Health Technology Assessment 2004; Vol. 8: No. 4

A systematic review of the role of bisphosphonates in metastatic disease

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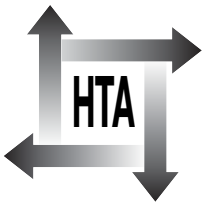
D Wonderling, C Normand and K Broadley

February 2004

Health Technology Assessment
NHS R&D HTA Programme



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A systematic review of the role of bisphosphonates in metastatic disease

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Declared competing interests of authors: none

Published February 2004

This report should be referenced as follows:

Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.
A systematic review of the role of bisphosphonates in metastatic disease. *Health Technol Assess* 2004;**8**(4).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

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This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure was replaced in 2000 by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

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The research reported in this monograph was funded as project number 98/30/01.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

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Abstract

A systematic review of the role of bisphosphonates in metastatic disease

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Objectives: To identify evidence for the role of bisphosphonates in malignancy for the treatment of hypercalcaemia, prevention of skeletal morbidity and use in the adjuvant setting. To perform an economic review of current literature and model the cost effectiveness of bisphosphonates in the treatment of hypercalcaemia and prevention of skeletal morbidity
Data sources: Electronic databases (1966–June 2001). Cochrane register. Pharmaceutical companies. Experts in the field. Handsearching of abstracts and leading oncology journals (1999–2001).
Review methods: Two independent reviewers assessed studies for inclusion, according to predetermined criteria, and extracted relevant data. Overall event rates were pooled in a meta-analysis, odds ratios (OR) were given with 95% confidence intervals (CI). Where data could not be combined, studies were reported individually and proportions compared using chi-squared analysis. Cost and cost-effectiveness were assessed by a decision analytic model comparing different bisphosphonate regimens for the treatment of hypercalcaemia; Markov models were employed to evaluate the use of bisphosphonates to prevent skeletal-related events (SRE) in patients with breast cancer and multiple myeloma.
Results: For acute hypercalcaemia of malignancy, bisphosphonates normalised serum calcium in >70% of patients within 2–6 days. Pamidronate was more effective than control, etidronate, mithramycin and low-dose clodronate, but equal to high dose clodronate, in achieving normocalcaemia. Pamidronate prolongs (doubles) the median time to relapse compared with clodronate or etidronate.
For prevention of skeletal morbidity, bisphosphonates compared with placebo, significantly reduced the OR for fractures (OR [95% CI], vertebral, 0.69 [0.57–0.84], non-vertebral, 0.65 [0.54–0.79], combined, 0.65 [0.55–0.78]) radiotherapy 0.67 [0.57–0.79] and hypercalcaemia 0.54 [0.36–0.81] but not orthopaedic surgery 0.70 [0.46–1.05] or spinal cord compression 0.71 [0.47–1.08]. However, reduction in orthopaedic surgery was significant in studies that lasted over a year 0.59 [0.39–0.88]. Bisphosphonates significantly increased the time to first SRE but did not affect survival. Subanalyses were performed for disease groups, drugs and route of administration. Most evidence supports the use of intravenous aminobisphosphonates. For adjuvant use of bisphosphonates, Clodronate, given to patients with primary operable breast cancer and no metastatic disease, significantly reduced the number of patients developing bone metastases. This benefit was not maintained once regular administration had been discontinued. Two trials reported significant survival advantages in the treated groups. Bisphosphonates reduce the number of bone metastases in patients with both early and advanced breast cancer.
Bisphosphonates are well tolerated with a low incidence of side-effects. Economic modelling showed that for acute hypercalcaemia, drugs with the longest

cumulative duration of normocalcaemia were most cost-effective. Zoledronate 4 mg was the most costly, but most cost-effective treatment. For skeletal morbidity, Markov models estimated that the overall cost of bisphosphonate therapy to prevent an SRE was £250 and £1500 per event for patients with breast cancer and multiple myeloma, respectively. Bisphosphonate treatment is sometimes cost-saving in breast cancer patients where fractures are prevented.

Conclusions: High dose aminobisphosphonates are most effective for the treatment of acute hypercalcaemia and delay time to relapse. Bisphosphonates significantly reduce SREs and delay the time to first SRE in patients with bony metastatic disease but do not affect survival. Benefit is demonstrated after administration for at least 6–12 months. The greatest body of evidence supports the use of intravenous aminobisphosphonates. Further evidence is required to support use in the adjuvant setting.

Contents

List of abbreviations

AEC	annual equivalent cost
alb	albumin
ARR	absolute risk reduction
ASCO	American Society of Clinical Oncology
ATP	adenosine triphosphate
BASO	British Association of Surgical Oncology
BMD	bone mineral density
BMU	bone multicellular unit
BNF	British National Formulary
BSP	bone sialoprotein
C#	combined fracture
Can$	canadian dollar
CCa	corrected calcium
C-erb-B2	human epidermal growth factor receptor-2 gene (HER 2)
CI	confidence interval
CTX	C-terminal cross-linking telopeptide of type I collagen
DARE	Database of Abstracts of Reviews of Effectiveness
ECOG	Eastern Co-operative Oncology Group
ECU	European currency unit
ER +ve	oestrogen receptor-positive
ER –ve	oestrogen receptor-negative
FDA	(US) Food and Drug Administration
FPP	farnesyl diphosphate
GGPP	geranylgeranyl diphosphate
GI	gastrointestinal
GTP	guanosine triphosphate
HCA	hypercalcaemia
HHCM	humoral hypercalcaemia of malignancy
HRG	healthcare resource group
IL-1	interleukin-1
IL-6	interleukin-6
LD_{50}	lethal dose 50
MMP-1	matrix-metalloproteinase-1
NcAMP	nephrogenic cyclic adenosine monophosphate
NICE	National Institute for Clinical Excellence
NNT	numbers needed to treat
NTX	N-terminal cross-linking telopeptide of type I collagen
NV#	non-vertebral fracture
OC	osteocalcin
ODF	osteoclast differentiation factor (now known as RANKL)
OECD	Organisation of Economic Cooperation and Development
OPG	osteoprotogerin
OR	odds ratio
Ortho	orthopaedic surgery
PAPAS	Pain, Palliative and Supportive Care Collaborative Cochrane Review Group
PICP	procollagen type I C propeptide
PINP	procollagen type I N propeptide
PR	progesterone receptor
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
PYD	pyridinoline

continued

List of abbreviations *continued*

QALY	quality-adjusted life-year
RANK	receptor-activated nuclear factor NF-kappaB
RANKL	receptor-activated nuclear factor NF-kappaB ligand (previously known as ODF)
RCT	randomised controlled trial
RT	radiotherapy
SCC	spinal cord compression
SRE	skeletal-related event
TGF-α	tumour growth factor-alpha
TGF-β	tumour growth factor-beta
TNF-α	tumour necrosis factor-alpha
TNF-β	tumour necrosis factor-beta
V#	vertebral fracture

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Bisphosphonates inhibit osteoclastic bone resorption and are used in malignant disease to treat hypercalcaemia, reduce skeletal morbidity associated with bone metastases and, less often, in the adjuvant setting to delay the development of bone metastases. As there are economic implications for the widespread use of these drugs, it is essential that their use is evidence based.

Objectives

1. To identify evidence for the role of bisphosphonates in malignancy for the
   (a) treatment of hypercalcaemia
   (b) prevention of skeletal morbidity
   (c) use in the adjuvant setting.
2. To perform an economic review of current literature and to model the cost-effectiveness of bisphosphonates in the treatment of hypercalcaemia and prevention of skeletal morbidity

Methods

Data sources

- Electronic databases: MEDLINE, CANCERLIT, EMBASE, Science Citation Index Expanded, pre-MEDLINE, Cochrane Register for Randomised Controlled Trials and Database for Abstracts of Reviews of Effectiveness, Health Economic Evaluations Database, National Health Service Economic Evaluations Database.
- Scanning of reference lists of included studies and key reviews.
- Pharmaceutical companies.
- Experts in the field.
- US Food and Drug Administration website.
- Hand-searching of abstracts from the meeting of American Society Clinical Oncology and European Congress Cancer Oncology 1999–2001; contents pages of *Journal Clinical Oncology* 2001, *European Journal of Cancer* 2001 and *Bone* 2001, together with abstracts printed in these journals 1999–2001.

Study selection

1. Hypercalcaemia review
   (a) randomised controlled trials (RCTs)
   (b) patients with hypercalcaemia of malignancy (elevated corrected serum calcium post-rehydration)
   (c) treated with a bisphosphonate.
2. Skeletal morbidity review
   (a) RCTs
   (b) patients with malignancy and bony metastases
   (c) treated with a bisphosphonate
   (d) studies measuring at least one skeletal-related event (SRE): pathological fractures (non-vertebral, vertebral, combined), radiotherapy, spinal cord compression, orthopaedic surgery, hypercalcaemia.
3. Adjuvant review
   (a) RCTs
   (b) patients with malignancy and no bony metastases
   (c) treated with a bisphosphonate.
4. Economic review
   (a) all studies included (not limited to RCTs)
   (b) information regarding cost/cost-benefit of bisphosphonate therapy.

Data extraction

All studies were assessed for inclusion then data extracted by two independent reviewers. Consensus was reached, with a third reviewer's decision being final. Studies were graded according to blinding and allocation concealment.

Data synthesis

Where possible, overall event rates were calculated by meta-analysis and pooled odds ratios (OR) given with 95% confidence intervals (CIs). Where data could not be combined, studies were reported individually and proportions compared using chi-squared analysis. Cost and cost-effectiveness were assessed by a decision analytic model comparing different bisphosphonate regimens for the treatment of hypercalcaemia; Markov models were employed to evaluate the use of bisphosphonates to prevent SRE in patients with breast cancer and multiple myeloma.

Results

Hypercalcaemia review

Owing to the heterogeneity of studies, results could not be combined in a meta-analysis. Pamidronate was more effective than control, etidronate, mithramycin and low-dose clodronate (600 mg) in achieving normocalcaemia. Pamidronate 90 mg was as effective as higher dose clodronate (1500 mg) and demonstrates a dose response from 30–60–90 mg. Pamidronate prolongs (doubles) the median time to relapse compared with clodronate and etidronate. Alendronate has similar efficacy to clodronate but is superior to etidronate in achieving normocalcaemia. A dose response is seen with ibandronate (up to 4 mg) and alendronate. Mean time to normocalcaemia for all bisphosphonates ranges from 2 to 6 days.

Skeletal morbidity review

Primary analysis

On meta-analysis, bisphosphonates, compared with placebo, significantly reduced the OR for vertebral fractures, non-vertebral fractures, combined fractures, radiotherapy and hypercalcaemia but not orthopaedic surgery or spinal cord compression. OR (95% CI): vertebral fractures, 0.692 (0.570 to 0.840), $p < 0.0001$; non-vertebral fractures, 0.653 (0.540 to 0.791), $p < 0.0001$; combined fractures, 0.653 (0.547 to 0.780), $p < 0.0001$; radiotherapy, 0.674 (0.573 to 0.791), $p < 0.0001$; spinal cord compression, 0.714 (0.470 to 1.083), $p = 0.113$; orthopaedic surgery, 0.698 (0.463 to 1.052), $p = 0.086$; and hypercalcaemia, 0.544 (0.364 to 0.814), $p = 0.003$.

Time to first SRE

Bisphosphonates (intravenous pamidronate and intravenous zoledronate) significantly increase the time to first SRE. The evidence for oral clodronate is conflicting.

Sub-analysis over time

The OR for radiotherapy was significantly reduced at all time points. Orthopaedic surgery showed a progressive reduction in OR with narrowing of the CI, reaching significance at 24 months. For hypercalcaemia, the reduction in the OR was significant at all time points except 18–24 months.

Sub-analysis of disease groups

Two results contrasted strongly with the primary analysis. Vertebral fractures were not significantly reduced in patients with breast cancer, OR (95% CI) 0.870 (0.656 to 1.154), $p = 0.334$. Hypercalcaemia was not significantly reduced in patients with myeloma, OR (95% CI) 0.968 (0.687 to 1.365), $p = 0.852$.

Sub-analysis of drugs

All outcomes except spinal cord compression reached significance with pamidronate, including orthopaedic surgery, $p = 0.009$. Clodronate significantly reduced the OR for vertebral fractures, non-vertebral fractures and hypercalcaemia. Zoledronate significantly reduced the OR for all outcomes except spinal cord compression and orthopaedic surgery. There was no difference, for any outcome, in trials directly comparing zoledronate with pamidronate.

Sub-analysis of route

Oral bisphosphonates significantly reduced the OR for vertebral fractures and non-vertebral fractures. Intravenous bisphosphonates significantly reduced the OR for all outcomes except spinal cord compression.

Survival

There was no survival benefit.

Adjuvant review

Clodronate significantly reduces the number of patients with primary operable breast cancer developing bone metastases. This benefit was not maintained once regular administration had been discontinued. Two trials reported significant survival advantages in the treated groups. These findings were not seen in trials of patients with advanced disease.

Toxicity

Bisphosphonates are well tolerated with a low incidence of side-effects

Economic review

Hypercalcaemia

Drugs with the longest cumulative duration of normocalcaemia were most cost-effective. Zoledronate 4 mg was the most costly but most cost-effective treatment (approximately £22,900 per life year gained). The estimates of cost-effectiveness were sensitive to amount of time in hospital.

Skeletal morbidity

The overall cost of bisphosphonate therapy to prevent an SRE was estimated at £250 and £1500 per event for patients with breast cancer and multiple myeloma, respectively. The model suggested that bisphosphonate treatment is sometimes cost-saving in breast cancer patients where fractures are prevented. The models were sensitive to the probability of averting an SRE, the unit cost of an SRE and the price of bisphosphonate treatment.

Conclusions

Bisphosphonates normalise serum calcium in >70% of patients with hypercalcaemia of malignancy within 2–6 days; pamidronate doubles the time to relapse compared with non-aminobisphosphonates. They significantly reduce SREs and delay the time to first SRE in patients with bony metastatic breast cancer and multiple myeloma. Benefit is seen at different time points for different SREs. Bisphosphonates do not affect survival. The current evidence is strongest for the efficacy of pamidronate and for the intravenous over the oral route of administration. In primary operable breast cancer, oral clodronate reduces the number of patients developing bone metastases.

Implications for healthcare

Bisphosphonate therapy appears cost-effective in the treatment of hypercalcaemia and for the prevention of skeletal morbidity, particularly for patients with breast cancer. The economic evidence reviewed was of limited quality, therefore any conclusions based on this evidence need to be interpreted with caution.

Recommendations for research

Hypercalcaemia

- RCT of bisphosphonate maintenance therapy to delay time to relapse in patients following first episode of hypercalcaemia
- trial of parathyroid hormone-related protein (PTHrP) blocker in combination with bisphosphonate in patients with very high levels of PTHrP.

Skeletal morbidity

- RCT using bisphosphonates for prevention of skeletal morbidity in patients with prostate cancer metastatic to bone
- trials to determine the optimum time to commence bisphosphonate therapy: at diagnosis of asymptomatic bone metastases or at first SRE?
- trial to compare efficacy of oral versus intravenous bisphosphonate
- a study to determine current clinical practice with respect to bisphosphonate use in UK oncology centres.

Adjuvant use

- extended use of bisphosphonates (>3 years) for primary prevention of bone metastases from breast cancer
- adjuvant use of bisphosphonates in patients with prostate cancer at high risk of developing bone metastases.

Economic analyses

The evidence base for estimating cost and cost-effectiveness is limited. Further cost and quality of life data are required to identify cost-effectiveness associated with reductions in SREs and delayed time to first SRE. Data on cumulative length of stay and response to successive treatments for patients with hypercalcaemia are needed.

Chapter 1
Introduction

Bisphosphonates

Bisphosphonates are synthetic analogues of naturally occurring pyrophosphate compounds that inhibit calcification. They have been useful in treating many disorders, such as metabolic bone disease, Paget's disease, osteoporosis and metastatic bone disease. They are also used in imaging procedures. New applications for the use of these drugs are still emerging.

The history and development of bisphosphonates

The major substances of biomineralisation are Ca^{2+} and CO_3^{2-} ions. The interaction between these two ions or their equivalents:

> "… cover(s) all major forms of solid-state formation in living beings, as well as many so-called 'dead' inorganic solidification processes …"

from sea bottom calcium carbonate sediments to coral reefs, egg shells, kidney stones and skeletons, to name but a few.[1]

Inorganic pyrophosphate inhibits the transformation of amorphous calcium phosphate into its crystalline form. Calcium phosphate in the form of calcium hydroxyapatite is the main constituent of the skeletal system. Pyrophosphate is hydrolysed and thereby inactivated by alkaline phosphatase, allowing the mineralisation of bone.

The fundamental property of bisphosphonates, which has been exploited by industry and medicine, is their ability to form bonds with crystal surfaces and to form complexes with cations in solution, close to or at a solid–liquid interface. Phosphates act by inhibiting crystallisation processes, such as the precipitation of calcium carbonate. In the 1930s, this role was discovered accidentally by Rosenstein:

> "… while fertilising orange trees via an irrigation system, he noticed that accidental addition of very little phosphate (1 ppm, or 10^{-6}) was already effective against undesirable crystal formation blocking his irrigation tubes."[1]

Many compounds were developed in the 1950s and 1960s for use in industry, such as etidronate. Applications are wide and bisphosphonates are used to inhibit scale on crystal surfaces and inhibit corrosion of metal surfaces and in solutions they form complexes with Ca^{2+} ions and are useful for example as water softeners.[1]

Fleisch and colleagues in 1968 isolated pyrophosphate from urine.[2] Inorganic pyrophosphate inhibits precipitation of calcium phosphate *in vitro*.[3,4] This group proposed that pyrophosphate, which is also present in plasma, prevented the calcification of tissues, and suggested that bone alkaline phosphatase destroyed pyrophosphate locally, thereby allowing amorphous phase calcium phosphate to crystallise and form new bone.[2]

Pyrophosphate undergoes rapid hydrolysis when given orally, so its therapeutic application was limited. It has a role in radionucleide bone scanning and in toothpaste to prevent dental plaque.[5] Since bisphosphonates are synthetic analogues of pyrophosphates, they have the same chemical activity, but greater stability. They were found to inhibit induced calcification *in vitro*[6] and bone resorption in animals.[7]

Bisphosphonates are analogues of pyrophosphate that are resistant to enzymatic hydrolysis. This accounts for the physiochemical property of bisphosphonates, namely their ability to prevent the formation and the dissolution of calcium phosphate crystals.

Over the years, first-, second- and now third-generation bisphosphonates have been developed. Changes in chemical structure have resulted in increased potency, without demineralisation of bone. There is now a growing body of evidence regarding the efficacy of these drugs in clinical settings.

Chemical structure

Bisphosphonates have two carbon–phosphate bonds. When these attach to the same carbon atom, they are properly called geminal (central) bisphosphonates. All bisphosphonates that act significantly on the skeleton are characterised by this P–C–P bond, in contrast to pyrophosphate, which has a P–O–P bond. It is this feature that

confers stability on the compound and is one of its most important properties, rendering it stable to heat and most chemical reagents.

Variations in effect between different bisphosphonates result from changes to the two lateral chains (R^1, R^2) on the carbon or by esterifying the phosphate groups.[5] Modification of the R^1 side-chain enhances the ability of the compound to bind to crystals in bone; R^2 determines the potency of the bisphosphonate.[8] Structures (**1**) and (**2**) show the basic structures of inorganic pyrophosphate and geminal bisphosphonate, respectively, where R^1 and R^2 represent different side-chains for each bisphosphonate. The addition of a hydroxyl (OH) or primary amino (NH_2) group increases the affinity for calcium ions, resulting in preferential localisation of these drugs to sites of bone remodelling.[9] Increasing the number of carbon atoms in the side-chain (i.e. the length) will initially increase and then decrease the magnitude of the effect on bone resorption.[10] Cyclic geminal bisphosphonates are the most potent compounds, particularly if they contain a nitrogen atom in the ring. The most active compound in this class, zoledronate, contains an imidazole ring.[10]

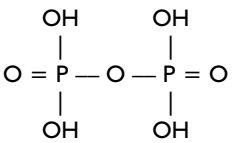
Chemical manipulations alter the properties of the compound, leading to the range of bisphosphonates that are available for use today. It is not possible to extrapolate results from one bisphosphonate to another because small changes in the structure can have major effects on the chemical properties of these compounds.[11] The first bisphosphonates to become commercially available for use in cancer patients were etidronate and clodronate. The aim in developing the next generation of bisphosphonates was to synthesise compounds which had more potent anti-resorptive activity, without increasing their ability to inhibit mineralisation. This was achieved by making changes to the R^2 side-chain. It has subsequently been discovered that nitrogen-containing bisphosphonates act by inhibiting the enzymes of the mevalonate pathway. This results in disruption of the biosynthesis of isoprenoid compounds which are essential for the post-translational modification of small guanosine triphosphonate (GTP)-binding proteins such as ras, rho and rac.[8,12] Bisphosphonates that resemble pyrophosphate such as clodronate and etidronate act as analogues of adenosine triphosphonate (ATP) and inhibit ATP-dependent intracellular enzymes.[8,12] *Tables 1* and *2* show the structures of the bisphosphonate compounds.

Pharmacokinetics

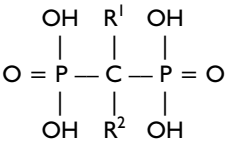
Bisphosphonates are synthetic compounds that appear to be absorbed, stored and excreted unchanged from the body.[10] Absorption of these drugs from the gastrointestinal tract is poor: <6% for etidronate and clodronate.[13,14] Absorption takes place by passive diffusion, primarily in the small intestine and, to a lesser extent, in the stomach,[10] and is reduced in the presence of food and calcium.[15] The plasma half-life is short, between 20 minutes to 2–3 hours, depending on the particular bisphosphonate and the rate at which an individual is able to clear the drug.[13,16]

By contrast, the bone half-life is very long, from months to years in humans, because of the high affinity of these drugs for solid-phase calcium phosphate, resulting in binding to hydroxyapatite and accumulation in bone.[9,17] Bisphosphonates become trapped in the bone and are only released when the bone is resorbed. Approximately 50% of the absorbed drug is located in the bone.[11] The pattern of uptake is thought to relate to areas where bone resorption and formation is taking place.[10] There is a suggestion that the inhibition of bone resorption reaches a new steady-state level, rather than becoming progressively lower. Once the drug is being administered in a clinically effective dose, the new steady state seems to be unaffected by further changes in dose or the use of a more potent drug.[8,18]

Bisphosphonates are excreted unaltered in the urine, probably by active secretion.[19] The side-chains of some bisphosphonates are metabolised. If bisphosphonates are infused rapidly in large quantities, they form insoluble aggregates in the blood.[10]

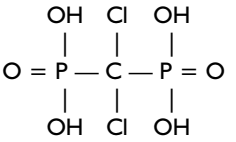
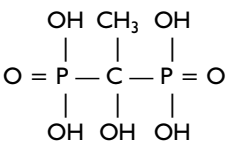
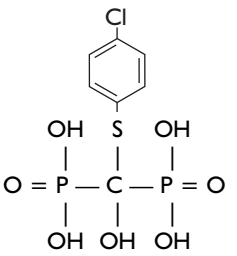


Inorganic pyrophosphate
(**1**)



Geminal bisphosphonate
(**2**)

TABLE 1 *Non-aminobisphosphonates: names, formulae and potency of compounds*

Generic drug name	Chemical name	Trade name(s)	CAS reference number(s)	Chemical structure	Potency[a]
Clodronate	Disodium (dichloromethylene) diphosphonate tetrahydrate	Bonefos, CL2MDP, Loron, Difosfonal, Ascredar, Ossiten, Lodronat, Clasteon, Lytos, Mebonat, Ostac, Clastoban	22560-50-5		×10
Etidronate	Disodium dihydrogen (1-hydroxyethylidene) diphosphonate	Didronal, Difosfen, Difosfen, Osteodidronel, Osteum	7414-83-7		×10
Tiludronate	Disodium dihydrogen {[(*p*-chlorophenyl)thio] methylene}diphosphonate hemihydrate	Skelid	14985-07-8		×10

[a] Relative potency to inhibit bone resorption in rats.[10]

Toxicology

Bisphosphonates are safe drugs with few side-effects. Toxicity is very low in animal studies and teratogenicity, mitogenicity and carcinogenicity studies are all negative.[19] The mechanism of death in lethal dose 50 (LD_{50}) studies is respiratory arrest due to muscular tetany as a result of hypocalcaemia.[19]

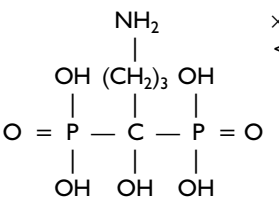
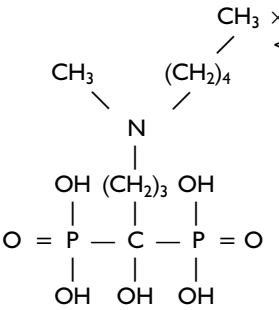
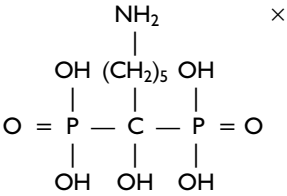
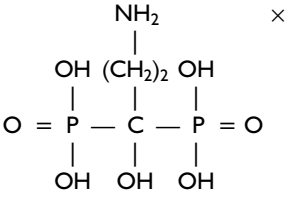
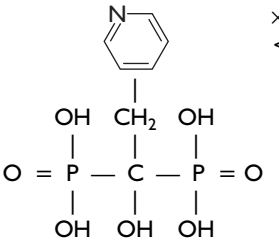
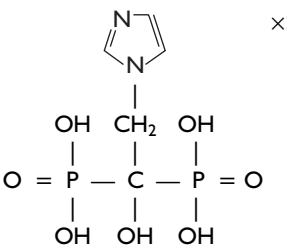
The most serious side-effect is renal failure, which can be avoided by slow intravenous infusion in plenty of fluid. It is thought to be due to a solid phase in the blood that subsequently lodges in the kidney.[5] The intravenous infusion rate should be <200 mg/h and the drug should be given in at least 250–500 ml of fluid to avoid adverse effects on renal function.[19] More potent bisphosphonates can be given faster in smaller volumes of fluid because the dose of drug required to achieve an equivalent clinical effect is much lower.

The commonest side-effect is transient pyrexia of 1–2°C for 24–48 hours, following the administration of aminobisphosphonates such as pamidronate (10% of patients), alendronate, neridronate and olpadronate.[16] It has not been reported with compounds that do not have a nitrogen molecule in their structure such as etidronate and clodronate.[19] The fever is accompanied by haematological changes that resemble an acute-phase response. It occurs on first-ever administration and does not generally recur when the patient is re-challenged with the drug.[19]

Oral administration can cause gastrointestinal (GI) side-effects; an incidence of 10% has been reported with clodronate, for example.[20] Minor GI side-effects are more common with the larger sized capsules or tablets of less potent bisphosphonates such as etidronate and clodronate, but serious adverse gastric events have not been documented with these drugs.[19] Amino compounds such as pamidronate are associated with more serious GI effects and occasionally with erosive oesophagitis and gastritis.[21,22] The effect may be dose-related and appears to be related to the direct contact of undissolved crystals with the mucosal lining of the GI tract. It can be mitigated by dissolving tablets in demineralised hot water or by ingesting the drug with a large volume of cold water and instructing the patient not to lie down for 30 minutes afterwards.[19]

Bisphosphonates do inhibit bone mineralisation. Osteomalacia has been found to occur as a result of using etidronate,[23] particularly if doses exceed 800 mg day.[19] However, the concentrations required to inhibit bone resorption, particularly with the newer bisphosphonates, are so low that

TABLE 2 *Aminobisphosphonates: names, formulae and potency of compounds*

Generic drug name	Chemical name	Trade name(s)	CAS reference number(s)	Chemical structure	Potency[a]
Alendronate	Aminohydroxybutylidene diphosphonic acid	Fosamax, Adronat, Alendros, Dronal	66376-36-1		×>100–<1000
Ibandronate	[1-Hydroxy-3-(methylpentylamino)propylidene]diphosphonic acid	Bondronat	114084-78-5		×>1000–<10,000
Neridronate	(6-Amino-1-hydroxyhexylidene) diphosphonic acid	AHDP	79778-41-9		×100
Pamidronate	Aminohydroxypropylidene bisphosphonate	APD, Aredia	57248-88-1 109552-15-0		×100
Risedronate	Sodium trihydrogen [1-hydroxy-2-(3-pyridyl) ethylidene]diphosphonate	Actonel	115436-72-1		×>1000–<10,000
Zoledronate	(1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) bisphosphonic acid monohydrate	Zometa	118072-93-8		×>10,000

[a] Relative potency to inhibit bone resorption in rats.[10]

they are unlikely to have a significant impact on mineral dissolution.[5]

Hypocalcaemia is usually mild, transient and asymptomatic.[24] Normal levels are rapidly restored provided that factors involved in the homeostasis of calcium are intact. Sufficient calcium and vitamin D intake needs to be ensured in patients with malignancy who have borderline or low calcium levels when commencing treatment with bisphosphonates.[19]

Adverse eye events are associated with pamidronate. Bilateral uveitis, scleritis and episcleritis have been reported in approximately one in 1000 patients receiving the drug. The clinical symptoms are mild and respond to topical corticosteroids. Symptoms recur on re-challenge with the drug and are more common in patients with a history of inflammatory eye disease. Ophthalmic side-effects appear to be linked to the administration of high-dose amino-bisphosphonates.[25–27]

Transient exacerbation of bone pain on initial exposure to intravenous pamidronate was documented in 6–40% of patients with Paget's disease[16] and has also been noted in patients with bone metastases.[19]

Mechanisms of action

It is now clear that bisphosphonates work by several different mechanisms, not all of which are clearly understood. Physiochemical effects resemble those of pyrophosphate and relate to the high affinity that these compounds have for solid-phase calcium phosphate.

Mineralisation or calcification is inhibited by physiochemical mechanisms.[5] They inhibit the formation and aggregation of calcium phosphate crystals,[28] block the transformation of amorphous calcium phosphate into hydroxyapatite[6, 29] and delay the aggregation of apatite crystals[30] and the dissolution of calcium phosphate crystals.[7]

However, the most important clinical effect is the inhibition of bone resorption and this is thought to be mediated principally by cellular mechanisms. Bisphosphonates reduce bone turnover, reducing both bone resorption and bone formation.[5] Proposed mechanisms of action include the inhibition of osteoclast recruitment and adhesion. The life span of osteoclasts is reduced, their activity is reduced and there appears to be modulation of the osteoclast–osteoblast interrelation.[5]

Bisphosphonates inhibit osteoclasts as they start to resorb bisphosphonate-containing bone. During bone resorption the space beneath the osteoclast is acidified by proton pumps in the ruffled border of the osteoclast membrane. The acidic pH results in dissolution of the bone mineral. The extracellular matrix is broken down by proteolytic enzymes. Concentrations of bisphosphonates in this microenvironment can reach very high levels. When osteoclasts ingest bisphosphonates, they lose their ruffled border and their cytoskeleton becomes disrupted.[8,12]

Bisphosphonates can be divided into two groups: first, those resembling pyrophosphate that act as analogues of ATP and inhibit ATP-dependent intracellular enzymes, and second, the aminobisphosphonates that inhibit enzymes of the mevalonate pathway disrupting the signalling functions of key regulatory proteins.[8,12,31,32]

The mevalonate pathway is involved in the production of sterols such as cholesterol and isoprenoid lipids from mevalonate. Farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP) are required for post-translational modification of small GTPases such as ras, rho and rac. These act as signalling proteins which are important in regulating a number of cell processes in osteoclasts. There is correlation between the ability of aminobisphosphonates to inhibit FPP synthase, one of the enzymes on the mevalonate pathway, and their potency *in vivo*.[12,33] This mechanism of action is now thought to be of prime importance in mediating the effects on osteoclasts.

The mechanism of action of bisphosphonates is still not completely understood. It is certain that they also affect osteoblast cells. It is probable that they influence the immune system and inhibit the adhesion of tumour cells.[5]

The clinical problem

The lifetime risk of developing cancer is one in three for the UK population. Nearly half of all deaths from cancer in the UK occur as a result of breast, prostate, lung and bowel carcinoma.[34]

Bone metastases: incidence and patterns of spread

Metastatic bone disease is a major cause of morbidity for patients. Complications resulting from secondary growths include pathological fracture, hypercalcaemia, nerve root compression,

spinal cord compression, bone marrow infiltration, intractable pain, incident pain and reduced mobility.[35,36] The therapeutic options for the treatment of complications and associated symptoms are numerous. However, none of the treatment strategies are completely satisfactory, even when used in combination. This group of patients continues to represent a major therapeutic challenge to the clinician.

Bone metastases most commonly result from breast, lung, prostate, renal and thyroid carcinomas.[36] They are rare in gastric carcinoma (affecting 5% of patients), but it is not clear if this is due to shorter natural history of the disease, as opposed to the pattern of spread.[37] Multiple myeloma also leads to considerable skeletal morbidity.[38] Bone metastases may be lytic, sclerotic or mixed. They are most frequently located in the axial skeleton, which reflects the distribution of the red marrow.[36] The most frequently affected sites are vertebrae, pelvis, ribs, femur and skull.[37]

Breast cancer

Breast cancer is the commonest cancer in women in the UK, with an incidence of 21,000 new cases every year, approximately 65:100,000.[39] Bone metastases are very common in patients with advanced breast cancer. In the UK, approximately 9000 women develop bone metastases each year.[40] Characteristically, patients with bone secondaries alone tend to have a protracted disease course when compared to those with visceral and in particular liver metastases. Median survival in patients with first relapse in bone is 20 months compared with 3 months in patients after first relapse in liver.[41] This may be a reflection of the histological tumour type; bone metastases are more commonly associated with well-differentiated, oestrogen-positive tumours.[41] Up to one-fifth of patients with metastatic bone disease will still be alive 5 years after diagnosis of bony metastases.[40]

Prostate cancer

Adenocarcinoma of the prostate is the commonest cancer in men in the UK over 65 years of age. The incidence in the UK is of the order of 23:100,000,[42] and in excess of 80% will have developed bone metastases by the time they die.[43] Bone metastases are usually osteoblastic in nature. Spread is commonly to well-vascularised sites of the skeleton.[43] Gleeson score and clinical staging at presentation correlate with subsequent development of bone metastases. Approximately 50% patients in the UK have bone secondaries at diagnosis.[44] The 5-year survival for patients in England and Wales is 43%.[44]

Multiple myeloma

The incidence of multiple myeloma increases sharply with age and is commonest in patients aged over 65 years with annual incidence of 4:100,000.[45] Median survival varies between 6 months and 5 years, depending upon various prognostic factors.[45] Most morbidity in this disease is due to osteolytic bone metastases and their complications.[46]

Hypercalcaemia

Incidence

Hypercalcaemia occurs in 10–20% of patients with malignant disease.[47] It is more common (20–40%) in patients with breast cancer, squamous cell lung cancer, renal cancer and multiple myeloma.[48] The term 'humoral hypercalcaemia of malignancy' (HHCM) "refers to a clinical, syndrome where a tumour secretes calcaemic factors that act both on the skeleton to increase bone resorption, and on the kidney to increase conservation of calcium".[48] In addition, metastases within the bone itself may have a local effect on bone resorption. There is no correlation between the presence and degree of bony metastases and incidence of hypercalcaemia.[49] The picture may be mixed, but the majority (90%) of patients with solid tumours will have evidence of a humoral component contributing to the elevation of serum calcium, irrespective of whether bone metastases are present or not.[50] It is therefore no longer correct to use the term HHCM only to describe patients with hypercalcaemia in the absence of skeletal metastases.

Physiology

Physiological regulation of serum calcium is maintained by parathyroid hormone (PTH). Secretion of PTH by the parathyroid glands is inversely related to ionised serum calcium. PTH stimulates bone resorption and increases renal calcium reabsorption. It also increases the hydroxylation of 25-hydroxy-vitamin D to 1,25-dihydroxy-vitamin D (calcitriol) in the kidney. Calcitriol increases absorption of calcium from the gut and also independently stimulates bone resorption (*Figure 1*). When the normal feedback mechanisms for calcium homeostasis fail, usually due to autonomous secretion of PTH or related proteins, hypercalcaemia results.

Serum calcium

Serum calcium exists in three different forms: an ionised fraction, a protein-bound fraction and a complexed fraction.[51] Approximately 40% of

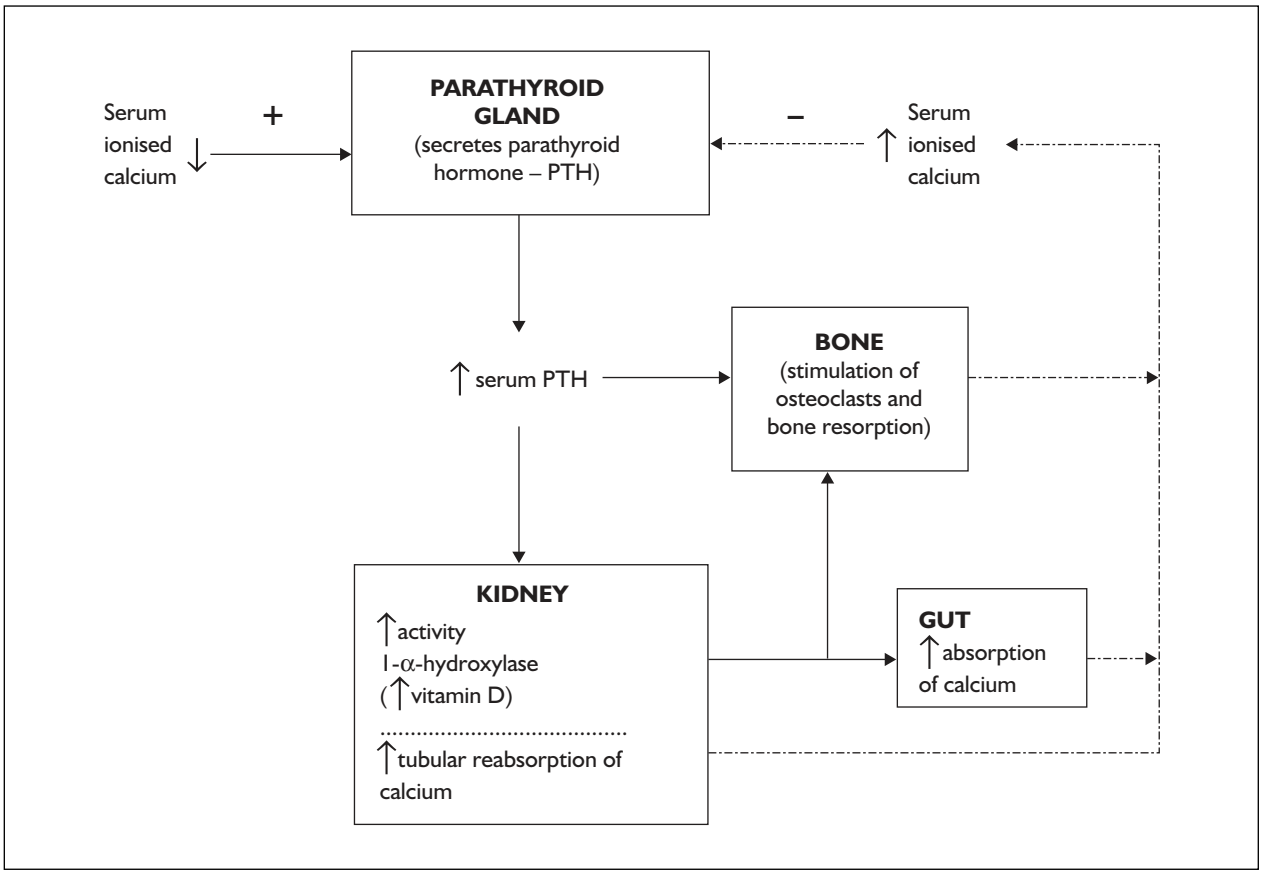


FIGURE 1 *Physiological regulation of serum calcium*

serum calcium is protein bound, mainly to albumin.[52] The other 60% is known as ultrafiltrable or diffusible; 45% is ionised and 15% is complexed with organic ions such as bicarbonate, citrate and lactate. All three forms of serum calcium exist in equilibrium, but it is the ionised calcium that is physiologically relevant and is under hormonal control.

Most laboratories measure total serum calcium. Direct measurement of ionised calcium is expensive and requires more stringent conditions and technical expertise.[53] Various formulae have been proposed for the correction of total serum calcium for differences in plasma protein concentration (*Table 3*). Formulae can be based on either plasma total protein, plasma albumin or plasma specific gravity.[71] Correction according to plasma albumin is preferred,[72] and different formulae have been validated in normal subjects and various disease states,[73] showing good correlation with measured values. Although these correction formulae have been criticised, they are widely accepted and applied, and will remain so until the measurement of ionised calcium becomes easier and more widely accessible.[74]

The exact proportion of total serum calcium bound to protein will depend on not only the total protein concentration, but also the pH of the serum and temperature. An acute acidosis or alkalosis will affect ionised calcium, whereas total calcium remains unaffected.[53] During venesection, problems can arise if there is prolonged haemostasis or changes in posture, resulting in concentration of plasma proteins. These factors increase the measured total serum calcium although ionised calcium is unaffected. In addition to quantitative differences, qualitative differences in the albumin or globulin fractions can alter the calcium-binding capacity of plasma proteins.

Correction of total serum calcium is particularly important in patients with malignancy, who often have low albumin. In these patients, measurement of total calcium is a poor indicator of ionised calcium, and it is necessary to use a standard correction factor.

Mechanism of hypercalcaemia

The two most common causes of hypercalcaemia are malignancy and primary hyperparathyroidism.

TABLE 3 *Formulae for correction of serum calcium*

Units for calcium (Ca) and albumin (alb)	Formula for correction of serum calcium	Study (cited reference[a])
Ca mmol/l, alb g/l	Ca + 0.02 (40 – alb)	Davis 1989[54] (a) Ostenstad 1992[56]
	Ca + 0.02 (45 – alb)	Gucalp 1994[57]
	Ca + 0.02 (46 – alb)	Sawyer 1990[58] (b)
	Ca + (0.02 × alb) + 0.8	Pecherstorfer 1996[60] (c) Ralston 1997[62]
Ca mg/dl, alb g/dl	Ca + 4 – alb	Warrell 1991[63] (d) Nussbaum 1993[65]
	Ca + 0.8 (4 – alb)	Nussbaum 1993[66]
	Ca + 0.8 (mid-ref. range alb – alb)	Gucalp 1992[67]
Ca mg/dl	Ca/(0.55 + proteins/160)	Body 1989[68] Rizzoli 1992[69] Zysset 1992[70]

[a] References cited in the listed studies for derivation of calcium correction: (a) Ref. 55; (b) Ref. 59; (c) Ref. 61; (d) Ref. 64.

In the latter, patients will have elevated PTH due to autonomous secretion by the parathyroid gland. In hypercalcaemia of malignancy, serum PTH is virtually always normal.[75] However, tumour cells can secrete parathyroid hormone-related protein (PTHrP). In one series, PTHrP was detected in 100% of patients with solid tumours and hypercalcaemia but no evidence of bone metastases was found.[48] In another series, 81% of hypercalcaemic patients with bone metastases had raised PTHrP, compared with 85% of those with no evidence of bone metastases.[50]

PTHrP is also present in a number of normal tissues (brain, breast and skin) and has a role in normal development.[76] Its structure is closely related to that of PTH, thus allowing it to interact with the PTH receptor and produce a similar physiological response. Sensitive assays have now been developed to measure serum PTHrP.[48] PTHrP is undetectable in the plasma of most normocalcaemic patients with malignancy, but will be detected in 80–90% of those with hypercalcaemia.[77]

PTH and PTHrP induce osteoclast-mediated bone resorption, resulting in release of calcium from the skeleton. They also act on the kidney to reduce excretion of the increased calcium load, by increasing tubular reabsorption of calcium. Hypercalcaemia itself decreases renal reabsorption of sodium and water resulting in polyuria. Patients find it difficult to increase oral intake to correct this because of nausea and anorexia. Thus a decrease in extracellular volume further increases serum calcium concentration and reduces glomerular filtration, which exacerbates the problem.

Although PTHrP is the most important stimulus to bone resorption,[48] other stimuli can be involved. For example, in some patients with lymphoma, tumour cells can convert 25-hydroxy-vitamin D to 1,25-hydroxy-vitamin D or secrete other stimulators of bone resorption.[78] In haematological malignancy, these mechanisms are thought to be of greater importance as serum PTHrP is elevated in <50% of cases,[79] and abnormalities of renal function play a greater role.[78] Local bone metastases also stimulate osteoclasts by paracrine mechanisms, including secretion of PTHrP and various cytokines, interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), tumour necrosis factor-beta (TNF-β), and tumour growth factor-alpha (TGF-α).[48,76]

Clinical signs and symptoms

Clinical manifestations of hypercalcaemia are varied and may be difficult to distinguish from symptoms due to underlying malignancy. They are often related to the rapidity of onset of hypercalcaemia, and therefore someone with a mildly elevated calcium can be symptomatic whilst another with a moderately elevated calcium is asymptomatic. Symptoms can be broadly divided into gastrointestinal, renal and neurological effects. Anorexia, nausea and vomiting and constipation are common. Renal dysfunction results in polyuria and polydipsia and rarely nephrocalcinosis. Confusion, drowsiness and coma can also occur if hypercalcaemia is left untreated.[80]

Treatment

There are four aims of treatment: correction of dehydration, inhibition of bone resorption, increasing renal excretion of calcium and treatment of the underlying malignancy. Rehydration itself may correct mild hypercalcaemia simply by increasing the intravascular volume and promoting hypercalcuria. All patients should receive rehydration whether or not they require additional therapy.[75] Treatment of the underlying malignancy is the single most important factor in determining prognosis in these patients.[81] A number of different drugs apart from bisphosphonates have been used in the treatment of hypercalcaemia.

Plicamycin

Plicamycin (also known as mithramycin) was initially used as an antineoplastic agent and acts by inhibiting RNA synthesis in osteoclasts.[75] It is given intravenously, 25 µg/kg over 4–6 hours, and this can be repeated after 24 hours if indicated. One study found that, at these doses, 92% of patients with hypercalcaemia of malignancy became normocalcaemic.[82] Plicamycin results in an early fall in serum calcium approximately 12 hours after administration with a nadir at 48–72 hours.[83] The duration of normocalcaemia varies from weeks to months. The main problem limiting the use of this drug is toxicity.[83] Side-effects include nausea, local irritation at injection site, reversible hepatotoxicity,[84] nephrotoxicity, thrombocytopaenia and myelosuppression.[76,83]

Calcitonin

Calcitonin is a naturally occurring peptide which inhibits bone resorption and increases renal calcium excretion. It is usually given as salmon calcitonin 4–8 units/kg every 12 hours by either subcutaneous or intramuscular injection.[75] Its advantage is the rapid onset, reducing serum calcium within a few hours, but this effect is often mild, 0.5 mmol/l, and short-lived [median (range) 1 (1–4) days].[85,86] Repeated administration has decreased efficacy, owing to down-regulation of calcitonin receptors on the surface of osteoclasts. Side-effects are minimal, with some nausea and flushing and occasional abdominal cramps.[76]

Gallium nitrate

Gallium nitrate does not impair osteoclast function directly, but adsorbs on and decreases the solubility of hydroxyapetite crystals. It also stimulates bone formation and therefore movement of calcium into the bone. It is usually given at a dose of 200 mg/m^2 in 1 litre of fluid and this can be repeated daily over 5 days.[83] In one randomised controlled trial (RCT) of gallium nitrate versus calcitonin,[85] serum calcium normalised in 75% of patients by day 5, reaching a nadir at day 7. The median duration of normocalcaemia was 6 days (range 1–15 days). The most important side-effect is renal impairment; patients should be well hydrated and this drug should not be given with aminoglycosides or amphotericin. Gallium nitrate can also cause gastrointestinal side-effects and anaemia.[75]

Glucocorticoids

Glucocorticoids are most useful in haematological malignancies since they inhibit growth of neoplastic lymphoid cells and also decrease intestinal absorption by counteracting the effects of vitamin D.[83] Hydrocortisone, 200–300 mg, is given intravenously for 3–5 days.[75] If used, they are sometimes combined with calcitonin.

Other

The use of loop diuretics such as furosemide is controversial. It acts to increase renal excretion of calcium, but should only be used when intravascular volume has been replaced, since otherwise it will further exacerbate dehydration and kidney function. It is the diuretic of choice in patients who become overloaded during fluid replacement since thiazide diuretics act to increase renal reabsorption of calcium.[75]

Intravenous phosphate should not be used since it leads to formation of calcium–phosphate complexes which can then precipitate in blood vessels, lungs and kidneys. Oral inorganic phosphate (2–3 g/day) is effective in one-third of cases but poorly tolerated owing to nausea and diarrhoea and should be avoided in patients with renal impairment.[47]

Octreotide is a somatostatin analogue and has been used to treat hypercalcaemia secondary to neuroendocrine tumours when other measures have failed.[87]

Skeletal morbidity

Bone structure

Macroscopic structure

Macroscopic bone in adults consists of two types: compact bone tissue and cancellous bone tissue. Compact bone, sometimes called cortical bone, is hard and dense and is found in flat bones, the shafts of long bones and as a thin covering over all other bones. Cancellous bone tissue, also called

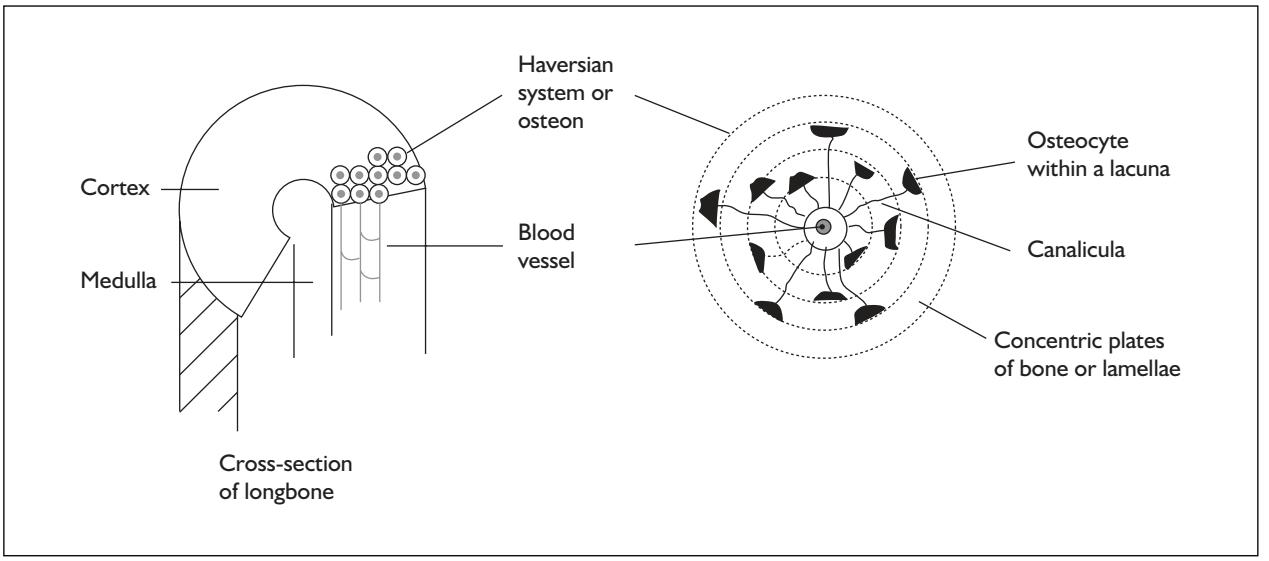


FIGURE 2 *Microscopic structure of compact bone*

trabecular or spongy bone, is located inside the ends of long bones, in short bones and as a layer between two layers of compact bone, such as the scapula and ribs. The hollow centre of long bones contains yellow bone marrow, which consists predominantly of fat cells.

Microscopic structure[90]

Compact bone is made up of microscopic units called osteons or Haversian systems in the shape of tubes. They consist of plates of bone, lamellae, arranged concentrically around a central canal containing blood vessels. Between the plates of bone are minute spaces, lacunae, which contain osteocytes. The spaces are connected to each other and the central Haversian canal by tiny canals called canaliculi (*Figure 2*).

In cancellous bone, the lamellae are irregularly arranged and there are no Haversian canals. The plates of bone, or trabeculae are nourished from the surface. The vessels are in the interstitial spaces which are filled with marrow.

Bone consists of mineral and matrix. The organic matrix, called osteoid, consists predominantly of the protein collagen, arranged as fibres. The fibres are aligned in parallel to the tension stresses to which the bone is subject. The mineral apatite, which consists of calcium and phosphate, is deposited on the collagen fibres in the form of needle-shaped crystals.

Bone remodelling

In the adult, bone is constantly being turned over, old fatigued bone being replaced with new bone. The remodelling rate is between 2 and 10% of bone per year; approximately 80% of the cancellous bone is turned over in comparison with 20% of cortical bone.[90] The precise mechanisms by which bone remodelling is initiated is unclear. Several factors influence the process, for example, vitamins (A, C, D), hormones (growth hormone, thyroid and parathyroid hormone, oestrogen, testosterone) and mechanical loading.[89,90]

The bone multicellular unit (BMU) or bone remodelling unit is responsible for resorbing old bone and forming new bone. It consists of two types of cells, osteoclasts, which dissolve bone, and osteoblasts, which form new bone. Both cell types originate in the bone marrow.

Osteoclast regulation

Osteoclasts are derived from the haematopoetic monocyte–macrophage cell lineage, whereas osteoblasts come from the mesenchymal lineage in the bone marrow. The development of osteocytes is under the control of osteoblasts which produce colony-stimulating factors, osteoclast differentiation factor and cytokines that influence the differentiation pathway of these cells.[91,92] There is also evidence that osteocytes may participate in osteoclast recruitment and possibly activation, particularly at sites of microdamage.[93] Differentiation of osteoclast precursor cells requires direct cell–cell contact with primed osteoblasts or bone marrow stromal cells.[94] A membrane-bound factor called osteoclast differentiation factor (ODF) [now known as receptor-activated nuclear factor NF-kappaB ligand (RANKL)] has recently been isolated from

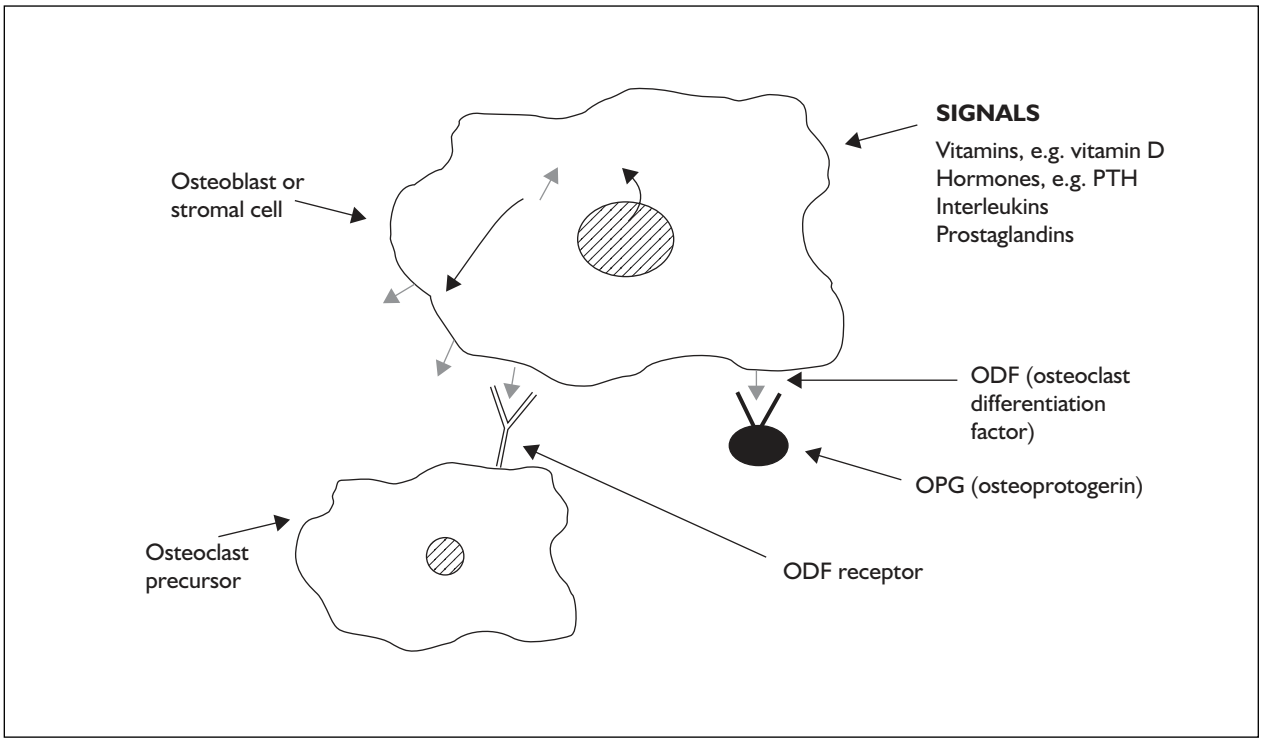


FIGURE 3 *Maturation of an osteoclast precursor*

the surface of osteoblasts and stromal cells.[94] ODF binds to receptor-activated nuclear factor NF-kappaB (RANK), a member of the TNF-α receptor family, which is located on the surface of osteoclasts and their precursors, thereby promoting osteoclast maturation.[94] Osteoprotogerin (OPG) was isolated in 1997[95] and appears to act as a naturally occurring ODF antagonist. It has been proposed that the ODF/OPG ratio determines the effective activity of ODF to promote osteoclast formation and therefore plays a central role in the regulation of bone turnover. OPG overexpression leads to osteopetrosis[95] and underexpression results in osteoporosis (*Figure 3*).[96]

Bone resorption

The BMU travels from left to right, resorbing bone that is old or damaged. The direction is mechanical in the case of long bones and metabolic in the axial skeleton.[93] It is the role of the osteoclast to resorb bone. It performs this task by sealing off an environment between the cell and the bone called the clear zone. The cell rim attaches itself to peptide sequences in the matrix by means of cell membrane receptors called integrins. The cell membrane within this microenvironment is called the ruffled border.[90] It secretes two substances which resorb the bone. Hydrogen ions are secreted by means of a proton ATPase; this dissolves the bone mineral. Proteolytic enzymes digest the matrix (*Figure 4*).[90]

Bone formation

The osteoclasts excavate a trench which is filled with an organic matrix secreted by osteoblasts. This matrix is calcified extracellularly. Linking of osteoclast resorption and osteoblast bone formation is called coupling. The linear resorption rate of osteoclasts is approximately 50 µm and the formation rate is about 1 µm/day. New pre-osteoclasts are continually recruited to maintain resorption of the bone. The termination of the trench occurs when the osteoclast supply is switched off, the life span of an osteoclast being about 16 days. The timing of apoptosis of osteoclasts determines the depth of erosion.[93] Osteoblast recruitment continues until the trench is filled. It takes about 3 months to rebuild a new bone structural unit (*Figure 5*).

Markers of bone formation and resorption

A number of breakdown products are excreted as bone is resorbed and remodelled. These are measurable in the serum and the urine. Techniques for measuring bone resorption markers, such as the urinary hydroxyproline/creatinine ratio, have been available for a number of years, but lacked specificity and were never used clinically to any

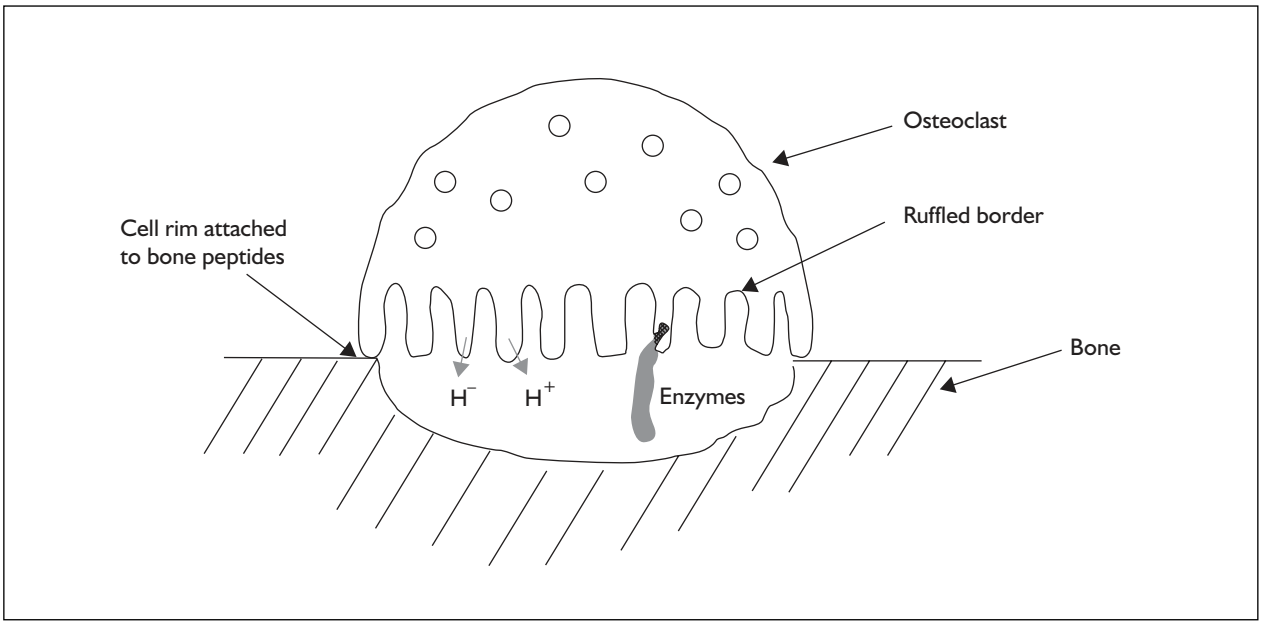


FIGURE 4 *Structure of a resorbing osteoclast. Adhesion rim and ruffled border create a microenvironment at the bone surface. Hydrogen ions (H^+) and enzymes are secreted to resorb bone.*

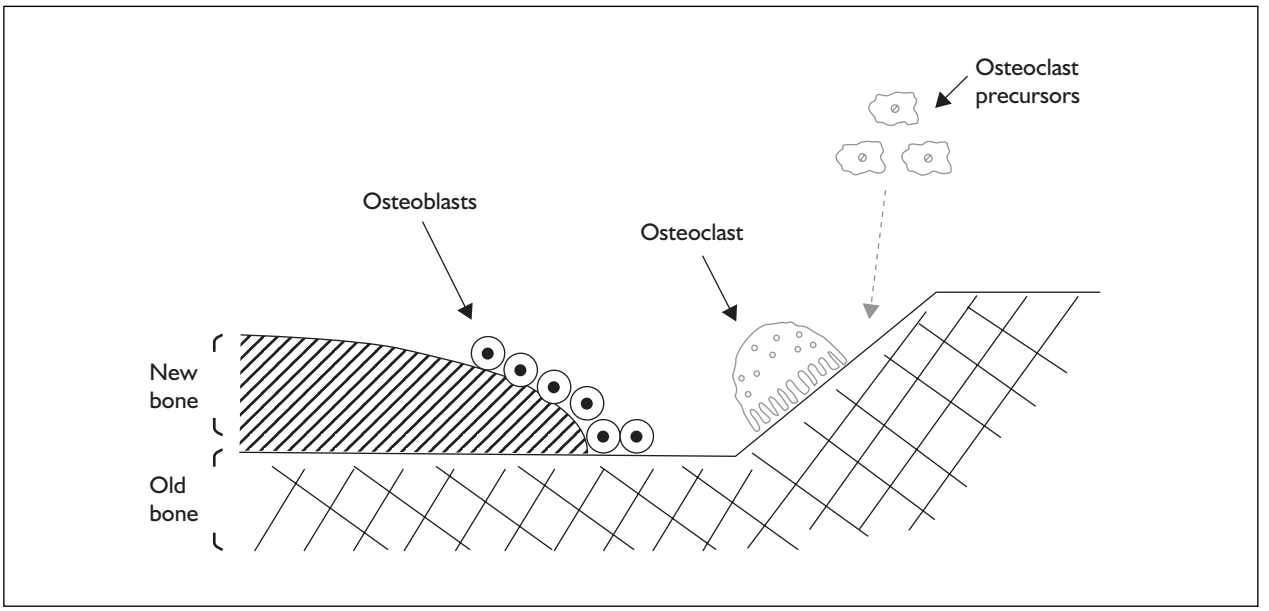


FIGURE 5 *Bone resorption and formation*

great extent. Several newer and more accurate markers have now been isolated. This field is now being revisited to examine the clinical application of these new markers, for example in the diagnosis of bone metastases and the monitoring of treatment.[97,98] Markers can be classified as those which reflect bone formation and those which reflect bone resorption. There are now more than 20 of these. Examples of bone formation markers include total alkaline phosphatase and bone alkaline phosphatase, type 1 collagen propeptides such as procollagen type I N propeptide (PINP), procollagen type I C propeptide (PICP) and osteocalcin (OC). Examples of bone resorption markers include collagen pyridinum cross-links such as pyridinoline (PYD) and type 1 collagen telopeptide breakdown products, N-terminal cross-linking telopeptide of type I collagen (NTX), C-terminal cross-linking telopeptide of type I collagen (CTX) and bone sialoprotein (BSP).[97,98]

The pathophysiology of bone metastases

'Seed and soil' hypothesis

'What is it that decides what organs shall suffer in a case of disseminated cancer?'[99] In 1889, Paget proposed that metastatic growth in the bone was dependent on the characteristics of two factors: the 'seed' and the 'soil'. Every "single cancer cell must be regarded as an organism, alive and capable of development. When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil."[99] There is much to support this hypothesis today and our understanding of the mechanisms involved has developed significantly over the last two to three decades.

The 'soil'

Access by micrometastases to the bone most commonly occurs via the bloodstream. The bone microenvironment is unique and contains several growth factors which encourage the growth of cancer cells.[100] Growth factors are more abundant in areas of bone resorption. Some animal work supports the concept that certain factors within the bone may regulate and control the division of metastatic cells.[101]

Metastatic cells appear to disturb the bone microenvironment, altering its regulatory mechanisms and influencing the 'soil', thereby making it more conducive to the development of metastases. There is evidence for increased turnover of all elements of bone, both resorption and formation.[37] Second, the amount of new bone formed does not always equal the bone resorbed, although the mechanisms for this are far from clear.[37] Third, there is uncoupling between the osteoclasts and osteoblasts, resulting in both independent resorption of bone without formation and the deposition of new bone at sites of quiescent bone, not preceded by resorption.[37]

The 'seed'

Not all metastatic cancer cells in the bone marrow develop into clinically detectable metastases.[101] There are particular inherent characteristics of some cancer cells which contribute to the establishment and growth of metastases within the bone microenvironment.

Highly motile metastatic breast cancer cells are more likely than cells with low motility to become established in the bone *in vitro*; this feature is independent of their osteolytic capacity.[102] Another important feature is the ability of cells to adhere to specific components of bone, such as collagen or endothelial cells. Adhesion molecules and their relevant substrate have been isolated for several cancer cell lines.[101]

The mechanisms by which cancer cells stimulate osteoclasts, to resorb bone, varies from one tumour type to another. Myeloma tumours, for example, produce cytokines TNF-β (lymphotoxin), IL-1 and IL-6. Solid tumours produce PTHrP, TNF, prostaglandins and other factors.[37,103–105] Cancer cells can induce osteolysis directly via a variety of enzymes *in vitro*, independently of osteoclasts.[106] Prostate cancer cells produce proteins capable of stimulating osteoblasts, which are thought to play a role in the formation of sclerotic metastases seen with this type of cancer.[107,108]

There are a number of primary tumour features that are considered to have a bearing on the development of bone metastases.[101,109] Much of the work in this field is at an experimental stage and the evidence is based on studies using animal models and cell lines. For example, the expression by cells of human epidermal growth factor receptor-2 gene (HER2) (c-erb-B2) appears to predispose the host to the development of bone metastases.[110] Bone sialoprotein is a glycoprotein found in mineralising tissues; it is produced ectopically by some solid tumours and has a role in the attachment of metastatic cells to bone mineral.[111]

The story is best developed for PTHrP, produced ectopically by a range of solid tumours; it has the ability to stimulate osteoclasts.[100] "Evidence is accumulating that there is a vicious cycle between osteoclasts, osteoblasts and cancer cells during the development and progression of bone metastases."[112] As bone is resorbed by osteoclasts, growth factors are released from the bone, such as tumour growth factor-beta (TGF-β), which stimulates the production of PTHrP from tumour cells within the bone microenvironment. PTHrP increases the expression of RANKL on the surface of osteoblasts, which binds to RANK on osteoclasts, resulting in increased osteoclast activity.[112] ODF receptor is identical with RANK (*Figure 6*). More than 90% of breast cancer cells from bone metastases express PTHrP, compared with 50% for the primary breast tumour and 70% for visceral metastases.[109] This supports the role of the bone microenvironment in enhancing the production of PTHrP by tumour cells.

Action of bisphosphonates in relation to tumour cells in the bone

Bisphosphonates inhibit bone resorption by a variety of mechanisms. New mechanisms are

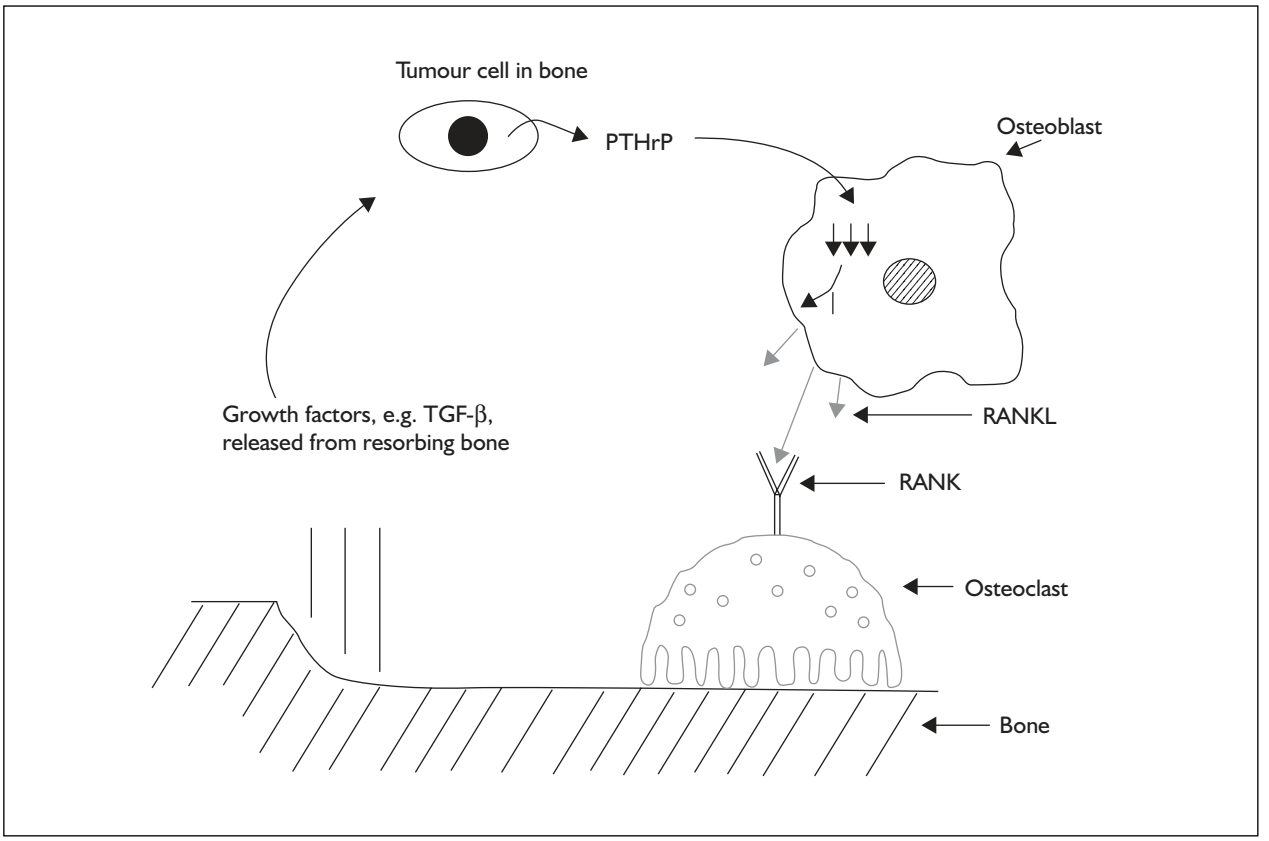


FIGURE 6 *Role of PTHrP in tumour induced osteolysis*

emerging in addition to those already discussed. Although the most important action appears to be that related to the inhibition of osteoclast activity, it is now clear that aminobisphosphonates affect other elements in the bone microenvironment and may have a direct action on tumour cells. Aminobisphosphonates have been shown to inhibit other enzymes, for example matrix-metalloproteinase-1 (MMP-1), which has a role to play in bone resorption.[113] They have also been found to directly inhibit the adhesion of tumour cells within bone.[113]

Adjuvant use of bisphosphonates

"Can we, by affecting the 'soil' of the microenvironment in which deposits of tumour cells grow, influence the behaviour of 'seeds', the tumour micrometastases themselves?".[114] Several of the mechanisms described before indicate that bisphosphonates influence the microenvironment, thereby making bone less favourable to the establishment and growth of bony metastases. The possibility that bisphosphonates may delay, reduce or even prevent bone metastases is clinically very important.

As early as 1980, Galasko and colleagues demonstrated an inhibitory effect of bisphosphonates (clodronate and etidronate) on tumour osteolysis in a mouse mammary cancer cell line.[115] Further animal work in the 1990s indicated that there might be an application for bisphosphonates in the adjuvant setting. Using a rat model for breast cancer, the bisphosphonate risedronate reduced the incidence, size and number of sites of bone metastases compared with placebo.[116] Similarly, pretreatment of Wistar–Lewis rats with clodronate inhibited the development of bone metastases in comparison with controls.[117] More recently, studies using breast and prostate cancer cell lines have provided evidence for a direct cellular effect of bisphosphonates. In a laboratory setting, bisphosphonates appear both to prevent cellular invasion and to exert an inhibitory effect on the proteolytic activity of matrix metalloproteinases through zinc chelation, thereby reducing cancer cell growth.[118,119]

In humans, there is evidence that bisphosphonates have a role in the treatment of symptomatic bone disease by reducing skeletal morbidity. In view of these findings, several investigators have attempted to determine whether pretreatment

TABLE 4 *Bisphosphonates: licensed uses, recommended dose and cost in UK*

Generic drug name	Trade name (UK)	Licensed use	Recommended dose	Cost: oral treatment, 1 month (£)	Cost: intravenous treatment per vial (£)
Alendronate	Fosamax	Osteoporosis	10 mg/day	23.12	–
Etidronate	Didronel	Paget's disease Osteoporosis	5 mg/kg/day for 6 months Cyclical: 400 mg/day for 14 days followed by calcium carbonate 1.25 g for 76 days	43.88 40.20 (90-day cycle)	
Pamidronate	Aredia	Hypercalcaemia Osteolytic bone metastases (pain) Paget's disease	15–90 mg 90 mg every 3–4 weeks 30 mg week 1, then 60 mg/week	15 mg: 27.27 30 mg: 54.53 90 mg: 155.80	
Risedronate	Actonel	Paget's disease Osteoporosis	30 mg/day for 2 months 5 mg/day	152.81 21.83	
Clodronate	Bonefos, Loron	Hypercalcaemia Osteolytic bone metastases (pain)	1500 mg 1600/1040 mg/day	– 174.16/174.18	300 mg: 13.78
Tiludronate	Skelid	Paget's disease	400 mg/day for 3 months	198	
Zoledronate	Zometa	Hypercalcaemia	4 mg		4 mg: 195

Source: *British National Formulary*, September 2001.[122]

with bisphosphonates, before bone metastases develop, would decrease the incidence of metastatic bone disease and its clinical consequences. There may also be a role for bisphosphonates in the prevention of osteoporosis occurring as a result of hormonal treatment for breast and prostate cancers, or premature menopause in the case of breast cancer patients.

In up to one-third of breast cancer patients, the first site of relapse occurs in bone, with or without soft tissue metastases.[114] Lymph node-positive and oestrogen receptor-positive (ER +ve) breast cancer patients have higher sites of relapse in bone compared with node-negative and oestrogen receptor-negative (ER –ve) patients.[114]

At present, the adjuvant use of bisphosphonates is not recommended outside clinical trials in the USA or UK.[40,120] The financial implication of the adjuvant use of bisphosphonates has not been studied. A systematic review of the data currently available will help to identify areas for future research and inform the development of evidence-based guidelines for clinical practice if sufficient data are available.

Economic evaluation

This systematic review, which considers the role of bisphosphonates in metastatic disease, will examine the evidence from RCTs to determine whether bisphosphonates are effective in treating hypercalcaemia of malignancy and reducing skeletal morbidity. Data from another systematic review[121] have considered whether bisphosphonates are effective analgesics in patients with malignancy.

If bisphosphonates reduce both skeletal-related events (SREs) and hypercalcaemia (HCA) of malignancy, and improve quality of life and pain control, then they will have positive consequences for health services and patients. This may be seen by a decrease in any of the following: orthopaedic surgery, radiotherapy, analgesic use, hospital admissions, time spent in hospital, outpatient visits and community support.

However, there are a number of costs involved in giving bisphosphonate treatment. The cost of different drugs, as stated in the *British National Formulary* (BNF),[122] is given in *Table 4*. In

addition, other costs such as those associated with administration of the drug must be considered.

Once treatment has been initiated, repeated doses of the drug are usually required and may be continued until the patient is close to death. At present there is little evidence to determine the duration of treatment. The American Society of Clinical Oncology (ASCO) guidelines recommend the use of bisphosphonates in women with breast cancer who have radiological evidence of lytic bone destruction and are receiving systemic therapy for their cancer. They suggest that the drug is continued until "there is a substantial decline in the patient's performance status". They state that patients may also benefit from bisphosphonates for bone pain and that they may prevent osteoporosis in women following treatment-induced menopause. ASCO does not recommend the use of bisphosphonates for asymptomatic bone metastases or in the adjuvant setting outside trials.[120] The British Association of Surgical Oncology (BASO) recommends the use of bisphosphonates for the treatment of acute hypercalcaemia and for the prevention of osteoporosis in patients in whom hormone replacement therapy should be avoided. They are less clear about their use in patients with bone metastases and were unable to draw up national guidelines, but suggested that sub-groups of patients most likely to benefit from long-term bisphosphonate treatment should be identified.[40]

Prostate and breast cancer are common cancers in men and women, respectively, and both of these tumours commonly metastasise to bone. Therefore, use of bisphosphonates to prevent cancer-associated SREs could represent a considerable financial burden to the NHS. Even among the wealthiest healthcare systems there have been calls to restrict the prescribing of bisphosphonates to those situations where it can be shown to be cost-effective. Johnson[123] presents some survey evidence indicating that cost is a major factor for palliative care physicians in both the NHS and the UK private sector, when choosing whether or not to use bisphosphonates, and which bisphosphonate to choose. However, bisphosphonate therapy is likely to eliminate some health service costs by reducing skeletal morbidity. The cost of treating skeletal morbidity is substantial. It has been estimated that it accounts for 63% of hospital costs involved in treating breast cancer patients in the USA.[124] The cost of bisphosphonate therapy should be weighed against the cost savings in other parts of the health service and the associated health gain.

By reviewing the economic literature so far, and constructing economic models, we aim to provide a useful addition to previous published literature on the economic consequences of bisphosphonate therapy. This will be based on comprehensive data regarding the efficacy of these drugs from this systematic review and will use unit costs that are typical in today's NHS. Cost of administration of bisphosphonates might be completely offset by the cost savings from treatment of SREs. If not, the relative value for money, cost-effectiveness, of the drugs needs to be assessed. These analyses add to earlier work by incorporating some of the considerable costs of social care that are associated with skeletal morbidity.

The key economic questions are:

- Is administration of bisphosphonates in patients with bone metastases cost-saving/cost-effective?
- Are there some groups of patients for whom it is more cost-effective?
- How does choice of drug and dosage affect cost and cost-effectiveness?

Chapter 2
Methods

Objective

The objective of this review was to examine the role of bisphosphonates in metastatic disease. This was divided into three parts:

- Are bisphosphonates effective in the treatment of hypercalcaemia due to malignancy?
- Do bisphosphonates reduce skeletal morbidity in patients with bone metastases?
- Do bisphosphonates delay the onset of bone metastases in patients with malignancy?

Search strategy

Three potential sources of material for inclusion in this review were identified: electronic databases, reference lists from RCTs and review articles, and consultation with experts in the field.

A comprehensive search strategy was constructed, consisting of three parts. The first identified all studies with cancer. The second identified all studies using bisphosphonates (CAS numbers, generic, chemical and national, European and international trade names for each drug, *Tables 1* and *2*). The third was a recognised filter for identifying RCTs.[125] This search was applied to MEDLINE (1966–present), CANCERLIT (1975–present), and adapted for EMBASE (1980–present), Science Citation Index Expanded (1981–present) and pre-MEDLINE electronic databases. The full MEDLINE search strategy is included in Appendix 1. The last search was run on 19 June 2001.

In addition, we searched the Cochrane and Database of Abstracts of Reviews of Effectiveness (DARE) databases for relevant studies. All reference lists of identified studies for inclusion in the review, and key reviews, were scanned for further studies.

A number of experts in the field were identified and contacted to see if they were aware of other studies, published or unpublished. Several drug companies were approached for information regarding their products and the US Food and Drug Administration (FDA) website was explored for further information.

Abstracts from ASCO 1997–2001 were searched on-line using all generic names of individual bisphosphonates and bisphosphonate*, diphosphonate*; contents pages of *Journal Clinical Oncology* 2001, *European Journal of Cancer* 2001 and *Bone* 2001, together with abstracts printed in these journals 1999–2001, were searched by hand. A decision was made by the steering group not to search grey literature for the main review, because the yield from such work would be negligible[126] and time constraints did not allow for this. Members of the steering group and experts contacted would be expected to identify any further relevant work in this field.

Methods of the review

The review was conducted according to Cochrane guidelines. Titles and abstracts of articles identified by the search strategy were reviewed. Letters, case reports, editorials and reviews were removed by hand. Any studies that were clearly not RCTs were also excluded. If no electronic abstract was available, or it was unclear, full text articles were obtained.

Studies were divided into three groups, in relation to the three questions proposed as part of this review: hypercalcaemia, skeletal morbidity and adjuvant applications.

In each group, resulting studies were assessed by two independent reviewers, using inclusion/exclusion sheets developed for this review (Appendices 2–4). A proportion (10%) of all studies were also assessed by a third reviewer to ensure consistency. Where there was disagreement between reviewers, it was agreed that this would be discussed, with the third reviewer's decision being final.

Studies identified for inclusion were data extracted using data extraction forms (Appendices 5–7). Information was collated using an Excel spreadsheet.

Statistical analysis

Outcome data are usually reported in various forms by different authors. Preliminary analyses were undertaken to summarise individual study outcome data. For the majority of studies, outcome data were extracted in dichotomous form as proportions; chi-squared tests were performed

to compare groups. Some studies reported outcomes as continuous data in the form of means. Where these were accompanied by standard deviations, *t*-tests and one-way analysis of variance were performed as appropriate to compare the groups. Finally, some studies looked at survival data, and where a survival analysis was undertaken the results are discussed. All preliminary analyses were performed using Stat Xact.[127]

Where possible, results of comparable studies were statistically combined in a meta-analysis. The studies had to be comparable with respect to methods, intervention groups and measurement of outcome. All meta-analyses were performed using dichotomous data with the odds ratio (OR) being used as the summary measure for each outcome. We aimed to combine survival data using hazard ratios as the summary measure. Studies in the meta-analysis were weighted using the inverse variance method. Clinical heterogeneity was expected to exist between these studies with respect to intervention, duration of treatment, population and length of follow-up; therefore, it was decided *a priori* that a random effects model would be applied to all meta-analyses.

Sub-group analyses were performed to examine the effect of treatment over time, in different disease types, using different bisphosphonates and routes of administration.

All meta-analyses were performed in the statistical package Intercooled Stata 7.0.[128]

Methodological quality of included studies

All studies were RCTs. They were assessed and graded for allocation concealment according to Cochrane guidelines[129] (A, adequate; B, unclear; C, inadequate; D, not used). Blinding of studies was recorded as open, single-blind or double-blind. All studies were included at this stage irrespective of blinding or allocation concealment.

Hypercalcaemia review

Objectives

The primary objective of this review was to establish the efficacy of bisphosphonates in treating hypercalcaemia of malignancy. Secondary objectives were to compare the efficacy of different bisphosphonates, doses, route of administration, tolerability and duration of response.

Criteria for considering studies for hypercalcaemia review

Types of studies

Only RCTs were included in the review.

Types of participants

Patients with hypercalcaemia of malignancy after intravenous rehydration, defined as: corrected serum calcium above upper limit of normal reference range for each laboratory. There was no age limit, and no distinction was made between first or subsequent episodes of hypercalcaemia.

Types of interventions

Oral or intravenous bisphosphonate in the experimental arm, compared with another bisphosphonate, another recognised treatment for hypercalcaemia, placebo or control group.

Outcome measures

The primary outcome measure used was normalisation of serum-corrected serum calcium. Secondary outcome measures were time to normalisation of serum-corrected calcium, measured from day of administration of drug, toxicity, time to relapse and changes in bone resorption markers and serum parathyroid hormone.

Skeletal morbidity review

Objectives

The primary objective of this review was to establish whether bisphosphonates reduce skeletal morbidity in patients with bony metastatic disease (metastatic deposits in the bone having been confirmed by X-ray, scan or biopsy). Secondary objectives were to compare the effect of bisphosphonates on the time to disease progression, survival, quality of life and toxicity.

Criteria for considering studies for skeletal morbidity review

Types of studies

Only RCTs were included in the review.

Types of participants

Patients with proven malignant disease and bony metastases, which had been confirmed by X-ray, scans or biopsy, were included in the review. Patients with multiple myeloma were included, but other haematological malignancies were excluded.

Types of interventions

Oral or intravenous bisphosphonate in the experimental arm, compared with another bisphosphonate, placebo or standard care.

Outcome measures

The primary outcome measure was a reduction in skeletal morbidity as reflected by a decrease in:

- number of pathological fractures (vertebral and non-vertebral)
- need for radiotherapy (RT)
- incidence of spinal cord compression (SCC)
- orthopaedic procedures
- episodes of hypercalcaemia.

Pain relief was not included since a separate systematic review, 'Bisphosphonates as analgesics for bone pain secondary to bone metastases', was already in progress. This work was being done by Wong and Wiffen[121] at the Pain, Palliative and Supportive Care Collaborative Cochrane Review Group (PAPAS); permission was obtained for the work by PAPAS to be cited in this report.

Secondary outcome measures were:

- time to first SRE
- survival
- performance status [as measured by Eastern Co-operative Oncology Group (ECOG) or Karnofsky scores]
- quality of life
- toxicity.

Adjuvant review

Objectives

The primary objective of this review was to examine whether bisphosphonates delay the development of bone metastases (confirmed by X-ray, scan or biopsy) in patients with malignancy and no prior evidence of bony metastases. This was measured by the number of patients developing bony metastases and time to first relapse in bone.

Secondary objectives included the effect of bisphosphonates, given in an adjuvant setting, on the development of distant (non-bony) metastases and survival.

Criteria for considering studies for adjuvant review

Types of studies

Only RCTs were included in this review.

Types of participants

Patients with histologically proven malignant disease and no evidence of bony metastases (by X-ray, scan or biopsy) were included in the review. Patients with multiple myeloma were included; all other haematological malignancies were excluded.

Types of interventions

Oral or intravenous bisphosphonate in the experimental arm compared with placebo.

Outcome measures

The primary outcome measures were:

- the number of patients developing bone metastases (confirmed by X-ray, bone scan or biopsy), during the study period, in each group
- Time to first relapse in bone.

Secondary outcome measures were:

- survival
- number of patients developing non-bony metastases
- time to development of non-bony disease.

Economic review

A review was undertaken to identify studies that had investigated the economics of using bisphosphonates in metastatic disease. On the basis of this review and review of the clinical literature, cost analyses were conducted for the following areas:

- treatment of cancer-associated hypercalcaemia
- prevention of SREs in patients with multiple myeloma
- prevention of SREs in patients with breast cancer and bony metastases.

Literature review

A systematic search was carried out using similar cancer and drug terms to those used in the main review. The filter for RCTs was replaced with search terms to identify cost data (Appendix 8). The following databases were searched on 29 August 2001: MEDLINE-PubMed (1966–present), EMBASE (1980–present), Science Citation Index (1981–present), Social Science Citation Index (1981–present), Health Economic Evaluations Database (1958–present) and NHS Economic Evaluations Database (1968–present). Data were extracted using a data extraction form (Appendix 9). Estimates of cost and cost-effectiveness were converted to 2001 UK £ sterling using purchasing power parities [source: Organisation of Economic Cooperation and Development (OECD)] and the health component of the UK harmonised index of consumer prices

(source: Office for National Statistics). Where studies did not state the year of costing, it was assumed to be the year of publication for conference abstracts or the year prior to publication for full articles.

Cost analysis of treatment of cancer-associated hypercalcaemia

It was not possible to evaluate the overall clinical effect using meta-analysis; therefore, separate cost analyses were carried out for each of four selected RCTs.[62,66,130,131] The studies were selected on the basis of their relevance to policy, in addition to the quality of the study design and sample size. For example, the comparison of zoledronate and pamidronate[131] was included even though it had been excluded from the main part of the clinical review. The costs associated with each arm of each of the four trials were calculated to enable the comparison of:

- zoledronate and pamidronate[131]
- pamidronate and intravenous clodronate[130]
- different doses of pamidronate[66]
- different doses of ibandronate.[62]

When comparing one treatment strategy with another, the economic outcome measures of interest were:

- incremental cost per patient
- incremental cumulative duration of normocalcaemia
- incremental cost per extra day of normocalcaemia.

The model

The analysis was undertaken with primary reference to the cost implications for the NHS, a health service perspective. The cost components considered were (a) drug costs and (b) costs associated with increased stay in hospital. The cost of treating side-effects associated with the drugs was not estimated, because the frequency of serious side-effects was negligible and there were no statistically significant differences in side-effects between trial arms in any of the four studies.

For each arm of each study, both an expected cost, $E(C_i)$, that is, mean cost per-patient, and also an expected response duration, $E(t_i)$, was calculated. For each strategy, the incremental cost per patient was calculated as the expected cost of that strategy minus the expected cost of the next most effective strategy, $E(C_a) - E(C_b)$. The incremental cumulative duration of normocalcaemia was calculated in the same manner $[E(t_a) - E(t_b)]$. The incremental cost per extra day of normocalcaemia is calculated as the incremental cost per patient divided by the incremental cumulative duration of normocalcaemia:

$$[E(C_a) - E(C_b)]/(E(t_a) - E(t_b)]$$

The expected outcomes were calculated using the decision analytic model represented in *Figure 7*. Data on response rate and time to first relapse were taken from the four studies (*Table 5*). The studies followed patients until the time of first relapse only and did not report data on length of stay. Hence in addition to trial data, the decision model was constructed using the following estimates and assumptions derived from clinical experience:

- After relapse patients would have up to two further treatments (and up to two additional relapses) with the same drug regimen.
- With each successive treatment both the response rate and the time to relapse diminish by one-third.
- At the time of relapse, one-quarter of patients will die of causes other than hypercalcaemia (before further treatment).
- Patients receiving bisphosphonate treatment would spend 7 days in hospital/hospice.
- Those who do not respond to treatment will die after a further 7 days in hospital.
- On responding to the drug, patients spend time in normocalcaemia at home with their families.

For ease of presentation, *Figure 7* includes only two treatment arms; however, three of the four studies compare three different treatment options and this is reflected in the decision models. None of the four studies evaluated the strategy of best supportive care without bisphosphonate therapy, but this 'do nothing' option is included in this analysis, as is common practice in economic evaluation. It was assumed that these patients only go through the dying phase and hence have a life expectancy of just 7 days spent in hospital/hospice.

Duration of normocalcaemia

The expected cumulative duration of normocalcaemia for a particular drug regimen is determined not just by the time to relapse but also by the response rate.

To measure the expected (i.e. mean) cumulative response duration requires knowing the mean time to relapse for each treatment. The studies, however, all reported median time to first relapse; therefore, medians were used as a proxy for

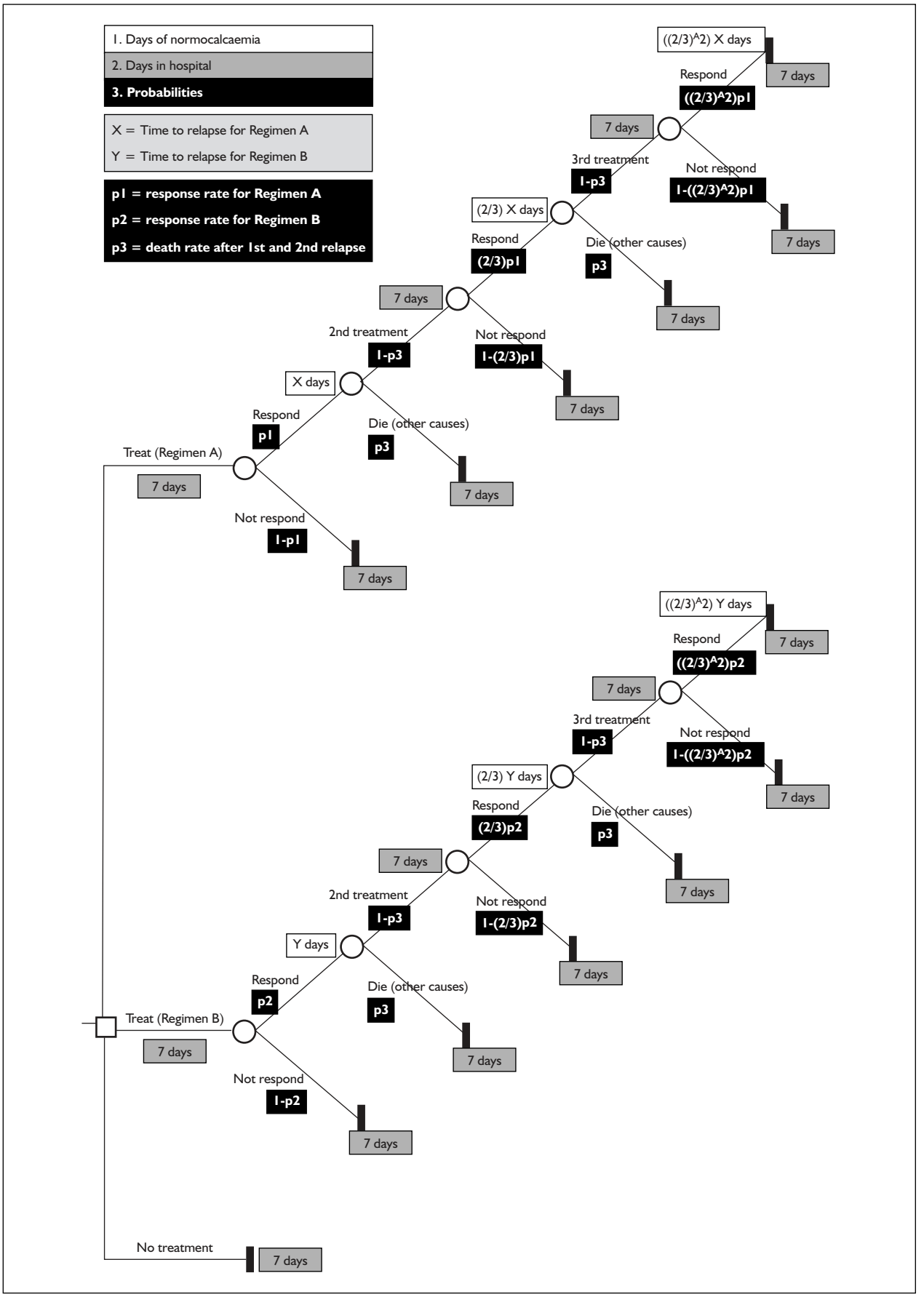


FIGURE 7 *Decision analytic model comparing two drug regimens for the treatment of cancer-associated hypercalcaemia*

TABLE 5 *Study-specific data for hypercalcaemia models*

	Purohit *et al.*[130]	Major *et al.*[131]	Ralston *et al.*[62]	Nussbaum *et al.*[66]
Sample size	41	275	131	50
Regimen A	Pamidronate 90 mg	Zoledronate 8 mg	Ibandronate 6 mg	Pamidronate 90 mg
Regimen B	Clodronate 1500 mg	Zoledronate 4 mg	Ibandronate 4 mg	Pamidronate 60 mg
Regimen C	N/A	Pamidronate 90 mg	Ibandronate 2 mg	Pamidronate 30 mg
*p*1 = response rate for Regimen A (%)	100	87	78	100
*p*2 = response rate for Regimen B (%)	80	88	76	61
*p*4 = response rate for Regimen C (%)	N/A	70	50	40
X = time to first relapse for Regimen A: median (mean) (days)	28	40	11	6 (10.8)
Y = time to first relapse for Regimen B: median (mean) (days)	14	30	12	5 (13.3)
Z = time to first relapse for Regimen C: median (mean) (days)	N/A	17	12	4 (9.2)
Drug cost per treatment for Regimen A (£)	155.80	390.00	261.24	155.80
Drug cost per treatment for Regimen B (£)	68.90	195.00	174.16	109.60
Drug cost per treatment for Regimen C (£)	N/A	155.80	87.08	54.53

means. Given the skew in the distribution of time to first relapse, this means that the model is underestimating the cumulative duration of normocalcaemia. Only Nussbaum and colleagues[66] reported estimates of mean time to first relapse and these were used as part of the sensitivity analysis.

Costs

The cost of drug treatment was taken from the BNF for September 2001,[122] except for ibandronate, which is not yet marketed in the UK. In the NHS, drug costs vary between hospitals according to local contracts; however, for the purposes of this study the prices recorded in the BNF were taken to be broadly representative. The manufacturer of ibandronate, Roche, declined to give a price but said that the per-month price would be similar to the price of Loron (oral clodronate). Hence 4 mg of ibandronate was assumed to have the monthly price of Loron, and the prices of 2 and 6 mg were estimated in proportion to that.

The expected drug cost varies between strategies, not just because the cost of the drug varies but also because the number of treatments varies according to the response rate of the particular drug regimen.

The expected cost of time in hospital will be higher for more responsive drug regimens because patients will come back for further treatment when they relapse. Hence hospital stay costs add to the drug cost associated with bisphosphonate therapy.

The daily cost of an inpatient stay, £153, was calculated using the NHS Reference Cost database. It was calculated as the mean cost per day across 208 NHS trusts of an inpatient stay pertaining to bone metastases (Healthcare Resource Groups: H53 and H54) in a non-surgical specialty.

The NHS Reference Cost database[132] contains accounting cost data from NHS hospital trusts. Each trust reports an average cost per hospital episode, categorised by type of visit, such as outpatient and elective inpatient, clinical specialty and Healthcare Resource Group (HRG). An HRG provides an indication of the nature of treatment and also the resources likely to be spent in delivering it. The Reference Cost 2000 database contains information for 69.4 million hospital episodes amounting to 88% of annual expenditure on services by NHS hospitals. Accounting practices do vary between hospitals but the costs should reflect the full cost of the service (including direct, indirect and overhead costs), as described in the NHS Costing Manual.[133]

The costs are in UK £ sterling at 2000/2001 prices. It was not necessary to discount future costs or effects, as the median time to relapse was no more than a few weeks in all four studies.

Sensitivity analysis

For each of the four analyses, a sensitivity analysis was conducted to see how the results would change if there were changes in:

- the death rate from other causes

- the rate at which response diminishes after each relapse
- the time in hospital estimated for a treatment episode
- the unit cost of a day spent in hospital
- the time to relapse
- the response rate.

Cost analysis of preventing skeletal morbidity

The aim of this analysis was to estimate the costs associated with using bisphosphonate in the preventative setting and the cost savings resulting from delaying and postponing SREs. The studies that have investigated the effects of bisphosphonates in preventing SREs have focused mainly on patients with multiple myeloma or patients with primary breast cancer and bony metastases. Hence, the following questions were considered:

- What is the net effect on costs of using bisphosphonates to prevent SREs in patients with multiple myeloma?
- What is the net effect on costs of using bisphosphonates to prevent SREs in patients with breast cancer and bony metastases?

The main economic outcome measures of interest were:

- incremental cost (or cost saving) per patient
- number of SREs averted per patient
- incremental cost per SRE averted.

The model

The analysis was undertaken with primary reference to the cost implications for the NHS, a health and social service perspective. The cost items included in the model were:

- cost to the hospital of providing bisphosphonate therapy
- inpatient and outpatient hospital costs associated with treating SREs; fractures, hypercalcaemia, surgery and RT
- community health service costs associated with palliation of bone pain
- community health service costs associated with the longer term care of patients with pathological fractures.

The cost of treating side-effects from the drug was not included because of the rarity of serious side-effects (see *Table 23*). The cost of treating SCC was not estimated because there is not good evidence of a reduction in incidence associated with bisphosphonate use. Costs to patients and their families were not included. There would in reality be additional costs associated with patients attending for their bisphosphonate infusion, but cost savings associated with the reduced incidence of SREs would at least partially offset these costs.

Markov models were used to estimate the duration of bisphosphonate therapy, the number of SREs averted and the associated costs and cost savings involved. Generally, a Markov model is used to estimate the expected outcome from a chain of events occurring over time.[134] As with decision analyses (probability trees), risks or probabilities are applied to particular outcomes, such as cost and quality of life, to produce an expected outcome. However, decision analytic models become extremely complicated when an event occurs more than once, sporadically, as for example in the case of bone fractures. A Markov model overcomes this complexity by assuming that the probability of an event in the next time period is determined by the health state in the current time period but not by the path that the individual has taken before that period. This simplification means that the model cannot be used to predict the pathway of an individual. However, it can be used to estimate, accurately, the number and timing of events in a population if the probability data are reasonably precise.

Figure 8 shows a Markov cycle tree that indicates the number of possible health states and the paths that can be taken from each health state. There is a cost associated with each health state and there is a probability associated with each possible path between health states. For each primary cancer type (breast cancer and multiple myeloma), two Markov models were produced, one for the bisphosphonate arm and one for the no-bisphosphonate arm. Each model estimated overall treatment costs by applying monthly mortality rates and skeletal event rates to the monthly cost associated with bisphosphonate therapy and the cost associated with each SRE. Each model consisted of 48 monthly cycles to correlate with the longest time horizon of the studies examined in the literature. In order to estimate total incremental cost, a long time horizon is desirable; however, the longer the horizon the more we have to extrapolate from the results of the clinical trials. Costs would not change greatly if the model were extended over a longer period because most patients would die before the fifth year; furthermore, the process of discounting diminishes costs in later years.

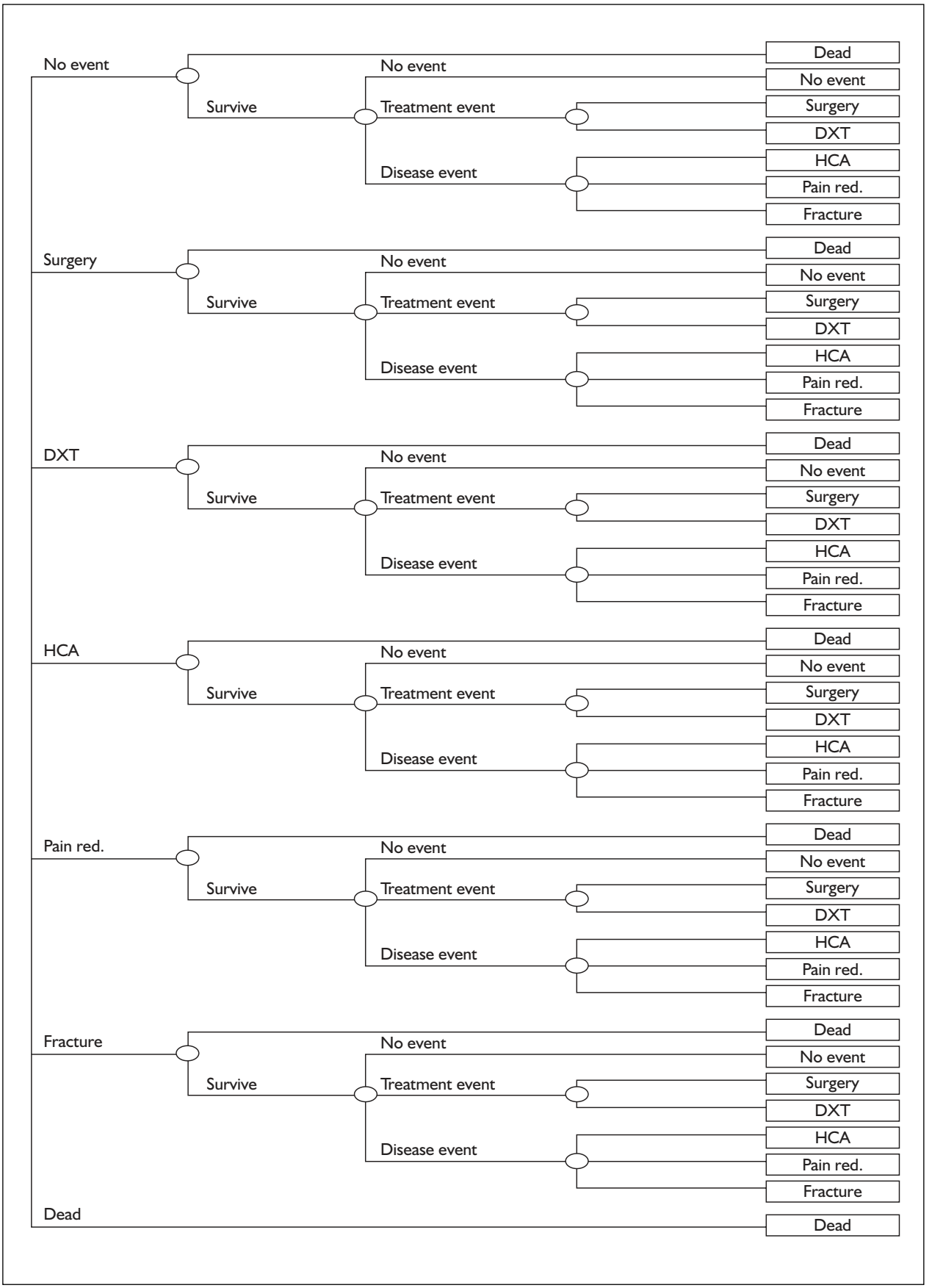


FIGURE 8 *Markov model of use of bisphosphonates to prevent skeletal events. HCA, hypercalcaemia; DXT, radiotherapy; Pain red., pain reduction.*

TABLE 6 *Event rates and unit costs*

	Unit cost (£)	Monthly incidence (%): breast cancer			Monthly incidence (%): multiple myeloma		
		No-bisphosphonate arm *A*	Relative risk *B*	Bisphosphonate arm *C = A × B*	No-bisphosphonate arm *D*	Relative risk *E*	Bisphosphonate arm *F = D × E*
Death	–[a]	3.8	100.0	3.8	2.4	100.0	2.4
Vertebral fracture	2017	7.5	90.5	6.8	7.3	64.8	4.7
Non-vertebral fracture	2017	11.7	79.4	9.3	2.0	51.5	1.0
Hypercalcaemia	3503	3.1	50.8	1.6	2.4	97.6	2.3
RT	708	10.0	71.2	7.1	9.1	77.8	7.1
Orthopaedic surgery	2036	1.3	58.6	0.7	–[b]	–[b]	–[b]

[a] Not costed because the incidence is the same for both the no-bisphosphonate and bisphosphonate arms.
[b] Not measured in trials.

Probabilities

The monthly mortality rates were calculated using the survival data from the largest studies that measured survival. In each case, median survival from the placebo arm was extracted. For breast cancer 18 months was used – the estimate from both Lipton and colleagues[135] and Hultborn and colleagues.[136] For multiple myeloma, the midpoint was used between the estimates of McCloskey and colleagues[137] and Berenson and colleagues[138] – 29 months. Monthly mortality rates were then derived on the following basis: if p = monthly death rate and t = the median survival (in months), then we can say that the proportion surviving t months will be

$$(1 - p)' = 0.5$$

and, by rearranging,

$$p = 1 - 0.5^{1/t}$$

This assumes that the mortality rate is constant over the 4-year course of the disease. In the model, it was assumed that the mortality was the same in both the bisphosphonate arm and no-bisphosphonate arm.

For the no-bisphosphonate arm, the monthly incidence rates of the following SREs were extracted from the literature (*Table 6*):

- vertebral fracture
- non-vertebral fracture
- hypercalcaemia
- RT
- orthopaedic surgery.

For breast cancer, only Lipton and colleagues[135] and Theriault and colleagues[139] had reported incidence rates. The estimates by Lipton and colleagues were used as they subsume the data from Theriault and colleagues. However, Lipton and colleagues did not present separate estimates for vertebral and non-vertebral fractures, and therefore these were taken from Theriault and colleagues. For multiple myeloma, there were no studies reporting the incidence rates of individual skeletal events. Berenson and colleagues[138] reported a combined skeletal morbidity incidence rate (for all fractures and radiotherapy). To derive approximate incidence rates for each type of SRE, we applied the relative frequency of each event to the overall morbidity rate. For example, Berenson and colleagues[138] found 46% of the placebo arm had one or more fractures and 45% had one or more RT episodes. Assuming the ratio of fractures to RT is 46:45 and the total number of events is 2.2 per person per year,[138] then the number of fractures is 1.11 per year and the number of RT sessions is 1.09 per year. The frequency of orthopaedic surgery was not recorded in any of the multiple myeloma studies, hence this event was only included in the breast cancer model.

For the bisphosphonate arm, the monthly incidence rates of each SRE were calculated by multiplying the incidence rate in the no-bisphosphonate arm by an estimated relative risk. The relative risk for each SRE was calculated by random effects meta-analysis, using the same methods and the same data as for the clinical review. For multiple myeloma, the relative risks for RT and non-vertebral fractures were each derived

from a single study, Berenson and colleagues[138] and McCloskey and colleagues,[137] respectively, as there were no other relevant data.

As with mortality rate, SRE incidence rates in both the bisphosphonate and no-bisphosphonate arm were assumed to be constant over the 4-year course of the disease.

In addition to avoiding these SREs, it was assumed that bisphosphonate therapy would alleviate bone pain in a proportion of patients. On the basis of the overall number needed to treat estimated by Wong and Wiffen,[121] it was estimated that one in seven patients would have their bone pain fully alleviated each month.

Hospital costs

The estimates of treatment effect are based on studies that used a variety of drug regimens. In the model, the cost of bisphosphonate therapy was based on monthly cycles of 90 mg pamidronate – the most commonly used therapy in the larger studies. The monthly cost of the drug was taken from the BNF for September 2001.[122] The cost of a clinical oncology outpatient visit was added. This was calculated using the mean cost of such a visit recorded in the NHS Reference Cost database[132] (see the section 'Costs', p. 22).

The cost of each type of SRE (excluding hypercalcaemia) was also taken from the NHS Reference Cost database (*Table 6*). Fractures and orthopaedic surgery were given a mean cost of an inpatient stay with the HRG associated with bone malignancy, using non-surgical and surgical specialities, respectively. RT has separate codes. Based on two previous studies,[140,141] we assumed that an episode consisted of three RT sessions, in an outpatient setting. The cost of a clinical oncology outpatient appointment was added to the RT cost of each session.

The cost of an episode of hypercalcaemia was taken from the results of our own costing analysis. Three similar incremental cost estimates were derived for 90 mg pamidronate from three studies.[66,130,131] The simple mean of these three estimates was calculated and used as the unit cost of hypercalcaemia in the Markov model.

Costs of community care

The literature relating to community health service costs and social care costs associated with skeletal morbidity is limited, therefore these costs are difficult to approximate. Some studies have investigated community resource use for elderly patients with osteoporosis.[142–147] Resource use for cancer-associated fractures is likely to be different because the duration of the care required may be different, for two reasons: first the fractures in these patients do not heal, and second their life expectancy is relatively short.

In order to calculate the cost of treating bone pain, a treatment protocol for a 'typical patient' who is experiencing bone pain was devised by the project team (*Table 7*). The protocol was divided into three stages (stages 1, 2 and 3) according to severity of bone pain. The annual cost of each stage of the protocol was costed using the BNF for drug prices, standard average NHS costs for community care services (including staff travel costs)[148] and NHS Reference costs for hospital services. For each stage, a monthly cost was calculated by dividing the relevant annual cost by 12. To calculate the cost savings attributable to bisphosphonates, the probability of alleviating bone pain (1/7)[121] that month was multiplied with the monthly cost. In year 1 of the model, the monthly cost of the stage 1 protocol was used; in year 2, the stage 2 protocol was used; and in years 3 and 4, the stage 3 protocol was used.

The project team also devised pathways for 'typical patients' with pathological long bone fractures (*Table 8*). There were two separate protocols for patients requiring different levels of intensity of care. The monthly cost of each protocol was calculated using, standard average NHS costs for community care services (including staff travel costs)[148] and NHS Reference costs[132] for hospital services and, where data were lacking, the retail prices of selected retailers. An annual equivalent cost (AEC) was estimated for capital equipment included in the package. The AEC was calculated assuming a life expectancy for the equipment of 5 years and a discount rate of 6%. It was not possible to determine the duration of care required per fracture, or the proportion that would require the more intensive package, therefore fracture care costs were not incorporated into the main results. The incidence of long bone fractures as a proportion of all non-vertebral fractures was estimated to be 61% using data from the placebo arm of the trial reported by McCloskey and colleagues.[137]

General costing conventions

All costs were in UK £ sterling at 2000/2001 prices. All future costs were discounted at 6%, as recommended by the UK Treasury[150] and the National Institute for Clinical Excellence

TABLE 7 *Cost of treating bone pain in the community*

Component	Unit cost (£)	Frequency	Number per year	Cost per year (£)	Source of unit cost
Year 1					
Oncology outpatient visit	92.00	3-monthly	4	368	NHS Reference Costs 2000[132]
Coproxamol (4 × 2 tablets)	0.10	Daily	365	35	BNF Sept. 2001,[122] p. 209
Tramadol (4 × 100g)	0.79	Daily	365	289	BNF Sept. 2001[122]
Codanthramer (2 × 2 capsules)	1.71	Daily	365	626	BNF Sept. 2001[122]
Haloperidol (1.5 mg nocte)	0.04	Daily	365	14	BNF Sept. 2001[122]
		Total cost per year =	**1331**		
		Cost per month =	**111**		
Year 2					
Oncology outpatient visit	92.00	3-monthly	4	368	NHS Reference Costs 2000[132]
Palliative chemotherapy (daycase)	232.00	2-monthly	6	1392	NHS Reference Costs 2000[132]
Palliative nurse visit (1 hour)[a]	67.10	2-weekly	26	1745	Netten *et al.*,[148] p. 100
GP clinic consultation	26.00	Monthly	12	312	Netten *et al.*,[148] pp. 103–4
District nurse (0.5 hours)	28.60	Weekly	52	1487	Netten *et al.*,[148] p. 97
Codanthramer (2 × 2 capsules)	1.71	Daily	365	626	BNF Sept. 2001[122]
Haloperidol (1.5 mg nocte)	0.04	Daily	365	14	BNF Sept. 2001[122]
Morphine (6 × 20 mg, tablets)	0.65	Daily	365	236	BNF Sept. 2001,[122] p. 213
		Total cost per year =	**6179**		
		Cost per month =	**515**		
Year 3					
As for year 2				6179	
Palliative nurse visit (1 hour)[b]	67.10	2-weekly	26	1745	Netten *et al.*[148]
Palliative medicine outpatient visit	96.34	Monthly	12	1156	NHS Reference Costs 2000[132]
Hospice day visit (including 1 hour physiotherapy)	84.00	Weekly	52	4368	Douglas H-R, personal communication; Netten *et al.*,[148] p. 89, for cost of physiotherapy
Hospice stay (nights)[c]	235.00	2 weeks p.a.	14	3290	NHS Reference Costs 2000[132]
Occupational therapist (1 hour)	47.10	Once	1	47	Netten *et al.*,[148] p. 115
		Total cost per year =	**6785**		
		Cost per month =	**1399**		

[a] Cost of a NHS community nurse specialist for HIV/AIDS is used as a proxy.
[b] Cost of a NHS community nurse specialist for HIV/AIDS is used as a proxy.
[c] Used the mean daily cost of a palliative medicine inpatient stay as a proxy.

(NICE).[151] Likewise, health effects, such as the number of SREs, were discounted at 1%. The main results were also presented using a number of other discounting conventions, including discounting both costs and health effects at 0% (i.e. not discounting), 3% and 5%, to allow comparison with overseas studies, as recommended by the Washington Panel on Cost-effectiveness.[152] There are a number of reasons for putting a lower weight on costs (and benefits) that are incurred in the future. One reason is that money available in the present can be invested to earn interest and therefore accumulate value; thus, a pound today is valued more than a pound available in 1 year's time. To account for this time preference, healthcare expenditures occurring in the future are discounted to their present value.

Sensitivity analysis

A sensitivity analysis was conducted to assess the robustness of the results to each of the following parameters:

- the cost of the drugs
- the survival rate
- the rates of SREs, including bone pain
- the hospitalisation rate associated with fractures
- the unit costs of skeletal events.

We looked at the results to see if they would change when rates were increased over time to test

TABLE 8 *Cost of treating pathological fracture in the community*

Component	Unit cost (£)	Frequency	Number per month	Cost per month (£)	Source of unit cost
Home care – lower cost package					
Oncology outpatient visit	92.00	Monthly	1	92	NHS Reference Costs 2000[132]
Palliative nurse visit (1 hour)[b]	67.10	Weekly	4	268	Netten *et al.*,[148] p. 100
District nurse (1 hour)	56.10	Weekly	4	224	Netten *et al.*,[148] p. 97
Social services (1 hour/day for shopping/cleaning)	10.31	Daily[b]	36	371	Netten *et al.*,[148] p. 113
Social services (1 hour/day for personal care)	10.31	Daily[c]	36	371	Netten *et al.*,[148] p. 113
		Total cost per month =		**1327**	
Home care – higher cost package					
Palliative nurse visit (1 hour)[a]	67.10	Weekly	4	268	Netten *et al.*,[148] p. 100
GP home visit (1/2 hour)	99.69	Weekly	4	399	Netten *et al.*,[148] pp. 103–4
District nurse (1 hour – morning & twilight service)	57.20	Daily	30	1716	Netten *et al.*,[148] p. 97
Social services (1 hour/day for shopping/cleaning)	10.31	Daily[b]	36	371	Netten *et al.*,[148] p. 113
Social services (3 hours/day for personal care)	10.31	3 × daily[b]	108	1113	Netten *et al.*,[148] p. 113
Occupational therapist (2 hours)	93.10	Once[c]	0.17	16	Netten *et al.*,[148] p. 115
Wheelchair, unpowered	54.00	Annual[d]	0.08	5	Netten *et al.*,[148] p. 85
Hoist	235.00	Annual[d]	0.08	20	Netten *et al.*,[148] p. 86
Pressure-relieving mattress	38.93	Annual[d]	0.08	3	Rimmer[149]
Commode (mobile)	40.36	Annual[d]	0.08	3	www.medisave.co.uk
Mattress variator	127.97	Annual[d]	0.08	11	www.medisave.co.uk
Hospital bed (fixed height)	166.57	Annual[d]	0.08	14	www.hospital-beds.co.il
		Total cost per month =		**3939**	

[a] Cost of a-NHS community nurse specialist for HIV/AIDS was used as a proxy.
[b] The frequency is stated as 36 per month (instead of 30) so that Saturdays get a weighting of 1.5 and Sundays 2.0 (Netten *et al.*[148]).
[c] For number per month a life expectancy of 6 months was assumed.
[d] Discount rate = 6%, equipment life = 5 years.

the assumption of constant rates of death and SREs. We tested to see whether the conclusion of Beusterien and colleagues[153] that bisphosphonate patients had shorter length of stay would effect the results. The potential cost savings attributable to reduced incidence of SCC was assessed.

Chapter 3
Results

Retrieval of studies

Searches of the electronic databases and subsequent removal of irrelevant or duplicate citations produced 191 articles. In addition, 11 studies were identified from consultation with experts, handsearching and identification of unpublished data through drug companies. Full text copies of these articles were obtained and reviews or clear non-RCTs were removed. This resulted in 45 articles for inclusion in the hypercalcaemia review, 95 for the skeletal morbidity review and 30 for the adjuvant review (*Figure 9*).

Hypercalcaemia review

Twenty-six papers and two abstracts fulfilled inclusion criteria for this review, and they are described in *Table 9*. Details of the 17 excluded studies are given in *Table 10*. Of the included studies, two papers contained duplicate information of studies reported elsewhere.[159,163]

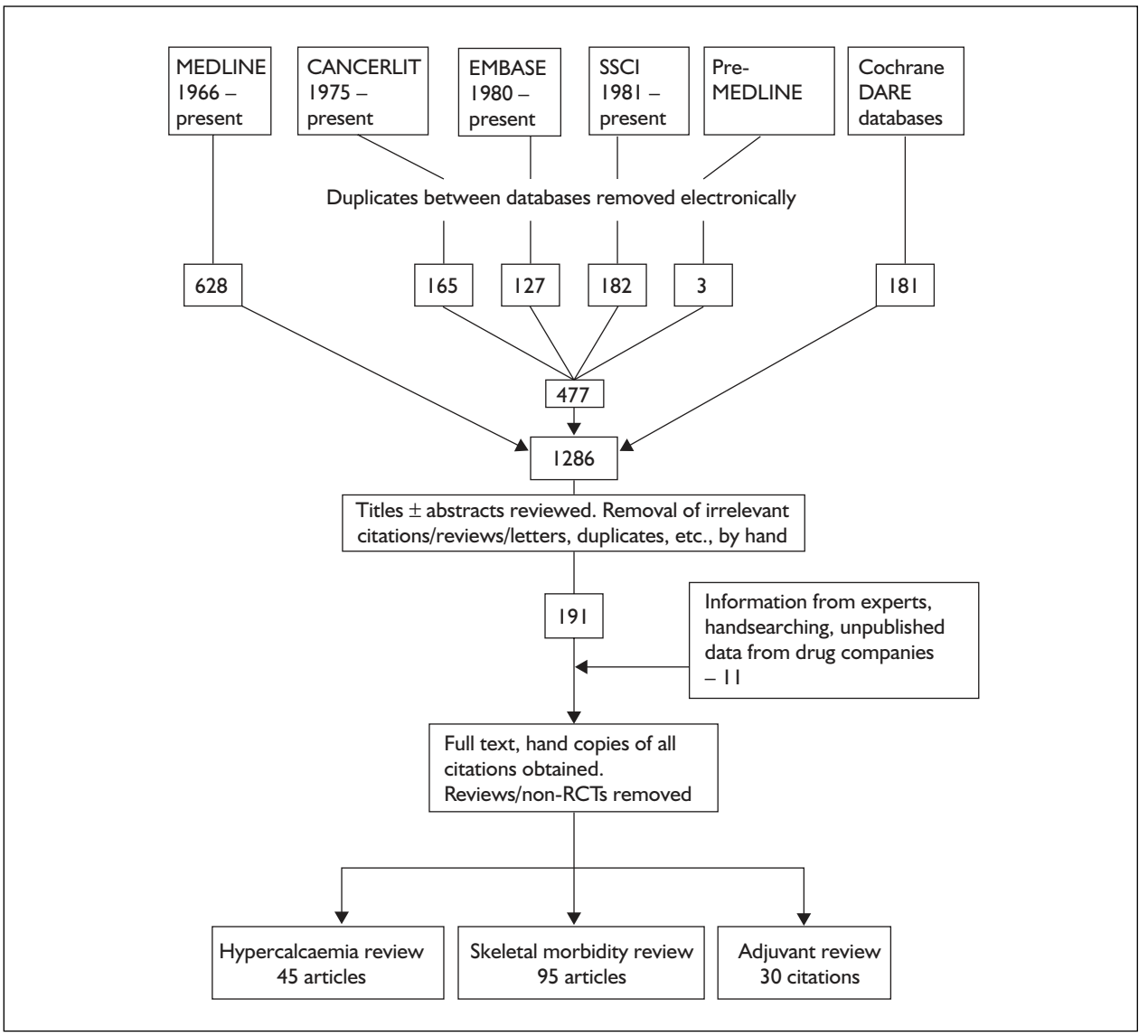


FIGURE 9 *Flow diagram of identification of articles for inclusion in each part of the review*

TABLE 9 *Hypercalcaemia review: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Bertheault-Cvitkovic, 1995[154]	RCT Double blind	62 pts All cancer types Entry CCa: >12.0 mg/dl (*>3.0 mmol/l*)	A – gallium nitrate 200 mg/m^2/d i.i. for 5 d B – pamidronate 60 or 90 mg i.v. over 24 h for 1 d	Pts achieving normocalcaemia: A 73%; B 62% Time to normocalcaemia (d) [median]: A 6; B 5	Meeting abstract	B
Body, 1989[68]	RCT Open	33 pts 13 M/20 F All cancer types Entry CCa: >2.55 mmol/l	A – pamidronate 0.5 mg/kg/d i.v. in 250 ml Nsaline over 2 h for 3 d B – pamidronate 1.5 mg/kg i.v. in 1 l Nsaline over 24 h for 1 d C – pamidronate 0.5 mg/kg i.v. in 1 l Nsaline over 24 h for 1 d	Pts achieving normocalcaemia [x/y]: A 11/11; B 11/11; C 10/11 Time for mean gp CCa to reach normocalcaemia (d): A 4; B 4; C 7 Time to relapse[a] (d), [Median (range)]: A 7 (2–42); B 8 (2–26); C 8 (0–120)	All groups: significant decrease in urinary Ca/Cr ratio	B
Davis, 1989[54]	RCT Open	27 pts 17 M/10 F All cancer types Entry CCa: >3.0 mmol/l	A – pamidronate 30 mg i.v. in 500 ml Nsaline over 4 h for 1 d B – pamidronate 30 mg/d i.v. in 500 ml Nsaline over 4 h for 2 d C – pamidronate 60 mg i.v. in 500 ml Nsaline over 8 h for 1 d	Pts achieving normocalcaemia [x/y]: A 4/9; B 4/7; C 3/8 Time to normocalcaemia: no difference between groups, range 2–12 d Time to relapse[b] (d) [range]: A 8–22; B 13–34; C 7–25		B

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Dodwell, 1992[155]	RCT Open	50 pts All cancer types Entry CCa: >2.9 mmol/l	A – pamidronate 60 mg i.v. in 500 ml Nsaline over 2 h B – pamidronate 60 mg i.v. in 500 ml Nsaline over 4 h C – pamidronate 60 mg i.v. in 500 ml Nsaline over 8 h D – pamidronate 60 mg i.v. in 500 ml Nsaline over 24 h	Pts achieving normocalcaemia [x/y]: A 8/9; B 10/11; C 14/15; D 15/15 Time to normocalcaemia: no significant difference between groups, median 5 d Time to relapse[b] (d) [median (range)]: no difference between groups, 21 (11–47)		B
Fukumoto, 1994[156]	RCT Open	79 pts 45 M/30 F All cancer types Entry CCa: >2.75 mmol/l	A – YM175 2.5 mg i.v. in 500 ml Nsaline over 3–4 h B – YM175 5 mg i.v. in 500 ml Nsaline over 3–4 h C – YM175 10 mg i.v. in 500 ml Nsaline over 3–4 h	Pts achieving normocalcaemia [x/y]: A 5/26; B 8/30; C 11/23 Time to normocalcaemia: no data Time to relapse: no data		B
Gallacher, 1991[157]	RCT Open	32 pts All cancer types Entry CCa: >2.8 mmol/l	A – pamidronate 30 mg i.v. in 500 ml Nsaline over 4 h B – pamidronate 90 mg i.v. in 1 l Nsaline over 24 h	Pts achieving normocalcaemia [x/y]: A 10/16; B 8/16 Time to normocalcaemia (d) [mean]: A 6; B 6 Time to relapse: data not comparable	Definition of time to relapse does not compare with other studies PTH, NcAMP, urinary Ca/Cr, renal tubular threshold for phosphate reabsorption (TmPO4) were also measured	B

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Gucalp, 1992[67]	RCT Double blind	65 pts 37 M/28 F All cancer types Entry CCa: >3.0 mmol/l	A – Nsaline control B – pamidronate 60 mg i.v. in 500 ml Nsaline over 4 h C – pamidronate 60 mg i.v. in 1 l Nsaline over 24 h	Pts achieving normocalcaemia [x/y]: A 5/23; B 18/23; C 14/23 Time for mean gp CCa to reach normocalcaemia (d): A not reached; B 5; C 4 Time to relapse[a] (d) [median (range)]: A 6 (3–57); B 6 (1–59); C 11 (1–62)		B
Gucalp, 1994[57]	RCT Double blind	69 pts 31 M/38 F All cancer types Entry CCa: >3.0 mmol/l	A – pamidronate 60 mg i.v. in 1 l Nsaline over 24 h B – etidronate 7.5 mg/kg/d i.v. in 250 mls Nsaline over 2 h for 3 d	Pts achieving normocalcaemia [x/y]: A 21/30; B 14/35 Time to normocalcaemia: no data Time to relapse: data not comparable	Time to normocalcaemia and time to relapse, data are combined for complete and partial responders	B
Hasling, 1986[158]	RCT Double blind	20 pts 4 M/16 F All cancer types Entry CCa: >2.85 mmol/l	A – etidronate 7.5 mg/kg/d i.v. over 3 h for 3–5 d B – placebo	Pts achieving normocalcaemia [x/y]: A 11/12; B 2/6 Time to normocalcaemia (d) [range]: A 0–4; B 0–3 Time to relapse: no data	Same study as Hasling, 1987[159]	B

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Hasling, 1987[159]	RCT Double blind	20 pts 4 M/16 F All cancer types Entry CCa: >2.85 mmol/l	A – etidronate 7.5 mg/kg/d i.v. over 3 h for 3–5 d B – placebo		Duplicate publication of Hasling, 1986,[158] therefore **not** duplicated in analyses	B
Morton, 1988[160]	RCT Open	30 pts All cancer types Entry CCa: >2.8 mmol/l	A – pamidronate 60 mg i.v. in 500 ml Nsaline over 8 h for 1 d B – pamidronate 30 mg i.v. in 250 ml Nsaline over 4 h, d 1 & d 2 C – pamidronate 15 mg i.v. in 125 ml Nsaline over 2 h, d 1–4	Pts achieving normocalcaemia [x/y]: A, B, C: 28/30 Time to normocalcaemia (d) [median]: A 7; B 5; C 3 Time to relapse (d): A, B, C: mean 21	Urinary Ca, urinary OHP/Cr were also measured	B
Nussbaum, 1993[65]	RCT Double blind	59 pts 37 M/22 F All cancer types Entry CCa: >2.88 mmol/l	A – alendronate 2.5 mg i.v. in 250 ml Nsaline over 2 h B – alendronate 5 mg i.v. in 250 ml Nsaline over 2 h C – alendronate 10 mg i.v. in 250 ml Nsaline over 2 h D – alendronate 10 mg i.v. in 250 ml Nsaline over 24 h E – alendronate 15 mg i.v. in 250 ml Nsaline over 2 h	Pts achieving normocalcaemia [x/y]: A 2/13; B 9/11; C + D 15/25; E 9/10 Time to normocalcaemia (d) [median]: A not reached; B 5; C + D 5; E 4 Time to relapse[b] (d) [median]: A–E; 15		A

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Nussbaum, 1993[66]	RCT Double blind	50 pts 32 M/18 F All cancer types Entry CCa: >3.0 mmol/l	A – pamidronate 30 mg i.v. over 24 h B – pamidronate 60 mg i.v. over 24 h C – pamidronate 90 mg i.v. over 24 h	Pts achieving normocalcaemia [x/y]: A 6/15; B 11/18; C 17/17 Time for mean gp CCa to reach normocalcaemia (d): A 4; B 5; C 4 Time to relapse[a] (d) [mean (median)]: A 9.2 (4); B 10.8 (6) C 13.3 (5);	PTH, urinary Ca/Cr, urinary OHP/Cr were also measured	A
Ostenstad, 1992[56]	RCT Open	28 pts All cancer types Entry CCa: >2.8 mmol/l	A – pamidronate 30–90 mg (depending on baseline CCa) i.v. in 11 Nsaline over 12 h B – mithramycin 1.25 mg i.v. in 500 ml Nsaline over 4 h	Pts achieving normocalcaemia [x/y]: A 14/14; B 3/11 Time for mean gp CCa to reach normocalcaemia (d): A 2; B 3 Time to relapse: insufficient data		B
Pecherstorfer, 1996[60]	RCT Double blind	174 pts 86 M/65 F All cancer types Entry CCa: >2.7 mmol/l Stratified by serum CCa and tumour type	A – ibandronate 0.6 mg i.v. in 500 ml Nsaline over 2 h B – ibandronate 1.1 mg i.v. in 500 ml Nsaline over 2 h C – ibandronate 2.0 mg i.v. in 500 ml Nsaline over 2 h	Pts achieving normocalcaemia [x/y]: A 22/50; B 24/46; C 37/55 Time to normocalcaemia: no data Time to relapse[a] (d) [median]: A 11; B 17; C 12	Urinary collagen cross-links were also measured	B

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Purohit, 1995[130]	RCT Double blind	41 pts All cancer types Entry CCa: >2.7 mmol/l	A – pamidronate 90 mg i.v. in 500 ml Nsaline over 4 h B – clodronate 1500 mg i.v. in 500 ml Nsaline over 4 h	Pts achieving normocalcaemia [x/y]: A 19/19; B 16/20 Time to normocalcaemia (d) [median]: A 4; B 3 Time to relapse[b] (d) [median (range)]: A 28 (10–28+); B 14 (7–21); $p < 0.01$	Urinary Ca/Cr, urinary OHP/Cr were also measured	B
Ralston, 1985[161]	RCT Open	39 pts All cancer types Entry CCa: >2.7 mmol/l	A – pamidronate 15 mg i.v. in 250 ml Nsaline daily until normocalcaemia B – mithramycin 25 μg/kg i.v. in 500 ml 5% dextrose, d 1 and repeated d 3 if CCa >2.9 mmol/l C – prednisolone 40 mg p.o. daily (or i.v. equivalent) and calcitonin 400 IU s.c. t.d.s. for d 1–9	Pts achieving normocalcaemia [x/y]: median group CCa failed to reach normocalcaemia for all groups. Time to normocalcaemia: no data Time to relapse: no data		C

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Ralston, 1989[162]	RCT Open	48 pts All cancer types Entry CCa: >2.8 mmol/l	A – etidronate 7.5 mg/kg i.v. in 500 ml Nsaline over 2 h, d 1–3, then 20 mg/kg/d p.o. B – clodronate 600 mg i.v. in 500 ml Nsaline over 6 h, d 1 C – pamidronate 30 mg i.v. over 4 h	Pts achieving normocalcaemia [x/y]: A 5/16; B 6/16; C 14/16 Time to normocalcaemia: no data Time to relapse[b] (d) [median (range)]: A 10.5 (6–20); B 12 (9–45); C 29 (18–90)	Urinary Ca/Cr ratio was also measured	C
Ralston, 1997[62]	RCT Double blind	131 pts 58 M/67 F All cancer types Entry CCa: >3.0 mmol/l	A – ibandronate 2 mg i.v. in 500 ml Nsaline over 2 h B – ibandronate 4 mg i.v. in 500 ml Nsaline over 2 h C – ibandronate 6 mg i.v. in 500 ml Nsaline over 2 h	Pts achieving normocalcaemia: A 50%; B 75.6%; C 77.5% Time for mean group CCa to reach normocalcaemia (d): A not reached; B 4; C 4 Time to relapsea (d) [median]: A 12; B 12; C 11	PTH-rP, urinary Ca/Cr ratio were also measured	C
Rizzoli, 1992[69]	RCT Double blind	64 pts 34 M/30 F All cancer types Entry CCa: >2.7 mmol/l	A – alendronate 7.5 mg i.v. in 500 ml Nsaline over 4–6 h B – clodronate 600 mg i.v. in 500 ml Nsaline over 4–6 h	Pts achieving normocalcaemia [x/y]: A 12/30; B 14/34 Time to normocalcaemia: non-comparable data Time to relapse: non-comparable data	Urinary Ca/Cr ratio was also measured	B

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Rizzoli, 1992[69]	RCT Double blind	18 pts All cancer types Entry CCa: >2.7 mmol/l	A – alendronate 2.5 mg i.v. in 500 ml Nsaline over 4–6 h B – alendronate 5 mg i.v. in 500 ml Nsaline over 4–6 h C – alendronate 10 mg i.v. in 500 ml Nsaline over 4–6 h	Pts achieving normocalcaemia [x/y]: A 1/7; B 2/5; C 4/6 Time to normocalcaemia: non-comparable data Time to relapse: non-comparable data	Urinary Ca/Cr ratio was also measured	B
Rizzoli, 1999[163]	Combines results of two RCTs by Ralston[62] and Pecherstorfer[60]				Two trials considered individually, therefore this study was **not** included in analyses	B
Rotstein, 1992[164]	RCT Double blind	44 pts All F Breast cancer Entry ionised Ca: >1.6 mmol/l Stratified by number of previous episodes of hypercalcaemia	A – clodronate 300 mg i.v. in 500 ml Nsaline over 3 h, d 1–7 or until serum ionised Ca <1.4 mmol/l B – placebo, 500 mls Nsaline i.v. over 3 h, d 1–7, or until serum ionized Ca <1.4 mmol/l	Pts achieving normocalcaemia [x/y]: A 17/21; B 4/19 Time to normocalcaemia (d) [range]: A (3–7); B (2–7) Time to relapse: no data	Urinary Ca/Cr, urinary OHP/Cr were also measured	B
Sawyer, 1990[58]	RCT Open	25 pts All cancer types Entry CCa: >2.9 mmol/l Stratified by baseline serum Ca, renal function and tumour type	A – pamidronate 1 mg/bg (max. 75 mg) i.v. in 500 ml Nsaline over 4 h B – pamidronate 1 mg/kg (max. 75 mg) i.v. in 500 ml Nsaline over 24 h	Pts achieving normocalcaemia [x/y]: A, B: 21/23 Time to normocalcaemia (d) [mean]: A 4; B 5 Time to relapse: no data		C

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Vinholes, 1997[165]	RCT Double blind	31 pts All cancer types Entry CCa: >2.7 mmol/l	A – pamidronate 90 mg i.v. in 500 ml Nsaline over 4 h B – clodronate 1500 mg i.v. in 500 ml Nsaline over 4 h		Subset analyses of Purohit.[130] Looking at bone resorption markers therefore adds no additional data to primary study and **not** included in analyses	C
Warrell, 1991[63]	RCT Double blind	71 pts 39 M/32 F All cancer types Entry CCa: >3.0 mmol/l Stratified by tumour type and performance status I	A – gallium nitrate 200 mg/m^2 i.v. in 1 l 5% dextrose over 24 h, d 1–5 B – etidronate 7.5 mg/kg i.v. in 250 ml Nsaline over 4 h, d 1–5	Pts achieving normocalcaemia [x/y]: A 28/34; B 16/37 Time for mean gp CCa to reach normocalcaemia (d): A 6; B not reached Time to relapse[a] (d) [median (range)]: A 8 (0–54); B 0 (0–23)		A
Warrell, 1997[166]	RCT Double blind	108 pts Entry CCa: A/C >11.5 mg/dl (*2.88 mmol/l*); B/D >13.5 mg/dl (*3.38 mmol/l*)	A – alendronate 10 mg over 4 h i.v. B – alendronate 15 mg over 4 h i.v. C + D – etidronate 7.5 mg/kg/d i.v. for 3 d	Pts achieving normocalcaemia: A 75%; B 82%; C 33%; D 32% Time to normocalcaemia (d) [median]: A + B 3; C + D 4 Time to relapse (d) [median]: A + B 12; C + D 6	Meeting abstract	B

continued

TABLE 9 *Hypercalcaemia review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Wimalawansa, 1994[167]	RCT Open	34 pts All cancer types Entry CCa: >2.8 mmol/l	A – pamidronate 60 mg i.v. in 1 l Nsaline over 5–6 h every 2 weeks B – pamidronate 60 mg i.v. in 1 l Nsaline over 5–6 h every 3 weeks		Both groups received identical treatment for initial treatment of hypercalcaemia, therefore treatment of hypercalcaemia not randomised. Prevention study	B
Zysset, 1992[70]	RCT Double blind	23 pts 12 M/18 F All cancer types Entry CCa: >2.87 mmol/l	A – alendronate 10 mg i.v. in 250 ml Nsaline over 2 h B – alendronate 10 mg i.v. in 250 ml Nsaline over 24 h	Pts achieving normocalcaemia [x/y]: A 7/10; B 9/10 Time to normocalcaemia (d) [mean]: A 6; B 5 Time to relapse (d) [mean (SEM)]: A 31 (6); B 27 (5)	Urinary Ca, urinary OHP were also measured	B

Abbreviations: CCa, corrected calcium; d, days; NcAMP, nephrogenic cyclic adenosine monophosphate; Nsaline, normal saline; OHP, hydroxyprotein; pts, patients; SEM, standard error of the mean.

[a] Definition time to relapse: measured from day normocalcaemia reached.

[b] Definition time to relapse: measured from day of treatment with bisphosphonate.

TABLE 10 *Hypercalcaemia review: excluded studies*

Study	Reason for exclusion
Atula, 2001[168] [meeting abstract]	Randomisation between study centres unclear
Berenson, 1998[46]	Review which summarises findings of other RCTs
Canfield, 1987[169]	Review which summarises findings of other RCTs
Chapuy, 1980[170]	Patients were not rehydrated prior to measurement of serum calcium
Daragon 1991[171] [meeting abstract]	Serum calcium was not corrected for serum albumin
Delmas, 1982[172]	Not clear from paper whether patients were rehydrated prior to measurement of serum calcium
Jung, 1983[173]	Study looking at pharmacokinetics of bisphosphonates. Not relevant to review question
Major, 2001[131]	Patients were not rehydrated prior to measurement of serum calcium
Martinez, 1997[174]	Study looking at effect of bisphosphonates on vitamin D metabolites. Not relevant to review question
Mundy, 1983[175]	Study mixed patients with primary hyperparathyroidism and those with metastatic disease
Murray, 1990[176] [meeting abstract]	Not clear whether serum calcium corrected for albumin
Pecherstorfer, 2001[177] (additional data – personal communication)[176]	Patients were not rehydrated prior to measurement of serum calcium
Ralston, 1988[179]	Summary of 3 studies. One is a randomised controlled trial and has been included (Ralston, 1985[161]). The other two have insufficient information regarding methodology to be included as RCTs
Singer, 1991[180]	Patients were not rehydrated prior to measurement of serum calcium. Not all serum calcium measurements were corrected for serum albumin
Siris, 1983[181]	Study just looking at bone resorption markers. Not relevant to review question
Thurlimann, 1992[182]	Patients were not rehydrated prior to measurement of serum calcium
Witte, 1987[183]	Patients were not rehydrated prior to measurement of serum calcium

One paper gave additional information on results of bone resorption markers from a previously reported study.[165] Another paper looked at the prevention of hypercalcaemia using two versus three weekly infusions of pamidronate and thus the initial treatment dose was the same in both groups, leaving no control.[167] The paper by Rizzoli and colleagues contained results from two separate studies, which for methodological reasons were treated separately.[69] Therefore, data were used from 25 studies in the following analyses (*Figure 10*).

The studies were designed to answer one or more of the following:

- efficacy of an individual bisphosphonate
- comparison of different doses of a bisphosphonate
- comparison of different times of administration of a bisphosphonate.

Owing to heterogeneity of studies and the limited data for varying end-points, it was not possible statistically to combine data in a meta-analysis. *Tables 11*, *12* and *13* summarise the end results from included studies, for each of the three questions above. More detailed results are presented below.

Bisphosphonates were given intravenously in all studies included in this part of the review. Results are expressed as the percentage of patients (total number in group) achieving a given outcome. In the majority of studies allocation concealment was graded as 'unclear', except where stated otherwise.

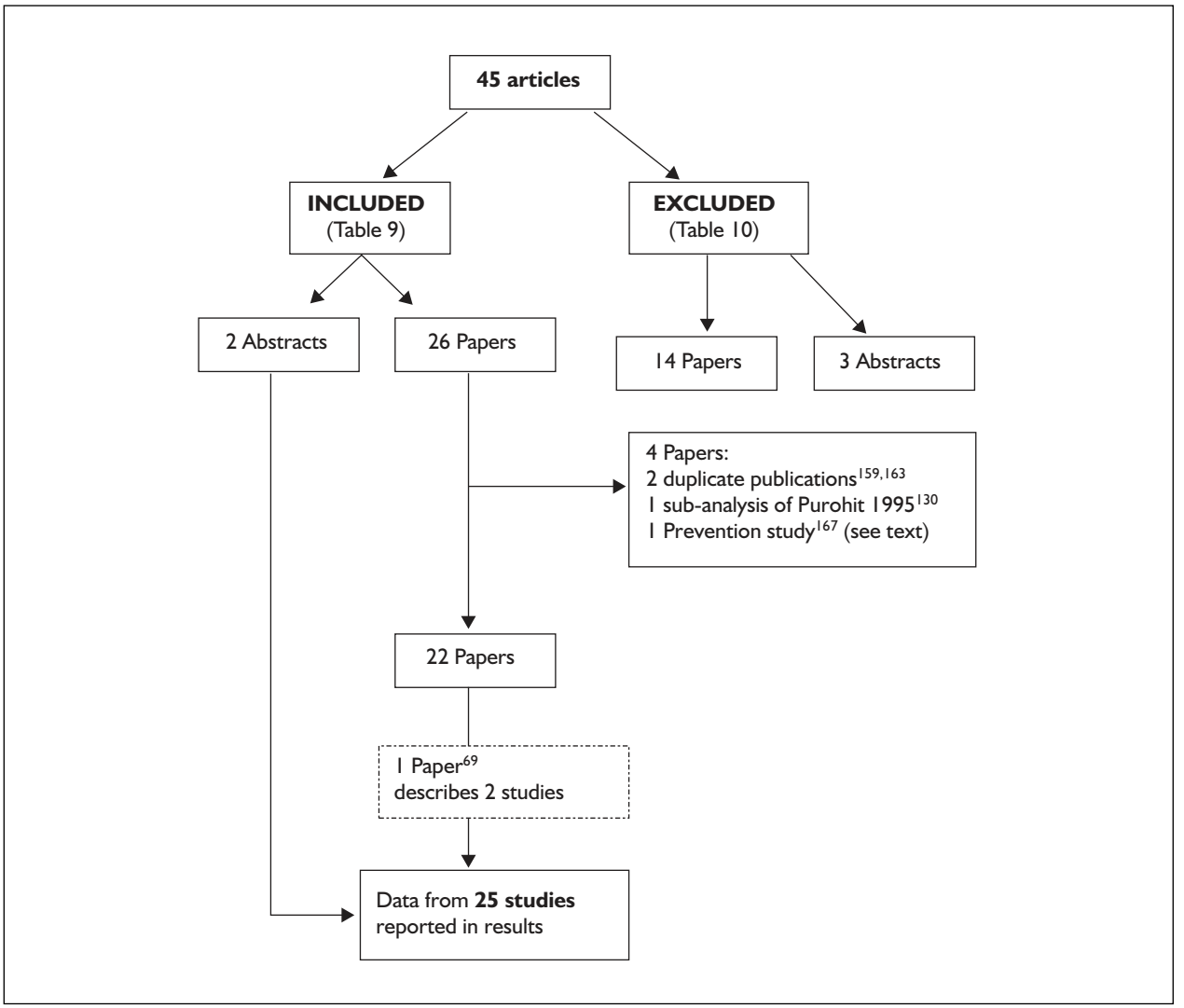


FIGURE 10 *Flow diagram: hypercalcaemia review*

Primary outcome: number of patients achieving normocalcaemia

Pamidronate

Efficacy

Gucalp and colleagues[57] showed that pamidronate 60 mg was better than control. In their study, 70% (46) versus 22% (23) of patients achieved normocalcaemia. Ostenstad and colleagues[56] found that pamidronate 30–90 mg [according to serum corrected calcium (CCa) at entry] was better than mithramycin 1.2 mg/kg, 100% (14) versus 27% (11) of patients reaching normocalcaemia. Bertheault-Cvitkovic and colleagues suggested that a single dose of 60 mg of pamidronate was less effective than five consecutive doses of 200 mg/m^2/day gallium nitrate; 73% versus 62% of patients reached normocalcaemia.[154] However, this was a meeting abstract and no level of significance was given, or total numbers of patients in each group.

Compared with other bisphosphonates, pamidronate 60 mg was more effective than etidronate 7.5 mg/kg on days 1–3, with 70% (30) versus 40% (35) patients becoming normocalcaemic, respectively.[67] An open study, using a lower dose of pamidronate, 30 mg, also found that pamidronate was more effective than etidronate.[162] In addition, this study showed that pamidronate 30 mg was more effective than clodronate 600 mg. In the pamidronate, etidronate and clodronate arms, 88% (16) versus 33% (16) versus 38% (16) of patients became normocalcaemic, respectively.[162] Purohit and colleagues performed a double-blind study,[130] in which the entry calcium was lower (2.7 mmol/l). They found higher doses of pamidronate (90 mg) and clodronate (1500 mg) to be equally effective with 100% (19) and 80% (20) patients reaching normocalcaemia.

TABLE 11 *Summary of efficacy of bisphosphonates in achieving normocalcaemia (for full details of study design and results see, Table 9)*

Comparison	Study	Bisphosphonate/i.v. dose	Comparison	*p*-Value[a]
Bisphosphonate vs no active drug	Gucalp, 1994[57]	Pamidronate 60 mg	Control	<0.0001
	Rotstein, 1992[164]	Clodronate 300 mg/d, 7 d	Placebo	<0.0003
	Hasling, 1986[158]	Etidronate 7.5 mg/kg/d, 3–5 d	Placebo	<0.022
Bisphosphonate vs recognised treatment	Ostenstad, 1992[56]	Pamidronate 30–60 mg	Mithramycin 1.2 mg/kg	<0.0001
	Bertheault-Cvitkovic, 1995[154]	Pamidronate 60 mg	Gallium nitrate 200 mg/m^2/d	Insufficient data
	Warrell, 1991[63]	Etidronate 7.5 mg/kg/d, 3 d	Gallium nitrate 200 mg/m^2/d	<0.001 (in favour gallium)
Bisphosphonate vs another bisphosphonate	Gucalp, 1992[67]	Pamidronate 60 mg	Etidronate 7.5 mg/kg/d, 3 d	<0.024
	Ralston, 1989[162]	Pamidronate 30 mg	Etidronate 7.5 mg/kg/d, 3 d	<0.003
	Ralston, 1989[162]	Pamidronate 30 mg	Clodronate 600 mg	<0.009
	Purohit, 1995[130]	Pamidronate 90 mg	Clodronate 1500 mg	<0.106
	Rizzoli, 1992[69]	Alendronate 7.5 mg	Clodronate 600 mg	<1.000
	Warrell, 1997[166]	Alendronate 10–15 mg	Etidronate 7.5 mg/kg/d, 3 d	<0.003

[a] *p*-Value: comparison of proportion of patients achieving normocalcaemia in each group calculated using Pearson's chi-squared, StatXact.[127]

TABLE 12 *Summary of dose finding studies for hypercalcaemia (for full details of study design and results, see Table 9)*

Bisphosphonate	Study	Doses compared (mg)	*p*-Value[a]
Pamidronate	Davis, 1989[54]	30 vs 60	<1.000
	Gallacher, 1991[157]	30 vs 90	<0.722
	Body, 1989[68]	30 vs 90	Both 100% effective
	Nussbaum, 1993[66]	30 vs 60 vs 90	<0.001
Ibandronate	Pecherstorfer, 1996[60]	0.6 vs 1.1 vs 2	<0.051
	Ralston, 1997[62]	2 vs 4 vs 6	<0.009
Alendronate	Rizzoli, 1992[69]	2.5 vs 5 vs 10 vs 15	<0.186
	Nussbaum, 1993[65]	2.5 vs 5 vs 10	<0.001
Incadronate	Fukumoto, 1994[156]	2.5 vs 5 vs 10	<0.077

[a] *p*-Value: comparison of proportion of patients achieving normocalcaemia in each group calculated using Pearson's chi-squared, StatXact.[127]

TABLE 13 *Summary of studies comparing administration of bisphosphonates using different dosing regimens (for full details of study design and results, see Table 9)*

Bisphosphonate	Study	Total dose	Dosing Regimen	*p*-Value[a]
Pamidronate	Dodwell, 1992[155]	60 mg	2 h vs 4 h vs 8 h vs 24 h	<0.770
	Sawyer, 1990[58]	1 mg/kg	4 h vs 24 h	Insufficient data
	Gucalp, 1994[57]	60 mg	4 h vs 24 h	<0.337
	Davis, 1989[54]	60 mg	30 mg 4 h days 1+2 vs 60 mg 8 h day 1	<1.000
	Morton, 1988[160]	60 mg	60 mg 8 h days 1 vs 30 mg 4h days 1+2 vs 15 mg 2 h days 1, 2, 3, 4	Insufficient data
	Body, 1989[68]	90 mg	1.5 mg/kg 24 h day 1 vs 0.5 mg/kg 2 h on days 1, 2, 3	<1.000
Alendronate	Nussbaum, 1993[65]	10 mg	2h vs 24h	Insufficient data
	Zysset, 1992[70]	10 mg	2h vs 24h	<0.582

[a] *p*-Value: comparison of proportion of patients achieving normocalcaemia in each group calculated using Pearson's chi-squared, StatXact.[127]

In summary, pamidronate works better than control (no treatment),[57] mithramycin,[56] etidronate (7.5 mg/kg)[67,162] and low-dose clodronate (600 mg).[162] However, pamidronate and higher dose clodronate (1500 mg) were equally effective.[130]

Dose studies
Davis and Heath showed no significant difference in efficacy between 30 and 60 mg of pamidronate;[54] 44% (9) versus 33% (8) of patients became normocalcaemic. This open study defined the entry calcium as CCa >3.0 mmol/l.

Two further studies showed no significant difference in 30 versus 90 mg pamidronate,[68,157] 100% (11) versus 100% (11) and 63% (16) versus 50% (16) of patients became normocalcaemic, respectively. Both were open studies, and their entry calcium was lower than the previous study (2.8 and 2.55 mmol/l, respectively) and therefore a higher percentage of patients reached normocalcaemia.

In contrast, we found one double-blind study with good allocation concealment.[66] The entry calcium was defined as CCa > 3.0 mmol/l. There was a significant difference between 30-, 60- and 90-mg doses; 40% (15) 61% (18) versus 100% (17) patients became normocalcaemic. A dose response was demonstrated, with the decline in CCa greater in the 90-mg versus the 30- or 60-mg group ($p < 0.001$).

In summary, four studies[54,66,68,157] compared different doses of pamidronate. Three open studies[54,68,157] showed no significant difference between 30, 60 and 90 mg of pamidronate, but the results should be interpreted with caution. One well-designed study[66] showed increasing efficacy with increasing doses of pamidronate.

Time studies
Six studies compared the time of administration of a given dose of pamidronate.[54,57,58,68,155,160] Dodwell and colleagues[155] looked at 50 patients, and found no difference between 60 mg of pamidronate given over 2, 4, 8 or 24 hours, with 89–100% of patients in each arm becoming normocalcaemic. Similarly, two studies[57,58] showed no significant difference between the same dose, given over 4 and 24 hours with 91% (23) and 61% (23) versus 78% (23) of patients becoming normocalcaemic, respectively. Two studies were open, with entry calcium >2.9 mmol/l,[58,155] and one was double blind with entry calcium >3.0 mmol/l.[57]

Two studies[54,160] compared 60 mg pamidronate administered either on day one or divided over days one and two, in a total of 48 patients. One of these studies[160] also divided the dose over days 1–4. Both studies were open and patients had an entry calcium of 3.0 and 2.8 mmol/l, respectively. They found no significant difference between groups, with 33–93% of patients becoming normocalcaemic. Body and colleagues[68] compared 1.5 mg/kg of pamidronate as a single infusion versus 0.5 mg/kg on three consecutive days. There were no differences between groups; 95% (22) of patients reached normocalcaemia.

In summary, six studies[54,57,58,68,155,160] compared a variety of time regimens to deliver pamidronate. None of the studies demonstrated any difference in the efficacy of pamidronate in relation to the time over which the drug was delivered to the patient

Other bisphosphonates
Efficacy
One double-blind study[158] found etidronate, 7.5 mg/kg for 3–5 days to be more effective than placebo, with 92% (12) versus 33% (6) of patients becoming normocalcaemic, respectively. Clodronate[164] 300 mg daily for up to 7 days was more effective than placebo, with 81% (21) versus 21% (19) became normocalcaemic.

Warrell and colleagues[63] found that gallium nitrate 200 mg/m^2/day was more effective than etidronate 7.5 mg/kg. This was a double-blind trial, with good allocation concealment; 82% (34) versus 43% (37) of patients became normocalcaemic, respectively.

One double-blind study[69] compared alendronate 7.5 mg with clodronate 600 mg. There was no difference between the two, with 40% (30) and 41% (34) of patients achieving normocalcaemia, respectively. A double-blind study by Warrell and colleagues[166] of 108 patients compared a single dose of 10–15 mg alendronate (depending on baseline CCa) with three consecutive doses of etidronate, 7.5 mg/kg/day. Alendronate was more effective, with 75–82% of patients reaching normocalcaemia compared with 33%.

In summary, these studies suggest that low-dose clodronate (300 mg) and etidronate perform better than placebo.[158] Etidronate is not as effective as gallium nitrate.[63] Two studies compared one bisphosphonate against another and found that alendronate was equal to

clodronate (600 mg)[69] and superior to etidronate.[166]

Dose studies
Two larger, double-blind studies compared different doses of ibandronate 0.6, 1.1, 2 mg[60] and 2, 4, 6 mg.[62] The first found 2 mg to be significantly better than 0.6 mg, and the second found both 4 and 6 mg to be significantly better than 2 mg. In the first study, entry calcium was >2.7 mmol/l and 67% (55) of the 2-mg group became normocalcaemic. In the second, entry calcium was >3.0 mmol/l and 50% (45) of the 2-mg group, 75.6% (44) of the 4-mg group and 77.5% (42) of the 6-mg group became normocalcaemic.

Different doses of alendronate were compared in two trials.[65,69] Normocalcaemia was achieved in 14% (7) and 15% (13) patients who received 2.5 mg, 40% (5) and 82% (11) who received 5 mg, 67% (6) and 60% (25) who received 10 mg and 90% (10) of patients who received 15 mg. The trial performed by Nussbaum and colleagues[65] had good allocation concealment and demonstrated a significant dose response. The trial by Rizzoli and colleagues[69] was a smaller open trial, and results did not reach statistical significance.

One study compared different doses (2.5, 5 and 10 mg) of incadronate (YM175);[156] 19% (26), 27% (30) and 48% (23) of patients became normocalcaemic respectively, demonstrating a trend towards a dose response ($p < 0.1$).

In summary, a dose response was suggested with three bisphosphonates. Ibandronate showed increasing efficacy with increasing doses from 0.6 to 4 mg, but doses of 4 and 6 mg were equivalent.[60,62] Alendronate showed an increasing dose response at 2.5, 5, 10 and 15 mg.[65] Similarly, incadronate suggests an increasing dose response at 2.5, 5 and 10 mg, although this trend was not statistically significant.

Time studies
Two studies found no difference in the time of administration of 10 mg aledronate (<4 versus 24 hours). Both were double-blind studies with good allocation concealment and patients had an entry calcium of >2.87 mmol/l. In one study[65] 60% (25) of patients became normocalcaemic and in the other study[70] 80% (20) became normocalcaemic.

In summary, the time over which these bisphosphonates are delivered makes no difference to the efficacy of the drug.

Secondary outcomes

Time to normocalcaemia

Nineteen of the included studies gave data for time to normocalcaemia (*Table 9*). In most cases, the mean/median time for patients who reached normocalcaemia is quoted, and in a few, the time for the mean group calcium to reach normocalcaemia is given. None of these studies detected a significant difference between different bisphosphonates or different doses/times of administration of any single bisphosphonate. The mean time to normocalcaemia when treated with any bisphosphonate ranged from 2 to 6 days.

Time to relapse

Nineteen of the included studies measured time to relapse (*Table 9*). In some studies this was measured as time from administration of the drug to recurrence of hypercalcaemia and in others as time from documented normocalcaemia to recurrence of hypercalcaemia. None of the studies differentiated between first or subsequent episodes of hypercalcaemia at entry, and the entry CCa varied between studies. In some cases those who failed to reach normocalcaemia are not included in the analyses, and in others a time to relapse of zero days is given to those failing to achieve normocalcaemia. Thus the disparity between studies means that individual results are not directly comparable.

Pamidronate
Gucalp and colleagues[57] compared 60 mg pamidronate with control in 69 patients. They found a median (range) time from normocalcaemia to relapse of 11 (1–62) and 6 (3–57) days, respectively.

Nussbaum and colleagues[66] compared three doses of pamidronate (30, 60 and 90 mg) in 50 patients. This study was double blind with good allocation concealment. Mean times from normocalcaemia to relapse were 9.2, 10.8, and 13.3 days, respectively; however these differences did not reach statistical significance.

Three studies reported finding a significant difference between treatment groups when comparing pamidronate with another bisphosphonate. The first[130] was a double-blind study that compared 90 mg of pamidronate with 1500 mg of clodronate in 41 patients. Time to relapse was defined as time from administration of the drug to recurrence of hypercalcaemia. Patients treated with pamidronate relapsed at a median (range) 28 (10–28+) days versus 14 (7–21) days

for clodronate ($p < 0.01$). The second[162] was an open study with 48 patients. Time to relapse in patients treated with pamidronate 30 mg was significantly longer than either clodronate 600 mg or etidronate 7.5 mg/kg: median (range), 29 (18–90) versus 12 (9–45), 10.5 (6–20) days respectively. The third[67] states that pamidronate 60 mg was better than etidronate 7.5 mg/kg: median (range) 7(1–31) versus 5(2–32) days. However, no level of significance is given and these data are unclear since initial complete and partial responders are pooled.

Six other studies using pamidronate were small (<50 patients) open studies.[54,56,68,155,157,160] None of these showed a significant difference between treatment groups. Median time to relapse for these studies ranged between 4 and 21 days.

Other bisphosphonates

Two double-blind studies[60,62] compared a range of doses of ibandronate (0.6–6 mg). The median time to relapse quoted ranged from 11–17 days.

Two double-blind studies,[65,70] with good allocation concealment, compared different dose and time schedules of alendronate. Zysset and colleagues[70] looked at 23 patients treated with 10 mg of alendronate administered over 2 or 24 hours. The mean time to relapse was 31 and 27 days, respectively. Nussbaum and colleagues[65] looked at 59 patients given a range of aledronate doses (2.5–15 mg) and found no difference between groups, the median time to relapse being 15 days. An abstract by Warrell and colleagues reports data from a double-blind study of 108 patients comparing 10–15 mg alendronate with 7.5 mg/kg/day etidronate;[166] median time to relapse was 12 versus 6 days.

Warrell and colleagues[63] compared 71 patients treated with gallium nitrate versus etidronate and found no difference between the two groups; less than 50% patients on etidronate reached normocalcaemia.

In summary, the studies are not comparable because the method of measuring time to relapse is not standardised. A number of studies were underpowered.

The three studies with robust methodology show that pamidronate gives a longer time to relapse than control,[57] clodronate[130,162] or etidronate.[162] One study showed a trend of increasing time to relapse with increasing doses of pamidronate, but this did not reach statistical significance.[66] None of the other different dosing regimens seem to affect time to relapse.[60,62,65,70]

One study showed no difference in time to relapse between etidronate and gallium nitrate.[63]

Serum and urinary bone resorption markers; serum PTH

A number of studies measured a variety of urinary bone resorption markers.[58,60,62,66,68–70,130,157,160,162,164] In all cases the urinary calcium/creatinine (Ca/Cr) ratio fell from baseline by days 3–8 following treatment with bisphosphonate. In some studies the urinary hydroxyproline/creatinine (OHP/Cr) ratio was also measured. The results are inconsistent but suggest a decrease with bisphosphonate treatment, although this does not always reach statistical significance. In all cases, only a subset of patients entered into the study have data for these markers. One paper[162] compared pamidronate, clodronate and etidronate and demonstrated that pamidronate was the most effective in reducing urinary Ca/Cr ($p < 0.05$ and $p < 0.01$, respectively).

Four papers measured serum PTH in some of their patients,[62,66,156,157] however, the data collected were limited. Gallacher and colleagues[157] subdivided patients according to whether they had normal or elevated nephrogenic cyclic adenosine monophosphate (NcAMP) at baseline. Increased NcAMP, with low serum PTH, suggests elevated renal action of PTHrP. They found that 100% (11) patients with normal NcAMP achieved normocalcaemia whereas only 41% (17) patients with elevated NcAMP achieved normocalcaemia.

Toxicity

Pamidronate

A summary of the reported side-effects from included studies using pamidronate is displayed in *Table 14*. Fever was the commonest side effect. Several asymptomatic biochemical abnormalities were recorded, the most frequent being hypocalcaemia and hypophosphataemia. In most cases no action was required to correct the biochemical abnormality. Infrequently recorded side-effects included infusion site reactions, xanthopsia and nausea and vomiting.

Other bisphosphonates

A summary of the reported side-effects from included studies using other bisphosphonates (clodronate, etidronate, alendronate, ibandronate, incadronate) is displayed in *Table 15*. The toxicity findings were very similar to those for pamidronate, with fever being the commonest

TABLE 14 *Hypercalcaemia review: side-effects reported from included studies using pamidronate*

Study	No. of patients in study on pamidronate	Side-effects: (% of patients)		
		Biochemical	Fever	Other
Body, 1989[68]	33	$\downarrow Ca^{2+}$ 39	9	
Davis, 1989[54]	27	$\downarrow Ca^{2+}$ 7 $\downarrow K^{+}$ 19	7	
Dodwell, 1992[155]	50	$\downarrow Ca^{2+}$ 8	8	
Gallacher, 1991[157]	32		13	
Gucalp, 1994[57]	46	$\downarrow Ca^{2+}$ 2 $\downarrow PO_4^{2-}$ 30	22	9 site reaction
Gucalp, 1992[67]	30	$\downarrow Ca^{2+}$ 17 $\downarrow PO_4^{2-}$ 7	17	7 site reaction
Morton, 1988[160]	30	$\downarrow Ca^{2+}$ 13	17	3 xanthopsia
Nussbaum, 1993[65]	50	$\downarrow Ca^{2+}$ 6 $\downarrow K^{+}$ 54 $\downarrow PO_4^{2-}$ 40[a]	20	
Purohit, 1995[130]	20		15	
Sawyer, 1990[58]	25			12 nausea and vomiting

[a] 24 low at baseline.

TABLE 15 *Hypercalcaemia review: side-effects reported from included studies using other bisphosphonates*

Study	Drug	No. of patients in study on drug	Side-effects: percentage of patients		
			Biochemical	Fever	Other
Rotstein, 1992[164]	Clodronate	25	$\downarrow Ca^{2+}$ 16 $\downarrow K^{+}$ 32 $\downarrow Mg^{2+}$ 16		4 diarrhoea
Gucalp, 1992[67]	Etidronate	35	$\downarrow Ca^{2+}$ 6	9	3 altered taste
Hasling, 1986[158]	Etidronate	12	$\downarrow Ca^{2+}$ 50		
Warrell, 1991[63]	Etidronate	37	$\downarrow PO_4^{2-}$ 11 $\uparrow Cr$ 11		
Nussbaum, 1993[65]	Alendronate	59	$\downarrow Ca^{2+}$ 14 $\uparrow$LFTs 14		3 pain at infusion site
Zysset, 1992[70]	Alendronate	23	$\downarrow Ca^{2+}$ 17	35	
Ralston, 1997[62]	Ibandronate	131	$\downarrow Ca^{2+}$ 5	21	
Pecherstorfer, 1996[60]	Ibandronate	174	$\downarrow Ca^{2+}$ 2 $\uparrow$LFTs <1 $\downarrow$Plts <1	6	<1 nausea <1 oesophagitis
Fukumoto, 1994[156]	Incadronate	79	$\uparrow$LFTs 2	19	<1 nausea <1 headache <1 skin eruption

side-effect, followed by asymptomatic biochemical abnormalities. Infrequently documented side-effects included diarrhoea, altered taste, site reactions, nausea, oesophagitis, headache and skin eruption.

Summary

Pamidronate

The efficacy of pamidronate in achieving normocalcaemia is better than control,[57] etidronate,[67,162] mithramycin,[57] and low-dose clodronate (600 mg).[162] Pamidronate 90 mg was found to be as effective as clodronate given at a higher dose (1500 mg).[130] The best evidence suggests that pamidronate demonstrates a dose response from 30 to 60 to 90 mg.[66]

Pamidronate demonstrated a longer time with relapse when compared with clodronate[130,162] and etidronate.[162] The median time to relapse is approximately double that of the drugs with which it is compared. One study showed a trend towards increasing time to relapse with increasing dose of pamidronate.[66]

Other bisphosphonates

When considering the efficacy of bisphosphonates in achieving normocalcaemia, clodronate and etidronate performed better than placebo.[158,164] Two studies compared one bisphosphonate against another and found that alendronate had similar efficacy to clodronate[69] but was superior to etidronate.[166] A dose response was demonstrated with ibandronate up to 4 mg,[60,62] and alendronate up to 15 mg.[65] A dose study using incadronate showed a trend towards a dose response.[156]

All bisphosphonates

Differences in scheduling of bisphosphonates, such as 4 hours versus 24 hours, or dividing the dose over consecutive days, made no difference to the efficacy of any of the drugs.[54,57,58,68,155,160]

The mean time to normocalcaemia for all of the bisphosphonates in the studies ranged from 2 to 6 days.

Bisphosphonates are well tolerated with low incidence of side-effects.

Skeletal morbidity review

Forty-seven papers, describing 30 studies, fulfilled the inclusion criteria for this review, and they are described in *Table 16*. Details of 48 excluded studies are given in *Table 17*. Where multiple papers describe parts of the same study, these are grouped together and included as a single item in all analyses.

It was not possible to include data from all 30 studies in the meta-analysis (*Figure 11*), and those not included are discussed in more detail below. Data extracted from 18 studies were eligible for inclusion in the meta-analyses. For three of these studies, data could only be used for time to the first SRE. Three studies compared two bisphosphonates; 12 studies compared a bisphosphonate with placebo or control.

Studies presented data in one of two ways:

- Proportions of patients with given outcome in treatment and control groups, at fixed time points (e.g. 6,12,18, 24 months). [Individual data for different time points are used in the sub-analysis 'Time to normocalcaemia' (p. 44). In all other analyses, data measured at the latest time point were used.]
- Proportions of patients with a given outcome in treatment and control groups, and median length of time on study. [These data are not used in the subanalysis 'Time to normocalcaemia' (p. 44).

Where forest plots are given, studies are ordered by length of study, starting with the longest study followed by studies in decreasing time order.

Primary analyses

Reduction in skeletal morbidity end-points

Bisphosphonates, compared with placebo, significantly reduced the OR for vertebral, non-vertebral and combined fractures, RT and hypercalcaemia. Reductions in orthopaedic surgery and spinal cord compression were not significant. The following pooled OR (95% CI) were calculated: vertebral fractures 0.692 (0.570 to 0.840), $p < 0.0001$; non-vertebral fractures 0.653 (0.540 to 0.791), $p < 0.0001$; combined fractures 0.653 (0.547 to 0.780), $p < 0.0001$; RT 0.674 (0.573 to 0.791), $p < 0.0001$; hypercalcaemia 0.544 (0.364 to 0.814), $p = 0.003$; orthopaedic surgery 0.698 (0.463 to 1.051), $p = 0.086$; and SCC 0.714 (0.470 to 1.083), $p = 0.113$. *Figure 12(a–g)* shows the forest plots for each individual skeletal morbidity end-point, and *Table 18* summarises the pooled ORs for each outcome, together with the number of trials and patients included in the analyses.

TABLE 16 *Skeletal morbidity review: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Ausili-Cefaro, 1999[184]	RCT Open	(No pts recruited) Breast cancer >70 years old Eligible for 2nd-line hormone therapy or chemo Painful bony metastases with no previous radiotherapy	A – pamidronate 90 mg i.v. 2 h in 250 ml Nsaline × 9 (+ RT) B – control group RT	Protocol only – no results Pathological # SCC Hypercalcaemia		B
Belch, 1991[185]	RCT Double blind	166 pts 104 M/62 F Multiple myeloma No previous chemo (steroids or RT allowed)	A – etidronate 5–20 mg/kg/day p.o. to death or withdrawal B – placebo chemo (melphalan, prednisolone)	Median time on study: 44.4 months Pathological # (C#): A 20/92; B 21/74; $p < 0.368$ Hypercalcaemia: A 23/92; B 14/74; $p < 0.453$ Survival: NS	Also measured vertebral index (NS) Bone pain Progression of bony metastases	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Berenson, 1996[138] Berenson, 1998[46] Berenson, 1998[186]	RCT Double blind	392 pts 217 M/137 F Multiple myeloma Durie–Salmon stage III, at least 1 osteolytic lesion Stratified by 1st-line or 2nd+-line chemo	A – pamidronate 90 mg i.v. 4 h 500 ml 5% dextrose every 4 weeks × 9 B – placebo 500 ml 5% dextrose i.v. 4 h	Outcomes measured at: 3, 6, 9, 12, 15, 18, 21 months Pathological # (C#, V#): (C#) 21 months A 62/196; B 66/181; $p < 0.330$ (V#) 21 months A 31/196; B 49/181; $p < 0.008$ RT: 21 months A 50/196; B 61/181; $p < 0.090$ SCC: NS Ortho procedure: NS Hypercalcaemia: 21 months A 18/196; B 16/181; $p < 1.000$ Time to 1st SRE: $p < 0.016$ (log-rank test) Survival [median]: N,. 26 vs 24 months, $p < 0.377$	ECOG 9 months Quality of life (Spitzer index) 9 months Pain and analgesic use 9 months	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Berenson, 2001[187] Berenson, 2001[188]	RCT Double blind	280 pts 67 M/213 F Breast cancer and multiple myeloma All pts at least 1 osteolytic lesion Myeloma pts: previous SRE or failed 1st line chemo	A – zoledronate 0.4 mg i.v. 5 minutes in 50 ml Nsaline every 4 weeks B – zoledronate 2 mg i.v. 5 minutes in 50 ml Nsaline every 4 weeks C – zoledronate 4 mg i.v. 5 minutes in 50 ml Nsaline every 4 weeks D – pamidronate 90 mg i.v. 2 h in 250 ml Nsaline every 4 weeks	Outcomes measured at: 10 months Pathological # (C#): A 19/68; B 16/72; C 14/67; D 15/73; $p < 0.723$ RT: A 16/68; B 14/72; C 14/67; D 13/73; $p < 0.857$ SCC: A 1/68; B 0/72; C 2/67; D 2/73; $p < 0.545$ Ortho procedure: A 5/68; B 2/72; C 2/67; D 3/73; $p < 0.547$ Hypercalcaemia: A 5/68; B 2/72; C 0/67; D 2/73; $p < 0.103$ Time to 1st SRE: $p < 0.05$ D vs A Survival: not recorded	ECOG Pain and analgesic scores Bone mineral density	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Brincker, 1998[189]	RCT Double blind	304 pts 160 M/140 F Multiple myeloma Stratified by: randomised to interferon, not randomised to interferon, not eligible for interferon	A – pamidronate 300 mg/d p.o. to withdrawal, death or end of trial B – placebo chemo (melphalan, prednisolone)	Median (range) time on study 544 (4–1702) vs 551 (2–1659) d Outcomes: number of events Pathological # (NV#, V#): (N#) A 28/152; B 40/148; $p < 0.098$ (V#) A 84/152; B 99/148; $p < 0.044$ RT: A 45/152; B 62/148; $p < 0.030$ Ortho procedure: A 5/152; B 11/148; $p < 0.129$ Hypercalcaemia: A 11/152; B 22/148; $p < 0.042$ Time to 1st SRE [median]: NS, 440 vs 414 d; $p < 0.33$ Survival [median]: NS, 1183 vs 1063 d; $p < 0.9$	Progression of bony metastases Pain and analgesic use Height	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Conte, 1994[190] Conte, 1996[191] Ford, 1996[192]	RCT Open	295 (F) pts Breast cancer Osteolytic or mixed metastases Progressive disease at entry and eligible for 1st line chemo. No restriction on amount of previous hormonal therapy	A – pamidronate 45 mg i.v. 1 h in 250 ml Nsaline every 3 weeks until progressive disease B – control no treatment	Median follow-up 249 vs 168 d Outcomes: number of events Pathological # (C#): A 34/143; B 32/152; $p < 0.580$ RT: A 66/143; B 83/152; $p < 0.163$ Ortho procedure: A 4/143; B 8/152; $p < 0.380$ Hypercalcaemia: A 8/143; B 13/152; $p < 0.371$ Time to 1st SRE [median]: NS, 533 vs 490 d Survival [median]: NS, 592 vs 642 d	Performance status (WHO) Pain and analgesic use Time to progressive bony disease	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Daragon, 1993[193]	RCT Double blind	104 pts 44 M/50 M Multiple myeloma Durie–Salmon stage II or III	A – etidronate 10 mg/kg/d oral for 4 months B – placebo	Outcomes measured at: 4 months Pathological # (C#): A 2/49; B 1/45; $p < 1.000$ Hypercalcaemia: NS Survival [median]: NS, 43 vs 46 months	Also measured vertebral index (NS) Progression of bony metastases Pain and analgesic use Performance status (Karnofsky) Not included in meta-analysis as <6 months	B
Delmas, 1982[194]	RCT Double blind	13 pts Multiple myeloma Excluded if >10 courses chemo on entry	A – clodronate 1.6 g/d oral for 18 months B – placebo	Outcomes measured at: 6–18 months (4 pts 6 months, 5 pts 12 months, 4 pts 18 months) Pathological # (NV#, V#): (NV#) A 0/7; B 3/6; $p < 0.103$ (V#) A 1/7; B 4/6; $p < 0.070$ Hypercalcaemia: A 1/7; B 0/6; $p < 1.000$	Progression of bony disease Bone pain Bone histomorphometry	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Diel, 1999[195]	RCT Open	361 pts Breast cancer	A – clodronate 2.4 g/d oral B –clodronate 900 mg i.v. every 3 weeks C – pamidronate 60 mg i.v. every 3 weeks	Median time on study: 18 months Pathological # (V#): A 11/112; B 19/103; C 16/103; $p < 0.183$	Meeting abstract Bone pain	B
Elomaa, 1983[196] Elomaa, 1987[197] Elomaa, 1988[198]	RCT Double blind	34 (F) pts Breast cancer Pts with bone metastases that had progressed on hormone therapy and chemo	A – clodronate 1.6–3.2 g/d oral for 3–9 months B – placebo	Outcomes measured at: 12 months Pathological # (N#): A 1/17; B 4/17; $p < 0.335$ RT: A 3/17; B 10/17; $p < 0.032$ Hypercalcaemia: A 1/17; B 4/17; $p < 0.335$ Survival: NS, 14/17 vs 9/17 patients alive at 12 months	Analgesic use Disease progression (new bone metastases) (261) reports data on 1-y follow-up period post-treatment	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Glover, 1994[199]	RCT Open	61 (F) pts Breast cancer Painful bony metastases Excluded pts with history of fracture, SCC, hypercalcaemia within 3 months	A – pamidronate 30 mg i.v. 4 h every 2 weeks × 6 B – pamidronate 60 mg i.v. 4 h every 4 weeks × 3 C – pamidronate 60 mg i.v. 4 h every 2 weeks × 6 D – pamidronate 90 mg i.v. 6 h every 4 weeks × 3	Outcome measured at: 3 months Pathological # (C#): NS, two events Radiotherapy: NS, one event Hypercalcaemia: No events	Pain and analgesic use Progression of bony disease Not comparable to other studies – all patients on pamidronate at different dosing regimens for 3/12	B
Gomez-Pastrana, 1996[200]	RCT Double blind	28 (F) pts Breast cancer	A – clodronate 300 mg/d i.v. for 5 d followed by 1600 mg/d oral for 6 months B – placebo	Outcomes measured at: 6 months Pathological # Hypercalcaemia	Pain study No data on skeletal morbidity outcomes in text	A
Harris, 1993[201]	RCT Open	72 (F) pts Breast cancer	A – pamidronate 30 mg i.v. every 3 weeks for 3 months B – control group	Outcomes measured at: 3 months Pathological # (C#): A 3/36; B 3/36; $p < 1.000$ RT: A 10/36; B 15/36; $p < 0.322$ SCC: A 2/36; B 2/36; $p < 1.000$ Hypercalcaemia: A 2/36; B 0/36; $p < 0.493$ Survival: NS	Meeting abstract Data not included in meta-analysis as <6 months	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Heim, 1995[202] Clemens, 1993[203]	RCT Open	170 pts 77 M/80 F Multiple myeloma Stratified by Durie–Salmon stage and presence of osteolytic metastases	A – clodronate 1.6 mg/d oral for 12 months B – control group	Outcomes measured: Pathological # Hypercalcaemia	Pain and analgesic use Progression of bony disease Data not extractable in format for this review, therefore results not included	A
Holten-Verzantvoort 1993[204] Holten-Verzantvoort, 1987[205] Cleton, 1989[206] Holten-Verzantvoort, 1991[207]	RCT Open	205 (F) pts Breast cancer	A – pamidronate 300–600 mg/d oral to death or withdrawal B – control No treatment	Median (range) time in study: 18 (1–66) vs 21 (1–53) months Pathological # (C#): A 6/81; B 10/80; $p < 0.305$ RT: A 22/81; B 43/80; $p < 0.001$ Ortho procedure: A 4/81; 8/80; $p < 0.247$ Hypercalcaemia: A 4/81; B 17/80; $p < 0.002$ Time to 1st SRE [median]: NS, 14 vs 11 months, $p < 0.10$ Survival [median]: NS, 25 vs 24 months, $p < 0.98$	There were problems with study methodology and changes of dose in treatment group due to GI toxicity therefore data from this study not included in meta-analysis	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Hortobagyi, 1998[208] Hortobagyi, 1996[209]	RCT Double blind	382 (F) pts Breast cancer Stage IV breast cancer, on chemo, at least 1 osteolytic metastasis >1 cm diameter Stratified by ECOG	A – pamidronate 90 mg i.v. 2 h in 250 ml 5% dextrose every 3–4 weeks × 24 B – placebo 250 ml 5% dextrose i.v. 2 h every 3–4 weeks × 24	Outcome measured at: 3, 6, 9, 12, 15, 18, 21, 24 months Pathological # (NV#, V#, C#): (NV#) 24 months A 42/185; B 74/197; $p < 0.002$ (V#) 24 months A 47/185; B 51/197; $p < 1.000$ (C#) 24 months A 67/185; B 96/197; $p < 0.017$ RT: 24 months A 51/185; B 88/197; $p < 0.001$ SCC: 24 months A 4/185; B 7/197; $p < 0.545$ Ortho procedure: 24 months A 9/185; B 24/197; $p < 0.017$ Hypercalcaemia: 24 months A 13/185; B 30/197; $p < 0.017$ Time to 1st SRE [median]: 13.9 vs 7 months; $p < 0.001$ Survival [median]: NS, 14.8 vs 14.0 months; $p < 0.82$	ECOG QUAL Bone pain and analgesic use Radiological response in bone	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Hultborn, 1999[136] Hultborn, 1996[210]	RCT Double blind	404 (F) pts Breast cancer Pts entered at diagnosis of skeletal spread or on change of systemic Tx due to disease progression	A – pamidronate 60 mg i.v. 1 h in 500 ml Nsaline every 3–4 weeks × 24 B – placebo 500 ml Nsaline i.v. 1 h every 3–4 weeks × 24	Median time on study: 12 vs 11.5 months Pathological # (NV#): A 30/201; B 31/203; $p < 1.000$ RT: A 54/201; B 65/203; $p < 0.276$ SCC: A 5/201; B 6/203; $p < 1.000$ Ortho procedure: A 12/201; B 17/203; $p < 0.441$ Hypercalcaemia: A 5/201; B 17/203; $p < 0.014$ Time to 1st SRE [median]: 11.8 vs 8.4 months $p < 0.006$ Survival [median]: NS, 18.3 months	Performance status (WHO) Pain and analgesic score	A
Kraj, 2000[211] Kraj, 2000[212]	RCT Open	46 pts 26 M/20 F Multiple myeloma All receiving chemo	A – pamidronate 60 mg i.v. over 4 h every 4 weeks B – control Standard chemo	Outcomes measured at: 12, 21 months Pathological #, Radiotherapy, SCC: individual data not given Hypercalcaemia: NS Survival [median]: NS, 20 vs 19 months; $p < 0.45$	ECOG Pain and analgesic use Progression of bone metastases Mean SRE/yr (#, RT, SCC) Significant, $p < 0.013$	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Kristensen, 1999[213]	RCT Open	100 (F) pts Breast cancer Untreated or 1st-line treatment for <6 months	A – clodronate 1.6-3.2 g/d oral for 24 months B – control group	Only recorded 1st SRE for each patient Pathological # (NV#, V#, C#): (C#) A 3/49; B 13/51; $p < 0.013$ RT: A 8/49; B 4/51; $p < 0.230$ Hypercalcaemia: A 3/49; B 4/51; $p < 1.000$ Time to 1st SRE: $p < 0.015$ Survival [median (95% CI)]: NS, 18.3 (16.3 to 20.3) vs 18.0 (15.7 to 20.2) months	WHO performance status Quality of life – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Hospital Anxiety and Depression Scale (HADS) Pain and analgesic use Time to progressive bony metastases Time to 1st SRE and survival included in analyses	B
Lahtinen, 1992[214] Laasko, 1994[215]	RCT Double blind	350 pts 166 M/170 F Multiple myeloma Pts newly diagnosed, commenced on melphalan–prednisolone	A – clodronate 2.4 g/d oral for 24 months B – placebo	Outcome measured at: 24 months Pathological # (NV#,V#): (NV#) A 26/108; B22/95; $p < 1.000$ (V#) A 33/108; B 38/95; $p < 0.185$ Hypercalcaemia: NS	203/350 pts had baseline and follow-up X-rays, therefore data not included in meta-analysis Pain and analgesic use Progression of bony lesion (209) is a subset analysis looking at cost data	B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Lipton, 2000[135] Theriault, 1996[216]	RCT Double blind	754 (F) pts Breast cancer			Pooled results from Hortobagyi (1998)[208] and Theriault (1999)[139] Trials considered individually as shown	A
Martoni, 1991[217]	RCT Double blind for 1 week then open	38 (F) pts Breast cancer Progressive disease Stratified by type of bone metastases (osteolytic, osteoblastic, mixed), systemic treatment (chemo vs hormonal)	A – clodronate 300 mg/d i.v. 3 h in 250 ml Nsaline for 1 week, followed by 100 mg/d i.m. for 3 weeks followed by 100 mg/alt days i.m. for 2 months B – control 250 ml/day Nsaline 3 h i.v. for 1 week followed by standard care	Outcomes measured at: 3 months Pathological # (C#): A 0/17; B 2/16; $p < 0.103$ Hypercalcaemia: A 1/17; B 3/16; $p < 0.335$	Pain and analgesic use Number of bony metastases Data not included in meta-analysis as <6 months	B
McCloskey, 1998[137]	RCT Double blind	614 pts 318 M/218 F Multiple myeloma Excluded if previous chemo	A – clodronate 1.6 g/d oral for 24 months B – placebo	Median time on study 33.6 months Pathological # (NV#, V#): (NV#) A 15/264; B 29/272; $p < 0.041$ (V#) A 41/264; B 60/272; $p < 0.060$ RT: NS Hypercalcaemia: A 39/264; B 48/272; $p < 0.413$ Time to 1st SRE: NS Survival [median (95% CI)]: NS, $p < 0.74$, OR 0.97, 2.9 (2.4 to 3.4) vs 2.8 (2.5 to 3.5) y	Performance status QUAL Pain Height	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Paterson, 1993[218]	RCT Double blind	173 (F) pts Breast cancer	A – clodronate 1.6 g/d oral for 36 months B – placebo	Median time on study: 14 vs 14.5 months Pathological # (NV#, V#): (NV#) A 19/85; B 24/88; $p < 0.486$ (V#) A 38/85; B 46/88; $p < 0.363$ RT: A 34/85; B 42/88; $p < 0.359$ Hypercalcaemia: A 20/85; B 31/88; $p < 0.099$ Time to 1st SRE: NS Survival: 35% vs 14% patients alive at 2 y		A
Robertson, 1995[219]	RCT Double blind	55 pts All cancer types Bone pain secondary to progressive bony disease, failed 1st-line antitumour therapy	A – clodronate 1.6 g/d oral B – placebo	Median (range) time on study: 8 (0.7–17.3) months Pathological # (C#): A 4/27; B 2/28; $p < 0.422$ SCC: A 0/27; B 3/28; $p < 0.236$ Hypercalcaemia: A 0/27; B 2/28; $p < 0.491$ Survival [median (range)]: NS, 240 (25–518) vs 240 (20–486) d		B

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Theriault, 1999[139]	RCT Double blind	372 (F) pts Breast cancer Pts on stable hormonal therapy 2 osteolytic metastases or 1 osteolytic (>1 cm diameter) + extraskeletal metastases Stratified by ECOG score	A – pamidronate 90 mg i.v. 2 h in 250 ml 5% dextrose every 3–4 weeks × 24 B – placebo 250 ml 5% dextrose i.v. 2 h every 3–4 weeks × 24	Outcome measures at: 6, 12, 18, 24 months Pathological # (NV#, V#, C#): (NV#) 24 mths A 66/182; B 75/189; $p < 0.522$ (V#) 24 months A 50/182; B 58/189; $p < 0.568$ (C#) 24 mths A 81/182; B 102/189; $p < 0.078$ RT: 24 months A 56/182; B 76/189; $p < 0.065$ SCC: 24 months A 7/182; B 6/189; $p < 0.783$ Ortho procedure: 24 months A 13/182; B 20/189; $p < 0.277$ Hypercalcaemia: 24 months A 8/182; B 19/189; $p < 0.045$ Time to 1st SRE [median]: 10.4 vs 6.9 months; $p < 0.049$ Survival [median (95% CI)]: 23.2 (19.3 to 25.8) vs 23.5 (18.7 to 27.4); $p < 0.685$	ECOG QUAL Bone pain and analgesic use	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Tubiana-Hulin, 2001[220] Hulin, 1994[221]	RCT Double blind	144 (F) pts Breast cancer	A – clodronate 1.6 g/d p.o. for 12 months B – placebo	Only recorded 1st SRE for each patient Pathological # (C#): A 8/73; B 7/71; $p < 1.000$ RT: A 7/73; B 13/71; $p < 0.153$ Hypercalcaemia: A 0/73; B 4/71; $p < 0.057$ Time to 1st SRE [median (range)]: 18.1 (1.2–12.2) vs 6 (1.1–12.2) months; $p < 0.05$	Time to progressive bony metastases Time to 1st SRE included in analyses	B
Unpublished data A[a] Rosen, 2002[222]	RCT Double blind	773 pts Solid tumours excluding breast/prostate	A- zoledronate 8/4 mg i.v. every 3 weeks for 9 months B – zoledronate 4 mg i.v. every 3 weeks for 9 months C – placebo	Outcome measured at: 9 months Pathological # (NV#, V#, C#): (NV#) A 21/266; B 26/257; C 29/250 (V#) A 13/266;B 20/257; C 30/250 (C#) A 31/266; B 40/257; C 53/250 RT: A 70/266; B 69/257; C 81/250 SCC: A 7/266; B 7/257; C 10/250 Ortho procedure: A 14/266; B 11/257; C 9/250 Hypercalcaemia: A 2/266; B 0/257; C 8/250 Time to 1st SRE [median]: A 7.2; B 7.56; C 5.1 months	Performance status QUAL Bone pain and analgesic use	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Unpublished data B[b] Rosen, 2001[223]	RCT trial Double blind	1648 pts Breast cancer and multiple myeloma	A – zoledronate 8/4 mg i.v. every 3–4 weeks for 12 months B – zoledronate 4 mg i.v. every 3–4 weeks for 12 months C – pamidronate 90 mg i.v. every 3–4 weeks for 12 months	Outcome measured at: 13 months Pathological # (NV#, V#, C#): (NV#) A 135/524; B 145/561; C 148/555 (V#) A 84/524; B 109/561; C 108/555 (C#) A 179/524; B 200/561; C 203/555 RT: A 112/524; B 85/561; C 112/555 SCC: A 12/524; B 11/561; C 16/555 Ortho procedure: A 15/524; B 21/561; C 31/555 Hypercalcaemia: A 5/524; B 7/561; C 12/555 Time to 1st SRE [median]: A 11.54; B 12.26; C 11.70 months; NS	Performance status QUAL Bone pain and analgesic use	A

continued

TABLE 16 *Skeletal morbidity review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Unpublished data C[c] Saad, 2002[224]	RCT Double blind	643 pts Prostate cancer	A – zoledronate 8/4 mg i.v. in 50–100 ml Nsaline over 5–15 minutes every 3 weeks for 15 months B – zoledronate 4 mg i.v. in 50–100 ml Nsaline over 5–15 mins every 3 weeks for 15 months C – placebo	Outcome measured at: 15 months Pathological # (NV#, V#, C#): (NV#) A 22/221; B 22/214; C 33/208 (V#) A 17/221; B 8/214; C 17/208 (C#) A 33/221; B 28/214; C 46/208 RT: A 53/221; B 49/214; C 61/208 SCC: A 11/221; B 9/214; C 14/208 Ortho procedure: A 6/221; B 5/214; C 7/208 Hypercalcaemia: A 0/221; B 0/214; C 2/208 Time to 1st SRE [median]: A 11.93; B not reached; C 10.55 months	Performance status QUAL Bone pain and analgesic use	A

Abbreviations: chemo, chemotherapy; CI, confidence interval; NS, not significant; ortho, orthopaedic surgery; OR, odds ratios; #, fractures.
[a] Murphy R, Novartis Pharmaceuticals: personal communication, 2001.
[b] Murphy R, Novartis Pharmaceuticals: personal communication, 2001.
[c] Murphy R, Novartis Pharmaceuticals: personal communication, 2001.

TABLE 17 *Skeletal morbidity review: excluded studies*

Study	Reason for exclusion
Abdulkadyrov, 1993[225]	Russian paper. On translation, did not fulfil criteria for a RCT
Abildgaard, 1998[226]	Histomorphometric study of a subset of patients from Brinker *et al.*[189]
Adami, 1989[227]	Pain study; did not measure any of the primary outcome measures of this review
Arican, 1999[228]	Pain study; did not measure any of the primary outcome measures of this review
Attardo-Parrinello, 1987[229]	Not an RCT
Ausgabe, 1997[230]	German paper. This review mentions recruitment for an RCT of hormone-resistant prostate cancer, patients randomised to one of three arms: epirubicin, clodronate, or epirubicin + clodronate. Study centre contacted for update on progress. No reply received
Body, 1999[231]	Meeting abstract. Outcomes measured as events/year. Further data not available from authors
Cascinu, 1998[232]	Pain study; did not measure any of the primary outcome measures of this review
Coleman, 1997[233]	Pain study; did not measure any of the primary outcome measures of this review
Coleman, 1998[234]	Pain study; did not measure any of the primary outcome measures of this review
Coleman, 1999[235]	Study measuring bone resorption markers. No measurement of any of the primary outcome measures of this review
Conte, 1991[236]	Study measuring bone resorption markers. No measurement of any of the primary outcome measures of this review
Costa, 1993[237]	Portuguese paper. On translation, did not fulfil criteria for an RCT
Dearnaley, 2001[238]	Meeting abstract. Did not report any of the primary outcome measures of this review
Diel, 1999[239]	Meeting abstract. Pain and quality of life study; did not measure any of the primary outcome measures of this review
Elomaa, 1992[240]	Pain study; did not measure any of the primary outcome measures of this review
Elomaa, 1996[241]	Bone resorption marker study; did not measure any of the primary outcome measures of this review
Ernst, 1992[242]	Pain study; did not measure any of the primary outcome measures of this review
Ernst, 1997[243]	Pain study; did not measure any of the primary outcome measures of this review
Fernandez-Conde, 1997[244]	Histomorphometric study; did not measure any of the primary outcome measures of this review
Gessner, 2000[245]	Economic study; costs of terminal care for patients with osteolytic bone disease treated with pamidronate
Jung, 1983[173]	Calcium kinetics study; did not measure any of the primary outcome measures of this review
Koeberle, 1999[246]	Pain study; did not measure any of the primary outcome measures of this review
Kylmala, 1993[247]	Pain study; did not measure any of the primary outcome measures of this review
Kylmala, 1997[248]	Pain study; did not measure any of the primary outcome measures of this review
Lipton, 1994[249]	Pain study; did not measure any of the primary outcome measures of this review
Lipton, 1996[250]	Not an RCT
Lipton, 1998[251]	Not an RCT
Merlini, 1990[252]	Not an RCT
Moiseenko, 1998[253]	Russian paper. On translation, pain study, no measurement of any of the primary outcome measures of this review
O'Rourke, 1995[254]	Pain study; did not measure any of the primary outcome measures of this review
Peest, 1996[255]	Primary outcome, measurement of bone resorption markers. Did not measure any of the primary outcome measures of this review
Piga, 1998[256]	Pain study; did not measure any of the primary outcome measures of this review
Poliakov, 1999[257]	Russian paper. On translation, not an RCT, pain study, no measurement of any of the primary outcome measures of this review
Ringenberg, 1987[258]	Maintenance of normocalcaemia study; included mixed haematological malignancies
Schiller, 1987[259]	Maintenance of normocalcaemia study

continued

TABLE 17 *Skeletal morbidity review: excluded studies (cont'd)*

Slaby, 1997[260]	Czech paper. Measured bone resorption markers
Smith, 1989[261]	Pain study; did not measure any of the primary outcome measures of this review
Strang, 1997[262]	Pain study; did not measure any of the primary outcome measures of this review
Taube, 1993[263]	Histomorphometric study; did not measure any of the primary outcome measure of this review
Taube, 1994[264]	Histomorphometric study; did not measure any of the primary outcome measures of this review
Terpos, 2000[265]	Pain study; did not measure any of the primary outcome measures of this review
Thurlimann, 1994[266]	Not an RCT
Vinholes, 1996[267]	Not an RCT
Vinholes, 1997[268]	Pain study; did not measure any of the primary outcome measures of this review
Vinholes, 1999[269]	Measured bone resorption markers; did not measure any of the primary outcome measures of this review
Zhang, 1997[270]	Chinese paper. On translation, pain study, no measurement of any of the primary outcome measures of this review
Zhang, 1999[271]	Chinese paper. On translation, pain study, no measurement of any of the primary outcome measures of this review

Time to first skeletal event

Ten of the studies included in the analysis recorded time to first skeletal related event for patients treated with bisphosphonate versus control[137–139,208,210,213,218,220] (Murphy R, Novartis Pharmaceuticals: two personal communications, 2001). It was not possible statistically to combine data from different studies. Eight studies showed a significant increase in time to first SRE for the bisphosphonate-treated group; four used intravenous pamidronate,[138,139,208,210] two intravenous zoledronate (Murphy R, Novartis Pharmaceuticals: two personal communications, 2001), and two oral clodronate.[213,220] In contrast, two studies using oral clodronate[137,218] did not show a significant difference in time to first SRE. One study comparing zoledronate with pamidronate showed no difference in time to first SRE between the two drugs (Murphy R, Novartis Pharmaceuticals: personal communication, 2001). *Table 16* records data given by individual studies.

Secondary analyses

Reduction in skeletal morbidity with bisphosphonates over time

Figure 13 is a high–low plot, showing the OR (95% CI) for non-vertebral fractures, RT, orthopaedic surgery and hypercalcaemia at fixed time points. The time points represented are ≥ 6–<12 months, ≥ 12–<18 months, ≥ 18–<24 months and ≥ 24 months. *Table 19* summarises the pooled ORs for each outcome at each time point, together with the number of trials and patients included in the analyses.

This sub-analysis contains fewer data than the primary analysis. Bisphosphonates, compared with placebo, significantly reduced the OR for RT at all time points. For non-vertebral fractures, the OR showed a trend towards significance, remaining fairly stable over time. For orthopaedic surgery, there is a clear trend towards a reduction in the OR, with narrowing of the CI with time. The reduction in the OR reaches significance at 24 months. For hypercalcaemia, the reduction in the OR is highly significant at 6–12 months, significant at 12–18 months and highly significant, with a narrow CI, at 24 months. At 18–24 months there is a trend towards a reduction in the OR, with widening of the CI.

Reduction in skeletal morbidity with bisphosphonates: disease groups

Breast cancer

Five trials of patients with breast cancer (n = 1364) had data for one or more skeletal morbidity end-point. Bisphosphonates, compared with placebo, significantly reduced the OR for non-vertebral fractures, combined fractures, RT, orthopaedic surgery and hypercalcaemia, but not for SCC or vertebral fractures. This contrasts with the primary analysis, which showed a significant decrease in vertebral fractures when all disease groups were combined. In addition, the reduction in need for orthopaedic surgery is significant in this sub-analysis (p = 0.009). *Table 20* summarises the pooled ORs for each outcome, together with the number of trials and patients included in the analyses.

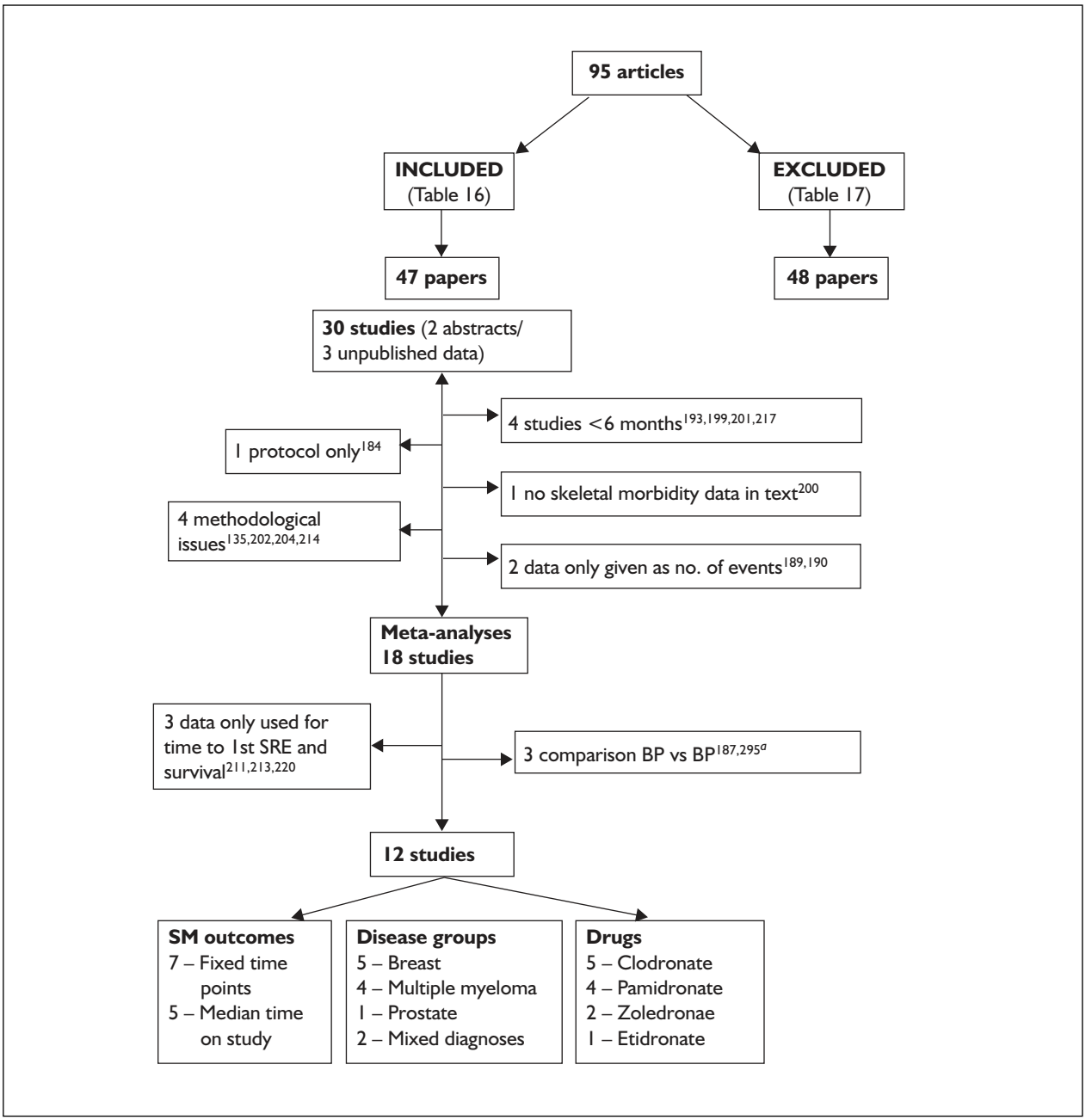


FIGURE 11 *Flow diagram: skeletal morbidity review.* [a] *Also Murphy R, Navartis Pharmaceuticals personal communication, 2001.*

Myeloma

Three trials of patients with multiple myeloma (n = 1079) had data for one or more skeletal morbidity end-points. Unfortunately, data could only be pooled for vertebral fractures, combined fractures and hypercalcaemia. *Table 20* summarises the pooled ORs for each outcome, together with the number of trials and patients included in the analyses. Bisphosphonates, compared with placebo, significantly reduced the OR for vertebral fractures, but not for combined, although only 543 patients contributed to the latter analysis. The pooled OR (95% CI) for hypercalcaemia from the three studies is 0.968 (0.687 to 1.365), $p < 0.852$. This contrasts with the primary analysis, which showed a significant decrease in hypercalcaemia when all disease groups were combined. *Figures 14* and *15* show forest plots for vertebral fractures and hypercalcaemia, respectively, in the breast and myeloma sub-groups.

Prostate cancer

One trial (643 patients) compared zoledronate with placebo in patients with prostate cancer (Murphy R, Novartis Pharmaceuticals: personal communication, 2001). There was a significant

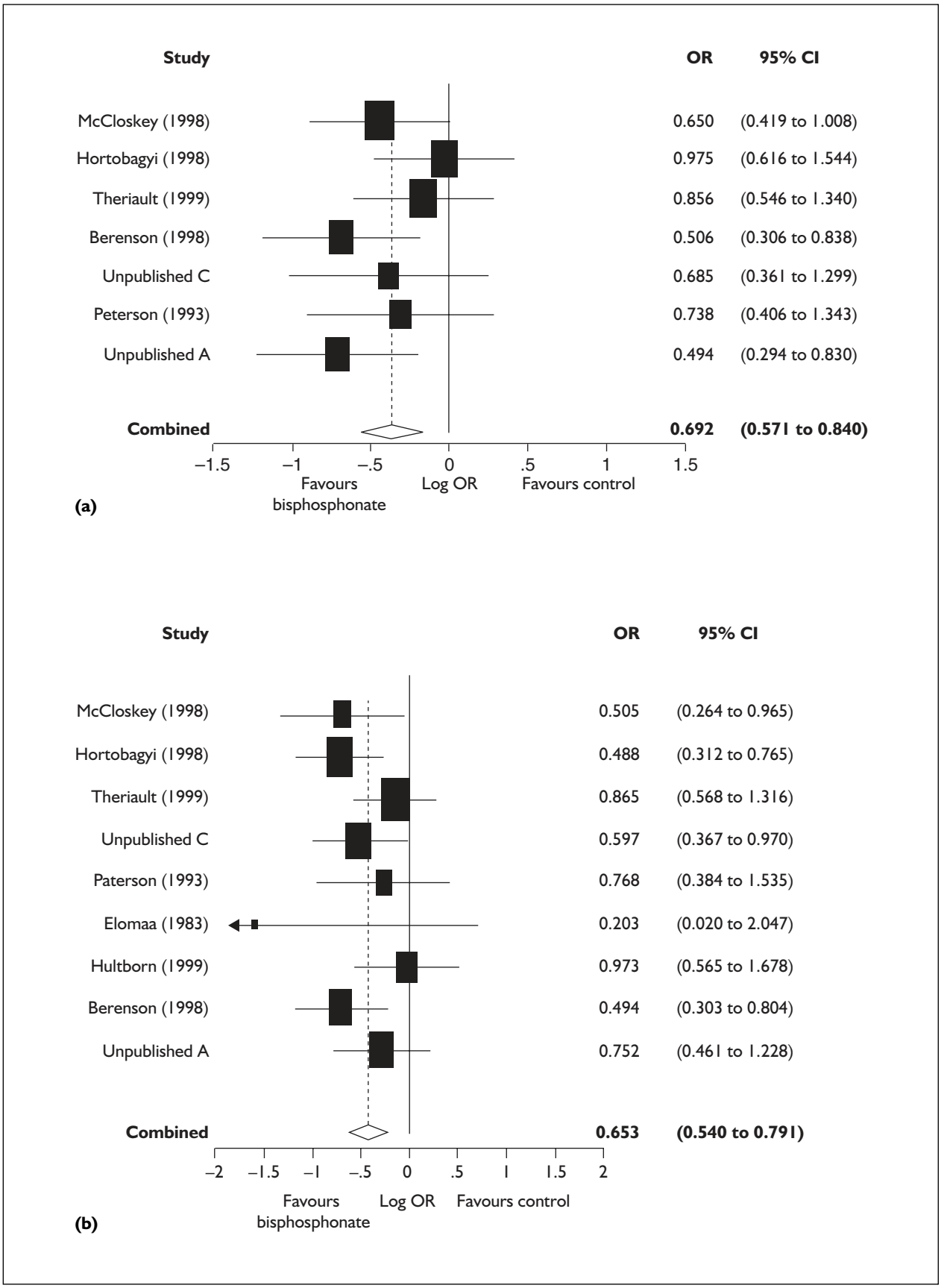
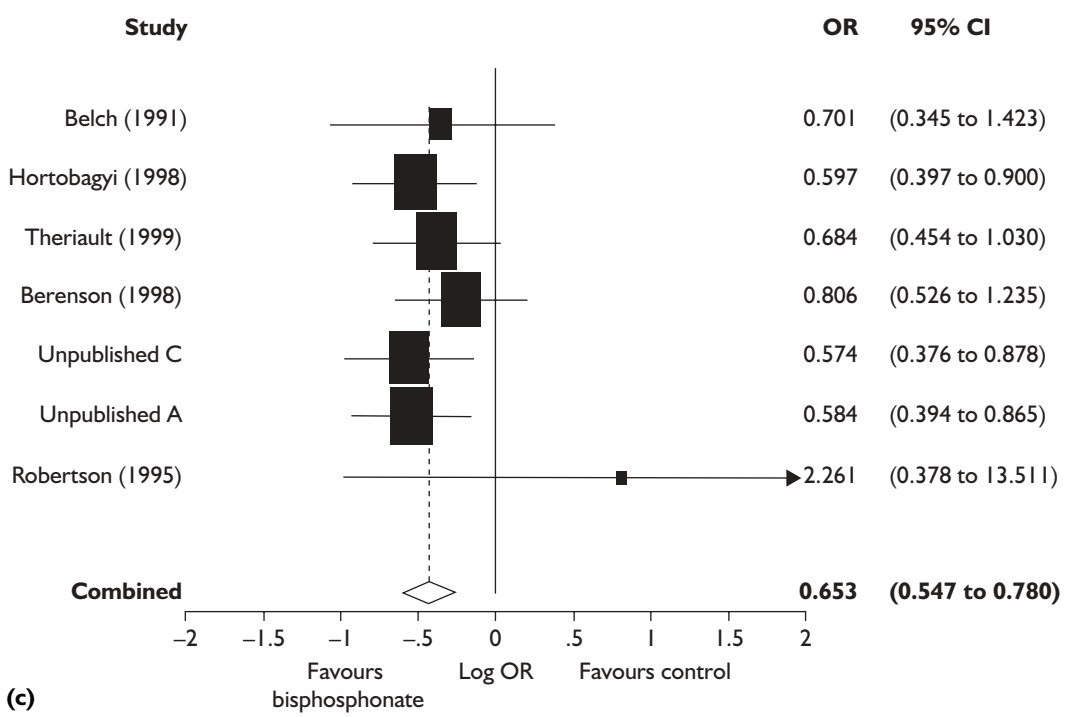


FIGURE 12 *Forest plots of skeletal morbidity end-points: (a) vertebral fractures (total no. of patients = 4567); (b) non-vertebral fractures (4015); (c) combined fractures (3644); (d) RT (4469); (e) SCC (2628); (f) orthopaedic surgery (3885); (g) hypercalcaemia (3894). [Studies ordered by length of study, pooled OR (95% CI).]*



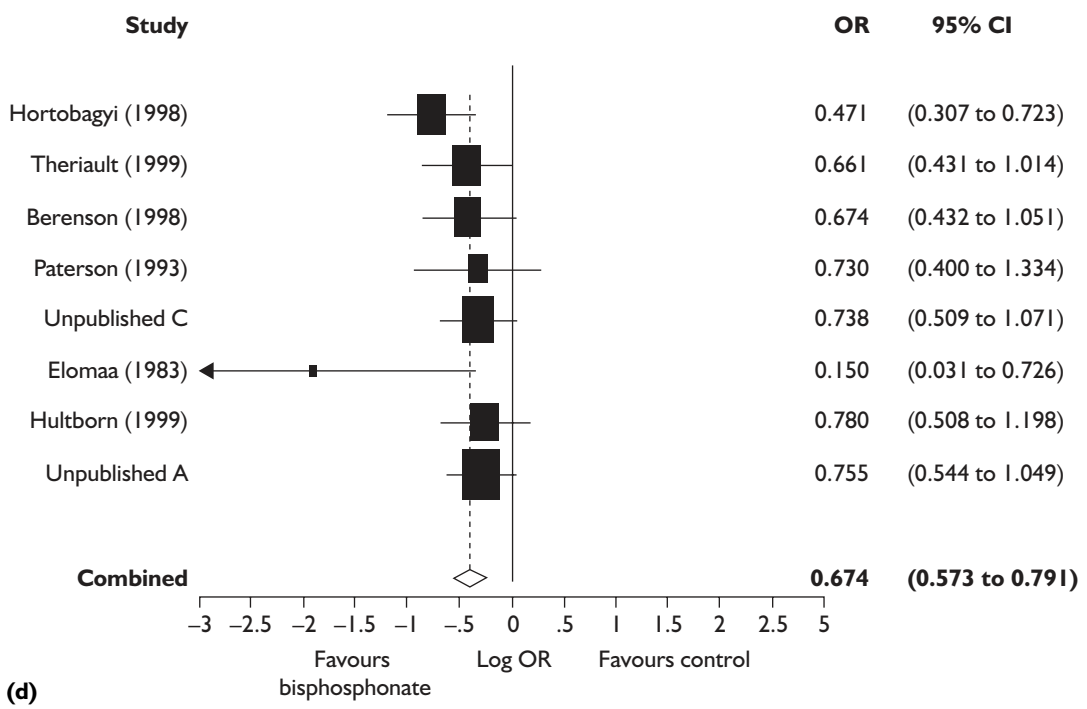


FIGURE 12 *(cont'd) Forest plots of skeletal morbidity end-points: (a) vertebral fractures (total no. of patients = 4567); (b) non-vertebral fractures (4015); (c) combined fractures (3644); (d) RT (4469); (e) SCC (2628); (f) orthopaedic surgery (3885); (g) hypercalcaemia (3894). [Studies ordered by length of study, pooled OR (95% CI).]*

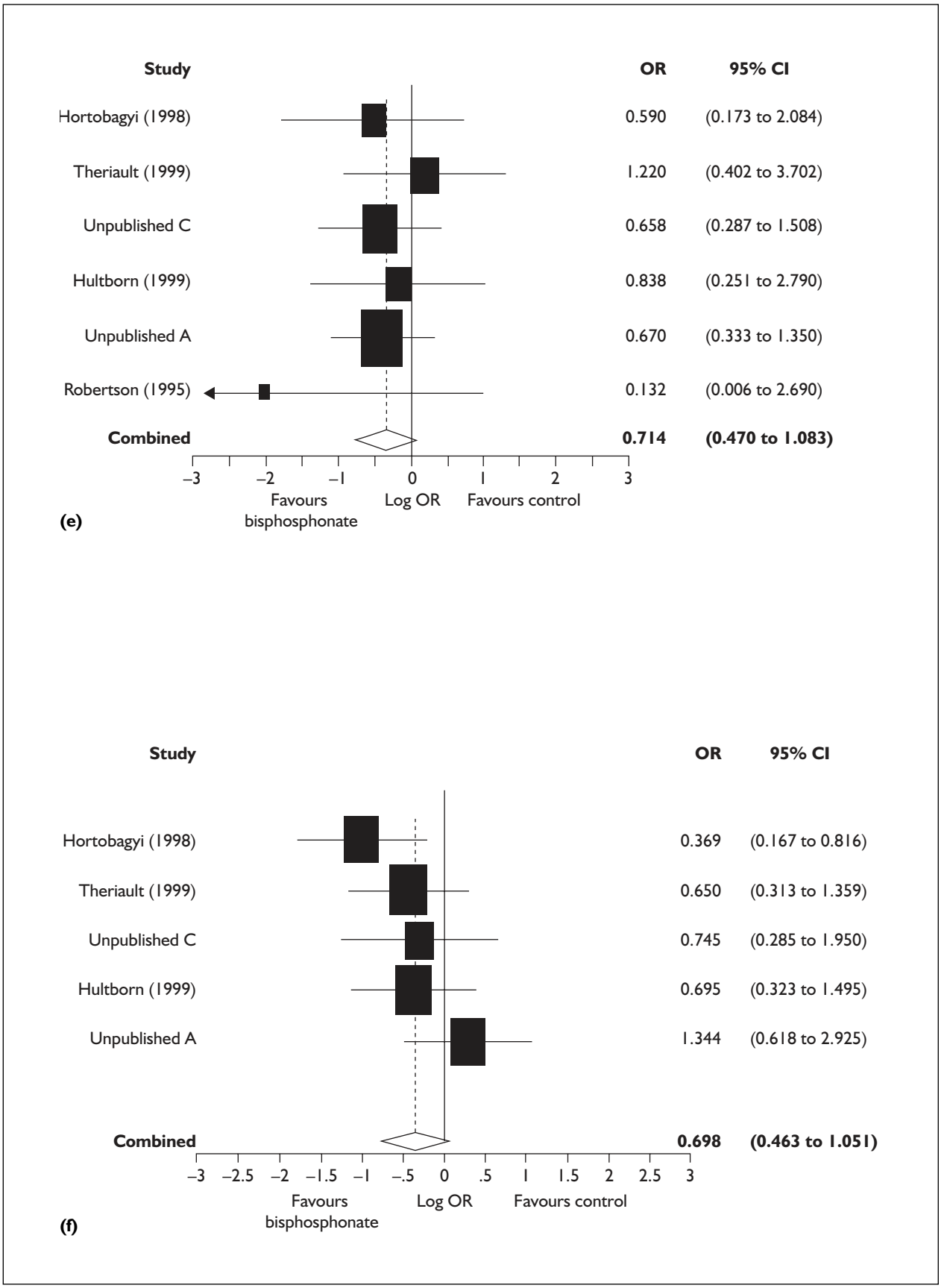


FIGURE 12 *(cont'd) Forest plots of skeletal morbidity end-points: (a) vertebral fractures (total no. of patients = 4567); (b) non-vertebral fractures (4015); (c) combined fractures (3644); (d) RT (4469); (e) SCC (2628); (f) orthopaedic surgery (3885); (g) hypercalcaemia (3894). [Studies ordered by length of study, pooled OR (95% CI).]*

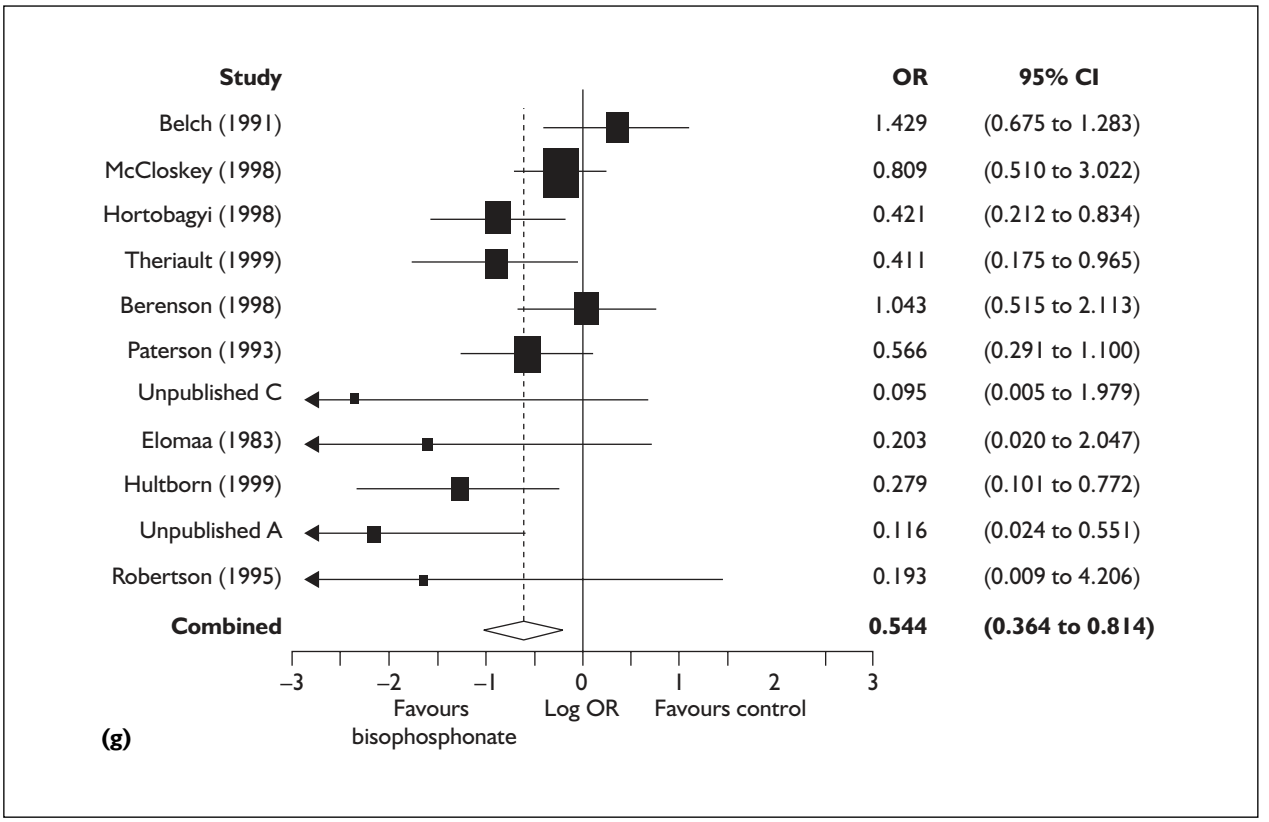


FIGURE 12 *(cont'd) Forest plots of skeletal morbidity end-points: (a) vertebral fractures (total no. of patients = 4567); (b) non-vertebral fractures (4015); (c) combined fractures (3644); (d) RT (4469); (e) SCC (2628); (f) orthopaedic surgery (3885); (g) hypercalcaemia (3894). [Studies ordered by length of study, pooled OR (95% CI).]*

TABLE 18 *Summary statistics of skeletal morbidity end-points, from pooled analysis [Figure 12(a–g)]*

	OR	Lower CI	Upper CI	No. of studies	No. of patients	*p*-Value
Vertebral fractures	0.692	0.571	0.840	7	3238	0.0001
Non-vertebral fractures	0.653	0.540	0.791	9	3376	0.0001
Combined fractures	0.653	0.547	0.780	7	2758	0.0001
RT	0.674	0.573	0.791	8	3140	0.0001
SCC	0.714	0.470	1.083	6	2628	0.113
Orthopaedic surgery	0.698	0.463	1.051	5	2556	0.086
Hypercalcaemia	0.544	0.364	0.814	11	3894	0.003

reduction in combined fractures in the 4-mg treatment group and a trend towards significance for RT.

Reduction in skeletal morbidity with bisphosphonates: drugs

Table 21 summarises the pooled ORs for each skeletal morbidity outcome, together with the numbers of trials and patients included in this sub-analysis.

Pamidronate (intravenous)

Four trials (1534 patients) compared pamidronate with control or placebo.[138,139,208,210] Bisphosphonates significantly reduced the OR for non-vertebral, vertebral and combined fractures, RT, orthopaedic surgery and hypercalcaemia, but not for SCC.

Clodronate (oral)

Five trials (811 patients) compared oral clodronate

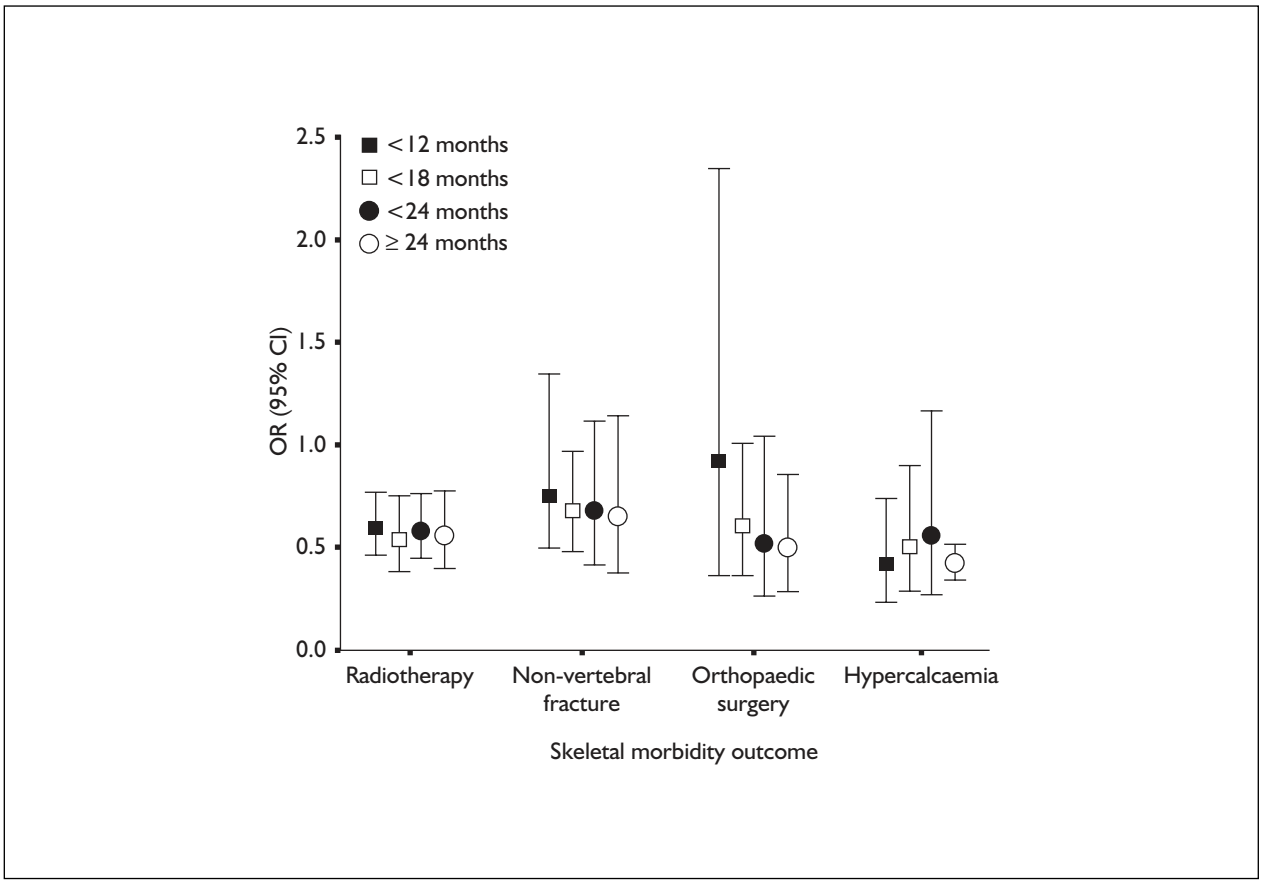


FIGURE 13 *High–low plot of OR for CIs for skeletal morbidity end-points with time*

TABLE 19 *Summary statistics from pooled analysis at fixed time points for RT, non-vertebral fractures, orthopaedic surgery and hypercalcaemia*

	Time point (months)	OR	Lower CI	Upper CI	No. of studies	No. of patients	*p*-Value
Radiotherapy	≥ 6–<12	0.600	0.468	0.770	4	1903	0.0001
	≥ 12–<18	0.536	0.380	0.757	5	1807	0.0001
	≥ 18–<24	0.580	0.443	0.760	3	1130	0.0001
	≥ 24	0.558	0.401	0.777	2	753	0.001
Non-vertebral fractures	≥ 6–<12	0.753	0.498	1.139	4	1903	0.179
	≥ 12–<18	0.678	0.477	0.96	4	1430	0.031
	≥ 18–<24	0.681	0.414	1.118	2	753	0.129
	≥ 24	0.650	0.371	1.139	2	753	0.132
Orthopaedic surgery	≥ 6–<12	0.922	0.362	2.351	3	1526	0.866
	≥ 12–<18	0.607	0.365	1.009	3	1396	0.054
	≥ 18–<24	0.524	0.262	1.046	2	753	0.067
	≥ 24	0.493	0.283	0.859	2	753	0.013
Hypercalcaemia	≥ 6–<12	0.417	0.235	0.741	5	1916	0.003
	≥ 12–<18	0.503	0.282	0.898	5	1807	0.02
	≥ 18–<24	0.557	0.266	1.165	3	1130	0.12
	≥ 24	0.418	0.342	0.511	2	753	0.0001

TABLE 20 *Summary statistics from sub-group analysis of skeletal morbidity end-points in breast and myeloma disease groups*

Disease group	Skeletal morbidity outcome	OR	Lower CI	Upper CI	No. of studies	No. of patients	*p*-Value
Breast	Vertebral fractures	0.870	0.656	1.154	3	926	0.334
	Non-vertebral fractures	0.720	0.520	0.996	5	1364	0.047
	Combined fractures	0.640	0.479	0.854	2	753	0.002
	RT	0.611	0.454	0.822	5	1364	0.001
	SCC	0.874	0.441	1.728	3	1157	0.697
	Orthopaedic surgery	0.558	0.360	0.867	3	1157	0.009
	Hypercalcaemia	0.427	0.292	0.625	5	1364	0.0001
Myeloma	Vertebral fractures	0.583	0.419	0.812	2	913	0.001
	Combined fractures	0.776	0.539	1.120	2	543	0.175
	Hypercalcaemia	0.968	0.687	1.365	3	1079	0.852

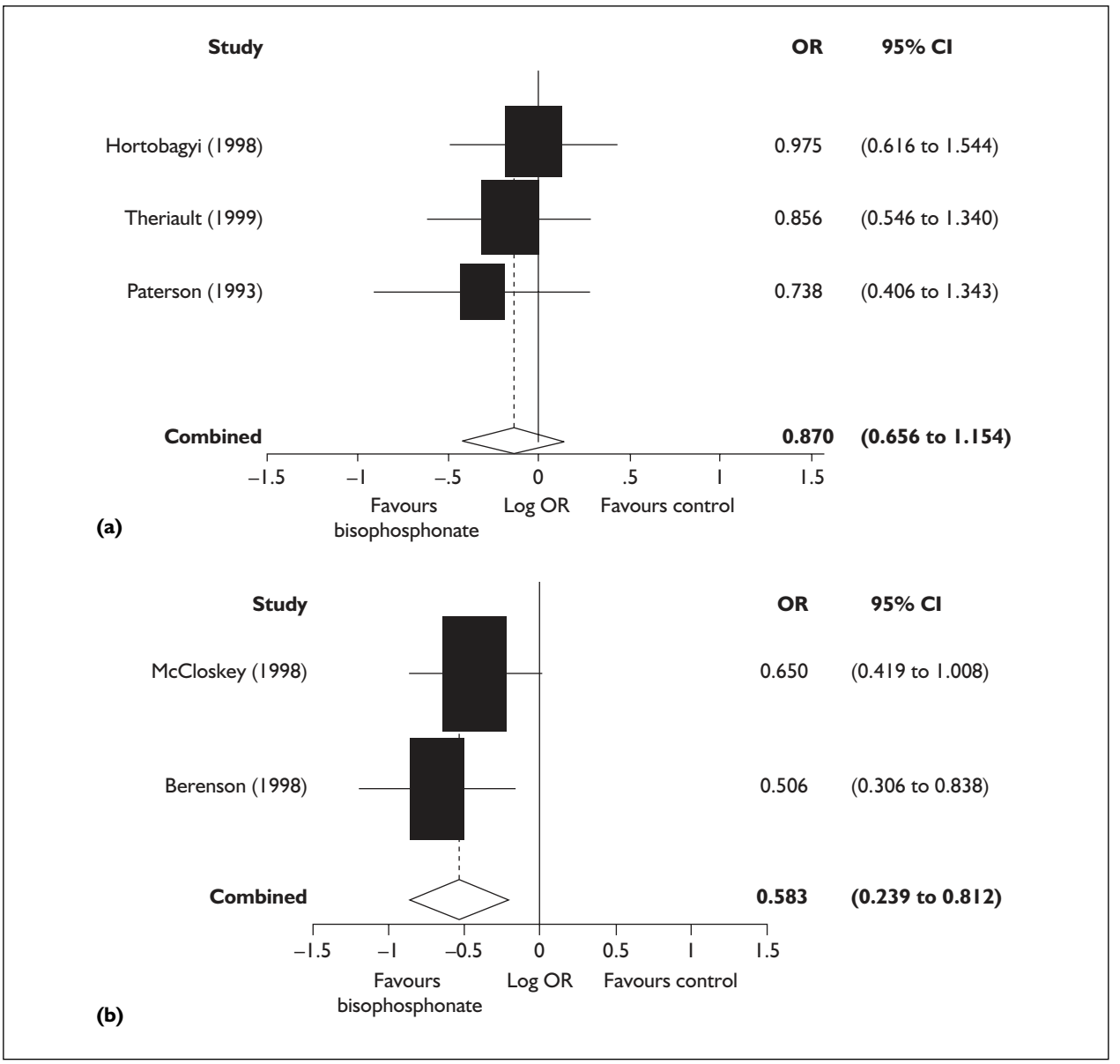
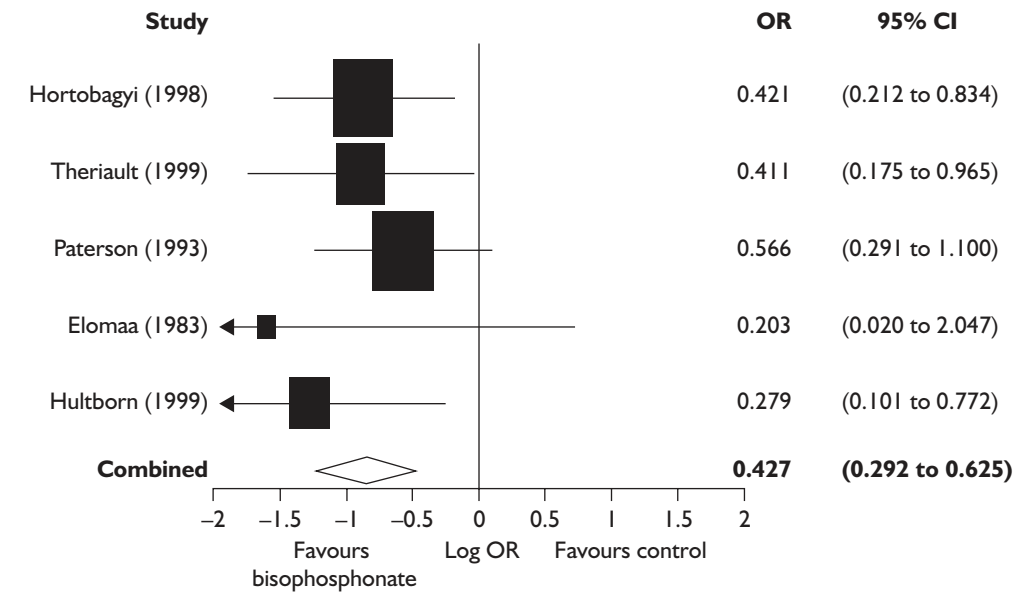
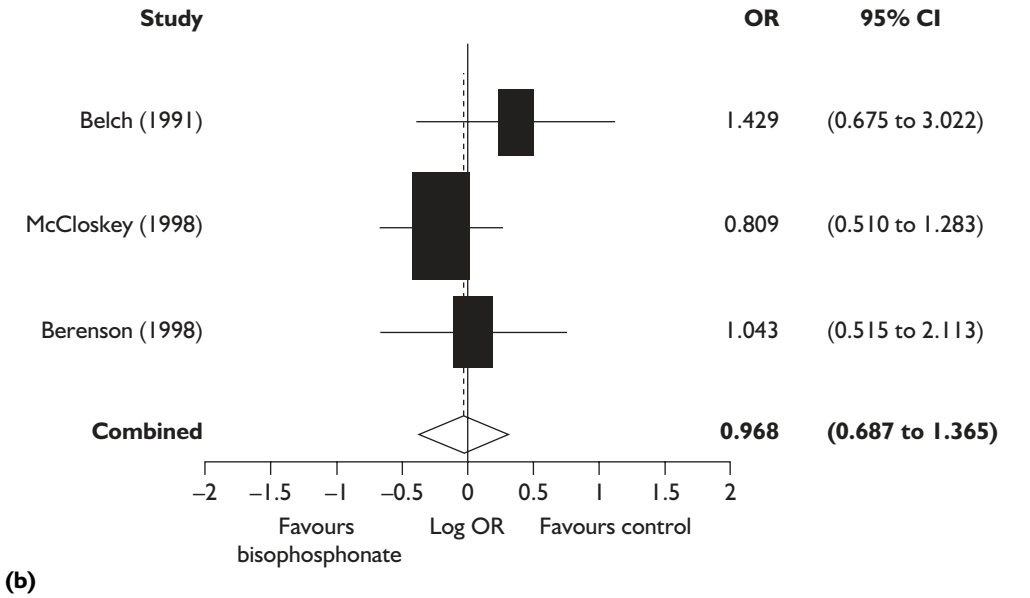


FIGURE 14 *Forest plots of vertebral fractures for sub-group analyses of disease groups: (a) breast and (b) myeloma [studies ordered by length of study, pooled OR (95% CI)]*



(a)



(b)

FIGURE 15 *Forest plots of hypercalcaemia for sub-group analyses of disease groups: (a) breast and (b) myeloma [studies ordered by length of study, pooled OR (95% CI)]*

TABLE 21 *Summary statistics from sub-group analysis of skeletal morbidity end-points with different bisphosphonates, pamidronate, clodronate, zoledronate, and zoledronate versus pamidronate*

Bisphosphonate	Skeletal morbidity outcome	OR	Lower CI	Upper CI	No. of studies	No. of patients	*p*-Value
Pamidronate	Vertebral fractures	0.759	0.579	0.995	3	1130	0.046
	Non-vertebral fractures	0.642	0.468	0.881	4	1534	0.006
	Combined fractures	0.688	0.541	0.874	3	1130	0.002
	RT	0.635	0.512	0.788	4	1534	0.0001
	SCC	0.874	0.441	1.728	3	1157	0.697
	Orthopaedic surgery	0.558	0.360	0.867	3	1157	0.009
	Hypercalcaemia	0.501	0.287	0.875	4	1534	0.015
Clodronate	Vertebral fractures	0.679	0.477	0.969	2	709	0.032
	Non-vertebral fractures	0.587	0.369	0.933	3	743	0.024
	RT	0.394	0.087	1.790	2	207	0.228
	Hypercalcaemia	0.696	0.481	1.006	5	811	0.054
Zoledronate	Vertebral fractures	0.542	0.343	0.856	2	1416	0.009
	Non-vertebral fractures	0.670	0.474	0.944	2	1416	0.022
	Combined fractures	0.579	0.434	0.773	2	1416	0.0001
	RT	0.748	0.584	0.956	2	1416	0.021
	Orthopaedic surgery	0.664	0.389	1.135	2	1416	0.135
	Hypercalcaemia	0.111	0.028	0.445	2	1416	0.002
Zoledronate vs pamidronate	Vertebral fractures	1.619	0.496	5.286	2	1860	0.425
	Non-vertebral fractures	1.619	0.443	5.923	2	1860	0.466
	Combined fractures	0.759	0.410	1.404	2	1860	0.379
	RT	0.691	0.338	1.412	2	1860	0.311
	Orthopaedic surgery	0.564	0.267	1.192	2	1860	0.134

with control or placebo; however, not all trials measured all skeletal morbidity end-points.[137,194,196,218,219] On meta-analysis there was a significant reduction in the ORs for vertebral and non-vertebral fractures and hypercalcaemia. The OR for RT was reduced to 0.394, with a wide CI (0.087 to 1.790); only two of the smaller studies (207 patients) contribute to this analysis.

Zoledronate (intravenous)

Two trials (1416 patients) compared intravenous zoledronate with placebo (Murphy R, Novartis Pharmaceuticals: two personal communications, 2001). On meta-analysis there was a significant reduction in the odds ratio for fractures (non-vertebral, vertebral and combined) radiotherapy and hypercalcaemia, but neither orthopaedic surgery or spinal cord compression reached significance.

Zoledronate (intravenous) versus pamidronate (intravenous)

Two trials (1860 patients) compared zoledronate with pamidronate[187] (Murphy R, Novartis Pharmaceuticals: two personal communications, 2001). There was no significant difference between these two drugs in reducing any of the skeletal morbidity end-points.

Reduction in skeletal morbidity with bisphosphonates: route of administration

Oral

Five studies used oral bisphosphonates (four clodronate[137,196,218,219] and one etidronate[185]). Oral bisphosphonates significantly reduced the ORs for vertebral and non-vertebral fractures. A reduction in combined fractures would be expected, but only two small studies[185,219] (total of 215 patients) contributed to this analysis, which did not reach significance. Reduction in need for RT was not significant ($p = 0.228$, 193 patients). Hypercalcaemia was not significantly reduced, $p < 0.263$; this analysis is weighted by one myeloma study,[137] which contributes over half of the patients. The study using etidronate[185] was not significant for any outcome. None of these trials measured orthopaedic surgery as a skeletal morbidity outcome. *Table 22* summarises the pooled ORs for each skeletal morbidity outcome, together with the numbers of trials and patients included in this sub-analysis.

TABLE 22 *Summary statistics from sub-group analysis of skeletal morbidity end-points for oral and intravenous routes of administration*

Administration	Skeletal morbidity outcome	OR	Lower CI	Upper CI	No. of studies	No. of patients	*p*-Value
Oral	Vertebral fractures	0.679	0.477	0.969	2	695	0.032
	Non-vertebral fractures	0.587	0.369	0.933	3	729	0.024
	Combined fractures	0.933	0.348	2.502	3	632	0.89
	RT	0.394	0.087	1.790	2	193	0.228
	Hypercalcaemia	0.782	0.508	1.203	5	1064	0.263
Intravenous	Vertebral fractures	0.690	0.522	0.913	5	2543	0.009
	Non-vertebral fractures	0.776	0.629	0.957	6	2947	0.018
	Combined fractures	0.641	0.533	0.771	5	2543	0.0001
	RT	0.661	0.562	0.777	6	2947	0.0001
	SCC	0.738	0.484	1.124	5	2573	0.157
	Orthopaedic surgery	0.698	0.463	1.051	5	2570	0.086
	Hypercalcaemia	0.402	0.222	0.728	6	2930	0.003

Intravenous

Six trials studied intravenous bisphosphonates versus control and the results mirror the primary analysis[138,139,208,210] (Murphy R, Novartis Pharmaceuticals: two personal communications, 2001). Bisphosphonates significantly reduced the OR for vertebral, non-vertebral and combined fractures, RT and hypercalcaemia, but not for orthopaedic surgery or SCC. *Table 22* summarises the pooled ORs for each skeletal morbidity outcome, together with the numbers of trials and patients included in this sub-analysis.

Survival

None of the individual studies demonstrated a significant difference in survival between patients treated with bisphosphonates and controls. We were unable statistically to combine data from different studies, as survival data were not reported in enough detail in publications. *Table 16* records the data given by individual studies.

Quality of life, performance status

Very few data could be extracted from papers regarding performance status and quality of life. Eight studies measured performance status,[137–139,187,190,193,210,213] and three of these also measured quality of life.[138,139,213] In many studies data were only available for analysis on a subset of patients.

Performance status was measured by ECOG score or Karnofsky score. Berenson and colleagues[138] showed a statistically significant change in mean group ECOG score at 9 months compared with baseline: 0.1 pamidronate group versus 0.44 control group, $p < 0.05$. McCloskey and colleagues[137] state that the prevalence of poor performance status was lower in those treated with clodronate versus placebo: 18.3% versus 30.5%, respectively, $p < 0.025$. All other studies found no significant difference between groups.

Berenson and colleagues[138] showed a mean change in the Spitzer quality of life index at 9 months of –0.24 in the treatment versus –0.7 in the control group, but no level of significance is given. The other two studies found no difference between groups.

Toxicity

All bisphosphonates were generally well tolerated. *Table 23* summarises the more serious and common adverse events reported in the trials. Essentially oral medications were associated with increased incidence of GI side-effects, but these were often mirrored in placebo groups. Aminobisphosphonates were associated with a higher proportion of acute-phase reactions.

Studies not included in meta-analysis

Three studies[199,201,217] were of 3 months' duration and one[193] 4 months' duration. In these studies pain was the primary outcome measure. None of the skeletal morbidity outcomes reached significance and in each case 0–3 events were recorded for each group, except for one study[201] that had 10 and 15 patients requiring RT. Less than 6 months was not considered long enough for a change in skeletal morbidity to be demonstrated. In these studies small numbers of events occur, with relatively small numbers of patients in each study.

TABLE 23 *Summary of serious and common side-effects of bisphosphonates reported in skeletal morbidity trials*

Treatment	Study	No. of patients on drug	Side-effect	Patients affected (%)
Pamidronate, i.v.	Berenson[138]	196	Anaemia (grade 3/4)	16
	Theriault [139]	182	Leucopenia	9
	Hultborn[210]	201	Myelotoxicity	1a
	Berenson[138]	196	Myalgia	25
	Kraj[211]	73		7
	Glover[199]	61		7
	Berenson[187]	73	Local reaction at injection site	4
	Conte[190]	143		9
	Theriault[139]	182		6
	Glover[199]	61		3
	Conte[190]	143	Fever	6
	Lipton[135]	367		14
	Diel[195]	103		7
	Glover[199]	61		18
	Conte[190]	143	Rigors	2
	Berenson[187]	73	Elevated creatinine (grade 3)	3
	Berenson[138]	196	Symptomatic hypocalcaemia	<1[a]
	Hortobagyi[209]	185		<1[a]
	Lipton[135]	367		<1
	Kraj[211]	73		3
	Conte[190]	143	Elevated aspartate transminase	<1[a]
	Kraj[211]	73		<1
	Hortobagyi[209]	185	Bone pain post-infusion	<1[a]
	Kraj[211]	73		9
	Berenson[138]	196	Allergic reaction	<1[a]
	Hortobagyi[209]	185	Increased weakness, fatigue, SOB	<1[a]
	Lipton[135]	367		<1
	Theriault[139]	182	Dyspnoea and interstitial pulmonary	<1
	Lipton[135]	367	infiltrates	<1
	Theriault[139]	182	Ophthalmic events	<1
	Lipton[135]	367		<1
Pamidronate p.o.	Holten-Verzantvoort[204]	81	Nausea and vomiting	22[a]
	Brincker[189]	152		16
	Holten-Verzantvoort[204]	81	Stomatitis	<1[a]
	Holten-Verzantvoort[204]	81	Anaemia	<1[a]
	Brincker[189]	152	Oesophageal ulceration	1
	Brincker[189]	152	GI haemorrhage	3
Clodronate p.o.	Paterson[218]	85	Difficulty swallowing capsules	16 (18 in placebo group)
	Diel[195]	112	GI (general)	13
	Kristensen[213]	49		4[b]
	Paterson[218]	85		2
	Kristensen[213]	?	Nausea	5[a]
	Paterson[218]	85		21
	Kristensen[213]	49	Diarrhoea	4[a]
	Paterson[218]	85		5
	Kristensen[213]	49	'Sensations in the skeleton'	2[b]

continued

TABLE 23 *Summary of serious and common side-effects of bisphosphonates reported in skeletal morbidity trials (cont'd)*

Treatment	Study	No. of patients on drug	Side-effect	Patients affected (%)
Etidronate i.v.	Darragon[193]	49	Erythema	<1
Zoledronate i.v.	Unpublished[c]	2048	Side-effect profile similar to pamidronate (detailed data not available)	

[a] Withdrawn from study.
[b] Dose reduction.
[c] Murphy R, Novartis Pharmaceuticals; three personal communications, 2001.
SOB, shortness of breath.

One study reported a protocol only, and gave no results.[184] One study, measuring pain as the primary outcome, stated that the number of fractures and episodes of hypercalcaemia had been measured but we were unable to extract data from the report.[200]

Four other studies were excluded from meta-analyses owing to methodological issues.[135,200,202,204] Lipton and colleagues[135] combine data from two RCTs[139,209] and these have been included separately in the analyses. Heim and colleagues[202] report analyses of their results by sub-groups, according to how long they remained in the study. We were unable to extract the primary data from this report. In the study by Holten-Verzantvoort and colleagues,[204] the dose of bisphosphonate was changed part way through the study and we were unable to extract usable data from the report. Lahtinen and colleagues[214] measured fractures as the primary outcome but only 203 of the 350 patients had X-rays at baseline and follow-up.

Two studies measured numbers of events rather than numbers of people with an event and we were unable to obtain data in this format from the authors.[189,190]

Adjuvant review

Seven studies fulfilled the inclusion criteria for this review[272–278] (*Figure 16*). In addition, there were seven abstracts relating to these studies,[279–285] and four published papers[286–289] reporting bone mineral density measurement in subsets of patients from two of the larger studies.[276,277] Details of included and excluded studies are given in *Tables 24* and *25*.

Of the seven studies, one was excluded from the analysis because it only reported bone mineral density (BMD) measurements in patients with prostate cancer.[278]

The remaining six studies all recruited patients with breast cancer and no skeletal metastases. Three studies looked at the role of adjuvant bisphosphonates in primary operable breast cancer[272,276,277] and the other three studies examined the role of bisphosphonates in patients with advanced breast cancer.[273–275]

Primary operable breast cancer

Diel and colleagues,[272] Powles and colleagues[276] and Saarto and colleagues[277] recruited patients with primary operable breast cancer, but no metastatic disease. Diel and colleagues also required positive bone marrow aspirate for tumour cells. All studies gave oral clodronate 1600 mg/day for 2–3 years. Diel and colleagues and Powles and colleagues report data at the end of the treatment period, Powles and colleagues also report findings after an additional follow-up observation period of 3 years. Saarto and colleagues only report findings at the end of 5 years, consisting of 3 years' treatment followed by a 2-year observation period.

The primary end-point for these studies was the number of patients who developed bone metastases. At the end of treatment, *Figure 17* shows pooled results for Diel and colleagues[272] and Powles and colleagues.[276] Both studies report significant benefit in the reduction of number of patients developing bone metastases; meta-analysis of the 1371 patients gave a pooled OR (95% CI) of 0.411 (0.249 to 0.677), $p < 0.0001$. In addition, Diel and colleagues showed that for those patients who develop bone metastases, the mean number of bone metastases per patient was

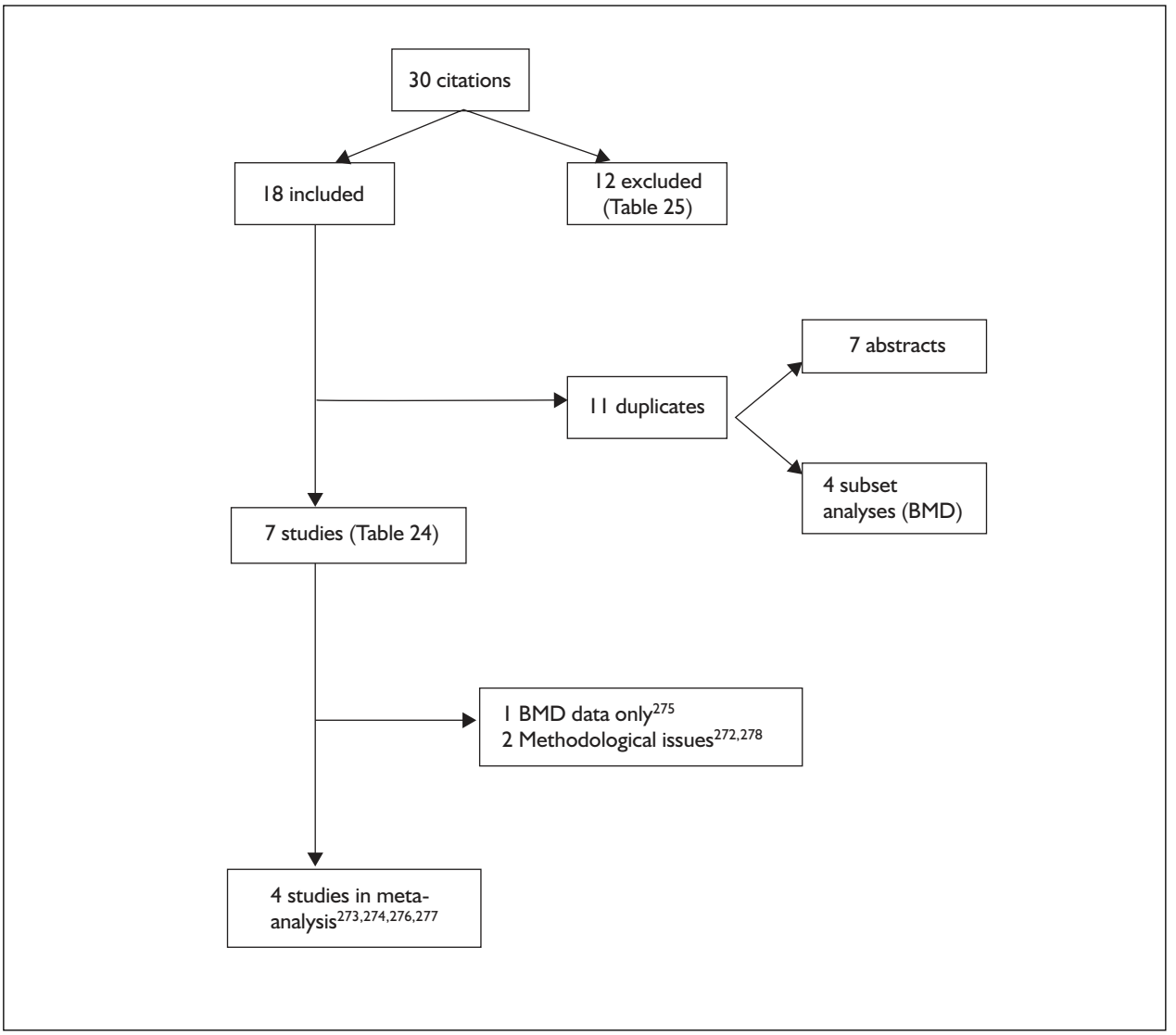


FIGURE 16 *Flow diagram: adjuvant review. BMD, bone mineral density.*

significantly reduced in the treatment group (3.1 versus 6.3; $p < 0.004$). They also demonstrated a difference in the median time to development of bone metastases between the treatment and control groups (23 versus 16 months).

Powles and colleagues[276] and Saarto and colleagues[277] treated patients for 2 and 3 years, respectively, and analysed the results at the end of an additional observation period of 3 and 2 years, respectively. Powles and colleagues found that the benefit observed during the treatment period was not maintained in the observation period, with 63/530 versus 80/539 ($p < 0.127$) patients developing bone metastases. Saarto and colleagues only reported results following an observation period. The study found no significant difference between the groups; 29/149 versus 24/150 patients had developed bone metastases by the end of the trial. The results from the Saarto study may be confounded by the fact that groups were not comparable at baseline, with significantly more patients in the treatment group having ER/progesterone receptor (PR) negative hormone receptor status. When the treatment group was compared with the control group, 48/139 versus 33/143 patients were found to be ER negative ($p < 0.023$) and 62/139 versus 44/143 ($p < 0.011$) were PR negative.

Secondary end-points included measurement of the number of patients developing non-bony metastases. Diel and colleagues found a significant reduction in number of patients developing non-bony metastases (13/157 versus 27/145; $p < 0.003$). This finding was not reproduced by the Powles study. No difference was found in the

TABLE 24 *Adjuvant review: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Diel, 1998[272] Diel, 1997[279] [meeting abstract]	RCT Open	302 pts Breast cancer (Tumour stage 1–4, Nodes 0–2) Bone marrow aspirate positive No evidence skeletal disease/distant metastases No neoadjuvant chemo/hormone therapy	A – clodronate 1600 mg p.o./day for 2 y B – control, standard follow-up	Median time in study 36 months Pts developing bone metastases: A 12/157; B 25/145 $p < 0.003$ Pts developing visceral metastases: A 13/157; B 27/145; $p < 0.003$ Median time to bony metastases (months): A 23; B16 Survival: A 6 pts died; B 22 pts died; $p < 0.001$	Mean no. of bony metastases per pt: A 3.1; B 6.3; $p < 0.004$	B
Holten-Verzantvoort, 1996[273]	RCT Open	124 pts Breast cancer Locally advanced disease (III B) or non-bony metastases	A – pamidronate 300 mg/d until death/toxicity B – control	Median length of time on study: A 19 months; B 34 months Pts developing bone metastases: A 23/65; B16/59	Many early withdrawals and length of time in study different for treatment vs controls. Data not included in meta-analysis	B
Kanis, 1996[274]	RCT Double blind	133 pts Breast cancer Locally advanced disease or non-bony metastases	A – clodronate 1600 mg/d for 3 y B – placebo	Analysis 1 y after last patient recruited Pts developing bone metastases: A 15/66; B 19/67 Survival: A 47 pts died; B 52 pts died	Total no. of bone metastases: A 32; B 63; $p < 0.005$	A

continued

TABLE 24 *Adjuvant review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Mardiak, 2000[275]	RCT Double blind	73 pts Breast cancer Stage III or IV No prior chemo/hormone therapy No evidence of bone metastases	A – clodronate 1600 mg/d for 2 y B – placebo	Median (range) time on study: 84 (57–193) months Pts developing bone metastases: A 9/37; B 7/36 Median time to development bone metastases (months): A 13.4; B 28.4 Pts developing non-bony metastases: A 16/37; B 16/36 Median time to development of non-bony metastases (months): A 20.2 B 16.3	Not intention to treat analysis Methodological problems (see text)	B
Unpublished data (now published[276])	RCT Double blind	1069 pts Breast cancer Primary operable disease No metastases	A – clodronate 1600 mg/d for 2 y B – placebo	End of 2 y: Pts developing bone metastases: A 12/530; B 28/539; $p < 0.016$ Pts developing non-bony metastases: A 38/530; 39/539	Median follow –up (2 y treatment plus observation period): 5.5 y Pts developing bone metastases: A 63/530; B 80/539; $p < 0.127$ Pts developing non-bony metastases: A 112/530; B 128/539; $p < 0.257$ Survival: A 98 pts died; B 129 pts died; $p < 0.047$	A

continued

TABLE 24 *Adjuvant review: characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Saarto, 2001[277] Saarto, 2001[288] Saarto, 1997[289] Vehmanen, 2001[287]	RCT Open	299 pts Breast cancer Newly diagnosed operable disease (T1–3, N1–2, M0)	A – Clodronate 1600 mg/d p.o. for 3 y plus 2 y follow-up B – standard treatment	Analysis at 5 y Pts developing bone metastases: A 29/149; B 24/150 Pts developing non-bony metastases: A 60/149; B 36/150 Survival: A 42 pts alive B 24 pts alive	Groups were not equal at baseline for hormone receptor status Refs 287–289: all subsets looking at BMD	B
Smith, 2001[278]	RCT Open	47 pts Prostate cancer Advanced/recurrent disease No bone metastases	A – leuprolide plus pamidronate 60 mg i.v. every 12 weeks (× 4 cycles) B – leuprolide	No outcome measures relevant to this study BMD study		B

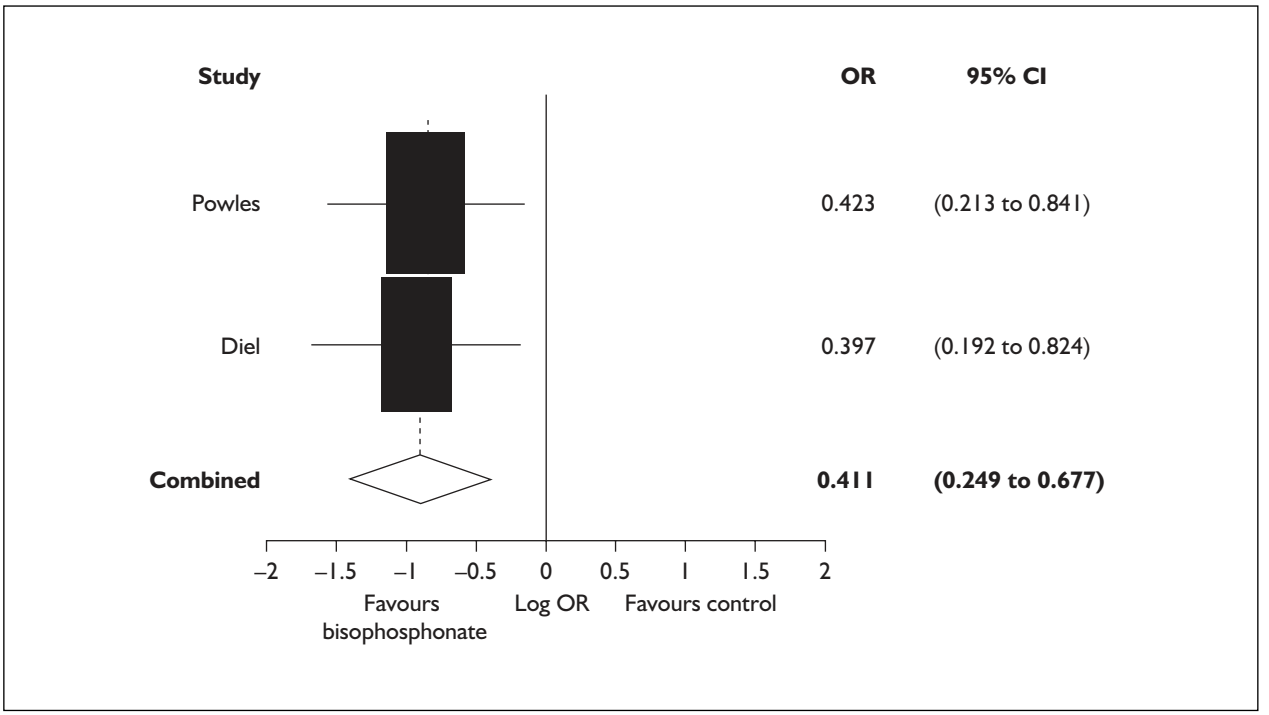


FIGURE 17 *Forest plot of number of patients developing bone metastases, adjuvant studies [pooled OR (95% CI)]*

TABLE 25 *Adjuvant review: excluded studies*

Study	Reason for exclusion
Blay, 1998[290]	Editorial
Boissier, 2000[118]	*In vitro* work
Colleoni, 2000[291]	Not an adjuvant study
Dearnaley, 2001[238]	Patients had bone metastases on entry
Diel, 1999[292]	Not an adjuvant study
Galasko, 1980[115]	Not an adjuvant study
Hidalgo, 2001[293]	Review
Lee, 2001[119]	*In vitro* work
Lokeshwar, 1999[294]	Review
Rutqvist, 1994[295]	Protocols of proposed studies
Smith, 1999[296]	Editorial
Wolff, 1999[297]	Review

incidence of non-bony metastases in the treatment and control groups. Saarto and colleagues recorded increased numbers of patients in the treatment group developing non-bony metastases (60/149 versus 36/150; $p < 0.002$) but this may be due to unequal groups at baseline for hormone receptor status (see above).

Diel and colleagues and Powles and colleagues both found survival benefits in the treatment groups ($p < 0.001$, $p < 0.047$, respectively). Saarto and colleagues found that an increased number of patients died in the treatment group.

Advanced breast cancer

Three trials investigated the use of bisphosphonates in patients with advanced breast cancer but no skeletal metastases.

We were unable to use data from two of these studies for methodological reasons.[273,275] In the trial by Holten-Verzantvoort and colleagues,[273] the median length of time on study was significantly different for treatment and control groups (19 versus 34 months). In addition, there were many early withdrawals (approximately 50%) from the trial. In the treatment group, 14 patients died and 15 patients withdrew because of GI side-effects from oral pamidronate, 300 mg/day. In the control group, 26/59 patients died.

Methodological problems were evident in the trial by Mardiak and colleagues.[275] This study treated patients for 2 years with oral clodronate 1600 mg/day, and reported results after a follow-up period, with a median (range) time on study of 7 (4.75–16) years. No interim results were reported at the end of the 2-year treatment period. Of the initial 73 patients recruited, 10 were not evaluated for response in the final analysis (seven clodronate, three placebo). Survival data are reported as 59.4 versus 54.7 months for the two groups. This is shorter than the median time on trial. The range of median time on study is not consistent with the methods section, which

reports that the trial started recruiting patients in 1990.

Kanis and colleagues[274] treated patients with advanced breast cancer in a placebo-controlled study, using oral clodronate 1600 mg/day, for 3 years. The number of patients completing 3 years of treatment was small: 8/66 treatment versus 10/67 control. Although the numbers of patients developing bone metastases were similar in both groups (15/66 versus 19/67), the number of bone metastases in all patients was significantly different between the two groups (32 versus 63; $p < 0.005$). There was no difference in survival.

Summary of results

Bisphosphonates, specifically clodronate, given in the adjuvant setting to patients with primary operable breast cancer with no metastatic disease significantly reduces the number of patients developing bone metastases. One trial demonstrated a delay in the time to development of bone metastases. The benefit observed during the treatment period does not seem to be maintained at the same level once regular administration of bisphosphonates has been discontinued. Two trials reported significant survival advantages in the treated groups.

Bisphosphonates reduce the number of bone metastases in patients with both early and advanced breast cancer.

Economic evaluation

Literature review

The search strategy identified 150 abstracts, which were reviewed. Of these, eight articles contained drug-pricing information (*Table 26*) and 14 papers contained economic analyses (*Table 27*). In addition, nine papers commented on the economic analyses. A summary of these papers is given in *Table 28*.

Hypercalcaemia

A direct comparison of the price per infusion of intravenous bisphosphonates, as reported in the BNF,[122] indicates the following ranking:

- clodronate 1500 mg £68.90
- pamidronate 60 mg £109.60
- pamidronate 90 mg £155.80
- oral clodronate 1600 mg £174.16
- zoledronate 4 mg £195.00.

Clearly the variation in price reflects the quantity of each drug prescribed but also, to some extent, the different levels of effectiveness of the different drugs. In the BNF, oral clodronate is more expensive than intravenous clodronate but the administration of oral clodronate is less costly because it does not require the use of outpatient facilities.

The Consumers Association[304] reported that the treatment of cancer-associated hypercalcaemia in the UK was less costly per month with pamidronate, etidronate or clodronate than with calcitonin (*Table 26*). Likewise, Kellihan and Mangino[301] found the cost of pamidronate therapy in the USA to be comparable to that of gallium nitrate therapy but more expensive than calcitonin and plicamycin treatment. Clearly, the relative cost of bisphosphonates compared with an alternative varies according to the exact dosage prescribed. It also may vary according to the geographical context – bisphosphonates appear to be considerably more expensive in the USA than in the UK, for example.

Gallacher[315] has argued that the additional costs associated with pamidronate compared with intravenous clodronate are likely to be at least partly offset by a reduced need for subsequent bisphosphonate treatment. However, there is no clear evidence on this matter as trials tend to follow up patients up to first relapse only.

There is only one previous study that has estimated the net effect on total hospital costs of using bisphosphonates for severe hypercalcaemia. Puolijoki and Liippo[312] had a sample of seven men with primary lung cancer, painful rib metastases and hypercalcaemia. Each was rehydrated and then prescribed oral clodronate 2400–1600 mg daily. Mean survival was 4.5 months. After treatment, five patients could be cared for at home for a mean of 41 days representing a total saving of £55,000. Such savings would certainly offset the cost of the drugs, which would amount to approximately £7000 at current BNF prices.[122] This would suggest that bisphosphonate use in hypercalcaemia is cost-saving but, without a control group, one has to be cautious in accepting the savings as 'incremental' costs savings. First, it is not clear if costs are avoided or merely shifted from the hospital to the patient's family and/or primary care facilities. Furthermore, patients who are not given bisphosphonates are likely to spend less overall time in hospital because they will die without treatment. The time in hospital is likely to be postponed, rather than avoided, and it is more likely that the time will be extended for the period where the calcium level is returning to normal.

TABLE 26 *Papers considering the price of bisphosphonate use in cancer care*

Study	Country	Site of primary cancer	Drugs compared	Price stated[a]
Durie, 2001[334]	USA	Multiple myeloma	Pamidronate	$700 per vial ($1500–3000 per month for completion of treatment)
Beijnen and Koks, 1990[299]	The Netherlands	Various	(1) Pamidronate, (2) etidronate	Material costs: (1) NLG 0.12; (2) NLG 900
Kao, 1997[300]	USA	Breast cancer	Pamidronate	$700 per vial ($8400 per year)
Strong and McPherson, 1998[298]	USA	Various	Pamidronate	$575 per vial, wholesale
Kellihan and Mangino, 1992[301]	USA	Various (hypercalcaemia)	(1) Pamidronate, (2) etidronate, (3) calcitonin, (4) gallium nitrate, (5) plicamycin	Cost per treatment: (1) $312–468; (2) $382–636; (3) $117–233; (4) $460; (5) $69–139
Madeline *et al*., 1999[302]	France	Multiple myeloma	Pamidronate	FF1600 per vial (FF1.6m in France in 1997)
Anon., 2000[303]	USA	Multiple myeloma	Pamidronate	$3500 per year
Consumers Association, 1990[304]	UK	Various (hypercalcaemia)	(1) Pamidronate, (2) etidronate, (3) clodronate, (4) calcitonin	Cost per month: (1) £93; (2) £100, oral = £120; (3) £75, oral = £175; (4) £350–700

[a] NLG, Netherlands guilder; FF, French franc.

TABLE 27 *Papers containing economic analyses of bisphosphonate use in cancer care*

Study	Country	Site of primary cancer	Drug	Dosage (mg)	Specific context	Source of event and resource use data	Sample size (median time on study)	Type of analysis[a]
Balducci, 1998[305]	USA	Breast	Pamidronate	90 monthly	Prevention of skeletal morbidity	Not stated	Not stated	Cost analysis
Beusterien *et al.*, 2001[153]	USA	Breast	Pamidronate	90 monthly	Prevention of skeletal morbidity	Retrospective case note review	295 (12 months[b])	Resource use analysis
Biermann *et al.*, 1991[124]	USA	Breast	Clodronate (oral)	Not stated	Prevention of skeletal morbidity	Retrospective case note review	457 (not stated)	Cost analysis
Bruce *et al.*, 1999[306]	UK	Multiple myeloma	Clodronate (oral)	1600 daily	Prevention of skeletal morbidity	McCloskey *et al.*, 1998[137]	536 (34 months)	Cost analysis
Coyte *et al.*, 2001[307]	Canada	Multiple myeloma	Pamidronate	Not stated	Home i.v. vs hospital i.v.	Retrospective case note review	48 (6 months[c])	Cost analysis
DesHarnais Castel *et al.*, 2001[308]	USA	Various	Zoledronate Pamidronate	4 90	Comparison of i.v infusion costs	Time and motion study	Not stated	Cost analysis
Dranitsaris, 2001[140]	Canada	Multiple myeloma	Pamidronate	90 monthly	Prevention of skeletal morbidity	Berenson *et al.*, 1998[46]	392 (9 months)	Cost–benefit analysis
Dranitsaris and Hsu, 1999[141]	Canada	Breast	Pamidronate	90 monthly	Prevention of skeletal morbidity	Hortobagyi *et al.*, 1996[209]	382 (9 months)	Cost–utility analysis
Gessner *et al.*, 2000[245]	Switzerland	Various	Pamidronate	(a) 60, (b) 90 monthly	Treatment of bone pain	Koeberle *et al.*, 1999[246]	70 (11 months)	Cost analysis
Guignard *et al.*, 1997[309]	France	Breast	Clodronate (oral)	Not stated	Prevention of skeletal morbidity	Retrospective case note review	57 (12 months)	Cost analysis
Hillner *et al.*, 2000[310]	USA	Breast	Pamidronate	90 monthly	Prevention of skeletal morbidity	Hortobagyi *et al.*, 1998[208]; Theriault *et al.*, 1999[139]	382 (12 months); 372 (16months)	Cost–utility analysis
Laakso *et al.*, 1994[215]	Finland	Multiple myeloma	Clodronate (oral)	2,400 daily	Prevention of skeletal morbidity	Lahtinen *et al.*, 1992[214]	312 (24 months[d])	Cost analysis
Marchetti *et al.*, 2000[311]	Italy	Breast	Pamidronate	90 monthly	Prevention of skeletal morbidity	Two RCTs – not specified	Not stated	Cost–utility analysis
Puolijoki and Liippo, 1992[312]	Finland	Lung	Clodronate (oral)	2,400–1600 daily	Treatment of hypercalcaemia	Prospective single cohort evaluation	7 (5 months)	Cost analysis

[a] Cost analyses do not include an overall measure of health outcome. Cost–utility analyses measure health outcomes in terms of quality-adjusted life-years (QALYs) gained. Cost–benefit analyses put a monetary value on health outcomes.
[b] 14.7 months in late pamidronate group, 9.0 months in early pamidronate group, 10.6 months in non-pamidronate group.
[c] Mean not median.
[d] Follow-up was 'up to 24 months'.

TABLE 28 *Papers commenting on economic analyses of bisphosphonate use in cancer care*

Study	Country	Site of primary cancer	Specific context
Elomaa, 2001[313]	Finland	Various	Various
Fulfaro *et al.*, 1998[314]	Italy	Various	Treatment of bone pain
Gallacher, 1996[315]	UK	Various	Treatment of hypercalcaemia
Hillner, 2000[316]	USA	Breast	Various
Hillner *et al.*, 2000[120]	USA	Breast	Various
McCloskey and Libretto, 1998[317]	UK	Multiple myeloma	Various
McCloskey *et al.*, 2001[318]	UK	Breast and multiple myeloma	Various
Pereira *et al.*, 1998[319]	Canada	Various	Treatment of bone pain
Wisloff *et al.*, 1999[335]	Norway	Multiple myeloma	Various

Treatment of bone pain

The only economic analysis of the use of the bisphosphonates specifically for cancer-associated bone pain was carried out in Switzerland by Gessner and colleagues.[245] They made a before and after comparison of patients who had 6 months' bisphosphonate treatment followed by 6 months without. The 70 patients had a variety of primary cancers: breast 60% and multiple myeloma 21%. The result was a significant reduction in pain by 20–30% on an analogue scale. The costs, which included hospitalisation and RT costs, were higher in the treatment period, 1290 versus 1050 ECU (European currency unit) per month, although this was not statistically significant at the 5% level.

Prevention of skeletal morbidity – multiple myeloma

There were three economic analyses of the use of bisphosphonates to prevent skeletal events in patients with multiple myeloma (*Tables 29–31*).

Laakso and colleagues[215] based their cost analysis on the RCT reported by Lahtinen and colleagues[214] with 156 patients receiving 2400 mg of oral clodronate per day and 156 receiving placebo. They found that one fracture was prevented per patient. They found a cost saving from reduced hospitalisation of 27 Finnish marks per day. However, this was more than offset by the cost of the therapy of 78 Finnish marks per day. Neither the difference in event costs nor the difference in overall cost was statistically significant, but this is unsurprising given the relatively small sample size.

Bruce and colleagues[306] constructed a 4-year state transition model based on the MRC VI myelomatosis trial.[137] The economic data were based on 207 patients from the trial. Those in the intervention group received 1600 mg/day of oral clodronate and those in the control group a placebo. They costed the following adverse events:

- severe hypercalcaemia
- vertebral fracture
- rib fracture
- arm fracture
- leg fracture.

As with Laakso and colleagues,[215] there were cost savings from the reduced number of events to the value of £1484 per patient but these were more than offset by the cost of clodronate therapy, amounting to £4862 per patient. The overall difference was £3377 (95% CI: £2605 to £4150). This additional cost was associated with a 50% reduction in hypercalcaemia, a 48% reduction in the incidence of non-vertebral fractures and a 45% reduction in the incidence of vertebral fractures. They did not consider the treatment of bone pain but commented that the cost of treating bone pain was so small compared with overall costs that it was unlikely to affect costs.

Dranitsaris[140] conducted the only cost–benefit analysis of bisphosphonate use in cancer. The use of 90 mg pamidronate 4-weekly was evaluated. The incremental costs were calculated on the basis of the results from Berenson and colleagues[46] and included RT and non-surgical treatment of fractures. They measured the benefit of therapy by asking a sample of 100 multiple myeloma patients of their willingness to pay to avoid (a) a fracture and (b) an incident of RT. They estimated the incremental cost to be Can$4153 per patient, which more than offset the willingness to pay of Can$3364. This gives an overall loss to society but the confidence interval is consistent with a moderate benefit to society.

TABLE 29 *Economic studies of the prevention of skeletal events using bisphosphonates: (a) Methods and context and (b) Effectiveness*

(a) Methods and context

	Paper	Country	Time horizon (months)	Drug brand	Events costed	Primary outcome measure(s)
Multiple myeloma	Laakso *et al*., 1994[215]	Finland	24	Clodronate (oral)	Inpatient day	Incremental cost per patient per day
	Bruce *et al*., 1999[306]	UK	48	Clodronate (oral)	Fracture (vertebral, rib, arm, leg), hypercalcaemia	Incremental cost per patient
	Dranitsaris, 2001[140]	Canada	9	Pamidronate	Fracture, RT	Incremental cost per patient, net benefit
Breast cancer	Guignard *et al.*, 1997[309]	France	12	Clodronate (oral?)	Inpatient day, RT	Incremental cost per patient
	Hillner *et al.*, 2000[310]	USA	24	Pamidronate (chemotherapy arm and hormone therapy arm)	RT, surgery, SCC, hypercalcaemia, 'other fracture'[a]	Incremental cost per patient Incremental cost per SRE averted Incremental cost per QALY gained
	Marchetti *et al.*, 2000[311]	Italy	24	Pamidronate (chemotherapy arm and hormone therapy arm)	Vertebral fracture (acute and chronic), non-vertebral fracture (acute and chronic), chronic bone pain	Incremental cost per patient Incremental cost per QALY gained
	Dranitsaris and Hsu, 1999[141]	Canada	12	Pamidronate	Non-vertebral fracture, hypercalcaemia, RT, surgery	Incremental cost per patient Incremental cost per QALY gained

[a] 'Other fractures were either asymptomatic or required only oral analgesics'.

(b) Effectiveness

	Paper	Events averted (per patient)[a]	QALYs gained (per patient)
Multiple myeloma	Laakso *et al.*, 1994[215]	2 osteolytic bone lesions; 1 vertebral fracture; Inpatient days, not stated	Not measured
	Bruce *et al.*, 1999[306]	45% of vertebral fractures; 48% of non-vertebral fractures; 60% of hypercalcaemia	Not measured
	Dranitsaris, 2001[140]	ARR: 13% fractures; 8% RT sessions	Not measured
Breast cancer	Guignard *et al.*, 1997[309]	Inpatient stays, 19% patients; RT sessions – 22% patients	Not measured
	Hillner *et al.*, 2000[310]	1.13 SREsb (chemotherapy arm) 0.82 SREsb (hormone therapy arm)	0.037 (chemotherapy arm) 0.025 (hormone therapy arm)
	Marchetti *et al.*, 2000[311]	Not stated	0.035 (chemotherapy arm) 0.082 (hormone therapy arm)
	Dranitsaris and Hsu, 1999[141]	Non-vertebral fractures, 10% patients; hypercalcaemia, 6% patients; RT, 14% patients; surgery, 6% patients; Any SREb – 16% patients	0.15

[a] In Dranitsaris and Hsu[141] and Guignard *et al*.[309] these are based on number of persons with one or more events rather than numbers of events. Bruce *et al*.[306] present relative reductions in number of events. Hillner *et al*.[310] and Laakso *et al*.[215] present number of events averted per patient. Dranitsaris[140] presents the 'absolute risk reduction (ARR) for pathological fractures and radiation treatment to the bone'.

TABLE 30 *Economic studies of the prevention of skeletal events using bisphosphonates: cost results (original currencies)*

	Study	Currency[a]	Incremental drug cost	Incremental SRE cost	Incremental total cost	Event cost savings as a proportion of drug therapy cost (%)	Cost-effectiveness
Multiple myeloma	Laakso *et al.*, 1994[215]	Finnish mark 1990	78 per day	–27 per day	51 per day	35	Not estimated
	Bruce *et al.*, 1999[306]	UK £1997	4862	–1484	3377	31	Not estimated
	Dranitsaris, 2001[140]	Can$1998	5373	–1220	4153	23	Net loss to society of Can$789 per patient
Breast cancer	Guignard *et al.*, 1997[309]	FF1998	21750	–13766	7984	63	Not estimated
	Hillner *et al.*, 2000[310] – chemotherapy	US$1998	10564	–6596	3968	62	$3940 per SRE averted, $108,200 per QALY gained
	Hillner *et al.*, 2000[310] – hormone therapy	US$1998	12101	–4416	7685	36	$9390 per SRE averted, $305,300 per QALY gained
	Marchetti *et al.*, 2000[311] – chemotherapy arm	US$2000	Not stated	Not stated	1676	Not stated	$45,700 per QALY gained
	Marchetti *et al.*, 2000[311] – hormone therapy arm	US$2000	Not stated	Not stated	2358	Not stated	$28,700 per QALY gained
	Dranitsaris and Hsu, 1999[141]	Can$1999	5970	–3170	2800	53	Can$18,700 per QALY gained

[a] Can$ = Canadian dollar.

TABLE 31 *Economic studies of the prevention of skeletal events using bisphosphonates: cost results (2001 UK £)*

	Study	Incremental drug cost (£)	Incremental SRE cost (£)	Incremental total cost (£)	Event cost savings as a proportion of drug therapy cost (%)	Cost-effectiveness
Multiple myeloma	Laakso *et al.*, 1994[215]	10.54 per day	–3.65 per day	6.89 per day	35	Not estimated
	Bruce *et al.*, 1999[306]	5453	–1664	3788	31	Not estimated
	Dranitsaris, 2001[140]	3267	–741	2525	23	Net loss to society of £480 per patient
Breast cancer	Guignard *et al.*, 1997[309]	2290	–1449	840	63	Not estimated
	Hillner *et al.*, 2000[310] – chemotherapy	7452	–4653	2799	62	£2779 per SRE averted, £76,330 per QALY gained
	Hillner *et al.*, 2000[310] – hormone therapy	8536	–3115	5421	36	£6624 per SRE averted, £215,375 per QALY gained
	Marchetti *et al.*, 2000[311] – chemotherapy	Not stated	Not stated	1132	Not stated	£30,831 per QALY gained
	Marchetti *et al.*, 2000[311] – hormone therapy	Not stated	Not stated	1590	Not stated	£19,362 per QALY gained
	Dranitsaris and Hsu, 1999[141]	3546	–1883	1663	53	£11,108 per QALY gained

The setting of the intervention can also affect its cost-effectiveness. Coyte and colleagues[307] compared a system of intravenous infusion of pamidronate completed at home with a system that was purely hospital based. They found that there were overall cost savings to the hospital associated with freeing up chemotherapy chairs. In addition, there were further savings to the patients and families associated with parking fees and loss of work/leisure time. DesHarnais Castel and colleagues[308] estimated that the cost of intravenous infusion was lower for patients receiving 4 mg zoledronate than for those receiving 90 mg pamidronate to the amount of US$48 per visit, excluding the cost of the drugs.

Prevention of skeletal morbidity – solid tumours with bone metastases

All of the economic literature in this area has looked at patients with primary breast cancer. There are seven such studies in the literature, although three are excluded from the main comparison:

- Biermann and colleagues[124] were the first to carry out a study. It is excluded on the grounds that it did not use real data on reduction of SREs. The cost savings were estimated speculatively on the basis of hypothesised reductions in SREs. They estimated that there would be cost savings from bisphosphonate therapy as long as it resulted in a reduction of events by 20% or more. Of the studies reviewed, this one appeared to have the lowest estimate of drug cost and the highest estimates of SRE unit costs. Therefore, not surprisingly, their conclusions about the cost-effectiveness of bisphosphonates were more optimistic than the other studies.
- Balducci[305] only published an abstract. He examined the cost of prevention of skeletal events but the methods and results were described obscurely and are not reported here. An unsuccessful attempt was made to contact the author.
- Beusterien and colleagues[153] measured resource use rather than cost. They concluded that in addition to having fewer inpatient stays, patients on bisphosphonates who did visit had a length of stay of only 50% of that of patients not on bisphosphonates.

Guignard and colleagues[309] reported that there were substantial cost savings in RT and in hospitalisation after 12 months for patients with metastatic breast cancer. However, these savings did not completely offset the cost of clodronate treatment. Overall there was an incremental cost of 7984 FF per patient per year. This cost was associated with 9% fewer patients having an event in the year (70% versus 79%), which they deem to be 'favourable' in terms of cost-effectiveness.

Dranitsaris and Hsu[141] constructed a decision analytic model based on the RCT reported by Hortobagyi and colleagues.[209] Those in the intervention group (n = 185) received a 90-mg intravenous infusion of pamidronate 4-weekly (maximum 12 cycles) and those in the control group (n = 195) a placebo infusion. They costed the following adverse events:

- severe hypercalcaemia
- orthopaedic surgery
- RT
- non-surgical treatment of non-vertebral fractures.

They found an additional cost associated with the pamidronate arm of Can$2800 or Can$18,700 per QALY gained. They considered this a 'reasonable cost'; however, given the incidence of the disease, this suggested a cost of Can$10m per year for Ontario, which means that "difficult decisions would have to be made about which patients to treat with pamidronate and where the funding should be allocated from".

Hillner and colleagues[310] constructed a simple Markov model based on a hypothetical cohort meeting the entry Criteria for the Aredia Breast Cancer Study Group protocols 18 and 19 as reported by Hortobagyi and colleagues[208,209] and Theriault and colleagues[139] Incidence of SREs was taken from these trials and the results were reported separately for the group receiving systemic hormone therapy and that receiving systemic chemotherapy. Both intervention groups received 90-mg intravenous pamidronate every month. They costed the following adverse events:

- severe hypercalcaemia
- orthopaedic surgery
- SCC
- RT
- non-surgical treatment of other fractures.

For the chemotherapy patients, they found an additional cost associated with the pamidronate arm of $3968 or $108,200 per QALY gained. For the hormonal group, bisphosphonate therapy was more costly, and less cost-effective, because these patients lived longer and had fewer SREs.

Marchetti and colleagues[311] constructed a Markov model based on two RCTs, presumably Hortobagyi and colleagues[208] and Theriault and colleagues.[139] The details of the study are not clear as it is published only as a conference abstract. As with Hillner and colleagues,[310] the results were reported separately for the group receiving systemic hormone therapy and that receiving systemic chemotherapy. Both intervention groups received 90-mg intravenous pamidronate every month. They costed the following adverse events using hospital charges:

- chronic bone pain
- vertebral fractures (acute and chronic costs)
- non-vertebral fractures (acute and chronic costs).

They describe the benefits of the programme in terms of gain in life expectancy. This is a curious choice, given that the evidence that bisphosphonates extend life is very weak. Unlike Hillner and colleagues, they find bisphosphonate therapy to be more cost-effective for the hormonal therapy group at $28,689 per QALY gained.

Dranitsaris and Hsu[141] and Marchetti and colleagues[311] had found bisphosphonate treatment to be borderline cost-effective, whereas Hillner and colleagues[310] found it to be much less cost-effective. A key difference contributing to this discrepancy is the estimated QALY gains. Dranitsaris and Hsu estimated 0.15 QALYs gained, but Hillner and colleagues only 0.037 (chemotherapy group) or 0.025 (hormonal group). The reason for this difference is unclear but the fact that Hillner and colleagues ascribed a reduced quality of life only for the month in which the SRE occurs might suggest that they are underestimating the gains associated with preventing events. It is not clear how long the estimated duration of an SRE is in the Dranitsaris and Hsu model. Other differences were the 50% lower cost of bisphosphonate therapy in the Canadian study and their assumption that all non-vertebral fractures were assumed to be hospitalised.[120,316]

Issues arising from the economic literature

The economic analyses of pain control and anti-hypercalcaemia were poorly controlled and of a small size and hence should be treated cautiously.

The studies of prevention of SREs were of better quality. Despite the heterogeneity of participants, they all concluded that the cost savings associated with reduced adverse events did not fully offset the cost of the therapy for both breast cancer and multiple myeloma. The incremental cost per patient ranged between £800 and £5400 (*Table 31*), with the variation only partly reflecting the different time horizons of the models. The proportion of therapy cost being offset by event cost savings varied between 23 and 63%. The studies did not find significant differences in cost but this must be more to do with lack of power (the sample size was relatively small in all studies) than magnitude of effect, especially as in all studies the effect was in the same direction, that is, bisphosphonate therapy raised overall costs.

The three studies that estimated the cost per QALY gained reported different levels of cost-effectiveness although even the most cost-effective estimate was only marginally cost-effective. The difference in estimates appears to rest largely on methodological differences in the calculation of quality of life improvements.

All of the studies considered costs largely from a hospital perspective rather than a societal one – a few suggested that the patient costs associated with bisphosphonate therapy are relatively small. This may be true for the administration of the drugs but the community care costs associated with fracture care might be considerable. Omission of the cost of social care, be it provided by the family, the community health service or the social services, might substantially underestimate the cost savings to society associated with bisphosphonate therapy.

The studies had varying time horizons from 9-months to 4 years. Statistics such as cost per month or cost per year would allow better comparison between them but not perfectly so, as the incidence of events might be different in those patients who survive for longer. Most did not present such figures; therefore, direct comparison is difficult, but one could surmise that the incremental cost varies approximately between £1000 and £4000 per annum.

Only one of the studies was set in the UK NHS and we should be cautious about generalising the results of foreign studies to the UK setting. Treatment costs for SREs, as with treatment costs generally, are likely to be much higher in the USA than in the UK. This would imply that cost savings are potentially smaller in the UK but the cost of bisphosphonate therapy will also be smaller.

Important omissions from the literature are:

- studies evaluating bone pain control or hypercalcaemia control
- studies comparing different drug regimens in the prevention of skeletal morbidity
- studies concerned with other cancers that commonly metastasise to bone.

Cost analysis of treatment of cancer-associated hypercalcaemia

Costs and days to relapse were calculated separately for four published clinical trials. For each trial these outcomes are calculated for each arm and then incrementally – one arm compared with the next most effective drug arm.

Cumulative duration of normocalcaemia

Table 32 shows the cumulative duration of normocalcaemia (per patient) and the number of drug treatments per patient, by trial and drug arm. The cumulative duration of normocalcaemia ranged from 1.8 to 46.6 days depending on the estimated responsiveness and time to first relapse of each drug regimen. For 90 mg of pamidronate, used in three of the trials, the estimated cumulative duration of normocalcaemia varied considerably between studies, reflecting the observed differences in response rate and time to first relapse. Underlying these differences were the differences in entry criteria of the studies. The study with the longest duration of effect had the lowest average serum calcium level on entry.

The estimated differences in time in hospital were due to differences in response rates. The average cumulative time in hospital between drug regimens ranged from 17 to 22 days. Average survival, which was calculated as cumulative duration of normocalcaemia plus cumulative time in hospital, varied from 18 to 68 days between drug regimens. The average number of drug treatments per patient varied between 1.4 and 2.1, depending on the response rate of the drug regimen.

Costs

The costs associated with bisphosphonate therapy are shown in *Table 33*. Drug costs vary according to the cost of a single dose and also according to the number of treatments per patient. Drug cost varied between £74 and £754 per patient. Hospital stay costs were dependent on the cumulative time in hospital estimated for each drug regimen. They varied between £2500 and £3300 per patient. Therefore, the differences between arms, cost increments, were estimated to be greater in terms of hospital stay costs than drug costs. Hence differences in hospital stay are driving the differences in overall cost. Total cost, drugs and stays ranged from £2600 to £3700 per patient.

Cost-effectiveness

Table 34 shows the extra cost, incremental cost, associated with an extra day of response, comparing each strategy with the next most effective strategy – the first column of numbers shows the extra drug cost per extra day and the second the extra total cost per extra day.

For example, in the analysis of the trial reported by Purohit and colleagues,[130] the extra total cost per patient associated with pamidronate compared with clodronate was estimated to be £509 (*Table 33*). The extra cumulative duration of normocalcaemia was 24.7 days (*Table 32*), hence the extra cost per extra day was £21 (£509/24.7).

The final column of *Table 33* shows cost per year of life gained (365.25 × cost per day gained). The denominator here is estimated from the incremental survival, which is greater than the incremental duration of normocalcaemia.

We cannot calculate incremental cost-effectiveness ratios for ibandronate 6 mg because the 4-mg regimen was found to have both a lower cost and a better health outcome, hence treatment at 4 mg dominates 6 mg.

Where a treatment has a lower incremental cost-effectiveness ratio than the next most effective treatment, the former has extended dominance over the latter. For example, in the analysis of Purohit and colleagues[130] the incremental cost-effectiveness of pamidronate is only 10,314 per life-year compared with 25,587 for clodronate. In such circumstances we would eliminate the dominated treatment, in this case clodronate, and compare the more cost-effective treatment pamidronate with the next most effective strategy, in this case the no-treatment option. Clodronate is eliminated, in this example because the same duration of normocalcaemia can be achieved at a lower cost per day using pamidronate, hence pamidronate is unequivocally better value for money.

For the same reason, extended dominance, we also eliminate the following drug strategies:

- zoledronate 4 mg and zoledronate 2 mg – Major and colleagues[131]

TABLE 32 *Comparison of hypercalcaemia treatment strategies – survival and number of treatments*

		Days per patient							
		Response (normocalcaemia)		Hospital		Survival		Drug treatments per patient	
Study	**Treatment**	**No.**	**Increment**	**No.**	**Increment**	**No.**	**Increment**	**No.**	**Increment**
Purohit *et al.*[130]	Pamidronate 90 mg	39.4	24.7	21.9	2.0	61.3	26.7	2.1	0.3
	Clodronate 1500 mg	14.7	14.7	19.9	12.9	34.6	27.6	1.8	1.8
	No bisphosphonate treatment	0.0		7.0		7.0		0.0	
Major *et al.*[131]	Zoledronate 8 mg	46.6	10.8	20.5	–0.2	67.2	10.6	1.9	0.0
	Zoledronate 4 mg	35.9	20.8	20.7	1.8	56.6	22.6	2.0	0.3
	Pamidronate 90 mg	15.0	15.0	18.9	11.9	34.0	27.0	1.7	1.7
	No bisphosphonate treatment	0.0		7.0		7.0		0.0	
Nussbaum *et al.*[66]	Pamidronate 90 mg	8.4	4.7	21.9	3.7	30.3	8.4	2.1	0.5
	Pamidronate 60 mg	3.8	1.9	18.2	1.7	22.0	3.6	1.6	0.2
	Pamidronate 30 mg	1.8	1.8	16.5	9.5	18.4	11.4	1.4	1.4
	No bisphosphonate treatment	0.0		7.0		7.0		0.0	
Ralston *et al.*[62]	Ibandronate 6 mg	11.1	–0.6	19.6	0.2	30.8	-0.5	1.8	0.0
	Ibandronate 4 mg	11.7	4.6	19.5	2.2	31.2	6.8	1.8	0.3
	Ibandronate 2 mg	7.1	7.1	17.3	10.3	24.4	17.4	1.5	1.5
	No bisphosphonate treatment	0.0		7.0		7.0		0.0	

TABLE 33 *Comparison of hypercalcaemia treatment strategies – costs*

		Drug cost per patient (£)		Hospital stay cost per patient (£)		Total cost per patient (£)	
Study	**Treatment**	**Cost**	**Increment**	**Cost**	**Increment**	**Cost**	**Increment**
Purohit *et al.*[130]	Pamidronate 90 mg	331	204	3344	305	3675	509
	Clodronate 1500 mg	127	127	3039	1969	3166	2096
	No bisphosphonate treatment	0		1070		1070	
Major *et al.*[131]	Zoledronate 8 mg	754	372	3137	–26	3891	347
	Zoledronate 4 mg	381	116	3163	269	3544	385
	Pamidronate 90 mg	266	266	2894	1824	3160	2090
	No bisphosphonate treatment	0		1070		1070	
Nussbaum *et al.*[66]	Pamidronate 90 mg	331	156	3344	563	3675	719
	Pamidronate 60 mg	175	101	2780	255	2956	356
	Pamidronate 30 mg	74	74	2525	1455	2599	1529
	No bisphosphonate treatment	0		1070		1070	
Ralston *et al.*[62]	Ibandronate 6 mg	472	162	3003	27	3475	189
	Ibandronate 4 mg	310	182	2976	334	3286	517
	Ibandronate 2 mg	128	128	2642	1572	2770	1699
	No bisphosphonate treatment	0		1070		1070	

TABLE 34 *Comparison of hypercalcaemia treatment strategies – cost-effectiveness*

Study	Comparison		Incremental drug cost per extra day of normocalcaemia (£)	Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)
	Treatment A	Treatment B			
Purohit *et al.*[130]	Pamidronate 90 mg	Clodronate 1500 mg	8	21	6970
	Clodronate 1500 mg	No bisphosphonate treatment	9	142	27735
Major *et al.*[131]	Zoledronate 8 mg	Zoledronate 4 mg	35	32	11944
	Zoledronate 4 mg	Pamidronate 90 mg	6	18	6214
	Pamidronate 90 mg	No bisphosphonate treatment	18	139	28311
Nussbaum *et al.*[66]	Pamidronate 90 mg	Pamidronate 60 mg	33	154	31399
	Pamidronate 60 mg	Pamidronate 30 mg	52	184	36140
	Pamidronate 30 mg	No bisphosphonate treatment	40	835	49207
Ralston *et al.*[62]	Ibandronate 6 mg	Ibandronate 4 mg	N/A	N/A	N/A
	Ibandronate 4 mg	Ibandronate 2 mg	39	112	27681
	Ibandronate 2 mg	No bisphosphonate treatment	18	239	35690

TABLE 35 *Comparison of hypercalcaemia treatment strategies – cost-effectiveness (eliminating strategies subject to dominance or extended dominance)*

Study	Treatment A	Treatment B	Incremental drug cost per extra day of response (£)	Incremental total cost per extra day of response (£)	Incremental total cost per life-year gained (£)[a]
Purohit *et al.*[130]	Pamidronate 90 mg	No bisphosphonate treatment	8	66	17500
Major *et al.*[131]	Zoledronate 8 mg	No bisphosphonate treatment	16	60	17100
Nussbaum *et al.*[66]	Pamidronate 90 mg	No bisphosphonate treatment	39	308	40800
Ralston *et al.*[62]	Ibandronate 4 mg	No bisphosphonate treatment	26	189	33400

[a] Rounded to the nearest £100.

- pamidronate 60 mg and pamidronate 30 mg – Nussbaum and colleagues[66]
- ibandronate 2 mg – Ralston and colleagues.[62]

Table 35 shows the new incremental cost-effective ratios after the elimination of dominated strategies. Of the remaining strategies, zoledronate 8 mg is apparently the most cost-effective. Pamidronate 90 mg has a similar level of cost-effectiveness when based on the Purohit[130] study, but is substantially less cost-effective when calculated from the Nussbaum[66] results.

Sensitivity analysis

The results of all four analyses were tested for sensitivity to the data and assumptions of the model (*Tables 36–39*). Changing the following parameters tested the results:

- the death rate of other causes
- the rate at which response diminishes after each relapse
- the time assumed for a treatment episode
- the unit cost of a day spent in hospital
- the time to relapse
- the response rate.

The results were not tested for sensitivity to drug price because it is clear from *Table 33* that drug costs are a small component of total cost.

The results seemed to be sensitive only to:

1. The amount of time in hospital during a treatment episode. Time in hospital increases incremental costs substantially.
2. The time to relapse. For the baseline results, median time to first relapse was used as an estimate of mean time to first relapse because three of the studies only reported medians. Nussbaum and colleagues,[66] who reported both, gave means that were approximately twice the size of the median. Doubling the time to relapse, not surprisingly, has a large impact on cost-effectiveness, where there are relatively high response rates.

On two occasions, a sensitivity analysis brought about a swing in relative cost-effectiveness. This occurred when assuming that the stay in hospital for treatment was zero days – this is equivalent to including only drug costs and not hospital costs. This had the effect of making zoledronate 4 mg relatively more cost-effective than 6 mg, and ibandronate 2 mg more cost-effective than 4 mg.

Taking into account all of these uncertainties gives a broad range of cost-effectiveness for the drug regimens considered. For zoledronate 8 mg, for example, the cost per extra day of normocalcaemia could range from £9 to £152 and the cost per life-year gained between £2200 and £40,600. The use of bisphosphonates to treat cancer-associated hypercalcaemia is likely to be considered good value for money at the lower end of this range but of more marginal cost-effectiveness at the upper end.

Cost analysis of preventing skeletal morbidity – breast cancer

Table 40 shows the number of events per breast cancer patient and the costs per patient over 4 years from diagnosis of bone metastases, as estimated using a Markov model.

Number of skeletal-related events

The model estimated that 84% of patients would be dead by the end of the fourth year (*Table 40*). It was assumed that patients in the bisphosphonate arm would be treated with monthly cycles of pamidronate 90 mg until death, or up to the end of the fourth year. This amounted to 21.5 months of treatment per patient on average.

It was estimated that for every 100 patients treated with bisphosphonates, 179 SREs would be averted – 54 non-vertebral fractures, 16 vertebral fractures, 34 episodes of hypercalcaemia, 64 episodes of RT and 12 episodes of surgery (*Table 40*). In addition, bone pain was reduced for an average of 3.2 months per patient.

Costs

The cost of bisphosphonate therapy, including the use of outpatient facilities, was £5237 per patient (*Table 40*). This cost was partly (59%) offset by cost savings from the reduced incidence of SREs – comparable to that of the previous economic analyses (36–63%). In addition, cost savings associated with reduced incidence of bone pain offset 32% of the cost. Hence the overall incremental cost of bisphosphonate use in this context was estimated to be £444 per patient.

The cost savings associated with reduced fracture care are potentially large (*Table 41*), and are dependent on both the intensity and duration of care required. If the less costly package of care is required for just 3 months per long bone fracture, this would imply that bisphosphonate therapy is cost-saving overall. If more intensive care is required or the duration of care is longer, then the incremental cost savings associated with the therapy could be considerable.

TABLE 36 *Economic analysis of Purohit and colleagues[130]– sensitivity analysis (excluding strategies where there is dominance or extended dominance)*

			Comparison			
	Sensitivity analysis	**Detail**	**Treatment A**	**Treatment B**	**Incremental total cost per extra day of normocalcaemia (£)**	**Incremental total cost per life-year gained (£)[a]**
0	Baseline		Pamidronate 90 mg	No bisphosphonate treatment	66	17500
1	Probability of death from other causes – low	P3 =0 %	Pamidronate 90 mg	No bisphosphonate treatment	74	19000
2	Probability of death from other causes – high	P3 = 50%	Pamidronate 90 mg	No bisphosphonate treatment	58	15600
3	Diminishing of response – fast	Drug is 50% less effective after each relapse	Pamidronate 90 mg	No bisphosphonate treatment	74	19000
4	Diminishing of response – slow	Drug is 75% less effective after each relapse	Pamidronate 90 mg	No bisphosphonate treatment	61	16600
5	Treatment time – short	0 days (therefore cumulative time in hospital is the same for all patients)	Pamidronate 90 mg	No bisphosphonate treatment	8	3100
6	Treatment time – long	14 days	Pamidronate 90 mg	No bisphosphonate treatment	124	25800
7	Cost of an inpatient stay – high	75th centile of reference cost distribution = £194 per day	Pamidronate 90 mg	No bisphosphonate treatment	82	21600
8	Cost of an inpatient stay – low	25th centile of reference cost distribution = £109 per day	Pamidronate 90 mg	No bisphosphonate treatment	53	14300
9	Time to relapse – longer	Assume mean time to relapse is double the median time to relapse	Pamidronate 90 mg	No bisphosphonate treatment	33	10200

continued

TABLE 36 *Economic analysis of Purohit and colleagues[130]– sensitivity analysis (excluding strategies where there is dominance or extended dominance) (cont'd)*

Sensitivity analysis	Detail	Comparison		Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)[a]
		Treatment A	Treatment B		
10 Response rate – high	100% for optimal strategy (same as baseline in this case)	Pamidronate 90 mg	No bisphosphonate treatment	66	17500
11 Response rate – Low	50% for optimal strategy	Pamidronate 90 mg	No bisphosphonate treatment	109	24500
12 All of the above – high cost	1, 3, 6, 7 and 11 combined	Pamidronate 90 mg	No bisphosphonate treatment	294	44100
13 All of the above – low cost	2, 4, 5, 8, 9 and 10 combined	Pamidronate 90 mg	No bisphosphonate treatment	4	1300

[a] Rounded to the nearest £100.

TABLE 37 *Economic analysis of Major and colleagues[131] – sensitivity analysis (excluding strategies where there is dominance or extended dominance)*

Sensitivity analysis	Detail	Comparison		Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)[a]
		Treatment A	Treatment B		
0 Baseline		Zoledronate 8 mg	No bisphosphonate treatment	60	17100
1 Probability of death from other causes – low	P3 = 0%	Zoledronate 8 mg	No bisphosphonate treatment	35	18600
2 Probability of death from other causes – high	P3 = 50%	Zoledronate 8 mg	No bisphosphonate treatment	29	15600
3 Diminishing of response – fast	Drug is 50% less effective after each relapse	Zoledronate 8 mg	No bisphosphonate treatment	35	18500
4 Diminishing of response – slow	Drug is 75% less effective after each relapse	Zoledronate 8 mg	No bisphosphonate treatment	30	16200

continued

TABLE 37 *Economic analysis of Major and colleagues[131] – sensitivity analysis (excluding strategies where there is dominance or extended dominance) (cont'd)*

Sensitivity analysis	Detail	Comparison		Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)[a]
		Treatment A	Treatment B		
5 Treatment time – short	0 days (therefore cumulative time in hospital is the same for all patients)	Zoledronate 8 mg	Zoledronate 4 mg	35	12600
		Zoledronate 4 mg	No bisphosphonate treatment	11	3900
6 Treatment time – long	14 days	Zoledronate 8 mg	No bisphosphonate treatment	30	24300
7 Cost of an inpatient stay – high	75th centile of reference cost distribution = £194 per day	Zoledronate 8 mg	No bisphosphonate treatment	32	20500
8 Cost of an inpatient stay – low	25th centile of reference cost distribution = £109 per day	Zoledronate 8 mg	No bisphosphonate treatment	33	14300
9 Time to relapse – longer	Assume mean time to relapse is double the median time to relapse	Zoledronate 8 mg	No bisphosphonate treatment	16	9700
10 Response rate – high	100% for optimal strategy	Zoledronate 8 mg	No bisphosphonate treatment	31	15900
11 Response rate – low	50% for optimal strategy	Zoledronate 8 mg	No bisphosphonate treatment	27	23000
12 All of the above – high cost	1, 3, 6, 7 and 11 combined	Zoledronate 8 mg	No bisphosphonate treatment	152	40600
13 All of the above – low cost	2, 4, 5, 8, 9 and 10 combined	Zoledronate 8 mg	No bisphosphonate treatment	9	2200

[a] Rounded to the nearest £100.

TABLE 38 *Economic analysis of Nussbaum and colleagues[66] – sensitivity analysis (excluding strategies where there is dominance or extended dominance)*

			Comparison		
	Sensitivity analysis	Detail	Treatment A	Treatment B	Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)[a]
0	Baseline		Pamidronate 90 mg	No bisphosphonate treatment	308	40800
1	Probability of death from other causes – low	P3 = 0%	Pamidronate 90 mg	No bisphosphonate treatment	346	42500
2	Probability of death from other causes – high	P3 = 50%	Pamidronate 90 mg	No bisphosphonate treatment	271	38900
3	Diminishing of response – fast	Drug is 50% less effective after each relapse	Pamidronate 90 mg	No bisphosphonate treatment	344	42400
4	Diminishing of response – slow	Drug is 75% less effective after each relapse	Pamidronate 90 mg	No bisphosphonate treatment	285	39600
5	Treatment time – short	0 days (therefore cumulative time in hospital is the same for all patients)	Pamidronate 90 mg	No bisphosphonate treatment	39	14300
6	Treatment time – long	14 days	Pamidronate 90 mg	No bisphosphonate treatment	578	46700
7	Cost of an inpatient stay – high	75th centile of reference cost distribution = £194 per day	Pamidronate 90 mg	No bisphosphonate treatment	381	50400
8	Cost of an inpatient stay – low	25th centile of reference cost distribution = £109 per day	Pamidronate 90 mg	No bisphosphonate treatment	247	32700
9	Time to relapse – longer	Assume mean time to relapse is double the median time to relapse	Pamidronate 90 mg	No bisphosphonate treatment	154	30000

continued

TABLE 38 *Economic analysis of Nussbaum and colleagues[66] – sensitivity analysis (excluding strategies where there is dominance or extended dominance) (cont'd)*

Sensitivity analysis	Detail	Comparison		Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)[a]
		Treatment A	Treatment B		
10 Response rate – high	100% for optimal strategy (same as baseline in this case)	Pamidronate 90 mg	No bisphosphonate treatment	308	40800
11 Response rate – low	50% for optimal strategy	Pamidronate 90 mg	No bisphosphonate treatment	506	47500
12 All of the above – high cost	1, 3, 6, 7 and 11 combined	Pamidronate 90 mg	No bisphosphonate treatment	1373	65200
13 All of the above – low cost	2, 4, 5, 8, 9 and 10 combined	Pamidronate 90 mg	No bisphosphonate treatment	16	6000

[a] Rounded to the nearest £100

TABLE 39 *Economic analysis of Ralston and colleagues[62] – sensitivity analysis (excluding strategies where there is dominance or extended dominance)*

			Comparison		
Sensitivity analysis	**Detail**	**Treatment A**	**Treatment B**	**Incremental total cost per extra day of normocalcaemia (£)**	**Incremental total cost per life-year gained (£)[a]**
0 Baseline		Ibandronate 4 mg	No bisphosphonate treatment	189	33400
1 Probability of death from other causes – low	P3 = 0%	Ibandronate 4 mg	No bisphosphonate treatment	208	35000
2 Probability of death from other causes – high	P3 = 50%	Ibandronate 4 mg	No bisphosphonate treatment	170	31800
3 Diminishing of response – fast	Drug is 50% less effective after each relapse	Ibandronate 4 mg	No bisphosphonate treatment	206	34800
4 Diminishing of response – slow	Drug is 75% less effective after each relapse	Ibandronate 4 mg	No bisphosphonate treatment	178	32500
5 Treatment time – short	0 days (therefore cumulative time in hospital is the same for all patients)	Ibandronate 4 mg Ibandronate 2 mg	Ibandronate 2 mg No bisphosphonate treatment	39 18	14400 6600
6 Treatment time – long	14 days	Ibandronate 4 mg	No bisphosphonate treatment	351	41000
7 Cost of an inpatient stay – high	75th centile of reference cost distribution = £194 per day	Ibandronate 4 mg	No bisphosphonate treatment	232	41200
8 Cost of an inpatient stay – low	25th centile of reference cost distribution = £109 per day	Ibandronate 4 mg	No bisphosphonate treatment	152	26900
9 Time to relapse – longer	Assume mean time to relapse is double the median time to relapse	Ibandronate 4 mg	No bisphosphonate treatment	94	22500
10 Response rate – high	100% for optimal strategy	Ibandronate 4 mg	No bisphosphonate treatment	157	30400

continued

TABLE 39 *Economic analysis of Ralston and colleagues[62] – sensitivity analysis (excluding strategies where there is dominance or extended dominance) (cont'd)*

Sensitivity analysis	Detail	Comparison		Incremental total cost per extra day of normocalcaemia (£)	Incremental total cost per life-year gained (£)[a]
		Treatment A	Treatment B		
11 Response rate – low	50% for optimal strategy	Ibandronate 4 mg	No bisphosphonate treatment	257	38400
12 All of the above – high cost	1, 3, 6, 7 and 11 combined	Ibandronate 4 mg	No bisphosphonate treatment	691	58100
13 All of the above – low cost	2, 4, 5, 8, 9 and 10 combined	Ibandronate 4 mg	No bisphosphonate treatment	9	3300

[a] Rounded to the nearest £100.

TABLE 40 *Use of bisphosphonates to prevent skeletal events in metastatic breast cancer – events and costs*

	No. of events per patient			Cost per patient (£)		
	Bisphospho-nate arm	No-bisphospho-nate arm	Increment	Bisphospho-nate arm	No-bisphospho-nate arm	Increment
Deaths	0.84	0.84	0.00			
Bisphosphonate therapy (months)	21.5	0.00	21.5	5237	0	5237
Non-vertebral fracture	2.07	2.60	–0.54	3947	4973	–1026
Vertebral fracture	1.51	1.67	–0.16	2893	3197	–304
Hypercalcaemia	0.35	0.69	–0.34	1159	2283	–1124
RT	1.59	2.23	–0.64	1065	1496	–431
Surgery	0.16	0.28	–0.12	315	538	–223
	5.68	*7.47*	*–1.79*	*9380*	*12487*	*–3107*
Pain reduction (months)	3.2	0.00	3.2	–1686	–	–1686
Total cost (per patient)				12931	12487	444

TABLE 41 *Use of bisphosphonates to prevent skeletal events in metastatic breast cancer – cost of fracture care*[a]

No. of months of care per fracture	Lower cost community care package		Higher cost community care package	
	Cost per fracture (£)	Incremental cost of bisphosphonate therapy per patient (£)	Cost per fracture (£)	Incremental cost of bisphosphonate therapy per patient (£)
0	0	400	0	400
1	1300	0	3900	–800
2	2700	–400	7900	–2100
3	4000	–900	11800	–3400
4	5300	–1300	15800	–4700
5	6600	–1700	19700	–6000
6	8000	–2200	23600	–7300
7	9300	–2600	27600	–8600
8	10600	–3000	31500	–9900
9	11900	–3500	35400	–11200
10	13300	–3900	39400	–12500
11	14600	–4300	43300	–13800
12	15900	–4800	47300	–15100

[a] Rounded to the nearest £100.

Even if we ignore these rather uncertain cost savings, it could be argued that the preventive use of bisphosphonate therapy is good value for money (cost-effective). *Table 42* shows that the results of the model, excluding savings from reduced fracture care, equate to a cost of £250 per SRE averted or £1645 per fracture averted, using the UK's convention of discounting costs at 6% and health effects at 1%.

From *Table 42*, it is clear that the results are not sensitive to the discount rates employed. This is not very surprising, given that the time horizon of the model is only 4-years, and much of the cost is incurred in the first 2 years.

Sensitivity analysis

The results, excluding fracture care cost savings, were tested for sensitivity to the data and

TABLE 42 *Cost-effectiveness of bisphosphonate therapy in preventing skeletal events – breast cancer (not including savings from reduced fracture care)*

	Effect discount rate %	Cost discount rate (%)				
		6[a]	5	4	3	0
Incremental cost per patient (£)	N/A	**444**	433	422	410	373
Incremental cost per year of therapy (£)	N/A	**248**	242	236	229	208
Incremental cost per fracture averted (£)	6	674	657	640	622	565
	5	668	652	635	617	560
	4	662	646	629	612	555
	3	656	640	624	606	550
	2	651	635	618	601	545
	1	**645**	629	612	595	540
	0	638	623	607	590	535
Incremental cost per SRE averted (£)	6	262	255	249	242	219
	5	259	253	246	240	218
	4	257	251	244	238	216
	3	255	249	242	235	214
	2	253	246	240	233	212
	1	**250**	244	238	231	210
	0	248	242	236	229	208
Incremental cost per QALY gained (£)[b]	0	**1380**	1346	1311	1275	1157

[a] Figures in bold are consistent with the UK government discounting convention.
[b] Using QALYs gained from Dranitsaris and Hsu[141] adjusted up to account for duration of treatment 22 months (compared with 10 months): $0.15 \times 22/10 = 0.33$.

assumptions of the model (*Table 43*). The results were not sensitive to the survival rate, the inclusion of SCC or the assumption of constant event rates. Costs and cost-effectiveness were sensitive to the price of bisphosphonates, the probability of averting an event and the unit costs associated with events.

Taking into account all of these uncertainties, the cost consequence of bisphosphonate therapy could lie anywhere between saving £19,000 per patient to augmenting costs by £4000 per patient. The cost per SRE averted could be anything up to £13,000.

Cost analysis of preventing skeletal morbidity – multiple myeloma

Table 44 shows the number of events per multiple myeloma patient and the costs per patient over 4 years from diagnosis, as estimated using a Markov model.

Number of skeletal-related events

The model estimated that 68% of patients would be dead by the end of the fourth year (*Table 44*). It was assumed that patients in the bisphosphonate arm would be treated with monthly cycles of pamidronate 90 mg until death, or up to the end of the fourth year. This amounted to 28.2 months of treatment per patient on average.

It was estimated that for every 100 patients treated with bisphosphonates, 162 SREs would be averted – 28 non-vertebral fractures, 74 vertebral fractures, two episodes of hypercalcaemia and 58 episodes of RT (*Table 44*). In addition, bone pain was reduced for an average of 4.1 months per patient.

Costs

The cost of bisphosphonate therapy, including the use of outpatient facilities, was £6710 per patient (*Table 44*). This cost was partly (35%) offset by cost savings from the reduced incidence of skeletal events – comparable to that of the previous economic analyses (33–35%). In addition, cost savings associated with reduced incidence of bone pain offset 29% of the cost. Hence the overall incremental cost of bisphosphonate use in this context was estimated to be £2396 per patient.

As with breast cancer, the cost savings associated with reduced fracture care are potentially large (*Table 45*), and are dependent on both the intensity and duration of care required. If the less

TABLE 43 *Use of bisphosphonates to prevent skeletal events in metastatic breast cancer – sensitivity analysis (not including savings from reduced fracture care)*

		Incremental cost per patient (£)		Incremental cost per SRE averted (£)	
Sensitivity analysis	**Description**	**Low**	**High**	**Low**	**High**
Baseline	Results as reported in Table 42 (costs discounted at 6% and effects at 1%)	444		250	
Median survival	A = Hortobagyi *et al.*[208] lower confidence limit (12 months); B =Theriault *et al.*[139] upper confidence limit (27 months)	243	582	109	437
Event rates	A = using lower confidence limit for the relative risks; B = using upper confidence limit for the relative risks	–1473	2888	N/A – cost-saving	7383
Drug costs	A = 1,500 mg i.v. clodronate (£68.90); B = 4 mg zoledronate (£195)	–1392	1273	N/A – cost-saving	717
Event costs	A = 25th centile of reference cost distribution; B = 75th centile of reference cost distribution	–583	2226	N/A – cost-saving	1254
Surgery cost	£18,000 from Hillner *et al.*[310]	–864		N/A – cost-saving	
Graduating survival and event rates	Year 2 = 150% of Year 1; Year 3 = 150% of Year 2; etc. Year 1 is set so that median survival is the same as the baseline estimate	12		6	
Differential in length of stay	Inpatient unit costs of the bisphosphonate arm are 50% of the no-bisphosphonate arm – Beusterian *et al.*[153]	–3713		N/A– cost-saving	
Pain reduction – no. needed to treat (NNT)	A =lower confidence limit for NNT=5; B = upper confidence limit for NNT=12 646	–230	1147	N/A – cost-saving	
Inclusion of spinal cord compression treatment	£14,000 per event from Hillner *et al.*[310]; incidence (no-bisphosphonate) = 0.07 per year from Lipton *et al.*;[135] relative risk of 0.878 from metal analysis	148		250	
Hospitalisation rate for fractures	40% have inpatient stay, 60% have outpatient visit[120]		1206		679
All of the above		–19434	5904	N/A – cost-saving	13153

TABLE 44 *Use of bisphosphonates to prevent skeletal events in multiple myeloma – events and costs*

	No. of events per patient			Cost per patient (£)		
	Bisphospho-nate arm	No-bisphospho-nate arm	Increment	Bisphospho-nate arm	No-bisphospho-nate arm	Increment
Deaths	0.68	0.68	0.00			
Bisphosphonate therapy (months)	28.2	0.0	28.2	6710	0	6710
Non-vertebral fracture	0.30	0.58	–0.28	567	1100	–533
Vertebral fracture	1.36	2.10	–0.74	2567	3961	–1394
Hypercalcaemia	0.67	0.69	–0.02	2209	2263	–55
RCT	2.04	2.62	–0.58	1352	1738	–386
	4.37	5.99	–1.62	6694	9063	–2368
Pain reduction (months)	4.1	0.0	4.1	–1946	–	–1946
Total cost (per patient)				11458	9063	2396

TABLE 45 *Use of bisphosphonates to prevent skeletal events in multiple myeloma – cost of fracture care*[a]

No. of months of care per fracture	Lower cost community care package		Higher cost community care package	
	Cost per fracture (£)	Incremental cost of bisphosphonate therapy per patient (£)	Cost per fracture (£)	Incremental cost of bisphosphonate therapy per patient (£)
0	0	2400	0	2400
1	1300	2200	3900	1700
2	2700	1900	7900	1000
3	4000	1700	11800	400
4	5300	1500	15800	–300
5	6600	1300	19700	–1000
6	8000	1000	23600	–1700
7	9300	800	27600	–2400
8	10600	600	31500	–3000
9	11900	300	35400	–3700
10	13300	100	39400	–4400
11	14600	–100	43300	–5100
12	15900	–300	47300	–5800

[a] Rounded to the nearest £100.

costly package of care is required for 11 months per long bone fracture then this would imply that bisphosphonate therapy is cost-saving overall. If more intensive care is required then cost savings are more likely.

Even if we ignore these rather uncertain cost savings, it could be argued that the preventative use of bisphosphonate therapy is reasonably good value for money (cost-effective). *Table 46* shows that the results of the model, excluding savings from reduced fracture care, equate to a cost of £1497 per skeletal event averted or £2376 per fracture averted, discounting at 6%.

As with breast cancer, it is clear that the results are not sensitive to the discount rates employed (*Table 46*).

TABLE 46 *Cost-effectiveness of bisphosphonate therapy in preventing skeletal events – multiple myeloma (not including savings from reduced fracture care)*

	Effect discount rate %	Cost discount rate (%)				
		6[a]	5	4	3	0
Incremental cost per patient (£)	N/A	**2396**	2406	2417	2428	2464
Incremental cost per year of therapy (£)	N/A	**1019**	1023	1028	1033	1048
Incremental cost per fracture averted (£)	6	2507	2518	2529	2541	2578
	5	2481	2492	2503	2515	2552
	4	2455	2466	2477	2489	2525
	3	2429	2440	2451	2462	2498
	2	2402	2413	2424	2435	2471
	1	**2376**	2386	2397	2408	2443
	0	2349	2359	2370	2381	2416
Incremental cost per SRE averted (£)	6	1579	1586	1594	1601	1624
	5	1563	1570	1577	1585	1608
	4	1547	1554	1561	1568	1591
	3	1530	1537	1544	1551	1574
	2	1514	1520	1527	1534	1557
	1	**1497**	1504	1510	1517	1539
	0	1480	1487	1493	1500	1522

[a] Figures in bold are consistent with the UK government discounting convention.

Sensitivity analysis

The results, excluding fracture care cost savings, were tested for sensitivity to the data and assumptions of the model (*Table 47*). The results were not sensitive to the survival rate or the assumption of constant event rates. Cost was more sensitive to the unit costs of skeletal events, the hospitalisation rate and the pain reduction number needed to treat. Costs were most sensitive to the probability of averting an event and the cost of bisphosphonate therapy.

Taking into account all of these uncertainties, at one extreme bisphosphonates could save £6000 per patient and at the other extreme they not only amount to a cost of £8000 per patient but they also increase the number of SREs.

Preventing skeletal morbidity – breast cancer and multiple myeloma compared

Median survival in the trials covered was higher for multiple myeloma than for metastatic breast cancer. As a consequence, patients were on bisphosphonate therapy for longer and the cost of therapy was greater. Also as a consequence of this parameter, there were more months of pain reduction and therefore greater cost savings.

The relative risks were smaller for the multiple myeloma patients for some events, for example vertebral fractures, and for breast cancer patients for others, hypercalcaemia and surgery, which was not included in the multiple myeloma model. Overall, the cost savings attributable to reduced SREs was similar for both patient groups, but the higher therapy costs for multiple myeloma patients resulted in a higher incremental cost.

The cost per fracture averted was three and a half times higher for multiple myeloma and the cost per SRE averted was nearly six times higher. The potential cost savings attributable to reduced need for fracture care were greater for the breast cancer patients, as the evidence appears to show that bisphosphonates are more effective at preventing non-vertebral fractures in this group. Bisphosphonate therapy for multiple myeloma patients is much less likely to be cost-saving than it is for breast cancer patients.

TABLE 47 *Use of bisphosphonates to prevent skeletal events in multiple myeloma – sensitivity analysis (not including savings from reduced fracture care)*

Sensitivity analysis		Description	Incremental cost per patient (£)		Incremental cost per SRE averted (£)	
			Low	High	Low	High
0	Baseline	Results as reported in Table 46 (costs discounted at 6% and effects at 1%)	2396		1497	
1	Median survival	A = Berenson *et al.*[138] (24 months); B = McCloskey *et al.*[137] – upper confidence limit (42 months)	2274	2599	1405	1557
2	Event rates	A = using lower confidence limit for the relative risks; B = using upper confidence limit for the relative risks	384	6144	139	N/A – events not averted
3	Drug costs	A = 1500 mg i.v. clodronate (£68.90); B = 4 mg zoledronate (£195)	42	3457	27	2160
4	Event costs	A = 25th centile of reference cost distribution; B = 75th centile of reference cost distribution	1420	3607	887	2254
5	Graduating survival and event rates	Year 2 = 150% of Year 1; Year 3 = 150% of Year 2; etc. etc. Year 1 is set so that median survival is consistent with baseline assumption	2155		1143	
6	Differential in length of stay	Inpatient unit costs of bisphosphonate arm are 50% of the no-bisphosphonate arm – Beusterien *et al*[153]	1008		630	
7	Pain reduction – number needed to treat	A = lower confidence limit for NNT = 5; B = upper confidence limit for NNT = 12	1617	3206	1010	2004
8	Hospitalisation rate for #	40% inpatient stay, 60% outpatient visit[120]		3499		2187
9	All of the above		–5670	8243	N/A – cost saving	N/A – event not averted

Chapter 4
Discussion

Hypercalcaemia review

Bisphosphonates are now the drug of choice for the treatment of acute hypercalcaemia of malignancy. It is standard practice to give intravenous bisphosphonate therapy together with intravenous fluids. Fluids are important because patients are often dehydrated, which can exacerbate hypercalcaemia. This review demonstrates that bisphosphonates as a class of drugs are effective, with over 70% of patients reaching normocalcaemia. Bisphosphonates are well tolerated and serious side-effects are rare. A meta-analysis was not undertaken owing to the heterogeneity of the data in the included studies, thus limiting the conclusions that can be reached.

Rehydration will partially lower serum calcium, depending on the degree to which the patient is dehydrated. Therefore, in order to look at the true effect of bisphosphonates in a trial setting, it was decided that serum calcium should have been measured after rehydration in studies included in this review. Our review therefore excluded three recent studies comparing different bisphosphonates. These were well-designed RCTs, comparing pamidronate with zoledronate,[131] ibandronate[177,178] and clodronate.[168]

Major and colleagues[131] studied 287 patients with CCa ≥ 3.0 mmol/l. Patients were randomised to 4 or 8 mg of zoledronate or 90 mg of pamidronate. Zoledronate was more effective than pamidronate, with 88.4% ($p < 0.002$) and 86.7% ($p < 0.015$) vs 69.7% of patients, respectively, reaching normocalcaemia by day 10. In addition, the median duration of normocalcaemia was greater with zoledronate, 32 and 43 days versus 18 days, respectively.

In a further study, ibandronate 2–4 mg and pamidronate 15–90 mg, depending on baseline CCa, were equally effective with 76.5% (33) and 75% (34) patients reaching normocalcaemia, respectively.[177,178] Sub-group analyses (based on 17 patients) suggested that ibandronate was superior in normalising the mean group calcium in patients with baseline CCa ≥ 3.5 mmol/l. An abstract by Atula and colleagues[168] showed that pamidronate 90 mg was as effective as clodronate 1500 mg, but superior to a lower dose of clodronate (900 mg). This supports the findings of previous studies by Purohit and colleagues[130] and Gucalp and colleagues.[57]

It could be argued that a more potent bisphosphonate might improve the percentage of patients reaching normocalcaemia, and the study by Major and colleagues[131] supports this hypothesis. However, in a number of studies this was not the case,[130,168,171] although these studies were not statistically powered to demonstrate superiority of one bisphosphonate against another.

There is some evidence that more potent bisphosphonates give a longer time to relapse. Aminobisphosphonates are more effective than non-aminobisphosphonates in delaying relapse; pamidronate gives a longer time to relapse than clodronate[130,162] or etidronate.[162] Aminobisphosphonates vary in potency; zoledronate is 100 times more potent than pamidronate and gave a median time to relapse of 43 (8 mg) versus 18 (90 mg) days, respectively.[131]

There is evidence to support a dose response for a number of bisphosphonates.[60,62,65,66,131] One study also showed a trend of increasing time to relapse with increasing doses of pamidronate, but this did not reach statistical significance.[66] The study by Major and colleagues[131] suggests that 8 mg of zoledronate delays time to relapse compared with 4 mg. Pharmaceutical companies currently recommend higher doses for higher initial baseline calcium. If however, there is a significant increase in time to relapse at higher doses, a higher initial dose may be more cost-effective.

Clinical experience suggests that subsequent episodes of hypercalcaemia become increasingly difficult to treat. This raises a number of questions. Is this simply due to the poor prognosis associated with advanced cancer, in particular when no further anticancer therapy is available? Do patients become resistant to one drug with time? Does the renal mechanism of hypercalcaemia become more prominent with advancing disease? None of the included studies distinguished between first and subsequent episodes of hypercalcaemia. Interestingly, there

are case reports of patients being resistant to one bisphosphonate, but responsive to another (Baxter C, Jamal H, Cheung J, Differential response to biphosphonates in a patient with malignant hypercalcaemia: personal communication, 2002). One study in patients with Paget's disease found that 16% of patients failed to show a biochemical response to pamidronate, but did subsequently respond to alendronate or tiludronate.

Is there any value in giving prophylactic bisphosphonates to patients after the first episode of hypercalcaemia? Ringenberg and Ritch[258] showed that oral etidronate 20 mg/kg/day was more effective than placebo in prolonging time to relapse in those patients with hypercalcaemia who responded to initial therapy. Median time to relapse was 29 days in the treatment arm versus 11 days for placebo. A similar study by Schiller and colleagues[259] found a median time to relapse of 55 versus 28 days, but these differences were not statistically significant.

Kristensen and colleagues[81] found that survival in breast cancer patients with their first episode of hypercalcaemia was related to baseline serum calcium and was worse if no systemic treatment was available. Other studies have performed sub-group analyses and shown that the initial level of PTHrP correlates with poor response to bisphosphonates.[320,321] Wimalawansa found that patients with the highest levels of PTHrP had a worse prognosis with shorter duration of normocalcaemia after pamidronate, although PTHrP did not correlate with baseline corrected calcium.[50]

Bisphosphonates act on bone to inhibit osteoclastic resorption of bone, the increased bone resorption being stimulated by PTHrP or local cytokines. Bisphosphonates have no effect on the renal action of PTHrP.[162] Therefore, development of drugs to inhibit the renal tubular resorption of calcium mediated by PTHrP are needed: specific inhibitors of PTHrP action, antibodies to PTHrP or inhibitors of PTHrP production. Animal work has shown that PTHrP antibodies can reverse experimentally induced hypercalcaemia and prolong survival in athymic mice.[322] However, PTHrP is a complex molecule and involved in a number of different physiological processes,[323] and concern has therefore been raised regarding the potential adverse effects of generalised blockade of PTHrP action.

Time to normocalcaemia is not affected by different bisphosphonates. Dosing regimens did not affect outcome; therefore, on economic grounds, bisphosphonates should be given rapidly, in a small volume of fluid. The rate is limited by renal side-effects, since too rapid administration can lead to deposition of calcium complexes in the kidney and subsequent renal failure. In the treatment of hypercalcaemia, the time required to give adequate volume for rehydration is likely to be the factor limiting infusion times and therefore length of stay. It may be clinically beneficial and more cost-effective to treat patients with a higher dose of bisphosphonate regardless of initial presenting calcium.

Skeletal morbidity review

Several important questions need to be addressed in relation to bisphosphonate therapy for patients with bone metastases. When should bisphosphonate therapy commence, when should it stop and who should we treat? Which drug should be used, what is the optimum dose, by which route should it be delivered and what is the most effective scheduling regimen?

The primary analysis shows a highly significant reduction in vertebral, non-vertebral and combined fractures, radiotherapy and hypercalcaemia for patients receiving bisphosphonates. From the calculated pooled ORs, the risk of an SRE for those taking bisphosphonates is 65.3% of the risk compared with the risk for those patients not taking bisphosphonates for non-vertebral fractures, 69.2% for vertebral fractures, 65.3% for combined fractures, 67.4% for RT and 54.4% for hypercalcaemia.

In the primary analysis, the reduction in the need for orthopaedic fractures did not reach significance. However, the sub-analysis of pamidronate showed a significant effect, $p = 0.009$. The studies in this analysis were all of at least 1 year duration. In addition, the sub-analysis at fixed time points clearly demonstrates an increasing benefit with time for the reduction in the need for orthopaedic surgery in patients treated with bisphosphonates (*Figure 13*). This finding is supported by the contribution to the primary analysis of one study of 9 months' duration (Murphy R, Novartis Pharmaceuticals: personal communication, 2001). This study favours control rather than bisphosphonate (*Figure 12d*). If only the results of studies of at least 12 months' duration are analysed, then a significant benefit of bisphosphonates in reducing

orthopaedic surgery is clearly demonstrated, OR (95% CI) 0.587 (0.393 to 0.875), $p = 0.009$.

The primary analysis showed no reduction in the incidence of SCC. This is a rare event in comparison with the other skeletal morbidity end-points and therefore a greater number of patients would be needed to show a significant difference between treatment and control groups.

Although there is no survival advantage to be gained by taking bisphosphonates to prevent skeletal morbidity, there is a delay in time to first SRE. The evidence for this is clear for intravenous bisphosphonates (pamidronate, zoledronate) but conflicting for oral clodronate. A delay in time to first SRE is likely to have a major impact on patients' quality of life, although there is little objective evidence to support this from the studies available. It is important that good quality of life data are collected in future studies. A delay in time to first SRE will also translate into cost-savings for the NHS in these patients, where survival is the same for both groups.

Studies examining the proportion of patients with a given outcome at fixed time points help to determine the minimum length of time that patients need to be treated with bisphosphonates in order to gain some benefit. There is no evidence that treatment with bisphosphonates for less than 6 months has an impact on skeletal morbidity.[193,199,201,217] This may reflect the small numbers of patients and low event rate in these studies. However, it may be inappropriate to treat patients with bone metastases if they have a poor prognosis. The data suggest that patients need at least 6 months of treatment to benefit from a reduction in skeletal morbidity (with the exception of pain relief). Wong and Wiffen[121] calculated numbers needed to treat (NNT) from a meta-analysis of studies using bisphosphonates to treat bone pain. They showed that one patient benefits from 'some pain relief' for every six that are treated, OR 2.37 (95% CI: 1.61 to 3.5). The maximum response to pain relief is likely to be observed by 4 weeks of treatment.[121]

The OR for bisphosphonates reducing the need for RT is highly significant at 6 months. There is a trend towards a reduction in non-vertebral fractures by 6 months, but this does not reach significance. This is likely to be a reflection of the smaller numbers of patients (753–1130) used in the fixed time-point analyses compared with the larger numbers (3376) used in the primary analyses. Orthopaedic procedures do reach significance, but not until 24 months. Again, this can be partly explained by a lack of power, 2556 in the primary analyses compared with 753 in the secondary analyses. The facts that the ORs decrease and the CIs narrow at successive time points suggest that there is also a real effect with time. In other words, it may be a reflection of the time needed for treatment with bisphosphonates to have an impact on particular skeletal morbidity end-points.

Episodes of hypercalcaemia are significantly reduced at <12 months; the p value then reverts to a non-significant result at <18 months, with increasing significance for subsequent time points. The fluctuation in the results for hypercalcaemia is due to inclusions of different studies at different time points. In particular, studies in patients with multiple myeloma influence the results, as discussed below.

Analyses of different disease groups showed significant reductions in all skeletal morbidity end-points for breast cancer except for vertebral fractures and SCC. In contrast, multiple myeloma analyses showed significant results for reduction of vertebral fractures, but not hypercalcaemia episodes. These differences are not seen in the overall analyses, which have greater numbers of patients. However, the difference may be explained by greater disease activity in the vertebrae in myeloma, resulting in preferential localisation of bisphosphonates to this site. It is interesting that in the myeloma group prevention of hypercalcaemia is not significant ($p < 0.852$). Since 1079 patients contribute to this analysis, this may be a real effect. It is thought the mechanisms leading to hypercalcaemia are different in myeloma. The authors are aware that two Cochrane reviews are currently in progress considering bisphosphonate use in myeloma and breast cancer.

Body and colleagues found that more patients failed to respond to bisphosphonates with each successive episode of hypercalcaemia: 10, 31 and 85% of patients for first, second and third episodes, respectively.[324] Decreased responsiveness of hypercalcaemia is linked to rising levels of PTHrP, which acts by increasing bone resorption and enhancing tubular calcium reabsorption, especially in tumours other than breast.[327] In multiple myeloma a number of cytokines in addition to PTHrP are released, such as IL-1, IL-6 and TNF. These stimulate bone resorption and may well have a role in hypercalcaemia of malignancy.[48] Additionally, if renal mechanisms

become predominant, the effect of bisphosphonates will be mitigated because their site of action is in the bone.

Sub-group analyses of different bisphosphonates show that studies using pamidronate show significant results for all end-points except SCC. Clodronate studies showed significant efficacy for reduction of hypercalcaemia and vertebral and non-vertebral fractures. RT did not reach significance but this is likely to be because the analysis was underpowered (207 patients). Zoledronate studies demonstrated significant efficacy for fractures (vertebral, non-vertebral and combined) and RT. No difference between zoledronate and pamidronate was demonstrated in a direct comparison of these two drugs (Murphy R, Novartis Pharmaceuticals: personal communication, 2001).

Intravenous bisphosphonates have much better bioavailability than oral bisphosphonates. Most of the studies using oral bisphosphonates showed no significant results for any of the skeletal morbidity end-points, when considered individually.[137,185,189,204,214,219] A number show trends towards significance, or are significant for one or more end-points.[194,196,218,220] However, when the results were combined in a meta-analysis, significance was reached for vertebral and non-vertebral fractures. Trials using intravenous bisphosphonates have significant results for several outcomes[138,139,208] (Murphy R, Novartis Pharmaceuticals: personal communication, 2001). It may be argued that the trials which showed non-significant results using intravenous bisphosphonates were using the drug at too low a dose.[190,210]

Diel and colleagues[195] compared continuous oral clodronate (2.4 g/day) versus interval therapy (900 mg intravenous clodronate or 60 mg intravenous pamidronate every 3 weeks) in an RCT with a median observation period of 18 months. They showed a reduction in the number of patients with vertebral fractures in the oral clodronate group [11 (112)] compared with intravenous clodronate [19 (103)] and intravenous pamidronate [16 (103)]. They concluded that continuous administration of bisphosphonates was probably more effective than interval therapy, although this did not reach statistical significance ($p < 0.183$).

New bone markers have been isolated in recent years, which give more accurate measurement of bone resorption and formation. We do not know if different cancers induce osteoclasts to resorb bone at different rates or whether the rate of bone resorption is constant, intermittent or accelerates during the course of an individual's disease. Differences may be due to the different cytokines and hormones that tumours produce in the bone microenvironment, which may be responsible for differential effects on osteoclasts. The application of new technology will allow us to gain greater insights into the rates and patterns of bone resorption in different cancers and patients. This may enable us to tailor bisphosphonate therapy to either individuals or different cancers, hopefully leading to more efficient and cost-effective use of bisphosphonates with increased clinical benefit to patients.

Do some patients acquire or have inherent resistance to particular bisphosphonates? Joshua and colleagues[325] found that 16% of patients with Paget's disease failed to respond to increasing doses of intravenous pamidronate, but that the majority of the non-responders achieved full biochemical remission with the use of alendronate or tiludronate. This suggests that some individuals are resistant to individual bisphosphonates but not to the whole class of drugs. A case report described a patient with resistant hypercalcaemia who had failed to respond to treatment with intravenous pamidronate, but demonstrated a partial biochemical response to intravenous clodronate (Baxter C, Jamal H, Cheung J, Differential response to bisphosphonates in a patient with malignant hypercalcaemia: personal communication, 2002).

Bisphosphonates have no impact on survival when given in this setting to patients with breast cancer and multiple myeloma. However, they clearly have a major impact on the quality of life of patients by delaying the time to first SRE and reducing skeletal morbidity. Unfortunately, no conclusions can be drawn from quality of life data from the studies included in this review.

Bisphosphonates are well tolerated with a very low incidence of serious side-effects (*Tables 14*, *15* and *23*). Ali and colleagues[326] followed a small cohort of patients ($n = 22$) on intravenous pamidronate and zoledronate for a mean duration of 3.6 years (range, 2.2–6.0 years). No serious adverse toxicity was described. They showed that the fracture rate was no greater in the subsequent compared to the first 2 years on treatment. This small trial suggests that the drugs are safe to administer on a long-term basis.

Most of the evidence for the use of bisphosphonates in skeletal morbidity comes from

trials with breast cancer and multiple myeloma patients. One study (Murphy R, Novartis Pharmaceuticals: personal communication, 2001) compared zoledronate with placebo in patients with prostate cancer, demonstrating a significant reduction in combined fractures, and a trend towards a reduction in need for RT. This study may not have been long enough to show a reduction in need for orthopaedic procedures. Preliminary results from another study comparing oral clodronate with placebo[238] in patients with prostate cancer indicates that treatment delays development of skeletal morbidity.[238] Further results from this study will be available in the near future.

We would hypothesise that bisphosphonate treatment would work better if started as early as possible in the disease process, for example at diagnosis of bone metastases, in order to prevent the development of SREs. Animal work has demonstrated the effect of prophylactic administration of bisphosphonates to prevent tumour-induced osteolysis in rats.[327] The most important clinical effect of bisphosphonates is the inhibition of bone resorption;[5] bisphosphonates are more effective at preserving intact bone than repairing damaged bone.[327] Currently there is no prospective clinical evidence to confirm when bisphosphonates should be commenced, but the increase in time to first SRE in patients treated with bisphosphonates strongly favours earlier treatment.

Adjuvant review

The results of the review demonstrate that patients with primary operable breast cancer benefit from adjuvant bisphosphonates. Although the number of studies is small, two are well designed and sufficiently powered to show a reduction in the number of patients developing bone metastases.[272,276] The trial by Saarto and colleagues[277] is difficult to interpret because there were significantly more hormone receptor negative patients in the treatment group, which is likely to have an impact on the results. ER –ve tumours relapse earlier in bone,[328] do not respond as well to hormone treatment and have a shorter disease free-interval and survival.

The beneficial effects of bisphosphonates do not appear to be maintained off treatment. This may be related to the fact that bisphosphonates are preferentially absorbed at sites of bone turnover[10] and are 'used up' as bone is resorbed by osteoclasts. Bisphosphonate trapped in bone that is quiescent is inert. Hence it may be necessary to expose the patient to continuous bisphosphonates to ensure adequate levels at sites of metastatic activity within the bone microenvironment.

Bisphosphonates reduce the number of bone metastases in patients with early and advanced breast cancer, but the clinical significance of this is not clear. In clinical practice, reduced numbers of bone metastases may not translate into reduced morbidity, since a single bone metastasis may result in an SRE.

The trial by Diel and colleagues[272] demonstrated a reduction in the number of patients developing visceral metastases in the treated group, but these findings have not been reproduced in other studies.

A survival advantage has been demonstrated for patients with primary operable breast cancer in two trials,[272,276] but this was not seen in those patients with more advanced disease.[272] The results for patients with advanced breast cancer are far less clear. This is due to a lack of evidence available for this sub-group of patients; two trials had poor methodology[273,275] and the third had relatively small numbers of patients completing the study.[274] More trials are needed in this group of patients to clarify the use of bisphosphonates. Animal work suggests that the earlier bisphosphonates are given, the more effective they are,[327,329] suggesting a preventive role. The question of when bisphosphonate treatment should be commenced has still not been answered. Should they be started either in all patients at high risk of developing bone metastases in the future, or at the point at which bone metastases are diagnosed, or when the patient develops their first SRE? The emerging evidence suggests that the earlier bisphosphonates are given the more effective they are and that they may need to be given for life.

An important aspect of the application of bisphosphonates in the adjuvant setting is the identification of sub-groups of breast cancer patients who are most likely to benefit from treatment. Adjuvant chemotherapy has an impact on loco-regional and distant soft-tissue relapse, but it does not significantly reduce the incidence of relapse in bone or viscera.[328] Tamoxifen has been shown to reduce the incidence of metastases, including bone, in some patients.[330] There is a need for additional treatment modalities to limit

the development and extent of bone metastases, considering it is the first site of relapse in over 25% of breast cancer patients.[114] Bisphosphonates are site-specific, concentrating in bone, and would complement the existing treatment regimens employed in the adjuvant setting.

There are a number of prognostic indicators that can be used to identify patients most at risk of relapse in bone. Lymph node-positive disease increases the risk, with four or more nodes positive carrying the highest risk. The cumulative incidence of bone metastases, at any time, in patients with four or more nodes at diagnosis is 14.9% at 2 years and 40.8% at 10 years.[291] Larger primary tumours and ER +ve tumours also carry an increased risk of relapse in bone. Although ER +ve tumours have an increased incidence of relapse in bone, ER –ve tumours relapse earlier in bone.[291] When considering patterns of spread from a clinical perspective, patients with first relapse in loco-regional or distant soft tissue sites appear to be at higher risk of developing bone metastases.[291] There is some evidence to suggest that early microdissemination via lymphatic and haematogenous systems are independent events.[331] For patients with lymph node negative breast cancer, the presence of micrometastatic cells in the bone marrow is an independent risk factor for the development of bone metastases.[331]

Further work is now needed on several fronts. Bisphosphonates need to be trialled for longer treatment periods in patients with primary operable breast cancer. The more potent aminobisphosphonates need to be randomised against non-aminobisphosphonates in the adjuvant setting. There may be some advantage to be gained by using amino and non-aminobisphosphonates in combination because they work by different mechanisms. The case for the adjuvant use of bisphosphonates in patients with advanced disease is not clear owing to lack of trials. Bisphosphonates need to be trialled in other groups of patients who are at high risk of developing bone metastases, for example, patients with prostate cancer.

Several trials are currently in progress and the results of these trials should become available over the next few years.

Economic evaluation

To assess the costs and cost-effectiveness of using bisphosphonates in metastatic disease, a review of the health economic literature was conducted. This, along with the hypercalcaemia and skeletal morbidity reviews, formed the basis of economic analyses. As a result knowledge was accumulated in two areas:

- the cost-effectiveness of treating hypercalcaemia
- the cost-effectiveness of preventing skeletal morbidity.

Treatment of hypercalcaemia

No cost-effectiveness analyses of treating hypercalcaemia were found in the literature. Based on data from effectiveness studies, and unit costs estimated from routine data sources, we constructed a decision-analytic model to evaluate the cost-effectiveness. After excluding zoledronate 8 mg because of its toxic side-effects, the most costly strategy was zoledronate 4 mg, but this is likely to be the most cost-effective, £22,900 per life-year gained, because it appears to have the longest cumulative duration of normocalcaemia of the drug regimens considered here. It is difficult to compare studies, however, when they have different entry criteria for serum calcium and when not all studies rehydrated patients prior to measurement of baseline calcium.

When we consider the cost-effectiveness, cost per life-year gained, of bisphosphonate therapy for hypercalcaemia compared with the cost-effectiveness of other healthcare interventions, we find that it is not the most cost-effectiveness intervention. However, zoledronate 4 mg and pamidronate 90 mg, when calculated according to Purohit and colleagues,[130] probably represent fairly good value for money compared with a number of treatments that have been recommended by NICE.[332,333] NICE uses cost-effectiveness as one of its criteria for assessing health technology. Ibandronate 4 mg and pamidronate 90 mg, when calculated according to Nussbaum and colleagues,[66] represent lower levels of cost-effectiveness. Ibandronate 6 mg does not seem to be cost-effective because it appears to be no more effective than 4 mg.

The analysis was constructed using the best available evidence. However, gaps in the evidence base mean that there are reasons to be cautious about drawing conclusions about cost-effectiveness:

1. The trials on which the effectiveness data were based were fairly small, with sample sizes ranging from 44 to 275, and had different entry criteria. Consequently, the estimated cost-

effectiveness varied according to which clinical trial the effectiveness data came from, for example, the estimate of cost-effectiveness of 90 mg pamidronate varied between studies from £66 and £308 per extra day of response.
2. The trials reported median time to first relapse. In the model, these estimates were used to approximate the mean time to first relapse but because of the skew of time to first relapse, this represents a bias. Therefore, the estimates of cost per extra day of normocalcaemia may be overestimates.
3. Lack of information in the literature meant that a number of estimates had to be made on the basis of clinical expertise. Given this, meaningful CIs for cost-effectiveness estimates could not be calculated. The sensitivity analysis investigated the effects of a wide range of estimates, and this indicated that there is a wide range in the estimates of cost-effectiveness. For example, for zoledronate 8 mg, the cost per life-year gained varied from £2200 to £40,600.
4. The results were particularly sensitive to the estimate of the amount of time spent in hospital during a treatment episode. The shorter the time in hospital, the smaller are hospital costs as a proportion of total costs. When time in hospital is reduced substantially below the 7 days assumed in the baseline analysis, pamidronate 90 mg becomes the most cost-effective, using the data from the study by Purohit and colleagues.[130]

For a precise estimate of the cost-effectiveness of different bisphosphonate regimens, one needs to know the amount of time patients spend in hospital under each regimen. This is a major weakness of the current evidence base.

Preventing skeletal morbidity

Data on the cost or cost-effectiveness associated with the preventative use of bisphosphonates was extracted from seven studies, only one of which was conducted for the UK context. All seven found that the cost savings from SREs averted were not large enough to offset completely the costs associated with bisphosphonate therapy. Three studies measured cost-effectiveness. Two found the programme to be moderately cost-effective and the other one found it not to be cost-effective. The one cost–benefit analysis estimated a slight loss to society. None of the studies had measured the cost savings attributable to a reduced need for care in the community for bone pain and fracture care.

Markov models were constructed to estimate the incremental costs associated with preventative bisphosphonate therapy in patients with (a) metastatic breast cancer and (b) multiple myeloma. It was estimated that use of bisphosphonates in this context costs £250 per SRE averted in breast cancer patients and £1497 in multiple myeloma patients. Using the amount of QALYs gained, as estimated by Dranitsaris and Hsu,[141] the cost-effectiveness for breast cancer would amount to £1340 per QALY gained. This would generally be considered to be highly cost-effective. The prevention of skeletal morbidity in patients with multiple myeloma is less cost-effective than for patients with breast cancer and bone metastases. This is because the incidence of SREs is lower for patients with multiple myeloma.[318]

The analysis was constructed using the best available evidence. However, gaps in the evidence base mean that these results should be treated with caution. Given the use of data from various sources, meaningful confidence intervals for cost-effectiveness estimates could not be calculated. Sensitivity analyses were conducted and suggested that the costs and cost-effectiveness estimates lie within a broad range. Cost-effectiveness was particularly sensitive to the probability of averting a skeletal event, the unit costs of skeletal events and the price of the bisphosphonate regimen.

One innovation of this review was the estimation the cost savings associated with a reduced need for fracture and bone pain care. We omitted the fracture cost savings from the main results because we were uncertain of the quantity or intensity of fracture care required. If the number of months of care required per fracture is high then it seems likely that the preventive use of bisphosphonates actually saves the health service money even in multiple myeloma patients. Even if the number of months is smaller it could substantially improve the estimated cost-effectiveness.

For a precise estimate of the cost-effectiveness of preventative bisphosphonate use, one needs to know the amount of community health care required for patients with pathological fractures. This is another weakness of the current evidence base.

Implications for health service

On the basis of the best available evidence, the use of bisphosphonate therapy in both a treatment

and a preventative setting appears to be cost-effective for appropriately selected patients. It is likely to be more cost-effective than a number of treatments already recommended by NICE, for example, riluzole for motor neuron disease, implantable cardiac defibrillators for arrythmias and orlistat for obesity.[332]

Bisphosphonates are likely to be most cost-effective in the prevention of skeletal morbidity in patients with breast cancer and skeletal metastases and may actually be cost-saving, when fracture care and/or other variables are taken into account. For the treatment of multiple myeloma, they are less likely to be cost-saving, but may still represent very reasonable value for money.

If, as some studies suggest, the impact of bisphosphonates on skeletal morbidity is greater the longer the duration of treatment, then those patients with a longer life expectancy could be prioritised. However, the length of life required for the treatment to be cost-effective may be fairly short, although there is no evidence available on this matter.

Treatment of hypercalcaemia is likely to be less cost-effective than prevention because it seems to increase the time patients spend in hospital, although this is based on expert opinion only. In the treatment of hypercalcaemia, those drugs with the longest cumulative duration of normocalcaemia were most cost-effective.

There is considerable uncertainty around our estimates of cost-effectiveness owing to gaps in the evidence base. It is perhaps more likely that our baseline estimates of incremental cost are overestimates rather than underestimates because:

- in the absence of data on mean time to relapse we used median time instead
- we were unable to estimate the fracture care cost savings with any precision.

Chapter 5
Conclusions

Hypercalcaemia review

Bisphosphonates normalise serum calcium in >70% of patients with hypercalcaemia of malignancy. The mean time to normocalcaemia ranges from 2 to 6 days when treated with any bisphosphonate. A dose effect is demonstrated for normalisation of serum calcium. There is a suggestion that increasing doses may also delay time to relapse. An aminobisphosphonate, pamidronate, doubles the time to relapse when compared with non-aminobisphosphonates, clodronate or etidronate. More potent bisphosphonates, zoledronate compared with pamidronate, further delay time to relapse.

Skeletal morbidity review

Bisphosphonates significantly reduce SREs in patients with bone metastases from breast cancer and multiple myeloma. Bisphosphonates delay time to the development of first SREs.

The evidence suggests that the benefits of bisphosphonate treatment reach significance at different time points for different events. For example, the analgesic effect occurs early at <1 month,[121] there is a significant reduction in need for RT by 6 months and a significant reduction in the need for orthopaedic surgery by 24 months.

Prevention of vertebral fractures in patients with multiple myeloma is highly significant, but is not significant for breast cancer patients. This may reflect increased localisation of bisphosphonates to sites of increased disease activity. Bisphosphonates do not prevent hypercalcaemia in patients with multiple myeloma, presumably owing to the increased importance of renal mechanisms in these patients.

In drug sub-analyses, pamidronate is significant for all end-points except SCC. Zoledronate is similar to pamidronate but the reduction in orthopaedic surgery does not reach significance because of the shorter duration of these trials (9 and 15 months). The data are less robust for clodronate but reduced numbers contribute to the analysis. Regarding route of administration, intravenous bisphosphonates are effective. It is difficult to draw conclusions regarding oral bisphosphonates as numbers are small for most outcomes, and disease type clearly influences outcomes.

There is no survival advantage for patients when bisphosphonates are given in this setting. Bisphosphonates are well tolerated with low toxicity and the evidence supports their use in all patients with bone metastases to decrease skeletal morbidity.

Adjuvant review

In patients with primary operable breast cancer, clodronate significantly reduces the number of patients developing bone metastases. The benefit observed during the treatment period is not maintained once the drug has been discontinued. Two trials report a significant survival advantage. More studies are needed for patients with advanced breast cancer but no bone metastases.

Economic evaluation

On the basis of the best available evidence, the use of bisphosphonate therapy in both the treatment of hypercalcaemia and particularly the prevention of skeletal morbidity is cost-effective. However, there is much uncertainty around the estimates of cost and cost-effectiveness. In particular, there is little or no information regarding the length of stay in hospital for patients being treated for hypercalcaemia or the quantity of community care required for patients with pathological fractures.

Chapter 6

Recommendations for further research

Hypercalcaemia

- RCTs of maintenance therapy using bisphosphonates to delay time to relapse in patients following their first episode of hypercalcaemia.
- For patients with very high PTHrP, drugs which block PTHrP action on the kidney need to be trialled in combination with bisphosphonates, for example, daily calcitonin with an aminobisphosphonate.
- Work to identify the reasons for poor response in patients with resistant hypercalcaemia. Trials to identify extent of resistance and whether treatment with a different bisphosphonate (amino versus non-amino) would be effective.

Skeletal morbidity

- Further RCTs trialling bisphosphonates in patients with prostate cancer metastatic to bone are required, given that this is a common cancer in men over 65 years, frequently metastasises to bone and has a relatively long prognosis.
- Further trials are required to confirm the optimum time to commence bisphosphonate therapy in patients with bone metastases. Should they be commenced at diagnosis of asymptomatic bone metastases or at first skeletal related event?
- Bisphosphonate use appears to vary between centres in the UK. A study to determine current clinical practice in oncology centres with respect to bisphosphonate use for patients with metastatic bone disease from breast cancer, myeloma and prostate cancer is needed.
- An RCT to compare directly the efficacy of one bisphosphonate versus another, in particular an oral preparation with an intravenous preparation, is needed. Scheduling should also be researched, for example, administration of intravenous bisphosphonates for 6 months followed by oral therapy for maintenance.
- Further areas for research include the use of bone resorption markers to tailor the use of bisphosphonates to individual patients and/or cancer types. It may be possible to deliver more potent bisphosphonates less frequently than on a 4-weekly cycle, which is currently accepted clinical practice.
- Should bisphosphonates be continued after progression of bone metastases? A trial randomising patients with progressive disease to bisphosphonates or placebo should be performed to answer this question.
- A trial to determine whether interval therapy is superior to continuous administration.

Adjuvant

There are several trials currently in progress and the results of these will be available over the next few years.

- An RCT using bisphosphonates, in patients with primary operable breast cancer, over an extended time period.
- Other disease groups such as prostate cancer need to be studied in the adjuvant setting.
- Other drugs, particularly aminobisphosphonates, need to be studied in this patient group, and whether or not a dose effect exists.
- Patients with advanced disease, but no skeletal metastases, need to be studied to see if onset of bone metastases can be delayed and also to determine whether bisphosphonates are more effective at reducing skeletal morbidity when given earlier.

Economic

To assess the cost-effectiveness of bisphosphonate therapy, trials are needed to collect and report data on the following:

- total or mean cumulative duration of normocalcaemia (hypercalcaemia treatment)
- total or mean time in hospital (especially hypercalcaemia treatment studies)
- incidence rates for each type of skeletal event (prevention)
- patients use of hospital and community health services for fracture and bone pain (prevention).

It would be useful if hypercalcaemia trials were to follow up patients until death instead of until first relapse.

The CIs around the relative risk of particular skeletal events were very broad, even when results were combined using meta-analysis. This was particular true of multiple myeloma studies. Larger trials with longer follow-up would be useful in the assessment of cost-effectiveness.

The relative cost-effectiveness of different drug regimens in the preventative setting is difficult to assess because of the lack of comparable effectiveness data. Cost-effectiveness was sensitive both to the cost of the drug and the probability of averting skeletal events. More costly drug regimens will only be more cost-effective if they substantially reduce skeletal events compared with commonly used regimens such as pamidronate 90 mg. The use of newer more costly drugs should be evaluated by comparing their additional (incremental) costs and additional (incremental) effectiveness.

Acknowledgements

This review was conducted jointly by Drs Ross and Saunders, and was funded by the Health and Technology Assessment Research and Development group. We are grateful for the support of the Systematic Reviews Training Unit at the Institute of Child Health. Novartis Pharmaceutical Company, Professor T Powles and Dr D Dearnaley, Royal Marsden Hospital, and Dr P Wiffen, Pain, Palliative and Supportive Care Collaborative Review Group, Oxford, all kindly supplied their unpublished data for inclusion in this review. Many thanks are due to members of the steering group for their advice and support.

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References

1. Blomen LJ. History of bisphosphonates: discovery and history of non-medical uses of bisphosphonates. In Bijvoet OL, Fleisch H, Canfield RE, Russell RG, editors. *Bisphosphonate on bones*. Amsterdam: Elsevier, 1995. pp. 111–24.
2. Fleisch H, Bisaz S. Isolation from urine of pyrophosphate, a calcification inhibitor. *Am J Physiol* 1962;**203**:671–5.
3. Fleisch H, Russell RG, Bisaz S. *Influence of pyrophosphate on the transformation of amorphous to crystalline calcium phosphate*. Berlin: Springer, 1968. pp. 49–59.
4. Fleisch H, Russell RG, Bisaz S. The influence of pyrophosphate analogues (diphosphonates) on the precipitation and dissolution of calcium phosphate invitro and invivo. *Calcif Tissue Res* 1968;**2**:49–59.
5. Fleisch H. Bisphosphonates: mechanism of action. *Endocrine Rev* 1998;**9**:80–100.
6. Francis M, Russell RG, Fleisch H. Diphosphonates inhibit formation of calcium phosphate crystals *in-vitro* and pathological calcification *in-vivo*. *Science* 1969;**165**:1264–6.
7. Fleisch H, Russell RG, Francis M. Diphosphonates inhibit hydroxyapatite dissolution *in-vitro* and bone resorption in tissue culture and *in-vivo*. *Science* 1969;**165**:1262–4.
8. Russell RG, Rogers M, Frith JC, Luckman SP, Coxon FP, Benford HL, *et al*. The pharmacology of bisphosphonates and new insights into their mechanisms of action. *J Bone Miner Res* 1999; **14**(Suppl 2):53–65.
9. Jung A, Bisaz S, Fleisch H. The binding of pyophosphate and two diphosphonates by hydroxyappatite crystals. *Calcif Tissue Res* 1973;**11**:269–80.
10. Fleisch H. Bisphosphonates – preclinical. In Fleisch H, editor. *Bisphosphonates in bone disease; from the laboratory to the patient*. London: Parthenon, 1995. pp. 31–65.
11. Fleisch H. Bisphosphonates: pharmacology and use in the treatment of tumour induced hypercalcaemic and metastatic bone disease. *Drugs* 1991;**42**:919–44.
12. Rogers MJ, Frith JC, Luckman SP, Coxon FP, Benford HL, Monkkonen J, *et al*. Molecular mechanisms of action of bisphosphonates. *Bone* 1999;**24** (5 Suppl):73s–79s.
13. Yakatan GJ, Poyner WJ, Talbert RL, Floyd BF, Slough CL, Ampulski RS, *et al*. Clodronate kinetics and bioavailability. *Clin Pharmacol Ther* 1982; **31**:402–10.
14. Recker RR, Hassing GS, Lau JR, Saville PD. The hyperphosphatemic effect of disodium ethane-1-hydroxy-1,1-diphosphonates: renal handling of phosphorus and the renal response to parathyroid hormone. *J Lab Clin Med* 1973;**81**:258–66.
15. Francis MD, Martodam RR. Chemical, biochemical and medicinal properties of the diphosphonates. In Hilderbrand JD, editor. *The role of bisphosphonates in living systems*. Boca Raton, FL: CRC Press, 2001. pp. 55–96.
16. Fitton A, McTavish D. Pamidronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1991; **41**:289–318.
17. Barnett B, Stickland L. Structure of disodium dihydrogen 1-hydroxyethylidenediphosphonate tetrahydrate: a bone growth regulator. *Acta Crystallogra B* 1979;**35**:1212–14.
18. Coleman RE, Purohit OP, Vinholes J. New roles for bisphosphonates in cancer therapy. *Prog Palliative Care* 1996;**4**:39–43.
19. Adami S, Zamberlan N. Adverse effects of bisphosphonates: a comparative review. *Drug Saf* 1996;**14**:158–70.
20. Kanis J, McCloskey E. The use of clodronate in disorders of calcium and skeletal metabolism. In: Lomax P, Vessel E, editors. *Progress in basic and clinical pharmacology*. Basel: Karger, 1990. pp. 89–136.
21. Lufkin EG, Argueta R, Whittaker MD, Cameron AL, Wong VH, Egan KS, *et al*. Pamidronate: an unrecognised problem in gastrointestinal tolerability. *Osteoporos Int* 1994;**4**:320–2.
22. Maconi G, Bianchi Porro G. Multiple ulcerative esophagitis caused by alendronate. *Am J Gastroenterol* 1995;**90**:1889–90.
23. Boyce BF, Smith L, Fogelman I, Johnston E, Ralston S, Boyle IT. Focal osteomalacia due to low dose diphosphonate therapy in Paget's disease. *Lancet* 1984;**i**:821–4.
24. Mian M, Beghe F, Caprio A, Aloj R, Bertelli A. Tolerability and safety of clodronate therapy in bone diseases. *Int J Clin Pharmacol Res* 1991; **ii**:107–14.

25. Siris ES. Bisphosphonates and iritis. *Lancet* 1993; **341**:436.

26. Ghose K, Waterworth R, Trolove P, Highton J. Uveitis associated with Pamidronate. *Aust NZ J Med* 1994;**24**:320.

27. Macarol V, Fraunfelder FT. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Opthalmol* 1994;**118**:220–4.

28. Fleisch H, Russell RG, Bisaz S, Muhlvauer RC, Williams DA. The inhibitory effect of phosphonates on the formation of calcium phosphate crystals *in vitr*o and on aortic and kidney calcification *in vivo*. *Eur J Clin Invest* 1970; **1**:12–18.

29. Francis MD. The inhibition of calcium hydroxyapatite crystal growth by polyphosphonates and polyphosphates. *Calcif Tissue Res* 1969; **3**:151–62.

30. Hanson N, Felix R, Bisaz S, Fleisch H. Aggregation of hydroxyapatite crystals. *Biochim Biophys Acta* 1976;**451**:549–59.

31. Luckman SP, Hughes DE, Coxon FP, Russell RG, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 1998;**13**:581–9.

32. Coxon FP, Helfrich MH, Van't Hof R, Sebti S, Ralston SH, Hamilton A, *et al*. Protein geranylgeranylation is required for osteoclast formation, function and survival: inhibition by bisphosphonates and GGTI-298. *J Bone Miner Res* 2000;**15**:1467–76.

33. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, *et al*. Structure–activity relationships for inhibition of farnesyl diphosphate synthase *in vitro* and inhibition of bone resorption *in vivo* by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001;**296**:235–42.

34. Cancer Research Campaign. *Cancer statistics: mortality – UK*. London: Cancer Research Campaign, 2001. pp. 1–6.

35. Healey JH, Brown HK. Complications of bone metastases. Surgical management. *Cancer* 2000; **88**:2940–51.

36. Coleman RE. Skeletal complications of malignancy. *Cancer (Suppl)* 1997;**80**:1588–94.

37. Kanis JA. Bone and cancer: pathophysiology and treatment of metastases. *Bone* 1995;**17** (2 Suppl): 101S–105S.

38. Kanis JA, McCloskey EV. Bisphosphonates in multiple myeloma. *Cancer* 2000; **88** (12 Suppl): 3022–32.

39. Souhami R, Tobias J, editors. Breast cancer. In *Cancer and its management*. Oxford: Blackwell Science, 1998. pp. 216–34.

40. Bishop HM, Cameron DA, Coleman R, Davies AM, Dewar JA, Evans A, *et al*. British Association of Surgical Oncology Guidelines. *Eur J Surg Oncol* 1999;**25**:3–23.

41. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987;**55**:61–6.

42. In Souhami R, Tobias J, editors. Genitourinary cancer. *Cancer and its management*. Oxford: Blackwell Science, 1998. pp. 308–33.

43. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer* 2001;**88**:2989–94.

44. Cancer Research Campaign. Cancer of the prostate. Factsheet 20. London: Cancer Research Campaign, 1994. pp. 1–5.

45. Souhami R, Tobias J, editors. Myeloma and other paraproteinaemias. In *Cancer and its management*. Oxford: Blackwell Science, 1998. pp. 470–82.

46. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, *et al*. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. *J Clin Oncol* 1998;**16**:593–602.

47. Twycross R. Biochemical syndromes. In Twycross R, editor. *Symptom management in advanced cancer*. Oxford: Radcliffe Medical Press, 1997. pp. 132–42.

48. Grill V, Rankin W, Martin TJ. Parathyroid hormone-related protein (PTHrP) and hypercalcaemia. *Eur J Cancer* 1998;**34**:222–9.

49. Ralston SH, Fogelman I, Gardner MD, Boyle IT. Relative contribution of humoral and metastatic factors to the pathogenesis of hypercalcaemia of malignancy. *BMJ* 1984;**288**:1405–8.

50. Wimalawansa SJ. Significance of plasma PTH-rP in patients with hypercalcemia of malignancy treated with bisphosphonate. *Cancer* 1994;**73**:2223–30.

51. Siggaard-Andersen O, Thode J, Fogh-Andersen N. What is 'ionised calcium'? *Scand J Clin Lab Invest* 1983;**43** (Suppl.165):11–15.

52. Raman A. The calcium fractions of normal serum. *Clin Biochem* 1971;**4**:141–6.

53. Kanis JA, Yates AJ. Measuring serum calcium. *BMJ* 1985;**290**:728–9.

54. Davis JR, Heath DA. Comparison of different dose regimes of aminohydroxypropylidene-1,1-bisphosphonate (APD) in hypercalcaemia of malignancy. *Br J Clin Pharmacol* 1989;**28**:269–74.

55. Leading article. Correcting the calcium. *BMJ* 1977;**1**:598.

56. Ostenstad B, Andersen OK. Disodium pamidronate versus mithramycin in the management of tumour-associated hypercalcemia. *Acta Oncol* 1992;**31**:861–4.

57. Gucalp R, Theriault R, Gill I, Madajewicz S, Chapman R, Navari R, *et al*. Treatment of cancer-associated hypercalcemia. Double-blind comparison of rapid and slow intravenous infusion regimens of pamidronate disodium and saline alone. *Arch Intern Med* 1994;**154**:1935–44.

58. Sawyer N, Newstead C, Drummond A, Cunningham J. Fast (4-h) or slow (24-h) infusions of pamidronate disodium (aminohydroxypropylidene diphosphonate (APD)) as single shot treatment of hypercalcaemia. *Bone Miner* 1990;**9**:121–8.

59. Raman A. The calcium fractions of normal serum. *Clin Biochem* 1971;**4**:141–6.

60. Pecherstorfer M, Herrmann Z, Body JJ, Manegold C, Degardin M, Clemens MR, *et al*. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. *J Clin Oncol* 1996;**14**:268–76.

61. Portale AA. Blood calcium, phosphorus and magnesium. In Flavus MJ, editor. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. Richmond, VA: William Byrd, 1990. pp. 62–4.

62. Ralston SH, Thiebaud D, Herrmann Z, Steinhauer EU, Thurlimann B, Walls J, *et al*. Dose–response study of ibandronate in the treatment of cancer-associated hypercalcemia. *Br J Cancer* 1997;**75**:295–300.

63. Warrell RPJ, Murphy WK, Schulman P, O'Dwyer PJ, Heller G. A randomized double-blind study of gallium nitrate compared with etidronate for acute control of cancer-related hypercalcemia. *J Clin Oncol* 1991;**9**:1467–75.

64. Payne RB, Carver ME, Morgan DB. Interpretation of serum total calcium: effects of adjustment for albumin concentration frequency of abnormal values and on detection of change in the individual. *J Clin Pathol* 1979;**32**:56–60.

65. Nussbaum SR, Warrell RP Jr, Rude R, Glusman J, Bilezikian JP, Stewart AF, *et al*. Dose–response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. *J Clin Oncol* 1993;**11**:1618–23.

66. Nussbaum SR, Younger J, Vandepol CJ, Gagel RF, Zubler MA, Chapman R, *et al*. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *Am J Med* 1993;**95**:297–304.

67. Gucalp R, Ritch P, Wiernik PH, Sarma PR, Keller A, Richman SP, *et al*. Comparative study of pamidronate disodium and etidronate disodium in the treatment of cancer-related hypercalcemia. *J Clin Oncol* 1992;**10**:134–42.

68. Body JJ, Magritte A, Seraj F, Sculier JP, Borkowski A. Aminohydroxypropylidene bisphosphonate (APD) treatment for tumor-associated hypercalcemia: a randomized comparison between a 3-day treatment and single 24-hour infusions. *J Bone Min Res* 1989;**4**:923–8.

69. Rizzoli R, Buchs B, Bonjour JP. Effect of a single infusion of alendronate in malignant hypercalcaemia: dose dependency and comparison with clodronate. *Int J Cancer* 1992;**50**:706–12.

70. Zysset E, Ammann P, Jenzer A, Gertz BJ, Portmann L, Rizzoli R, *et al*. Comparison of a rapid (2-h) versus a slow (24-h) infusion of alendronate in the treatment of hypercalcemia of malignancy. *Bone Miner* 1992;**18**:237–49.

71. Berry EM, Gupta MM, Turner SJ, Burns RR. Variation in plasma calcium with induced changes in plasma specific gravity, total protein and albumin. *BMJ* 1973;**4**:640–3.

72. Payne R. Interpretation of serum calcium in patients with abnormal serum proteins. *BMJ* 1973;**4**:643–6.

73. Gardner MD, Dryburgh FJ, Fyffe JA, Jenkins AS. Predictive value of derived calcium figures based on the measurement of ionised calcium. *Ann Clin Biochem* 1981;**18**:106–9.

74. Payne RB, Carver ME, Morgan DB. Interpretation of serum total calcium: effects of adjustment for albumin concentration on frequency of abnormal values and on detection of change in the individual. *J Clin Pathol* 1979;**32**:56–60.

75. Bilezikian JP. Management of acute hypercalcaemia. *N Engl J Med* 1992; **326**:1196–203.

76. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Saf* 1999;**21**:389–406.

77. Walls J, Bundred N, Howell A. Hypercalcaemia and bone resorption in malignancy. *Clinical Orthop* 1995;**312**:51–63.

78. Mundy GR. Hypercalcaemia associated with hematologic malignancies. In Mundy GR, editor. *Calcium homeostasis: hypercalcaemia and hypocalcaemia*. London: Martin Dunitz, 1990. pp. 100–15.

79. Grill V, Martin TJ. Hypercalcaemia of malignancy. *Rev Endocr Metab Disord* 2001;**1**:253–63.

80. Bajorunas DR. Clinical manifestations of cancer related hypercalcaemia. *Semin Oncol* 1990; **17** [2 (Suppl 5)]:16–25.

81. Kristensen B, Ejlertsen B, Mouridsen HT, Loft H. Survival in breast cancer patients after the first episode of hypercalcaemia. *J Intern Med* 1998; **244**:189–98.

82. Elias EG, Reynoso G, Mittleman A. Control of hypercalcaemia with mithramycin. *Ann Surg* 1972;**175**:435.

83. Chisholm MA, Malloy AL, Taylor AT. Acute management of cancer related hypercalcaemia. *Ann Pharmacother* 1996;**30**:507–13.

84. Green L, Donehower RC. Hepatic toxicity of low doses of mithramycin in hypercalcaemia. *Cancer Treat Rep* 1984;**68**:1379–81.

85. Warrell RP, Israel R, Frisone M, Synder T, Gaynor JJ, Bockman RS. Gallium nitrate for acute treatment of cancer related hypercalcaemia. *Ann Inter Med* 1988;**108**:669–74.

86. Wineski LA. Salmon calcitonin in the acute management of hypercalcaemia. *Calcif Tissue Int* 1990; Suppl 46:S26–S30.

87. Harrison M, James N, Broadley K, Bloom SR, Armour R, Wimalawansa S, *et al*. Somatostatin analogue treatment for malignant hypercalcaemia. *BMJ* 1990;**300**:1313–14.

88. Riggs BL. Are biochemical markers for bone turnover clinically useful for monitoring therapy in individual osteoporotic patients? *Bone* 2000; **26**:551–2.

89. Mundy GR. Hormonal factors which regulate bone resorption. In Mundy GR, Martin TJ, editors. Physiology and pharmacology of bone. New York: Springer, 1993. pp. 215–38.

90. Fleisch H. Bone and mineral metabolism. In Fleisch H, editor. *Bisphosphonates in bone disease. From the laboratory to the patients*. New York: Parthenon, 1995. pp. 11–28.

91. Manolagas SC. Role of cytokines in bone resorption. *Bone* 1995;**17**(2 Suppl):63s–67s.

92. Manolagas SC, Jilka RL. Bone marrow, cytokines and bone remodelling. *N Engl J Med* 1995; **332**:305–11.

93. Parfitt AM, Mundy GR, Roodman GD, Hughes DE, Boyce BF. A new model for the regulation of bone resorption with particular reference to the effects of bisphosphonates. *J Bone Miner Res* 1996;**11**:150–9.

94. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S, *et al*. Osteoclast differentiation factor is a ligand for osteoprotogerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. *Proc Natl Acad Sci USA* 1998;**95**:3597–602.

95. Simonet WS, Lecey DL, Dunstan C, Kelley M, Chang M, Luthy R, *et al*. Osteoprotogerin: a novel secreted protein involved in the regulation of bone density. *Cell* 1997;**89**:309–19.

96. Bucay N, Sarosi I, Dunstan C, Morony S, Tarpley J, Capparelli C, *et al*. Osteoprotogerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev* 1998;**12**:1260–8.

97. Fontana A, Delmas PD. Markers of bone turnover in bone metastases. *Cancer* 2000;**88**:2952–60.

98. Demers LM, Costa L, Lipton A. Biochemical markers and skeletal metastases. *Cancer* 2000; **88**:2919–26.

99. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet* 1889;**i**:571–3.

100. Guise TA. Molecular mechanisms of osteolytic bone metastases. *Cancer* 2000;**88**:2892.

101. Orr FW, Lee J, Duivenvoorden WCM, Singh G. Pathophysiologic interactions in skeletal metastasis. *Cancer* 2000;**88**:2912–18.

102. Lemieux P, Harvey J, Guise TA, Dallas M, Oesterreich S, Yin JJ, *et al*. Low cell motility induced by hsp27 overexpression decreases osteolytic bone metastases of human breast cancer cells *in-vivo*. *J Bone Miner Res* 1999;**14**:1570–5.

103. Rabbani SA, Gladu J, Harakidas P, Jamison B, Goltzman D. Overproduction of parathyroid hormone related peptide results in increased osteolytic skeletal metastases by prostate cancer cells *in-vivo*. *Int J Cancer* 1999;**80**:257–64.

104. Garrett IR. Bone destruction in cancer. *Semin Oncol* 1993;**20** (3 Suppl 2):4–9.

105. Zhang Y, Fujita N, Oh-hara T, Morinaga Y, Nakagawa T, Yamada M, *et al*. Production of interleukin-11 in bone derived endothelial cells and its role in the formation of osteolytic bone metastases. *Oncogene* 1998;**16**:693–703.

106. Eilon G, Mundy GR. Direct resorption of bone by human breast cells *in-vitro*. *Nature* 1978;**276**:726–8.

107. Zhau HE, Li C, Chung LWK. Establishment of human prostate carcinoma skeletal metastasis models. *Cancer* 2000;**88**:2995–3001.

108. Autzen P, Robson CN, Bjartell A, Malcolm AJ, Johnson MI, Neal DE, *et al*. Bone morphogenetic protein 6 in skeletal metastases from prostate cancer and other common human malignancies. *Br J Cancer* 1998;**78**:1219–23.

109. Roodman GD. Biology of osteoclast activation in cancer. *J Clin Oncol* 2001;**19**:3562–71.

110. Engebraaten O, Fodstad O. Site specific experimental metastases patterns of two human breast cancer cell lines in nude rats. *Int J Cancer* 1999;**82**:219–25.

111. Kim RH, Sodek J. Transcription of the bone sialoprotein gene is stimulated by v-Src acting through an inverted CCAAT box. *Cancer Res* 1999;**59**:565–71.

112. Yoneda T, Michigami T, Yi B, Williams PJ, Niewolna M, Hiraga T. Actions of bisphosphonate on bone metastasis in animal models of breast carcinoma. *Cancer* 2000;**88**:2979–88.

113. Mundy GR, Yoneda T, Hiraga T. Preclinical studies with zoledronic acid and other bisphosphonates: impact on the bone microenvironment. *Semin Oncol* 2001;**28** (2 Suppl 6):35–44.

114. Paterson AHG. The potential role of bisphosphonates as adjuvant therapy in the prevention of bone metastases. *Cancer* 2000; **88**:3038–46.

115. Galasko CS, Samuel AW, Rushton S, Lacey E. The effect of prostagladin synthesis inhibitors and diphosphonates on tumour-mediated osteolysis. *Br J Surg* 1980;**67**:493–6.

116. Hall DG, Stoica G. Effect of bisphosphonate risedronate on bone metastases in a rat mammary adenocarcinoma model system. *J Bone Miner Res* 1994;**9**:221–30.

117. Krempien B. Morphological findings in bone metastasis, tumorosteopathy and anti-osteolytic therapy. In Diel IJ, Kaufman M, Bastert G, editors. *Metastatic bone disease: fundamental and clinical aspects*. Berlin: Springer, 1994. pp. 59–85.

118. Boissier S, Ferreras M, Peyruchaud O, Magnetto S, Ebetino F, Colombel M, *et al*. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. *Cancer Res* 2000;**60**:2949–54.

119. Lee M, Fong E, Singer FR, Guenette R. Bisphosphonate treatment inhibits the growth of prostate cancer cells. *Cancer Res* 2001;**61**:2602–8.

120. Hillner BE, Ingle JN, Berenson JR, Janjan NA, Albain KS, Lipton A, *et al*. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel. *J Clin Oncol* 2000;**18**:1378–91.

121. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane Review). Cochrane Database Syst. rev. Oxford: Update Software, 2002; (2). CD002068.

122. BMA. *British National Formulary*. London: BMA and Royal Pharmaceutical Society of Great Britain, 2001. pp. 364–7.

123. Johnson IJ. Use of bisphosphonates for the treatment of metastatic bone pain. A survey of palliative physicians in the UK. *Palliat Med* 2001; **15**:141–7.

124. Biermann WA, Cantor RI, Fellin FM, Jakobowski J, Hopkins L, Newbold RC III. An evaluation of the potential cost reductions resulting from the use of clodronate in the treatment of metastatic carcinoma of the breast to bone. *Bone* 1991; **12** (Suppl 1):S37–S42.

125. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

126. Cook AM, Finlay IG, Edwards AGK, Hood K, Higginson IJ, Goodwin DM, *et al*. Efficiency of searching the grey literature in palliative care. *J Pain Symptom Manage* 2001;**22**:797–801.

127. StatXact 4.0.1. Cambridge, MA: Cytel Software, 2001.

128. Stata. Stata statistical software: release 7.0. College Station, TX: Stata, 2001.

129. Cochrane Library. Selection bias. In: Clarke M, Oxman AD, editors. *Cochrane Reviewers Handbook 6.3* [updated June 2001]. The Cochrane Library, Issue 3. Oxford: Update Software. 2001, updated quarterly.

130. Purohit OP, Radstone CR, Anthony C, Kanis JA, Coleman RE. A randomised double-blind comparison of intravenous pamidronate and clodronate in the hypercalcaemia of malignancy. *Br J Cancer* 1995;**72**:1289–93.

131. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, *et al*. Zoledronic acid is superior to pamidronate in the treatment of hypercalcaemia of malignancy: a pooled analysis of two randomised, controlled clinical trials. *J Clin Oncol* 2001;**19**:558–67.

132. NHS Executive. *Reference Costs 2000*. Leeds: Department of Health, 2000.

133. NHS Executive. *NHS Costing Manual*. Leeds: Department of Health, 2000.

134. Beck J, Pauker S. The Markov process in medical prognosis. *Med Decis Making* 1983;**3**:419–58.

135. Lipton A, Theriault R, Hortobagyi GN, Simeone J, Knight RD, Mellars K, *et al*. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases. *Cancer* 2000;**88**:1082–90.

136. Hultborn R, Gundersen S, Ryden S, Holmberg E, Carstensen J, Wallgren UB, *et al*. Efficacy of pamidronate in breast cancer with bone metastases: a randomized, double-blind placebo-controlled multicenter study. *Anticancer Res* 1999; **19**(4C):3383–92.

137. McCloskey EV, MacLennan IC, Drayson MT, Chapman C, Dunn J, Kanis JA. A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. MRC Working Party on Leukaemia in Adults. *Br J Haematol* 1998;**100**: 317–25.

138. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, *et al*. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 1996;**334**:488–93.

139. Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF, *et al*. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. *J Clin Oncol* 1999; **17**:846–54.

140. Dranitsaris G. Pamidronate for the prevention of skeletal related events in multiple myeloma. What does the public think it is worth? *Int J Technol Assess Health Care* 2001;**15**:108–22.

141. Dranitsaris G, Hsu T. Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer. *Support Care Cancer* 1999;**7**:271–9.

142. Autier P, Haentjens P, Bentin J, Baillon JM, Grivegnee AR, Closon MC. Costs induced by hip fractures: a prospective controlled study in Belgium. *Osteoporos Int* 2000;**11**:373–80.

143. Brainsky A, Glick H, Lydick E, Epstein R, Fox KM, Hawkes W. The economic cost of hip fractures in community-dwelling older adults: a prospective study. *J Am Geriatr Soc* 1997;**45**:281–7.

144. Lane A. Direct costs of osteoporosis for New Zealand women. *Pharmacoeconomics* 1996;**9**:231–45.

145. Pientka L, Friedrich C. The costs of hip fracture in Germany; a prospective evaluation. *Z Gerontol Geriatr* 1999;**32**:326–32.

146. de Laet CE, van Hout BA, Burger H, Weel AE, Hofman A, Pols HA. Incremental cost of medical care after hip fracture and first vertebral fracture. *Osteoporos Int* 1999;**10**:66–72.

147. Dolan P, Torgeson DJ. The cost of treating osteoporotic fractures in the United Kingdom female population. *Osteoporos Int* 1998;**8**:611–17.

148. Netten A, Rees T, Harrison G. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit, University of Kent and Canterbury, 2001.

149. Rimmer C. Establishing the cost of comfort. Effectiveness of pressure sore prevention. *Prof Nurse* 1992;810–15.

150. HM Treasury. *Appraisal and evaluation in central government*. 1997. Norwich: The Stationery Office.

151. NICE. *Guidance for manufacturers and sponsors*. London: National Institute for Clinical Excellence (NICE). 2001.

152. Weinstein NC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;**276**:1253–8.

153. Beusterien KM, Hill MC, Ackerman SJ, Zacker C. The impact of pamidronate on inpatient and outpatient services among metastatic breast cancer patients. *Support Care Cancer* 2001;**9**:169–76.

154. Bertheault-Cvitkovic F, Tubiana-Hulin M, Chevalier B, Clavel M, Rossy JF, Warrell RP. Gallium nitrate (GN) versus pamidronate (APD) for acute control of cancer-related hypercalcaemia (CRH): interim results of a randomised double-blind multi-national study (meeting abstract). *Proc Annu Meet Am Soc Clin Oncol* 1995;**14**:A369.

155. Dodwell DJ, Howell A, Morton AR, Daley-Yates PT, Hoggarth CR. Infusion rate and pharmacokinetics of intravenous pamidronate in the treatment of tumour-induced hypercalcaemia. *Postgrad Med J* 1992;**68**:434–9.

156. Fukumoto S, Matsumoto T, Takebe K, Onaya T, Eto S, Nawata H, *et al*. Treatment of malignancy-associated hypercalcemia with YM175, a new bisphosphonate: elevated threshold for parathyroid hormone secretion in hypercalcemic patients. *J Clin Endocrinol Metab* 1994;**79**:165–70.

157. Gallacher SJ, Ralston SH, Fraser WD, Dryburgh FJ, Cowan RA, Logue FC, *et al*. A comparison of low versus high dose pamidronate in cancer-associated hypercalcemia. *Bone Mineral* 1991;**15**:249–56.

158. Hasling C, Charles P, Mosekilde L. Etidronate disodium for treating hypercalcaemia of malignancy: a double blind, placebo-controlled study. *Euro J Clin Invest* 1986;**16**:433–7.

159. Hasling C, Charles P, Mosekilde L. Etidronate disodium in the management of malignancy-related hypercalcemia. *Am J Med* 1987;**82**(2A):51–4.

160. Morton AR, Cantrill JA, Craig AE, Howell A, Davies M, Anderson DC. Single dose versus daily intravenous aminohydroxypropylidene biphosphonate (APD) for the hypercalcaemia of malignancy. *BMJ* 1988;**296**:811–14.

161. Ralston SH, Gardner MD, Dryburgh FJ, Jenkins AS, Cowan RA, Boyle IT. Comparison of aminohydroxypropylidene diphosphonate, mithramycin, and corticosteroids/calcitonin in treatment of cancer-associated hypercalcaemia. *Lancet* 1985;**ii**:907–10.

162. Ralston SH, Gallacher SJ, Patel U, Dryburgh FJ, Fraser WD, Cowan RA, *et al*. Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. *Lancet* 1989;**ii**:1180–2.

163. Rizzoli R, Thiebaud D, Bundred N, Pecherstorfer M, Herrmann Z, Huss HJ, *et al*. Serum parathyroid hormone-related protein levels and response to bisphosphonate treatment in hypercalcemia of malignancy. *J Clin Endocrinol Metab* 1999;**84**:3545–50.

164. Rotstein S, Glas U, Eriksson M, Pfeiffer P, Hansen J, Soderqvist J, *et al*. Intravenous clodronate for the treatment of hypercalcaemia in breast cancer patients with bone metastases – a prospective randomised placebo-controlled multicentre study. *Eur J Cancer* 1992;**28A**:890–3.

165. Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Evaluation of new bone resorption markers in a randomized comparison of pamidronate or clodronate for hypercalcemia of malignancy. *J Clin Oncol* 1997;**15**:131–8.

166. Warrell R, Mullane M, Bilezikian J, Edelstein M, Mallette M, Stepanavage M, *et al*. Treatment of cancer associated hypercalcaemia with alendronate sodium: a randomised double-blind comparison with etidronate (meeting abstract). *Proc Annu Meet Am Soc Clin Oncol* 1997.

167. Wimalawansa SJ. Optimal frequency of administration of pamidronate in patients with hypercalcaemia of malignancy. *Clin Endocrinol* 1994;**41**:591–5.

168. Atula S, Tahtela R, Nevalainen J, Pyikkanen L. Single IV infusion of clodronate 1500mg is effective in the treatment of hypercalcaemia of malignancy. *Eur J Cancer* 37 (Suppl 6), 2001;S354.

169. Canfield RE, Siris ES, Jacobs TP. Dichloromethylene diphosphate action in hematologic and other malignancies. *Bone* 1987;**8**(suppl. 1):557–562.

170. Chapuy MC, Meunier PJ, Alexandre CM, Vignon EP. Effects of disodium dichloromethylene diphosphonate on hypercalcemia produced by bone metastases. *J Clin Invest* 1980;**65**:1243–7.

171. Daragon A, Peyron R, Serrurier D, Deshayes P. Treatment of hypercalcemia of malignancy with intravenous aminohydroxypropylidene bisphosphonate. Results of a stratified, double-blind, randomized two-month dose-response study. *Curr Ther Res Clin Exp* 1991;**50**:10–21.

172. Delmas P, Chapuy MC, Vignon E, Briancon D, Charhon S, Meunier PJ. Dichloromethylene diphosphonate (Cl2MDP) treatment of hypercalcaemia produced from bone metastases. *Nouv Presse Med* 1982;**11**:1471–4.

173. Jung A, Chantraine A, Donath A, van Ouwenaller C, Turnill D, Mermillod B, *et al*. Use of dichloromethylene diphosphonate in metastatic bone disease. *N Engl J Med* 1983;**308**:1499–501.

174. Martinez ME, Pastrana P, Sanchez-Cabezudo MJ, Jariego C, Del Campo MT. Effect of clodronate on calcidiol serum levels in women with breast cancer. *Calcif Tissue Int* 1997;**61**:148–50.

175. Mundy GR, Wilkinson R, Heath DA. Comparative study of available medical therapy for hypercalcemia of malignancy. *Am J Med* 1983;**74**:421–32.

176. Murray R, Pitt P, Jerums G. A randomised trial of varying doses of aminohydroxypropylidene bisphosphonate (APD) in the treatment of hypercalcaemia of malignancy. Seventeenth annual scientific meeting, Clinical Oncology Society of Australia, 1990; IS28.

177. Pecherstorfer M, Steinhauer EU, Pawsey S. Ibandronic acid is more effective than pamidronate in lowering serum calcium in patients with severe hypercalcaemia of malignancy (HCM) and has at least equal efficacy to pamidronate in HCM patients with lower baseline calciums. Results of a randomised, open-label, comparative study. *Proc Am Soc Clin Oncol* 2001; **20**:abstract 1535.

178. Pecherstorfer M, Steinhauer EU, Pawsey S. Ibandronic acid is more effective than pamidronate in lowering serum calcium in patients with severe hypercalcaemia of malignancy (HCM) and has at least equal efficacy to pamidronate in HCM patients with lower baseline calciums. Results of a randomised, open-label, comparative study. *Proc Am Soc Clin Oncol* 2001; **20**;abs 1535

179. Ralston SH, Alzaid AA, Gallacher SJ, Gardner MD, Cowan RA, Boyle IT. Clinical experience with aminohydroxypropylidene bisphosphonate (APD) in the management of cancer-associated hypercalcaemia. *Q J Med* 1988;**68**:825–34.

180. Singer FR, Ritch PS, Lad TE, Ringenberg QS, Schiller JH, Recker RR, *et al*. Treatment of hypercalcemia of malignancy with intravenous etidronate. A controlled, multicenter study. *Arch Intern Med* 1991;**151**:471–6.

181. Siris ES, Hyman GA, Canfield RE. Effects of dichloromethylene diphosphonate in women with breast carcinoma metastatic to the skeleton. *Am J Med* 1983;**74**:401–6.

182. Thurlimann B, Waldburger R, Senn HJ, Thiebaud D. Plicamycin and pamidronate in symptomatic tumor-related hypercalcemia: a prospective randomized crossover trial. *Ann Oncol* 1992;**3**:619–23.

183. Witte RS, Koeller J, Davis TE, Benson AB III, Durie BG, Lipton A, *et al*. Clodronate. A randomized study in the treatment of cancer-related hypercalcemia. *Arch Intern Med* 1987; **147**:937–9.

184. Ausili-Cefaro G, Capirci C, Crivellari D, Fontana V, Mandoliti G, Olmi P, *et al*. Radiation therapy vs radiation therapy + pamidronate (Aredia) in elderly patients with breast cancer and lytic bone metastases: a GROG–GIOGER randomized clinical trial. *Rays* 1999; **24** (Suppl 2):49–52.

185. Belch AR, Bergsagel DE, Wilson K, O'Reilly S, Wilson J, Sutton D, *et al*. Effect of daily etidronate on the osteolysis of multiple myeloma. *J Clin Oncol* 1991;**9**:1397–402.

186. Berenson JR. The efficacy of pamidronate disodium in the treatment of osteolytic lesions and bone pain in multiple myeloma. *Rev Contemp Pharmacother* 1998;**9**:195–203.

187. Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, *et al*. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001;**91**:1191–200.

188. Berenson JR. Zoledronic acid in cancer patients with bone metastases: results of phase I and II trials. *Semin Oncol* 2001;**28** [2 (Suppl 6)]:25–34.

189. Brincker H, Westin J, Abildgaard N, Gimsing P, Turesson I, Hedenus M, *et al*. Failure of oral pamidronate to reduce skeletal morbidity in multiple myeloma: a double-blind placebo-controlled trial. Danish–Swedish co-operative study group. *Br J Haematol* 1998;**101**:280–6.

190. Conte PF, Giannessi PG, Latreille J, Mauriac L, Koliren L, Calabresi F, *et al*. Delayed progression of bone metastases with pamidronate therapy in breast cancer patients: a randomized, multicenter phase III trial. *Ann Oncol* 1994;**5** (Suppl 7):S41–S44.

191. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, *et al*. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. *J Clin Oncol* 1996;**14**:2552–9.

192. Ford JF. Pamidronate in the treatment of bone metastases – the European experience. *Br J Clin Pract Suppl* 1996;**87**:3–4.

193. Daragon A, Humez C, Michot C, Le Loet X, Grosbois B, Pouyol F, *et al*. Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. *Eur J Med* 1993;**2**:449–52.

194. Delmas P, Charhon S, Chapuy MC, Vignon E, Briancon D, Edouard C, *et al*. Long-term effects of dichloromethylene diphosphonate (CL2MDP) on skeletal lesions in multiple myeloma. *Metab Bone Dis and Relat Res* 1982;**4**:163–8.

195. Diel IJ, Marschner N, Kindler M, Lange O, Untch M, Hurtz HJ, *et al*. Continuous oral versus intravenous interval therapy with bisphosphonates in patients with breast cancer and bone metastases. *J Clin Oncol (ASCO)* 1999; abs 488.

196. Elomaa I, Blomqvist C, Grohn P, Porkka L, Kairento AL, Selander K, *et al*. Long-term controlled trial with diphosphonate in patients with osteolytic bone metastases. *Lancet* 1983; **i**:146–9.

197. Elomaa I, Blomqvist C, Porkka L, Lamberg-Allardt C, Borgstrom GH. Treatment of skeletal disease in breast cancer: a controlled clodronate trial. *Bone* 1987;**8** (Suppl 1):S53–S56.

198. Elomaa I, Blomqvist C, Porkka L, Holmstrom T, Taube T, Lamberg-Allardt C, *et al*. Clodronate for osteolytic metastases due to breast cancer. *Biomed Pharmacother* 1988;**42**:111–16.

199. Glover D, Lipton A, Keller A, Miller AA, Browning S, Fram RJ, *et al*. Intravenous pamidronate disodium treatment of bone metastases in patients with breast cancer. *Cancer* 1994;**74**:2949–55.

200. Gomez-Pastrana E, Velasco JG, Requena A, Martinez-Salazar FJ, Martinez ME, Calero F. Clinical and biochemical valuation of clodronate in tumoral osteolysis by bone metastases of breast cancer. *Prog Obstet Gynecol* 1996;**39**:357–64.

201. Harris AL, Millward M, Tomkin K, Cantwell BM, Carmichael J, Wilson R, *et al*. Randomised trial of aminoglutethamide and hydrocortisone with and without disodium pamidronate (APD) in patients with advanced postmenopausal breast cancer and bone metastases. In *Conference proceedings. Osteoclast inhibition in the management of malignancy related bone disorders*. Seattle, WA: Hogrefe and Huber, 1993.

202. Heim ME, Clemens MR, Queirber W, Pecherstorfer M, Boewer C, Herold M, *et al*. Prospective randomised trial of dichloromethylene bisphosphonate (clodronate) in patients with multiple myeloma requiring treatment. A multicenter study. *Onkologie* 1995;**18**:439–48.

203. Clemens MR, Fessele K, Heim ME. Multiple myeloma: effect of daily dichloromethylene bisphosphonate on skeletal complications. *Ann Hematol* 1993;**66**:141–6.

204. Holten-Verzantvoort AT, Kroon HM, Bijvoet OL, Cleton FJ, Beex LV, Blijham G, *et al*. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;**11**:491–8.

205. Holten-Verzantvoort AT, Bijvoet OL, Cleton FJ, Hermans J, Kroon HM, Harinck HI, *et al*. Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* 1987;**ii**:983–5.

206. Cleton FJ, Holten-Verzantvoort AT, Bijvoet OL. Effect of long-term bisphosphonate treatment on morbidity due to bone metastases in breast cancer patients. *Recent Results Cancer Res* 1989;**116**:73–8.

207. Holten-Verzantvoort AT, Zwinderman AH, Aaronson NK, Hermans J, Emmerik B, Dam FS, *et al*. The effect of supportive pamidronate treatment on aspects of quality of life of patients with advanced breast cancer. *Eur J Cancer* 1991;**27**:544–9.

208. Hortobagyi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoff C, *et al*. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. *J Clin Oncol* 1998;**16**:2038–44.

209. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, *et al*. Efficacy of pamidronate in reducing skeletal complications in

patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996;**335**:1785–91.

210. Hultborn R, Gundersen S, Ryden S, Holmberg E, Carstensen J, Wallgren UB, *et al*. Efficacy of pamidronate in breast cancer with bone metastases: a randomized double-blind placebo controlled multicenter study. *Acta Oncol* 1996; **35** (Suppl 5):73–4.

211. Kraj M, Poglod R, Pawlikowski J, Maj S, Nasilowska B. Effect of pamidronate on skeletal morbidity in myelomatosis. Part 1. The results of the first 12 months of pamidronate therapy. *Acta Pol Pharm* 2000;**57**:113–16.

212. Kraj M, Poglod R, Pawlikowski J, Maj S. The effect of long-term pamidronate treatment on skeletal morbidity in advanced multiple myeloma. *Acta Haematol Pol* 2000;**31**:379–89.

213. Kristensen B, Ejlertsen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999;**246**:67–74.

214. Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. *Lancet* 1992;**340**:1049–52.

215. Laakso M, Lahtinen R, Virkkunen P, Elomaa I. Sub-group and cost–benefit analysis of the Finnish multicentre trial of clodronate in multiple myeloma. *Br J Haematol* 1994;**87**:725–9.

216. Theriault R. Pamidronate in the treatment of osteolytic bone metastases in breast cancer patients. *Br J Clin Pract Suppl* 1996;**87**:8–12.

217. Martoni A, Guaraldi M, Camera P, Biagi R, Marri S, Beghe F, *et al*. Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. *Oncology* 1991;**48**:97–101.

218. Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;**11**:59–65.

219. Robertson AG, Reed NS, Ralston SH. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;**13**:2427–30.

220. Tubiana-Hulin M, Beuzeboc P, Mauriac L, Barbet N, Frenay M, Monnier A, *et al*. Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. *Bull Cancer* 2001;**88**:701–7.

221. Hulin MT, Beuzeboc P, Mauriac L, Clavel M, Barbet N, Frenay M, *et al*. Double blind placebo controlled trial of oral clodronate in patients with bone metastases from breast cancer. *Ann Oncol* 1994;**5** (Suppl 8):198.

222. Rosen LS, Gordon D, Tchekmedyian S, Hirsch V, Yanagihara R, Coleman RE, *et al*. Zoledronic acid significantly reduces skeletal related events in patients with bone metastases from solid tumours. *Proc Am Soc Clin Oncol* 2002; Abs1179.

223. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, *et al*. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer* 2001; **7**:377–87.

224. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002; **94**:1458–68.

225. Abdulkadyrov KM, Bessmelisev SS. Bonefos efficacy in combined treatment of multiple myeloma. *Terapeut Arkh* 1993;**65**(12):70–2.

226. Abildgaard N, Rungby J, Glerup H, Brixen K, Kassem M, Brincker H, *et al*. Long-term oral pamidronate treatment inhibits osteoclastic bone resorption and bone turnover without affecting osteoblastic function in multiple myeloma. *Eur J Haematol* 1998;**61**:128–34.

227. Adami S, Mian M. Clodronate therapy and metastatic bone disease in patients with prostatic carcinoma. *Recent Results Cancer Res* 1989; **116**:s67–s72.

228. Arican A, Icli F, Akbulut H, Cakir M, Sencan O, Samur M, *et al*. The effect of two different doses of oral clodronate on pain in patients with bone metastases. *Med Oncol* 1999;**16**:204–10.

229. Attardo-Parrinello G, Merlini G, Pavesi F, Crema F, Fiorentini ML, Ascari E. Effects of a new aminodiphosphonate (aminohydroxybutylidene diphosphonate) in patients with osteolytic lesions from metastases and myelomatosis. Comparison with dichloromethylene diphosphonate. *Arch Intern Med* 1987;**147**:1629–33.

230. Ausgabe A. Behandlung des hormonrefraktären Prostatakarzinomsmit schmerzhaften Knochenmetastasen. *Urologe* 1997;**36**:568.

231. Body JJ, Lichinitser MR, Diehl I, Schlosser K, Pfarr E, Cavalli F, *et al*. Double-blind placebo-controlled trial of intravenous ibandronate in breast cancer metastatic to bone. *Proc Annu Meet Am Soc Clin Oncol* 1999;**18**:A2222.

232. Cascinu S, Graziano F, Alessandroni P, Ligi M, Del Ferro E, Rossi D, *et al*. Different doses of pamidronate in patients with painful osteolytic bone metastases. *Support Care Cancer* 1998; **6**:139–43.

233. Coleman RE, Purohit OP, Vinholes J, Zekri J. High dose pamidronate: clinical and biochemical effects in metastatic bone disease. *Cancer* 1997; **80**:1686–90.

234. Coleman RE, Houston SJ, Purohit OP, Rubens RD, Kandra A, Ford J. A randomised phase II study of oral pamidronate for the treatment of bone metastases from breast cancer. *Eur J Cancer* 1998; **34**:820–4.

235. Coleman RE, Purohit OP, Black C, Vinholes JJ, Schlosser K, Huss H, *et al*. Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease. *Ann Oncol* 1999; **10**:311–16.

236. Conte N, Di Virgilio R, Da Rin G, Roiter I, Pavan P, Legovini P, *et al*. Clodronate treatment increases serum osteocalcin in normocalcemic osteolytic bone metastases. *Oncology* 1991;**48**:54–7.

237. Costa L, Moreira C, Da Costa EB. Pamidronato dissódico (APD) no tatamento das metástases ósseas. [Disodium pamidronate (APD) in the treatment of bone metastases]. *Acta Méd Port* 1993;**6**:71–3.

238. Dearnaley DP, Sydes MR. Preliminary evidence that oral clodronate delays symptomatic progression of bone metastases from prostate cancer: first results of the MRC Pr05 trial. *J Clin Oncol (ASCO)* 2001;Abs 693.

239. Diel IJ, Lichinitser MR, Body JJ, Schlosser K, Moecks J, Cavalli F, *et al*. Improvement of bone pain, quality of life and survival time of breast cancer patients with metastatic bone disease treated with intravenous ibandronate. *Eur J Cancer* 1999;**35** (Suppl 4):S83.

240. Elomaa I, Kylmala T, Tammela T, Viitanen J, Ottelin J, Ruutu M, *et al*. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostate cancer. *Int Urol Nephrol* 1992;**24**:159–66.

241. Elomaa I, Risteli L, Laakso M, Lahtinen R, Virkkunen P, Risteli J. Monitoring the action of clodronate with type I collagen metabolites in multiple myeloma. *Eur J Cancer* 1996;**32A**:1166–70.

242. Ernst DS, MacDonald N, Paterson AHG, Jensen J, Brasher P, Bruera E. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *J Pain Symptom Manage* 1992;**7**:4–11.

243. Ernst DS, Brasher P, Hagen N, Paterson AHG, MacDonald N, Bruera E. A randomised controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage* 1997;**13**:319–26.

244. Fernandez-Conde M, Alcover J, Aaron JE, Ordi J, Carretero P. Skeletal response to clodronate in prostate cancer with bone metastases. *Am J Clin Oncol* 1997;**20**:471–6.

245. Gessner U, Koeberle D, Thuerlimann B, Bacchus L, Horisberger B. Economic analysis of terminal care for patients with malignant osteolytic bone disease and pain treated with pamidronate. *Support Care Cancer* 2000;**8**:115–22.

246. Koeberle D, Bacchus L, Thurlimann B, Senn HJ. Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomised double-blind trial. *Support Care Cancer* 1999;**7**:21–7.

247. Kylmala T, Tammela T, Risteli L, Risteli J, Taube T, Elomaa I. Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *Eur J Cancer* 1993;**29A**(6):821–5.

248. Kylmala T, Taube T, Tammela T, Risteli L, Risteli J, Elomaa I. Concomitant IV and oral clodronate in the relief of bone pain – a double blind placebo controlled study in patients with prostate cancer. *Br J Cancer* 1997;**76**:939–42.

249. Lipton A, Glover D, Harvey H, Grabelsky S, Zelenakas K, Macerata R, *et al*. Pamidronate in the treatment of bone metastases: results of 2 dose-ranging trials in patients with breast or prostate cancer. *Ann Oncol* 1994;**5** (Suppl 7):s31–s35.

250. Lipton A. Zolendronate in the treatment of osteolytic bone metastases. *Br J Clin Pract Suppl* 1996;**87**:21.

251. Lipton A, Demers L, Curley E, Chinchilli V, Gaydos L, Hortobagyi G, *et al*. Markers of bone resorption in patients treated with pamidronate. *Eur J Cancer* 1998;**34**:2021–6.

252. Merlini G, Parrinello GA, Piccinini L, Crema F, Fiorentini ML, Riccardi A, *et al*. Long-term effects of parenteral dichloromethylene bisphosphonate (CL2MBP) on bone disease of myeloma patients treated with chemotherapy. *Hematol Oncol* 1990;**8**(1):23–30.

253. Moiseenko VM, Blinov NN, Semiglazov VV, Konstantinova MM, Trishkina EA. Randomised trial of two intravenous schedules of bonefos (clodronate) in patients with painful bone metastases. *Vopr Onkol* 1998;**44**:725–8.

254. O'Rourke N, McCloskey E, Houghton F, Huss H, Kanis JA. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *J Clin Oncol* 1995;**13**:929–34.

255. Peest D, Deicher H, Fett W, Harms P, Braun HJ, Planker M, *et al*. Pyridinium cross-links in multiple myeloma: correlation with clinical parameters and use for monitoring of intravenous clodronate therapy – a pilot study of the German Myeloma Treatment Group (GMTG). *Eur J Cancer* 1996;**32A**:2053–7.

256. Piga A, Bracci R, Ferretti B, Sandri P, Nortilli R, Acito L, *et al*. A double blind randomised study of oral clodronate in the treatment of bone metastases from tumours poorly responsive to chemotherapy. *J Exp Clin Cancer Res* 1998; **17**:213–17.

257. Poliakov PI, Larionova NA, Bychenkov OA, Moskin VG. An experience with combined therapy of radiation and Bonephos for osteolytic metastases of breast cancer. *Vopr Onkol* 1999;**45**:311–13.

258. Ringenberg QS, Ritch PS. Efficacy of oral administration of etidronate disodium in maintaining normal serum calcium levels in previously hypercalcemic cancer patients. *Clin Ther* 1987;**9**:318–25.

259. Schiller JH, Rasmussen P, Benson AB, III, Witte RS, Bockman RS, Harvey HA, *et al*. Maintenance etidronate in the prevention of malignancy-associated hypercalcemia. *Arch Intern Med* 1987;**147**:963–6.

260. Slaby J, Spicka I, Hulejová H, Spacek P, Cieslar P, Klener P. Effect of clodronate in patients with multiple myeloma. *Cas Lék Cesk* 1997;**136**:57–60.

261. Smith JA. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomised, prospective, double-blind, placebo-controlled study. *J Urol* 1989;**141**:85–7.

262. Strang P, Nilsson S, Brandstedt S, Sehlin J, Borghede G, Varenhorst E, *et al*. The analgesic effect of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Res* 1997;**17**:4717–22.

263. Taube T, Elomaa I, Blomqvist C, Beneton MN, Kanis JA. Comparative effects of clodronate and calcitonin on bone in metastatic breast cancer: a histomorphometric study. *Eur J Cancer* 1993;**29A**:1677–81.

264. Taube T, Kylmala T, Lamberg-Allardt C, Tammela T, Elomaa I. The effect of clodronate on bone in metastatic prostate cancer. Histomorphometric report of a double-blind randomised placebo-controlled study. *Eur J Cancer* 1994;**30A**:751–8.

265. Terpos E, Palermos J, Tsionos K, Anargyrou K, Viniou N, Papassavas P, *et al*. Effect of pamidronate administration on markers of bone turnover and disease activity in multiple myeloma. *Eur J Haematol* 2000;**65**:331–6.

266. Thurlimann B, Morant R, Jungi WF, Radziwill AJ. Pamidronate for pain control in patients with malignant osteolytic bone disease: a prospective dose effect study. *Support Care Cancer* 1994;**2**:61–5.

267. Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Metabolic effects of pamidronate in patients with metastatic bone disease. *Br J Cancer* 1996;**73**:1089–95.

268. Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Ann Oncol* 1997;**8**:1243–50.

269. Vinholes J, Coleman R, Lacombe D, Rose C, Tubiana-Hulin M, Bastit P, *et al*. Assessment of bone response to systemic therapy in an EORTC trial: preliminary experience with the use of collagen cross-link excretion. *Br J Cancer* 1999; **80**:221–8.

270. Zhang L, Guan Z, He Y. Randomised comparative clinical trial of treatment of bone metastatic diseases by infusion of palidronate and clodronate. *Chin J Cancer* 1997;**16**:430–2.

271. Zhang J, Chu Y, Xie S. Treatment of metastatic bone pain with Bonin either alone or combined with chemotherapy. *Chin J Clin Oncol* 1999; **26**:762–4.

272. Diel IJ, Solomayer EF, Costa SD, *et al*. Reduction in new metatases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; **339**:357–63.

273. Holten-Verzantvoort AT, Hermans J, Beex LV, Blijham G, Cleton FJ, Eck-Smit BC, *et al*. Does supportive pamidronate treatment prevent or delay the first manifestation of bone metastases in breast cancer patients? *Eur J Cancer* 1996;**32A**:450–4.

274. Kanis JA, Powles T, Paterson AH, McCloskey EV, Ashley S. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. Bone 1996;**19**:663–7.

275. Mardiak J, Bohunicky L, Chovanec J, Salek T, Koza I. Adjuvant clodronate therapy in patients with locally advanced breast cancer – long-term results of a double blind randomised trial. *Neoplasma* 2000;**47**:177–80.

276. Powles T, Paterson S, Kanis JA, McCloskey EV, Ashley S, Tidy A, *et al*. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002;**20**:3219–24.

277. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. Adjuvant clodronate treatment does not reduce skeletal metastases in node positive breast cancer. *J Clin Oncol* 2001;**19**:10–17.

278. Smith MR, McGoven FJ, Zietman AL, *et al*. Pamidronate to prevent bone loss during androgen depravation therapy for prostate cancer. *N Engl J Med* 2001;**345**:948–55.

279. Diel IJ, Solomayer EF, Goerner R, Gollan C, Wallweiner D, Bastea G. Adjuvant treatment of breast cancer patients with the bisphosphonate clodronate reduces incidence and number of bone and non-bone metastases. *J Clin Oncol (ASCO)* 1997; Abs 461.

280. Powles T, Tidy A, Ashley S, Kanis J, Paterson AD. Clodronate decreases the incidence of bone metastases in patients with advanced or metastatic breast cancer but no clinical evidence of bone metastases. *Br J Cancer* 1995;**71** (Suppl 24):15.

281. Powles T, McCloskey E, Paterson AH, Ashley S, Tidy A, Kanis J. Oral clodronate will reduce the loss of bone mineral density in women with primary breast cancer. *J Clin Oncol (ASCO)* 1997; Abs 460.

282. Powles T, Paterson AH, Nevantaus A, Legault S, Pajunen M, Tidy A, *et al*. Adjuvant clodronate reduces the incidence of bone metastases in patients with primary operable breast cancer. *J Clin Oncol (ASCO)* 1998;Abs 468.

283. Powles T, Paterson S, Ashley S, Rosenqvist K, Tidy A, Nevantaus A, *et al*. A placebo controlled trial of clodronate for prevention of bone metastases in patients with primary operable breast cancer. *Bone* 2000;**26** (3 Suppl):42S.

284. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. No reduction of bone metastases with adjuvent clodronate treatment in node-positive breast cancer patients. *J Clin Oncol (ASCO)*, 1999; Abs 570.

285. Vehmanen L, Saarto T, Blomqvist C, Virkkunen P, Elomaa I. The effect of adjuvant clodronate on bone mineral density (BMD) in pre- and postmenopausal breast cancer patients. A randomized 5 year follow-up study. *Eur J Cancer* 1999;**35** (Suppl 4):S159.

286. Powles T, McCloskey E, Paterson AH, Ashley S, Tidy A, Nevantaus A, *et al*. Oral clodronate and reduction in loss of bone mineral density in women with operable primary breast cancer. *J Nat Cancer Inst* 1998;**90**:704–8.

287. Vehmanen L, Saarto T, Elomaa I, Makela P, Valimaki M, Blomqvist C. Long-term impact of chemotherapy induced ovarian failure on bone mineral density (BMD) in pre-menopausal breast cancer patients. The effect of adjuvant clodronate treatment. *Eur J Cancer* 2001;**37**:2373–8.

288. Saarto T, Vehmanen L, Elomaa I, Valimaki M, Makela P, Blomqvist C. The effect of clodronate and antioestrogens on bone loss associated with oestrogen withdrawal in postmenopausal women with breast cancer. *Br J Cancer* 2001;**84**:1047–51.

289. Saarto T, Blomqvist C, Valimaki M, Makela P, Sarna S, Elomaa I. Chemical castration induced by adjuvant cyclophosphamide, methotrexate and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomised study in premenopausal breast cancer patients. *J Clin Oncol* 1997;**15**:1341–7.

290. Blay JY. Traitement adjuvant du cancer du sein localisé à haut risque de rechute: et maintenant les diphosphonates. *Bull Cancer* 1998;**85**:741.

291. Colleoni M, O'Neill A, Goldhirsch A, Gelber RD, Bonetti M, Thurlimann B, *et al*. Identifying breast cancer patients at high risk for bone metastases. *J Clin Oncol* 2000;**18**:3925–35.

292. Diel IJ, Solomayer EF, Seibel MJ, Pfeilschifter J, Maisenbacher H, Gollan C, *et al*. Serum bone sialoprotein in patients with primary breast cancer is a prognostic marker for subsequent bone metastasis. *Clin Cancer Res* 1999;**5**:3914–19.

293. Hidalgo M, Eckhardt SG. Development of matrix metalloproteinase inhibitors in cancer therapy. *J Nat Cancer Inst* 2001;**93**:178–93.

294. Lokeshwar BL. MMP inhibition in prostate cancer. *Ann N Y Acad Sci* 1999;**878**:271–89.

295. Rutqvist LE. Randomized adjuvant breast cancer trials in Sweden. *Cancer* 1994;**74** (3 Suppl):1156–9.

296. Smith TJ, Hillner BE. Clodronate reduced the incidence of bony and visceral metastases in patients with breast cancer and tumour cells in the bone marrow. *Evid Based Med* 1999;**4**:43.

297. Wolff AC, Abeloff MD. Adjuvant systemic management of early stage carcinoma of the breast. *Surg Oncol* 1999;**8**:93–101.

298. Strong KM, McPherson ML. Pamidronate. *Am J Hospice Palliative Care* 1998;**15**:54–5.

299. Beijnen JH, Koks CHW. Didronel IV met 100% korting (I). *Pharm Weekbl* 1990;**125**:383–4.

300. Kao G. Pamidronate and metastatic breast disease. *N Engl J Med* 1997;**336**:1609.

301. Kellihan MJ, Mangino PD. Pamidronate. *Ann Pharmacother* 1992;**26**:1262–9.

302. Madeline I, Berton B, Paubel P, Faure P. Impact budgétaire des anticancéreux et des médicaments des thérapeutiques adjuvantes depuis 10 ans à l'hôpital Saint-Louis. *Haematologie* 1999;**5** (Suppl 1):89–91.

303. Anon., Multiple myeloma: QALY gains from optimal therapy. *Drugs Ther Perspect* 2002;**16**:12–16.

304. Consumers Association. Treating cancer associated hypercalcaemia. *Drug Ther Bull* 1990;**28**:85–7.

305. Balducci L. Cost effectiveness of pamidronate in the treatment of breast cancer in the metastatic and adjuvant setting [meeting abstract 1599]. *Proc Am Soc Clin Oncol* 1998;**17**:415a.

306. Bruce NJ, McCloskey EV, Kanis JA, Guest JF. Economic impact of using clodronate in the management of patients with multiple myeloma. *Br J Haematol* 1999;**104**:358–64.

307. Coyte PC, Dobrow MJ, Broadfield L. Incremental cost analysis of ambulatory clinic and home-based intravenous therapy for patients with multiple myeloma. *Pharmacoeconomics* 2001;**19**:845–54.

308. DesHarnais Castel L, Bajwa K, Markle JP, Timbie JW, Zacker C, Schulman KA. A microcosting analysis of zoledronic acid and pamidronate therapy in patients with metastatic bone disease. *Support Care Cancer* 2001;**9**:545–51.

309. Guignard E, Dardenne J, Pelc A, *et al*. Economic assessment of clodronate in the preventive treatment of bone resorption in patients with metastatic breast cancer. *Eur J Cancer* 1997; **33**(Suppl 9):S25.

310. Hillner BE, Weeks JC, Desch CE, Smith TJ. Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol* 2000;**18**:72–9.

311. Marchetti N, Liberato NL, Tamburlini A, Barosi G. Cost-effectiveness of pamidronate in breast cancer patients with skeletal metastases. *J Med Decis Making* 2000;**20**:477.

312. Puolijoki H, Liippo K. Symptomatic hypercalcaemia in lung cancer. *Respir Med* 1992; **86**:359–60.

313. Elomaa I. Use of bisphosphonates in skeletal metastases. *Acta Oncol* 2001;**39**:445–54.

314. Fulfaro F, Casuccio A, Ticozzi C, Ripamonti C. The role of bisphosphonates in the treatment of painful metastatic bone disease: a review of phase III trials. *Pain* 1998;**78**:157–69.

315. Gallacher SJ. Formulary management of drugs for cancer-associated hypercalcaemia. *Pharmacoeconomics* 1996;**9**:39–50.

316. Hillner BE. The role of bisphosphonates in metastatic breast cancer. *Semin Radiat Oncol* 2000;**10**:250–3.

317. McCloskey EV, Libretto SE. Use of bisphosphonates in the treatment of multiple myeloma. *Hematology* 1998;**3**:291–8.

318. McCloskey E, Guest JF, Kanis JA. The clinical and cost considerations of bisphosphonates in preventing bone complications in patients with metastatic breast cancer or multiple myeloma. *Drugs* 2001;**61**:1253–74.

319. Pereira J, Mancini I, Walker P. The role of bisphosphonates in malignant bone pain: a review. *J Palliative Care* 1998;**14**:25–36.

320. Gurney H, Grill V, Martin TJ. Parathyroid hormone related protein and response to pamidronate in tumor induced hypercalcaemia. *Lancet* 1993;**341**:1611–13.

321. Walls J, Ratcliffe WA, Howell A, Bundred NJ. Response to intravenous bisphosphonate therapy in hypercalcaemic patients with and without bone metastases: the role of parathyroid hormone-related protein. *Br J Cancer* 1994;**70**:169–72.

322. Kukreja SC, Shevrin DH, Wimbiscus SA, Ebeling PR, Danks JA, Rodda CP, *et al*. Antibodies to parathyroid hormone related protein lower serum calcium in athymic mouse models of malignancy associated hypercalcaemia due to human tumours. *J Clin Invest* 1988;**82**:1798–802.

323. Bayne MC, Illidge TM. Hypercalcaemia, parathyroid hormone-related protein and malignancy. *Clin Oncol* 2001;**13**:377.

324. Body JJ, Louviaux I, Dumon JC. Decreased efficacy of bisphosphonates for recurrences of tumour-induced hypercalcaemia – mechanisms and influence of tumour type. *J Clin Oncol. (ASCO)* 1998; Abs 169.

325. Joshua F, Epstein M, Major G. Bisphosphonate resistance in Paget's disease. *Bone* 2000; **27** (4 Suppl):24S.

326. Ali SM, Hortobagyi G, Harvey H, Seaman J, Knight R, Costa L, *et al*. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. *J Clin Oncol* 2001;**19**:3434–7.

327. Krempien B, Manegold C. Prophylactic treatment of skeletal metastases, tumour-induced osteolysis and hypercalcaemia in rats with the bisphosphonate CL2MBP. *Cancer* 1993;**72**:91–8.

328. Goldhirsch A, Gelber RD, Price KN, Castiglione M, Coates AS, Rudenstam CM, *et al*. Effect of systemic adjuvant treatment on the first sites of breast cancer relapse. *Lancet* 1994;**343**:377–81.

329. Krempien B, Wingen F, Eichmann T, Muller M, Schmahl D. Protective effects of prophylactic treatment with APD on the development of tumour osteopathies in the rat: experimental studies with the Walker carcinosarcoma 256. *Oncology* 1988;**45**:41–6.

330. Fisher B, Costantino J, Redmond C, Poisson R, Bowman D, Couture J, *et al*. A randomised clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have oestrogen-receptor-positive tumours. *N Engl J Med* 1989; 320(8):479–84.

331. Braun S, Cevalti BS, Assemi C, Janni W, Kentenich CR, Schindlbeck C, *et al*. Comparative analysis of micrometastasis to the bone marrow and lymph nodes of node-negative breast cancer patients receiving no adjuvant therapy. *J Clin Oncol* 2001;**19**:1468–75.

332. Raftery J. NICE: faster access to modern treatments? Analysis of guidance on health technologies. *BMJ* 2001; **323**:1300–3.

333. Rawlings M. *Completed technology appraisals 2000/2001*. London: National Institute for Clinical Excellence, 2001.

334. Durie, BGM, Multiple myeloma. *Oncol Spectrums* 2001;**1**:113.

335. Wisloff F, Gulbrandsen N, Nord E. Therapeutic options in the treatment of multiple myeloma. *Pharmacocconomics* 1999;**16**:329–41.

Appendix 1

Search strategy: MEDLINE (Ovid)

Database: MEDLINE <1966 to present>

1. randomized controlled trial.pt.
2. randomized controlled trials.sh.
3. random allocation.sh.
4. double blind method.sh.
5. single blind method.sh.
6. 1 or 2 or 3 or 4 or 5
7. animal.sh.
8. human.sh.
9. 7 not (7 and 8)
10. 6 not 9
11. clinical trial.pt.
12. exp clinical trials/
13. (clin$ adj3 trial$).ti,ab.
14. ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
15. placebos.sh.
16. placebo$.ti,ab.
17. random.ti,ab.
18. research design.sh.
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 19 not 9
21. 20 not 10
22. comparative study.sh.
23. exp "evaluation studies."/
24. follow-up studies.sh.
25. prospective studies.sh.
26. (control$ or prospectiv$ or volunteer$).ti,ab.
27. 21 or 22 or 23 or 24 or 25
28. 26 not 9
29. 28 not (10 or 21)
30. exp Neoplasms/
31. neoplas$.af.
32. cancer$.af.
33. carcino$.af.
34. malignan$.af.
35. (bon$ adj5 lesion$).af.
36. or/30-35
37. exp diphosphonates/
38. bisphosphonate$.af.
39. diphosphonate$.af.
40. etidron$.af.
41. didron$.af.
42. difosfen.af.
43. osteodidronel.af.
44. osteum.af.
45. "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
46. 7414-83-7.rn.
47. or/40-46
48. Pamidronate.af.
49. APD.af.
50. aredia.af.
51. "disodium 3-amino-1-hydroxypropylidenebisphosphonate".af.
52. 109552-15-0.rn.
53. 57248-88-1.rn.
54. or/48-53
55. clodronate.af.
56. CL2MDP.af.
57. bonefos.af.
58. loron.af.
59. ascredar.af.
60. lodronat.af.
61. lytos.af.
62. ostac.af.
63. clastoban.af.
64. clasteon.af.
65. difosfonal.af.
66. ossiten.af.
67. mebonat.af.
68. "disodium (dichloromethylene)diphosphonate tetrahydrate".af.
69. 22560-50-5.rn.
70. or/55-69
71. tiludron$.af.
72. skelid.af.
73. "disodium dihydrogen{[(p-chlorophenyl)thio]methylene}diphosphonate hemihydrate".af.
74. 149845-07-8.rn.
75. or/71-74
76. risedron$.af.
77. actonel.af.
78. "sodium trihydrogen[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate".af.
79. 115436-72-1.rn.
80. or/76-79
81. alendron$.af.
82. fosamax.af.
83. adronat.af.
84. alendros.af.
85. dronal.af.
86. "aminohydroxybutylidene diphosphonic acid".af.
87. 66376-36-1.rn.
88. or/81-87

89. neridron$.af.
90. AHDP.af.
91. "(6-amino-1-hydroxyhexylidene)diphosphonic acid".af.
92. 79778-41-9.rn.
93. or/89-92
94. zoledron$.af.
95. zometa.af.
96. 118072-93-8.rn.
97. or/94-96
98. ibandron$.af.
99. bondronat.af.
100. "(1-hydroxy-3-[methylpentylamino]propylidene)diphosphonic acid".af.
101. 114084-78-5.rn.
102. or/98-101
103. olpadron$.af.
104. OPD.af.
105. "(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.
106. 63132-39-8.rn.
107. or/103-106
108. incadron$.af.
109. YM175.af.
110. YM 175.af.
111. 138330-18-4.rn.
112. or/108-111
113. minodron$.af.
114. YM529.af.
115. YM 529.af.
116. 127657-42-5.rn.
117. or/113-116
118. or/37-39,47,54,70,75,80,88,93,97,102,107,112,117
119. 118 and 36
120. 119 and (10 or 21 or 29)

Appendix 2

Hypercalcaemia inclusion/exclusion sheet

Reference Manager No		Reviewer	JRR
Lead Author			YS
Year			PE

Patient Population:

Number of patients (xx M / yy F)		Age yrs [mean ± SD **OR** median (IQR)]	
Cancer type [all or specify]			
Histological Dx	Y / N / NR	Haem malig Inc	Y / N / NR
Metastatic Disease	Y / N / NR	Bone mets	Y / N / NR
Hypercalcaemia?	primary / secondary / both / NR Prevention of ↑Ca		
Exclusion Criteria			
Previous Bisphosphonate	Y / N / NR		

Study Design / follow-up:

Randomised	Y / N	How?	
Allocat^{n} conceal^{mt}	A B C D		
Blinding	Single / double / open		
Primary end point			
Secondary end point(s)			
Grps comparable at baseline	Y / N / ?	If N / ? why not?	
Grps identical Tx + intervention	Y / N / ?	If N / ? why not?	

Tx in each arm	**Treatment Arm (A)**	
	Drug / Route / oral / IV / Dose / inf rate	
	Control Arm	
	Drug / Route / oral / IV / Dose / inf rate	
	Treatment Arm (B)	
	Drug / Route / oral / IV / Dose / inf rate	
	Treatment Arm (C)	
	Drug / Route / oral / IV / Dose / inf rate	
Definition ↑Ca (how calc cCa)		
Rehydration (24-48 hrs)	Y / N	

Conclusion:

RCT	Y / N	Reason(s) for exclusion:
For inclusion	Y / N	

Appendix 3

Skeletal morbidity: inclusion/exclusion sheet

Reference Manager No		Reviewer	JRR
Lead Author			YS
Year			PE

Patient Population:

Number of patients (xx M / yy F)		Age yrs [mean ± SD **OR** Median range/IQR]	
Cancer type [all or specify]			
Confirmed Malignancy	Y / N	Confirmed Bony Mets	Y / N Xray / Bone scan / Biopsy
Exclusion Criteria			

Study Design / follow-up:

Randomised	Y / N	How?	
Allocat^{n} conceal^{mt}	A B C D		
Blinding	Single / double / open		
Primary end point			
Defined end point(s)	Hypercalcaemia pathological fracture (vertebral / non-vertebral) radiotherapy cord compression orthopaedic procedures Performance status (Karnofsky / ECOG) Quality of Life Survival Time to disease progression Other:		Y / N Y / N Y / N Y / N Y / N Y / N Y / N
Grps comparable at baseline	Y / N / ?	If N / ? why not?	
Grps identical Tx + intervention	Y / N / ?	If N / ? why not?	

Tx in each arm	**Treatment Arm (A)**	
	Drug / Route / oral / IV / Dose / inf rate	
	Control Arm	
	Drug / Route / oral / IV / Dose / inf rate	
	Treatment Arm (B)	
	Drug / Route / oral / IV / Dose / inf rate	
	Treatment Arm (C)	
	Drug / Route / oral / IV / Dose / inf rate	

Conclusion:

RCT	Y / N	Reason(s) for exclusion:
For inclusion	Y / N	

Appendix 4

Adjuvant review inclusion/exclusion sheet

Reference Manager No		Reviewer	
Lead Author			
Year			

Patient Population:

Number of patients (xx M / yy F)		Age yrs [mean ± SD **OR** median (IQR)]	
Cancer type [all or specify]			
Histological Dx	Y / N / NR	Haem malig Inc	Y / N / NR
Metastatic Disease	Y / N / NR	Confirmed NO Bone Mets	Y / N Xray / Bone scan / Biopsy
Exclusion Criteria			
Previous Bisphosphonate	Y / N / NR		

Study Design / follow-up:

Randomised	Y / N	How?	
Allocat^{n} conceal^{mt}	A B C D		
Blinding	Single / double / open		
Primary end point	Development of skeletal metastases Y / N Time to first skeletal metastases Y / N		
Secondary end point(s)	Survival Y / N Development of non-bony metastases Y / N Time to non-bony metastases Y / N		
Grps comparable at baseline	Y / N / ?	If N / ? why not?	

Tx in each arm	**Treatment Arm (A)**	
	Drug / Route / oral / IV / Dose / inf rate	
	Control Arm	
	Drug / Route / oral / IV / Dose / inf rate	
	Treatment Arm (B)	
	Drug / Route / oral / IV / Dose / inf rate	
	Treatment Arm (C)	
	Drug / Route / oral / IV / Dose / inf rate	

Conclusion:

RCT	Y / N	Reason(s) for exclusion:
For inclusion	Y / N	

Appendix 5

Hypercalcaemia data extraction sheet

Reference Manager No	
Lead Author	
Year	

Flow diagram
Age:

Group	Age (yrs)	Stats: Mean/Median (SD/IQR/Range)	n=

Outcomes:

1) Normocalcaemia (within 10 days)

Group	No of pts NormoCa x / y	Baseline CCa for grp (mean ± SD)

2) Time to normocalcaemia (days)

Group	Value (spread)	STATS	n=	Comments

3) Time to relapse (days)

Group	Value (spread)	STATS	n=	Comments

4) Survival (Could additional data be req from Au Y / N)

	Comments

5) Bone resorption markers

Specify marker	Group	Value (units) baseline	Value (units) post Tx	Comments

6) Toxicity

Side effect	n=	Asymp (Y/N)	Comments

Appendix 6

Skeletal morbidity data extraction sheet

ID Number						
Ref Mx No(s)						
Lead Author						
Year						

Flow diagrams

(i) How papers fit together – indicate which paper(s) data taken from
(ii) numbers of patients randomised / treated / drop outs

ID_____

Ref Mx No		Author		Year		Reviewer	JR / YS

		Group A					Group B				
MONTH											
Path # V / N / C	x (N)										
	rate										
DXT	x (N)										
	rate										
SCC	x (N)										
	rate										
Ortho	x (N)										
	rate										
HyperCa	x (N)										
	rate										

Time to disease progression **STUDY ID:_____**

Radiologist blinded Y / N **Study length :_____**

Definitions:

	Group A		Group B	
	mean / median	SD / SEM / IQR / range	mean / median	SD / SEM / IQR / range
Bone mets				
1st SRE				

PERFORMANCE STATUS / QUALITY OF LIFE

SURVIVAL

TOXICITY

Appendix 7

Adjuvant data extraction sheet

Reference Manager No		Reviewer	
Lead Author			
Year			

Flow Diagram:

Age:

Group	Age (yrs)	Stats: Mean/Median (SD/IQR/Range)	n=

Outcomes:

Patients developing bone metastases	No. patients	No. events	Event rate
BP			
Placebo			
Time to development bone metastases	**Mean/Median (SD/SQR/range)**	**n=**	
BP			
Placebo			
Patients developing non-bony metastases	**No. patients**	**No. events**	**Event rate**
BP			
Placebo			

Survival:

	Clod	Placebo	Comments
At 6 months			
At 1 years			
At 2 years			
At 4 years			

Appendix 8

Economics search strategy
Last searched: 29 August 2001

PubMed search

1	bisphosphonate OR diphosphonate OR disphosphonate OR biphosphonate OR bisphosphonates OR diphosphonates OR disphosphonates OR biphosphonates OR diphosphonates[MESH]
2	clodronate OR pamidronate OR etidronate OR alendronate OR ibandronate OR risedronate OR zoledronate OR tiludronate OR APD OR aredia OR didronel OR benefos OR loron OR skelid OR actonel OR fosamax OR neridronate OR olpadronate OR OPD OR amino-olpadronate OR "amino-olpadronate" OR incadronate OR etidronic OR clodronic OR pamidronic OR alendronic OR ibandronic OR risedronic OR zoledronic OR tiludronic OR neridronic OR olpadronic OR incadronic OR etidron* OR osteum OR cl2mdp OR ostac OR tiludron* OR clodron* OR etidron* OR pamidron* OR minodron* OR risedron* OR alendron* OR zoledron* OR neridron* OR ibandron* OR olpadron* OR incadron* OR YM175 OR "YM 175"
3	neoplasm OR neoplasms OR cancer OR cancers OR "multiple myeloma" OR myeloma OR myelomas OR neoplasms[MESH]
4	Cost OR costs OR cost-effective OR cost-effectiveness OR costeffective OR costeffectiveness OR cost-benefit OR benefit-cost OR cost-effect* OR costeffect* OR cost-benefi* OR benefit-cost* OR benefitcost* OR costbenefi* OR cost-utility OR economic OR cost-utility* OR costutility* OR economics OR econom* OR economics[MESH] OR "cost-effective" OR "cost-effectiveness" OR "cost-benefit" OR "benefit-cost" OR "cost-utility" OR costing OR costings OR costed OR QALY* OR life-year* OR lifeyear* OR utility OR hospitali*
5	#1 OR #2
6	#5 AND #3
7	#6 AND #4

Appendix 9

Cost data extraction form

Basics

Drug(s) name and dosages	
Is the control group 'no treatment' or an alternative drug regime?	
What is the denominator (e.g. cost per patient per year)? Is it usable?	

Does the cost estimate include the following (and are these cost components stated separately):

Component	Is it included? (Y/N)	Magnitude (treatment group)	Magnitude (control group)
Drug costs			
Staff time			
Consumables, running costs			
Overheads			
Treatment of skeletal events			
Patient costs			
Any other cost item			
All costs			

Add additional information on reverse, if necessary

Context

Clinical context (incl. Patient group)	
Currency and year of cost	
Country	

Details of resources used

Staff time	
Staff grade	
Treatment of skeletal events	
Other	

Source information

Which trial is the study based on?	
Sample size	
Nature of statistical analysis	
Model used	

Add additional information on reverse, if necessary

Summary of results

Health outcomes
Resource use/costs
Cost-effectiveness

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We look forward to hearing from you.

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ISSN 1366-5278