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COMMENTARIES

The U.S. National Osteoporosis Foundation (NOF) Guidelines: Recommendations for Pharmacologic Treatment

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New thoughtful and comprehensive guidelines from the U.S. National Osteoporosis Foundation (NOF) include valuable information and guidance about nutrition, exercise, prevention of falls and rehabilitation after fracture. This *Commentary* focuses on the recommendations for drug therapy (Table 1).

Among men and women age 50 or older, the following should be treated with FDA-approved pharmacologic therapy:
- A history of hip or radiographic or clinical vertebral fracture; OR
- Bone density T-scores <-2.5 at the femoral neck, total hip, or lumbar spine; OR
- Low bone mass (*i.e.*, osteopenia: T-scores of -1 to -2.5 at the femoral neck, or total hip, or lumbar spine) and any of the following:
o A secondary cause of osteoporosis that increases fracture risk; OR
o A 10-year risk of hip fracture >3% by the WHO Index; OR
o A 10-year "major osteoporotic fracture" >20% by the WHO Index; OR
o A history of any fracture

Table 1. U.S. National Osteoporosis Foundation guidelines for recommending pharmacologic therapy (http://www.nof.org/professionals/Clinicians_Guide.htm).

These recommendations are based on a cost-effectiveness analysis that concluded that drug treatment is "cost-effective" if the patient has ≥3% 10-year risk of hip fracture (1). Treatment would generally be cost-effective for women who meet any one of the NOF criteria (2). In addition to recommending treatment for BMD T-scores below -2.5, the guidelines recommend treatment for those with 'low bone mass' ("osteopenia") and risk factors that put their risk above an absolute risk of fracture. The guidelines should decrease drug treatment for women in their 50s with "osteopenia"

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who have low risks of fracture. On the other hand, these guidelines would increase the number of older women, over age 65, including many with hip T-scores >-2.5 because age and risk factors indicate that their risk of fracture is higher than the threshold. Table 2, excerpted from the cost-effectiveness analysis supporting the new guidelines, illustrates this shift (1).

Race and gender	Age	Increased relative risk vs. average at which treatment becomes cost-effective*
White women		
	55	2.3
	60	1.6
	65	1.3
	70	0.9
	75	0.4
	80	0.3
White men		
	55	8.1
	60	3.4
	65	2.3
	70	1.9
	75	1.0
	80	0.7

Table 2. Increased relative risk of fracture compared with the average for that gender, race, and age above which treatment is cost-effective (adapted from Tosteson (1)). * The analysis included the impact of clinical vertebral fractures along with fractures of the wrist, humerus, pelvis, and tibula/fibula (for women).

The table shows that, under the assumptions used for the analysis, most elderly white women should be recommended for treatment with drugs to prevent fracture. A relative risk of 1.0 in the column labeled “Increased relative risk…” means that it would be cost-effective to treat a person with an average risk of fracture for his or her age. Relative risks above 1.0 mean that treatment is cost-effective if the profile of risk factors indicates a higher than average risk. For example, a 55-year-old woman should be treated if her risk factors and BMD increase her risk of hip fracture by at least 2.3-fold above average. A relative risk below 1.0 means that treatment is cost-effective unless the profile of risk factors indicates a lower than average risk. For example, at age 75, a woman should be treated unless her risk factors and BMD reduce her risk by at least 60% below average. Dawson-Hughes and colleagues note that pharmacologic treatment is cost-effective for the average 68 year old woman (2). Thus, treatment would be recommended for most women age 70 or older (Table 2).

To confirm these conclusions, we analyzed data from the Study of Osteoporotic Fractures (SOF). Despite its name, SOF did not preferentially include women with osteoporosis. Rather, white women age ≥65 years were recruited from population-based listings in 4 U.S. cities at a time (~1987) when there had been little publicity about osteoporosis and bone densitometry was not clinically available. Compared with white women ≥ age 65 in NHANES III, women in SOF have slightly higher age-adjusted mean femoral neck BMD (0.62 vs 0.65 mg/cm^2) and fewer have femoral neck T-scores <-2.5 (30 vs 20%) and risk factor profiles are similar. Thus, estimates from SOF will underestimate the proportion of older white women in the U.S. recommended for treatment. WHO 10-year probabilities of hip

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and "major osteoporotic fractures" were calculated for SOF, but are not available for NHANES. We have preliminarily and conservatively estimated that the NOF Guidelines would recommend drug therapy for more than two-thirds of white women ≥ age 65. This fits the implications from Table 2.

When guidelines recommend drug therapy for such a large proportion of older women, it is important that they be based on very solid evidence.

Assumptions Underlying the NOF Guidelines: Efficacy of Treatment

The NOF cost-effectiveness analysis depends on many assumptions. Most importantly, it assumes that pharmacological treatment reduces the risk of all clinical fractures by 35% regardless of bone density or presence of vertebral fracture. Modest changes in this assumption – say, from 35% to 20% efficacy – will change the estimated cost-effectiveness by tens of thousands of dollars per QALY and change the number of elderly women and men recommended for drug therapy by millions (3).

The models are based on alendronate as a prototype for the efficacy, safety and cost of pharmacologic treatment. In women with osteoporosis, defined by having vertebral fractures and/or femoral neck T-scores ≤-2.5, FDA-approved treatments reduce the risk of vertebral fractures by 35% to 70% and some treatments, including alendronate, also reduce the risk of nonvertebral fractures by 20% to 40%. There is less certainty about the efficacy of drug therapy in women (and men) without osteoporosis. Recent systematic reviews of trials of alendronate and all FDA-approved treatments (4;5) concluded that bisphosphonates reduce the risk of vertebral fractures but found no significant reductions in risk of other osteoporotic nonvertebral fractures in women without vertebral fractures or osteoporosis by BMD. An older review reached similar conclusions (6). The Fracture Intervention Trial (FIT II) found that alendronate reduced clinical fractures by 14% in women with a femoral neck T-score ≤-1.6 who had no vertebral fracture and treatment was less effective in those with femoral neck T-scores >-2.5 (7). Subsequent analyses of FIT have found no significant reduction in clinical fractures in women at higher risk because of a previous clinical fracture (Ryder K, *et al*. *J Gen Intern Med*. 2008, in press). On the other hand, in the Women's Health Initiative, estrogen therapy reduced the risk of clinical vertebral, nonvertebral, and hip fractures by about one-third in postmenopausal women not selected on the basis of BMD or history of fractures and clodronate reduced the risk of clinical fractures by 20% in women age ≥75 years who were included without regard to BMD (8).

Many of the older women – and men – who would be treated under the NOF Guidelines would not have "osteoporosis" defined by hip BMD T-scores above -2.5 and no vertebral fracture. If drug therapy, besides estrogen, reduces their risk of clinical fractures, evidence to date suggests that the reduction is less than the 35% assumed by the new guidelines.

Other Specifications and Assumptions

The U.S. NOF Guidelines also recommend treating women with T-scores at the lumbar spine <-2.5 even if their femoral neck or total hip BMD T-score is above -2.5. Kanis *et al*. have pointed out that adding women with a spine BMD T-score <-2.5 adds more women who have a lower risk of hip and nonvertebral fracture; this has an effect that is similar to including all women who have a femoral neck T-score between -2.5 and -2.0 (9). As above, the degree of efficacy of bisphosphonate therapy on nonvertebral fractures in this expanded lower risk population is not certain.

The NOF cost-effectiveness analysis specifies that the drug costs $600 per year. In the U.S., generic alendronate costs about $400 per year and the price may fall further. At $300 per year with a 35% reduction in fracture risk, treatment is cost-effective if the 10-year hip fracture risk exceeds 1.4% (2);

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treatment would be recommended for most white women age 60 years or older white men age 65 years or older (Table 2).

The recommended treatment threshold is based on the costs and assumed efficacy of alendronate. It also assumes that treatment has no adverse effects. The threshold would be higher for more expensive drugs, drugs that do not reduce the risk of nonvertebral fracture, and drugs that have adverse effects. The guidelines follow the simpler approach: a physician may choose any drug for a patient who qualifies for treatment based on the lower threshold (2;10).

Recommendations for individuals should take account of their informed preferences (11). Dawson-Hughes *et al*. point out, “specific treatment recommendations should be personalized through shared decision-making between patient and physician” (2). Specifically, the guidelines say that “patient preferences may indicate treatment for people with 10-yr fracture probabilities below these levels.”

Summary

The new U.S. NOF guidelines include important information about preventing fractures and mitigating their consequences. Their emphasis on treating based on fracture risk is appealing. They would restrain the treatment of relatively young women with "osteopenia." On the other hand, they would recommend pharmacologic therapy for most elderly white women and a substantial fraction of elderly white men. Drug therapy might be very beneficial and worthwhile for all of these people. Or drug therapy might provide relatively little benefit for those who have low bone mass (“osteopenia”) and risk factors. This important question should be answered by a randomized trial. In the meantime, the recommendations about drug therapy should be tempered by the uncertainty about how much drug treatments benefit women and men who do not have osteoporosis.

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