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# Are we taking full advantage of the growing number of pharmacological treatment options for osteoporosis?

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We are becoming increasingly aware that the manner in which our skeleton ages is not uniform within and between populations. Pharmacological treatment options with the potential to combat age-related reductions in skeletal strength continue to become available on the market, notwithstanding our current inability to fully utilize these treatments by accounting for an individual's unique biomechanical needs. Revealing new molecular mechanisms that improve the targeted delivery of pharmaceuticals is important; however, this only addresses one part of the solution for differential age-related bone loss. To improve current treatment regimes, we must also consider specific biomechanical mechanisms that define how these molecular pathways ultimately impact whole bone fracture resistance. By improving our understanding of the relationship between molecular and biomechanical mechanisms, clinicians will be better equipped to take full advantage of the mounting pharmacological treatments available. Ultimately this will enable us to reduce fracture risk among the elderly more strategically, more effectively, and more economically. In this interest, the following review summarizes the biomechanical basis of current treatment strategies while defining how different biomechanical mechanisms lead to reduced fracture resistance. It is hoped that this may serve as a template for the identification of new targets for pharmacological treatments that will enable clinicians to personalize care so that fracture incidence may be globally reduced.

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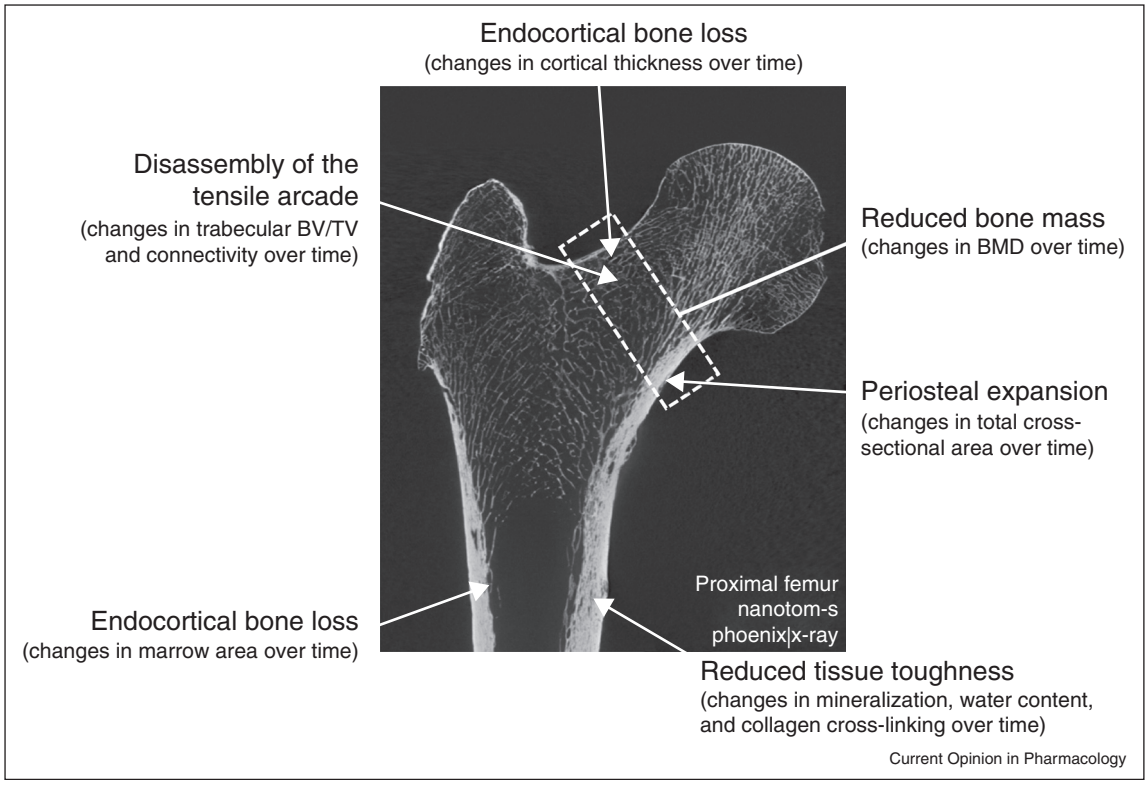
## Introduction

A common goal for the pharmacological treatment of osteoporosis is to reduce fracture incidence. Most treatments have been centered on improving bone mineral density (BMD), which is a non-invasive measure of bone mass. This is an appropriate place to begin given that DEXA is a commonly available technology used to screen individuals for osteoporosis and because most pharmacological treatments have traditionally centered on slowing age-related bone loss [1]. However, we have known for quite some time that osteoporosis is not simply a bone loss disease [2–4], but that there are many age-related changes in bone structure and composition that contribute to the gradual decline in fracture resistance (Figure 1). As the number of pharmacological treatment options steadily increases and as research provides greater insight into skeletal aging, there will be new opportunities for developing the technologies and scientific approaches which will enable physicians to treat individuals in ways that will improve bone strength more strategically. The physician currently has pharmacological treatment options that target bone loss, bone gain, or both (Figure 2). *How does the physician decide which of these options should be used to most effectively treat each individual patient for low bone mass?* Surprisingly, the introduction of new pharmacological treatment options has surpassed our ability to differentially diagnose and treat individuals based on their individual pathway to fracture susceptibility (Figure 1). This is a major problem because it means that we may not be taking full advantage of the treatments currently available or in the pipeline. Current pharmacological treatment options for osteoporosis include the use of antiresorptive therapies, such as bisphosphonates (e.g. alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, RANKL-inhibitors (e.g. denosumab), strontium ranelate, and selective estrogen modulators (e.g. raloxifene), as well as anabolic intermittent parathyroid hormone (teriparatide). Ongoing pre-clinical and clinical trials are currently examining anti-resorptive cathepsin-K inhibitors (e.g. odanacatib), and anabolic Wnt-pathway inhibitors (e.g. sclerostin, dickkopt-1) [5] for their efficacy in postmenopausal osteoporotic patients. More detailed information about the mechanisms of action for these emerging therapeutics can be found in a companion paper in this journal by Ng and Martin.

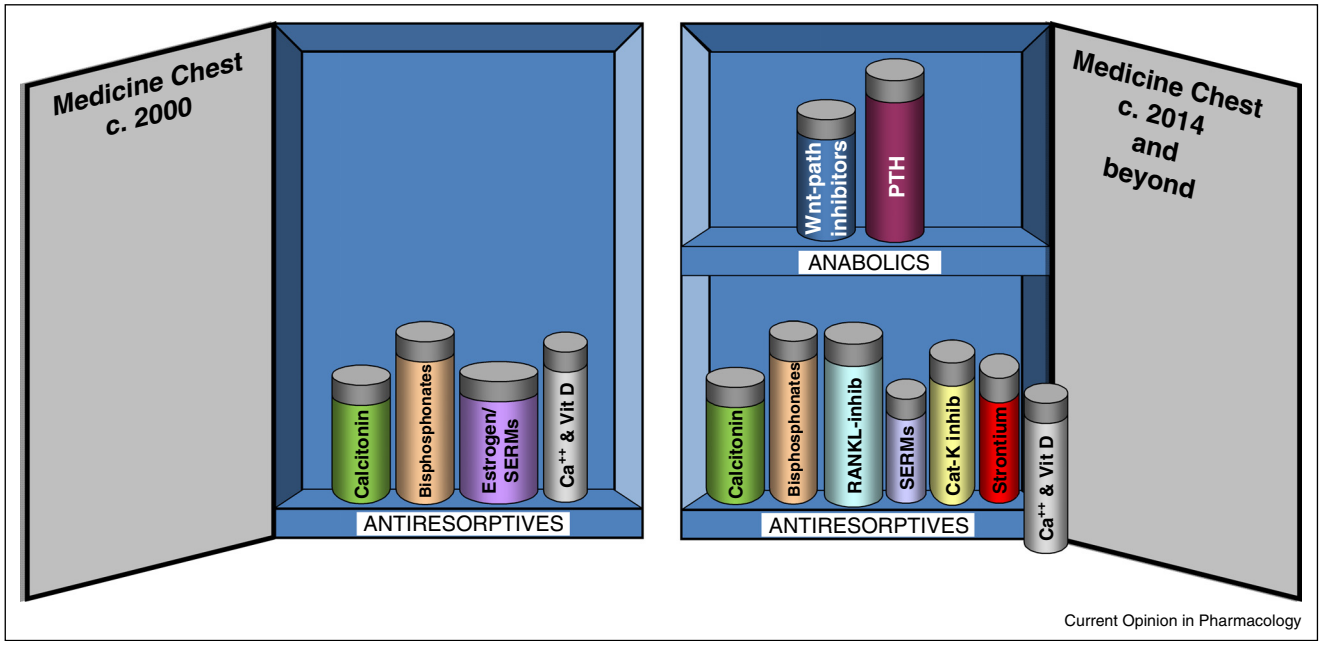
The goal of this review paper is to briefly summarize the biomechanical basis of current treatment strategies and to define how understanding the different biomechanical mechanisms leading to reduced fracture resistance may help identify new targets for pharmacological treatments that allow physicians to treat locally (i.e. personally) to reduce fracture incidence globally.

**Figure 1**




Sagittal section of a human proximal femur (25 micron voxel size; nanotom-s, phoenix|x-ray, GE Measurement & Control; Wunstorf, Germany) showing the many changes in structure and tissue-level mechanical properties that occur with aging. Potential biomarkers for each pathway are shown in parentheses.

**Figure 2**




The number of available pharmacological treatment options and those in the pipeline has steadily increased over the last two decades. Examples of antiresorptive and anabolic treatments are shown in the medicine chests.