HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal - Appraisal Consultation Document (ACD)

On

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

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Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

TO: NICE	FROM: NHS Quality Improvement Scotland

Section 1. Comments on the NICE ACD - PRIMARY

In this section, we are particularly interested in receiving your comments on the ACD under the following general headings:

1. Whether you consider that all the relevant evidence has been taken into account.

This ACD is long overdue. Unfortunately as a consequence of this – it hasn't included some of the more recent SMC –approved drugs such as intact PTH & iv zoledronic acid. Given that the primary prevention ACD aims to reduce fracture incidence, it is instructive to report the prevalence of the risk factors, cited in this ACD among women who have actually presented with new clinical fractures. It would appear that a strategy that depends exclusively on possession of 1 or more independent risk factors for fracture – even assuming that these patients' fracture risk could be eliminated completely- is likely to fail to impact on fracture incidence, at least in women age 70+ or 75+. In those <65yr – the prevalence of these risk factors suggests that these independent risk factors are more relevant, provided alcohol access doesn't attenuate the efficacy of alendronate and provided the falls & fracture relationship associated with alcohol excess don't over-ride the potential fracture risk benefits of treatment.The extremely low prevalence of IBD (composite of Crohn's disease & ulcerative colitis) in our fracture population suggests that a strategy that uses this as a criterion will not impact on fracture incidence at all. Ankylosing spondylitis is also extremely rare in our population. Our data suggest that the primary prevention strategy proposed by NICE is not clinically relevant to our population.

Independent risk factors for fracture

	Parental (maternal) hip fracture	Alcohol excess	RA
≥75 (n=2551)	4.5%	0.7%	1.9%
≥70 (n=3806)	5.2%	1%	1.9%
<65 (n=3117)	8%	5.8%	1.7%

Indicators of low BMD

	BMI <22	IBD	Early menopause*
≥75 (n=2551)	23.8%	0.7%	20.7%
≥70 (n=3806)	21%	0.7%	22.1%
<65 (n=3117)	13.8%	0.6%	25.7%

* reflects hx of menopause<45 irrespective of retention of ovaries during hysterectomy; no data on use of HRT

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence..

What is proposed by NICE is irrelevant to women who actually experience fractures in Scotland –see above data.

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

These recommendations will be unlikely to impact on preventing fractures in Scottish women.

Section 1. Comments on the NICE ACD - Secondary

In this section, we are particularly interested in receiving your comments on the ACD under the following general headings:

This ACD is long overdue. Unfortunately as a consequence of this – it hasn't included some of the more recent SMC –approved drugs such as intact PTH & iv zoledronic acid.

The ACD is controversial because it recommends different treatment thresholds for different drugs – based on the cost of drug. The consequence of this is a scenario that is highly politically charged. If a patient doesn't tolerate generic alendronate (& I believe firmly that that is and should be first choice given its efficacy and relatively low cost) – then this ACD requires a significantly lower BMD to justify any alternative treatment to reduce fracture risk. It is doubtful if that is ethically justifiable – it is unlikely to be politically acceptable.

1. Whether you consider that all the relevant evidence has been taken into account.

This ACD suggests that treatment of women >75yr with fracture doesn't necessitate prior DXA. Among women ≥75yr with fractures (all sites), the percentages with osteoporosis, osteopaenia & normal BMD are 50%, 44% & 6% respectively. There is a prerequisitve to have confirmed osteoporosis to justify treatment in younger women – and yet there is an assumption that women ≥75yr will necessarily repond to blind treatment with alendronate. Our data suggest that 50% of such women will not have osteoporosis –is the potential for adverse effects justifiable given that it is unlikely that half those being treated empirically may not have prospect of deriving benefit?

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence..

See above

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

Beyond treatment with alendronate – the substratification for treatment appears complex – to the extent of being impractical. The complexity is added to because of the further requirement for risk factors termed 'independent risk factors for fracture'. The relevance of this concession is debatable given the low prevalence of each of these. Among 8901 women age ≥50yr with fractures (all sites) presenting to the North Glasgow Fracture Liaison Service, the prevalence of the key risk' independent risk factors for fracture' is:Parental (maternal) hip fracture – 6.4%, RA (all grades of severity) – 1.9%, Alcohol excess – 3.1%. Only 9 patients overall had 2 of the required risk factors. At best this may a cynical veneer to create the illusion of addressing other aspects of osteoporosis risk – but in reality these risk factors are irrelevant to those women from the West of Scotland who do present with new fractures to our A&E and acute orthopaedic services.

[redacted]

Section 1. Comments on the NICE ACD Primary and Secondary

In this section, we are particularly interested in receiving your comments on the ACD under the following general headings:

1. Whether you consider that all the relevant evidence has been taken into account.

In general I am happy that relevant evidence has been considered in this review. I do have some concern though that there is an acceptance that BMD measurement is not necessary in some situations over the age of 75 years. This guidance is restricted to the treatment of women with osteoporosis and specifically excludes women with osteopenia. Excluding women from BMD measurement implies that there is an expectation that these women will have osteoporosis. However it is well recognised that even in the context of women presenting with fracture a large proportion of elderly women do not have osteoporosis. This is illustrated for example by Seeman et al. who demonstrated that in a population of women over the age of 80 years presenting with fracture approximately one third did not have osteoporosis. This limitation is not acknowledged but should be.

In general terms anti-osteoporosis therapies are most effectively used where BMD proven osteoporosis is present. This is because the absolute benefit of treatment is greatest in this context. This however is overly simplistic as a large proportion of women with osteopenia may be at equal (or higher) absolute fracture risk depending on what other fracture risk factors are present. These patients therefore will receive equal (or higher) absolute benefit of treatment with intervention. Since most fractures occur in osteopenic (not osteoporotic) women; these patients are disadvantaged by this guideline.

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

   In general I would accept the summaries of cost-effectiveness as reasonable interpretations of the evidence. There is some conflict though between this document and the work carried out by WHO. WHO state alcohol use of 3 units per day – NICE state 4 units per day. NICE do not include current smoking as a risk factor whereas this is included by WHO.

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

   I am concerned about the differing levels of thresholds for intervention amongst the different treatments. Whilst these are consistent with the modelling used; these will pose difficulties in practical implementation. The implications of these thresholds is that if a patient cannot tolerate generic alendronic acid unless their BMD is sufficiently low they will then have to be told that they are no longer eligible for therapy. I do not think this is appropriate.

[redacted]

Reviewer 1

Comments on the NICE ACD - Primary

In this section, we are particularly interested in receiving your comments on the ACD under the following general headings:

1. Whether you consider that all the relevant evidence has been taken into account.

A significant amount of evidence has been taken into account. I may have overlooked it but I did not see the agreement between T scores of less than minus 2.5 SD and drug effectiveness. Paragraph 4.2.6 mentioned a model prepared under the auspices of WHO and academic in confidence – is this where the link is made ?

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

I can understand the summaries but I am not sure about the details due to my lack of understanding between scores and drug effectiveness,

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

I would welcome a clinical view point

Comments on the NICE ACD - Secondary

In this section, we are particularly interested in receiving your comments on the ACD under the following general headings:

1. Whether you consider that all the relevant evidence has been taken into account.

A substantial amount of evidence has been taken into account

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

I cannot relate the precise and low T Scores to clinical evidence or drug effectiveness – could this be part of the fracture risk algorithm or is it elsewhere?

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

Since I am not sure of the clinical relevance of the low T scores, I cannot comment on whether the provisional recommendations are a suitable basis

24 April 2008