A Review of the Efficacy and Side Effects of Antiresorptive Drugs

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INTRODUCTION

Currently in the United States, over 10 million people are affected by osteoporosis, while an estimated 34 million are believed to be at high risk for this crippling bone disease. Postmenopausal women, whose estrogen levels have declined, compose one of the highest-risk groups for this disease. Due to the heightened activity of osteoclasts, osteoporosis sufferers are likely to experience a bone fracture later on in life. Approximately 1 in every 2 women over the age of 50 develops an osteoporosis-related bone fracture. Women represent a substantial portion of the 1.5 million fractures endured by both males and females each year.¹

Two types of drugs effectively treat and prevent osteoporosis.² Bone formation medications stimulate osteoblast activity, while antiresorptive drugs inhibit osteoclast uptake and degradation of the calcified matrix.²,³ Antiresorptive drugs appear to generate more promising results for osteoporosis sufferers and have already received FDA approval.⁴ Four types of antiresorptive drugs are commonly used to treat osteoporosis and prevent the degradation of bone: bisphosphonates, which include alendronate and risedronate sodium; hormone replacement therapy (HRT), and the second-generation SERM, raloxifene.² Although these drugs vary slightly in their modes of action, they all aim to increase bone mineral density (BMD) and halt bone resorption.

Since each of the antiresorptive drugs regulates osteoclast activity differently, it is uncertain which drug most effectively targets and minimizes the degradative effect of the osteoclasts. In addition, it has been shown that raloxifene, HRT, alendronate, and risedronate serve as both agonists and antagonists in other tissues in the body. This ability to target other tissues might lead to unwanted side effects, including
gastrointestinal adverse effects, breast cancer, and deep venous thromboembolic (VTE) disease. Potential health benefits unrelated to bone functioning have been shown to accompany raloxifene and HRT. Such benefits include an increase in high density lipoproteins (HDL), a reduction of low density lipoproteins (LDL), and a decreased risk of colorectal cancer. In order to fully evaluate the usefulness of each antiresorptive drug for osteoporosis sufferers, it is imperative that research on these potential side effects also be examined. This review will investigate recent research on the efficacy of each antiresorptive drug not only in terms of its direct effect on BMD, bone turnover markers, and fracture risk, but also in terms of its inadvertent health risks and benefits.

**METHODOLOGY**

Through the use of various medical and scientific journals, this review analyzed and evaluated the various antiresorptive drugs. In order to obtain appropriate studies, the databases, Pubmed, Ebsco, and Lexis Nexus were used. The following terms were initially searched for in each of the databases: *alendronate and osteoporosis, risedronate and osteoporosis, hormone replacement therapy and osteoporosis, and raloxifene and osteoporosis*. Due to the large number of studies generated from these search terms, the search terms had to be refined to be more specific. Depending on which efficacy parameter was being examined, an additional search term of *BMD, bone turnover markers, fracture risk, or side effects* was added to each of the search terms previously mentioned. To further limit the number of studies reviewed, a cohort restriction and date restriction were imposed on the studies. Whenever possible, only studies displaying the effects of antiresorptive drugs on postmenopausal women were used. Only double-blind
experiments conducted on a large population over an extended period of time were reviewed. Furthermore, reviewed studies were limited to those that have been published within the last five years, so that the most up-to-date data was presented. The figures included in this review were used to give a graphical representation of the results. In most cases, the study failed to supply the observed results in numerical form and instead opted to present the results in a figure. In order to ensure the most accurate presentation of such data, the original figures and tables were included in the review.

RESULTS

Efficacy

Increase in Bone Mineral Density (BMD)

*Hormone Replacement Therapy (HRT)*

Villareal et al\(^7\) analyzed the effect of HRT on BMD as well as on bone turnover markers in women aged 75 or older in a randomized controlled trial (RCT). In this double-blind, placebo-controlled trial lasting from September 1995 to August 2001, 67 women with mild to moderate physical frailty were examined. Patients exhibiting 2 of the 3 following parameters were considered to display mild to moderate physical frailty: (1) 11-18mL/min per kg of body weight for low peak aerobic power, (2) self-admitted need for assistance with 2 necessary activities of daily living (ADLs) or 1 basic ADL, and (3) a test score of 18 to 22 on a range of 0-36 on the modified physical performance test. Patients either received 0.625mg/d of conjugated estrogen combined with 5mg/d of medroxyprogesterone for 13 days every three months (n=45) or a placebo (n=22). After 9 months, patients receiving conjugated estrogen and medroxyprogesterone displayed a 4.3% increase in lumbar spine BMD compared to 0.4% (95% CI) increase exhibited by
the placebo patients. An increase of 1.7% in total hip BMD was observed in patients taking the HRT, while a decrease of 0.1% from the baseline was observed in the placebo patients.

In a randomized double-blind, placebo controlled study, Recker and colleagues examined 128 women who were older than 65. Eligible patients displayed a spinal BMD less than or equal to 0.90g/cm$^2$ at baseline. Patients either received 0.3mg/d of conjugated equine estrogen (CEE) and 2.5mg/d medroxyprogesterone (n=53) or a placebo (n=54). After 3 years, patients treated with HRT demonstrated a 4.0% increase in spinal BMD, while the placebo group demonstrated a 0.35 decrease in spinal BMD.

**Raloxifene**

Studies performed by Ettinger et al and Prestwood et al suggested that raloxifene increased overall BMD significantly when compared to the placebo. Ettinger et al examined 7705 postmenopausal women with osteoporosis from 25 countries to determine the effect of raloxifene on femoral neck and spine BMD. The patients were separated into 1 of 2 subgroups. If the subject displayed a femoral neck or lumbar spine BMD t score of less than -2.5, then they were grouped into the first study group (n=5064). The second study group (n=2641) similarly exhibited low BMD t scores, but also had suffered at least one fracture prior to the start of the study. Within each of these subgroups, patients were randomized to receive either 60mg/d of raloxifene, 120mg/d of raloxifene, or the placebo. Each patient also received daily calcium (500mg) and cholecalciferol (400 to 600IU) supplements. At the end of the 3-year trial, the patients receiving 60mg/d demonstrated a 2.1% increase in femoral neck BMD compared to the
placebo; patients receiving 120mg/d exhibited an increase of 2.4% when compared to the placebo group. The spinal BMD of patients being administered 60mg/d increased by 2.6% when compared to the placebo, while the spinal BMD of patients receiving 120mg/d increased by 2.7% when compared to the placebo group.

Prestwood et al\textsuperscript{10} demonstrated the effects of raloxifene and CEE on BMD when taken separately in a phase II randomized, double-blind study. Over the course of 6 months, 51 Caucasian women who had been postmenopausal for at least 5 years prior to the start of the study were examined. Eligible patients were between 55 and 85 years of age and exhibited a baseline lumbar spine BMD score between 1 SD above and 3 SD below peak bone mass. Patients received either 0.625 CEE (n=26) or 60mg raloxifene (n=25) daily. The study showed a substantial increase in lumbar spine, femoral neck, trochanter, and total body BMD. Theses increases can be seen in Figure 1.

Figure 1. BMD changes from baseline of patients receiving 60mg/d raloxifene (RLX) or 0.625mg/d CEE for 6 months. From: \textit{J Clin Endocrinol Metab}. 2000;85:2197-2202.
Alendronate

Bone and colleagues\textsuperscript{11} researched the efficacy of alendronate, CEE, alendronate and CEE, and a placebo in elevating BMD. A 2-year study including 425 postmenopausal women showed that alendronate when administered daily in amounts of 10mg increased lumbar spine BMD by 6.0%. The lumbar spine BMD decreased by 0.6% in the placebo group. Downs et al\textsuperscript{12} performed a randomized study of 299 women ranging in age from 45 to 84 who had been postmenopausal for at least 5 years and had been diagnosed with osteoporosis. Researchers administered either 10mg/d of alendronate, 200mg IU/d calcitonin, or a placebo to patients in 24 centers across the United States. BMD increases were observed in patients receiving either alendronate or calcitonin. Patients receiving calcitonin experienced an increase in BMD of 1.18% in the lumbar spine, 0.47% in the trochanter, and 0.58% in the femoral neck. However, more substantial increases were noted in the alendronate group with BMD increases of 5.16%, 4.73%, and 2.78% in the spine, trochanter, and neck respectively.

Greenspan and colleagues\textsuperscript{13} examined the effects of a weekly alendronate dosing on BMD in a 2-year double-blind study. Patients (n=1258) were postmenopausal women between the ages of 42 and 95 and exhibited a lumbar spine or femoral neck BMD t score of -2.5, which is characteristic of osteoporosis sufferers. Patients were randomized to receive 70mg alendronate once a week (n=519), 35mg alendronate twice a week (n=369), or 10mg alendronate every day (n=370). Results indicated that lumbar spine BMD increased by 6.8%, 7.0%, and 7.4% in the group receiving alendronate once a week, twice a week, and everyday respectively. Increases of 4.1%, 4.3%, and 4.3% in total hip
BMD were seen in the once-weekly, twice-weekly, and daily treatment groups respectively.

**Risedronate**

In a study of 36 patients receiving 30mg weekly risedronate, BMD increases of 1.9% and 2.1% were observed in the trochanter and hip respectively. Patients between the ages of 46 and 86 also received daily supplements of 400IU/d of vitamin D and 1200mg/d of calcium. Similar results were noted in a 3-year randomized double-blind study conducted by Harris and colleagues of 2458 ambulatory postmenopausal women. Eligible subjects were younger than 85 and had sustained 2 or more radiographically identified vertebral fractures (T4-L4, inclusive) or 1 vertebral fracture and low lumbar-spine (L1-L4) BMD (defined as ≤0.83 g/cm² [Hologic instrument] or ≤0.94 g/cm² [Lunar instrument]). Eligible patients were postmenopausal for at least 5 years prior to the start of the study. Patients were randomized to receive 2.5mg/d risedronate, 5.0mg/d risedronate, or a placebo. After the first year, the 2.5mg/d risedronate group was dropped from the study due to an amendment to the protocol that was not further explained in the study. Those patients receiving 5mg of risedronate a day exhibited an increase in lumbar spine BMD of 5.4% compared to the 1.1% increase observed in placebo patients. Femoral neck BMD increased by 1.6% in risedronate-receiving patients and decreased by 1.2% in placebo-receiving patients. Femoral trochanter BMD increased by 3.3% in the risedronate group and decreased by 0.7% in the placebo group.
Decrease in Bone Turnover Markers

Hormone Replacement Therapy

The Villareal et al\textsuperscript{7} study of 67 women with mild to moderate physical frailty observed the alterations in such bone turnover markers as bone-specific alkaline phosphatase (BSAP) and urine N-telopeptide (NTx). Patients in this study either received 0.625mg/d of conjugated estrogen with 5mg/d of medroxyprogesterone for 13 days every 3 months or a placebo. Results of the study indicated that HRT reduced BSAP levels by 24%. Urine N-telopeptide levels decreased by 48% in patients undergoing HRT.

Ralofixene

Levels of urinary cross-linked N- and C- telopeptides of type I collagen (NTx and CTx respectively) and deoxypyridinoline cross-links (DPYr) were observed by Prestwood and colleagues.\textsuperscript{10} In this study, 51 women with a baseline lumbar spine BMD score between 1 SD above and 3 SDs below peak bone mass were followed for 3 years. Patients received either 0.625mg/d of CEE or 60mg/d of raloxifene. CTx levels decreased by 23% in the raloxifene group. Similarly, NTx levels decreased by 22% with raloxifene. Raloxifene demonstrated a potential to decrease DPYr by 16%.

Alendronate

Alendronate’s efficacy in abating bone turnover markers was researched by Downs et al.\textsuperscript{12} In this study of 299 postmenopausal women, patients either received 10mg/d of alendronate, 200mg IU/d calcitonin, or a placebo. A 43% decrease of BSAP
levels in the alendronate group was observed compared to a 2% reduction in the placebo group. Furthermore, alendronate reduced urinary NTx by 62%.

*Risedronate*

Raisz and colleagues\(^1^6\) investigated the short-term effects of risedronate on biochemical markers of bone turnover, including DPYr, NTx, and CTx, in postmenopausal women. An overall decrease in the resorption markers was observed. DPYr decreased by 28%, NTx by 61%, and CTx by 73% after 2 weeks of treatment.

**Decreased Fracture Risk**

*Hormone Replacement Therapy*

A study\(^1^7\) conducted by the Women’s Health Initiative (WHI) monitored 16 608 postmenopausal women with intact uteruses aged 50-79 to determine the effects of HRT on fracture risk. The study lasted from 1997-2002. A woman was considered postmenopausal if she had failed to experience vaginal bleeding for 6 months prior to the start of the study, had undergone a hysterectomy, or had ever used postmenopausal medication, including HRT, raloxifene, alendronate, and risedronate. Patients either received CEE, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet or a placebo. Those patients that received HRT (n=8506) suffered from one third fewer hip and clinical vertebral fractures than the patients receiving placebo (n=8102). An overall decrease of 24% in total fractures was observed in the HRT group.
**Raloxifene**

The Ettinger et al\(^9\) study of 7705 women separated into 2 different groups based on the presence or absence of previous vertebral fractures (n=2641 and n=5064, respectively) illustrated a reduced relative risk (RR) of 0.7 for vertebral fracture in those patients receiving raloxifene versus those who received the placebo. The study groups received either 60mg/d (group 1) or 120mg/d (group 2) of raloxifene. Both groups displayed a decreased incidence of new vertebral fractures. No difference between the preventative effects of 60mg/d raloxifene or 120mg/d raloxifene was observed when the data from group 1 and 2 were combined. However, when the data from group 2 was analyzed by itself, a difference in raloxifene’s preventative effects was found. Women in study group 2 receiving 120mg/d raloxifene displayed a lower incidence of vertebral fractures (10.7%) than the women in study group 1 receiving 60mg/d raloxifene (14.7%). The incidence of nonvertebral fractures, including wrist and hip fractures, was not affected by raloxifene treatment.

**Alendronate**

Over a period of 4 years, the effects of alendronate on fracture risk in low BMD women were researched by Cummings and colleagues.\(^{18}\) Limitations restricted the eligible test population to women with less than 0.68g/cm\(^2\) in femoral neck BMD and without a previous vertebral fracture. A cohort of 4432 women, ranging in age from 54 to 81, participated in this 2-year randomized, blinded, and placebo-controlled study in which patients received alendronate (n=2214) or a placebo (n=2218). During the first 2 years, alendronate patients received 5mg/d. However, after 2 years, the dosage was
increased to 10mg/d due to other research which suggested that more substantial increases in BMD could be seen with 10mg/d. In alendronate patients, results indicated a 36% decrease in clinical fractures (RH=0.64, 95% CI) in women with baseline femoral neck BMD t scores of less than -2.5. Women with baseline femoral neck BMD t scores greater than -2.0 SDs demonstrated a 22% decrease in the risk for clinical fractures. A 44% decrease in vertebral fracture risk was observed in women with baseline femoral neck BMD t scores of less than -2.5.

Black et al\textsuperscript{19} generated similar fracture reduction results in an approximately 3-year study of 3658 women who had been postmenopausal for at least 2 years prior to the start of the study. Eligible women had to exhibit baseline femoral neck BMD equal to or less than 0.68 g/cm\textsuperscript{2} and were separated into 1 of 2 study groups. The vertebral fracture arm (n=2027) contained women who had previously suffered from a vertebral fracture, while the clinical fracture arm (n=1631) included women without previous histories of vertebral fractures. All women were given alendronate, and only those women whose baseline calcium intake was below 1000mg/d were given daily supplements of 500mg elemental calcium and 250IU of vitamin D. The original 5mg/d dosage of alendronate was changed to 10mg/d 2 years into the study due to other research which suggested that more substantial increases in BMD could be seen with 10mg/d. An overall decrease of 48% (RR=0.52, 95% CI) in radiological vertebral fractures was observed when the data from study group 1 and 2 were combined. In the 2 alendronate groups combined, the risk for multiple vertebral fractures was reduced by 87% (RR=0.13), for clinical vertebral fractures by 45% (RR=0.55), and for hip fractures by 53% (RR=0.47).
Risedronate

The ability of risedronate to reduce the risk of fractures was investigated by Harris et al.\textsuperscript{15} A cohort of 2458 ambulatory postmenopausal women were examined in this 3-year randomized double-blind study in which patients either received 2.5mg/d risedronate, 5mg/d risedronate, or a placebo. After the first year, the 2.5mg/d risedronate group was dropped from the study due to an amendment of the protocol that was not further explained in the study. After 1 year, the vertebral fracture risk was decreased by 65\% in those patients taking 5mg/d risedronate. The chance of vertebral fractures was decreased by 41\% in the 5mg/d risedronate group following 3 years of treatment. After 3 years of treatment, women taking 5mg/d risedronate illustrated a 39\% decrease in non-vertebral fracture risk compared to the placebo.

Side Effects

Hormone Replacement Therapy versus Raloxifene

Cancer

An increased risk for breast cancer was noted in patients using HRT to treat osteoporosis,\textsuperscript{17} while a decreased risk was associated with raloxifene.\textsuperscript{9} The WHI\textsuperscript{17} study lasted 5 years and included 16 608 postmenopausal women with intact uteruses. Results revealed a 26\% increase in breast cancer risk in HRT patients. The Ettinger\textsuperscript{9} study of 7705 postmenopausal women with osteoporosis found a RR of 0.3 for raloxifene patients. Several studies\textsuperscript{9,17} examined the probability of incurring other cancers, including colorectal and endometrial. HRT reduced the risk for colorectal cancer by 37\%.\textsuperscript{17} A raloxifene trial\textsuperscript{9} discovered endometrial cancer in 4 women out of 2557 women in the
60mg/d group, in 2 women out of 2572 women in the 120mg/d group, and in 4 women out of 2576 women in the placebo group.

*Pulmonary embolism/deep vein thrombophlebitis*

When used separately, HRT and raloxifene exhibit similar effects on the risk for pulmonary embolism or deep vein thrombophlebitis.\(^9,17\) WHI noted that the risk for pulmonary embolism and deep vein thrombophlebitis individually was twofold greater for patients taking HRT than those not taking it.\(^17\) Studies executed by Ettinger et al\(^9\) indicate that during the study 8 patients receiving the placebo experienced either pulmonary embolism or deep vein thrombophlebitis compared to 25 and 24 patients in the 60mg/d and 120mg/d raloxifene groups respectively. Raloxifene, regardless of dose, imposes a RR for deep vein thrombophlebitis of 3.1 (95% CI) on its users.

*Cardiovascular Disease and Serum Levels*

In the WHI study,\(^17\) HRT was shown to elevate the risk for any CHD by 22%. However, in a double-blind randomized, parallel trial in which Walsh et al\(^20\) examined 390 postmenopausal women, HRT and raloxifene seemed to decrease the risk of CHD. Patients received 60mg/d raloxifene, 120mg/d raloxifene, HRT (conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d), or a placebo. HRT was found to reduce LDL-C by 14%. Furthermore, it increased HDL\(_2\)-cholesterol by 33% and HDL-C by 11%. Triglyceride levels increased by 22% as a result of HRT treatment. This study also suggested that both doses of raloxifene demonstrated a less substantial increase in these factors than HRT. Raloxifene reduced LDL-C levels by
12%, increased HDL\textsubscript{2}-cholesterol levels by 15%, and exhibited no statistically significant effect on HDL-C or triglyceride levels when compared to placebo.

**Alendronate versus Risedronate**

Bisphosphonates seem to induce limited adverse side effects, among which are upper gastrointestinal ulcers and upper GI mucosal changes. A study conducted by Lanza and colleagues\textsuperscript{5} suggested that gastric ulcers occurred in 13.2\% of the group receiving alendronate. The Lanza et al\textsuperscript{5} study examined 515 postmenopausal women who were randomized to receive 5mg/d risedronate, or 10mg/d alendronate for 2 weeks. While reviewing the effects of alendronate and risedronate on the upper gastrointestinal tract, Lanza and colleagues\textsuperscript{5} observed 3 alendronate patients with esophageal ulcers, 1 alendronate patient with a duodenal ulcer, no esophageal ulcers in risedronate patients, and 2 duodenal ulcers in risedronate patients. The Lanza et al\textsuperscript{21} study included men and postmenopausal women who received either 40 mg/d alendronate (n=90), 30 mg/d risedronate (n = 89), or placebo with aspirin 650 mg for the last 7 days (n = 20). Both the alendronate and risedronate group demonstrated decreased gastroduodenal irritation when compared to the group receiving a placebo and aspirin.

In the study by Harris et al,\textsuperscript{15} 4.2\% of the women in the 5mg/d risedronate group complained of gastrointestinal adverse effects and decided to undergo gastrointestinal tract endoscopy. Similarly, 3.7\% of the placebo group complained of the same gastrointestinal adverse effects and underwent gastrointestinal tract endoscopy. Nine cases of duodenitis in risedronate patients compared to 2 in the placebo group were
noted. Duodenal ulcers appeared in 1 patient undergoing risedronate treatment, while they appeared in 3 placebo-receiving patients.

In a 10 week study conducted by Lanza and colleagues, the tolerability of a weekly alendronate dose was examined. A cohort of 277 men (n=90) and women (n=187) participated in this parallel, double-blind, placebo-controlled study. Subjects were between the ages of 45 and 80 and had suffered no recent gastrointestinal diseases prior to the start of the study. Each patient was randomly assigned to receive 70mg of alendronate once a week (n=126), a placebo once a week (n=126), or a weekly placebo for the first 9 weeks and a weekly placebo followed by 650mg of aspirin during the last week (n=25) in order to generate a positive control and to actually observe lesions. In order to ensure blinding, patients not receiving aspirin during the last week were given placebos that were similar in appearance to aspirin. As part of the methodology, patients took their medication in the morning before eating or drinking anything. Additionally, patients drank a full glass of water with the medication and remained upright for at least 30 minutes after the medication and before eating or drinking anything. Various scales were followed in order to evaluate patients’ endoscopic condition following treatment. Table 1 lists and explains the scales.
Table 1. Endoscopic scale used to evaluate patients’ conditions following treatment. From: *Am J Gastroenterol*. 2002; 97(1):58-64.

Results obtained from the alendronate and placebo group displayed similar mean gastric erosion scores with the alendronate group exhibiting a mean score of 0.32 and the placebo group illustrating a mean score of 0.35. Figure 2 and 3 respectively display the gastric erosion and duodenal erosion scores of patients in each of the treatment groups.

Figure 2. Distribution of gastric erosion scores at the final endoscopy. From: *Am J Gastroenterol*. 2002; 97(1):58-64.

Figure 3. Distribution of duodenal erosion scores at the final endoscopy. From: *Am J Gastroenterol*. 2002; 97(1):58-64.
Lanza and colleagues\textsuperscript{22} concluded that a weekly dose of 70mg is well tolerated and would increase patient compliance. The lack of gastric or duodenal adverse side effects was attributed to the patients’ adherence to the dosing instructions of alendronate.

**COMMENTS**

The efficacy of each drug was evaluated in terms of its ability to increase BMD, decrease bone turnover markers, reduce fracture risk, and impart minimal side effects on its user. Highly efficacious agents are those that accomplish all 4 of these tasks. Studies conducted by Villareal et al\textsuperscript{7} and Recker et al\textsuperscript{8} noted an increase in lumbar spine and total hip BMD in those patients treated with hormone replacement therapy. Not only do the studies agree on the ability of hormone replacement therapy to increase BMD, but also on the magnitude of HRT’s ability to increase lumbar spine BMD with Villareal et al\textsuperscript{7} documenting a 4.3\% increase and Recker et al\textsuperscript{8} noting a 4.0\% increase. Raloxifene’s ability to increase femoral neck, lumbar spine, trochanter, and total BMD was proven by Ettinger et al\textsuperscript{9} and Prestwood et al.\textsuperscript{10} Bone and colleagues,\textsuperscript{11} Downs et al,\textsuperscript{12} and Greenspan\textsuperscript{13} found alendronate to be an efficacious agent in terms of its ability to increase lumbar spine, trochanter, and femoral neck BMD. Risedronate’s ability to elevate trochanter, hip, lumbar spine, and femoral neck BMD was documented by Delaney et al\textsuperscript{14} and Harris et al.\textsuperscript{15} All of the drugs exhibited similar effects on BMD with no drug displaying substantially higher BMD increases than another. Furthermore, each of the drugs only exhibited a minimal increase in BMD with the greatest increase being 6.0\%.\textsuperscript{11} These minimal increases can be attributed to the focus of antiresorptive drugs on inhibiting osteoclast activity, not stimulating osteoblasts to reform bone.
All studies\textsuperscript{7,10,12,16} noted a decrease in bone turnover markers in patients taking hormone replacement therapy, raloxifene, alendronate, or risedronate. Since all the studies\textsuperscript{7,10,12,16} on bone turnover markers examined the change in urine N-telopeptide, the ability of each drug to decrease the concentration of this marker was used to evaluate the efficacy of each drug. Villareal et al\textsuperscript{7} found a 48% decrease of urine N-telopeptide in patients taking hormone replacement therapy, while Prestwood et al\textsuperscript{10} only documented a 22% decrease of urine N-telopeptide in those patients taking raloxifene. The drastic difference between these percentages suggests that hormone replacement therapy is more effective than raloxifene at reducing bone turnover markers. Alendronate was shown by Downs et al\textsuperscript{12} to decrease urine N-telopeptide by 62%. Similarly, risedronate was found to decrease urine N-telopeptide by 61\%.\textsuperscript{16} Alendronate and risedronate seem to be comparable and better than hormone replacement therapy and raloxifene in their ability to decrease bone turnover markers.

Each drug was shown to decrease the risk of fractures.\textsuperscript{9,15,17-19} However, hormone replacement therapy, alendronate, and risedronate all appear to have a heightened effect on fracture risk when compared to raloxifene. Hormone replacement therapy reduced the risk of vertebral fractures by one third,\textsuperscript{17} while alendronate was shown to decrease vertebral fracture risk by 44\%\textsuperscript{18} and 45\%.\textsuperscript{19} Risedronate decreased fracture risk by 41\%.\textsuperscript{15} Raloxifene was only shown to reduce the risk of vertebral fractures by 14.7\%.\textsuperscript{9} The disparity in these percentages suggests that when used separately, hormone replacement therapy, alendronate, or risedronate demonstrate a greater reduction in fracture risk than raloxifene. In order to more effectively compare these drugs in terms of their ability to
decrease fracture risk, a study involving and comparing all 4 drugs would need to be performed.

The most drastic differences between the drugs were seen in their potential side effects. Hormone replacement therapy was found to increase the risk of breast cancer by 26%\textsuperscript{17}, while raloxifene was shown to impart a RR of 0.3 on its users.\textsuperscript{9} In studies\textsuperscript{9,17} examining the incidence of pulmonary embolism or deep vein thrombophlebitis, it was found that when used separately, both hormone replacement therapy and raloxifene drastically increased the risk for these conditions. The effect of hormone replacement therapy on cardiovascular disease is inconclusive due to the variable results obtained from two studies.\textsuperscript{17,20} While the WHI study\textsuperscript{17} found an elevated risk of 22% for any CHD in those patients taking hormone replacement therapy, Walsh et al\textsuperscript{20} noted a favorable change in serum levels and subsequently a preventative effect of HRT on cardiovascular disease. The cohort size of the WHI study\textsuperscript{17} was 16 608 postmenopausal women, while the Walsh et al study\textsuperscript{20} only included 390 postmenopausal women. The larger cohort size in the WHI study\textsuperscript{17} suggests more accurate results. Furthermore, the WHI study\textsuperscript{17} lasted for 5 years as opposed to the Walsh et al study\textsuperscript{20} which terminated after 6 months. Walsh et al\textsuperscript{20} similarly observed a substantial decrease in the serum levels of patients taking raloxifene.

Alendronate and risedronate, individually, failed to demonstrate any adverse or beneficial side effects. Although one study conducted by Lanza and colleagues\textsuperscript{5} observed gastric ulcers in 13.2% of the group taking 10mg/d alendronate, this study was only conducted for 2 weeks, which may explain the prevalence of these gastric ulcers. Other studies\textsuperscript{15,21,22} have shown that no substantial difference exists between the
prevalence of gastrointestinal adverse effects in the placebo and in either the alendronate or risedronate group. The lack of adverse side effects in patients taking alendronate or risedronate suggests that they may be more tolerable and suitable than hormone replacement therapy and raloxifene for patients suffering from osteoporosis.

In order to prescribe the most suitable medication, practitioners must examine the patient’s medical history. Those patients that demonstrate a predisposition for breast cancer or high blood pressure should abstain from taking hormone replacement therapy or raloxifene and instead try alendronate or risedronate. For those patients who suffer from gastrointestinal problems, hormone replacement therapy or raloxifene may be the best option, although it is possible to take risedronate or alendronate if the patient complies with the strict dosing instructions. In order to ensure that gastrointestinal side effects do not arise in patients taking either alendronate or risedronate, it is imperative that patients take the medication in the morning before eating or drinking anything. Furthermore, patients must drink a full glass of water with the medication and remain upright for at least 30 minutes after the medication and before eating or drinking anything. These strict dosing instructions may affect patient compliance. Due to alendronate’s and risedronate’s mode of action, those patients with renal insufficiencies should not take alendronate or risedronate to treat their osteoporosis. Patients whose kidneys filter CrCl at a rate lower than 35ml/min or CrCl at rate lower than 30mL/min should not take alendronate or risedronate respectively.

Although a patient’s medical history should be the determining factor when deciding which antiresorptive drug to use to treat their osteoporosis, alendronate seems to be the most efficacious agent. When administered on a weekly basis, alendronate has
been proven to be as effective as daily alendronate doses.\textsuperscript{13} Furthermore, Lanza and colleagues\textsuperscript{22} have found once-weekly alendronate to be tolerable. Since alendronate increases BMD, decreases bone turnover markers, reduces fracture risk, imparts limited if any side effects on its users, and is convenient, weekly alendronate seems to be the most efficacious antiresorptive agent for the treatment of osteoporosis.

In order to identify the most efficacious antiresorptive drug, further studies need to be conducted to examine the effect of hormone replacement therapy and raloxifene when taken separately on the risk for cardiovascular disease. Furthermore, studies evaluating the efficacy and tolerability of weekly risedronate samples may provide patients with an alternative to weekly alendronate.
REFERENCES


