NEW ADVANCES IN THE TREATMENT OF OSTEOPOROSIS

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INTRODUCTION

Osteoporosis is a major cause of morbidity and mortality affecting millions of people in the U.S. and throughout the world (1). As our population ages the impact of this disease will continue to mount. The primary clinical manifestations of this disorder are fragility fractures. Hip fractures are the most important sequelae of osteoporosis. About 50% of patients sustaining a hip fracture are left with some impairment in physical function a year following fracture (2). About 9% of previously independent patients reside in a nursing home a year after sustaining a hip fracture (3,4). Vertebral fractures are associated with acute and chronic pain, postural deformity, depression, anxiety, fear of future fractures and functional impairment (5,6).

From basic science to the clinical arena, there have been great strides made in our understanding and ability to effectively treat this disorder. This review will focus on recent pharmacologic advances in the treatment of postmenopausal osteoporosis.

Osteoporosis has been defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (7). This definition is instructive in that it recognizes factors in addition to bone mass which contribute to bone quality. The microarchitectural status of bone is likely an important determinant of response to therapy and resistance to fracture. Table 1 lists some of the bone and non-bony factors at play in determining fracture risk, especially in the older patient. The list emphasizes the complex nature of fracture risk especially with respect to hip fracture. The majority of this discussion, however, will center on vertebral fractures.

Table 1. AGE-RELATED RISK FACTORS

BONE	FALLS
Reduced Bone Mass	Mechanics of Falling
	Postural Response
Accumulated Microdamage	Sensory Loss
	Orthostatic Hypotension
Architectural Weakness	Neurologic Disease
	Co-Morbidity
Osteocyte Cell Death	Polypharmacy

The clinical diagnosis of osteoporosis is made by the presence of a fragility or non-traumatic fracture. However, the advent of reliable means to measure bone mass coupled with the inverse

relationship of bone mass and fracture risk, have prompted some to favor making the diagnosis based on low bone mass alone (8). Although a threshold bone mass is associated with an increased fracture risk (concept of fracture threshold), the correlation between bone mass and fracture is linear. For every standard deviation (SD) below peak vertebral bone mineral density (BMD) there is an approximately doubling of vertebral fracture risk (9). For woman older than age 65 years, each SD decrease in femoral neck bone mineral density increases the age-adjusted risk for hip fractures by 2.6 (10). That is with progressive decline in bone mass fracture risk continues to increase. Furthermore, in patients with severe reductions in bone mass some alteration in microarchitecture may have already taken place (11,12,13).

In view of these considerations a panel of experts assembled by the World Health Organization (WHO) recommended a new diagnostic classification for osteoporosis and osteopenia for "practical use" based on bone mineral density (8). Under the WHO scheme a bone density of ≥ 2.5 SD below the mean value for premenopausal (T score) white women would be defined as having osteoporosis. Those with reduced bone mass and at least one fragility fracture is defined as "established" or severe osteoporosis (see Table 2). A criticism of the WHO definition is that only 70 to 80% of bone strength is attributable to bone mass (10), the cutoff value is relatively arbitrary and will identify some individuals that will never fracture just as there are some with higher values that will, and it does not account for other risk factors such as age and prior fracture (14).

Table 2. GENERAL DIAGNOSTIC CATEGORIES IN WOMEN*

Normal	BMD or BMC <1 below young adult mean value
Low bone mass (osteopenia)	BMD or BMC >1 but <2.5 SD below young adult mean value
Osteoporosis	BMD or BMC >2.5 SD below young adult mean value
Severe osteoporosis (established osteoporosis)	BMD or BMC >2.5 SD below young adult mean value in the presence of at least one fragility fracture

BMD=Bone Mineral Density
BMC=Bone Mineral Content
SD=Standard Deviation
*WHO Criteria

Table 3 lists the estimated lifetime fracture risk for 50-year-old white women and men (15). The lifetime risk of hip fracture for black women is 5.6% and 2.8% for black men. Melton has calculated that a 50 year-old-white women has a 40% chance of sustaining an

osteoporotic fracture over her lifetime. He calculates 425,000 of the 1,010,000 white women who reach menopause annually will sustain a fracture. This may be a conservative figure because many vertebral fractures are not diagnosed so the rate is likely much higher. However, many of these fractures are arguably clinically non-significant. One study reported that 25% of vertebral fractures were asymptomatic (16).

Table 3. ESTIMATED LIFETIME FRACTURE RISK IN 50-YEAR-OLD WHITE WOMEN AND MEN[a]

	Women % (95% CI[b])	Men % (95% CI)
Proximal femur fracture	17.5 (16.8, 18.2)	6.0 (5.6, 6.5)
Vertebral fracture[c]	15.6 (14.8, 16.3)	5.0 (4.6, 5.4)
Distal forearm fracture	16.0 (15.2, 16.7)	2.5 (2.2, 3.1)
Any of the three	39.7 (38.7, 40.6)	13.1 (12.4, 13.7)

[a] Age 50 years was chosen because this is about the average age of menopause in women

[b] Confidence interval

[c] Using incidence of clinically diagnosed fractures only

Using the WHO definitions a total of about 26 million post menopausal white women have osteopenia or osteoporosis. 16.8 million with osteopenia and 9.4 have osteoporosis. Fifty-one percent or 4.8 million are estimated to have established osteoporosis. Melton points out that these seemingly large figures are similar to the estimated 52 million adults that require dietary intervention for elevated cholesterol or the 30-54 million Americans that have hypertension (28). Furthermore, the argument remains that the consequence of these risk factors are significant, may be preventable and should not be considered a normal consequence of aging.

Table . PROPORTION (%) OF ROCHESTER, MINNESOTA, WOMEN WITH BONE MINERAL MEASUREMENTS MORE THAN 2.5 STANDARD DEVIATIONS BELOW THE MEAN FOR YOUNG NORMAL WOMEN[a]

Age group	Lumbar spine (%)	Either hip site (%)	Midradius (%)	Spine, hip or midradius (%)
50-59	7.6	3.9	3.7	14.8
60-69	11.8	8.0	11.8	21.6
70-79	25.0	24.5	23.1	38.5
≥80	32.0	47.5	50.0	70.0
Total[b]	16.5	16.2	17.4	30.3

[a] Mean is from 48 subjects under age 40 who were randomly samples from the Rochester, Minnesota population. None of them was known to have any disorder that might influence bone metabolism.

[b] Age-adjusted to the population structure of 1990 United States white women 50 years of age and older.

RISK FACTORS

A number of prospective and cross-sectional studies have assessed risk factors for osteoporosis (10,17-27,29). Bone mineral density measurements at any site predicts fracture risk but values at the site of interest are most precise in defining risk (10). Torgerson, et al (29) found that women between 45 and 49 without risk factors had a 2 year probability of fracture of 0.008 compared to 0.40 in women at highest risk of fracture. The later defined as lowest quarter of BMD, >1 previous fracture, family history (maternal grandmother) of hip fracture, and non-menstruating status. Hui (17) and colleagues found that the strength of a particular risk factor was dependent on the particular fracture studied. Both age and low bone density were associate with increased risk, however, age was a stronger predictor of hip fracture and low forearm bone density was a stronger predictor of fractures at the distal forearm. Ross (26) found that both reduced bone mass and prevalent fractures were independently important predictors of new vertebral fractures and that the combination was a better predictor than either alone. A prevalent fracture increases fracture risk at least as great as a decline in 1 SD of bone mass. Table 4 lists the correlates of spinal and proximal femur BMD in a multivariable regression analysis from a cross-sectional study of the 7963 participants in the Study of Osteoporotic Fractures Research Group (23). The models predicted 21 and 25% of the difference between subjects BMD at the femoral neck and lumbar spine.

Table 4. Correlates of Axial and Appendicular Bone Mineral Density*

Variable	Lumbar Spine	Femoral Neck	Distal Radius†
Age		−−	−−
Weight	+++	+++	+++
Height	++	++	++
Fracture in mother	−−	−−	−−
Age at menopause	+	+	++
Estrogen use	+++	+++	+++
Quadriceps strength		++	
Grip strength			+++
Thiazide use	+++	++	+++
Nonthiazide diuretic use	++		
Current smoker			−−
Number of alcoholic drinks in lifetime	+		
Dietary calcium intake		++	+
Lifetime caffeine intake			−
Non–insulin-dependent diabetes mellitus		+++	+++
Gastric surgery			−−
Recent or past activity	+	+	

* Correlations are taken from multivariable analyses. Symbols are used to indicate positive (+) and negative (−) effects on bone mineral density. The strength of the correlation is indicated by the number of symbols: Three symbols indicate 3% or greater change in bone mineral density per unit change in variable (see Tables 4 and 5 for definitions of unit change); two symbols, a 1% to 3% change; and one symbol, a change of less than 1%.

† Distal radial correlations obtained from Bauer and colleagues (8).

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PHARMACOLOGIC ADVANCES

During the past year two anti-resorptive agents, nasal calcitonin (Fosamax) and alendronate (Miacalcin) have been approved by the FDA for the treatment of osteoporosis and a bone forming agent, slow-release sodium fluoride (Neosten) is under FDA review. This review will focus primarily on these new agents. In addition, the role of estrogen and calcium will be briefly discussed.

There are two groups of pharmacologic agents to consider in the management of osteoporosis, antiresorptive agents (estrogen, calcium, calcitonin, and bisphosphonates) which decrease bone resorption and medications that stimulate bone formation (i.e. fluoride). Only medications that fall into the first category are currently approved for the treatment and prevention of osteoporosis.

It is well established that estrogen therapy given in the perimenopausal period is effective in maintaining bone mass (30). Estrogens appear to impair the release of bone resorbing cytokins. Early institution of estrogen replacement therapy reduces the risk of vertebral fractures and appears to reduce the risk of hip fracture at least in the two decades of estrogen therapy in users. Estrogen remains the recommended agent of choice in preventing postmenopausal bone loss. The decision to use estrogen for the prevention or treatment of osteoporosis will depend on patient preference and how, with the help of the physician, the risk and benefits of taking estrogen are weighed. For some patients, a bone density determination may assist in deciding on therapy. The lowest effective dose of conjugated estrogen (or its equivalent) that preserves bone density is 0.625 mg daily. Transdermal estrogen (estradiol) preparations also effectively inhibit postmenopausal bone loss (31,32). For women with an intact uterus, use of a progestational agent is necessary to reduce the risk of uterine cancer. There have been few randomized controlled trials to assess estrogens efficacy in reducing fractures. Lufkin et al (31) reported a reduction in vertebral fractures using 17B estradiol and increased spine and hip BMD. The short duration of the study limits interpretation of their findings. A number of case-controlled and cohort studies have suggested a reduction in fractures. Yet, the benefit of initiating estrogen therapy for the first time in late menopause (over 70 years) is still debated. There remains little evidence that those who have not previously taken estrogen therapy will benefit from initiating therapy for the first time at an age of highest risk for added fractures. Felson (33) and colleagues found that women from the Framingham study cohort that received estrogen therapy for longer than 7 years had higher BMD compared with those without therapy, but this effect was no longer present for women older than 75. Another report from the Framingham Study (34) found that estrogen therapy in women 65-74 years old was associated with a 63% reduction in hip fracture, but only an 18% reduction for those older than 75.

Ettinger (35) et al, determined that estrogen started within 3 years of menopause and used for at least 5 years resulted in a decline in vertebral fractures. Recently Ettinger and colleagues (36) extended their initial study by adding a mean of 8 years to the observation period and observed more than a tripling of the number of osteoporotic fractures. As a group, they once again showed that wrist and vertebral fractures were less common on those receiving estrogen. However, the rate of fractures in those more than 20 years since menopause was not different between groups. There was no protection among women over 80 years, whose fracture rate was greatest (See Fig. 1).

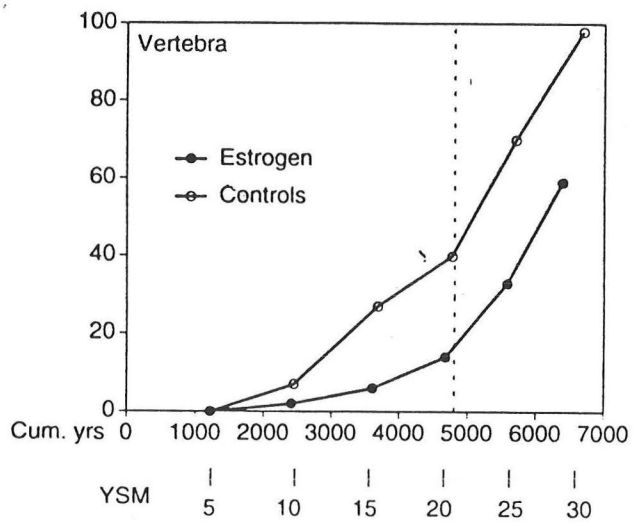

Fig. . Numbers of fractures according to type by cumulative patient-years and years since menopause (YSM) for 245 women who used estrogen and for controls. The *vertical line* at 4800 patient-years indicates the division between the previous study and the current study.

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Certainly, women at risk for osteoporosis (e.g. low body mass index) should strongly consider initiating estrogen replacement therapy at menopause. Because there is some evidence that increased bone loss may ensue after cessation of estrogen, older women (37) should probably be maintained on replacement therapy indefinitely although some of the data just presented does not completely support this position.

Sufficient intake of calcium remains critical throughout life and should be emphasized. Calcium supplementation is important in maintaining bone density during menopause but by itself does not appear as effective as estrogen during the early post-menopausal

period. Calcium supplementation can eliminate bone loss in osteoporotic patients and healthy older patients (38,39,40). The lack of efficacy in blocking bone resorption noted in some trials may be related to dose and bioavailability of the form used (40,41). The provision of modest doses of calcium and vitamin D to elderly patients with marginal intake of these nutrients resulted in an abrupt decrease in fractures (42).

The beneficial effect of calcium is primarily related to the reduction of PTH mediated bone resorption. With age, intestinal calcium absorption is reduced due to decreased production of 1,25 OH_2D and perhaps vitamin D independent factors. This causes an increase in parathyroid hormone secretion which mediates bone resorption. In this way calcium homeostasis is maintained at the expense of bone mass. The adequate provision of calcium and vitamin D decreases PTH levels and reduces bone resorption. In addition, PTH preferentially effects areas high in cortical bone such as the hip and distal forearm and may explain why calcium supplementation seems to be more effective in reducing cortical bone loss.

Women over the age of 65 years on estrogen replacement therapy should consume at least 1000 mg of elemental calcium daily and 1500 mg for those not receiving estrogen (43). Men over 65 years should consume 1500 mg of calcium daily. In the elderly, we favor calcium citrate because of its greater gastrointestinal absorption and apparent effectiveness in maintaining bone mass at axial and appendicular skeletal sites. Men and women over 65 years should consume 400-800 I.U. of vitamin D daily.

Nasal Salmon Calcitonin

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland. It inhibits osteoclastic activity thereby preventing bone resorption (44). Salmon calcitonin has an advantage to mammalian hormone because of greater potency and longer duration of action. The parenteral form of calcitonin has been approved by the FDA for the treatment of postmenopausal osteoporosis. However, its mode of administration, cost, and side effects (particularly flushing, nausea and vomiting), has limited its use. Last year the FDA approved a nasal spray formulation of salmon calcitonin easing administration and avoiding many of the side effects associated with parenteral usage. Indication for use is for woman with postmenopausal osteoporosis that are greater than five years post-menopause. A month supply of intranasal calcitonin at the recommended dose of 200 IU a day is about $56.

Intranasal calcitonin has been studied in multiple clinical trials (45-56). Table 5 summarizes randomized trials of at least 2 years duration (47,48,50,51,53-56). From this review it appears nasal calcitonin has a modest effect in maintaining bone mass in the spine with no affect in maintaining hip or forearm bone mass. Many

of the studies were carried out in healthy women and so relevance to those with reduced bone mass or established osteoporosis is uncertain. In the study by Overgaard et al '92 (50), reduced forearm bone mass was required for inclusion. There appeared to be a dose response with small increases (1%) in spinal mass per 100 IU of nasalcalcitonin compared to placebo. There was no influence at the hip. This study also reported a reduction of vertebral fractures by about two-thirds. However, the number of fractures in the study were small. Moreover, there is no evidence therapy resulted in a reduction in fractures in those with a baseline fracture. Although only 17 of 208 initially randomized patients had a baseline vertebral fracture, 3/15 on treatment and 0/2 on placebo experienced a new fracture. In fact, when these patients are included in the overall analysis significant reduction in fracture rate is lost.

COMPARISON OF PUBLISHED STUDIES*

Intranasal Salmon Calcitonin

Study	N (Baseline)	Age	YSM	DOSE	Baseline	Fx Outcome	Turnover	BMD Spine	HIP	Forearm	Duration
Reginster '95	251	53	0.5-6	50 5d/wk 200 5d/wk placebo**	Healthy	No data	No change	0.82% 2.03% -6.28%	No data	No data	2 yrs
Overgaard '89	52	52	2.5-5	100 placebo	Healthy	No data	No change	2.5% -5.7%	No data	No diff (-4%)	2 yrs
Overgaard '94	134	52	0.5-1.5	100 200 400 placebo	Healthy	No data	↓ T.O. @ 200 & 400 only	-1% No change No change -1%	No data	No diff (-1%)	2 yrs
Adami '95	75	60	11	100	> 2 SD	No data	No change	No change (-0.81%)	-1.83%	No data	
Overgaard '92	208	70	22	50 100 200 placebo	↓ BMC @ forearm 30% of normal	RR = 0.23	↓ T.O. but no dose reponse	2% 2% 3% 1%	No data	-1% -1% -1% -1%	2 yrs
Thamsborg '96	62	65	15	200 placebo	Baseline colles	No data	some ↓ T.O. ↓ erosion depths No change in activation frequency	2.5% 1.7%	-2.2% 1.6%	-1.2% -1.1%	2 yrs
Reginster '94	287		0.5-3	50 5d/wk placebo 5d/wk	Healthy	No data	No change	+1.8% -5.8%	No data	No data	3 yrs (N=186)
Reginster '94	100 (of 186)		0.5-3	50 5d/wk placebo 5d/wk	Healthy	No data	No change	1.1% -6.6%	No data	No data	5 yr

* At least 2 yrs duration

** Placebo treatment was typically 500 mg Ca as gluconolactate and carbonate

Table 5

Thasborg et al (56) studied intranasal salmon calcitonin in women a mean of 15 years since menopause. All subjects had a history of a fragility fracture (colle's) at baseline. Patients received 200 IU per day of intranasal salmon calcitonin or placebo and 500 mg of

calcium. There was no difference in bone mass at hip or spine in treatments. Histomorphometric analysis suggested that erosion depths were reduced but activation frequency was not. This suggests that therapy with calcitonin decreased existing osteoclastic resorption but had no effect in altering osteoclastic recruitment and numbers (as opposed to bisphosphonates which may decrease activation frequency as well as resorption depth (57,58)

Adami et al.(51) compared intranasal salmon calcitonin with alendronate in women with reduced bone mass (T score ≥ 2.5). Only 5% of subjects had prevalent fractures. Alendronate increased bone density in the hip and spine and reduced biochemical markers of turnover whereas calcitonin did not differ from placebo. The study was flawed in that the recommended or high doses of alendronate were used (10 to 20mg) compared to a low dose of nasal salmon calcitonin (100 IU compared to the recommended 200I.U).

A concern with the use of calcitonin is the apparent development of tachyphylaxis or escape phenomena. Receptor down-regulation and formation of antibodies may be responsible (59). Intermittent dosing has been suggested as a way to avoid this development.

Calcitonin has been reported to have central opioid properties and may be helpful in reducing pain from acute osteoporotic fractures(60). However, the clinical efficacy of calcitonin's analgesic properties is disputed among clinicians.
Intranasal calcitonin appears to be well tolerated and few patients have complained of nasal irritation. Baseline and periodic nasal examinations should be performed.

In summary, intranasal salmon calcitonin is a new and more convenient way to administer calcitonin. Physicians with patients who previously were candidates for calcitonin but could not tolerate the injectable form may want to consider this formulation. Unfortunately, the anti-resorptive effect of intranasal calcitonin (and calcitonin in general) is modest, limited to the spine, and evidence for it's anti-fracture efficacy is limited. This agent should be considered only after the adequate provision of calcium and estrogen has failed to maintain bone mass or estrogen therapy is deemed inappropriate.

Alendronate

The bisphosphonates are potent inhibitors of bone resorption. They are analogues of pyrophosphate but are resistant to enzymatic hydrolysis. A growing number of these agents are now available or under investigation. In the U.S. etidronate (Didronel) and pamidronate (Aredia) have been approved for the treatment of Paget's disease and hypercalcemia of malignancy. There has been widespread off label use of etidronate for the treatment of osteoporosis after 2 promising studies were published in 1990 showing decline in fractures and increase in bone density after 2

years (61,62). However, a follow-up report at 3 years found an increase in fracture rate in the treatment group (63,64). The FDA subsequently declined to approve this drug for treating osteoporosis. However, the FDA recently approved alendronate (Fosamax) making it the first drug in this class of agents approved for treating osteoporosis. Alendronate has been approved for women with postmenopausal osteoporosis defined by a low bone mass (>2 SD below premenopausal mean).

The bisphosphonates have 2 major effects on bone. They inhibit osteoclast-mediated bone resorption and impair mineralization of bone and cartilage. An important feature of the bisphosphonates is their relative selectivity at a given dose for inhibiting bone resorption versus mineralization. If an agent inhibits both bone resorption and mineralization at the same dose osteomalacic bone could result. This issue is a concern with the use of etidronate and is the reason for the cyclic dosing schedule of 2 weeks of therapy followed by a three month off period (63,64). This strategy allows for adequate mineralization of newly formed bone. On the other hand, the dose at which alendronate inhibits mineralization relative to its ability to inhibit bone resorption is reported to be 1000 to 1 (65). For this reason alendronate can be given on a daily basis and at least 3 year experience has found no evidence that osteomalacic bone is produced. The long term safety of these agents will need to be confirmed. The relative potency of the bisphosphonates to inhibit bone resorption also vary.

Table 6. RELATIVE POTENCY OF VARIOUS BISPHOSPHONATES TO INHIBIT METAPHYSEAL BONE RESORPTION IN VIVO

Agent	Relative Potency
Etidronate	1
Clodronate	10
Tiludronate	10
Pamidronate	100
Dimethyl pamidronate (mildronate)	500-1000
Alendronate	500-1000
EB 1053[a]	500-1000
Risedronate	1000-5000
BM 21.0955[b] (ibandronate)	10000

[a] Disodium 1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1, 1-bisphosphonate

[b] Nmethyl-N-pentylaminopropane hydroxybisphosphonate

As noted above, etidronate was the first bisphosphonate considered for treating osteoporosis in the U.S. In 1990, 2 studies were published finding etidronate increased spinal bone mass and reduced fractures (61,62). Watts et al (61) enrolled 429 women with established osteoporosis (at least one baseline spinal fracture)

and found patients receiving etidronate increased spine bmd approximately 5% from baseline and 4.0% from placebo. Femoral neck BMD increased about 3%. Typical for antiresorptive agents, the majority of increased spinal density occurred after the first 6 months of therapy (3.5-4.0%). New spinal fractures were reduced by about 50% in patients receiving etidronate. A four year follow-up study was reported by Harris and Watts et al (63). After the 2 yr trial patients were randomized to a 3rd yr of blinded study followed by open label during a 4th year in which all patients received etidronate (400 mg for 14 days). The increase in BMD noted over 2 years was maintained with at around 5% at 4 yrs from baseline. Increases in BMD at the hip was modest, about 1% There was no longer a significant reduction in fracture rate between etidronate and non-etidronate treatment due to an increase in fractures during year 3.

Storm and colleagues (62) performed a 3 yr (150 weeks) study in women with established osteoporosis (at least one spinal fracture) comparing etidronate with placebo (calcium and vitamin D). Bone mass at the spine increased 5.3% in the treatment over 3 yrs and there were fewer new vertebral fractures in the treatment group but this was not significant.

More recently, alendronate has been shown to significantly increase BMD at the lumbar spine as well as the hip (66-68). Ten mg of alendronate resulted in an 8.8% (compared to placebo) increase in the spine and 5.9% and 2.2% at the femoral neck and forearm respectively (68)(see Figure 2).

As anticipated with antiresorptive agents the most pronounced changes occurred during the first year (most rapidly during the first six months). The yearly changes in BMD during the subsequent 3 years of the study were approximately 5.5, 2.5, and 1% increase per year compared to baseline. The continued but diminished rate of increase in bone mass is likely a class effect of antiresorptive agents related to the ultimate recoupling of bone formation with resorption.

The increases in BMD observed with alendronate have been greater than calcitonin or etidronate. The favorable response at the hip to therapy with alendronate distinguishes it from calcitonin which has not improved or stabilized non-vertebral skeletal sites.

In addition, and most importantly, therapy with alendronate appears to have led to a reduction in vertebral fractures. The analysis of fracture data bears some scrutiny. Firstly, only 20% of patients had baseline compression fractures (established osteoporosis) and in this important group no decline in incident fractures were found p=.323(see Table 7). Secondly, although there are favorable trends in all groups (except those over age 65 yrs which is significant) it is only after pooling of the 2 studies (U.S. and multinational) that significance is achieved. Preliminary reports from the

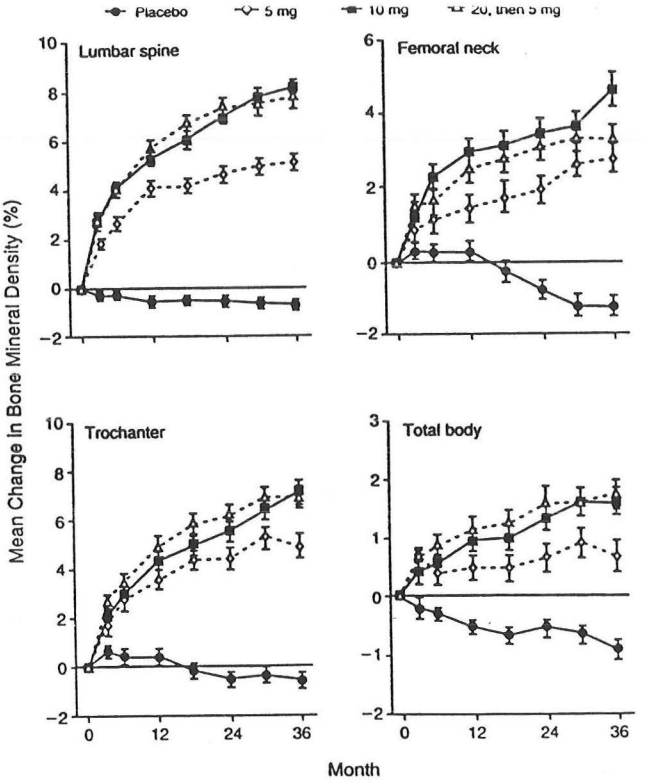

Figure 1. Mean (±SE) Changes in Bone Mineral Density from Base-Line Values in Women with Postmenopausal Osteoporosis Receiving Alendronate or Placebo for Three Years.

Data are shown for bone mineral density (measured by dual-energy x-ray absorptiometry) of the spine, femoral neck, trochanter, and total body. Data for the alendronate group are shown according to the dose: 5 or 10 mg per day for three years or 20 mg per day for two years followed by 5 mg per day in year 3.

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Figure 2

WOMEN WITH NEW VERTEBRAL FRACTURES DURING THE THREE-YEAR STUDY PERIOD

Group of Women	Placebo	Alendronate	P
	% of women with fractures (no./total no.)		
All	6.2 (22/355)	3.2 (17/526)	0.034
Age, <65 yr	4.7 (9/190)	3.7 (11/294)	0.591
Age, ≥65 yr	7.9 (13/165)	2.6 (6/232)	0.015
With previous fractures	19.1 (13/68)	13.4 (13/97)	0.323
Without previous fractures	2.0 (5/253)	1.0 (4/384)	0.328
In U.S. study	4.5 (8/177)	1.6 (4/258)	0.064
In multinational study	7.9 (14/178)	4.9 (13/268)	0.192

Table 7

Fracture Intervention Trial (69)suggest alendronate significantly reduced fracture rates in patients with established osteoporosis. Final report of this work is pending.

Although multiple dosing regimens have been studied, 10 mg/day appears to have the most favorable risk/benefit ratio and is the recommended daily dose. Adequate calcium and vitamin D should be assured and if supplements are needed they should be taken later in the day or evening so as not to interfere with GI absorption.

Because less than 1% (0.78%) of drug is absorbed it is critical that compliance to treatment recommendations are closely followed in order to maximize effectiveness and minimize side-effects (upper G.I. intolerance, ulcers). Alendronate should be taken with 6 to 8 oz. of **plain water** on an empty stomach at least 30 minutes before breakfast (study patients were instructed to wait 60 minutes (67). The medication should not be taken with juice or coffee or anything other than water because of the risk of eliminating absorption of the drug. Patients should remain standing or sitting (should not recline) to avoid impairing esophageal transit of the drug. This is due to concern it may cause esophageal erosions. In one study, intravenous alendronate was administered to 15 women with postmenopausal osteoporosis over four days (70). Markers of bone turnover decreased for a subsequent 6 months after therapy and BMD increased about 4%. Whether this or other IV bisphosphonates (71) would be an effective (cost and clinical) alternative is not known but could be attractive in some circumstances.

How do anti-resportive agents increase bone mass? Bisphosphonates promptly decrease bone resorption followed by a reduction in bone formation. During this period resorptive pits are being filled by the osteoblasts and a net increase in bone mass occurs (72,73). Ultimately, bone formation also falls but there is a temporal delay. Once bone formation declines the net increase in bone mass also declines and frequently after 2 years a new steady state is achieved. Depending on the rate of bone turnover (increased bone remodeling units) the increase in bone mass will vary with larger increases noted during increased turnover states and to a lesser degree during normal or low bone turnover states.
The long term effect of decreased bone formation is not know.
Safety of usage with alendronate beyond 4 years has not been established.

In general, bone turnover is increased for the first few years after menopause. Typically, bone turnover has been described as being normal or decreased late after menopause. More recently some studies have suggested that bone turnover remains elevated in the elderly, but less than during the perimenopausal period (74,75). The combination of age-related changes in osteoblast function and increased bone turnover due to secondary hyperparathyroidism (from impaired calcium absorption) account for age-related bone loss. The primary factor(s) operating in a particular individual is

variable and there is likely considerable patient heterogeneity. In general, markers of bone turnover have not been helpful in predicting response to therapy. They should have a role in clinical management in the future but remain primarily a research tool at present(77),

Slow-release sodium fluoride

In November 1995 the Metabolic Diseases Advisory Panel for the Food and Drug Administration unanimously recommended approval of slow-release sodium fluoride (SR-NaF) or Neosten after review of nearly 14 years of clinical studies by Pak et al(78). If approved, SR-NaF will be the first bone forming agent available for the treatment of osteoporosis. NaF stimulates bone formation and results in a steady and substantial increase in cancellous bone (38,39).

The bone forming properties of fluoride are well known (79-81) and have been investigated by a number of groups for the treatment of osteoporosis. In 1990, Riggs et al reported their findings from a 4 year double-blind randomized trial comparing 75mg of NaF(given 90 mg daily and 60 mg daily on alternate days) and calcium carbonate (1500mg) to placebo and calcium (38). All patients enrolled had at least one (median 4) baseline vertebral fracture. Although spinal bone mineral density increased a median of 35% there were no differences in vertebral fractures between groups and an increase in nonvertebral fractures were noted in the subjects receiving fluoride. Furthermore, patients treated with fluoride were more likely to experience gastric symptoms (gastric pain, nausea and vomiting) believed caused by irritation and increased gastric acidity due to the conversion of NaF to HF. In addition, patients receiving NaF were 7 times more likely to suffer from lower-extremity pain syndrome. The later is believed to be due to the formation of abnormal and increased bone remodeling in weight-bearing portions of the skeleton as well as the occurrence of stress fractures. The conclusion from this work was that fluoride in the dosage used was neither effective nor safe for the treatment of postmenopausal osteoporosis(83).

In 1982 Pak and colleagues began clinical trials seeking to overcome the problems associated with fluoride therapy (39,84). Recently, the final report of the randomized controlled trial was published(39). One-hundred ten patients (99 completing at least one year of therapy) with established osteoporosis were randomized to receive either 25mg of SR-NaF twice a day or placebo for 14 months (1 cycle included 12 months active treatment and a 2 month off period). All subjects received 400 mg twice daily of calcium citrate continuously. Mean duration of therapy was about 3.5 years. Treatment with SR-NaF reduced the risk of subsequent vertebral fractures by 70%. Bone mass increased in the spine by 4.5 % each year(20% over 4 years), about 2.5% in the femoral neck per year, with no change in the forearm (see Figure 3). Bone mass was maintained at all sites in the placebo group. There were no

Figure 3

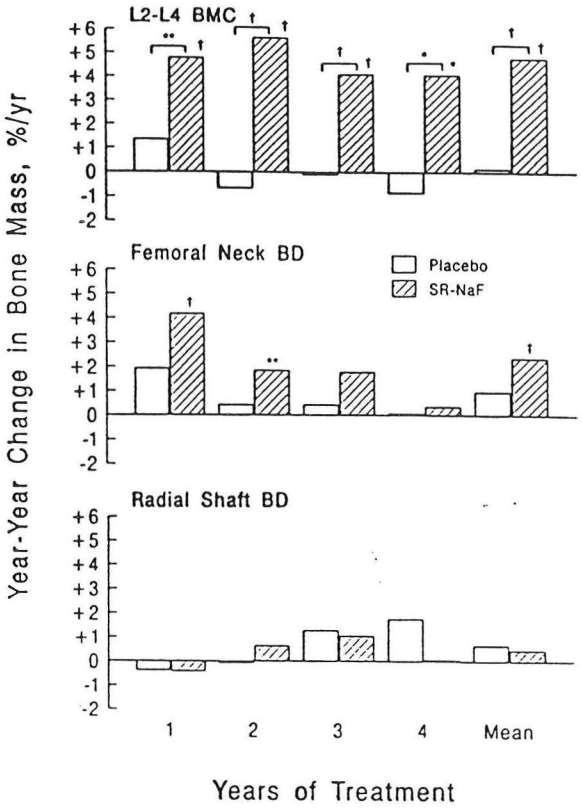


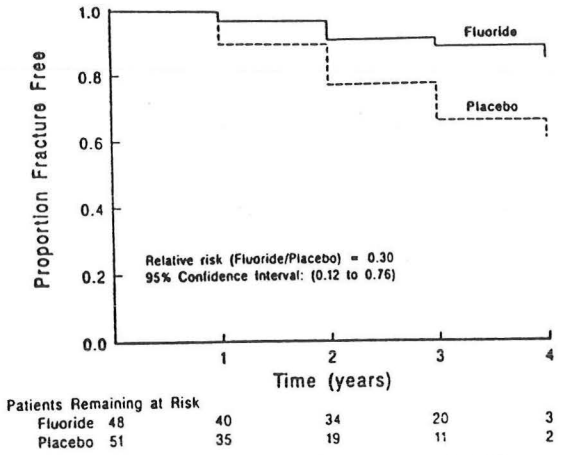
Figure 3. Effect of treatment on the L2–L4 bone mineral content (*BMC*) and on the bone density (*BD*) of the femoral neck and radial shaft. For each year, the percentage change of the value from the preceding year or from baseline was calculated. Thus, a year-to-year change, rather than a cumulative change, is shown. Symbols above the bars indicate a significant change from zero, whereas symbols above the brackets show significant changes between the group receiving placebo and the group receiving slow-release sodium fluoride (*SR-NaF*). $*P < 0.05$; $**P < 0.01$; $\dagger P < 0.001$.

reports of stress fractures or lower-extremity pain syndrome and no increase in GI complaints compared to placebo. Serum F levels were maintained well within the therapeutic threshold during the study and fell to baseline levels after the end of each cycle (12-14 month period). All methods to assess bone quality have determined the bone to be of normal quality with without evidence of osteomalacic or mosaic bone pattern(78).

Analysis of individual fracture rate (IVR) by baseline BMD (mild-moderate > 65% of premenopausal value or severe < 65%) found a greater treatment response in the mild-moderate group (P=0.004) compared those in the severe baseline BMD group (IVR P=0.19). However, when additional patients were added from randomized and non-randomized trials, SR-NaF was shown to be effective in severe bone loss as well RR .54, (P=0.03) comparable to the etidronate "high risk group" and by alendronate, most of whom did not have fractures (85) (see Figure 4).

The primary explanation for the efficacy and safety noted with SR-NaF compared to other studies is because of the maintenance of therapeutic serum F levels without exceeding the toxic threshold (about 195 ng/ml). In addition, the use of calcium citrate

Figure 4.



Proportion of patients without new spinal fractures during 4 years of treatment in the groups receiving slow-release sodium fluoride and placebo.

contrasts with calcium carbonate used in the Mayo clinic trial. Calcium citrate proved to be an effective antiresorbing agent and serum PTH fell in both groups which is likely due to the adequate provision of calcium and not a result of fluoride therapy. Of note, Riggs et al (82) has provided indirect support of the importance of maintaining serum F within the therapeutic window. They have re-analyzed their data and found evidence to suggest a direct relationship of lower serum F levels and lower rates of increased spinal mass to reduced vertebral fracture rates.

A second independent double-blind randomized controlled trial was begun in early 1993 by Rubin et al (86) to assess the efficacy of SR-NaF in elderly women with established osteoporosis. The Treatment of Senile Osteoporosis Study (TSOS) is a 40 month trial funded by the National Institute on Aging comparing SR-NaF, calcium citrate and vitamin D versus placebo, calcium citrate and vitamin D. TSOS trial differs from that reported by Pak et al (39) in that all patients are at least 65 years, receive 945 mg of elemental calcium in the form of calcium citrate vs. 800 mg, and 600 units of vitamin D (doses comparable to Chapuy et al (42) vs. no routine vitamin D supplementation. Outcome measures include spinal fractures, vertebral bone mass, safety and functional status.

Patients in the TSOS study follow the same regimen of SRNaF 25mg/twice a day (or placebo) for 12 months followed by a 2 months withdrawal period. An intermittent treatment design is used to permit adequate mineralization of newly formed bone and to avoid tachyphylaxis. Calcium and vitamin D supplementation is provided continuously. Seventy-seven patients have been enrolled. Table 8 reviews there baseline characteristics.

During the FDA advisory meet an interim analysis of vertebral fractures was presented. The integrity of the design was

Table 8

Baseline Presentations

	Nafril™	Placebo	P Value
No. Patients	39	38	
Age, yr	72.3±5.6	73.2±5.4	0.449
Weight, kg	61.6±12.0	60.8±10.3	0.763
Height, cm	157.5±6.7	156.6±6.2	0.565
L2-L4 BD, % Nl	72.7±9.8	70.8±12.4	0.459
Prevalent Spinal Fractures	2.8±2.12	2.4±1.95	0.423

Values are presented as mean ± SD. Significant difference between the two groups was determined by Student's T-test assuming equal variance. Prevalent fractures were identified visually by Dr. Rubin during recruitment.

maintained. At the time of analysis 51 subjects have completed at least one cycle and were evaluable for incident fracture determination (see Table 9). Although these are only interim findings, the risk reduction is very similar to the final findings of Pak et al. and supports SR-NaF's efficacy in treating established osteoporosis, specifically in older women.

Table 9

	Placebo	Slow Fluoride
N	27	24
Number of Cycles	35	31
Mean Cycles/Patient	1.3	1.3
New Fractures	8	2
GVFR*	8/35	2/31

* Group Vertebral Fracture Rate. RR .28 (95% CI .07-1.20). P = 0.087 in favor of slow-release NaF.

Conclusion.

Major advances have been made in the treatment of osteoporosis. Estrogen replacement therapy and calcium supplementation continue to be the mainstay of therapy for the prevention of postmenopausal bone loss. For women with established osteoporosis that are not candidates for estrogen therapy, alendronate and nasal calcitonin are alternative agents. Alendronate is an effective antiresorbing agent that produces modest increases in bone density at the spine and appendicular sites. It appears to be effective in reducing vertebral fractures but more information is needed. Presently

combined estrogen and alendronate therapy is not recommended but trials are ongoing. Upper gastrointestinal toxicity and poor GI absorption are its major drawbacks and will limit its usefulness in some populations. Safety beyond 4 years has not been demonstrated.

Intranasal calcitonin offers ease of usage and safety but its efficacy seems limited to maintenance of vertebral bone density and has no effect at cortical sites. One study found a decrease in fracture rate but the numbers of fractures were small and benefit was not seen in those with baseline fractures. Intranasal calcitonin is an alternative for patients that cannot tolerate or are not candidates for other antiresorbing agents. Although daily intranasal calcitonin is recommended an alterating regimen may be more effective . Parenteral calcitonin (not reviewed) is probably more effective but is generally not well tolerated and appears more effective in high turnover states or early menopausal states. This contrasts with intranasal calcitonin which has an indication of after 5 years postmenopause.

At the present time only antiresorbing agents are available. The approval and availabilitiy of SR-NaF would provide the first bone forming agent. Clinical investigations have demonstrated that it substantially reduces fracture rate in women with established osteoporosis. Side-effects historically associated with NaF are averted with the prescribed dose and slow-release formulation.

The availability of effective antiresorbing and bone forming agents provides physicians and patients with new opportunities to effectively treat this common disease. Antiresorbing agents are likely to be effective by decreasing bone turnover and preventing perforations which disrupt trabecular connectivity (87). Bone forming agents decrease fractures by increasing bone mass (normal bone) and bone strength. Some reconnectivity of trabecular struts is also possible depending on the severity of bone loss.

Finally, in this day of cost restraints Francis et al (88) performed a comparison of effectiveness and cost of treatment for vertebral fractures in England. Based on the formula used by Francis and colleagues, Table 10 is a similar analysis of agents in this country based on their predicted fracture reduction (from studies) and monthly cost. Baseline fracture rate was based on .229/pt/yr which is the rate of fracture in an untreated group of patients with estblished osteoporosis. Montly price for SR-NaF is based on speculation and other prices are from one pharmacy, not necessarily the best deal in town.

COST COMPARISON*

Table 10

Product	Monthly	Annually	Predicted Fx Reduction	Cost per Fx Averted
Premarin++	$17.36	$210	60%	$1,564
Prempro++	$22.45	$270	60%	$2,078
SR-NaF	$37.50+++	$450	70%	$2,976
Nasal Calcitonin+	$56.30	$675	67%	$4,669
Alendronate	$56.25	$675	52%	$6,005

\+ Data very limited supporting reduction in fracture rate
++ Reduction based on Cohort and case-controlled studies
+++ Based on estimation (unofficial) of $1.25/day.
* Based on formula by Francis et. al., 1995.

Issues for now and in the future:

1. Which patients should be screened? There remains controversy over the classification of osteoporsis and better predictors of fracture risk are needed. Population based screening is not recommended at the present time.

2. Further development of markers of bone turnover to assist in the diagnosis and selection of treatment are needed.

3.The development of non-invasive means to accurately assess bone strength.

4.Studies are needed to determine when or if patients would benefit from combination therapies.

5. Development of bisphosphonates with better absorption and GI tolerability .

6. Other agents.

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