NICE: its influence in treating osteoporosis in the UK and beyond

Ther Adv Musculoskel Dis
[2009] 1(2) 63–66

DOI: 10.1177/
1759720X09354945

© The Author(s), 2009.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Juliet Compston

Introduction

Rationing of healthcare is an inescapable consequence of the growing divide between increasing demands on health services and limited financial resources. In the UK the case of Child B, in which funding for treatment of a 10-year-old girl with leukaemia was refused by her Local Health Authority, brought the need for explicit rationing to public attention in 1995 [*The Independent*, 1995] and in 1999, the National Institute for Health and Clinical Excellence (NICE) was created. NICE is an independent organisation, accountable to the Secretary of State for Health, which produces guidance based on technology appraisals in several areas including the prescription of drugs in the National Health Service (NHS). The NHS is obliged to put recommendations arising from these appraisals into practice unless special circumstances apply.

The judgements made by NICE are often difficult and inevitably attract controversy. Nevertheless, in many disease areas NICE guidance has been positively received and the principle of using cost-effectiveness as a basis for recommendations about the use of technologies or drugs in the NHS is now widely accepted. The technology appraisals for osteoporosis, however, have fallen below the normally high standards of NICE, resulting in outdated and inappropriately restrictive guidance.

NICE guidance for osteoporosis

The history of NICE guidance for osteoporosis is long and complex. The scope of the appraisal was announced in April 2002 and guidance for secondary prevention of osteoporotic fracture in postmenopausal women was produced in January 2005 [NICE, 2005]. Subsequently the scope was broadened to include strontium ranelate, and new guidance for both primary and secondary prevention was issued in June 2007. Following a successful appeal against this guidance, new guidance was released in October 2008 [NICE 2008a, 2008b]. This was brought to judicial review in January 2009, as a result of which NICE was instructed to disclose and supply to consultees the full economic model on which the appraisals were based and to permit them to make further submissions or representations. The outcome of this process, which is currently ongoing, will determine whether the 2008 guidance will stand in its present form.

The complexity of the current guidance makes it difficult to summarise, but essentially all postmenopausal women presenting with a fragility fracture may receive alendronate if they are aged over 75 years; postmenopausal women under 75 years old with a fracture must be shown to have osteoporosis (ie a T-score ≤ -2.5) before being eligible for treatment. Primary prevention is mainly restricted to women aged 70 years or older, although younger postmenopausal women may

Correspondence to:
Juliet Compston
Professor of Bone
Medicine, Cambridge
University Hospitals NHS
Foundation Trust,
Hills Road,
Cambridge CB2 0QQ, UK
jec1001@cam.ac.uk

qualify for treatment if they have osteoporosis and clinical risk factors, the number and nature of which are age-dependent. In those women who cannot take alendronate, the use of alternative options (etidronate, risedronate, or strontium ranelate or, for secondary prevention only, raloxifene) requires more stringent criteria. For example, a woman aged 65–69 years with a fragility fracture must have a T-score of -3 or lower to qualify for etidronate or risedronate and a T-score between -3.0 and -4.0 (depending on the number of clinical risk factors) to be allowed strontium ranelate. For primary prevention a similar principle operates; a woman aged between 70 and 74 years with one clinical risk factor needs a T-score of -3.5 or -4 SD to qualify for risedronate or etidronate and strontium ranelate, respectively. Many women, therefore, who are unable to tolerate alendronate must wait until their bone mineral density (BMD) has decreased or they have a fracture before they can receive an alternative treatment (costing less than £350/year). This raises difficult ethical issues for physicians and particularly discriminates against the frail and elderly, who are most likely to be intolerant of alendronate. Furthermore, the complexity of the criteria required for second-line options in individual women makes it unworkable in the primary care setting.

Why is this guidance so restrictive, when generic formulations of alendronate are available, costing only £53.46/year at the time the guidance was issued? Even the second line options are relatively cheap, ranging from £85.65/year for etidronate to £333.71/year for strontium ranelate. Conversely, the costs to the health services of fragility fractures are enormous, estimated at over £2 billion per year [Dolan and Torgerson, 2000]. A contributor to the apparent poor cost effectiveness of treatment may be the limited time horizon of 10 years in the NICE model (in contrast to that used in their appraisal of another chronic disease, coronary heart disease) [Delmas and Siris, 2008]; in addition, a number of changes were made, in the absence of any new evidence, during the evolution of the appraisals in the assumptions on which the model is based. These included reduction in the efficacy estimate for alendronate, reduction in the disutility value for vertebral fractures, reduction in the cost per quality adjusted life year (QALY) threshold for primary prevention from £30,000 to £20,000, and a new assumption of disutility from side

effects that was then multiplied by an arbitrary factor of 10 [Kanis and Compston, 2008]. The cost of fractures is also almost half that of estimates based on empirical observation, and the cost of generic alendronate has fallen further.

There are also other inconsistencies in the use of the evidence base in the appraisal documents. Etidronate is positioned alongside risedronate as a second-line option, even though evidence for its antifracture efficacy in the spine would not be regarded as robust by modern standards and prospective evidence for nonvertebral fracture reduction is nonexistent. The choice of BMD-dependent and independent risk factors is idiosyncratic. Independent clinical risk factors are listed as an alcohol intake of 4 or more units daily, parental history of hip fracture and severe long-term rheumatoid arthritis. Evidence available at the time the appraisals were undertaken clearly demonstrates that the level of alcohol intake at which fracture risk increases is 3 units/day, and that current smoking and glucocorticoid therapy are also independent risk factors [Kanis *et al.* 2004, 2005a, 2005b]. Furthermore, the effect of rheumatoid arthritis on fracture risk is not limited to patients with severe long-term disease. BMD-dependent risk factors in NICE guidance are confined to low body mass index, defined as less than 22 kg/m^2 , and medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause, thus excluding many of the conditions that are known to be associated with low BMD [Poole and Compston, 2006].

The population included in current NICE guidance is restricted to postmenopausal women with osteoporosis as defined by a T-score ≤ -2.5 (although the latter is not mandatory for women aged over 75 years). Men are not included, neither are men or women treated with glucocorticoids. A postmenopausal woman aged less than 75 years who has a T-score higher than -2.5 does not qualify for treatment even if she has had one or more fractures. Newer interventions such as ibandronate and zoledronate, are not considered because they were not included in the original scope of the appraisal. And NICE guidance cannot be used with FRAX[®], the WHO-supported fracture risk assessment tool [Kanis, 2008; Kanis *et al.* 2008a], because its expression of risk as 10-year fracture probability cannot be translated into the

thresholds based on T-score, age and number of clinical risk factors that are used by NICE. Some of these omissions were to have been addressed by a clinical guideline linked to the technology appraisals, but development of this has been suspended and there is no indication as to when it will be resumed.

Despite more than 7 years of deliberations, therefore, the UK is faced with NICE guidance on osteoporosis that is inappropriately restrictive both in terms of its recommendations and the patient populations included, is out of date, and is unworkable in primary care, where the majority of management is based. Whilst the choice of alendronate as the first-line option is appropriate, the complexity of the recommendations for second-line treatments is likely to mean that many women who cannot tolerate alendronate will receive no further treatment. Most primary care organisations have specified targets for the prescribing of generic alendronate, which extend up to 90% of all prescriptions for bisphosphonates and, as part of this policy, switching patients to alendronate from other medications is now widely practised. This is often done in the form of a letter to the patient, without putting in place any arrangements for discussion about the change of therapy with a healthcare professional. The consequences of this policy are unknown, but a negative impact on treatment persistence seems probable. Finally, where no NICE guidance exists, for example in the treatment of men at high risk of fracture or in glucocorticoid-treated individuals, primary care organisations have no mandate to use bone protective therapy and in harsh economic climates may opt not to do so.

UK National Osteoporosis Guideline

The guidance recently produced by the National Osteoporosis Guideline Group (NOGG) in the UK fills the gaps that currently exist in NICE guidance for the management of osteoporosis [Compston *et al.* 2009]. The guideline is underpinned by cost-effectiveness analysis [Kanis *et al.* 2008b, 2008c] in which many of the assumptions used were similar to those used by NICE; however, a lifetime rather than a 10-year horizon was used in the NOGG analysis and the pessimistic assumptions about side effects used by NICE were not included, although examined in a sensitivity analysis. NOGG guidance includes men at increased risk of fracture, men and women treated with glucocorticoids, and all currently

approved interventions. In common with NICE guidance, it recommends treatment for postmenopausal women over the age of 75 years with a fragility fracture, without the need for dual energy x-ray absorptiometry (DXA), and proposes that alendronate should be the first-line option. However, whereas NICE requires a T-score ≤ -2.5 in most women for either primary or secondary prevention, the National Osteoporosis Guideline recognises the added contribution of independent clinical risk factors to fracture prediction and recommends the use of the WHO-supported fracture risk algorithm FRAX[®]. In addition, its approach to second-line therapy with other bisphosphonates, strontium ranelate or raloxifene is more pragmatic and does not require additional criteria for those who are unable to tolerate alendronate. A proposal for a combination of NICE and NOGG guidance that retains many of the main principles of NICE guidance but incorporates the greater workability and ethical acceptability of NOGG guidance in its approach to second-line therapy is currently being put forward to primary care organisations in the UK (Compston, in press).

Recent national guidelines from other countries are more in keeping with NOGG than NICE guidance in terms of their approach to fracture risk assessment and use of second-line therapies [Kanis *et al.* 2008d; Dawson-Hughes *et al.* 2008]. Nevertheless, particularly in countries lacking the resources required for technology appraisals, NICE is highly influential and its guidance on osteoporosis in the UK may be used by agencies as a basis for their own national guidance. This would be unfortunate, given the flawed development of the NICE guidance. The contribution made by NICE in many other disease areas to the appropriate utilisation of healthcare resources has rightly been praised; however, in the case of osteoporosis the fundamental principles of consistent use of the evidence base, transparency, and equity across disease states have not been observed. A solution would be a fresh NICE appraisal, as requested by the National Osteoporosis Society, with the parallel development of a clinical guideline that enfranchises all relevant patient populations and embraces the substantial advances that have been made in the management of osteoporosis.

Acknowledgement

JEC acknowledges the support of the NHS National Institute of Health Research.

Conflict of interest statement

JEC is Chair of the National Osteoporosis Guideline Group (NOGG).

References

Compston, J. (in press) Recent advances in the management of osteoporosis. *J R Coll Physicians*.

Compston, J., Cooper, A., Cooper, C., Francis, R., Kanis, J.A., Marsh, D. *et al.* (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* 62: 105–108.

Dawson-Hughes, B., Tosteson, A.N., Melton 3rd, L.J., Baim, S., Favus, M.J., Khosla, S. *et al.* (2008) National Osteoporosis Foundation Guide Committee (2008) Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int* 19: 449–458.

Delmas, P.D. and Siris, E.S. (2008) NICE recommendations for the prevention of osteoporotic fractures in postmenopausal women. *Bone* 42: 16–18.

Dolan, P. and Torgerson, D.J. (2000) The cost of treating osteoporotic fractures in the United Kingdom female population. *Osteoporos Int* 11: 551–552.

Kanis, J.A. on behalf of the World Health Organization Scientific Group (2008) Assessment of osteoporosis at the primary health-care level. *Technical Report*. WHO Collaborating Centre, University of Sheffield, UK.

Kanis, J.A. and Compston, J.E. (2008) NICE continues to muddy the waters of osteoporosis. *Osteoporos Int* 19: 1105–1107.

Kanis, J.A., Johansson, H., Oden, A., Johnell, O., De Laet, C., Melton, L.J. *et al.* (2004) A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 19: 893–899.

Kanis, J.A., Johansson, H., Johnell, O., Oden, A., De Laet, C., Eisman, J. *et al.* (2005a) Alcohol intake as a risk factor for fracture. *Osteoporos Int* 16: 737–742.

Kanis, J.A., Johnell, O., Oden, A., Johansson, H., De Laet, C., Eisman, J. *et al.* (2005b) Smoking and

fracture risk: a meta-analysis. *Osteoporos Int* 16: 222–228.

Kanis, J.A., Johnell, O., Oden, A., Johansson, H. and McCloskey, E. (2008a) FRAXTM and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 19: 385–397.

Kanis, J.A., Adams, J., Borgström, F., Cooper, C., Jönsson, B., Preedy, D. *et al.* (2008b) The cost-effectiveness of alendronate in the management of osteoporosis. *Bone* 42: 4–15.

Kanis, J.A., McCloskey, E.V., Johansson, H., Strom, O., Borgstrom, F. and Oden, A. and the National Osteoporosis Guideline Group. (2008c) Case finding for the management of osteoporosis with FRAXTM – assessment and intervention thresholds for the UK. *Osteoporos Int* 19: 1395–1408.

Kanis, J.A., Burlet, N., Cooper, C., Delmas, P.D., Reginster, J.Y., Borgström, F. *et al.* on behalf of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). (2008d) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 19: 399–428.

National Institute for Health and Clinical Excellence. Final appraisal determination. (2005) Alendronate, etidronate, risedronate and raloxifene for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, NICE: London.

National Institute for Health and Clinical Excellence. (2008a) Final appraisal determination. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (2008), NICE: London.

National Institute for Health and Clinical Excellence. (2008b) Final appraisal determination. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, NICE: London.

Poole, K.E. and Compston, J.E. (2006) Osteoporosis and its management. *Brit Med J* 333: 1251–1256.

The Independent, 11 March 1995, UK.