Comparing guidelines for treating osteoporosis

Guidelines for treating osteoporosis issued by NICE in October 2008 were controversial throughout the consultation process and legally challenged early in 2009. The National Osteoporosis Guideline Group released an alternative set of guidelines giving doctors more choice in prescribing and including treatment for men. While experts in the UK argued about treatment choices, the American College of Physicians released guidance for US practice. The USA is often seen as an early adopter of new treatments—does this translate into its guidance for doctors?

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How does a doctor treat a patient with osteoporosis? NICE guidance has repeatedly fallen short of what doctors and patient's groups call for. The NICE appraisal documents[1,2] were issued in October 2008, and were judged unlawful in February 2009.[3,4] Alternative guidelines were issued by the National Osteoporosis Guideline Group. Across the Atlantic, the American College of Physicians released recommendations in September 2008. How does the US view compare with those in the UK?

One point on which all groups agree is the definition of osteoporosis as a T-score of -2·5. This is bone mineral density of 2·5 standard deviations less than that of a heathy young female adult, and is measured clinically by dual absorption X-ray absorptiometry.

NICE Guidance

Two sets of guidelines were issued (table)—for primary prevention[1] and for secondary prevention[2] of osteoporotic fractures. Neither document deals with women with normal bone mineral density or osteopenia, even if they have a fragility fracture. Separate guidance is under development for corticosteroid-induced osteoporosis

Primary prevention

The first step is ensuring that the patient has no deficiency of calcium or vitamin D, with prescription of appropriate supplements if necessary. The recommendations for treatment of women who have not had a fragility fracture are complex (table), but alendronate is first-line treatment. The difficulty is that if a patient has any problem taking alendronate, no other treatment is recommended until the patient's bone-mineral density decreases further and they develop additional risk factors or indicators of osteoporosis (box).

Secondary prevention

Again, calcium and vitamin D levels should be adequate before further treatment options are considered. The recommendations are again complicated, but some differences from the primary prevention strategy are notable. Specifically in that additional treatment options become available at younger ages and with smaller decreases in bone-mineral density.

The patients that this guidance targets have already had a fragility fracture and are at high risk of further fractures, so you would expect more flexible treatment strategies. Raloxifene and

Box 1: Risk factors for osteoporosis

- Older age
- Female sex
- Current smoking
- Parental history of hip fracture*
- Alcohol intake of 3+ units a day*‡
- High caffeine intake
- Rheumatoid arthritis*
- Previous fragility fracture
- Low body-mass index (19–25 kg/m^2)§
- Weight loss of 10% or more of bodyweight
- Ankylosing spondylitis†
- Crohn's disease†
- Prolonged immobility†
- Untreated premature menopause†
- Use of glucocorticoids

*NICE risk factor. ‡4+ units in NICE guidance †NICE indicator. §Range of different thresholds between guidelines.

teriparatide are now recommended for secondary prevention in some patients, but the continued need for patients to deteriorate before switching to a different drug is counter-intuitive at best and unethical at worst.

NOGG

NOGG was formed by several organisations, including the Royal College of Physicians, the British Geriatrics Society, and the National Osteoporosis Society, which were unhappy with the guidelines issued by NICE. These guidelines were based on WHO's Fracture Risk Assessment Tool (FRAX), which calculates the 10-year probability of osteoporotic fracture. FRAX was launched in February 2008, which was too late for inclusion in NICE's appraisals.

Non-drug interventions

The best non-drug interventions are exercise and calcium supplementation, with or without vitamin D, which had grade A evidence for increasing bone-mineral density and grade B for reducing spine and hip fractures. Dietary calcium and smoking cessation were graded B for all outcomes. Reducing alcohol consumption had more effect on hip fracture rates (B) than on bone-mineral density or spine fracture (both C). Falls prevention programmes had some effect on both types of fracture (C), and hip protectors showed some efficacy (C).

Drug treatments

As for drug treatments, all approved treatments showed grade A evidence of efficacy against vertebral fracture—alendronate, etidronate, ibandronate, risedronate, zoledronate, calcitonin, calcitriol, raloxifene, strontium ranelate, teriparatide, recombinant human parathyroid hormone (1-84), and hormone replacement therapy. Not all drugs had best evidence in non-vertebral fracture and hip fracture, but those scoring top in all categories were alendronate, risedronate, zoledronate, and hormone replacement therapy.

NOGG's recommendations could not be simpler. Alendronate as first-line treatment because of efficacy and cost, then other bisphosphonates, strontium ranelate, or raloxifene if alendronate is not tolerated or is contraindicated. Parathyroid peptides (teriparatide, ecombinant human parathyroid hormone [1-84]) should be restricted to patients at very high risk, particularly for vertebral fractures because of their high cost. For men, use of approved treatments (alendronate, risedronate, and teriparatide) is endorsed.

Thresholds for treatment

The decision of which patients should be treated is still fairly complex. Those with previous fragility fracture should have treatment (ie, secondary prevention) without needing further investigation, but establishing bone-mineral density might be useful, especially for younger patients. For all men, and women without previous facture (ie, primary pervention), the 10-year probability of fracture should be calculated with FRAX.

Patients at the lower end of the probability scale do not need referred for further assessment. This ranges from 6% at age 50 years, increasing to 18% at 80 years. Patients with higher probabilities of fracture should be assessed further, and possibly treated. Patients with probabilities higher than the upper assessment threshold (9% at 50 years to 35% at 80 years) should be considered for treatment.

The US view

The American College of Physicians published a practical guideline[6] for treating osteoporosis on the basis of a systematic review of evidence from trials of drugs. Not all drugs available in the UK are licensed for use in osteoporosis in the USA. Etidronate for example is approved only for Paget's disease and heterotopic ossification, and strontium ranelate is not even mentioned in this guidance.

Treatment is recommended for men and women with known osteoporosis and for those who have had a fragility fracture; it should be considered for those at risk of osteoporosis. The choice of treatment should be made on the basis of risks and benefits to each individual patient. Bisphosphonates are suitable first-line options, but no evidence shows any to be superior to another, except that ibandronate has no evidence for reducing hip or non-vertebral fracture.

NICE on trial?

Doctors in the USA have more prescribing freedom because of their system of health-care funding. But the high monetary cost of prescribing what they like creates its own problems. WHO data[7] show that the total per capita healthcare expenditure USA in 2006 was double that of the UK at the average exchange rate. The USA also spends nearly double that of the UK in terms of gross domestic product (15·3% versus 8·4%). Despite this, people in the UK live a year longer and are far less likely to die between the ages of 15 and 60 years—137 per 1000 in USA versus 98 per 1000 in the UK.

Somehow we manage our health-care budget fairly effectively, although we always have room for improvement, and NICE has important roles in both controlling costs and setting out best practice. Regulatory bodies and doctors are concerned with the effectiveness of drugs for their patients. NICE puts a good deal of emphasis on cost-effectiveness. Well publicised debate on new cancer drugs costing tens of thousands of pounds for a few months' extra life is the extreme of the scale. Yet, these costs do not even compare with spending a few hundred pounds a year in the hope of avoiding disability and even death after hip fractures.

NICE has clearly produced the most obtuse guidelines of all three bodies. But for all its concern over cost-effectiveness, it did not include bone-mineral density scans in its financial model, apart from the initial scan that confirmed osteoporosis. These

	Primary prevention[1]	Secondary prevention[2]
Alendronate	Postmenopausal women younger than 65 years with 1 risk factor plus 1 indicator and confirmed osteoporosis Women aged 65–69 with at least 1 risk factor and confirmed osteoporosis Women aged 70+ with at least 1 risk factor or indicator and confirmed osteoporosis Women aged 75+ with at least 2 risk factors	Postmenopausal women with confirmed osteoporosis or aged 75+
Risedronate Editronate	Women unable to comply with administration of alendronate, or are intolerant or contraindicated to alendronate **and** Aged 65–69 with 1 risk factor and T=−3·5, or 2 risk factors and T=−3·0 Aged 70–74 with 0 risk factors and T=−3·5, or 1 risk factor and T=−3·0, or 2 risk factors and T=−2·5 Aged 75+ with 0 risk factors and T=−3·0, or 1 risk factor and T=3·0, or 2 risk factors and T=2·5	Women unable to comply with administration of alendronate, or are intolerant or contraindicated to alendronate **and** Aged 50–54 with 1 risk factor and T=−3·0, or 2 risk factors and T=−2·5 Aged 55–59 with 0 risk factors and T=−3·0, or 1 risk factor and T=−3·0, or 2 risk factors and T=−2·5 Aged 60–65 with 0 risk factors and T=−3·0, or 1 risk factor and T=−3·0, or 2 risk factors and T=−2·5 Aged 65–69 with 0 risk factors and T=−3·0, or 1 risk factor and T=−2·5, or 2 risk factors and T=−2·5 Aged 70+ with 0 risk factors and T=−2·5, or 1 risk factor and T=2·5, or 2 risk factors and T=2·5
Strontium ranelate	Women unable to comply with administration of alendronate and etidronate or risedronate, or are intolerant or contraindicated to alendronate and etidronate or risedronate **and** Aged 65–69 with 1 risk factor and T=−4·5, or 2 risk factors and T=−4·0 Aged 70–74 with 0 risk factors and T=−4·5, or 1 risk factor and T=−4·0, or 2 risk factors and T=−3·5 Aged 75+ with 0 risk factors and T=−4·0, or 1 risk factor and T=4·0, or 2 risk factors and T=3·0	Women unable to comply with administration of alendronate and etidronate or risedronate, or are intolerant or contraindicated to alendronate and etidronate or risedronate **and** Aged 50–54 with 1 risk factor and T=−3·5, or 2 risk factors and T=−3·5 Aged 55–59 with 0 risk factors and T=−4·0, or 1 risk factor and T=−3·5, or 2 risk factors and T=−3·5 Aged 60–65 with 0 risk factors and T=−4·0, or 1 risk factor and T=−3·5, or 2 risk factors and T=−3·5 Aged 65–69 with 0 risk factors and T=−4·0, or 1 risk factor and T=−3·5, or 2 risk factors and T=−3·0 Aged 70–74 with 0 risk factors and T=−3·0, or 1 risk factor and T=3·0, or 2 risk factors and T=2·5 Aged 75+ with 0 risk factors and T=−3·0, or 1 risk factor and T=2·5, or 2 risk factors and T=2·5
Raloxifene	Not recommended	
Teriparatide	Not mentioned	Women unable to comply with administration of alendronate and etidronate or risedronate, or are intolerant or contraindicated to alendronate and etidronate or risedronate or are intolerant of strontium ranelate or have had an unsatsfactory response to alendronate, risedronate, or etidronate, **and** Aged 55–64 with T=−4·0 and more than 2 fractures Aged 65+ with T=−3·5 and more than 2 fractures
Treating men	Not mentioned	Not mentioned

Table 1: Summary of NICE guidance

scans are the only reliable way of measuring bone mineral density. Thus, to establish if a patient has deteriorated to a point at which a treatment other than alendronate can be given, another scan must be done, increasing costs, risk to the patient, and changes standard clinical practice.

The peculiar case of NICE and the Professor

The financial model for determining cost-effectiveness of treatments for osteoporosis was supplied, under a confidentiality agreement, by Professor John Kanis of Sheffield University to Dr Stevenson who led the appraisal group. Professor Kanis holds the intellectual property relating to the risk algorithms and coefficients that power the model. The background to the development of the model has all been published in peer-reviewed journals. However, the coefficients used to construct a model are confidential. The principal reason for this is to protect the integrity of the model so that it is not abused. There are no commercial reasons for this confidentiality.[8]

After the release of NICE's guidelines, Servier Laboratories, manufacturers of strontium ranelate, with the support of the National Osteoporosis Society, took NICE to court.[4] Servier argued that the secrecy surrounding the financial model prevented rigorous scrutiny of the model and thus its accuracy could not be determined. The confidentiality of the model even contradicts NICE's own policies on transparency.

Regarding the availability of the model, Mr Justice Hoffman stated "very few people indeed apart from Dr Matthew Stevenson, who led the work of Sheffield University's School of Health and Related Research have ever seen it." A previous ruling in Eisai versus NICE put little value on agreements of confidentiality about the cost-effectiveness model used for Alzheimer's disease drugs. However, Mr Justice Hoffman judged that the duty of confidence between Professor Kanis, Dr Stevenson, and NICE was appropriate.

NICE's attempts to seek permission for wider disclosure of the model to interested parties consisted of a few emails, one telephone call, and one letter that was not received.[4] Professor Kanis offered NICE full use of WHO's Fracture Risk Assessment Tool (FRAX), which is also built on his algorithms and coefficients. He agreed in principle to wider disclosure, requesting discussion of the details with Mr Andrew Dillon, Chief Executive of NICE.

NICE seemed to misunderstand this request and in any event, no adequate attempts were made to have this discussion. During this time, Professor Kanis wrote an editorial for Osteoporosis International criticising NICE's lack of transparency.[4] Relations between Professor Kanis and NICE might have been strained because he had originally been invited by Mr Dillon to join the appraisal group, but some time later, he was removed because of perceived conflicts of interest, despite his full disclosure at the outset. Professor Kanis is also a key member of NOGG.

The judgement found in favour of Servier, ruling that NICE must now discuss with Professor Kanis the terms of disclosure of the financial model for all consultees. NICE must then permit all consultees to make further resubmissions, but NICE does not necessarily need to change its recommendations.[4]

This case shows NICE in a very poor light indeed. It has a public duty to every patient with, and at risk of, osteoporosis and its unprofessional methods of correspondence in this case publicly shows failure that is probably systematic. Until new guidance from NICE is available, doctors should use their own judgement for each patient, guided by the recommendations from NOGG and the American College of Physicians.

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