



<b>Title</b>	<b>A Systematic Review of the Role of Bisphosphonates in Metastatic Disease</b>
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<b>Reference</b>	Health Technol Assess 2004;8(04). Feb 2004. <a href="http://www.ncchta.org/execsumm/summ804.htm">www.ncchta.org/execsumm/summ804.htm</a>

## Aim

To identify evidence for the role of bisphosphonates in metastatic disease, in 3 areas: treating hypercalcaemia, preventing skeletal morbidity, and adjuvant use. To perform an economic review of the literature and construct Markov models to evaluate the cost effectiveness of bisphosphonates in treating hypercalcaemia and preventing skeletal morbidity.

## Conclusions and results

*Hypercalcaemia:* Due to the heterogeneity of studies, results could not be combined in a meta-analysis. Bisphosphonates are well tolerated with low incidence of side effects.

*Skeletal morbidity – Primary analysis:* On meta-analysis bisphosphonates, compared with placebo, significantly reduced the OR for V#, NV#, C#, RT and ↑Ca but not Ortho or SCC.

*Adjuvant Use:* Clodronate, given to patients with primary operable breast cancer with no metastatic disease significantly reduces the number of patients developing bone metastases. This benefit was not maintained once clodronate had been discontinued. Two trials reported significant survival advantages in treated groups but not in patients with advanced disease. Bisphosphonates reduce the number of bone metastases in early and advanced breast cancer.

*Economic review (Hypercalcaemia):* Drugs with the longest cumulative duration of normocalcaemia were most cost effective.

*Economic review (Skeletal morbidity):* The estimated cost to prevent SRE was £250 and £1,500 per event in patients with breast cancer and multiple myeloma respectively. The model suggested that bisphosphonate treatment is can save costs in breast cancer patients if fractures are prevented. The models were sensitive to the probability of averting SRE, the unit cost of SRE, and the price of bisphosphonate treatment.

## Recommendations

Bisphosphonates normalize serum calcium in >70% of patients with hypercalcaemia of malignancy within 2–6 days, they significantly reduce SREs and delay the time to first SRE in patients with bony metastatic breast cancer and multiple myeloma. Benefit appears at different times for different SREs. Bisphosphonates do not affect survival. The evidence is strongest for the efficacy of pamidronate and for intravenous over oral administration. In primary operable breast cancer, oral clodronate reduces the number of patients with bone metastases.

## Methods

See monograph for description of methods.

## Further research/reviews required

- 1) RCTs in other disease groups with a high incidence of skeletal metastases.
- 2) RCTs in the adjuvant setting over extended periods, with comparisons of newer more potent bisphosphonates, and oral vs IV routes of administration.
- 3) Further cost and quality of life data to identify cost effectiveness of reductions in SREs and delayed time to first SRE.
- 4) RCT to confirm optimum time to commence bisphosphonate therapy.
- 5) Studies to identify reasons for resistance to bisphosphonates, and develop drugs to block renal action of PTHrP.
- 6) RCT of maintenance therapy with bisphosphonates to delay time to relapse in hypercalcaemic patients.