EVIDENCE CENTRE CRITICAL APPRAISAL

The use of bisphosphonates in children and adolescents

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SUMMARY STATEMENT:

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REQUEST:

What is the evidence for the use of bisphosphonates in children and adolescents?

REQUESTED BY:

Dr Christine Rodda, Head, Paediatric Endocrinology and Diabetes, Department of Paediatrics, Monash Medical Centre, Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defined the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomized controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalizable, or have other methodologic difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request:

Search terms:

The following search terms were used to scour electronic databases and websites:

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient-related	Newborns, infants, children, adolescents
Intervention-related	Bisphosphonates, diphosphonates
Comparison-related	All others
Outcome-related	Fragility fractures, skeletal dysplasias, steroid-induced osteoporosis, osteogenesis imperfecta, humoral hypercalcemia of malignancy, hypophosphatasia, bony metastases, immobility osteoporosis

Resources Searched

We searched the following databases and Internet websites:

- Cochrane Library CD-ROM
- Best Evidence CD-ROM
- Medline (OVID)
- Pubmed
- National Guidelines Clearinghouse
- Agency for Health Care Policy and Research (AHCPR)
- NHS Centre for Reviews and Dissemination (NHS CRD)
- Aggressive Research Intelligence Facility (ARIF)
- Turning Research into Practice (TRIP)

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 15 October 1999. We only included articles published in the last 10 years. Critical appraisal was performed on the subset of studies published in English.

RESULTS:

From our sources we identified 94 articles which we categorised as follows:

Table 2. Study designs of articles retrieved by search

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	**7**
Controlled trials, cohort or case-control analytic studies	**9**
Descriptive case series	60
Consensus reports, non-evidence-based clinical practice guidelines	0
Narrative reviews	18

Articles were excluded from further appraisal as follows:

Table 3. Reasons for exclusion of articles retrieved by search

Reason for exclusion	Number
Level IV evidence	78
Adult subjects or individual subject ages not given	15

This left only one comparative study (Lepore 1991) available for critical appraisal. We are reasonably confident these articles represent the most important findings published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

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ARTICLES NOT CRITICALLY APPRAISED

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APPENDIX

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The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and Southern Health Care Network do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and Southern Health Care Network cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors of omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

Levels Of Evidence

As Defined By "A Guide To The Development, Implementation And Evaluation Of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 1998):

Level I		Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one properly designed randomised controlled trials.
Level III	-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series (either post-test or pre-test and post-test), opinions of respected authorities (narrative reviews), descriptive studies, reports of expert (i.e. consensus) committees, case studies.

Evidence Summary Therapy Bisphosphonates in children and adolescents	Lepore L, Pennesi M. Barbi E, Pozzi R. Treatment and prevention of osteoporosis in juvenile chronic arthritis with disodium clodronate. Clinical and Experimental Rheumatology 1991;9 (Suppl 6):33-35.
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Comparative study. Level III-2.
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	**Patients:** 13 patients, demographic data not given. **Intervention:** disodium clodronate 1200 mg/day in three divided doses for one year (n=7) **Comparison:** controls (n=6); nature of control group not indicated. **Outcome:** bone mineral density by CT scan **Incl & Excl Criteria:** not stated
VALIDITY: Methodology, rigour, selection, opportunity for bias	**Randomisation:** None stated **All patients accounted for:** Yes **Patients treated equally:** Unclear **Similar groups:** Unclear **Potential for bias:** No randomisation scheme. Comparability of groups uncertain. Inclusion and exclusion criteria not stated.
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	8% increase in bone mineral density in treatment group. 7% increase seen in controls. No substantial change in resum and urinary calcium. No haematologic abnormalities seen. Therapy well tolerated.
AUTHORS COMMENTS: Risk/benefit, limitations	"The small number of patients enrolled in our trial does not allow any definite conclusions to be drawn from the results. We believe, however, that our data are interesting and worthy of further study in order to evaluate the effectiveness of bisphosphonates in the prevention and/or treatment of osteoporosis in rheumatic diseases or consequent to corticosteroid treatment."
REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions	