

**Hormones and Healthy Bones**  
**Joint Project of**  
**National Osteoporosis Foundation and Association of Reproductive Health Professionals**

**Literature Review (January 2009)**  
**Agonists/Antagonists (SERMs)**

1. Ahlstrom M, Pekkinen M, Riehle U, Lamberg-Allardt C. Extracellular calcium regulates parathyroid hormone-related peptide expression in osteoblasts and osteoblast progenitor cells. *Bone*. 2008;42:483-90.  
Abstract: Parathyroid hormone-related peptide (PTHrP) has been shown to have anabolic effects on bone in women with postmenopausal osteoporosis. On the cellular level PTHrP promotes the recruitment of osteogenic cells and prevents apoptotic death of osteoblasts and osteocytes. The calcium concentration is considerably higher in the vicinity of resorbing osteoclasts than in the plasma. Therefore the osteoblasts are likely to be confronted by elevated extracellular calcium concentrations in the areas of resorptive activity. The present study was designed to assess the possibility that extracellular calcium could regulate PTHrP expression in osteoblastic cells. Adult human mesenchymal stem cells (hMSC) were cultured and differentiated by standard methods. The PTHrP release into the culture media was measured by an immunoradiometric assay and the expression of PTHrP, osteocalcin and Runx2 mRNA was assayed by real-time PCR. Increasing the extracellular calcium from 1 mM to 5 mM for 24 h resulted in a 4-6-fold increase in the PTHrP release. PTHrP mRNA was also increased by elevated calcium levels. The effect of calcium stimulation on PTHrP release could be seen within 60 min of treatment. The extracellular calcium sensing receptor (CaR) agonist neomycin mimicked the effects of calcium and the MEK/MAPK inhibitor PD98059 abolished the effect of calcium and neomycin. High extracellular calcium increased the mineralization of hMSC and the expression of osteocalcin, but this effect was not mimicked by neomycin. Our results show that in hMSC, elevated extracellular calcium levels increases both released PTHrP and PTHrP mRNA expression. The effect of calcium on PTHrP can be mimicked by activation of the CaR and can be diminished by inhibition of the MAPK signalling pathway.
2. Bennett GB, Feldman S, Martin H, Smith BC, Raineri BD. An opportunity for medication risk reduction, healthcare provider collaboration, and improved patient care: a retrospective analysis of osteoporosis management. *J Am Med Dir Assoc*. 2003;4:329-36.  
Abstract: OBJECTIVES: The objectives of this study were to examine the degree to which long-term care providers are compliant with product labeling regarding administration of alendronate in patients with renal insufficiency and presence of, or predisposition to, upper gastrointestinal disorders; and to observe differences, if any, in prescribing patterns between alendronate and calcitonin-salmon nasal spray in skilled nursing facilities. STUDY DESIGN: We studied retrospectively analyzed patient charts, including medication histories and laboratory data. SETTING: Our study comprised 134 skilled nursing facilities from 21 states. PARTICIPANTS: We studied postmenopausal women, age > or =65 years, receiving either alendronate or calcitonin-salmon nasal spray for a minimum of 2 weeks. MEASUREMENTS: Consultant pharmacists reviewed resident charts submitted the following data for each resident: 2-week history of alendronate or calcitonin use, 2-week history of H2 receptor antagonist or proton pump inhibitor use, most recently documented serum creatinine, actual body weight, and date of birth. RESULTS: Of 905 subjects in the analysis, 38.5% (n = 348) did not have documentation of serum

creatinine. Of the 267 alendronate patients for whom creatinine clearance could be calculated, more than half had renal insufficiencies of creatinine clearance  $<35$  mL/min/1.73 m<sup>2</sup> (51.3%, n = 137). In addition, despite widespread information regarding caution in using alendronate in patients with upper gastrointestinal disorders, we found that 33.9% (n = 151) of all alendronate patients were concurrently receiving either H<sub>2</sub> receptor antagonists or proton pump inhibitors. Although similar results were observed in the residents taking calcitonin, that agent has no precautions regarding its use in the renally impaired or in patients with gastrointestinal disorders. CONCLUSION: Data from this study indicate that long-term care clinicians might not be adequately differentiating patient profiles and safety criteria when initiating residents on osteoporosis pharmacotherapy, as evidenced by similar prescribing trends in both the alendronate and calcitonin groups. Given its package insert's statements regarding use of alendronate in the renally compromised, results from the alendronate group were particularly problematic as a result of the large number of residents with either insufficient renal function or undocumented serum creatinine. These data demonstrate that osteoporosis could be a disease state that should be more closely analyzed through drug utilization reviews and represent yet another opportunity for improved collaboration between medical directors and consultant pharmacists.

3. Biskobing DM. Update on bazedoxifene: a novel selective estrogen receptor modulator. *Clin Interv Aging*. 2007;2:299-303.

Abstract: In the elderly population, osteoporosis is a significant clinical problem leading to disability and even death. Many patients remain untreated, despite effective therapies, because of patients' unwillingness to take current therapies or inability to tolerate the therapies. For this reason, ongoing research continues to search for more effective and tolerable osteoporosis agents. Bazedoxifene is a selective estrogen receptor modulator (SERM) currently in development for osteoporosis prevention and treatment. A new drug application (NDA) for postmenopausal osteoporosis prevention was recently submitted to the FDA. Preclinical and clinical studies with bazedoxifene demonstrate more tissue selectivity than other SERMs. In particular, bazedoxifene has minimal if any agonist activity in the uterus and is able to antagonize effects of estrogen on the uterus. Animal studies and early clinical studies suggest effects in the bone similar to other SERMs with prevention of postmenopausal bone loss. Until more data on efficacy and safety are published, however, its role in osteoporosis is unknown.

4. Branca F, Lorenzetti S. Health effects of phytoestrogens. *Forum Nutr*. 2005:100-11. Abstract: Phytoestrogens are naturally occurring plant-derived phytochemicals, whose common biological roles are to protect plants from stress or to act as part of a plant's defense mechanism. Although composed of a wide group of nonsteroidal compounds of diverse structure, phytoestrogens have been shown to bind estrogen receptors and to behave as weak agonist/antagonist in both animals and humans. Phytoestrogens include mainly isoflavones (IF), coumestans, and lignans. These compounds are known to be present in fruits, vegetables, and whole grains commonly consumed by humans. IF are found in legumes--mainly soybeans--whereas flaxseed is a major source of lignans, and coumestans are significantly present in clover, alfalfa and soybean sprouts. 8-Prenyl flavonoids are common in vegetables. Bioavailability of IF requires an initial hydrolysis of the sugar moiety by intestinal beta-glucosidases to allow the following uptake by enterocytes and the flow through the peripheral circulation. Following absorption, IF are then reconstituted mainly to glucuronic acid and to a lesser degree to sulphuric acid. Gut metabolism seems

key to the determination of the potency of action. Several epidemiological studies correlated high dose consumptions of soy IF with multiple beneficial effects on breast and prostate cancers, menopausal symptoms, osteoporosis, atherosclerosis and stroke, and neurodegeneration. For the relief of menopausal symptoms a consumption of 60 mg aglycones/day has been suggested; for cancer prevention a consumption between 50 and 110 mg aglycones/day is considered beneficial to reduce risks of breast, colon and prostate cancer; to decrease cardiovascular risk a minimum intake of 40-60 mg aglycones/day, together with about 25 g of soy protein has been suggested. For improvement in bone mineral density, 60-100 mg aglycones/day for a period of at least 6-12 months could be beneficial.

5. Cranney A, Adachi JD. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. *Drug Saf.* 2005;28:721-30.  
Abstract: Raloxifene, a nonsteroidal benzothiophene, is a second-generation selective estrogen receptor modulator (SERM) that is an antiresorptive agent. Raloxifene is a non-hormonal agent that binds to the estrogen receptor and results in estrogen agonist effects on bone and the cardiovascular system and estrogen antagonist effects on endometrial and breast tissue. Raloxifene has diverse pharmacodynamic properties due to its differential interactions with the estrogen receptor and tissue selectivity. Raloxifene was the first SERM to be approved for the prevention and treatment of postmenopausal osteoporosis. In this review, we conducted a systematic search of the literature for trials that evaluated the following outcomes: bone density, fractures, quality of life, cardiovascular outcomes, safety and adverse events. Raloxifene at the approved dosage of 60 mg/day increased lumbar spine bone density by 2.5% relative to control after 2 years of therapy. A large fracture prevention trial confirmed that treatment with raloxifene 60 mg/day for 3 years decreased the relative risk of incident vertebral fractures by 30-50% in women with prevalent fractures or osteoporosis. Extraskelatal effects of raloxifene include a reduction in total cholesterol and low density lipoprotein cholesterol levels. Assessment of the safety profile revealed that raloxifene was not associated with endometrial hyperplasia and that there was a 72% reduction in the incidence of invasive breast cancer in raloxifene-treated postmenopausal women with osteoporosis. Adverse events associated with raloxifene included an increase in the absolute risk of venous thromboembolism and an increase in the risk of hot flashes and leg cramps. In comparison to other osteoporosis therapies, raloxifene has a lesser impact on bone mineral density, a similar effect on the occurrence of vertebral fractures, but no effect on the frequency of non-vertebral fractures. Raloxifene can be recommended for the prevention of vertebral fractures in women with osteopenia/osteoporosis who are not at high risk of non-vertebral fractures and who do not have a past history of venous thromboembolism.
6. Ferrari P. Cortisol and the renal handling of electrolytes: role in glucocorticoid-induced hypertension and bone disease. *Best Pract Res Clin Endocrinol Metab.* 2003;17:575-89.  
Abstract: Hypertension and osteoporosis are characteristic clinical features in patients with Cushing's syndrome or in those on glucocorticoid (GC) treatment. These two distinct complications of GC excess share one common denominator: an abnormal handling of cations, sodium (Na(+)) and calcium (Ca(2+)), either primarily or in part by the kidney tubule. The principal mechanism of GC-induced hypertension is overstimulation of the non-selective mineralocorticoid receptor (MR), resulting in renal Na(+) retention, volume expansion and finally to an increase in blood pressure. In mineralocorticoid target organs, such as the kidney, the MR is protected from GC occupation by the enzyme 11beta-

hydroxysteroid dehydrogenase type 2 (11 $\beta$ HSD2), a gate-keeping enzyme, which converts cortisol to receptor-inactive cortisone. This enzyme allows aldosterone to be the physiological agonist of the MR despite significantly higher circulating levels of cortisol. Kinetic properties of 11 $\beta$ HSD2 suggest that saturability of this enzyme can already be achieved at high-normal physiological plasma cortisol levels, thereby leading to overstimulation of the MR by cortisol in states of GC excess. The mechanisms of GC action on bone turnover are more complex. GCs increase bone resorption, inhibit bone formation and have an indirect action on bone by decreasing intestinal Ca(2+) absorption, but also inducing a sustained renal Ca(2+) excretion. The latter appears to be mediated through stimulation of the MR by GC. The prevention and treatment of GC-induced hypertension and osteoporosis include the use of the minimal effective dose of GC, some general measures, and the use of some specific drugs. Modulation of renal Na(+) and Ca(2+) excretion with some, but not all, diuretics represents an important specific (for hypertension) or supportive (for bone disease) therapeutic intervention.

7. Fontanges E, Fontana A, Delmas P. Osteoporosis and breast cancer. *Joint Bone Spine*. 2004;71:102-10.

Abstract: Osteoporosis affects one in three women after the menopause and the incidence of osteoporotic fractures increases steadily throughout life. Breast cancer is the most common cancer in women, both before and after the menopause. In younger women, recovery from breast cancer has been achieved using aggressive chemotherapy and radiotherapy that can adversely affect bone tissue or induce premature menopause. In postmenopausal women, breast cancer and osteoporosis are common, and although both are dependent on estrogens this leads to conflicting implications for the diagnosis and treatment: estrogens reduce the risk of fractures but increase the risk of breast cancer. Estrogen supplementation is, therefore, contraindicated in patients with a history of breast cancer. Selective estrogen response modifiers (SERMs) hold great promise, as they decrease both the fracture risk via an estrogen-agonist effect on bone and the breast cancer risk via an estrogen-antagonist effect on the breast tissue. SERMs can be used after successful treatment for breast cancer. Bisphosphonates, which are potent bone resorption inhibitors, are widely used both in cancer patients and in the prevention and treatment of spinal and peripheral osteoporotic fractures. Contraindications are exceedingly rare, and the satisfactory safety profile of these agents can be expected to improve further with newly developed modes of administration. Whether the bisphosphonates currently used to treat osteoporosis (alendronate and risendronate) have beneficial effects on skeletal events related to cancer progression remains to be determined, however. In sum, selection of the optimal treatment for osteoporosis in a patient with breast cancer involves assessment of the risk/benefit ratio of each treatment option, based on patient age, other risk factors for osteoporosis, and the stage of breast cancer progression.

8. Gallagher JC. Advances in bone biology and new treatments for bone loss. *Maturitas*. 2008;60:65-9.

Abstract: Recent advances in bone biology have led to a more detailed understanding of bone remodeling which is a process that leads to resorption of old bone and replacement by formation of new bone. The most important discoveries in this process of bone remodeling were those of the RANK Ligand/RANK/OPG system which is now recognized the dominant pathway regulating bone resorption. RANK Ligand (RANKL) is a cytokine belonging to the tumor necrosis factor family and is expressed by osteoblasts; it binds to membrane bound receptor RANK on osteoclasts and promotes differentiation of marrow

cells through various stages to multinucleated osteoclasts which resorb bone. Several hormones such as parathyroid hormone, calcitriol and prostaglandins stimulate RANK Ligand expression by osteoblasts. Osteoblasts also secrete osteoprotegerin (OPG) which is a soluble receptor that is a potent antagonist of osteoclast formation by binding and inactivating RANKL and OPG is therefore an important regulator of bone resorption. OPG is stimulated by estrogen. OPG has been genetically engineered and in human subjects is a potent inhibitor of bone resorption. Another method for preventing bone resorption is to develop antibodies against RANKL and this has been shown to be a successful strategy. A single subcutaneous injection of this antibody (Denosumab) every 6 months proved to be a potent inhibitor of bone resorption and clinical fracture trials using this agent are now underway. These are novel developments that have risen from basic research in bone biology and other discoveries in the bone remodeling process can be expected to lead to further treatment options for various bone diseases.

9. Haskell SG. Selective estrogen receptor modulators. *South Med J.* 2003;96:469-76.  
Abstract: Because of recent concerns about the long-term risks of estrogen replacement therapy in postmenopausal women, there is growing interest in a group of compounds known as selective estrogen receptor modulators (SERMs). The SERMs bind to estrogen receptors and have tissue-specific effects that allow them to function as estrogen agonists in some tissues and estrogen antagonists in other tissues. There are four SERMs currently marketed in the United States. These include the triphenylethylenes--clomiphene citrate (Clomid), tamoxifen, and toremifene--and the benzothiophene, raloxifene. Clomid is used primarily in the treatment of infertility. Tamoxifen is indicated for the treatment and prevention of breast cancer. It has an estrogen antagonist effect on breast tissue, but an estrogen-like effect on lipids, bone, and the endometrium. Toremifene has an antagonist/agonist profile similar to that of tamoxifen. Raloxifene is approved for the prevention of osteoporosis in postmenopausal women. It is thought to be an estrogen antagonist on the uterus and breast tissues and an estrogen agonist with respect to bone and serum lipids.
10. Lewiecki EM. Bazedoxifene and bazedoxifene combined with conjugated estrogens for the management of postmenopausal osteoporosis. *Expert Opin Investig Drugs.* 2007;16:1663-72.  
Abstract: Bazedoxifene acetate (WAY-140424; TSE-424) is an investigational non-steroidal indole-based selective estrogen receptor modulator (SERM) - also classified as an estrogen agonist/antagonist - that is being developed as a daily oral drug for the prevention and treatment of postmenopausal osteoporosis (PMO). Clinical studies have shown favorable effects on the skeleton, with prevention of bone loss in postmenopausal women without osteoporosis and reduction in vertebral fracture risk in women with PMO, without stimulation of endometrium or breast. Bazedoxifene combined with conjugated estrogens is an investigational tissue-selective estrogen complex, the first in a new class of therapeutic agents that pairs a selective estrogen receptor modulator with estrogens. Clinical trials with bazedoxifene/conjugated estrogens in postmenopausal women have shown skeletal benefit with improvement in menopausal vasomotor symptoms and little or no stimulation of endometrial or breast tissue. Bazedoxifene/conjugated estrogens is a potential agent for the prevention of PMO and control of menopausal symptoms.

11. Mackey JR, Joy AA. Skeletal health in postmenopausal survivors of early breast cancer. *Int J Cancer*. 2005;114:1010-5.

Abstract: Estrogen plays an important role in the skeletal health of all women. Many therapies used in the treatment of breast cancer reduce estrogen levels and have the potential to affect bone negatively by increasing the risk of osteoporosis and associated bone fractures. The long-term effects of systemic endocrine therapy on bone, therefore, are an important consideration in the adjuvant setting. Tamoxifen has been shown to have a moderate protective effect on postmenopausal bone due to its partial estrogen agonist activity; however, its long-term use is potentially associated with negative side effects, such as an increased risk of thromboembolic disease and endometrial cancer. Newer agents, the third-generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, for example, do not possess estrogen agonist effects and have improved breast cancer outcomes when compared to the standard 5 years of tamoxifen. However, patients treated with adjuvant AIs have been shown to have an increased incidence of osteoporosis and osteoporotic fractures. In order to select the optimal adjuvant therapy for each patient, it is important to assess the overall risk:benefit ratio for each endocrine strategy. All postmenopausal women should follow published guidelines to assess the risk of osteoporosis and, where appropriate, they should receive bone mineral density monitoring. Postmenopausal women with breast cancer who are at increased risk of osteoporotic fracture should be identified and managed with appropriate nonpharmacologic and pharmacologic measures.

12. Malluche HH, Koszewski N, Monier-Faugere MC, Williams JP, Mawad H. Influence of the parathyroid glands on bone metabolism. *Eur J Clin Invest*. 2006;36 Suppl 2:23-33.  
Abstract: Bone is a classic target tissue for parathyroid hormone (PTH), whose calcitropic effect is mediated largely via catabolic actions on this tissue. Paradoxically, PTH also exerts anabolic actions, with intermittent injections of PTH or its amino-terminal fragments causing an increase in bone formation and bone mass, actions that form the basis for the use of PTH in the treatment of osteoporosis. Besides vitamin D, PTH is the only other known bone anabolic agent. High-affinity PTH receptors (PTH-1R) have been detected on osteoblasts and osteoclasts (albeit in lower numbers). Bone turnover, which includes activation of osteoclasts and osteoblasts, appears to be best reflected not by absolute concentrations of PTH (which can vary based on the assay and antibody used) but by a balance of circulating full-length PTH-(1-84) and amino-terminally truncated C-PTH fragments. When PTH-(1-84) is predominant, bone turnover is promoted. Among PTH fragments, PTH-(7-84) appears to be the most potent antagonist of PTH-(1-84). The mechanisms involved in these effects are unclear although mediation via unique C-terminal receptors has been suggested. We propose that, within the range of total PTH (100-1000 pg mL<sup>-1</sup>), the ratio of PTH-(1-84)/C-PTH fragment is a valuable tool for diagnosis of bone turnover. Data indicate that at PTH levels < 100-150 pg mL<sup>-1</sup> and > 1000 pg mL<sup>-1</sup>, the ratio loses its predictive power. Assay type, patient characteristics (race, underlying renal disease) and treatment attributes (vitamin D, corticosteroids, phosphate binders) have an impact on the PTH ratio, and care should be used in interpreting assay results and making subsequent treatment decisions.

13. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol.* 2007;25:1038-42.  
Abstract: PURPOSE: Gonadotropin-releasing hormone (GnRH) agonists decrease bone mineral density (BMD) and increase fracture risk in men with prostate cancer. Annual zoledronic acid increases BMD in postmenopausal women, but its efficacy in hypogonadal men is not known. PATIENTS AND METHODS: In a 12-month study, 40 men with nonmetastatic prostate cancer who were receiving a GnRH agonist and had T scores more than -2.5 were randomly assigned to zoledronic acid (4 mg intravenously on day 1 only) or placebo. BMD of the posteroanterior lumbar spine and proximal femur were measured by dual-energy x-ray absorptiometry. RESULTS: Mean (+/- SE) BMD of the posteroanterior lumbar spine decreased by 3.1% +/- 1.0% in men assigned to placebo and increased by 4.0% +/- 1.0% in men assigned to zoledronic acid (P < .001). BMD of the total hip decreased by 1.9% +/- 0.7% in men assigned to placebo and increased by 0.7% +/- 0.5% in men assigned to zoledronic acid (P = .004). Similar between-group differences were observed for the femoral neck and trochanter. Serum N-telopeptide, a marker of osteoclast activity, decreased significantly after zoledronic acid treatment. CONCLUSION: In men receiving a GnRH agonist, a single treatment with zoledronic acid significantly increased BMD and durably suppressed serum N-telopeptide levels for 12 months. Annual zoledronic acid may be a convenient and effective strategy to prevent bone loss in hypogonadal men.
14. Pasaoglu G, Gok H, Mungan D, Sonel B, Yalcin P, Misirligil Z. Does the combination of inhaled steroids with long acting beta2 agonists decrease the risk for osteoporosis? A 1-year prospective follow-up study. *Rheumatol Int.* 2006;27:141-6.  
Abstract: Combination of inhaled corticosteroids (ICS) with long acting beta2 agonists has been used increasingly in the treatment of moderate-severe asthma, however there is indefinite data about their effect on bone loss. The aim of this study was to compare the effects of treatment with single ICS and combination of ICS with long acting beta2 agonists (combination therapy) on BMD and biomarkers of bone metabolism in adult patients with asthma over 1 year period. Forty-three patients with asthma were enrolled. Patients were separated into two groups according to their use of asthma drugs: single ICS or combination therapy (ICS plus long-acting inhaled beta2-agonist). Change in bone mineral density (BMD) and biochemical markers of bone metabolism were measured at baseline and at the end of 1 year. Mean ages and basal BMD of patients did not differ between the two groups (P > 0.05). The decrease in BMD was higher in the single ICS group than the combination therapy group, however there was no significant difference between them (P > 0.05). One year change (%) in BMD and biochemical markers of bone metabolism were not different between two groups (P > 0.05). In conclusion, use of ICS-in the range of doses used- does not seem to have an effect on the change of BMD. However, our data indicate a nonsignificant trend towards reducing bone loss with the use of combination therapy. Future studies are needed to provide definitive evidence for this trend to allow us suggesting combination therapy for minimizing bone loss.
15. Stump AL, Kelley KW, Wensel TM. Bazedoxifene: a third-generation selective estrogen receptor modulator for treatment of postmenopausal osteoporosis. *Ann Pharmacother.* 2007;41:833-9.  
Abstract: OBJECTIVE: To review clinical studies and other available literature regarding the development, pharmacology, toxicology, pharmacokinetics/pharmacodynamics, adverse effects, and place in therapy of bazedoxifene, a selective estrogen receptor

modulator (SERM), currently in Phase III clinical trials for the treatment and prevention of postmenopausal osteoporosis. DATA SOURCES: A literature search was performed of PubMed (1966-February 2007), International Pharmaceutical Abstracts (1970-February 2007), Web of Science (1975-February 2007), Biological Abstracts (1926-2007), and Google Scholar (2001-February 2007) databases, using the search terms bazedoxifene, TSE-424, Indole-33, WAY-140424, selective estrogen receptor modulator, and SERM. In addition, product information was requested from the manufacturer, and www.clinicaltrials.gov was searched for unpublished Phase III clinical trials in progress. STUDY SELECTION AND DATA EXTRACTION: Articles on Phase I and II trials were selected for review, as well as articles discussing preclinical development of bazedoxifene. At the time of writing, no articles on Phase III trials were available for review. Abstracts of unpublished data were reviewed, as was information provided by the manufacturer. DATA SYNTHESIS: Bazedoxifene is a third-generation SERM currently in Phase III clinical trials. It has been found to act as an agonist on skeletal tissue, with bone turnover reduced by 20-25% with doses of 20 or 40 mg daily. In addition, bazedoxifene has been found to be an antagonist on breast tissue and uterine tissue, demonstrating inhibition of breast tissue proliferation and decreased endometrial stimulation as the dose is increased. CONCLUSIONS: Current literature suggests that bazedoxifene will likely be safe and effective when used in the treatment of postmenopausal osteoporosis. Completion of Phase III clinical trials will more fully elucidate the safety and efficacy profile of bazedoxifene, as well as more clearly define its place in therapy.

16. Viereck V, Grundker C, Friess SC, et al. Isopropanolic extract of black cohosh stimulates osteoprotegerin production by human osteoblasts. *J Bone Miner Res.* 2005;20:2036-43. Abstract: An isopropanolic extract (iCR) from the rhizomes of *Cimicifuga racemosa* (black cohosh) is used as an alternative in the treatment of menopausal symptoms, and animal studies suggest positive skeletal effects. iCR stimulated osteoblastic OPG protein secretion by 3- to 5-fold as early as 12 h without affecting RANKL expression. The iCR effect, abrogated by the pure estrogen receptor antagonist ICI 182,780, also enhanced ALP activity (4-fold) and osteocalcin expression (3-fold), possibly contributing to the skeletal effects of black cohosh. INTRODUCTION: Despite its positive effects on the skeleton, estrogen replacement therapy is no longer recommended as first-line therapy for the prevention and treatment of postmenopausal osteoporosis because it increases cardiovascular, thromboembolic, and breast cancer risk. Recently, herbal therapeutics such as an isopropanolic extract (iCR) from the rhizomes of *Cimicifuga (=Actaea) racemosa* (black cohosh) are gaining interest as an alternative in the treatment of menopausal symptoms. Whereas animal studies in rats suggest positive skeletal effects, the mechanism of its actions on bone cells remain unclear. RANKL is essential for osteoclast formation and activation, while osteoprotegerin (OPG) neutralizes RANKL. MATERIALS AND METHODS: In this study, we assessed the effects of iCR on OPG and RANKL mRNA steady-state levels by semiquantitative RT-PCR and on protein production by an ELISA system in human osteoblasts (hOBs). RESULTS: Under serum-free conditions, treatment with iCR increased OPG mRNA levels and protein secretion of hOBs by 2- to 3-fold in a dose-dependent manner, with a maximum effect at a 10(6)-fold dilution of iCR ( $p < 0.001$ ) after 24-48 h. Time-course experiments indicated a stimulatory effect of iCR on osteoblastic OPG protein secretion by 3- to 5-fold ( $p < 0.001$ ) as early as 12 h, whereas RANKL expression was very low and was not found to be modulated by iCR. Of note, the stimulatory effect of iCR on OPG production was abrogated by the pure estrogen receptor antagonist ICI 182,780. Moreover, iCR enhanced two osteoblastic differentiation markers,

bone-specific alkaline phosphatase activity and osteocalcin expression, by up to 4- and 3-fold, respectively ( $p < 0.001$ ). CONCLUSIONS: Our data suggest that iCR enhances differentiation and increases the OPG-to-RANKL ratio of normal human osteoblasts. These effects may contribute to the positive skeletal effects of black cohosh.

17. Yirmiya R, Goshen I, Bajayo A, et al. Depression induces bone loss through stimulation of the sympathetic nervous system. *Proc Natl Acad Sci U S A*. 2006;103:16876-81.  
Abstract: Major depression is associated with low bone mass and increased incidence of osteoporotic fractures. However, causality between depression and bone loss has not been established. Here, we show that mice subjected to chronic mild stress (CMS), an established model of depression in rodents, display behavioral depression accompanied by impaired bone mass and structure, as portrayed by decreases in trabecular bone volume density, trabecular number, and trabecular connectivity density assessed in the distal femoral metaphysis and L3 vertebral body. Bone remodeling analysis revealed that the CMS-induced skeletal deficiency is accompanied by restrained bone formation resulting from reduced osteoblast number. Antidepressant therapy, which prevents the behavioral responses to CMS, completely inhibits the decrease in bone formation and markedly attenuates the CMS-induced bone loss. The depression-triggered bone loss is associated with a substantial increase in bone norepinephrine levels and can be blocked by the beta-adrenergic antagonist propranolol, suggesting that the sympathetic nervous system mediates the skeletal effects of stress-induced depression. These results define a linkage among depression, excessive adrenergic activity, and reduced bone formation, thus demonstrating an interaction among behavioral responses, the brain, and the skeleton, which leads to impaired bone structure. Together with the common occurrence of depression and bone loss in the aging population, the present data implicate depression as a potential major risk factor for osteoporosis and the associated increase in fracture incidence.