Osteoporosis: Treatment Gaps and Health Economics

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Introduction

Despite many advances in the diagnosis of osteoporosis, the assessment of fracture risk, the development of therapies to reduce the risk of fractures, and the production of best practice guidelines, many studies indicate that a minority of men and women at high fracture risk actually receive treatment (Harvey *et al.*, 2017a). Even in patients who sustain a fragility fracture, fewer than 20% actually receive therapies to reduce the risk of fracture in the year following the fracture (Giangregorio *et al.*, 2006; Kanis *et al.*, 2014a), with particularly poor rates of treatment for older women and those who live in long term care. Disparities in use of fracture risk assessment tools such as FRAX® vary one thousand-fold worldwide, with a far greater variability than the 30-fold range of crude, or 10-fold range of age-standardized hip fracture worldwide, indicating a large gap in service provision (Kanis *et al.*, 2012, 2014b). Limitations in access to the internet, lack of national assessment guidelines for osteoporosis in many countries, and the availability of alternative assessment algorithms may partially explain these differences (Kanis *et al.*, 2014b). Not only is lack of assessment and lack of treatment of those at very high risk of further fracture such as hip fracture a concern, most worrying is the downward trend in people being treated after hip fracture, demonstrated both in the USA and UK populations (Solomon *et al.*, 2014; Hawley *et al.*, 2016). The precise causes for this trend are likely to be several, including the recent reimbursement changes in the US, and the massive inflation of concerns regarding potential rare side effects of long-term bisphosphonate treatment such as osteonecrosis of the jaw and atypical femoral shaft fractures. In this review, we give an overview of the treatment gaps at all levels, potential underlying reasons, and possible approaches to help reverse the situation.

The Osteoporosis Treatment Gap

There are now data, from both Europe and the United States, demonstrating substantial disparities between the number of individuals at high fracture risk, or who have experienced a low trauma fracture, and the number who receive appropriate assessment and treatment for osteoporosis (Harvey *et al.* 2017a). Thus in the UK, analysis of the Clinical Practice Research Datalink (CPRD) has demonstrated substantial gaps in both primary and secondary prevention. The probability of being prescribed any antiosteoporosis drug after hip fracture in the UK increased from only 7% in 2000 to 46% in 2010 (Klop *et al.*, 2014). This trend was more marked in patients $\geq$75 years. The increase in prescribing of antiosteoporosis drugs was complemented by a similar increase in vitamin D/calcium provision. The cumulative incidence of antiosteoporosis therapy was greater at any given point in time in women (8% in 2000, 51% in 2010) than in men (4% in 2000, 34% in 2010). Despite $<$50% of hip fracture patients receiving treatment, more recent data suggest a plateau and a possible decrease in prescriptions from around 2011 (Hawley *et al.*, 2016). Furthermore, there appears to be substantial geographic heterogeneity in the UK amongst treatment rates following hip fracture. For example, in a CPRD analysis based on the UK healthcare regions, the odds ratio for antiosteoporosis medication following a hip fracture was 1.29 (95% CI: 0.89, 1.87) for the North East and 0.56 (95% CI, 0.43, 0.73) in South Central regions, the North West being the referent. These geographic differences in prescribing persisted over the 5-years of follow-up (Shah *et al.*, 2017). Additionally, data from the GLOW study, a prospective observational study of over 60,000 older women recruited from primary care practices in 10 countries across US, Europe, and Australia, showed that $>$80% of women with a fragility fracture did not receive osteoporosis treatment (Greenspan *et al.*, 2012).

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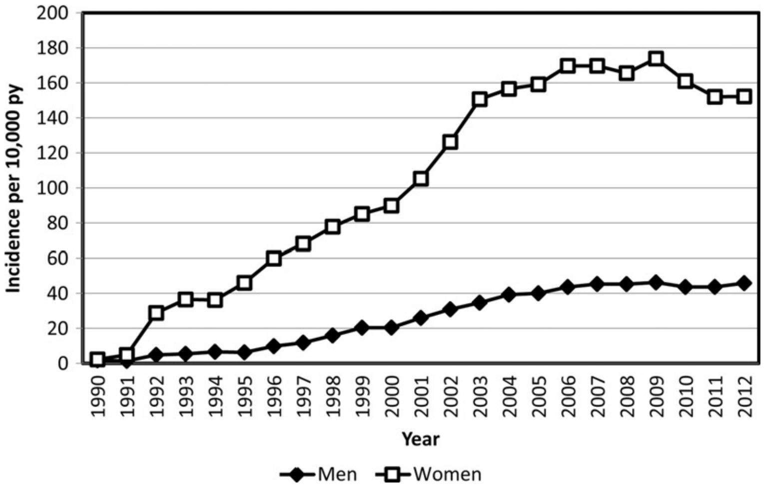

Fig. 1 Incidence of antiosteoporosis medication prescription from 1990 to 2012 in the UK population aged 50 years or over. Reproduced with permission from van der Velde, R.Y., Wyers, C.E., Teesselink, E., Geusens, P.P., van den Bergh, J.P., de Vries, F., Cooper, C., Harvey, N.C., van Staa, T.P. (2017). Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: Variation by age, sex, geographic location and ethnicity. *Bone* **94**, 50–55.

These differences by geography, ethnicity and time for secondary fracture prevention are consistent with findings relating to primary use of antiosteoporosis medications. Between 1990 and 2012, rates of antiosteoporosis medication prescription in the UK rose from 2.3 to 169.7 prescriptions per 10,000 person-years amongst women from 1990 to 2006, but this was followed by a plateau and then a 12% decrease over 2009 to 2012 (**Fig. 1**). Prescription rates rose less steeply in men from 1990 to 2007 and plateaued from 2008 onwards. There were marked differences in prescription of antiosteoporosis medications according to ethnicity and geographic location (van der Velde *et al.*, 2017).

In Europe, treatment uptake for osteoporosis increased progressively up to 2008, thereafter plateaued, and has subsequently fallen in more recent years (**Fig. 2**). The phenomenon is most marked in the case of the bisphosphonates and is evident on a country by country basis (Svedbom *et al.*, 2013). The number of patients treated in each country was computed from IMS Health sales data for 2010, adjusted for suboptimal adherence, and expressed as treatment years (Hernlund *et al.*, 2013). The use of hormone replacement therapy was excluded since the majority of women take this treatment for menopausal symptoms rather than for osteoporosis. The proportion of patients eligible for treatment depended on defining an intervention threshold that is, the risk of fracture above which treatment can be recommended. In this report, the intervention threshold set was at the FRAX-based 10-year fracture probability equivalent to women with a prior fragility fracture without knowledge of BMD as adopted in several European guidelines (Kanis *et al.*, 2013a; Lekamwasam *et al.*, 2012a; Compston *et al.*, 2017). Thus, the intervention threshold can be likened to a "fracture threshold" expressed in terms of fracture probability. The study showed a very wide inter-country variation in the treatment penetration of individuals at high risk for osteoporotic fractures. The treatment gap varied from 25% in Spain to 95% in Bulgaria. Large treatment gaps were identified in countries with populations at both high and low risk of fracture. In total in the EU, it was estimated that, out of the 21.3 million men and women who exceeded the risk level, 12.3 million were untreated in 2010 (Hernlund *et al.*, 2013). These figures are conservative since an undetermined proportion of low risk women will have received treatment (Diez-Perez *et al.*, 2011). In an international prospective study, low uptakes of pharmacological intervention after hip fracture was also observed. Amongst 1795 patients who sustained a low-energy hip fractures in ten countries (Australia, Austria, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain, and the United Kingdom), only 27% were prescribed pharmacological fracture prevention after the hip fracture (Svedbom *et al.*, 2013).

Data from the US suggest a similar pattern. In a large retrospective analysis of nearly 100,000 men and women aged 50 years or more who were hospitalized for hip fracture over a period of 1 year, based on U.S. administrative insurance claims data, the uptake of osteoporosis medication within 12 months after discharge from hospital was examined (Solomon *et al.*, 2014). The estimated probability of receiving osteoporosis medication within 12 months after discharge from hospital was 28.5% over this time period but varied by year. Indeed, the rates declined significantly over a 10-year interval, from 40.2% in 2002 to 20.5% in 2011 (Solomon *et al.*, 2014). Congruent findings come from analysis of the US Medical Expenditure Panel Survey, demonstrating a marked reduction in the prevalence of bisphosphonate use amongst women from 2007 onwards. Rates in men appeared to decline, albeit from a much lower baseline, over the same period (Jha *et al.*, 2015).

Reasons Underlying the Treatment Gap

There appear to be many factors in the poor rates of treatment for osteoporosis, including the insufficient implementation of strategies to effect primary and secondary prevention. Fundamentally, primary prevention is always made difficult by the concept

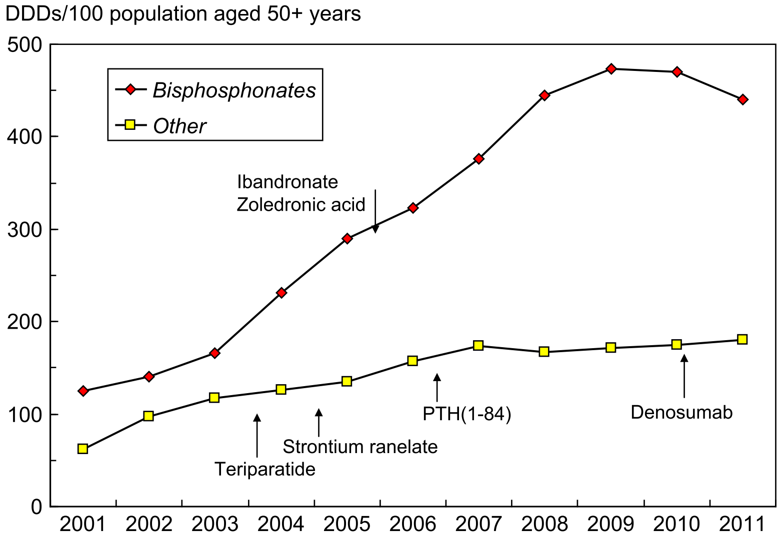

Fig. 2 Estimated sales (defined daily doses (DDDs)/100 population aged 50+ years) from 2001 to 2011 in the European Union. Reproduced with permission from Hernlund, E., Svedbom, A., Ivergard, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E.V., Jonsson, B., Kanis, J.A. (2013). Osteoporosis in the European Union: Medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Archives of Osteoporosis* **8**, 136.

of managing a future "risk", rather than treating a disease event which has already happened. However, a hip fracture, for example, is a devastating life event, with a 20% associated reduced survival compared with non-fracture peers (Harvey *et al.*, 2010); in the analogous situation of an acute myocardial infarction, it is difficult to imagine a situation in the developed world in which it would be acceptable for <50% of such cardiac patients receiving preventative treatments such as aspirin, statins, and anti-hypertensives (Austin *et al.*, 2008). It is apparent that musculoskeletal disease may be viewed both by patients and policymakers as a lower priority than outcomes such as myocardial infarction and cancer (Harvey *et al.*, 2017a). Conversely, the Global Burden of Disease initiative has demonstrated musculoskeletal disease to be a leading cause of disability worldwide (Harvey *et al.*, 2014). These observations suggest a mismatch between the severity of the condition, and associated perceptions; this is well documented in the large international GLOW cohort, in which many women underestimated their fracture risk compared with their peers (Siris *et al.*, 2011). Against this backdrop, studies cited above have clearly demonstrated a successful increase in antiresorptive treatment rates both in primary and secondary prevention over the last 15 years. Advances in risk assessment and policy, for example through the use of risk calculators such as FRAX (Kanis *et al.*, 2011, 2016), guidance on intervention (Kanis *et al.*, 2013a), together with the availability of generic bisphosphonates, have helped to improve the clinical situation. It is therefore tragic in the context of this maturing field that treatment rates, both before and after a fracture, have declined in recent years, despite inexorable expansion of the population at risk (Oden *et al.*, 2015). Two studies have suggested possible reasons for this. Jha *et al.* examined relationships between medication use (data from the Medical Expenditure Panel Survey and National Inpatient Sample in the US), internet search activity for alendronate between 2006 and 2010, and media reports of safety concerns (Jha *et al.*, 2015). Against the backdrop of a decline in bisphosphonate use by >50% between 2008 and 2012, there were marked spikes of internet search activity corresponding to events such as a 2006 lawsuit filed against Merck for Fosamax allegedly causing osteonecrosis of the jaw, a major ABC World News feature on Fosamax and atypical femoral fractures in 2010, and several other media reports of such rare, but serious side effects. Similar findings have come from the Australian Longitudinal Study on Women's Health (Peeters *et al.*, 2014). Consistent with the US data, total use of antiosteoporosis medications increased over the period 2000 to 2007 but then decreased from 2007 to 2010. Despite relaxing indications for bone density testing and a subsidy for antiosteoporosis medications, the decline coincided with adverse media stories such as a major report on osteonecrosis of the jaw in 2007 (Peeters *et al.*, 2014).

Whilst serious long-term adverse side-effects of bisphosphonates are very rare in absolute terms (with incidences in the range of 1/100,000 to 1/10,000 per year) (Adler *et al.*, 2016), the approach to risk/benefit communication has largely amongst the media (as demonstrated above) and unfortunately amongst physicians and policymakers, been very much on the side of declaring risk. Recognition that the underlying disease is associated with substantial morbidity and increased mortality, with fracture risk markedly reduced by antiosteoporosis medications, seems largely under-articulated in these discussions. Indeed, the recent UK National Institute for Health and Care Excellence (NICE) guidance on multi-morbidity (Farmer *et al.*, 2016) specifically targeted bisphosphonates for review after 3 years treatment despite evidence for longer term efficacy and safety being more reliable than for other treatments considered. Such concerns do very little to improve osteoporosis care in the setting of declining treatment rates overall. Reassuringly in terms of the risk-benefit ratio, a recent study in the Danish population has demonstrated that users of alendronate still have a reduced risk of fracture compared with matched controls even after 10 years use, and that the number of

Table 1 Number of central DXA units available in the EU27 countries per million of the general population

Country	*DXA units/million*	*Country*	*DXA units/million*	*Country*	*DXA units/million*
Austria	28.7	Germany	21.1	Netherlands	10.7
Belgium	53.0	Greece	37.5	Poland	4.3
Bulgaria	1.2	Hungary	6.0	Portugal	26.9
Cyprus	23.9	Ireland	10.0	Romania	2.4
Czech Republic	5.2	Italy	18.6	Slovakia	10.7
Denmark	14.6	Latvia	4.9	Slovenia	27.1
Estonia	8.9	Lithuania	3.4	Spain	8.4
Finland	16.8	Luxemburg	2.0	Sweden	10.0
France	29.1	Malta	9.7	UK	8.2

hip fractures prevented is still substantially greater than the number of subtrochanteric fractures occurring even by the end of a decade of bisphosphonate treatment (Abrahamsen *et al.*, 2016). It is patently clear that the field needs to dramatically improve its approach to communicating the risks and benefits of treatments, and to robustly counter ill-informed adverse media stories in a timely fashion.

Healthcare Policies and Osteoporosis Assessment

Osteoporosis, in comparison with comparable non-communicable diseases, has rarely attracted proportionate levels of attention from healthcare providers and governments, and an individual nation's policy on access to bone densitometry with dual-energy X-ray absorptiometry (DXA) and its reimbursement will greatly influence the assessment and treatment of this disease. The International Osteoporosis Foundation (IOF) has published various regional audits (https://www.iofbonehealth.org/regional-audits) covering the European Union, Eastern Europe and Central Asia, Latin America, North America, the Middle East and Africa, Asia Pacific in terms of epidemiology, burden and costs of osteoporosis. Taking Asia Pacific as an example, whilst Australia, Hong Kong, Japan, New Zealand, Republic of Korea and Singapore had 12–24 DXA machines per million of population, China, India, Indonesia, Pakistan, Philippines, Sri Lanka and Vietnam were greatly under-resourced with less than 1 DXA machine per million of population. In addition, BMD testing and osteoporosis treatment were not fully reimbursed by insurance or healthcare policies in many countries, which served as a barrier to accessing treatment.

In Europe, it was assumed that 11 DXA machines per million of population were needed to provide adequate osteoporosis care. 16 European countries fell into this category of adequate provision, and 9 countries were considered to have very inadequate provision with <8.4 DXA units per million (Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Luxembourg, Poland, Romania, and the United Kingdom). **Table 1** shows the number of DXA units per million of population in the EU27 countries as estimated in 2010 (Kanis *et al.*, 2013b). Reimbursement for DXA scans was extremely variable between EU member states in terms of the criteria required and level of imbursement awarded—interestingly in some countries reimbursement for DXA was only offered if the BMD measurement demonstrated osteoporosis (Bulgaria and Switzerland), only if after fracture (Germany), or only if seen by a specialist (Poland).

Though no official IOF audit is available for North America, reimbursement for treatment also varies greatly, depending on each individual patient's health insurance plan. However, healthcare reform is evolving in the USA from fee for service to supporting improved quality, prevention and care coordination with financial incentives to encourage healthcare professionals or systems to report on or improve patient outcomes. However, performance measures on osteoporosis assessment remain low compared to other major chronic diseases, and a major drop in reimbursement for DXA scans in the office setting has led to a fall in the number of DXA providers and more than 1 million fewer DXA scans performed per annum (Overman *et al.*, 2015). Recent evidence suggests that this coincides with a plateau in the secular decline in age- and sex-adjusted hip fracture rates which had been apparent up until 2012 (Lewiecki *et al.*, 2016).

Approaches to Closing the Gap

Identification of Patients at High Risk of Fracture

It is apparent from the evidence described above, that osteoporotic fractures place a huge burden on societies across the world. It is well known that osteoporosis is a silent disease until a fracture occurs. Patient perception of fracture risk is often underestimated (Grover *et al.*, 2014; Gregson *et al.*, 2014), so initiation of primary prevention is usually reliant on health care practitioners. It is unsurprising therefore that secondary prevention (identifying individuals for treatment on the basis of a low trauma fragility fracture occurring) is the approach most often taken as the starting point for fracture prevention. However, whatever approach is taken to the reduction of fracture risk, it is critically important to place this within the context of local factors, such as the background population fracture risk, prevalent patterns and risk factors, funding constraints and willingness of healthcare providers to pay for treatment.

Secondary Fracture Prevention

Following attendance to a healthcare practitioner with a new fracture, it is important to assess fracture risk in a straightforward way, and to treat if appropriate. Several methods have been explored—some staff based, some IT-based and others a combination of the two. The most successful systems usually focus on a multi-disciplinary Fracture Liaison Service (Eisman *et al.*, 2012; Mitchell, 2013), incorporating orthogeriatricians, rheumatologists, other physicians and clinical nurse specialists. They work in a multidisciplinary team to ensure that medical management of patients admitted with fracture is optimized, both whilst in hospital and for future fracture prevention, ideally with a lead clinician responsible for coordinating the team (Drew *et al.*, 2016). The International Osteoporosis Foundation has recently instituted "a global campaign to facilitate the implementation of coordinated, multi-disciplinary models of care for secondary fracture prevention." The "Capture the Fracture®" (http://www.capturethefracture.org/) initiative has provided guidance on secondary fracture prevention, and also a global map, with a quality grading scheme, on which, subject to application, secondary fracture prevention services can be documented (Akesson *et al.*, 2013). There is currently huge variation, not only between, but also within countries, and in the availability, scope and quality of secondary prevention facilities. The Capture the Fracture initiative, aimed at raising the quality and coverage of fracture liaison services providing secondary prevention for osteoporosis, should provide a clinically valuable and cost-effective contribution to service improvement (Mitchell *et al.*, 2016).

Further important initiatives around case finding of fragility fractures centre around vertebral fractures—around 12% of postmenopausal women with osteoporosis have at least one vertebral deformity, with less than a third of these individuals coming to clinical attention (Cooper *et al.*, 1992). Primary care based screening strategies (Clark *et al.*, 2012), and history-taking strategies distinguishing back pain likely to relate to vertebral fracture from other types of back pain may facilitate detection of these fractures (Clark *et al.*, 2016). In addition, consistent reporting of radiographs, CT scans and the incorporation of vertebral fracture assessment in DXA scans will help with secondary fracture prevention in individuals with prevalent osteoporotic vertebral fracture.

Primary Fracture Prevention

In osteoporosis, as in any non-communicable chronic disease, there is clearly a balance between the benefits of a systematic screening approach leading to widespread treatment, with associated increased cost and risk of side-effects, and a case-finding strategy focused on those at greatest individual risk, with associated problems of under-treatment. Although, DXA screening is standard in the US (at the age of 65 years in women, and age 70 in men, and in individuals over the age of 50 years who have suffered an adult fracture) (Cosman *et al.*, 2014), in the majority of countries population screening is not judged to be cost-effective and primary prevention is focused more on opportunistic case-finding, triggered by the presence of clinical risk factors (Kanis *et al.*, 2013a; Lekamwasam *et al.*, 2012a,b; Compston *et al.*, 2017). A seven-centre randomized controlled trial of the effectiveness and cost-effectiveness of screening older women in primary care for the prevention of fractures (the UK SCOOP study), in which approximately 12,500 older women were randomized to either normal care or screening and subsequent treatment (based upon the FRAX risk assessment tool), has recently demonstrated that this intervention leads to a reduction in hip fracture risk (Shepstone *et al.*, 2012, 2017).

Health Economic Considerations

There are two major approaches to the health economic assessment in a particular condition. Firstly, one can assess the cost-effectiveness of the intervention, and set the threshold for intervention, for example FRAX probability, accordingly. Alternatively, one can derive a clinically informed and appropriate intervention threshold, and use cost-effectiveness analysis to validate a threshold. The 2017 National Institute for Health and Care Excellence (NICE) updated Multiple Technology Appraisal (MTA) on bisphosphonate use in osteoporosis (NICE, 2017) illustrates how, for a common disorder, the former approach, with strict application of cost-effectiveness thresholds for relatively inexpensive drugs, may lead to counter-intuitive and potentially harmful guidance (Sims, 2017; Harvey *et al.*, 2017b). The MTA incorporates the development of fracture risk calculators based on individualized clinical risk factors, such as FRAX and QFracture, (both recommended by NICE for the assessment of fracture risk in certain sections of the population (NICE, 2012)), and also the widespread availability of low-cost generic forms of the main oral and intravenous bisphosphonates. This latter development has led, in the NICE analysis, to cost-effectiveness at very low risk thresholds, resulting in an appraisal which recommends that, amongst individuals who qualify for osteoporosis assessment on the basis of the NICE Clinical Guideline CG146 on fracture risk assessment (NICE, 2012), treatment with oral bisphosphonates may be instituted above a 1% probability of major osteoporotic fracture (hip, spine, wrist or humerus) over 10 years, or above 10% for intravenous bisphosphonates. These health-economic-derived thresholds create a real danger of excessive bisphosphonate prescription in the general population (Sims, 2017), with treatment of substantial numbers of people who are at very low individual fracture risk; for example, every person eligible for assessment under CG146, including all women aged ≥ 65 and men ≥ 75 years, would be recommended treatment if the MTA recommendations were interpreted as intervention thresholds (Kanis *et al.*, 2008). Very rare, but serious, side-effects of bisphosphonate treatment, such as atypical femur fracture and osteonecrosis of the jaw, would be observed far more commonly in the population than at present. Furthermore, the risk/benefit balance for individuals at low risk would be adversely affected, in contrast to the very clearly positive benefit/risk ratio associated with intervention at more clinically appropriate treatment thresholds (Adler *et al.*, 2016; Compston *et al.*, 2017; Rizzoli *et al.* 2011). In contrast, whilst the derivation of treatment thresholds is necessarily arbitrary, the UK National Osteoporosis Guideline Group (NOGG) used the second approach, developing its guidance on the basis of clinical appropriateness, setting the threshold at the age-specific 10-year FRAX probability of fracture equivalent to women having already sustained a fracture. Thus, economic thresholds were not used to set intervention thresholds but, more appropriately, to validate the use of clinically driven intervention thresholds. This approach, which avoids inappropriate over-treatment of older individuals and under-treatment of younger individuals, has been shown to be cost-effective (Kanis *et al.*, 2008), and has been adopted in many countries (Kanis *et al.*, 2016).

The cost effectiveness of individual therapies for osteoporosis have recently been comprehensively reviewed (Hiligsmann *et al.*, 2015). Of the 1794 articles identified across a range of databases, 39 studies fulfilled the inclusion criteria. These covered 14 different countries and within them 9 active interventions were assessed. When the interventions were compared with no treatment, active antiosteoporosis drugs were generally cost-effective in postmenopausal women aged over 60–65 years with low bone mass, especially amongst those with prior vertebral fractures. Factors which increased cost-effectiveness included higher individual fracture risk and medication adherence.

Summary

Whilst assessment for fracture risk, and use of antiosteoporosis medications, have increased markedly over the last 20 years, there is evidence from the United Kingdom, United States, and continental Europe that treatment rates have declined substantially in the last 5 years. Concerns amongst patients and clinicians around rare side effects of anti-resorptives, compounded by dramatic and widespread media reports, have been complemented by adverse changes in reimbursement in the US, and reflected in new guidance. Indeed, many doctors, dentists, and patients are now more frightened of the rare but serious side effects than they are of the disease and the fractures that arise. Notwithstanding, the lay press is simply the messenger bringing news and opinion from the scientific community, some or much of which may be ill-judged. The paradox arises that we seek to treat individual patients to the highest standards but at the same time bring disservice and disadvantage to the wider osteoporosis community. It is now time for us all to accept a long overdue collective responsibility for our failures and to work cohesively to improve the management of our patients.

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