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Cost-effective but clinically inappropriate: New NICE intervention thresholds in osteoporosis (Technology Appraisal 464)

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The creation of the UK National Institute for Clinical Excellence (NICE) in 1999 established rigorous processes for the assessment of health technologies, such as new pharmaceutical and biopharmaceutical products, to ensure that all National Health Service (NHS) patients in the UK would have equitable access to the most “viable” treatments, in terms of both clinical benefit and cost-effectiveness. Advice from NICE is aimed to end confusion or “uncertainty” over the value of treatments and to standardise access to healthcare across the UK, and indeed often influences approaches to guidance internationally. This has been particularly helpful in the case of expensive, specialist interventions, where technology appraisals have provided thresholds for access and usually informed clinical guideline development. However, the recent Technology Appraisal (TA464) on bisphosphonate use in osteoporosis [1] (which was published as a Final Appraisal Document without a period of consultation) has provided an object lesson in how, for a common disorder, the strict application of cost-effectiveness thresholds for relatively inexpensive drugs may lead to potentially harmful, and certainly counter-intuitive, guidance [2]. The original Technology

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Appraisals of osteoporosis treatments by NICE, published in 2008 and updated in 2011 [3,4], recommended varying risk thresholds across most of the medications then available [5]; in the absence of an accompanying Clinical Guideline, these thresholds were widely interpreted and adopted as intervention thresholds for clinical practice.

The recent appraisal incorporates two novel components of osteoporosis care which have emerged since the original guidance. First, fracture risk calculators based on individualized clinical risk factors, such as FRAX and QFracture, are now accessible and are recommended by NICE for the assessment of fracture risk in particular sections of the population [6]. Second, low cost generic forms of the main oral and intravenous bisphosphonates used in osteoporosis management are now available. The latter in particular has led, in the NICE analysis, to such treatments being cost-effective in people at very low risk of fracture. TA464 thus recommends that, amongst individuals who qualify for osteoporosis assessment on the basis of the NICE Clinical Guideline CG146 [6], treatment with oral bisphosphonates may be instituted at a 10-year probability of major osteoporotic fracture above 1%, or above 10% for intravenous bisphosphonates. These thresholds were derived purely on health economic grounds, and they raise the spectre of excessive bisphosphonate prescription in the general population [2], with treatment of substantial numbers of people who are at very low individual fracture risk. Indeed, based on a simulated UK population [7], it is apparent that all women aged 50 years or older are expected to have a FRAX probability greater than 1% (E McCloskey, personal communication), meaning that every woman eligible for assessment under CG146 would be recommended treatment if the current TA464 recommendations were interpreted as intervention thresholds. Such large-scale intervention would thus effectively constitute a population-based approach. At this level, serious but extremely rare side effects of bisphosphonate treatment, such as osteonecrosis of the jaw and atypical femur fracture, would be observed far more frequently in the population than at present; additionally, the benefit/risk balance for individuals at low risk would be adversely affected, in contrast to the demonstrably positive benefit/risk ratio associated with intervention at higher and more clinically appropriate treatment thresholds [8–10].

Presentation of guidance is everything. Busy clinicians and managers who might simply read the summary of the TA464 [1] are likely to recommend treatments for osteoporosis at these low fracture risks [2]. The NICE document does make reference to the guidance on assessment and intervention thresholds recently published by the UK National Osteoporosis Guideline Group (NOGG, accredited by NICE in 2017) [8], but NOGG is not cited in the NICE recommendations themselves. The discussion of the NOGG approach is accompanied by the erroneous statement that the NOGG thresholds have not been shown to be cost-effective. Importantly, the intervention thresholds of NOGG are higher at all ages than those deemed cost-effective in the current TA [11,1]. The formulation of treatment thresholds is necessarily a somewhat arbitrary process, but in contrast to the purely health-economic driven process of NICE, NOGG developed its guidance on the basis of clinical appropriateness, setting the threshold at the age-specific probability of fracture equivalent to that of an individual having already sustained a fracture. Critically, economic criteria were not used to set intervention thresholds but, more appropriately, to validate the implementation of clinically driven intervention thresholds. This approach, which avoids inappropriate under-treatment of younger individuals and over-treatment of older

individuals, has indeed been shown to be cost-effective [12], and has been incorporated into guidelines in many countries [13].

In conclusion, the appropriate clinical interpretation of the recent NICE MTA is that, whilst any treatment above the cost-effectiveness threshold will, at the population level, be cost-effective, it will frequently be clinically inappropriate for an individual. In order to avoid overtreatment, an aspiration recently espoused by NICE itself [14], it will be vital to continue to use validated approaches to risk assessment, and treatment thresholds that are both clinically appropriate as well as cost-effective, as proposed by the FRAX-NOGG system [8]. The widespread unthinking adoption of the NICE TA464 would risk a generation of older individuals prescribed a bisphosphonate, regardless of the benefit/risk balance for the individual, and a resulting increased burden of rare long-term side effects across the population. Given ongoing discussion about the role of pharmaceutical interventions in the prevention of several chronic non-communicable diseases [14], this would indeed be a harmful and counter-intuitive consequence of national guidance.

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