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Bone pain: current and future treatments

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Skeletal conditions are common causes of chronic pain and there is an unmet medical need for improved treatment options. Bone pain is currently managed with disease modifying agents and/or analgesics depending on the condition. Disease modifying agents affect the underlying pathophysiology of the disease and reduce as a secondary effect bone pain. Antiresorptive and anabolic agents, such as bisphosphonates and intermittent parathyroid hormone (1–34), respectively, have proven effective as pain relieving agents. Cathepsin K inhibitors and anti-sclerostin antibodies hold, due to their disease modifying effects, promise of a pain relieving effect. NSAIDs and opioids are widely employed in the treatment of bone pain. However, recent preclinical findings demonstrating a unique neuronal innervation of bone tissue and sprouting of sensory nerve fibers open for new treatment possibilities.

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Bone pain

Bone pain is a common and debilitating symptom of many malignant and non-malignant bone disorders. The treatment options are limited to classic analgesics and disease modifying agents and often insufficient in providing complete pain relief. Currently, only few (if any) therapies can attenuate bone pain without unwanted side effects [1••], and there is an unmet medical need of novel therapeutic options.

Clinically, bone pain is not well-characterized and the pain phenotype depends on the disease and the disease stage. A fracture will initially give rise to severe pain, often described as shooting or sharp. At stabilization of the bone a dull and aching pain will follow; a pain sensation which is also described for other bone disorders [2]. Chronic bone pain often results in a decreased functional status of the patient and a reduction in the quality of life. Bone pain occurs in a diverse group of skeletal disorders and tends to increase with age [1••]. Therefore, as the lifespan of individuals is increasing and with the decrease in skeletal health due to lifestyle factors such as obesity and reduction in daily physical activity, the burden that bone pain will exact on individuals and society is expected to increase significantly in the coming decades [1••,2,3].

One challenge of providing better treatment options has been the lack of focus on bone pain in clinical and basic research. However, in the last decade clinically relevant animal models of skeletal pain have been developed [4,5] and data on the underlying mechanisms of bone pain are beginning to emerge. These indicate that bone pain involves mechanisms that are distinct for this pain state and open for possible new mechanism based treatments. Importantly, animal studies suggest that bone tissue has a different innervation than skin, with bone having a high percentage of peptidergic and tropomyosin receptor kinase A (trkA) positive primary sensory neurons [6]. Also studies with knock-out mice have demonstrated that contrary to what is found for neuropathic pain, a normal function of the Nav1.7 sodium channels or Nav1.8-positive nociceptors was not required for the development of pain behavior in a model of cancer-induced bone pain [7•].

In this review we will focus on the current and future treatments targeting bone pain, emphasizing the pharmacological aspects of the treatment exemplified in a subset of non-malignant and malignant bone diseases.

Painful bone disorders

Bone pain is prevalent in most bone disorders including osteoporotic fractures, Paget's disease, osteogenesis imperfecta, fibrous dysplasia, bone metastasis, and multiple myeloma [8,9,10,11,12,13]. Furthermore, pain from osteoarthritis and even rheumatoid arthritis involves the bone [14]. Most of our existing knowledge on the mechanisms underlying bone pain stems from animal models of cancer-induced bone pain and there is a strong need to expand this research to the non-malignant bone diseases. Bone pain is considered nociceptive in nature, *i.e.* originating from damage of non-neural tissue and due to the activation of nociceptors, although recent findings suggest that there may be a neuropathic component as well [1••,15,16,17]. The pain may be caused by mechanical

distortion, fractures, increased bone turnover, demineralized bone and/or a disturbed microenvironment. This can lead to release of a plethora of inflammatory and pronociceptive mediators, nerve entrapment and sprouting of sensory and sympathetic nerve fibers; all of which drives nociceptive signaling [15,16,17,18,19,20,21,22,23,24].

Pain relieving agents

Therapies used in the management of bone pain can be divided into two categories: disease modifying agents and analgesics.

Disease modifying agents

Disease modifying agents affect bone turnover by either decreasing resorption and/or increasing bone formation and may slow or reverse disease progression, while as a secondary effect reduce bone pain. Figure 1 summarizes key targets in painful bone disorders.

Antiresorptive agents

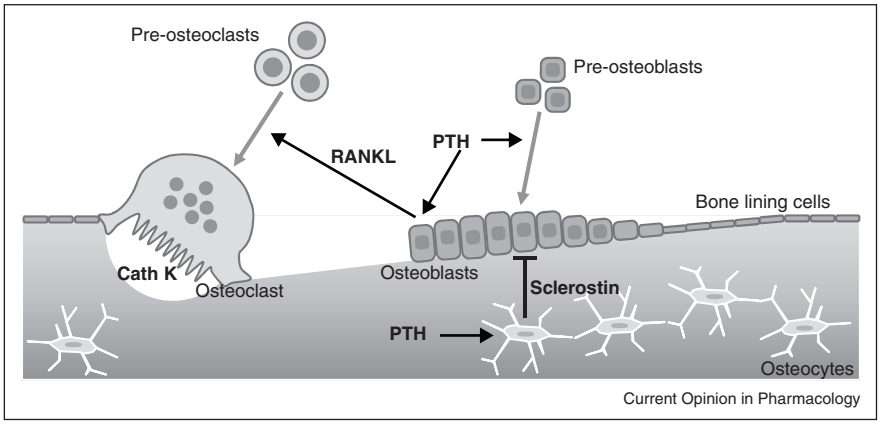
Bisphosphonates are used in a range of different metabolic bone diseases to reduce or prevent disease progression and to decrease symptoms and complications from the disease. Bisphosphonates bind to hydroxyapatite in the bone and are taken up by osteoclasts during bone resorption, which causes apoptosis of the osteoclasts leading to a decrease in bone resorption [25]. Bisphosphonates can be used in addition to radiotherapy and/or analgesics in the management of painful bone metastases and can provide some pain relief over time [26,27]. Bisphosphonate treatment also improves the quality of life including pain relief in Paget's disease [28,29•], osteogenesis imperfecta [30,31], osteoporotic fractures [9] and maybe fibrous dysplasia [32]. However, with long-term use the cyclic activity of osteoclasts and osteoblasts can be disrupted which will result in a decreased bone turnover comprising the strength and integrity of the bone [25].

A newer antiresorptive agent is denosumab; a human monoclonal antibody that blocks the receptor activator of nuclear factor-κB ligand (RANKL), a key activator of osteoclasts. Similar to the bisphosphonate zoledronic acid, denosumab significantly prevents or increases the time to skeletal related events in patients with solid tumors or multiple myeloma and a phase III trial suggested that denosumab could provide pain relief to patients suffering from metastatic bone disease. Denosumab extended the time to severe pain by approximately 1 month compared with zoledronic acid for patients with metastases from solid tumors [33•,34]. Denosumab could also be a relevant therapeutic option for alleviating pain in other metabolic bone disorders [35,36,37]; however, further studies are warranted to determine the efficacy.

Future antiresorptive agents

Cathepsin K inhibitors are a new class of antiresorptive agents that may hold promise of a bone pain relieving effect. The inhibitors are developed for the treatment of osteoporosis, as cathepsin K is the main proteolytic enzyme produced by osteoclasts and plays a fundamental role in the breakdown of bone matrix [25]. A phase II study, investigating the cathepsin K inhibitor odanacatib, demonstrated that the effects on bone mineral density (BMD) are comparable to those of bisphosphonates. But unlike bisphosphonates, which suppress both bone resorption and bone formation markers, odanacatib appears to suppress bone formation markers only transiently and the effects of

Figure 1



Bone pain can be caused by an altered bone turnover, demineralization of bone and a disturbed bone microenvironment. Disease modifying agents affect bone turnover and reduce as a secondary effect bone pain. Targets involve Cathepsin K (Cath K), nuclear factor-κB ligand (RANKL), intermittent parathyroid hormone (PTH) and sclerostin. Cath K is the main proteolytic enzyme excreted by osteoclasts and has a fundamental role in the breakdown of bone matrix [38,39]. RANKL is expressed by osteoblasts and act as a key factor for osteoclast differentiation and activation [33•,34]. PTH stimulates osteoblast differentiation, induces RANKL expression in osteoblasts and inhibits secretion of sclerostin from osteocytes [42,43]. Sclerostin is produced by osteocytes and inhibit bone formation by osteoblasts [47,48].