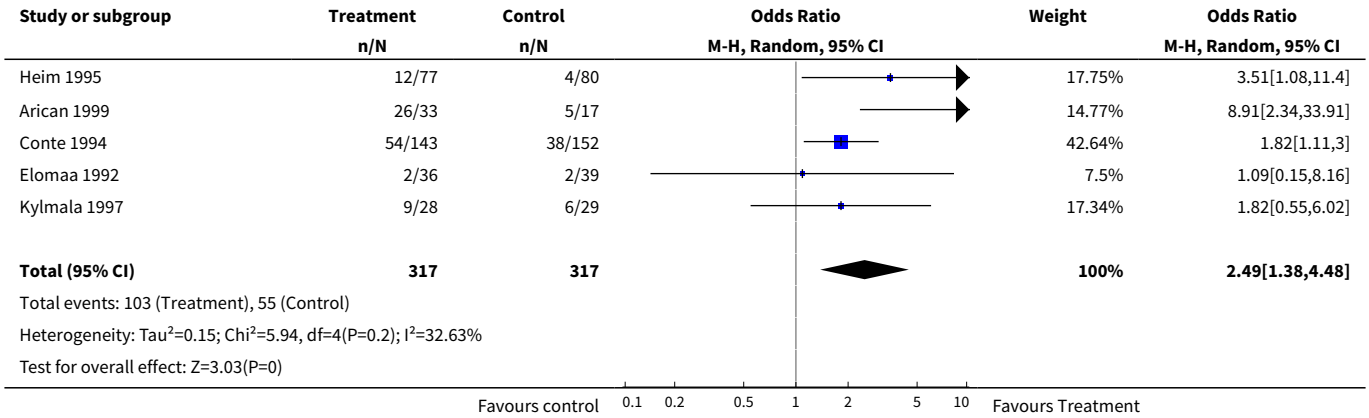




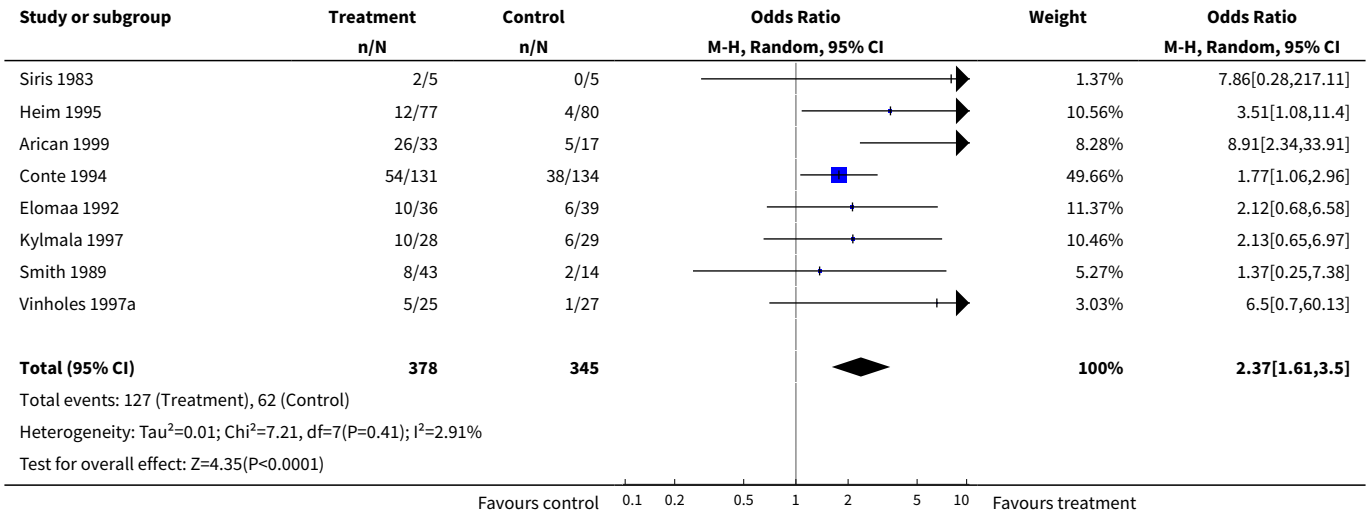
Analysis 1.2. Comparison 1 Proportion of patients with pain relief (Blinded and open control studies), Outcome 2 Proportion of patients with pain response at 8w (Blinded and open studies).



Analysis 1.3. Comparison 1 Proportion of patients with pain relief (Blinded and open control studies), Outcome 3 Proportion of patients with pain relief at 12w (Blinded and open studies).



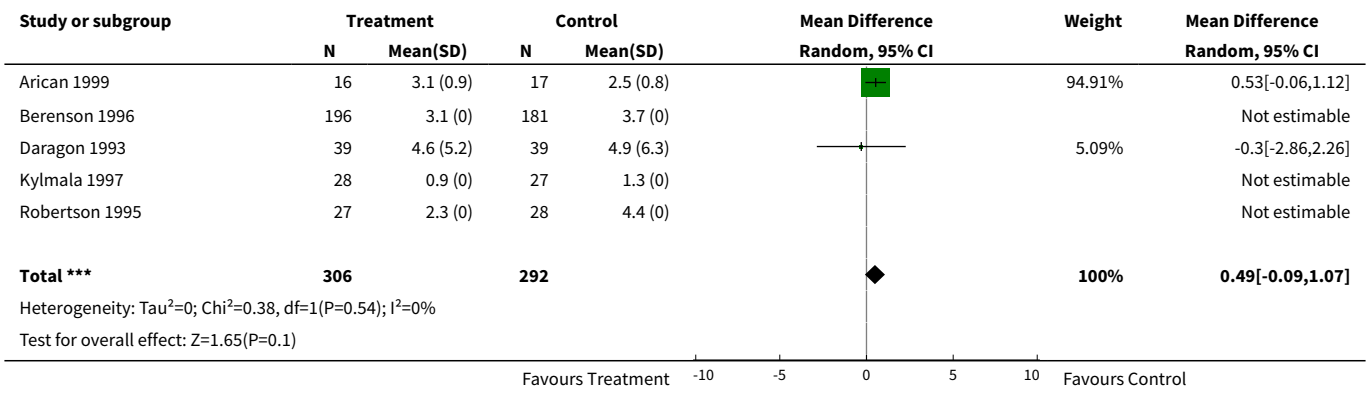
Analysis 1.4. Comparison 1 Proportion of patients with pain relief (Blinded and open control studies), Outcome 4 Proportion of patients with pain relief with best response within 12 weeks (blinded and open studies).



Comparison 2. Mean pain change (non standardized)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 mean pain score at 4 weeks	5	598	Mean Difference (IV, Random, 95% CI)	0.49 [-0.09, 1.07]
2 mean pain score at 8 weeks	1	377	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 mean pain score at 12 weeks	5	892	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Mean pain change (non standardized), Outcome 1 mean pain score at 4 weeks.



Analysis 2.2. Comparison 2 Mean pain change (non standardized), Outcome 2 mean pain score at 8 weeks.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Berenson 1996	196	3.1 (0)	181	3.5 (0)			Not estimable
Total ***	**196**		**181**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours Treatment -10 -5 0 5 10 Favours Control

Analysis 2.3. Comparison 2 Mean pain change (non standardized), Outcome 3 mean pain score at 12 weeks.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Arican 1999	16	2.7 (0)	14	3.4 (0)			Not estimable
Berenson 1996	196	2.4 (0)	181	3.4 (0)			Not estimable
Hortobagyi 1996a	185	2.6 (0)	195	2.5 (0)			Not estimable
Kylmala 1997	28	1.2 (0)	27	1.4 (0)			Not estimable
Piga 1998	27	6.4 (0)	23	6.4 (0)			Not estimable
Total ***	**452**		**440**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours Treatment -10 -5 0 5 10 Favours Control

Comparison 3. Proportion of patients with reduction in analgesics (Blinded and open studies)

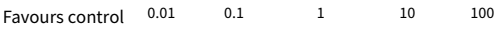
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with reduced analgesia at 4w (Blinded and open studies)	3	152	Odds Ratio (M-H, Random, 95% CI)	2.81 [1.24, 6.38]
2 Proportion of patients with reduced analgesia at 12w (Blinded and open studies)	3	182	Odds Ratio (M-H, Random, 95% CI)	2.37 [1.10, 5.12]

Analysis 3.1. Comparison 3 Proportion of patients with reduction in analgesics (Blinded and open studies), Outcome 1 Proportion of patients with reduced analgesia at 4w (Blinded and open studies).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Elomaa 1992	11/36	6/39		53.3%	2.42[0.79,7.43]
Ernst 1997	13/22	6/17		39.22%	2.65[0.72,9.8]
Martoni 1991	4/19	0/19		7.48%	11.32[0.57,226.72]
Total (95% CI)	**77**	**75**		**100%**	**2.81[1.24,6.38]**

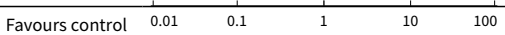
Favours control 0.01 0.1 1 10 100 Favours treatment

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Total events: 28 (Treatment), 12 (Control)					
Heterogeneity: Tau²=0; Chi²=0.93, df=2(P=0.63); I²=0%					
Test for overall effect: Z=2.47(P=0.01)					



Analysis 3.2. Comparison 3 Proportion of patients with reduction in analgesics (Blinded and open studies), Outcome 2 Proportion of patients with reduced analgesia at 12w (Blinded and open studies).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Kylmala 1997	8/28	5/29		37.19%	1.92[0.54,6.8]
Elomaa 1992	5/36	3/39		26.12%	1.94[0.43,8.76]
Piga 1998	22/27	13/23		36.69%	3.38[0.95,12.1]
Total (95% CI)	**91**	**91**		**100%**	**2.37[1.1,5.12]**
Total events: 35 (Treatment), 21 (Control)					
Heterogeneity: Tau²=0; Chi²=0.48, df=2(P=0.79); I²=0%					
Test for overall effect: Z=2.19(P=0.03)					

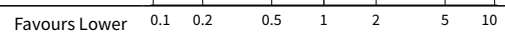


Comparison 4. Dose comparison studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with pain relief	3	126	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.62, 2.96]

Analysis 4.1. Comparison 4 Dose comparison studies, Outcome 1 Proportion of patients with pain relief.

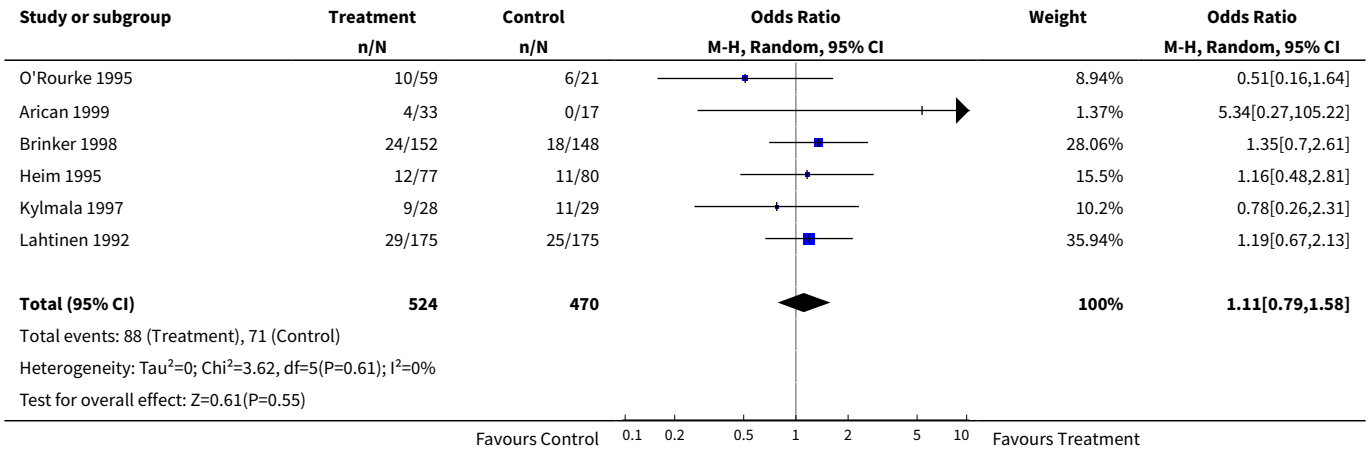
Study or subgroup	Higher dose n/N	Lower dose n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Arican 1999	13/17	13/16		21.37%	0.75[0.14,4.04]
Cascinu 1998	14/23	11/23		44.16%	1.7[0.53,5.47]
Coleman 1998	7/24	5/23		34.46%	1.48[0.39,5.58]
Total (95% CI)	**64**	**62**		**100%**	**1.36[0.62,2.96]**
Total events: 34 (Higher dose), 29 (Lower dose)					
Heterogeneity: Tau²=0; Chi²=0.63, df=2(P=0.73); I²=0%					
Test for overall effect: Z=0.78(P=0.44)					



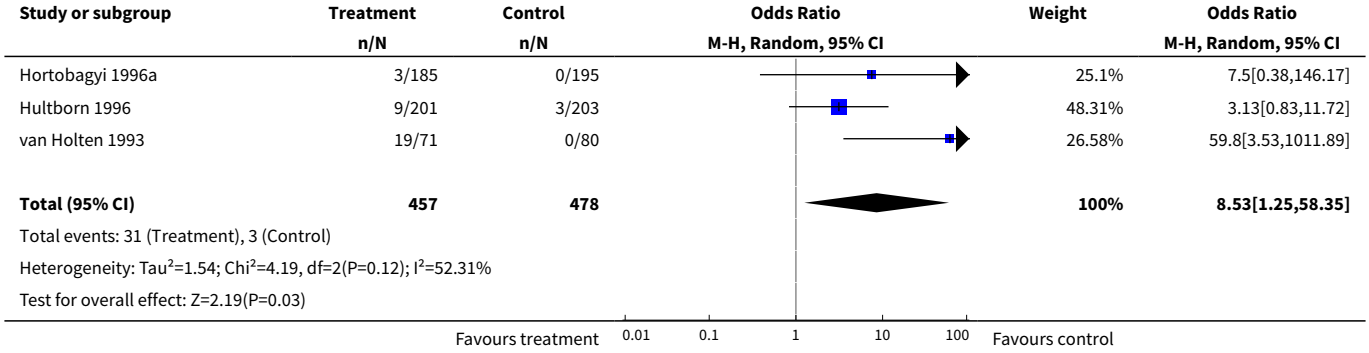
Comparison 5. Toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea and vomiting	6	994	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.79, 1.58]
2 Discontinuation of therapy	3	935	Odds Ratio (M-H, Random, 95% CI)	8.53 [1.25, 58.35]

Analysis 5.1. Comparison 5 Toxicity, Outcome 1 Nausea and vomiting.



Analysis 5.2. Comparison 5 Toxicity, Outcome 2 Discontinuation of therapy.



Comparison 6. Sensitivity analysis

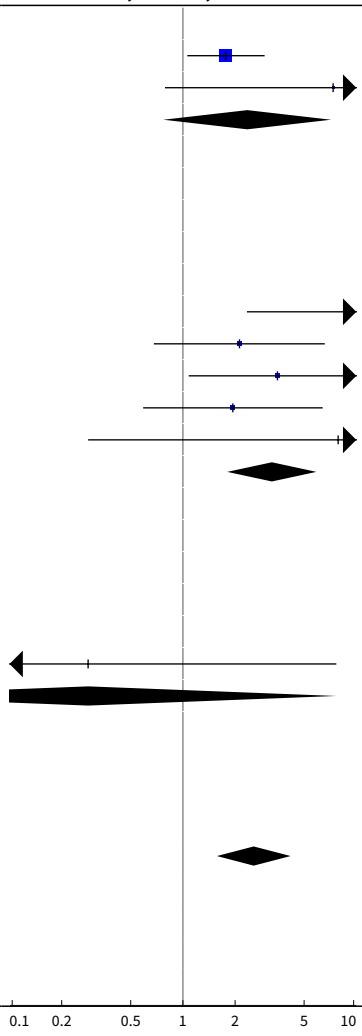
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Route/type of bisphosphonate.Best response within 12 weeks (blinded studies only)	8	685	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.57, 4.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pamidronate IV	2	313	Odds Ratio (M-H, Random, 95% CI)	2.35 [0.77, 7.15]
1.2 Clodronate PO	5	347	Odds Ratio (M-H, Random, 95% CI)	3.26 [1.80, 5.89]
1.3 Etidonrate IV	1	25	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.01, 7.67]
2 Primary disease site	8	685	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.57, 4.18]
2.1 Breast	2	275	Odds Ratio (M-H, Random, 95% CI)	1.83 [1.11, 3.04]
2.2 Prostate	3	155	Odds Ratio (M-H, Random, 95% CI)	1.81 [0.82, 4.02]
2.3 Multiple myeloma	1	157	Odds Ratio (M-H, Random, 95% CI)	3.51 [1.08, 11.40]
2.4 Any primary	2	98	Odds Ratio (M-H, Random, 95% CI)	8.47 [2.69, 26.67]
3 Study design (Blinded /open control) Pain relief using best response within 12 weeks	8	685	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.57, 4.18]
3.1 Blinded studies	6	478	Odds Ratio (M-H, Random, 95% CI)	1.92 [1.26, 2.92]
3.2 Open studies	2	207	Odds Ratio (M-H, Random, 95% CI)	5.29 [2.13, 13.15]
4 Pain as study entry criteria (Y/N) Pain relief using best response within 12 wks	8	685	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.57, 4.18]
4.1 Pain required	5	208	Odds Ratio (M-H, Random, 95% CI)	3.80 [1.42, 10.17]
4.2 No pain required	3	477	Odds Ratio (M-H, Random, 95% CI)	1.97 [1.27, 3.05]
5 Pain reporting (patient vs not specified) Pain relief using best response within 12 weeks	8	685	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.57, 4.18]
5.1 Patient reporting	5	550	Odds Ratio (M-H, Random, 95% CI)	2.00 [1.31, 3.06]
5.2 Not specified	3	135	Odds Ratio (M-H, Random, 95% CI)	4.30 [1.49, 12.41]
6 Blinded control, pain required, patient pain reporting, Pain relief using best response within 12 weeks	8	702	Odds Ratio (M-H, Random, 95% CI)	2.27 [1.45, 3.55]
6.1 Blinded control, pain required, patient pain reporting	2	73	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.08, 42.91]
6.2 Others	6	629	Odds Ratio (M-H, Random, 95% CI)	2.20 [1.43, 3.37]
7 Quality of studies	8	685	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.57, 4.18]
7.1 QS = 1	1	265	Odds Ratio (M-H, Random, 95% CI)	1.77 [1.06, 2.96]
7.2 QS = 2	3	282	Odds Ratio (M-H, Random, 95% CI)	3.80 [1.71, 8.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 QS = 3	1	25	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.01, 7.67]
7.4 QS = 4	1	55	Odds Ratio (M-H, Random, 95% CI)	1.94 [0.59, 6.40]
7.5 QS = 5	2	58	Odds Ratio (M-H, Random, 95% CI)	7.51 [1.18, 47.89]

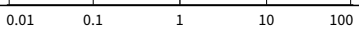
Analysis 6.1. Comparison 6 Sensitivity analysis, Outcome 1 Route/type of bisphosphonate.Best response within 12 weeks (blinded studies only).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
6.1.1 Pamidronate IV					
Conte 1994	54/131	38/134		38.45%	1.77[1.06,2.96]
Vinholes 1997a	5/22	1/26		4.48%	7.35[0.79,68.63]
Subtotal (95% CI)	**153**	**160**		**42.93%**	**2.35[0.77,7.15]**
Total events: 59 (Treatment), 39 (Control)					
Heterogeneity: Tau^2=0.33; Chi^2=1.49, df=1(P=0.22); I^2=32.85%					
Test for overall effect: Z=1.5(P=0.13)					
6.1.2 Clodronate PO					
Arican 1999	26/33	5/17		11.17%	8.91[2.34,33.91]
Elomaa 1992	10/36	6/39		14.53%	2.12[0.68,6.58]
Heim 1995	12/77	4/80		13.69%	3.51[1.08,11.4]
Kylmala 1997	10/28	6/27		13.45%	1.94[0.59,6.4]
Siris 1983	2/5	0/5		2.11%	7.86[0.28,217.11]
Subtotal (95% CI)	**179**	**168**		**54.94%**	**3.26[1.8,5.89]**
Total events: 60 (Treatment), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.74, df=4(P=0.44); I^2=0%					
Test for overall effect: Z=3.91(P<0.0001)					
6.1.3 Etidonrate IV					
Smith 1989	0/13	1/12		2.14%	0.28[0.01,7.67]
Subtotal (95% CI)	**13**	**12**		**2.14%**	**0.28[0.01,7.67]**
Total events: 0 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
Total (95% CI)	**345**	**340**		**100%**	**2.56[1.57,4.18]**
Total events: 119 (Treatment), 61 (Control)					
Heterogeneity: Tau^2=0.09; Chi^2=8.66, df=7(P=0.28); I^2=19.12%					
Test for overall effect: Z=3.76(P=0)					
Test for subgroup differences: Chi^2=2.19, df=1 (P=0.33), I^2=8.75%					



Analysis 6.2. Comparison 6 Sensitivity analysis, Outcome 2 Primary disease site.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
6.2.1 Breast					
Conte 1994	54/131	38/134		38.45%	1.77[1.06,2.96]
Siris 1983	2/5	0/5		2.11%	7.86[0.28,217.11]
Subtotal (95% CI)	**136**	**139**		**40.55%**	**1.83[1.11,3.04]**
Total events: 56 (Treatment), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.76, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=2.35(P=0.02)					
6.2.2 Prostate					
Elomaa 1992	10/36	6/39		14.53%	2.12[0.68,6.58]
Kylmala 1997	10/28	6/27		13.45%	1.94[0.59,6.4]
Smith 1989	0/13	1/12		2.14%	0.28[0.01,7.67]
Subtotal (95% CI)	**77**	**78**		**30.11%**	**1.81[0.82,4.02]**
Total events: 20 (Treatment), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.3, df=2(P=0.52); I^2=0%					
Test for overall effect: Z=1.46(P=0.14)					
6.2.3 Multiple myeloma					
Heim 1995	12/77	4/80		13.69%	3.51[1.08,11.4]
Subtotal (95% CI)	**77**	**80**		**13.69%**	**3.51[1.08,11.4]**
Total events: 12 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
6.2.4 Any primary					
Arican 1999	26/33	5/17		11.17%	8.91[2.34,33.91]
Vinholes 1997a	5/22	1/26		4.48%	7.35[0.79,68.63]
Subtotal (95% CI)	**55**	**43**		**15.65%**	**8.47[2.69,26.67]**
Total events: 31 (Treatment), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=3.65(P=0)					
Total (95% CI)	**345**	**340**		**100%**	**2.56[1.57,4.18]**
Total events: 119 (Treatment), 61 (Control)					
Heterogeneity: Tau^2=0.09; Chi^2=8.66, df=7(P=0.28); I^2=19.12%					
Test for overall effect: Z=3.76(P=0)					
Test for subgroup differences: Chi^2=6.57, df=1 (P=0.09), I^2=54.37%					

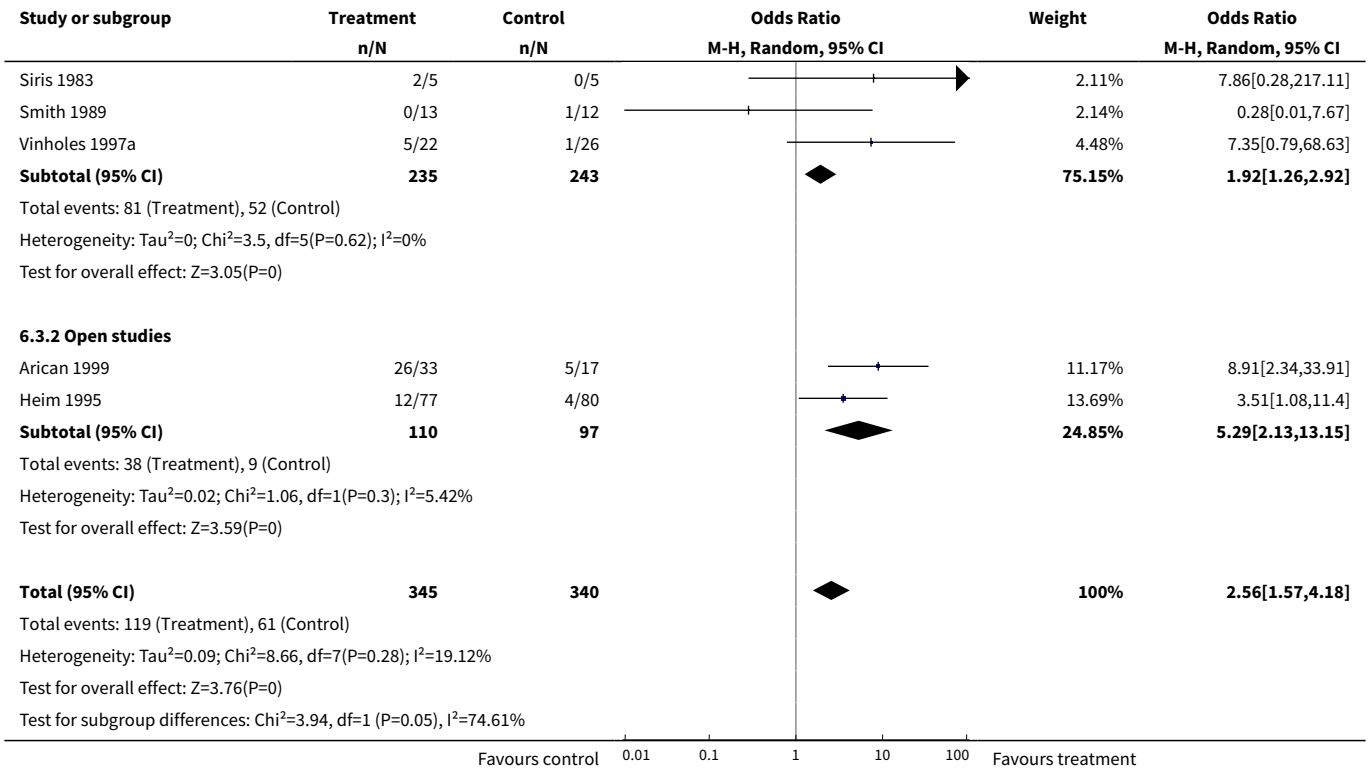


Favours control — Favours treatment

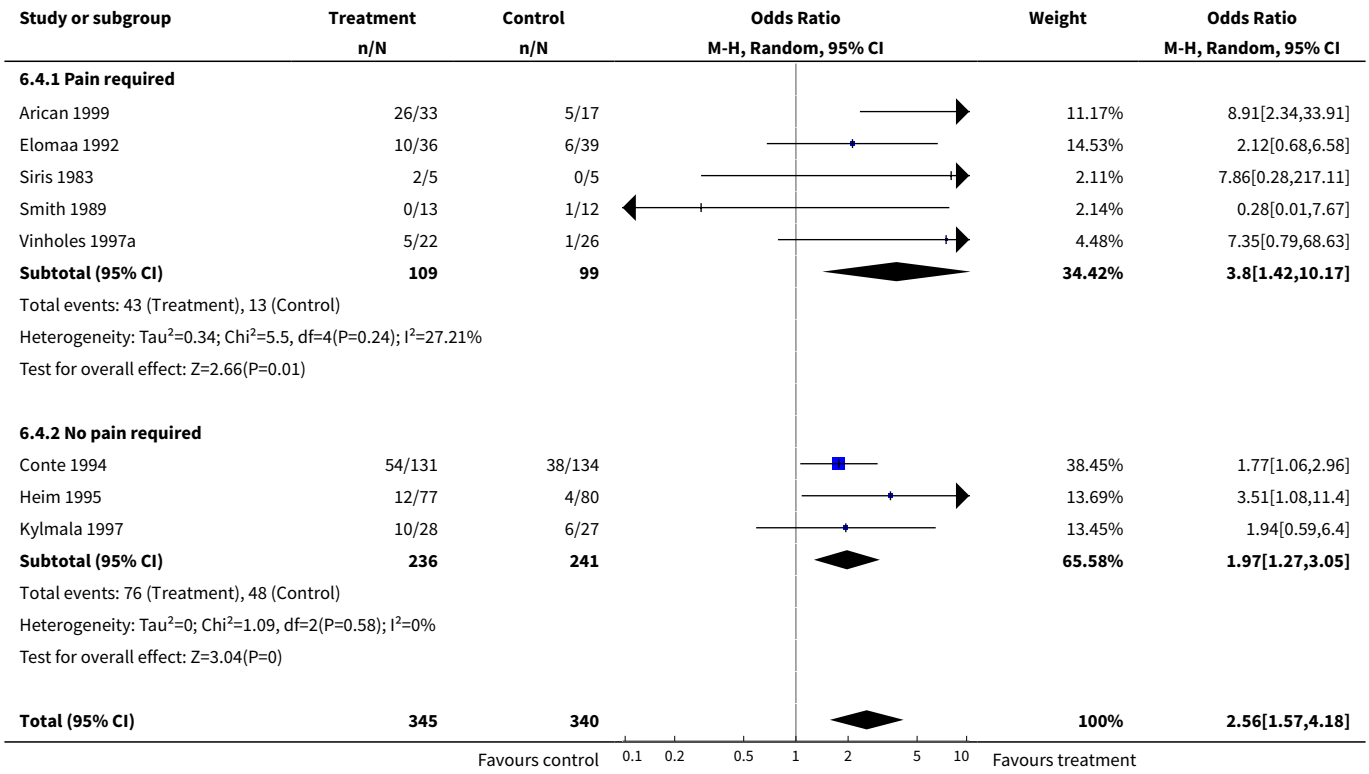
Analysis 6.3. Comparison 6 Sensitivity analysis, Outcome 3 Study design (Blinded /open control) Pain relief using best response within 12 weeks.

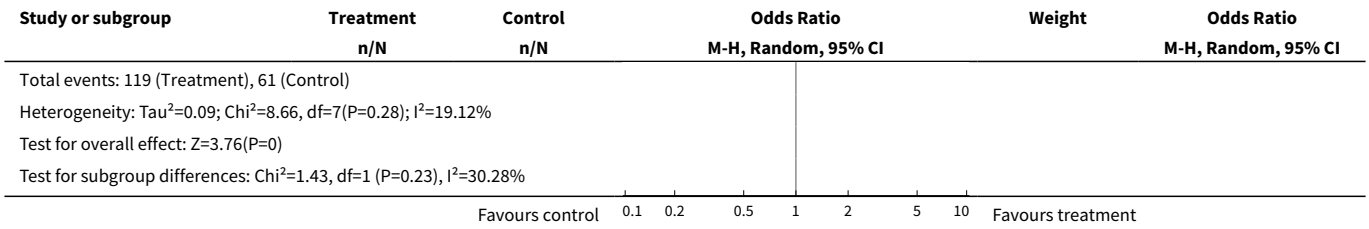
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
6.3.1 Blinded studies					
Conte 1994	54/131	38/134		38.45%	1.77[1.06,2.96]
Elomaa 1992	10/36	6/39		14.53%	2.12[0.68,6.58]
Kylmala 1997	10/28	6/27		13.45%	1.94[0.59,6.4]

Favours control — Favours treatment

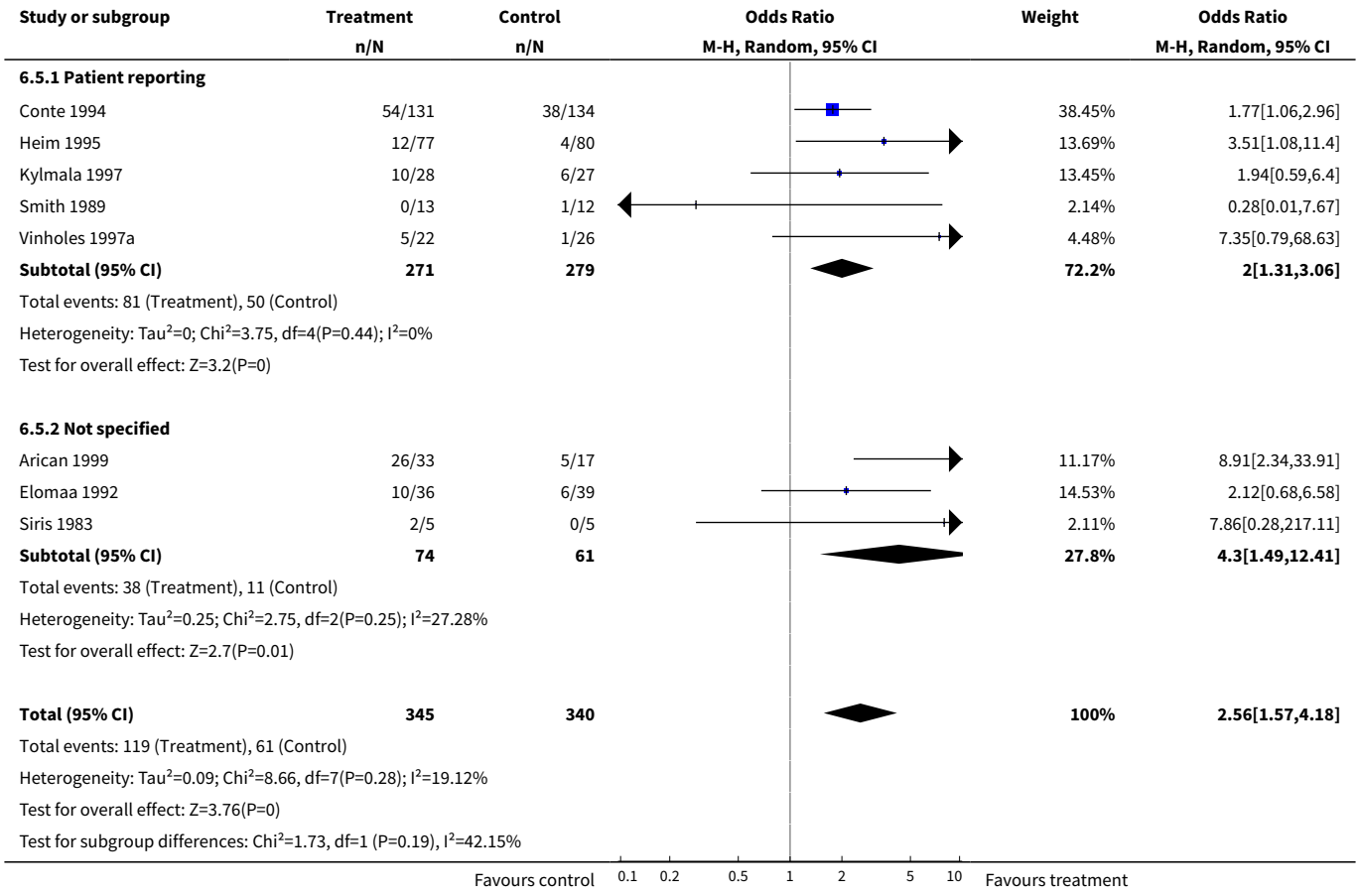


Analysis 6.4. Comparison 6 Sensitivity analysis, Outcome 4 Pain as study entry criteria (Y/N) Pain relief using best response within 12 wks.

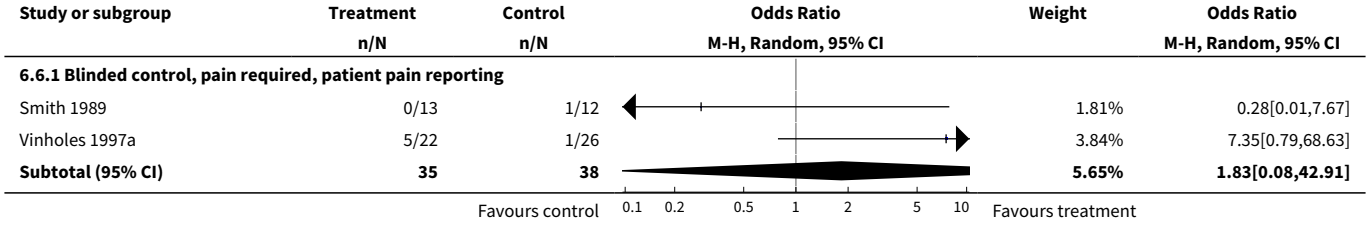


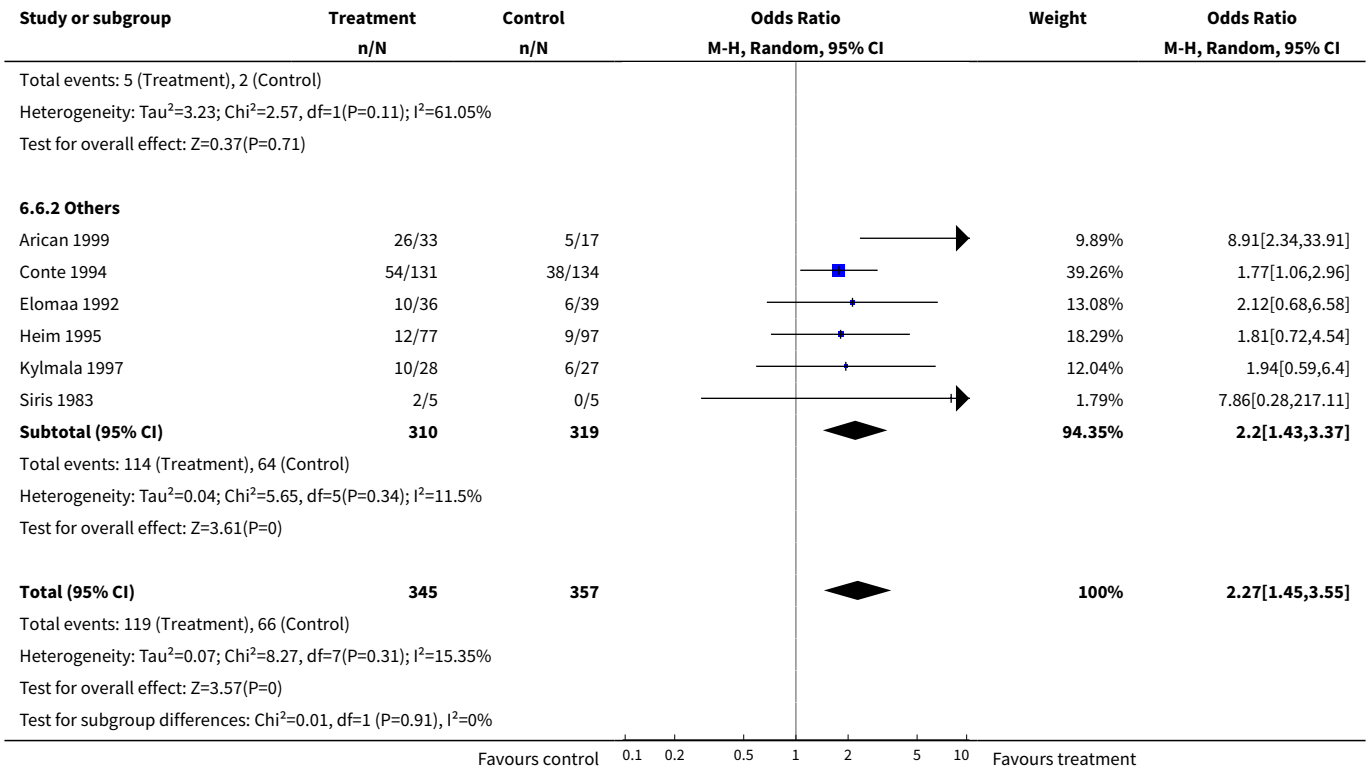


Analysis 6.5. Comparison 6 Sensitivity analysis, Outcome 5 Pain reporting (patient vs not specified) Pain relief using best response within 12 weeks.

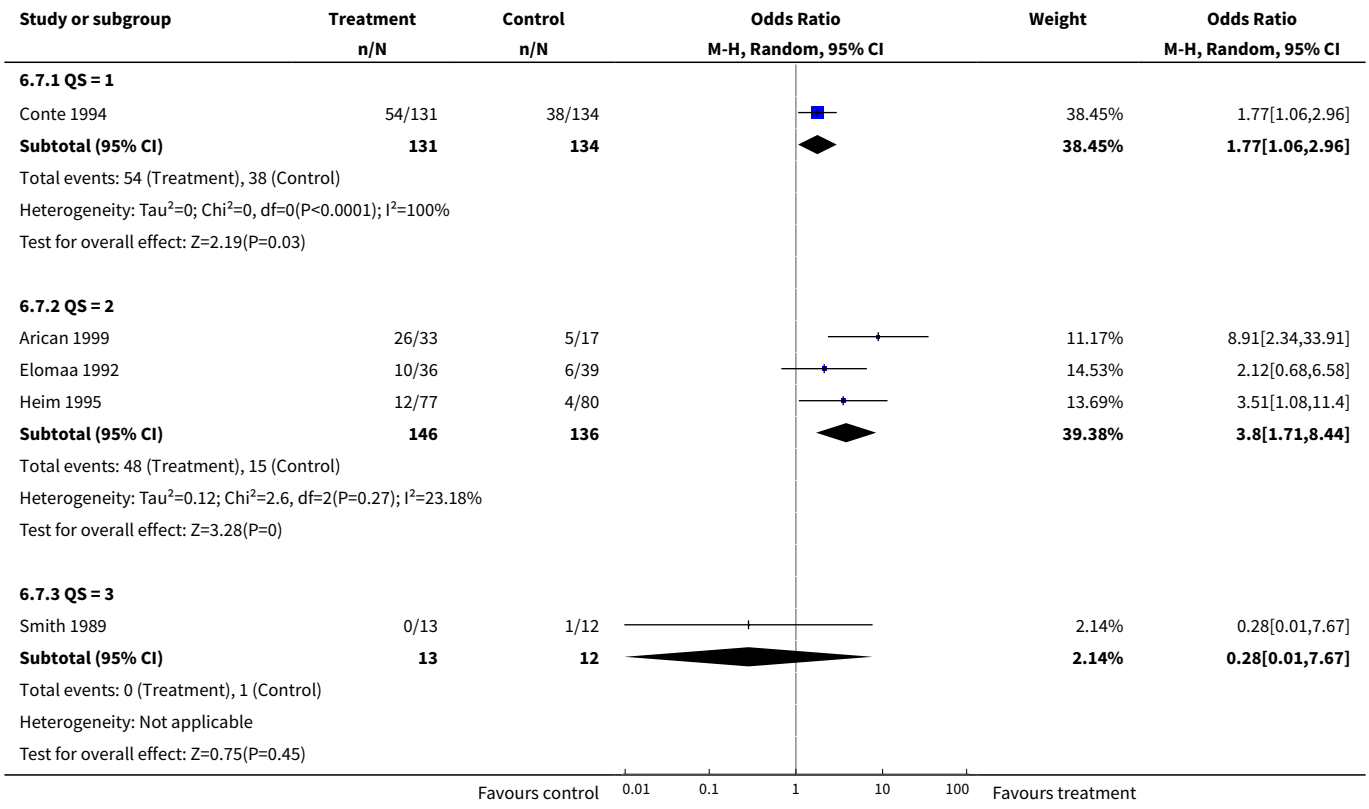


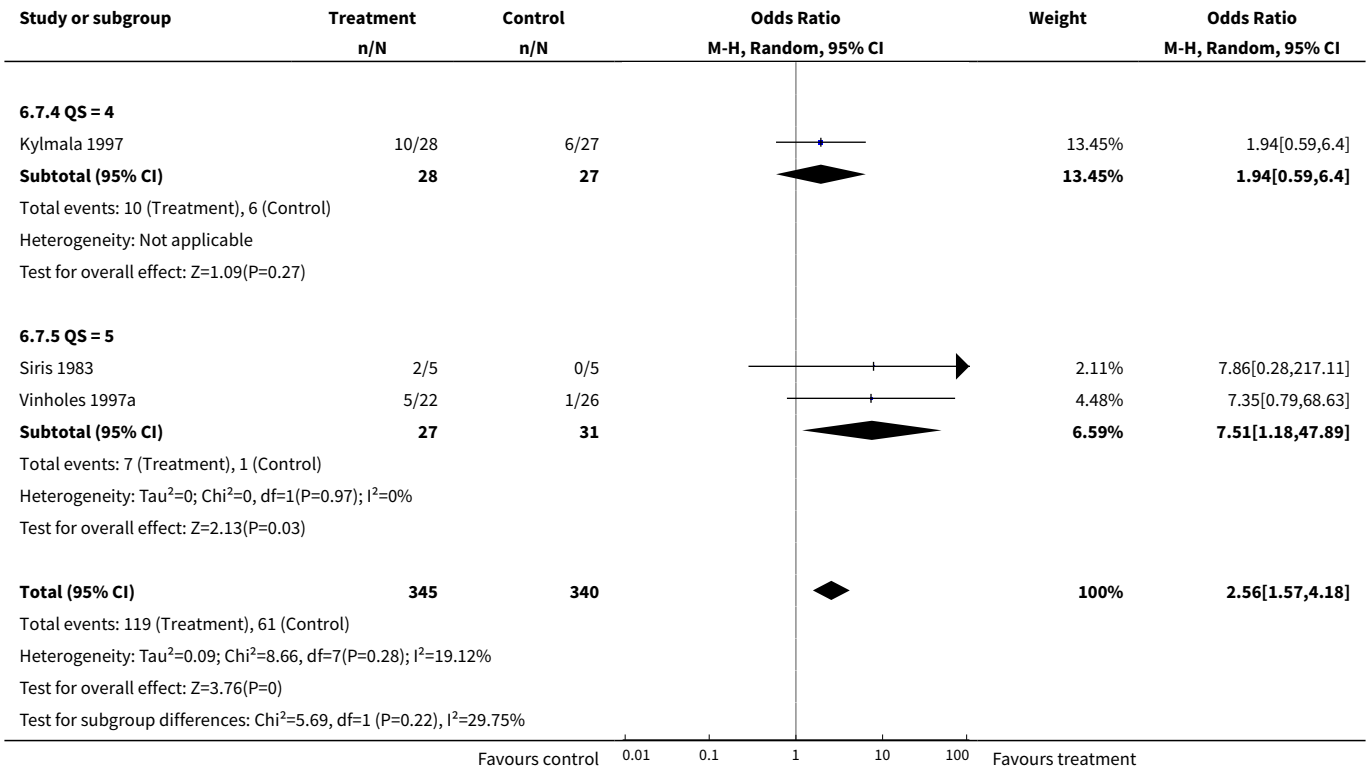
Analysis 6.6. Comparison 6 Sensitivity analysis, Outcome 6 Blinded control, pain required, patient pain reporting, Pain relief using best response within 12 weeks.





Analysis 6.7. Comparison 6 Sensitivity analysis, Outcome 7 Quality of studies.





ADDITIONAL TABLES

Table 1. Included studies by primary disease site

STUDY	BREAST	PROSTATE	MULTIPLE MYELOMA	LUNG	ANY PRIMARY
BLINDED STUDIES					
Theriault 1999	x				
Brinkler 1998			x		
Piga 1998					x
Vinholes 1997a					x
Strang 1997		x			
Kylmala 1997		x			x
Ernst 1997*					x
Hultborn 1996	x				
Hortobagyi 1996	x				

Table 1. Included studies by primary disease site *(Continued)*

Berenson 1996			x		
Robertson 1995			x		
O'Rourke 1995*					x
Daragon 1993			x		
Lahtinen 1992			x		
Elomaa 1992		x			
Ernst 1992					x
Martoni 1991	x				
Belch 1991			x		
Smith 1989*		x			
Siris 1983	x				
Demas 1982			x		
OPEN CONTROL					
Arican 1999*					x
Heim 1995			x		
Conte 1994	x				
Van Holten 1993	x				
ACTIVE CONTROL					
Koeberle 1999					x
Cascinu 1998					x
Moiseyenko 1998					x
Coleman 1998	x				
Glover 1994	x				

* studies with >1 active arms

Table 2. Studies by intervention (clodronate)

Study	placebo control	open control	400mg/d PO	800mg/d PO	1600mg/d PO	2400mg/d PO	3200mg/d PO	Others
Arican 1999		+		+	+			
Delmas 1982a	+				+			
Elomaa 1992	+							3.2g/dPO x1m then 1.6g/d PO x5m
Ernst 1992	+							600mg IV x1 dose
Ernst 1997	+							600mg IV x 1 dose vs 1500mg IV x1 dose
Heim 1995		+			+			
Kylmala 1997	+							300mg/d IV x5d, then 1.6g/d PO
Lahtinen 1992	+					+		
Martoni 1991	+							300mg/d IV x7d, 100mg/d IM x3w, 100mg alt d IM x2m
Moisenyenko 1998								300mgIV x5d vs 1.5gIV x1 dose then placebo x4 d
O'Rourke 1995	+		+		+		+	
Piga 1998	+				+			
Robertson 1995	+				+			
Siris 1983	+						+	
Strang 1997	+							300mg/d IV x3d, 600mg bid x4w PO

Table 3. Studies by intervention (Pamidronate IV)

study	Placebo control	Open control	40mg q3w IV	45mg q3w IV	60mg q3w IV	60mg q4w IV	90mg q3w IV	90mg q4w IV	others

Table 3. Studies by intervention (Pamidronate IV) *(Continued)*

Bereneson 1996	+						+	
Cascinu 1998				+	+		+	
Conte 1994		+		+				
Glover 1994						+	+	30 mg q2w vs 60 mg q2w
Hortobagyi 1996	+						+	
Hultborn 1996	+					+		
Koeberle 1999					+		+	
Theriault 1999	+						+	
Vinholes 1997a	+							120 mg x 1dose

Table 4. Studies by intervention (Pamidronate PO)

Study	Placebo control	Open control	150 mg/d	300 mg/d
Brinkler 1998	+		+	
Coleman 1998			+	+
Van Holten 1993		+		+

Table 5. Items sought for inclusion in 'Characteristics of included studies' table

Methods	Participants	Intervention	Outcomes	Notes
Number of study arms	Primary site (prostate vs breast vs multiple myeloma vs lung vs combination)	For each of intervention arm/ active control arm: name of bisphosphonate (etidronate, clodronate, pamidronate, others)	Which of the following pain measure outcome can be extracted from the study:	Oxford Quality Scale score (Jadad)
Study design (blind/ open/active controls)	Whether patients have to have bone metastases or not at the time of enrolment (bone mets vs bone mets not required)	Route of administration	Mean pain score pre and post treatment	Number and reason of dropouts
If crossover study, duration of washout period	Whether patients have to have pain prior to study enrolment (pain or pain not required)	Dose schedule	Proportion of patients with pain reduction	Other notes
Pain measurement tool used	Other interventions in study arm (chemotherapy / hormonal therapy/ others)	Duration of therapy	P value only for a pain measure	
Pain score expressed by : patient /physician/ unknown	Performance status measure (life expectancy / others)		Not reported as an endpoint	
Criteria of response for pain. This is only applicable if proportion of patients reponding is an outcome measure. Not specified infers that this is an outcome measure by definition not provided, not applicable infers that this is not an outcome measure used.	Other specifications for inclusion/exclusion		Which of the following analgesics change can be extracted from the data:	
Analgesic measurement tool used			proportion with analgesic reduction	
Criteria of response for analgesic			Others	

Table 5. Items sought for inclusion in 'Characteristics of included studies' table *(Continued)*

	Adverse effects for control, and study arm

WHAT'S NEW

Date	Event	Description
22 November 2013	Amended	See Published notes.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2002

Date	Event	Description
12 August 2009	Amended	Contact details updated.
13 May 2009	Amended	Contact details updated.
11 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The protocol and review were written jointly by both authors.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Princess Margaret Hospital, University Heath Network, Canada.
- Marie Curie Cancer Care, UK.
- Toronto Sunnybrook Regional Cancer Center, Cancer Care Ontario, Canada.

External sources

- No sources of support supplied

NOTES

This review is out of date, and the original authors are no longer available to update it. The contents of this review should be accepted for historical interest only as they may be misleading for current practice.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Non-Narcotic [therapeutic use]; Antineoplastic Agents [therapeutic use]; Bone Neoplasms [complications] [*drug therapy] [*secondary]; Clodronic Acid [therapeutic use]; Diphosphonates [*therapeutic use]; Etidronic Acid [therapeutic use]; Pain [*drug therapy]; Pamidronate; Randomized Controlled Trials as Topic

MeSH check words

Humans