

As a Clinical Specialist nominated by the British Geriatrics Society (BGS) and National Osteoporosis Society (NOS), I am grateful for the opportunity of commenting on the latest Appraisal Consultation Documents (ACDs). I was extremely disappointed at the proposed guidance, which still appears to be inappropriately restrictive and clinically unworkable. Following the decision of the Appeal Panel in December 2007, I welcome the fact that the Appraisal Committee now recognises the role for other treatments in patients in whom alendronate is either contraindicated or not tolerated. Nevertheless, I am concerned about the increasingly demanding bone mineral density (BMD) T-score thresholds for the use of risedronate (or etidronate), raloxifene, strontium ranelate and teriparatide. This will lead to situations where a patient who is unable to take or tolerate alendronate is denied alternative treatment, because their T-score is not low enough to justify a second line agent. This will be difficult for a clinician to explain and justify to an individual patient. It is also potentially discriminatory in that patients who otherwise fulfil the criteria for the use of alendronate, but have a contraindication such as oesophageal disease, may be denied access to alternative treatment if their T-score is not low enough. In order to address this issue, the Appraisal Committee should consider requesting further refinements to the cost effectiveness modelling, to take into account the increased cost of alternative treatments in the proportion of patients unable to take or tolerate alendronate. This would at least ensure more equitable access to treatment for patients, with or without contraindications to or serious side-effects from alendronate.

Has all the relevant evidence been taken into account?

The World Health Organization (WHO) has now published details of their model for predicting the ten year absolute risk of major osteoporotic fractures in general and hip fractures in particular (1). This Fracture Risk Assessment Tool (FRAXTM) is now freely available (<http://www.shef.ac.uk/FRAX>), where it may be accessed by health care professionals, patients, carers and the general public. The risk factors and their appropriate weighting was established from nine large prospective population-based studies from around the world and then validated in a further 11 independent cohorts with a similar geographic distribution (2). Although most previous studies of the efficacy of different osteoporosis treatments in the prevention of fractures recruited patients on the basis of low BMD and/or the presence of fractures, one recently presented study shows that the bisphosphonate clodronate is effective in reducing fracture risk in patients at high risk of fracture identified by FRAXTM (3).

It is unfortunate that although the NICE ACDs have used some of the risk factors included in the WHO FRAXTM tool, smoking has been omitted from the list of risk factors and the threshold for alcohol consumption has been increased from three or more to four or more units daily. Although FRAXTM may have its limitations in not including falls-related risk factors for fracture, on the basis that these are not necessarily modifiable by osteoporosis treatments, it is more evidence based than the proposed NICE guidance, which has selectively 'cherry picked' and manipulated the WHO risk factors. I therefore suggest that the Appraisal Committee consider fully incorporating FRAXTM in revised guidance, particularly as clinicians in primary and secondary care are already showing considerable interest in this tool.

At the Appeal Hearing in October 2007, considerable concern was expressed about the cost-effectiveness modelling underlying the NICE Technology Appraisals,

particularly as the model was not made available to the appellants. Although these criticisms were not upheld, considerable doubt remains about the validity of the assumptions made in the cost-effectiveness modelling, including the use of the ten year time horizon, the progressive lowering of the relative risk reduction at the hip for alendronate, the reduction in the disutility associated with vertebral fracture, the different QALY thresholds for primary and secondary prevention and the ten-times multiplier for the side effects of treatment. Concerns about the cost-effectiveness model were also highlighted in a recent Editorial published in *Bone*, written by the respective Presidents of the International Osteoporosis Foundation and National Osteoporosis Foundation (4). Although the price of generic alendronate is even lower than that used in the previous cost-effectiveness modelling, the resulting guidance remains highly restrictive. It appears that the assumptions used in the model have been uniformly conservative, rather than based on a best estimate. An alternative cost-effectiveness model has now been published, which uses a similar approach to the NICE model, but more realistic assumptions (5). This suggests that osteoporosis treatment is more cost-effective than the NICE model suggests in many situations.

Since work on these Technology Appraisals started in 2002, further treatments have been licensed for osteoporosis, including monthly oral and three monthly intravenous injections of ibandronate, annual intravenous infusions of zoledronate and parathyroid hormone 1-84. Although these agents are outside the scope of the current Technology Appraisals, I would urge that with the long delays in producing final guidance, serious consideration is given to including them at this late stage. This is particularly the case for intravenous zoledronate, which has been shown to be highly effective in reducing the risk of vertebral, hip and other non-vertebral fractures (6). Furthermore, it also decreases the risk of further fractures in patients with hip fractures, where a significant improvement in mortality was also seen (7). Compliance with annual infusion is also likely to be less of a problem than with daily or weekly oral bisphosphonate treatment.

Are the Summaries of Clinical and Cost Effectiveness Reasonable Interpretations of the Evidence and are the Preliminary Views on the Resource Impact and Implications for the NHS Appropriate?

As detailed above, there are a number of concerns about the cost-effectiveness modelling, which were highlighted in the recent Editorial in *Bone* (4) and by the NOS and other appellants at the Appeal Hearing. In particular, the different QALY thresholds for primary and secondary prevention appear illogical, as the opportunity cost in both situations is the same. The Appeal Panel stated that ‘the two circumstances of primary and secondary prevention of osteoporotic fractures were so similar that it would be advisable if the Final Appraisal Document for secondary prevention explained more clearly why a higher incremental cost per QALY had been accepted for secondary prevention as compared to that for primary prevention’. Paragraph 4.3.15 of the Primary Prevention ACD does not address this issue adequately, as it describes potential candidates for such intervention as asymptomatic. Patients with osteoporosis but without previous fractures who attend my Bone Clinic are very similar to those who have already fractured, in that many are frail, older women with co-morbid conditions, where a major low trauma fracture would be as devastating if it was the first or a subsequent fracture.

Are the Provisional Recommendations of the Appraisal Committee Sound and do they Constitute a Suitable Basis for the Preparation of Guidance to the NHS?

Given the relative lack of data to support the efficacy of etidronate in decreasing the risk of non-vertebral fractures, I am surprised that it is placed along side risedronate as an alternative second line treatment. Although this bisphosphonate is inexpensive, it is now rarely used in clinical practice, because of the complicated cyclical regimen and the poor data on anti-fracture efficacy. I therefore feel that the limitations of etidronate as a treatment option should be highlighted more clearly.

Although the ACDs provide guidance on the use of second line treatments in patients unable to take or tolerate alendronate, there are no longer any recommendations on management of patients who fail to respond to treatment. Although this may be difficult to define, this was attempted in TAG 87, where specific guidance on the management of such patients was provided.

I am concerned that the ACDs list independent clinical risk factors for fracture and indicators of low BMD separately, as this is potentially confusing to clinicians without a major interest in osteoporosis. Most of these risk factors and indicators of low BMD predict fracture, even after adjustment for BMD. The exception is untreated premature menopause, which may be a risk factor for the development of osteoporosis in younger postmenopausal women, but its effect on BMD and fracture risk later in life is uncertain. Furthermore, the proposed guidance does not weight these factors, but merely uses the total number, age and BMD to guide treatment decisions. The full inclusion of the FRAXTM would allow a simpler, more evidenced based approach to both the primary and secondary prevention of fractures.

Finally, I should like to highlight the lack of data on anti-fracture efficacy of alendronate in women above the age of 80 years, but remind the Appraisal Committee of research indicating that risedronate and strontium ranelate are safe and effective in decreasing fracture risk in this age group (8,9), so should be more readily available to this population. Furthermore, neither the draft NICE guidance nor FRAXTM use falls-related risk factors for fracture, on the basis that these are not necessarily modifiable by osteoporosis treatment. Nevertheless, prospective studies from the US, Australia and Europe show that the combination of low BMD and falls-related risk factors confers a greater risk of fracture than either one alone (10,11,12). As 90% of non-vertebral fractures occur after a fall and the number of falls is related to the risk of hip fracture (13), consideration should be given to the inclusion of falls as a 'permissive' risk factor for low trauma fractures in older women, to avoid disadvantaging this group.

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