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REVIEW OTHER

Understanding the Physiopathology of Pain Pathways for a Practical Approach of Cancer Pain Management

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Abstract Pain associated with cancer is often the first symptom reported with major repercussions on patient's quality of life. Mechanical compression, release of algogenic substances by the tumor or the complications of oncologic treatment represent the major causes. Nociceptive and neuropathic pain are both induced by different mediators that give rise to a neuroinflammation creating a peripheral and central sensitization responsible of chronic pain.

Understanding the pain pathway may orientate to the most appropriate treatment. Oral medication should be often reevaluated to consider multimodal analgesia including interventional pain procedures with intrathecal therapy and neuromodulation.

Keywords Cancer pain · Physiopathology · Interventional pain technique

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Cancer Pain: Introduction

Every year, more than 18 million cancers are diagnosed worldwide, and the incidence is constantly rising. It is one of the world's leading causes of morbidity and mortality. Pain associated with cancer is one of the most frequently reported symptoms, often the presenting symptoms of the disease, with often harmful consequences for patients. Indeed, the persistence of pain or its lack of relief has major repercussions on affective or emotional components, leading to increased anxiety, depression, irritability and even cognitive disorders. Consequently, this may reduce patient's quality of life and even life expectancy [1].

The improvement and development of specific treatments, such as certain immunotherapies, combined with improved early detection, has led to an increase in survival rates for many cancers [2]. At the same time, recent meta-analyses have shown only a slight decrease in the incidence of pain over the last few years, with an overall pain prevalence of 44.5%. Moderate-to-severe pain is reported in a third of cancer patients, but is most prevalent in over 50% of patients at advanced stages of the disease. So, despite improvements in oncological specific therapies, management of cancer pain remains a major public health issue [3, 4].

The aim of this review is to describe and translate the pathophysiological mechanisms of cancer pain, into as many therapeutic options as possible.

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Causes of Cancer Pain

Pain is often the first symptom of cancer, due to neoplastic invasion of various tissues (skin, bone, muscle and viscera). Thus, pain in oncology can have several different origins, often intertwined with each other. On one hand, the tumor itself, through mechanical compression, ischemic phenomena and the release of algogenic substances, can directly cause pain. On the other hand, specific treatments, such as radiotherapy, chemotherapy, immunotherapy or surgery, may also give rise to iatrogenic pain [5]. So-called sequelae pain may also be present in patients considered to be in remission. In fact, a recent study shows that around half of cancer survivors experience chronic pain following chemotherapy, radiotherapy or surgery [6].

The current view of cancer pain and therefore its management rely on the nosological classification of pain [7]. Nociceptive pain results from irritation or a reduction in the activation threshold of nociceptors located in superficial structures: skin, subcutaneous tissue, muscles and the skeletal-articular system (somatic pain) or in organs located in the thorax, abdomen and pelvis (visceral pain). This type of pain is generally due to the infiltration of tissues by a tumor or metastases, or to tissue damage following treatment directed against the tumor. On the other hand, tumor growth or treatments can cause direct lesions on the central or peripheral nervous system structures, resulting in neuropathic pain. This type of pain is often poorly tolerated and difficult to control. Pain in cancer patients is generally of mixed origin, and rarely manifests itself as a single semiological type [8]. Thus, current drug management based on oral opioid added with other co-analgesics and antidepressant or anticonvulsant medications, respectively for the nociceptive and neuropathic components, often proves limited effects particularly in the advanced phase of the disease [9].

Physiopathology of Cancer Pain

Physiology of Pain

The nociceptive system is made up of afferent fibers, with multiple specialized membrane receptors transducing the painful stimulus. Centripetal axons from spinal ganglion neurons synapse with second-order neurons in the dorsal horn of the spinal cord. The axons of the deutoneurons, responsible for the sensory-discriminative aspects of pain, then project to the thalamic nuclei, which relay the information to the cortical structures via a 3rd-order neuron. Other pathways, including brainstem, thalamic and cortical centers, are responsible for the affective and motivational components of pain stimuli. Descending inhibitory pathways interact with local circuits in the spinal cord to regulate transmission of the nociceptive message to higher centers [10]. This brief description of the nociceptive system is intended to emphasize that the mechanisms and pathways of nociception are ubiquitous. In other words, from a single anatomical substrate, all pain is conveyed by the components of the nociceptive system (Fig. 1).

Cancer Pain

Cancer pain is a complex entity, encompassing the characteristics of pathological, inflammatory and neuropathic pain, and capable of evolving according to the patient's life course. Thus, the concept of multimorphic pain proposes a dynamic vision, different from conventional nosological approaches that identify acute pain, chronic cancer pain and chronic pain secular to cancer treatments [11]. Chronic cancer pain generally manifests itself in the context of the progression of the disease where, in addition to the central sensitization mechanisms common to chronic pain, acute nociceptive mechanisms may be superimposed. This is the specific pathophysiological feature of most cancer pain, which is both nociceptive and neuropathic but also nociplastic. Like all chronic pain, it is part of a biopsychosocial model with its various components, not just the sensory-discriminative component. In fact, the representation of cancer, its management and its evolution, are different elements to be taken into consideration. The International Classification of Diseases (11th revision) classifies cancer pain into 2 main categories: chronic pain associated with cancer treatment, which we will not detail in this review [12, 13], and chronic cancer pain [14].

Physiopathology of Chronic Cancer Pain

The mechanism of cancer pain is a complex pathological process involving cellular, tissue and systemic changes that occur during tumor proliferation and invasion. Tumor tissue is composed of cancer cells and supporting stroma cells. This results in interactions between cancer/stromal cells, the peripheral and central nervous systems and the immune system [15, 16].

Somatic pain caused by the tumor and its environment provokes neurogenic inflammation in damaged tissue, leading to peripheral sensitization of sensory afferents. It is caused and exacerbated by tumor compression and induced ischemia of surrounding tissues, with the release of algogenic substances by tumor cells leading to direct and persistent activation of nociceptors [17]. These sensitization phenomena also follow the anatomical pathways of nociception in a centripetal way, leading to central sensitization phenomena [16]. Among the mechanisms of so-called

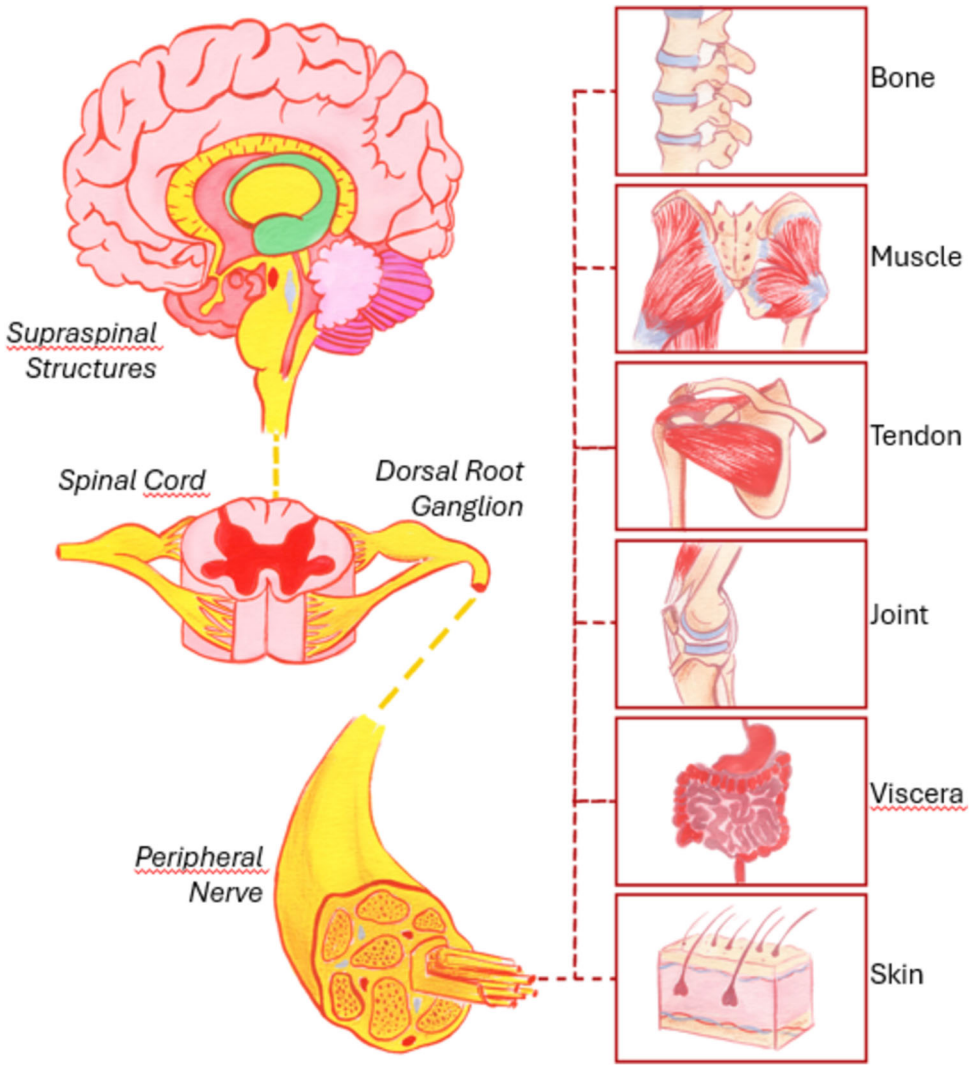

Fig. 1 Schematic representation of the somatic and visceral innervation by the nervous system: following activation of a nociceptor in the periphery, the nociceptive message is then sent to supraspinal structures via the peripheral nerve, the dorsal root ganglion and the spinal cord

nociceptive pain, it is interesting to focus on bone pain. Tumor-induced bone pain is the result of several mechanisms. Tumor growth in the bone marrow cavity stimulates stromal cells to secrete many inflammatory substances such as cytokines/chemokines, neurotrophic factors and colony-stimulating factors, triggering nociceptor activation. Tumor cells themselves also produce number of algogenic substances, capable of stimulating axonal nerve endings distributed throughout the bone [18]. On the other hand, parathyroid hormone-related protein secreted by tumor cells disrupts bone homeostasis, promoting bone resorption by osteoclasts [19]. Moreover, osteoclasts are known to release H + and Cl ions acidifying the environment, also contributing to osteolysis [20]. Thus, a decrease in local tissue pH is also associated with muscle and bone pain [21]. In addition, the production of neurotrophic factors, such as nerve growth factor, induces a pathological sprouting of sensory afferents [22] and increased expression of ion channels [23]. When cancer cells invade and damage nerve endings within the bone, the resulting pain involves a combination of persistent inflammation and neuropathological processes, leading to hyperexcitability from the spinal cord-to-supraspinal structures. In light of these pathophysiological mechanisms, the use of NSAIDs or corticosteroids reducing inflammation, the use of bisphosphonates or inhibitors of RANK ligand reducing the osteoclast/osteoblast imbalance, the use of cryotherapy and radiotherapy destroying the tumor itself or surgical stabilization to prevent the risk of fracture or in the case of a pathological fracture are all possible therapeutic options against tumor and its consequence.

Clinical pearl: pain coming from ischiopubic bone metastasis, for which various sessions of analgesic radiotherapy or cryotherapy of the lesion do not provide significant relief for the patient. If, despite various techniques targeting the tumor the pain persists, it is possible to consider modulating the

nociceptive message at spinal level using intrathecal analgesia.

Visceral pain is fundamentally different from somatic pain. Symptoms include diffuse, poorly localized pain, with certain particularities such as spasm and a heaviness sensation. Indeed, visceral receptors are sensitive to a wide range of mechanical stimuli (tumor compression or distension of hollow organs) or chemical stimuli (inflammatory substances released by injured tissue or tumor cells). This neuroinflammation, at the level of visceral afferents, will generate peripheral sensitization with centripetal repercussions at spinal or supraspinal level, as previously described [24]. Another distinctive feature of visceral pain is its dual innervation by the parasympathetic system (mainly vagus nerve, but also pelvic nerves for the lower part of the body) and spinal afferent fibers that travel through the orthosympathetic pathways [25, 26]. This makes the sympathetic system an interesting target for the treatment of visceral pain. Moreover, the afferents transmitting visceral pain, synapse with neurons in the intermediate gray matter near the ependyma, whose axons project into the medial dorsal column, along the posterior intermediate septum separating the Goll and Burdach tract [27]. The discovery of this sensory component in the medial dorsal spinal column has historically been a target for reducing visceral cancer pain by the section of medial fibers by midline myelotomy [28, 29]. Spinal visceral nociceptive modulation by intrathecal analgesia is therefore an interesting therapeutic option for patients with visceral pain.

Clinical pearl: in the case of pancreatic Cancer *with epigastric pain that is difficult to control with drug treatment, neurolysis of the celiac plexus may be proposed. If analgesia is ineffective or to transient, spinal modulation using intrathecal analgesia is an interesting and permanent option for patients* [30].

Neuropathic pain is defined as pain resulting from injury or disease affecting the somatosensory system [31]. Damage to the nervous system can be linked to tumor infiltration of nerve structures, neuroinflammatory activity of tumor cells, or may be related to cancer treatments (chemotherapy, radiotherapy, and surgery) [32]. Tumors are not strongly innervated by sensory neurons. However, rapid tumor growth damages nervous tissue by compression causing mechanical damage, ischemia and Wallerian degeneration [33]. Proteolytic enzymes produced by tumor cells can also damage sensory and sympathetic fibers, leading to neuropathic pain. Following a peripheral nerve damage, remodeling at both peripheral and central levels is widely described as peripheral and central sensitization. Peripheral changes include ectopic electrical activity, which is the cause of spontaneous pain. These are largely linked to changes in the expression and distribution of ion channels. The presence of abnormal connections between fibers, i.e., ephapses, is veritable "short-circuits" between the different nociceptive fibers. Finally, sensitization of nociceptive receptors has also been described: this is characterized by a reduction in their activation threshold, an increase in their response to supraliminal stimulation and the appearance of spontaneous activity [34]. This sensitization is largely linked to neurogenic inflammation phenomena resulting in the local release of cytokines and neuropeptides. Indeed, neuroinflammation is characterized by the activation of immune and/or glial cells around injured axons. These cells release these chemical mediators, which will modify nerve transmission and trigger the influx of other immune and/or glial cells. Moreover, this neuroinflammation is not confined to the area around the lesion, but spreads throughout the neuraxis, leading to central sensitization mechanisms [35, 36]. Intravenous or subcutaneous infusion of lidocaine [37, 38] or intravenous ketamine [39] could be considered in refractory cancer pain and have been described as both safe and efficacious. Ketamine is an effective analgesic in chronic pain conditions including cancer-related neuropathic pain. Sub-anesthetic concentrations of ketamine have shown opioid sparing ability by counteracting the central nervous system sensitization. In addition, it is difficult to target the tumor directly in the case of nerve invasion causing pain, apart from radiotherapy, because of the risk of further nerve damage. In addition to antineuropathic drug treatments, it is possible to modulate the nociceptive message in the periphery by continuous nerve block, at spinal level by intrathecal analgesia or by a spinal cord stimulator.

Clinical pearl: in the case of a lesion invading the sacral plexus, analgesic radiotherapy is initially used. If pain persists, intrathecal analgesia may be offered, because interventional radiological techniques are limited in cases of plexus invasion.

From a mechanistic point of view, cancer pain is divided into 2 types: nociceptive and neuropathic. However, the previous pathophysiological aspects demonstrated that chronic stimulation of primary afferents by tumor compression and its environment, leads to neuroinflammation mechanisms, ultimately inducing peripheral and central sensitization of the nociceptive system. Neuroinflammation provides a common anatomical and pathophysiological explanation of chronic pain [24]. In addition, a mixed nociceptive and neuropathic component is often clinically reported in cancer pain. Finally, this semiological and mechanistic dichotomy (nociceptive versus neuropathic) may be of pharmacological interest, but not fully relevant in terms of interventional pain techniques. The most

important aspect is the clinical impression added with a perfect topographical description of the painful symptoms in order to identify the pain generators and the anatomical substrate that drive the nociceptive message. Thus, the nociceptive pathway represents the target of interventional analgesic therapies, as well as the tumor itself.

Toward a New Approach to Cancer Pain Management

Current Cancer Pain Management

The World Health Organization (WHO) adopts a global approach, proposing strategies that are accessible to as many people as possible, with particular attention given to countries with low socioeconomic levels. Historically, the 3-step scale was created for cancer pain, with the aim of democratizing opioids. In 2019, a revision does not distinguish between the levels 2 and 3, which seem much closer to clinical practice in oncology. The distinction between nociceptive and neuropathic pain leads to the use of co-medication for the neuropathic component, such as antidepressants or anticonvulsants. Apart from cancer, these drugs used as first-line treatment often have a poor therapeutic response: number needed to treat (NNT) of 3.6, 6.4 and 7 for tricylic antidepressant, serotonin and noradrenaline reuptake inhibitors and gabapentinoids, respectively [40]. Moreover, topical treatments such as capsaicin and local injections using botulinum toxin are potential alternatives, particularly for localized neuropathic pain [41]. The literature highlights the relatively high persistence of pain associated with cancer or following its treatment [4] and it seems more evident that oral drug therapy alone is rapidly insufficient.

The Place of Interventional Pain Management

When pain persists, despite well-managed multimodal analgesia or in certain specific indications, interventional and surgical pain management techniques can be indicated. A 4th step of interventional techniques was proposed, grouping together the procedures that target the peripheral and central (epidural or intrathecal administration) nervous system or directly the tumor (radiotherapy and cryotherapy) [42]. However, this step proposes different interventional techniques with no place for a management algorithm, except for the intrathecal analgesia or for neurolytic blocks (coeliac plexus and superior hypogastric plexus). For example, interventional treatments for neuropathic pain are based on weak evidence and are not proposed to patients with neuropathic cancer pain [43]. Moreover, the WHO's 2019 revision, which has a universal and global view, pointed out these therapeutic possibilities. Unfortunately for patients, interventional pain management is often offered later in the treatment pathway, apart from established indications as cementoplasty and radiotherapy on the tumor or metastasis [44]. Currently, management of cancer pain is presented as two parts: in the first line, drugs with morphine and, in the event of insufficient analgesia, a second line with interventional treatments without recommendations concerning their use. Considering that the two types of treatment (medication and interventional) are complementary, they should be offered simultaneously. This current vision of cancer pain management is perhaps based on the postulate that "most of the time pain disappears when the cause is removed?" However, not every patient goes into remission, and even then sequelae of pain may persist.

Concept of Anatomical and Physiological Reasoning

Based on the pathophysiological mechanisms described above, and after a clinical and radiological assessment of a potential anatomical target, how can the pain generator be modulated?

In first line, various possibilities can be proposed to reduce the size of the tumor to get an effect on the mechanical compression and the associated inflammatory phenomena using radiotherapy, surgery, cryotherapy, radiofrequency or embolization. Secondly, if the previous techniques have failed or are not possible (e.g., no new exposure to radiation is possible, limited by the size or type of tumor), the next question is to find out which nerve structures are involved in the conduction of the message on the universal nociception pathways (Fig. 2). The latter, called neuromodulation, is defined as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" [45, 46].

The nervous system can be modulated in 2 ways: by an injection/single intervention or by an implanted device. The former may consist of chemical neurolysis, thermoablation or pulsed radiofrequency. None of these peripheral neuromodulation techniques has been shown to be superior to the other. For example, chemical or thermal neurolysis, which are lesional techniques, should be reserved for pure sensory nerves or mixed nerves in palliative patients. In case of visceral upper abdominal pain, coeliac plexus neurolysis is indicated, while for the pelvic area, superior hypogastric plexus neurolysis is preferred. Perineural pulsed radiofrequency, which is a nondestructive technique, can be used on mixed or sensory nerves. All of these techniques can be performed under radiological guidance (CT-scan and fluoroscopy for plexus and spinal interventions, ultrasound for peripheral nerves). Perineural

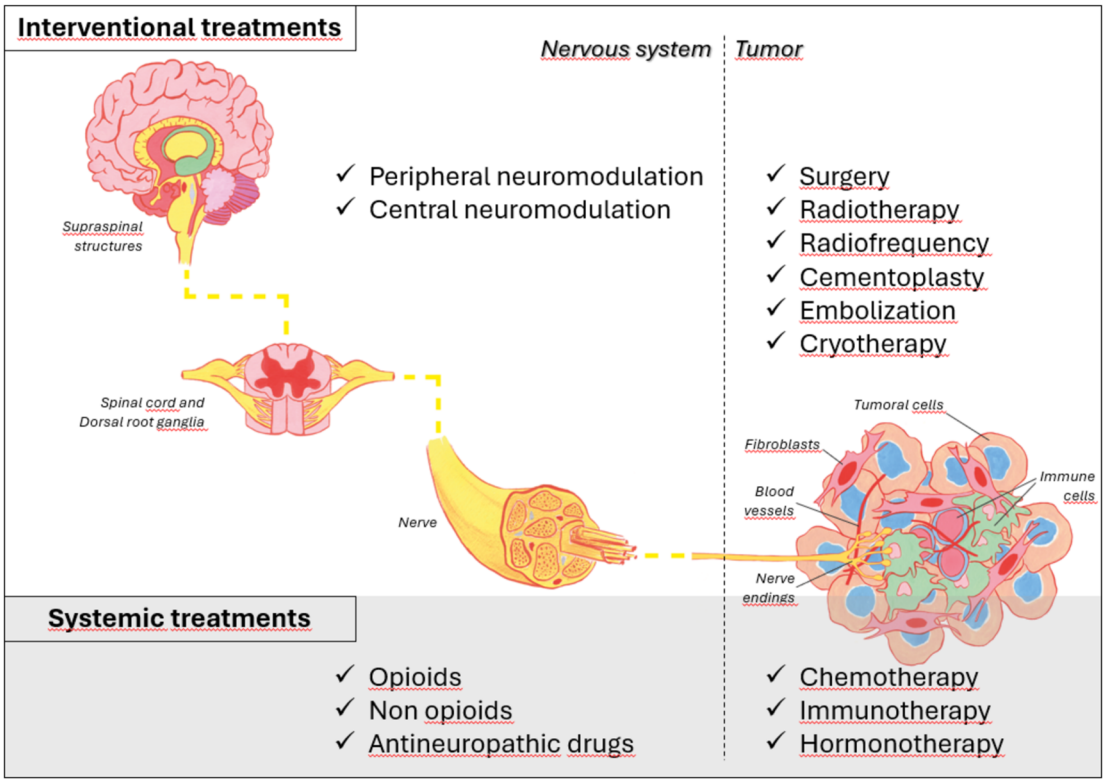

Fig. 2 Cancer pain management may be based on different combinations of therapeutic options: reducing the size of the tumor by interventional treatments (radiotherapy, surgery, cryotherapy, radiofrequency and embolization) or by systemic treatments directed against the tumor (chemotherapy, immunotherapy or hormone therapy) and modulating the message on the nociceptive pathways by systemic analgesic treatments (opioid, non-opioid or antineuropathic drugs) or by neuromodulation techniques along the peripheral or central nervous system

or epidural catheter can be proposed as a transitional possibility while awaiting a more permanent solution, either for patients in a palliative situation.

But for long-term efficiency, implanted device are often preferred. Chemical agents such as opioids, local anesthetics or ziconotide can be infused in the cerebrospinal fluid using this system, to get stronger results with lesser side effects by bypassing the oro-digestive cycle and the blood–brain barrier [47]. All neuromodulation techniques are still based on the historical pragmatism of interrupting pain pathways previously proposed in certain situations with DREZotomy or cordotomy for example [48].

Conclusion

The number of new cancers is constantly increasing each year in concomitance with patient survival, due to the progression of specific oncological management (prevention, early detection and treatments). However, the latest data in the literature highlight the persistence of a population of patients suffering from cancer pain. Currently, the overall management of these patients is relatively compartmentalized, with specific treatment initiated in the oncology department, and may limit drug pain management by the pain physician, as well as the interventional options offered often late at advanced stages of the disease. The choice of pain management should match and be systematically coordinated with the cancer treatment, the progression of the disease and the patient's wishes. In addition, the pain management strategy should be based on the concept of multimodal analgesia, derived from postoperative pain management, combining pharmacology and interventions simultaneously with the aim of improving the patient's outcome. We have already mentioned the common pathophysiological basis of chronic cancer pain. The interest is to highlight an up to date discussion fresh thinking of cancer pain, considering the painful territory and the anatomical substrate linked to the painful message, in addition to the mechanistic aspect. However, to elaborate such concept, it is necessary to organize, list and propose interventional options using structured recommendations.

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Declarations

Conflict of interests The authors declare that they have no conflict of interest.

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Informed Consent For this type of study, informed consent is not required.

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