CHALLENGES IN THE DIAGNOSIS AND MANAGEMENT OF OSTEOPOROSIS: THE ROLE OF THE MANAGED CARE PHARMACIST

An interview with Andrea S. Franks, PharmD, BCPS

An associate professor in the department of clinical pharmacy at the University of Tennessee, College of Pharmacy, Andrea S. Franks, PharmD, BCPS, also serves as Director of Education for the Knoxville Campus and as Associate Professor in the Department of Family Medicine at the University of Tennessee, Graduate School of Medicine. Dr Franks practices with University Family Physicians in inpatient and outpatient family medicine at the University of Tennessee Medical Center in Knoxville. Her academic lectures for pharmacy students are focused on women’s health (ie, osteoporosis, menopause, and incontinence), and she has received several teaching awards. Dr Franks’ practice and research interests include primary care, women’s health, tobacco cessation, and interdisciplinary practice and education. She is also a board-certified pharmacotherapy specialist and serves as a reviewer for several pharmacy and family medicine journals. In her previous position, Dr Franks worked alongside a geriatrician as part of a collaborative practice in a senior health clinic, managing and preventing osteoporosis.

A senior clinical editor for University of Tennessee Advanced Studies in Pharmacy (UTASiP) interviewed Dr Franks to provide readers with additional insight into the role of managed care pharmacists in current prevention and awareness efforts for patients with osteoporosis. A discussion of the major breakthroughs and challenges in the diagnosis and management of osteoporosis, therapeutic safety concerns, and emerging therapies is also included.

UTASiP: Despite the availability of preventive therapeutic agents, the incidence of osteoporosis and its associated costs continue to rise globally. Osteoporosis-related fractures cause over 432,000 hospital admissions and approximately 180,000 nursing home admissions annually in the United States. The cost to the healthcare system associated with osteoporosis-related fractures was estimated at $17 billion in 2005, with hip fractures accounting for 72% of fracture costs. What are some of the ways that pharmacists can help improve current prevention efforts aimed at identifying and treating patients with osteopenia and osteoporosis?

Dr Franks: Pharmacists in community-based and/or managed care settings can conduct osteoporosis screenings and educational programs. Pharmacists can evaluate patients’ medication profiles for drugs that may increase the risk of falls or cause bone loss (eg, heparin and corticosteroids); they can recommend calcium and vitamin D supplements for those who are taking medications for osteoporosis; and they can provide support and individual education regarding dosage and administration (especially for bisphosphonates and calcitonin). And very importantly, pharmacists can encourage adherence and persistence with these long-term medications.

Osteoporosis is a great subject for community service programs and presentations, particularly for groups of women and seniors. Osteoporosis is a disease state that has relevance for women of all ages because prevention really begins in childhood and adolescence, when good nutrition habits are estab-
lished. Presentations can focus on adequate calcium and vitamin D intake for the different stages of life, the importance of weight-bearing exercise throughout life, and fall risk reduction strategies for seniors. It is also a good opportunity to encourage attendees to ask their healthcare providers if they are candidates for bone mineral density (BMD) testing, and to educate the public about the risks of osteoporosis and the availability of medications to prevent and treat bone loss.

**UTASIP: The World Health Organization (WHO) has recently released an algorithm on absolute fracture risk called FRAX. Also referred to as a 10-year fracture risk model and 10-year fracture probability, this algorithm uses femoral neck (or total hip) BMD and other specific risk factors to estimate the likelihood of a person breaking a bone due to low bone mass or osteoporosis over a period of 10 years. Can you comment on the potential impact of this algorithm on the management of osteoporosis?**

*Dr Franks:* The US-adapted WHO algorithm provides a quick and easy assessment of fracture risk, based on key clinical factors, with or without BMD measurements. This diagnostic tool allows clinicians to identify and appropriately treat patients with low bone mass who do not necessarily meet the WHO criteria for osteoporosis (based on BMD alone), but who are at an increased fracture risk. These at-risk patients may be identified earlier, when interventions are most likely to prevent fractures. The impact of treatment is somewhat limited in advanced disease, when patients may have already experienced a fracture.

**UTASIP: In your opinion, what are some of the major breakthroughs that have occurred in the diagnosis and management of osteoporosis in recent years?**

*Dr Franks:* I believe that the development and marketing of antiresorptive agents, particularly oral bisphosphonates, in the mid 1990s was a breakthrough. These agents were accompanied by well-designed, controlled clinical trials that demonstrated fracture risk reduction at the hip, spine, and other non-vertebral sites. During this time, there was also an increase in diagnosis and treatment of osteoporosis, due to heightened awareness made possible by various public health campaigns (eg, Healthy People), the Surgeon General’s Report, the lay press, and perhaps aggressive pharmaceutical industry promotion. But despite this increase in awareness, osteoporosis remains undertreated. Screening and diagnostic advancements, particularly the availability of BMD testing, were also important milestones.

The more recent discovery and greater understanding of the receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway may lead to significant advances in osteoporosis prevention and/or treatment. Because this pathway regulates the balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation, it may allow us to target, more specifically, the underlying cause of bone loss. Although this pathway certainly offers potential new therapeutic targets (based on current research), we await further studies in order to formulate any definitive conclusions.

**UTASIP: What are some of the major challenges pertaining to current management of osteoporosis?**

*Dr Franks:* The major obstacles, in my opinion, include the need for long-term therapeutic adherence and persistence; safety, efficacy, and expense of current treatments; the aging population; and the challenges of prevention. The latter is greatly affected by lifestyle issues, such as poor nutrition and sedentary lifestyles, which begin in childhood and adolescence. The fact that this is a silent disease, where symptoms are not present, has significant implications for patient adherence and persistence with therapy.

**UTASIP: In recent years, safety concerns have risen over the association between long-term use of bisphosphonates and possible oversuppression of bone turnover, which may render bones brittle and more prone to spontaneous fractures. There have also been reports of osteonecrosis of the jaw following bisphosphonate treatment in oncology patients. Do you feel that these concerns are substantiated?**

*Dr Franks:* The concerns raised regarding potential oversuppression of bone turnover with bisphosphonates are largely based on animal models and on an earlier, small study of patients who sustained spontaneous non-spinal fractures while being treated with alendronate. Researchers did note that co-administration of estrogen and glucocorticoids appear to be a predisposing factor for this complication and called for

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larger studies to distinguish whether this fracture tendency was a direct result of bisphosphonate therapy or pre-existing bone disease. Thus far, biopsy studies examining the effects of bisphosphonates on bone histology (eg, mineralizing surface or microcracks) have not found any significant abnormalities or differences in suppression of bone remodeling in treated versus untreated patients. This potential complication may remain a theoretical concern, but there are certainly not enough data at this time to implicate one agent or class of agents.

Osteonecrosis of the jaw is rarely seen in patients being treated for osteoporosis (estimated between 1 in 10 000 and 1 in 100 000 patient-treatment years), and most often occurs in patients with cancer who are on very high doses of intravenous bisphosphonate (estimated between 1–10 per 100 patients). A typical post-menopausal patient with osteoporosis taking an oral bisphosphonate has a low risk of developing osteonecrosis. However, because bisphosphonates are incorporated into the bone and have very long half-lives, there are some related precautions that the medical and dental community should take. For example, dentists should use the least invasive procedure possible in patients receiving bisphosphonates, and patients should ideally take care of invasive dental work before initiating bisphosphonate therapy.

UTASp: The RANKL has been identified as an essential cytokine for the formation and activation of osteoclasts. The effects of RANKL are physiologically counterbalanced by the receptor OPG. Estrogen deficiency, glucocorticoid exposure, T-cell activation (eg, rheumatoid arthritis), and skeletal malignancies (eg, myeloma and metastases) enhance the ratio of RANKL to OPG and, thus, promote osteoclastogenesis and induce bone loss. RANKL blockade has been shown to prevent bone loss caused by osteoporosis and other disease states and may emerge as a therapy. Can you comment on this new avenue of research and its potential contribution to the management of osteoporosis?

Dr Franks: Although this is a relatively new development in osteoporosis treatment, it appears promising as a new mechanism of decreasing bone resorption via inhibition of formation and differentiation of osteoclasts. Preliminary data with a human monoclonal antibody to RANKL are promising, but more data are needed to define its role. Although improvements in markers of bone turnover and BMD are useful surrogate markers, the important clinical end point of fracture must be evaluated before an agent can be considered efficacious and cost effective.

UTASp: Taking into consideration the various advantages and disadvantages of current treatments for osteoporosis, what characteristics would you consider to be ideal in a new agent for osteoporosis?

Dr Franks: I consider important therapeutic qualities to include ease of administration, lack of adverse effects, cost effectiveness, and availability of long-term safety and efficacy data (outcomes as opposed to surrogate markers). An ideal treatment should also have a positive effect on bone preservation, even bone strengthening, without sacrificing the quality or microarchitecture of bone.

UTASp: With the exception of one approved anabolic agent (teriparatide) that stimulates bone formation, all other currently marketed therapies are considered antiresorptive. With such an imbalance in the number of available antiresorptive versus anabolic agents, do you feel that increasing bone formation is a viable therapeutic target?

Dr Franks: Clinical trials with parathyroid hormone (PTH) have provided evidence that anabolic agents targeting osteoblasts can increase BMD and reduce fracture risk. I believe that this research will ultimately lead to new agents targeting PTH or other anabolic pathways. However, at this time, teriparatide has limited clinical utility due to potentially serious adverse effects, and it is only recommended for short-term therapy in high-risk patients.

UTASp: There has been so much controversy regarding the use of hormone replacement therapy (HRT) for osteoporosis. For many years estrogen, alone or in combination with progesterone, played a pivotal role in the prevention of osteoporosis by increasing BMD and reducing the risk of fractures. Ironically, the study that ultimately confirmed estrogen's ability to reduce the risk of vertebral and hip fractures was the Women's Health Initiative (WHI) trial, which tied HRT with breast cancer and other ill effects, forever changing its role in the management of osteoporosis. Can you comment on how this research has impacted the management of postmenopausal osteoporosis?
Dr Franks: Prior to publication of the WHI results, HRT was widely used for prevention and treatment of postmenopausal osteoporosis. Following publication of the WHI trial and the accompanying media coverage, overall use of HRT fell significantly, but interestingly, use of HRT for osteoporosis decreased only slightly. During this time, prescriptions for medications to treat and prevent osteoporosis were increasing, and with the newly identified negative outcomes related to long-term use of HRT, many of these prescriptions were being written for bisphosphonates, which affirmed their role as first-line therapy for osteoporosis.

UTASp: Raloxifene, an estrogen agonist/antagonist that exhibits selective effects on estrogen receptors throughout the body, appears to exhibit several advantages over HRT in the prevention of postmenopausal osteoporosis. Because the agent has antagonist effects on the endometrium and breast, it does not appear to increase the risk of endometrial or breast cancer. Has there been an increase in use of raloxifene since the WHI trial?

Dr Franks: Medications for osteoporosis had a period of consistent growth from the mid 1990s through 2004. Prescribing of raloxifene did continue its steady increase during the time period following publication of the WHI trial, but it did not appear to be enhanced by that study. Raloxifene only has data demonstrating a reduction in vertebral (but not hip) fractures. Also, raloxifene increases the risk of deep vein thrombosis and/or pulmonary embolism to the same degree as HRT (2–3 times increased risk).

UTASp: Several conditions (eg, diabetes, malignancy, and chronic obstructive pulmonary disease), in addition to medications (eg, glucocorticoids, anticonvulsants, cyclosporine, proton pump inhibitors, selective serotonin reuptake inhibitors, and heparin), are associated with secondary osteoporosis, placing many different types of patients at risk for fractures. Loss of BMD is an increasingly common problem for women with breast cancer, especially because more women are becoming breast cancer survivors. And recently, a high incidence of osteoporosis has been observed in HIV-infected individuals with certain risk factors (eg, use of protease inhibitors and longer duration of HIV infection). What can be done to improve detection of these at-risk individuals and how can pharmacists help?

Dr Franks: The new National Osteoporosis Foundation clinician guide has augmented emphasis on other patients (besides postmenopausal females) who are at risk for osteoporosis. Patients with these diseases are fairly easy to identify because they are generally prescribed certain “trigger” medications. Thus pharmacists in any setting can target these high-risk patients for educational interventions or work with other clinicians to assure safe and appropriate use of medications, calcium, and vitamin D, as well as lifestyle modifications to prevent and treat osteoporosis. If patients are prescribed long-term treatment with any of the medications that can cause bone loss, pharmacists should work with other clinicians to identify an alternative medication, use the shortest course of therapy, and/or initiate preventive agents (eg, bisphosphonates, calcium, and vitamin D), if appropriate.