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REVIEW ARTICLE

Neurophysiological Mechanisms Related to Pain Management in Bone Tumors

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Abstract: ***Background*:** Primary and metastatic bone tumor incidence has increased in the previous years. Pain is a common symptom and is one of the most important related factors to the decrease of quality of life in patients with bone tumor. Different pain management strategies are not completely effective and many patients afflicted by cancer pain cannot be controlled properly. In this sense, we need to elucidate the neurophysiology of cancer-induced pain, contemplating other components such as inflammation, neuropathies and cognitive components regarding bone tumors, and thus pave the way for novel therapeutic approaches in this field.

***Aim*:** This study aims to identify the neurophysiology of the mechanisms related to pain management in bone tumors.

***Methods*:** Advanced searches were performed in scientific databases: PubMed, ProQuest, EBSCO, and the Science Citation index to get information about the neurophysiology mechanisms related to pain management in bone tumors.

***Results*:** The central and peripheral mechanisms that promote bone cancer pain are poorly understood. Studies have shown that bone cancer could be related to neurochemicals produced by tumor and inflammatory cells, coupled with peripheral sensitization due to nerve compression and injury caused by tumor growth. The activity of mesolimbic dopaminergic neurons, substance P, cysteine/glutamate antiporter, and other neurochemical dynamics brings us putative strategies to suggest better and efficient treatments against pain in cancer patients.

***Conclusion*:** Cancer-induced bone pain could include neuropathic and inflammatory pain, but with different modifications to the periphery tissue, nerves and neurochemical changes in different neurological levels. In this sense, we explore opportunity areas in pharmacological and non-pharmacological pain management, according to pain-involved mechanisms in this study.

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1. INTRODUCTION

Pain is a constant condition in humans. Despite this, it has been challenging to define since it has different contexts. The most accepted definition is that of Merskey (1979), modified by the International Association for the Study of Pain (IASP) taxonomy subcommittee. According to him pain is an "Unpleasant sensory or emotional experience associated with actual or potential tissue damage" [1]. This definition confers a multidimensional vision of pain. In this way, pain is not exclusively a sensation due to stimulation by nociceptors and neuropeptides, it also implies the existence of an emotional factor, which confers variability between individuals [2]. Therefore, we define pain as a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components [3]. Pain includes not only sensory components; emotional experiences are an important part of it [4]. Pain that occurs in response to injury (*e.g.* twisted joint, stressful impact) acti-

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vates nociceptors and stimulates the release of neuropeptides and other molecules. Bones have nociceptors, which allow transduction of painful stimuli in order to protect and promote efficient tissue repair. It has been shown that in the bone a variety of nociceptors exist. These differences lie in the histological features, the painful type (thermal, chemical, mechanical), the nervous fiber populations and its processing and response of the nervous system [5].

Cancer is a worldwide public health problem. This disease has a high economic, social and psycho-emotional impact on patients. Despite advances in cancer management, mortality rates remain high [6]. The quality of life of these patients is also affected, and one of the main reasons is the difficulty in managing cancer pain. Cancer pain (CP) has not yet been clearly understood, thus, pain management in cancer patients is a clinical challenge [7]. Cancer-associated pain can be present at any time during the course of the disease, but the frequency and intensity of cancer pain tend to increase with advancing stages of the disease. Between 75% and 90% of patients with metastatic or advanced cancer stage will experience significant cancer-induced pain [8]. CP can arise from different processes, either by direct tumor infiltration/involvement, as a result of diagnostic or therapeutic surgical procedures (such as biopsies and resection), or as a side effect of toxicity related to therapies used to treat cancer (for example, chemotherapy and radiation therapy) [9].

Incidence and prevalence of primary and secondary bone tumors (BT) have increased worldwide [10]. This has been attributed to high prevalence of bone metastasis, especially in developing countries, since the diagnoses of different types of cancer are made in advanced stages [11]. Recent studies have shown that the neurophysiological mechanisms in cancer-induced pain are important in tumor-genesis and additionally cause the sensitization of components of the nervous system that trigger nociceptive and neuropathic pain [12]. The management of pain in bone cancer, should be directed, not only to alleviate the suffering of the patients (which is essential), but also the possibility of reducing tumor stimuli should also be considered, therefore, the knowledge of the neurophysiological mechanisms of pain in bone cancer is fundamental therapeutic targets.

2. CANCER PAIN OVERVIEW

CP has characteristics related to the tumor type, like behavior and location. On the other hand, the psycho-emotional condition of the patients is usually linked to the final perception of the type and intensity of pain. Therefore, it is difficult to classify the type of cancer pain. According to the World Health Organization (WHO), there are different classifications of pain: related to the anatomical region (somatic, visceral and neuropathic), related to duration (acute and chronic), related to intensity (mild, moderate and severe) and related to the pathophysiology (nociceptive and neuropathic) [2, 13, 14].

2.1. Anatomic

Anatomic refers to the specific region or area of the body where pain is perceived or experienced [15].

a. *Somatic pain*: is the pain that occurs as a consequence of the activation of the nociceptors in the skin or the deep tissues. Is a well localized pain (*e.g*. bone metastases) [2].

b. *Visceral pain*: it arises after activation of the nociceptors by infiltration and/or compression of the thoracic, abdominal or pelvic viscera [2, 16]. Visceral pain is clinically characterized by the following factors: (1) it is not evoked from all viscera (organs such as liver, kidney, most solid viscera, and lung parenchyma are not sensitive to pain); (2) it is not always linked to visceral injury (cutting the intestine causes no pain and is an example of visceral injury with no attendant pain, whereas stretching the bladder is painful and is an example of pain with no injury); (3) it is diffused and poorly localized; (4) it is referred to other locations; and (5) it is accompanied with motor and autonomic reflexes, such as nausea, vomiting, and lower-back muscle tension.

c. *Neuropathic pain:* it was defined by the IASP as: ''pain initiated or caused by a primary lesion or dysfunction in the nervous system''. In 2008, a group of experts proposed a new definition: ''pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'' which was endorsed by the IASP in 2011 [17]. It is caused by a primary injury or dysfunction in the central or peripheral nervous system, with destruction and/or nerve involvement. This type of pain is generally described as paroxysmal discharges with a burning sensation or as pricks or numbness and tingling [2].

2.2. Duration

Term that refers to the time of perception of pain by the patient, and it is classified as acute and chronic.

a. *Acute:* it is defined as "the normal, predicted physiologic response to an adverse chemical, thermal, or mechanical stimulus associated with surgery, trauma, or acute illness" [18, 19]. Acute pain is caused by the activation of nociceptors due to tissue damage. This type of pain is usually associated to surgery, traumatic injury and inflammatory processes. Acute pain is an evolutive mechanism that allows us to protect damaged tissue. Acute pain is typically self-limited and resolves within days to weeks, however, in some cases, it can take up to 3 to 6 months [13].

b. *Chronic*. The IASP has defined chronic pain as that which lasts for longer than 3 months [20, 21]. It is commonly triggered by an injury or disease but may be perpetuated by other factors. The original injury may damage the nervous system in such a way as to be unable to restore itself to a normal state. All types of chronic pain lead people to seek health care, but they are often treated ineffectively. In this sense, chronic pain is unrelenting, and it is likely that stress, environmental, and affective factors superimpose on the original damaged tissue and contribute to the intensity and persistence of the pain [21]. Chronic pain

differs substantially from acute pain in terms of the persistence of pain and adaptive changes such as neuroplasticity that has been described at various levels of the nervous system [22]. In this sense, pain becomes chronic if it persists long after it can serve any useful function, becoming not just a symptom of injury or disease but a pathology in itself. Chronic pain covers persistent physical pain, disability, emotional disturbance, and social withdrawal symptoms, existing together and influencing each other. In contrast, physical pain could be from known or unknown sources; regardless, a chronic pain patient will undergo a number of biological, psychological, and social upheavals over the course of their illness [20]. The IASP recognizes common conditions associated with chronic pain and most importantly chronic pain can significantly affect quality of life [13].

2.3. Intensity

Classification system employs measures through visual, numerical, rating, and/or descriptor scales, typically self-assessed and is used for adolescent and adult patients (Pain assessment scales of The National Initiative on Pain Control™) [14]. Regarding children, the classification systems include adjective, numerical, visual analogue faces or color scales according to children's ages [23].

In Tables **1** and **2**, we show these scales.

2.4. Physiologic pathways

There are two types of cancer pains: nociceptive and neuropathic.

a. *Nociceptive pain:* is a normal bodily response to injury and can result from damaged tissues, such as internal organs, muscles, and/or bone. Pain is often associated with an inflammatory response because it aids in the healing process. Nevertheless, persistent inflammation needs to be addressed and managed accordingly to reduce the risk of developing pathologic somatic responses. Secondary diseases and conditions associated with persistent inflammation include rheumatoid arthritis, certain cancers, and atherosclerosis [14]. Generally, nociceptive pain is transient and could be either somatic or visceral. The peripheral nociceptors are activated usually by trauma, arthritic process, or cancer by a myriad of molecules such as prostaglandins, histamine, substance P or bradykinin that are released to the surrounding tissue and cause inflammation [12]. In this sense, nociceptive pain is a result of neuronal depolarization, allowing the transduction to the spinal cord *via* slow, non-myelinated C fibers and fast, myelinated Aδ fibers. In the spinal cord, the resulting incoming signals are then modulated and transmitted to second order neurons and then to the brain stem *via* ascending pathways by neurotransmitters. After that, the brain stem, as a mediator, transmits the signal to certain brain areas for the pain signals to be interpreted. Pain perception is regulated by descending pathways [12, 23]. Information about noxious stimuli is transmitted from the limbic system and midbrain structures down through the periaqueductal grey to the brainstem in the rostroventral medulla. Here the signals are filtered and subsequently passed to the dorsal horn of the spinal cord. The implicated neurotransmitters in the descending pathways are noradrenaline, which reduces pain, and serotonin (or 5-hydroxytryptamine), a bivalent neurotransmitter acting as facilitatory and inhibitory [33].

b. *Neuropathic pain,* according to the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG), is defined as ‘‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”. Some common conditions associated with neuropathic pain are diabetes, human immunodeficiency virus infection, amputation [14], trauma, surgery, herpes zoster virus infection, alcohol consumption, immune response, inherited, cancer and drug-induced factors (such as platinum derivatives, taxanes, vinca alkaloids, and others) [34]. As a result, there is a switch in the phenotype of the sensory neurons and their nociceptive signaling mechanisms. Alterations in the function of sodium channels (which generate pain signals), potassium channels (which inhibit pain signals) and calcium channels (which facilitate transmitter release) have been reported [33]. The pain produced is typically perceived as burning, tingling or ‘electric’ in character and can be combined with allodynia - in which non-painful stimuli evoke pain - and hyperalgesia. Neuropathic pain is more severe than nociceptive pain and harder to treat, nevertheless,

Table 1. Pain scales according with patient ages [24-30].

Recommended Age Range (Years)	Scale
3	Pieces of hurt (Poker Chip Tool)
4	Color scales
4-12	Faces scale
5-7	Visual analogue scales (VAS)
8-Adult	Numerical rating scales
9	Adjective scales

Table 2. Classification system intensity Pain [31, 32].

Types Scale	Caracteristics	Interpretation
Visual Scale	The Visual Analogue Scale (VAS) consists of a straight line with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be'.	No Pain Pain as bad as it could be
Numerical Scale	If descriptive terms like 'mild', 'moderate', 'severe' or a numerical scale is added to the VAS, one speaks of a Graphic Rating Scale (GRS).	0= No Pain 10= Pain as bad as it could be
Verbal Rating Scale	In a Verbal Rating Scale (VRS) adjectives are used to describe different levels of pain. The respondent is asked to mark the adjective which fits best to the pain intensity. As in the VAS, two endpoints such as 'no pain at all' and 'extremely intense pain' should be defined. Between these extremes, different adjectives which describe different pain-intensity levels are placed in the order of pain severity.	No pain at all Extremely intense pain
Test	Mc Gill Pain Questionnaire. It is one of the most used. More complex and large. It is useful to discriminate between patient kinds of pain.	Questions about location of pain, modifying factors pain, temporary pattern, the intensity of pain.
Test	Brief Pain Inventory. Originally developed for cancer pain, it is widely used in the clinic and research to assess the intensity and impact of pain and the effects of analgesic treatment.	Measure the intensity, location and quality of pain.

both neuropathic and nociceptive pain can coexist and become chronic in several conditions such as back pain and cancer pain [33, 34].

Neuropathic pain associated with lesions that affect the central or peripheral nervous system can be divided into 3 subgroups: sympathetically mediated, peripheral, or central.

3. BONE TUMORS PAIN AND NEUROPHYSIOLOGICAL ACTIVITY

The incidence of cancer pain-derived is approximately 75% to 90% of patients, many of whom have multiple pain sources [33, 35]. About 80% of individuals with an advanced disease experience pain of moderate-severe intensity and 50% of patients report inadequate pain control [9]. As mentioned before, cancer-induced pain is a multidimensional experience and its perception is influenced by many individual factors [36] and can be defined as a complex pain state with nociceptive, inflammatory, and neuropathic components. In this sense, cancer-associated bone pain is a consequence of a large number of sensory and sympathetic innervations of the bone periosteum, bone marrow and bone matrix.

It is important to mention that tumor cells cannot destroy bone by themselves, but rather, through the expression of inflammatory molecules such as nuclear factor kappa-B and the subsequent activation of its receptor (RANK / RANKL). These cells stimulate the activation and proliferation of osteoclasts, promoting an increase in bone resorption "bays", and then an acidic microenvironment that aides in the activation of sensory neurons in bone through ionic channels, such as the transient potential receptor vanilloid receptor 1 (TRPV1) and acid-sensitive ion channels. (ASIC) [12], transmitting the bone pain signal. Additionally, several mechanosensitive channels can also be activated due to an increase in tumoral volume and therefore, cause compression in the sensory nerve fibers. In addition, cancer cells produce a variety of chemical mediators (prostaglandins, nerve growth factor, bradykinin, and endothelin) that can activate or sensitize bone nociceptors. Nerve growth factor (NGF) binds to tyrosine kinase receptors on bone nociceptors and can modulate the sensitivity and expression of several other receptors and ion channels [37-39]. Increased levels of NGF have been associated with the sprouting of nerves and the formation of neuromas within the bone. Blocking NGF (NGF-sequestering antibodies) has been investigated as a potential therapy for pain in bone tumors and has shown promising results [36]. It has been demonstrated that bone tumors could promote neurogenesis and in this sense, they could establish reciprocal interaction with peripheral nerves. Bone tumor like other tumors, releases neuropeptides like neurotropic factors (NGF), axon guidance molecules (semaphorins) neurotransmitters (epinephrine, norepinephrine, dopamine, serotonin, histamine, gamma-aminobutyric acid, acetylcholine) and neuropeptides (neuropeptide Y, substance P, badykinin, CGRP, dynorphin) [12, 37, 38]. This feedback is possibly established as a pro-tumoral mechanism but ends up causing the activation and sensitization of bone nociceptors and different areas of the nervous system, which culminates in the generation of pain and its chronicity. Regarding glutamate, the transporter VGLUT1 [39] is involved in nociceptive (thermal or mechanical) transductions that release glutamate from peripheral primary afferent terminals. The glutamate released, presumably from the peripheral nerve endings, may contribute to sensitized nociception or pain pathology [40]. Yoneda *et al*. propose that the acidic environment, due to elevated aerobic glycolysis known as the "Warburg effect", generates a large amount of H+, and can activate nociceptors resulting in hyperalgesia at both the central and peripheral nervous levels [12, 41].

4. CURRENT PHARMACOLOGICAL TREATMENTS OF BONE TUMORS PAIN

The proper management of pain in bone tumors requires the identification of the pathophysiological origin of the type of pain, which can be mainly nociceptive, neuropathic or a mixture of both types of pain [42]. The adult skeleton is in-

nervated by finely myelinated tropomyosin kinase A (TrkA+) sensitive sensory nerve fibers (Aδ), while it does not receive innervation from larger touch-sensitive A-beta fibers and does not present C fibers without myelin (TrkA-) [43]. Bone sensory fibers are likely silent nociceptors, which are activated only in the event of trauma or injury. During the development of bone tumor, pain is initially an intrinsic process with the acid environment formation during bone resorption that is mainly of nociceptive origin [44, 45], but with pharmacological management to control cancer, its consequences appear and the pain begins to be neuropathic (chemotherapy-induced peripheral neuropathy), until finally, it predominates in the final stages [42]. Postherpetic neuralgia is a potential complication after acute reactivation of herpes zoster when patients have been treated with bortezomib, a proteasome inhibitor that makes reactivation of herpes zoster vulnerable [46]. Postherpetic neuralgia is a typical example of localized neuropathic pain, which is generally limited to a superficial, circumscribed, and easily identifiable area [47]. Thus, pain initially presents as central sensitization, then it is neuroplasticity, and finally, the pain becomes chronic. For this reason, pain treatment was initially managed primarily with antiresorptive therapy directed specifically at bone, protons released during bone resorption create an acidic bone microenvironment that excites bone sensory neurons *via* activation of ASIC3 [4, 45]. Bisphosphonates inhibit bone resorption, with a direct effect on apoptosis in osteoclasts [48], among the most used being Clodronate, Pamidronate intravenous [49] and Zoledronic Acid [50, 51]. Another route to reduce bone resorption is Denosumab (anti-RANKL-2) [52, 53], Tanezumab (anti NGF) [54, 55], and Pregabalin [56]. Corticosteroids such as Prednisone and Dexamethasone relieve pain between 30 to 70% [57], their use is particularly useful in patients during radiation therapy. Higher doses treat patients in emergencies such as fractures and spinal cord compression [58]. Analgesics are used when pain is becoming chronic; Acetaminophen is one of the non-opioid and non-steroidal anti-inflammatory drugs used in low doses, since these can generally affect the kidneys when used for a long time [59]. Opioids are still the most popular drug-treatment of severe cancer pain [60]. By modulating the ascending and descending pain pathways in the CNS [61], binding to mu opioid receptors (MOR), regulating calcium ion channels [60], opioids could modulate intracellular events such as adenylyl cyclase inhibition or receptor desensitization by internalization and/or degradation of these receptors through endocytosis [62]. Basically, opioids regulate several pain components, however, they can be supplemented with neuropathic pain modulators [63]. Some opioids such as codeine and morphine can accumulate in patients with kidney failure and have toxic effects; Oxycodone and hydromorphone require dose adaptation, whereas buprenorphine and fentanyl are considered first-line opioid drugs in patients with renal failure [64, 65]. Therapies for multiple types of cancer include immunosuppression with bortezomib, thalidomide and lenalidomide, which increases the risk of infections, and reactivation of the varicella zoster virus, which presents some comorbidity with, for example, multiple myeloma [66]. Thus, postherpetic neuralgia is a complication closely related to nerve pain, which is highly localized. Some topical pain treatments such as lidocaine and capsaicin [67, 68] inhibit nociceptive stimuli by blocking the potential action propagation; lidocaine, for example, inactivates the fast voltage-gated Na+ channels in the neuronal cell membrane and, capsaicin increases the intracellular calcium levels and disrupts mitochondrial electron chain in nociceptive fibers [69].

5. NOVEL STRATEGIES FOR NEUROPHARMACOLOGICAL MANAGEMENT OF BONE TUMOR PAIN

Loratadine, an antihistamine, is currently the most investigated drug for the treatment of cancer-induced bone pain. In patients with bone metastases, treatment with pegfilgrastim, a complementary drug that stimulates the production of neutrophils, causes severe pain [70-72]. Several clinical trials have analyzed the effect of loratadine for the prevention of pain in patients previously treated with pegfilgrastim. For example, in a clinical trial (NCT01712009), the difference in bone pain between breast cancer patients receiving chemotherapy and pegfilgrastim and prophylactic treatment with loratadine was estimated [73]. Participants received adjuvant or neoadjuvant chemotherapy and pegfilgrastim plus 10 mg prophylactic loratadine once daily for 5 days in each of the 4 cycles, at the beginning of pegfilgrastim administration. Patients with bone pain of all grades in cycle 1 had 42.5% under treatment with loratadine. Additionally, in a pilot study of 12 patients with various types of cancer (breast, genitourinary and colorectal) receiving chemotherapy and pegfilgrastim, they were treated with loratadine for 5 cycles of chemotherapy [74]. This treatment produced effective pain management in patients who developed pain from the first dose of pegfilgrastim. Likewise, combination therapy with famotidine and loratadine significantly reduced bone pain caused by filgrastim or pegfilgrastim in patients who received four-cycle myelosuppressive therapy [75].

Currently, two clinical trials (NCT04211259, NCT02305979), still in the patient recruitment phase, aim first, to analyze the effects of loratadine in reducing granulocyte-colony stimulating factor in patients with bone-pain multiple myeloma-related; and second, to evaluate the loratadine effects in bone-pain incidence and severity of patients with hematologic malignancies, patients undergoing mobilization of hematopoietic progenitor cells, and patients who have undergone an autologous hematopoietic cell transplant [76, 77].

Ibandronate, a nitrogen-containing bisphosphonate, has been tested for the treatment of bone pain in cancer [78]. Radiation therapy *vs*. ibandronate for pain reduction was compared in 470 patients with prostate cancer and bone pain. The pain response between the two treatments was not significantly different, so ibandronate could be considered when radiotherapy is not available [79]. Ibandronate and zoledronic acid combination therapy has been assayed in the treatment of bone pain in rats with lung cancer and bone metastases. The group of rats was treated subcutaneously with the combination of ibandronate plus zoledronic acid; it was significantly more effective compared to ibandronate or zoledronic acid monotherapy [80].

Clinical trials are currently underway to analyze the efficacy of ibandronate in treating pain in bone cancer. A phase III clinical trial (NCT00082927) is studying ibandronate to show how well it works compared to single-dose local radiation therapy in treating patients with localized metastatic bone pain; however, the results have not yet been published [81]. In addition, another clinical trial is testing the short-term efficacy for moderate to severe pain in ibandronate in 13 patients with breast cancer and bone metastases; wherein bone pain decreased in women with breast cancer and bone metastases following loading dose *i.v*. ibandronate which was well-tolerated with no renal safety concerns [82]. Similarly, another study is testing the short-term efficacy of ibandronate in patients, with moderate to severe pain, of breast cancer and bone metastasis; however, its results have not yet been published [83-85].

Zoledronic acid, another nitrogen-containing bisphosphonate, has also been used to reduce bone pain in cancer. In a phase III trial, men with castration-resistant prostate cancer, received zoledronic acid (4 mg) during 24 months, which reduced bone pain by 39% [86]. Another phase II clinical study determined the efficacy of the therapeutic combination of zoledronic acid with radiotherapy in patients with hepatocellular and colorectal carcinoma. This treatment caused the mean pain score to drop to 2.8 at 1 month and 2.1 at 3 months [87].

A clinical trial NCT00172029 assessed the efficacy and tolerability of zoledronic acid 4 mg infused over 15 minutes every 4 weeks for a total of 6 infusions, in combination with standard or reduced dose radiotherapy in patients with breast cancer and metastatic bone disease associated with pain [88]. A clinical trial NCT00375648 evaluated the efficacy and safety of 4 mg zoledronic acid administered intravenously every 3-4 weeks in the treatment of bone metastases-related pain in patients with prostate cancer [89]. Other two clinical trials (NCT00099177 and NCT00099203) will compare the efficacy of a regimen of intravenous and oral Bondronat with that of zoledronic acid in patients with malignant bone disease experiencing moderate to severe pain [90, 91].

Other drugs have been developed to try to relieve bone pain in cancer patients. Among them is resiniferatoxin, a phorbol-related diterpene, which was tested in a model of dogs with bone cancer pain, who, upon receiving 1.2 mg/kg of resiniferatoxin had a decrease in pain and no evidence of the development of deafferentation pain syndrome [92].

Saracatinib, a Src-kinase inhibitor, has been assayed as an analgesic for cancer-induced bone pain in a clinical trial with twelve patients with bone metastases; however, the data is insufficient to demonstrate that saracatinib has efficacy as analgesic [93]. Finally, pregabalin has been assayed in combination with palliative radiotherapy for cancer-induced bone pain; however, the results do not support the role of pregabalin in patients with cancer-induced bone pain receiving radiotherapy [94]. NGF sequestration, inhibition or other therapies that block NGF signaling are studied in animal models with encouraging results. NGF through its receptors (NGF / TrkA) and molecules that participate in its signaling (TRPV1) promotes changes in the activity and sensitivity of bone nociceptors [38]. A recombinant humanized monoclonal antibody to NGF, tanezumab, is found to be effective at reducing pain in patients with osteoarthritis, low back pain, and diabetic peripheral neuropathy with few side effects [37].

6. NON PHARMACOLOGICAL TREATMENTS OF BONE TUMOR PAIN

Non-pharmacologic approaches can be classified as Interventional (injection therapies, neural blockade and implant therapy), Rehabilitative (modalities, therapeutic exercise, occupational therapy, hydrotherapy, treatment for specific disorders), Psychological (psychoeducational interventions, cognitive behavioral therapy, relaxation therapy, hypnosis, guided imagery), Neurostimulation (transcutaneous, transcranial, implanted), and Integrative (acupuncture, massage, physical or movement) [95-97]. Some approaches are considered specifically for refractory pain. Among these are many interventional approaches, which consist of a large and varied group of injections, neural blockade approaches, and implant therapies. Other strategies (psychological, integrative and rehabilitative) are used by experienced clinicians when available, feasible, and desired by the patient, and consistent with the goals of care. Each of these strategies includes an array of specific interventions that vary in complexity and supporting research. Among the most useful are the so-called mind-body approaches, which are classified as both psychological and integrative interventions [98].

6.1. Interventional

Interventions can be considered at any point in the course of the disease; however, they can be especially useful in patients with less-than-adequate control of systemic analgesics and with serious side effects, or in patients with contraindications in opioids use. Interventional therapies include—but are not limited to— injections, neurolytic or non-neurolytic nerve blocks, and neuromodulation, such as targeted drug delivery and spinal cord stimulation [99]. Neural blockade therapy is a classic method of pain management, the role of it for chronic pain syndromes are still unknown. There is some evidence that neural blockade is a valid method for chronic pain [95]. They are achieved through the destruction of nerves that transmit pain. Most commonly, these procedures are performed using alcohol or phenol, but may also be performed by surgery or radiofrequency ablation of these nerves. Though neural blocks provide longer pain relief, serious side effects such as differentiation pain or motor weakness limit the use of this therapy [100].

a. *Radiofrequency*. Treatment is a minimally invasive technique with multiple therapeutic applications. Pulsed radiofrequency (PRF) has been proved to reduce neuropathic pain after nerve injury, even though the underlying mechanism remains unclear [95].

b. *Nerve blocks*. There are recent studies that state that interventions are more effective when started in the early stages of the disease, as shown by a randomized controlled trial of neurolytic sympathectomy to treat pain in abdominal or pelvic cancer; this study had two cohorts, one cohort with patients who received the in-

tervention early, and second cohort with patients who received it late, and it was observed the former that they employed less oral analgesics and reported a better quality of life. Therefore, nerve blocks can be considered earlier in treatment, if appropriate [99].

c. *Implantation of drug delivery* (IDD) system replaced the administered routes such as oral, intravenous, subcutaneous, transdermal, and transmucosal. The system consists of an implantable pump that stores and delivers medication through a catheter. Programmability is achieved by positioning an external device over the implanted pump to change the mode of drug delivery [95].

6.2. Rehabilitative

Occupational therapy can provide a very valuable role in both cancer patients as well as cancer survivors. Manipulation, soft tissue manipulation, heat, and massage have been reported to reduce discomfort in these patients [100].

6.3. Psychological

a. *Cognitive behavioral therapy* (CBT) refers to a broad range of treatments that aim to address maladaptive thinking, resulting in improved mood and behavior. This technique was first described for depression; its application has now expanded to other disorders such as anxiety, schizophrenia, eating disorders, and chronic pain [100].

b. *Relaxation therapy* trains the patient to engage a so-called relaxation response by repetitive focus on a word, sound, phrase, or body sensation, accompanied by mental focus, and guided imagery trains the patient to recall specific sights, smells, sounds, tastes, or somatic sensations to engender a positive cognitive and emotional state. There is evidence that these strategies can ameliorate pain and they hold promise of positive effects on other symptoms and broader quality of life domains. Their efficacy emphasizes the importance of cognition and emotions as mediators of symptom distress and quality of life, and draws attention to the continuing need for empathic communication and compassionate care by all professional staff [98]. Guided imagery and meditation training has also been used for the management of cancer pain. In this training, the patient is taught to focus on letting go of muscle tension through the use of imagery and suggestions for shift in pain perception. Taken together, psychosocial interventions may be helpful, when they are used in conjunction with conventional pharmacotherapy [100].

c. *Hypnosis.* This therapy involves inviting the patient to focus on his awareness and use his imagination to experience beneficial changes in symptoms and emotional responses. Hypnotherapy has been demonstrated to reduce anxiety and pain during diagnostic procedures, cancer treatment such as percutaneous treatment of tumors as well as in reducing pain in patients with advanced breast cancer [100].

6.4. Neurostimulation

Neural stimulation has been widely used in Europe for many years. It involves spinal cord stimulation (SCS), transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS), and Transcranial magnetic stimulation (TMS). Spinal cord stimulation consists of implantation of peri-epidural electrode in the posterior columns of the spinal cord at the spinal level of the dermatomes on which we want to produce the analgesic effect. The mechanism of function of SCS is that the stimulation is applied directly to the posterior horns of the spinal cord, but it does not allow us to conclude on the specific neurophysiological mechanisms of this analgesia. The stimulation may recruit afferents from the periphery, afferents from the spinal cord to the higher centers, local neuron circuits, and even fibers of the anterior horns of the spinal cord [95].

a. *Spinal cord stimulation* (SCS), also known as dorsal column stimulation, is a form of implanted neurostimulation. The ideal candidate has intractable, focal, isolated neuropathic pain that has failed conservative medical-pharmacological management. The incidence of neuropathic pain in cancer is estimated to be up to 40% [101]. It is a minimally invasive, outpatient technique that involves the placement of electrodes in the dorsal epidural space. The electrodes are connected to a pulse generator that is implanted under the skin, typically in the buttock area. Before neurostimulation management, all patients undergo a week-long trial to evaluate the effectiveness of the treatment. The purported mechanism of action is based on electrical stimulation of the dorsal horn, which most likely through several mechanisms suppresses the transmission of noxious stimuli from the peripheral nerves [35]. New modifications of the SCS have been introduced in recent years. One includes the use of high-frequency (10 kHz) stimulation that provides pain relief without the typical paresthesia experienced in the standard low-frequency SCS75 [35].

b. *Transcutaneous electrical nerve stimulation* (TENS) is widely employed to manage pain states, mainly because it is inexpensive, noninvasive, safe, and simple to use [102], it allows self-administration, and no potential for toxicity or overdose [103]. The neurobiological analgesic mechanisms of TENS are related to peripheral and central nervous systems modulation [104]. TENS uses electric fields to activate nerves in order to reduce neuropathic pain. The TENS unit is a small portable device, often battery-operated. It utilizes electrodes placed on the skin to a targeted therapeutic goal. This device has demonstrated high degree of user tolerance with few side effects, reducing overdose risk. TENS devices are user friendly, allowing control pulse width, intensity, and frequency. [105].

c. *Peripheral nerve stimulation* (PNS) is a neuromodulation technique in which an electrical current is applied to the peripheral nerves to ameliorate chronic pain through preferential activation of myelinated fi-

bers, inducing long-term depression of synaptic efficacy [95].

d. *Transcranial magnetic stimulation (TMS)* is a non-invasive technique. It involves placement of a wire coil (connected to a stimulator that discharges a high-current pulse) over the patient's cranium. The magnetic field produced penetrates the scalp of the patient and in turn induces the formation of electrical currents that excite or inhibit the neural tissue within the cortical and subcortical neural networks. The effect of TMS depends on the position of the coil, the parameters of the stimulation (for example, high or low frequency), and its duration. TMS delivered in the form of repetitive stimulations was shown to produce local changes that last longer than a single stimulation. The exact mechanism of TMS for pain relief is unknown but appears to work through affecting the levels of brain-derived neurotrophic factor (BDNF) [35].

e. *Transcranial direct current stimulation* (tDCS) is a non-invasive, easy-to-implement, and portable technique that involves applying low-intensity (1-2 mA) current to the patient's scalp using large sponge electrodes. The current penetrates the brain and modulates neuronal excitability. There are two types of stimulation: anodal (stimulating) and cathodal (inhibitory). tDCS works through affecting various neurotransmitter and BDNF levels influencing the maladaptive plasticity of pain pathways. Repeated sessions of anodal tDCS applied to the motor cortex contralateral to the pain side have been shown to be effective for various neuropathic pain syndromes [35].

6.5. Integrative Therapies

Integrative therapies are not the first line in cancer-related pain treatment; however, they could prove to be useful as an additional treatment in combination with traditional therapies. There are several integrative therapies. Nevertheless, the options could vary across medical centers, but some choices are outlined briefly below [99].

6.5.1. Acupuncture

Is part of traditional Chinese medicine and has been used for many years for the treatment of different health conditions. Electroacupuncture is a relatively recent variant of acupuncture, which consists of applying pulses of electrical current through needles inserted in specific places in the body called acupuncture points [100]. It is estimated that up to 31% of cancer patients employ acupuncture, however, the evidence is higly variable, showing in some cases contradictory results, and this could be because different studies explored multiple types of pain (chronic pain, neuropathic pain, post-thoracotomy pain, postoperative pain, *etc*.), supporting high risk of bias [100].

6.5.2. Mindfulness

Recently, mindfulness has been widely studied in a diversity of diseases, included pain control, and there is new evidence that reduces stress. In this sense, there are some studies that have explored the efficacy of this therapy in chronic cancer-related pain and in non-cancer-related pain; nevertheless, there is not sufficient evidence to confirm its usefulness in pain management [99].

CONCLUSION

The management of pain in bone cancer should be directed both to alleviate the suffering of the patients (which is essential), and to the possibility of reducing tumor stimuli, therefore, the knowledge of the neurophysiological mechanisms of pain in bone cancer is fundamental therapeutic target. Evidence has shown the effectiveness of both pharmacological and non-pharmacological treatments related to the neurophysiological mechanisms that cause pain in BT. However, more research is needed in order to elucidate the mechanisms of action of the therapies here reviewed for them to be applied on a large scale to help cancer patients efficiently manage chronic disease-inherent pain.

LIST OF ABBREVIATIONS

ASICs	=	Acid-Sensing Ion Channels
BDNF	=	Brain-Derived Neurotrophic Factor
BT	=	Bone Tumors
CBT	=	Cognitive Behavioral Therapy
CP	=	Cancer Pain
IASP	=	International Association for the Study of Pain
IDD	=	Implantation of Drug Delivery
MOR	=	Mu-Opiod Receptors
NGF	=	Nerve Growth Factor
NPH	=	Postherpetic Neuralgia
PNS	=	Peripheral Nerve Stimulation
PRF	=	Pulsed Radiofrequency
SCS	=	Spinal Cord Stimulation
tDCS	=	Transcranial Direct Current Stimulation
TENS	=	Transcutaneous Electrical Nerve Stimulation
TMS	=	Transcranial Magnetic Stimulation
TrkA	=	Myelinated Tropomyosin Kinase A
TRPV1	=	Vanilloid Receptor 1
VAS	=	Visual Analog Scale
WHO	=	World Health Organization

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The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Merskey, H.; Albe Fessard, D.; Bonica, J.J.; Carmon, A.; Dubner, R.; Kerr, F.W.L.; Lindblom, U.; Mumford, J.M.; Nathan, P.W.; Noordenbos, W.; Pagni, C.A.; Renaer, M.J.; Sternbach, R.A.; Sunderland, S. Recommended by the IASP Subcommittee on Taxonomy. Pain terms: a list with definitions and notes on usage. *Pain,* **1979**, *6*(3), 249-252. PMID: 460932

[2] Khosravi, S.P.; del Castillo R.A.; Pérez, M. G. Manejo del dolor oncológico. *An. Med. Interna (Madrid),* **2007**, *24*, 554-557. http://dx.doi.org/10.4321/S0212-71992007001100010

[3] Williams, A.C.; Craig, K.D. Updating the definition of pain. *Pain,* **2016**, *157*(11), 2420-2423. http://dx.doi.org/10.1097/j.pain.0000000000000613 PMID: 27200490

[4] Bernstein, L.R. A pragmatic, general definition of pain. *Pain Rep.,* **2020**, *5*(2), e813. http://dx.doi.org/10.1097/PR9.0000000000000813 PMID: 32441702

[5] Havelin, J.; King, T. Mechanisms underlying bone and joint pain. *Curr. Osteoporos. Rep.,* **2018**, *16*(6), 763-771. http://dx.doi.org/10.1007/s11914-018-0493-1 PMID: 30370434

[6] Solans, M.; Chan, D.S.M.; Mitrou, P.; Norat, T.; Romaguera, D. A systematic review and meta-analysis of the 2007 WCRF/AICR score in relation to cancer-related health outcomes. *Ann. Oncol.,* **2020**, *31*(3), 352-368. http://dx.doi.org/10.1016/j.annonc.2020.01.001 PMID: 32067678

[7] Money, S.; Garber, B. Management of cancer pain. *Curr. Emerg. Hosp. Med. Rep.,* **2018**, *6*, 141-146. http://dx.doi.org/10.1007/s40138-018-0170-9

[8] Mantyh, P.W. Cancer pain and its impact on diagnosis, survival and quality of life. *Nat. Rev. Neurosci.,* **2006**, *7*(10), 797-809. http://dx.doi.org/10.1038/nrn1914 PMID: 16988655

[9] Candido, K.D.; Kusper, T.M.; Knezevic, N.N. New Cancer Pain Treatment Options. *Curr. Pain Headache Rep.,* **2017**, *21*(2), 12. http://dx.doi.org/10.1007/s11916-017-0613-0 PMID: 28265859

[10] DelaGarza-Montano, P.; Estrada-Villaseñor, E.; Dominguez, R. R.; Martinez-Lopez, V.; Avila-Luna, A.; Alfaro-Rodriguez, A.; Garciadiego-Cazares, D.; Carlos, A.; Hernandez-Perez, A.D.; Bandala, C. Epidemiological Aspects of osteosarcoma, giant cell tumor and chondrosarcoma musculoskeletal tumors--experience of the National Rehabilitation Institute, Mexico City. *Asian Pac. J. Cancer Prev.,* **2015**, *16*(15), 6451-6455. http://dx.doi.org/10.7314/APJCP.2015.16.15.6451 PMID: 26434858

[11] Marko, T.A.; Diessner, B.J.; Spector, L.G. Prevalence of Metastasis at Diagnosis of Osteosarcoma: An International Comparison. *Pediatr. Blood Cancer,* **2016**, *63*(6), 1006-1011. http://dx.doi.org/10.1002/pbc.25963 PMID: 26929018

[12] Yoneda, T.; Hiasa, M.; Okui, T. Crosstalk between sensory nerves and cancer in bone. *Curr. Osteoporos. Rep.,* **2018**, *16*(6), 648-656. http://dx.doi.org/10.1007/s11914-018-0489-x PMID: 30343404

[13] WHO Normative Guidelines on Pain Management. **2007**.http://www.who.int/medicines/areas/quality_safety/delphi_study_pain_guidelines.pdf

[14] Orr, P.M.; Shank, B.C.; Black, A.C. The role of pain classification systems in pain management. *Crit. Care Nurs. Clin. North Am.,* **2017**, *29*(4), 407-418. http://dx.doi.org/10.1016/j.cnc.2017.08.002 PMID: 29107304

[15] European Commission Health in the European Union: Special EUROBAROMETER **2007**.http://ec.europa.eu/health/ph_publication/eb_health_en.pdf

[16] Cervero, F.; Laird, J.M.A. Visceral pain. *Lancet,* **1999**, *353*(9170), 2145-2148. http://dx.doi.org/10.1016/S0140-6736(99)01306-9 PMID: 10382712

[17] Bouhassira, D. Neuropathic pain: Definition, assessment and epidemiology. *Rev. Neurol. (Paris),* **2019**, *175*(1-2), 16-25. http://dx.doi.org/10.1016/j.neurol.2018.09.016 PMID: 30385075

[18] Carr, D.B.; Goudas, L.C. Acute pain. *Lancet.,* **1999**, *353*(9169), 2051-2058.

[19] Wurhman, E.; Cooney, M.F. Acute pain: assessment and treatment. *Medscape,* **2011**.https://www.medscape.com/viewarticle/735034_print

[20] Hylands-White, N.; Duarte, R.V.; Raphael, J.H. An overview of treatment approaches for chronic pain management. *Rheumatol. Int.,* **2017**, *37*(1), 29-42. http://dx.doi.org/10.1007/s00296-016-3481-8 PMID: 27107994

[21] IASP. Part III: Pain Terms, A Current List with Definitions and Notes on Usage. *Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy, edited by H. Merskey and N. Bogduk, ISAP Press, Seattle,* **1994**, 209-214. https://www.iasppain.org/PublicationsNews/Content.aspx?ItemNumber=1673

[22] Loeser, J.D.; Melzack, R. Pain: an overview. *Lancet.,* **1999**, *353*(9164), 1607-1609. http://dx.doi.org/10.1016/S0140-6736(99)01311-2

[23] von Baeyer, C.L. Children's self-reports of pain intensity: scale selection, limitations and interpretation. *Pain Res. Manag.,* **2006**, *11*(3), 157-162. http://dx.doi.org/10.1155/2006/197616 PMID: 16960632

[24] Hester, N.; Foster, R.; Kristensen, K. Measurement of pain in children: Generalizability and validity of the Pain Ladder and the Poker Chip Tool.*Tyler D, Krane E, eds. Pediatric Pain, Vol 15: Advances in Pain Research and Therapy*; New York: Raven Press, **1990**, pp. 79-84.

[25] Mahon, P.; Holsti, L.; Siden, H.; Strahlendorf, C.; Turnham, L.; Giaschi, D. Using colors to assess pain in toddlers: validation of "the rainbow pain scale"-a proof-of-principle study. *J. Pediatr. Oncol. Nurs.,* **2015**, *32*(1), 40-46. http://dx.doi.org/10.1177/1043454214555197 PMID: 25416519

[26] Hicks, C.L.; von Baeyer, C.L.; Spafford, P.A.; van Korlaar, I.; Goodenough, B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain,* **2001**, *93*(2), 173-183. http://dx.doi.org/10.1016/S0304-3959(01)00314-1 PMID: 11427329

[27] Cline, M.E.; Herman, J.; Shaw, E.R.; Morton, R.D. Standardization of the visual analogue scale. *Nurs. Res.,* **1992**, *41*(6), 378-380. http://dx.doi.org/10.1097/00006199-199211000-00013 PMID: 1437591

[28] von Baeyer, C.L.; Spagrud, L.J.; McCormick, J.C.; Choo, E.; Neville, K.; Connelly, M.A. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. *Pain,* **2009**, *143*(3), 223-227. http://dx.doi.org/10.1016/j.pain.2009.03.002 PMID: 19359097

[29] Pagé, M.G.; Katz, J.; Stinson, J.; Isaac, L.; Martin-Pichora, A.L.; Campbell, F. Validation of the numerical rating scale for pain intensity and unpleasantness in pediatric acute postoperative pain: sensitivity to change over time. *J. Pain,* **2012**, *13*(4), 359-369. http://dx.doi.org/10.1016/j.jpain.2011.12.010 PMID: 22424915

[30] Tesler, M.D.; Savedra, M.C.; Holzemer, W.L.; Wilkie, D.J.; Ward, J.A.; Paul, S.M. The word-graphic rating scale as a measure of children's and adolescents' pain intensity. *Res. Nurs. Health,* **1991**, *14*(5), 361-371. http://dx.doi.org/10.1002/nur.4770140507 PMID: 1891622

[31] Haefeli, M; Elfering, A. Pain assessment. *Eur Spine J.,* **2006**, *15*(1), 17-24. http://dx.doi.org/10.1007/s00586-005-1044-x

[32] Vicente, H.M.T.; Delgado, B. S.; Bandrés, M.F.; Ramírez, I., de la Torre, M.V.; Capdevila, G.L. Valoración del dolor. revisión comparativa de escalas y cuestionarios. *Rev. Soc. Esp. Dolor,* **2018**, *25*(4), 228-236. http://dx.doi.org/10.20986/resed.2018.3632/2017

[33] Besson, J.M. The neurobiology of pain. *Lancet.,* **1999**, *353*(9164), 1610-15. http://dx.doi.org/10.1016/S0140-6736(99)01313-6

[34] Pergolizzi, J.; Ahlbeck, K.; Aldington, D.; Alon, E.; Coluzzi, F.; Dahan, A.; Huygen, F.; Kocot-Kępska, M.; Mangas, A.C.; Mavrocordatos, P.; Morlion, B.; Müller-Schwefe, G.; Nicolaou, A.; Pérez Hernández, C.; Sichère, P.; Schäfer, M.; Varrassi, G. The development of chronic pain: physiological CHANGE necessitates a multidisciplinary approach to treatment. *Curr. Med. Res. Opin.,* **2013**, *29*(9), 1127-1135. http://dx.doi.org/10.1185/03007995.2013.810615 PMID: 23786498

[35] Payne, R. Anatomy, physiology, and neuropharmacology of cancer pain. *Med. Clin. North Am.,* **1987**, *71*(2), 153-167. http://dx.doi.org/10.1016/S0025-7125(16)30863-X PMID: 3546978

[36] Chwistek, M. Recent advances in understanding and managing cancer pain. *F1000Res.,* **2017**, *6,*945. http://dx.doi.org/10.12688/f1000research.10817.1

[37] Mancino, M.; Ametller, E.; Gascón, P.; Almendro, V. The neuronal influence on tumor progression. *Biochim. Biophys. Acta,* **2011**, *1816*(2), 105-118. PMID: 21616127

[38] Patel, M.K.; Kaye, A.D.; Urman, R.D. Tanezumab: Therapy targeting nerve growth factor in pain pathogenesis. *J. Anaesthesiol. Clin. Pharmacol.,* **2018**, *34*(1), 111-116. PMID: 29643634

[39] Miller, K.E.; Hoffman, E.M.; Sutharshan, M.; Schechter, R. Glutamate pharmacology and metabolism in peripheral primary afferents: physiological and pathophysiological mechanisms. *Pharmacol. Ther.,* **2011**, *130*(3), 283-309. http://dx.doi.org/10.1016/j.pharmthera.2011.01.005 PMID: 21276816

[40] Du, X.; Li, J.; Li, M.; Yang, X.; Qi, Z.; Xu, B.; Liu, W.; Xu, Z.; Deng, Y. Research progress on the role of type I vesicular glutamate transporter (VGLUT1) in nervous system diseases. *Cell Biosci.,* **2020**, *10*, 26. http://dx.doi.org/10.1186/s13578-020-00393-4 PMID: 32158532

[41] Nencini, S.; Ringuet, M.; Kim, D.H.; Chen, Y.J.; Greenhill, C.; Ivanusic, J.J. Mechanisms of nerve growth factor signaling in bone nociceptors and in an animal model of inflammatory bone pain. *Mol. Pain,* **2017**, *13*, 1744806917697011. http://dx.doi.org/10.1177/1744806917697011 PMID: 28326938

[42] Mantyh, P.W. The neurobiology of skeletal pain. *Eur. J. Neurosci.,* **2014**, *39*(3), 508-519. http://dx.doi.org/10.1111/ejn.12462 PMID: 24494689

[43] Castañeda-Corral, G.; Jimenez-Andrade, J.M.; Bloom, A.P.; Taylor, R.N.; Mantyh, W.G.; Kaczmarska, M.J.; Ghilardi, J.R.; Mantyh, P.W. The majority of myelinated and unmyelinated sensory nerve fibers that innervate bone express the tropomyosin receptor kinase A. *Neuroscience,* **2011**, *178*, 196-207. http://dx.doi.org/10.1016/j.neuroscience.2011.01.039 PMID: 21277945

[44] Jimenez-Andrade, J.M.; Mantyh, W.G.; Bloom, A.P.; Ferng, A.S.; Geffre, C.P.; Mantyh, P.W. Bone cancer pain. *Ann. N. Y. Acad. Sci.,* **2010**, *1198*, 173-181. http://dx.doi.org/10.1111/j.1749-6632.2009.05429.x PMID: 20536932

[45] Hiasa, M.; Okui, T.; Allette, Y.M.; Ripsch, M.S.; Sun-Wada, G.H.; Wakabayashi, H.; Roodman, G.D.; White, F.A.; Yoneda, T. Bone pain induced by multiple myeloma is reduced by targeting V-ATPase and ASIC3. *Cancer Res.,* **2017**, *77*(6), 1283-1295. http://dx.doi.org/10.1158/0008-5472.CAN-15-3545 PMID: 28254863

[46] Argyriou, A.A.; Cavaletti, G.; Bruna, J.; Kyritsis, A.P.; Kalofonos, H.P. Bortezomib-induced peripheral neurotoxicity: an update. *Arch. Toxicol.,* **2014**, *88*(9), 1669-1679. http://dx.doi.org/10.1007/s00204-014-1316-5 PMID: 25069804

[47] Schutzer-Weissmann, J.; Farquhar-Smith, P. Post-herpetic neuralgia - a review of current management and future directions. *Expert Opin. Pharmacother.,* **2017**, *18*(16), 1739-1750. http://dx.doi.org/10.1080/14656566.2017.1392508 PMID: 29025327

[48] Coluzzi, F.; Di Bussolo, E.; Mandatori, I.; Mattia, C. Bone metastatic disease: taking aim at new therapeutic targets. *Curr. Med. Chem.,* **2011**, *18*(20), 3093-3115. http://dx.doi.org/10.2174/092986711796391660 PMID: 21651483

[49] Berenson, J.R.; Lichtenstein, A.; Porter, L.; Dimopoulos, M.A.; Bordoni, R.; George, S.; Lipton, A.; Keller, A.; Ballester, O.; Kovacs, M.J.; Blacklock, H.A.; Bell, R.; Simeone, J.; Reitsma, D.J.; Heffernan, M.; Seaman, J.; Knight, R.D. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N. Engl. J. Med.,* **1996**, *334*(8), 488-493. http://dx.doi.org/10.1056/NEJM199602223340802 PMID: 8559201

[50] Rosen, L.S.; Gordon, D.; Kaminski, M.; Howell, A.; Belch, A.; Mackey, J.; Apffelstaedt, J.; Hussein, M.; Coleman, R.E.; Reitsma, D.J.; Seaman, J.J.; Chen, B.L.; Ambros, Y. Zoledronic acid *versus* pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J.,* **2001**, *7*(5), 377-387. PMID: 11693896

[51] Gimsing, P.; Carlson, K.; Turesson, I.; Fayers, P.; Waage, A.; Vangsted, A.; Mylin, A.; Gluud, C.; Juliusson, G.; Gregersen, H.; Hjorth-Hansen, H.; Nesthus, I.; Dahl, I.M.; Westin, J.; Nielsen, J.L.; Knudsen, L.M.; Ahlberg, L.; Hjorth, M.; Abildgaard, N.; Andersen, N.F.; Linder, O.; Wisløff, F. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. *Lancet Oncol.,* **2010**, *11*(10), 973-982. http://dx.doi.org/10.1016/S1470-2045(10)70198-4 PMID: 20863761

[52] Lipton, A.; Jun, S. RANKL inhibition in the treatment of bone metastases. *Curr. Opin. Support. Palliat. Care,* **2008**, *2*(3), 197-203. http://dx.doi.org/10.1097/SPC.0b013e32830baac2 PMID: 18685421

[53] Body, J.J.; Facon, T.; Coleman, R.E.; Lipton, A.; Geurs, F.; Fan, M.; Holloway, D.; Peterson, M.C.; Bekker, P.J. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin. Cancer Res.,* **2006**, *12*(4), 1221-1228. http://dx.doi.org/10.1158/1078-0432.CCR-05-1933 PMID: 16489077

[54] Halvorson, K.G.; Kubota, K.; Sevcik, M.A.; Lindsay, T.H.; Sotillo, J.E.; Ghilardi, J.R.; Rosol, T.J.; Boustany, L.; Shelton, D.L.; Mantyh, P.W. A blocking antibody to nerve growth factor attenuates skeletal pain induced by prostate tumor cells growing in bone. *Cancer Res.,* **2005**, *65*(20), 9426-9435. http://dx.doi.org/10.1158/0008-5472.CAN-05-0826 PMID: 16230406

[55] Sevcik, M.A.; Ghilardi, J.R.; Peters, C.M.; Lindsay, T.H.; Halvorson, K.G.; Jonas, B.M.; Kubota, K.; Kuskowski, M.A.; Boustany, L.; Shelton, D.L.; Mantyh, P.W. Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization. *Pain,* **2005**, *115*(1-2), 128-141. http://dx.doi.org/10.1016/j.pain.2005.02.022 PMID: 15836976

[56] Sjölund, K.F.; Yang, R.; Lee, K.H.; Resnick, M. Randomized study of pregabalin in patients with cancer-induced bone pain. *Pain Ther.,* **2013**, *2*(1), 37-48. http://dx.doi.org/10.1007/s40122-013-0009-8 PMID: 25135035

[57] Lim, F.M.Y.; Bobrowski, A.; Agarwal, A.; Silva, M.F. Use of corticosteroids for pain control in cancer patients with bone metastases: a comprehensive literature review. *Curr. Opin. Support. Palliat. Care,* **2017**, *11*(2), 78-87. http://dx.doi.org/10.1097/SPC.0000000000000263 PMID: 28306570

[58] Kumar, A.; Weber, M.H.; Gokaslan, Z.; Wolinsky, J.P.; Schmidt, M.; Rhines, L.; Fehlings, M.G.; Laufer, I.; Sciubba, D.M.; Clarke, M.J.; Sundaresan, N.; Verlaan, J.J.; Sahgal, A.; Chou, D.; Fisher, C.G. Metastatic spinal cord compression and steroid treatment: a systematic review. *Clin. Spine Surg.,* **2017**, *30*(4), 156-163. http://dx.doi.org/10.1097/BSD.0000000000000528 PMID: 28437329

[59] Fallon, M.; Giusti, R.; Aielli, F.; Hoskin, P.; Rolke, R.; Sharma, M.; Ripamonti, C.I. ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann. Oncol.,* **2018**, *29*, iv166-iv191. http://dx.doi.org/10.1093/annonc/mdy152

[60] Corder, G.; Castro, D.C.; Bruchas, M.R.; Scherrer, G. Endogenous and exogenous opioids in pain. *Annu. Rev. Neurosci.,* **2018**, *41*, 453-473. http://dx.doi.org/10.1146/annurev-neuro-080317-061522 PMID: 29852083

[61] Ferdousi, M.; Finn, D.P. Stress-induced modulation of pain: Role of the endogenous opioid system. *Prog. Brain Res.,* **2018**, *239*, 121-177. http://dx.doi.org/10.1016/bs.pbr.2018.07.002 PMID: 30314566

[62] Law, P.Y.; Wong, Y.H.; Loh, H.H. Molecular mechanisms and regulation of opioid receptor signaling. *Annu. Rev. Pharmacol. Toxicol.,* **2000**, *40*, 389-430.

http://dx.doi.org/10.1146/annurev.pharmtox.40.1.389 PMID: 10836142

[63] Coluzzi, F.; Raffa, R.B.; Pergolizzi, J.; Rocco, A.; Locarini, P.; Cenfra, N.; Cimino, G.; Mattia, C. Tapentadol prolonged release for patients with multiple myeloma suffering from moderate-to-severe cancer pain due to bone disease. *J. Pain Res.,* **2015**, *8*, 229-238.
http://dx.doi.org/10.2147/JPR.S83490 PMID: 26064064

[64] Coluzzi, F.; Pergolizzi, J.; Raffa, R.B.; Mattia, C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. *Ther. Clin. Risk Manag.,* **2015**, *11*, 515-523.
http://dx.doi.org/10.2147/TCRM.S79409 PMID: 25848298

[65] Coluzzi, F. Assessing and treating chronic pain in patients with end-stage renal disease. *Drugs,* **2018**, *78*(14), 1459-1479.
http://dx.doi.org/10.1007/s40265-018-0980-9 PMID: 30206801

[66] Kim, J.W.; Min, C.K.; Mun, Y.C.; Park, Y.; Kim, B.S.; Nam, S.H.; Koh, Y.; Kwon, J.H.; Choe, P.G.; Park, W.B.; Kim, I. Varicella-zoster virus-specific cell-mediated immunity and herpes zoster development in multiple myeloma patients receiving bortezomib- or thalidomide-based chemotherapy. *J. Clin. Virol.,* **2015**, *73*, 64-69.
http://dx.doi.org/10.1016/j.jcv.2015.10.018 PMID: 26546878

[67] Pickering, G.; Martin, E.; Tiberghien, F.; Delorme, C.; Mick, G. Localized neuropathic pain: an expert consensus on local treatments. *Drug Des. Devel. Ther.,* **2017**, *11*, 2709-2718.
http://dx.doi.org/10.2147/DDDT.S142630 PMID: 29066862

[68] Ghilardi, J.R.; Röhrich, H.; Lindsay, T.H.; Sevcik, M.A.; Schwei, M.J.; Kubota, K.; Halvorson, K.G.; Poblete, J.; Chaplan, S.R.; Dubin, A.E.; Carruthers, N.I.; Swanson, D.; Kuskowski, M.; Flores, C.M.; Julius, D.; Mantyh, P.W. Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. *J. Neurosci.,* **2005**, *25*(12), 3126-3131.
http://dx.doi.org/10.1523/JNEUROSCI.3815-04.2005 PMID: 15788769

[69] Anand, P.; Bley, K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br. J. Anaesth.,* **2011**, *107*(4), 490-502.
http://dx.doi.org/10.1093/bja/aer260 PMID: 21852280

[70] Moore, D.C.; Pellegrino, A.E. Pegfilgrastim-induced bone pain: a review on incidence, risk factors, and evidence-based management. *Ann. Pharmacother.,* **2017**, *51*(9), 797-803.
http://dx.doi.org/10.1177/1060028017706373 PMID: 28423916

[71] Xu, H.; Gong, Q.; Vogl, F.D.; Reiner, M.; Page, J.H. Risk factors for bone pain among patients with cancer receiving myelosuppressive chemotherapy and pegfilgrastim. *Support. Care Cancer,* **2016**, *24*(2), 723-730.
http://dx.doi.org/10.1007/s00520-015-2834-2 PMID: 26162536

[72] Lower, E.E.; Charif, M.; Bartelt, M. Reduced dose pegfilgrastim is associated with less bone pain without increased neutropenia: a retrospective study. *Cancer Chemother. Pharmacol.,* **2018**, *82*(1), 165-170.
http://dx.doi.org/10.1007/s00280-018-3607-7 PMID: 29869680

[73] Kirshner, J.J.; McDonald, M.C. III.; Kruter, F.; Guinigundo, A.S.; Vanni, L.; Maxwell, C.L.; Reiner, M.; Upchurch, T.E.; Garcia, J.; Morrow, P.K. NOLAN: a randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim. *Support. Care Cancer,* **2018**, *26*(4), 1323-1334.
http://dx.doi.org/10.1007/s00520-017-3959-2 PMID: 29147854

[74] Duggan, C.; Murphy, L.; Costello, V.; Leary, E.O.; Yousif, A.D.; Blazkova, S.; Dowling, M. Oral loratadine in the management of G-CSF-induced bone pain: a pilot study. *Br. J. Nurs.,* **2019**, *28*(4), S4-S11.
http://dx.doi.org/10.12968/bjon.2019.28.4.S4 PMID: 30811242

[75] Gavioli, E.; Abrams, M. Prevention of granulocyte-colony stimulating factor (G-CSF) induced bone pain using double histamine blockade. *Support. Care Cancer,* **2017**, *25*(3), 817-822.
http://dx.doi.org/10.1007/s00520-016-3465-y PMID: 27817104

[76] National Library of Medicine (U.S.). Loratadine for the Reduction of G-CSF Induced Bone Pain in Patients With Multiple Myeloma Undergoing Stem Cell Mobilization. **2020**. NCT04211259. Available at: https://clinicaltrials.gov/ct2/show/NCT04211259

[77] National Library of Medicine (U.S.). Evaluation of Loratadine for G-CSF Induced Bone Pain in Patients With Hematologic Malignancies. **2014**. NCT02305979. Available at: https://clinicaltrials.gov/ct2/show/NCT02305979

[78] Mhaskar, R.; Kumar, A.; Miladinovic, B.; Djulbegovic, B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. *Cochrane Database Syst. Rev.,* **2017**, *12*(12), CD003188.
http://dx.doi.org/10.1002/14651858.CD003188.pub4 PMID: 29253322

[79] Hoskin, P.; Sundar, S.; Reczko, K.; Forsyth, S.; Mithal, N.; Sizer, B.; Bloomfield, D.; Upadhyay, S.; Wilson, P.; Kirkwood, A.; Stratford, M.; Jitlal, M.; Hackshaw, A. A multicenter randomized trial of ibandronate compared with single-dose radiotherapy for localized metastatic bone pain in prostate cancer. *JNCI. J. Natl. Cancer Inst.,* **2015**, *107*(10), djv197.
http://dx.doi.org/10.1093/jnci/djv197 PMID: 26242893

[80] Wang, G.; Chen, J.; Ma, R.; Xu, W.; Yan, C.; Niu, C. Effects of zoledronic acid and ibandronate in the treatment of cancer pain in rats with lung cancer combined with bone metastases. *Oncol. Lett.,* **2018**, *16*(2), 1696-1700.
http://dx.doi.org/10.3892/ol.2018.8804 PMID: 30008855

[81] Purnell, H.; Monson, K. Single-Dose local radiation therapy compared with ibandronate in treating patients with localized metastatic bone pain. **2013**. Identifier NCT00082927. Available at: https://www.clinicaltrials.gov/ct2/show/NCT00082927

[82] Altundag, K.; Dizdar, O.; Ozsaran, Z.; Ozkok, S.; Saip, P.; Eralp, Y.; Komurcu, S.; Kuzhan, O.; Ozguroglu, M.; Karahoca, M. Phase II study of loading-dose ibandronate treatment in patients with breast cancer and bone metastases suffering from moderate to severe pain. *Onkologie,* **2012**, *35*(5), 254-258.
http://dx.doi.org/10.1159/000338369 PMID: 22868504

[83] National Library of Medicine (U.S.). A study to assess the short term efficacy of intravenous ibandronate (bondronat) in participants with metastatic bone pain due to breast cancer. **2015**. Identifier NCT02553707. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT02553707

[84] National Library of Medicine (U.S.). A study of loading doses of intravenous bondronat (ibandronate) in patients with breast cancer and malignant bone disease. **2014**. Identifier NCT00502736. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT00502736

[85] National Library of Medicine (U.S.). A study of loading doses of intravenous bondronat (ibandronate) in patients with breast cancer and metastatic bone disease. **2014**. Identifier NCT00478270. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT00478270

[86] Saad, F.; Eastham, J. Zoledronic Acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. *Urology,* **2010**, *76*(5), 1175-1181.
http://dx.doi.org/10.1016/j.urology.2010.05.026 PMID: 21056263

[87] Choi, J.; Lee, E.J.; Yang, S.H.; Im, Y.R.; Seong, J. A prospective Phase II study for the efficacy of radiotherapy in combination with zoledronic acid in treating painful bone metastases from gastrointestinal cancers. *J. Radiat. Res. (Tokyo),* **2019**, *60*(2), 242-248.
http://dx.doi.org/10.1093/jrr/rry092 PMID: 30445597

[88] National Library of Medicine (U.S.). Study comparing full-dose radiotherapy versus reduced dose in the management of bone metastasis in patients with breast cancer receiving zoledronic acid. **2014**. Identifier NCT00172029.

[89] National Library of Medicine (U.S.). Efficacy and safety of zoledronic acid in the treatment of bone metastases-related pain in patients with prostate cancer (TRAPEZE). **2017**. Identifier NCT00375648. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT00375648

[90] National Library of Medicine (U.S.). A study to assess the efficacy of intravenous/oral bondronat (ibandronate) in patients with metastatic bone disease experiencing moderate to severe pain. **2017**. Identifier NCT00099177. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT00099177

[91] National Library of Medicine (U.S.). Study to assess the efficacy of intravenous bondronat (ibandronate) in patients with malignant and painful bone disease. **2017**. Identifier NCT00099203. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT00099203

[92] Brown, D.C.; Agnello, K.; Iadarola, M.J. Intrathecal resiniferatoxin in a dog model: efficacy in bone cancer pain. *Pain,* **2015**, *156*(6), 1018-1024. http://dx.doi.org/10.1097/j.pain.0000000000000115 PMID: 25659068

[93] Danson, S.; Mulvey, M.R.; Turner, L.; Horsman, J.; Escott, K.; Coleman, R.E.; Ahmedzai, S.H.; Bennett, M.I.; Andrew, D. An exploratory randomized-controlled trial of the efficacy of the Src-kinase inhibitor saracatinib as a novel analgesic for cancer-induced bone pain. *J. Bone Oncol.,* **2019**, *19*, 100261. http://dx.doi.org/10.1016/j.jbo.2019.100261 PMID: 31667062

[94] Fallon, M.; Hoskin, P. J.; Colvin, L.A.; Fleetwood-Walker, S.M.; Adamson, D.; Byrne, A.; Laird, B.J. Randomized double-blind trial of pregabalin *versus* placebo in conjunction with palliative radiotherapy for cancer-induced bone pain. *J Clin Oncol.,* **2016**, *34*(6), 550-6. http://dx.doi.org/10.1200/JCO.2015.63.8221

[95] Xu, L.; Zhang, Y.; Huang, Y. Advances in the treatment of neuropathic pain. *Adv. Exp. Med. Biol.,* **2016**, *904*, 117-129. http://dx.doi.org/10.1007/978-94-017-7537-3_9 PMID: 26900067

[96] Vielhaber, A.; Portenoy, R.K. Advances in cancer pain management. *Hematol. Oncol. Clin. North Am.,* **2002**, *16*(3), 527-541. http://dx.doi.org/10.1016/S0889-8588(02)00016-3 PMID: 12170566

[97] Mercadante, S. Non pharmacological interventions and non-fentanyl pharmacological treatments for breakthrough cancer pain: A systematic and critical review. *Crit. Rev. Oncol. Hematol.,* **2018**, *122*, 60-63. http://dx.doi.org/10.1016/j.critrevonc.2017.12.016 PMID: 29458790

[98] Portenoy, R.K. Treatment of cancer pain. *Lancet,* **2011**, *25;377*(9784), 2236-47. http://dx.doi.org/10.1016/S0140-6736(11)60236-5

[99] Scarborough, B.M.; Smith, C.B. Optimal pain management for patients with cancer in the modern era. *CA Cancer J. Clin.,* **2018**, *68*(3), 182-196. http://dx.doi.org/10.3322/caac.21453 PMID: 29603142

[100] Liu, W.C.; Zheng, Z.X.; Tan, K.H.; Meredith, G.J. Multidimensional treatment of cancer pain. *Curr. Oncol. Rep.,* **2017**, *19*(2), 10. http://dx.doi.org/10.1007/s11912-017-0570-0 PMID: 28220448

[101] Dipan, P.; Saurabh, D.; Weber, G. Neuromodulation of cancer pain: current concepts and treatment strategies. *Topics in Pain Management,* **2016**, *31*(12), 1-10. http://dx.doi.org/10.1097/01.TPM.0000488727.32096.c9

[102] Searle, R.D.; Bennett, M.I.; Johnson, M.I.; Callin, S.; Radford, H. Transcutaneous electrical nerve stimulation (TENS) for cancer bone pain. *J. Pain Symptom Manage.,* **2009**, *37*(3), 424-428. http://dx.doi.org/10.1016/j.jpainsymman.2008.03.017 PMID: 18790599

[103] Bennett, M.I.; Johnson, M.I.; Brown, S.R.; Radford, H.; Brown, J.M.; Searle, R.D. Feasibility study of Transcutaneous Electrical Nerve Stimulation (TENS) for cancer bone pain. *J. Pain,* **2010**, *11*(4), 351-359. http://dx.doi.org/10.1016/j.jpain.2009.08.002 PMID: 19853518

[104] Mokhtari, T.; Ren, Q.; Li, N.; Wang, F.; Bi, Y.; Hu, L. Transcutaneous electrical nerve stimulation in relieving neuropathic pain: basic mechanisms and clinical applications. *Curr. Pain Headache Rep.,* **2020**, *24*(4), 14. http://dx.doi.org/10.1007/s11916-020-0846-1 PMID: 32072323

[105] Teoli, D.; An, J. Transcutaneous Electrical Nerve Stimulation (TENS). *StatPearls*; StatPearls Publishing: Treasure Island, FL, **2020**.