Original Article

THE BRITISH PAIN SOCIETY

British Journal of Pain
2014, Vol. 8(4) 154–162

DOI: 10.1177/2049463714545136
bjp.sagepub.com
SAGE

Cancer pain physiology

Sarah Falk[1], Kirsty Bannister[2] and Anthony H Dickenson[2]

Abstract

Mechanisms of inflammatory and neuropathic pains have been elucidated and translated to patient care by the use of animal models of these pain states. Cancer pain has lagged behind since early animal models of cancer-induced bone pain were based on the systemic injection of carcinoma cells. This precluded systematic investigation of specific neuronal and pharmacological alterations that occur in cancer-induced bone pain. In 1999, Schwei et al. described a murine model of cancer-induced bone pain that paralleled the clinical condition in terms of pain development and bone destruction, confined to the mouse femur. This model prompted related approaches, and we can now state that cancer pain may include elements of inflammatory and neuropathic pains but also unique changes in sensory processing. Cancer-induced bone pain results in progressive bone destruction, elevated osteoclast activity and distinctive nocifensive behaviours (indicating the triad of ongoing, spontaneous and movement-induced hyperalgesia). In addition, cancer cells induce an inflammatory infiltrate and release growth factors, cytokines, interleukins, chemokines, prostanoids and endothelins, resulting in a reduction of pH to below 5 and direct deformation of primary afferents within bone. These peripheral changes, in turn, drive hypersensitivity of spinal cord sensory neurons, many of which project to the parts of the brain involved in the emotional response to pain. Within the spinal cord, a unique neuronal function reorganization within segments of the dorsal horn of the spinal cord receiving nociceptive input from the bone are discussed. Changes in certain neurotransmitters implicated in brain modulation of spinal function are also altered with implications for the affective components of cancer pain. Treatments are described in terms of mechanistic insights and in the case of opioids, which modulate pain transmission at spinal and supraspinal sites, their use can be compromised by opioid-induced hyperalgesia. We discuss evidence for how this comes about and how it may be treated.

Keywords

Cancer pain, cancer-induced bone pain, peripheral and central pain mechanisms, spinal modulation, opioid-induced hyperalgesia

Introduction

Worldwide, more than 14 million new cases of cancer were diagnosed in 2012, and the incidence is rising.[1] As detection and treatment have improved, an increasing number of patients are living with chronic cancer or the long-term effects of surviving cancer. It is, therefore, important to focus on the physical and psychological consequences of living with this disease state. Cancer pain, and especially pain caused by metastasis of the primary cancer to the bone, is a common and highly debilitating complication for many

[1]Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[2]Departments of Neuroscience, Physiology and Pharmacology, University College London, London, UK

Corresponding author:
Anthony H Dickenson, Departments of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, WC1E 6BT London, UK.
Email: anthony.dickenson@ucl.ac.uk

cancer patients. Overall, 75–90% of patients with metastatic or advanced-stage cancer develop severe pain which significantly compromises their quality of life.[2]

Metastatic bone pain or cancer-induced bone pain is a complex pain state often involving background pain, spontaneous pain and incidence or movement-evoked pain.[3–5] The background pain is typically described as a dull continuous pain that increases in intensity as the disease is progressing and is generally treated fairly successfully with traditional analgesics. Therapeutically, the spontaneous and movement-evoked pains are much more difficult to manage, and the treatment is often associated with intolerable adverse effects.[6] These types of pain are often referred to as breakthrough pain, as they are experienced as episodes of extreme pain breaking through the underlying level of background pain. In addition, they are often unpredictable, rapid in onset and short in duration.[3,4] Besides the pain associated with the cancer itself, many patients also suffer from pain arising as a consequence of therapeutic interventions, such as surgery or chemotherapy. Overall, this means that the pain experienced by the patients is typically a synergy of nociceptive events, sometimes making it difficult to tease out the specific underlying mechanisms. In addition, most of the current analgesic therapies are based on non-cancer pain conditions, making them far from optimal for the treatment of cancer-associated pain.

One of the main reasons for the poor pharmacological targeting of cancer pain lies in the molecular complexity of the pain state. Cancer pain is regarded a mixed-mechanism pain state as it involves inflammatory, neuropathic and cancer-specific pain mechanisms. Currently, most of our knowledge about cancer pain is based on preclinical models of cancer-induced bone pain, which will, therefore, be the main focus of this review. Most animal models of cancer-induced bone pain are based on inoculation of cancer cells directly into the bone marrow of femur or tibia.[7] This has been the model of choice for studying cancer-associated pain as the cancer is restricted to single area that is easy to assess for pain behaviour evaluation, but also results in animals with a much better general health and with lower variability compared to models with systemic injections of cancer cells. Importantly, these models are also characterized by the same key mechanisms observed in the patients, including bone remodelling, pain and neurobiological changes in the periphery and at the level of the spinal cord.

Peripheral pain mechanisms

Cancer-induced bone pain involves a complex interplay of various peripheral mechanisms, adding to an alteration of the sensory impulses sent to the spinal cord, and causing a general state of hyperexcitability of the neurons in the dorsal horn.[8] Often inflammatory, neuropathic, ischaemic and cancer-specific mechanisms occur at the same time at the site of a tumour.[2,9] As the tumour grows, inflammatory infiltration will occur due to tissue damage of the surrounding tissue and release of various cytokines and inflammatory and pain mediators from the cancer cells and from a potential necrotic centre in larger tumours. The tumour cells might also cause direct damage to the sensory nerves by infiltration or compression, or inducing remodelling in the local microenvironment causing hyperinnervation or denervation of the bone, or stretching of the densely innervated periosteum.

Although the mechanisms involved in driving and maintaining cancer pain are less understood than some of the more classical pain states, such as inflammatory/nociceptive or neuropathic pain, both cancer-specific mechanisms and mechanisms shared with inflammatory and neuropathic pain have been identified.[2] It is now recognized that the bone is supplied by a dense network of sensory and sympathetic neurons innervating the bone marrow, the mineralized part of the bone and the periosteum.[10–12] Retrograde labelling and functional studies have demonstrated that the size, neurochemistry and segmental distribution of these neurons play a role in the nociceptive processing to the spinal cord.[13] The dense innervation of the bone puts the neuronal network in close contact with the microenvironment of the bone, and it is, therefore, not surprising that changes in the bone homeostasis can affect and sensitize the peripheral terminals of the sensory and sympathetic neurons altering the impulses to the spinal cord. In normal bone homeostasis, remodelling of the bone is balanced between osteoclast-induced bone resorption and osteoblast-mediated bone formation.[14] However, under pathological conditions, such as tumour growth, the balance is shifted resulting in osteolytic (net resorption) or osteoblastic (net deposition) bone lesions or both.[15] Most metastatic cancer types cause an overall net resorption resulting in disruption of the microarchitecture, and hence a decrease in the strength and resistance to bending of the bone, eventually leading to an increased risk of fractures and sometimes a systemic state of hypercalcemia.[16] Besides a general weakening of the bone, the growth of the tumour cells also initiates a vicious circle of molecular events in the microenvironment of the bone driven by osteoclast activation. The tumour cells interrupt the normal balance of the RANK–RANKL (receptor activator of nuclear factor kappa-B–Receptor activator of nuclear factor kappa-B ligand) system by increasing the release of RANKL from tumour cells, tumour-associated T-cells and osteoblasts.[17,18] The increased level of RANKL stimulates

the proliferation and activation of osteoclasts by activation of the RANK receptor expressed on the osteoclast precursor cells. In addition, the tumour cells secrete parathyroid hormone-related protein (PTHrP) also increasing the release of RANKL through stimulation of the osteoblasts. The increased amount of RANKL results in an increased osteoclast-mediated bone resorption causing not only bone degradation but also a local acidosis that can sensitize the sensory neurons through activation of acid-sensitive ion channels, such as the transient receptor potential cation channel 1 (TRPV1) and the acid-sensing ion channel 3 (ASIC3).[19] In addition, some cancer cells have a lower pH than normal cells, potentially adding to the local acidosis. To complete the vicious circle, the increased bone resorption is associated with release of Ca^{2+} and various growth factors, such as transforming growth factor beta (TGF-β) and insulin-like growth factor 1 (IGF1), overall stimulating additional growth of the tumour cells. Currently, the most effective treatment of pain associated with bone metastasis is based on an interruption of this vicious cycle, either by direct inhibition of the osteoclast activation or by decreasing the amount of free RANKL. In the clinic, bisphosphonates are now widely used to inhibit the osteoclast-induced bone resorption. The bisphosphonates bind to the bone and are taken up by the osteoclast by endocytosis as a part of the bone resorption. Once in the osteoclast, the bisphosphonates interfere with the normal metabolism of the cell, eventually leading to dysfunction and apoptosis. In both animal models and patients, bisphosphonates can effectively suppress bone resorption and alleviate pain.[20] And additional mode of action suggested to contribute to pain relief is the inhibition of the local acidosis otherwise produced by the bone-resorbing osteoclasts. Inhibiting the local acidosis might decrease some of the sensitization normally mediated through TRPV1 and ASIC3. Similarly, drugs such as osteoprotegerin and denosumab, which interfere with the RANK–RANKL binding and hence the osteoclast activation, have been demonstrated to effectively decrease bone resorption and bone pain in both animal models[21] and patients with different bone degenerative diseases including cancer-induced bone diseases.[22,23]

As mentioned, cancer-induced bone pain displays some of the characters observed in inflammatory pain conditions. The initial growth of the tumour and destruction of the surrounding tissue result in recruitment and infiltration of various inflammatory and immune cells such as macrophages, mast cells, neutrophils and T-lymphocytes, which eventually become part of the tumour-associated stromal cells together with endothelial cells and fibroblasts. These cells, in turn, release a number of growth factors, cytokines, interleukins, chemokines, prostanoids, endothelins, bradykinin, adenosine triphosphate (ATP) and so on of which several are speculated to contribute to the overall pain process by sensitizing or directly exciting the peripheral nerves.[2,19,24] Although non-steroidal anti-inflammatory drugs (NSAIDs) are routinely used in the clinic as a supplement to other stronger analgesics, the preclinical data are conflicting, and there is still a general lack of clinical data to support a significant effect in cancer pain.[2,17,25] The suggested additive effect of NSAIDs is likely to be associated with a reduced production of prostaglandins through inhibition of the cyclooxygenase (COX) pathway.[26,27]

Besides the cancer-associated and bone-associated pain, and the inflammatory component, an essential element in driving and maintaining cancer-induced bone pain is the peripheral nerves, especially the interface between the peripheral terminal and the local microenvironment in the bone. As mentioned, the bone is densely innervated by myelinated and unmyelinated sensory and sympathetic fibre. In healthy bones, the sensory and sympathetic fibres are normally not located in close proximity to each other; however, it has been demonstrated that the tumour cells can induce reorganization and sprouting of both fibre types, causing not only a general increase in the density of the fibres but also formation of neuroma-like structures with an abnormal intermingling of the two fibre types.[28] The remodelling of the sensory and sympathetic fibres has been speculated to contribute to the generation of the spontaneous breakthrough episodes often observed in cancer patients, as similar neuroma-like structures have been demonstrated in other conditions characterized by spontaneous ectopic pain episodes, such as complex regional pain syndrome.[28,29] The mechanism underlying the phenomenon is still not fully understood, but it has been suggested that the abnormal proximity of the sensory and sympathetic fibres facilitates excitation of the sensory neurons by release of various nociceptive factors from the sympathetic neurons. The reorganization of the sensory and sympathetic fibres is likely associated with increased release of nerve growth factor (NGF) for the tumour and tumour-associated cells. Jimenez-Andrade et al.[30] have demonstrated that preventive or late administration of anti-NGF can attenuate both sprouting and neuroma-like formations in mice, and also decrease the nociceptive behaviour without affecting the bone destruction or tumour growth. NGF has been demonstrated to have various pronociceptive actions in addition to remodelling of the peripheral nerve fibres. Through a series of intracellular signal pathways, NGF can both increase the expression on TRPV1 on the sensory nerves and sensitize the channel by phosphorylation.[31] In addition, NGF and its

receptor, neurotrophic tyrosine kinase receptor type 1 (TrkA), can form a complex that can be transported retrograde from the peripheral terminals to the cell body located in dorsal root ganglion (DRG), where it can initialize synthesis of neurotransmitters (substance P and calcitonin gene-related peptide), expression of receptor and channels (bradykinin receptor, P2X3, TRPV1, ASIC3 and sodium channels), transcription factors (Activating Transcription Factor 3 (ATF-3)) and structural molecules (neurofilaments and sodium-channel-anchoring molecule p11).[32] Furthermore, NGF has been suggested to modulate trafficking and expression of voltage-gated sodium channel (Nav) 1.8 and TRPV1.[33,34] Tanezumab, a monoclonal anti-NGF, has been successfully tested in clinic in the treatment of patients with osteoarthritis and lower back pain but was discontinued due to side-effect concerns.[35,36] However, anti-NGF might still be a potential treatment and palliation of cancer patients.

Various receptors and ion channels located on the peripheral nerves have been targeted in an attempt to understand and potentially treat cancer-induced bone pain. Channels that are highly expressed on the peripheral sensory neurons, either at the peripheral terminal or at the cells body, have been closely studied. These receptors, such as the P2X3 receptor[37,38] and TRPV1 receptor,[39] have an effect on the overall pain behaviour; however, a recent study has demonstrated that we might have to think beyond the traditional classification of nociceptive neurons and sensory processing to effectively target cancer-induced bone pain.[40] Traditionally, the nociceptors have been classified based on expression of specific ion channels and receptors, such as the Nav1.7 and Nav1.8, and it is generally accepted that more than 90% of the nociceptors express Nav1.8. However, in the study by Minett et al.,[40] it was demonstrated that the normal function of the Nav1.7- and Nav1.8-positive neurons was not critical for the development of pain behaviour in a mouse model of cancer-induced bone pain despite the fact that these Navs are highly essential for many other pain phenotypes. This also adds to the understanding of cancer-induced bone pain as a separate pain state, clearly highlighting that although some mechanisms are important for neuropathic, inflammatory and cancer-induced bone pain, some of the processing of the signal is also, at least partly, processed through completely different mechanisms in cancer-induced bone pain. This might be one of the key elements in understanding why the traditional analgesic therapies are failing in effectively treating cancer patients with metastatic bone pain.

Spinal events

Given the knowledge of the peripheral events in cancer pain, there are a number of potential targets for therapy, but another approach would be to modulate the central transmission of the painful messages, where the mechanisms of pain may be more common than the clearly different events behind tissue and nerve damage. Over time, the mouse models were validated further with the description of cancer-induced bone pain in different species, and the injection of mammary gland carcinoma cells into the tibia of rats, which resulted in astrocyte hypertrophy, progressive bone destruction and pain behaviour similar to the original mouse models,[41] which now provided the opportunity to measure neuronal activity at the level of the spinal cord in this species. The spinal cord is not only the first relay for incoming pain messages but also where central hyperexcitability is first established and where descending controls from the brain further act to change the level of excitability at these first relays. It is also a key site for opioid modulation of pain. Finally, the spinal cord sends ascending projections to the brain, both sensory areas and affective areas, hence being key to the establishment of the activity that will lead to the individual pain experience.

Clear changes are seen in the responses of the spinal cord neurons indicative of a hyperexcitability[17] in agreement with the idea of an ongoing central sensitization.[42] An important point is that the recording of sensory neurons allows the application of suprathreshold stimuli, unlike behaviour, that measures the threshold, so that the former enable the quantification of responses to high-intensity stimuli, and so allow the study of the underlying events that equate to the moderate to severe pains experienced by patients. These alterations are not the same as those seen in models of neuropathy or inflammation, supporting the concept of a unique pain state. Spinal neurons project in two main pathways. Projections run to the thalamus and then the cortex, providing information on the quality and location of the stimulus. Another pathway supplies the limbic brain via the parabrachial nucleus and so leads to the affective components of pain.[43] We have recently recorded from both populations of neurons and compared the coding of the spinal neurons to a selective heat stimulus and varied the area of skin stimulated. We then used the same stimulus in human psychophysics and recorded the electrocardiogram as well. The deep dorsal horn wide dynamic range (WDR) neurons, responding across the range of innocuous to noxious stimuli, coded the stimuli in perfect accord with the human pain experience, and the nociceptive-specific (NS) neurons, coded too, but were less well coded.[44] Thus, we can be confident that these neuronal responses can inform on human pain processing.

Recording in the superficial dorsal horn, compared to controls, cancer-induced bone pain leads to a greater proportion of WDR neurons which also showed hyperexcitable responses to mechanical, thermal and

electrical stimuli. This spinal lamina mainly projects to those brain areas involved in the affective component of pain, and hence the conclusion could be that there will be increased disruption of normal function that could lead to anxiety, depression and sleep problems seen in patients as well as a de novo ability of low-threshold inputs to be distressing.[45]

This change in neuronal populations has not yet been in other pain models but was confirmed in a murine model.[46] Furthermore, the catalogue of neuronal changes had very similar time-courses to the gradual development of pain behaviour,[47] suggesting a causal relationship between the measures.

A key link between the periphery and the central nervous system is the ability of calcium channels to open in response to action potentials in peripheral nerves and release transmitters such as glutamate and substance P on to receptors on spinal neurons, hence passing the pain messages on to the brain. The drugs gabapentin (GBP) and pregabalin (PGB) are effective in pain patients, mainly those with neuropathic pain, and modulate the activity of calcium channels. They do so by binding to the alpha-2 delta subunit of the channel and hence chronic GBP or PGB prevents the channel from being moved to its active site on the membrane where the transmitter is released.[48] The subunit is up-regulated after nerve injury so that the drugs have state-dependent effects. In the model of cancer-induced bone pain, researchers have reported that chronic treatment with GBP was able to reduce pain behaviour and, moreover, attenuated the hyperexcitable dorsal horn responses.[47] Behavioural effects of GBP have also been seen in the mouse models on both ongoing and movement-evoked pains.[49] Overall, the results suggest that abnormal transmitter release is an early stage in the subsequent spinal changes. This will include glutamate and one of its receptors, the *N*-methyl-D-aspartate (NMDA) receptor, has been widely implicated in neuronal excitability. Recent studies (Patel and Dickenson, unpublished) have shown the ability of low doses of systemic ketamine, the NMDA receptor blocker, to inhibit the responses of spinal WDR neurons in the model of cancer-induced bone pain, indicative of an intrinsic spinal hyperexcitabilty being driven by the NMDA receptor for glutamate, crucial to the induction of wind-up in these spinal neurons. The doses required were lower than those needed in control animals, suggesting that the spinal excitability is enhanced after cancer and forms a mechanistic basis for the use of ketamine in cancer pain patients.

The treatment with GBP also restored the neuronal population plasticity back towards the normal state *and* reset the neuronal populations, but when the treatment terminated, the abnormal state returned. This is not surprising since these agents are not able to change the peripheral events but are able to modulate the central consequences.

Since the spinal neurons project to the brain, in particular, the lamina I cells will impact upon descending controls that arise from altered amygdala, central grey and brainstem connectivity driven by the affective component of pain. Changes in peripheral and spinal signalling have impact on the processing of pain by the brain. A key system relaying in the rostroventral medulla (RVM) is a facilitatory 5-hydroxytryptamine (5-HT) drive, mediated by spinal 5-HT_3 receptors, that enhances both mechanical and thermal nociceptive transmission and allows WDR to produce a faithful coding of inputs.[50] We have reported enhancement of this system in cancer pain so that natural-evoked spinal neuronal responses in cancer animals are elevated by this descending pathway.[51] As in other models of various pain states, this RVM-generated 5-HT_3 descending pathway is not critical for the induction of the pain state but becomes active as the pain persists and so is important to the maintenance rather than the generation of chronic pain.[52,53] This would equate with the delayed appearance of co-morbidities too, as the limbic brain and descending pathways are slowly re-organized by the persistent pain messages.

The pharmacological events described so far act to attenuate excitability. As the World Health Organization (WHO) ladder suggests, opioids are the mainstay of treatment. Here, the ability of opioids to produce pain control is based on their actions to inhibit transmission of pain messages by activation of the opioid receptors. These are situated at key sites along the pain pathways with high numbers found at the level of the spinal cord. Most clinically used opioids act through the mu opioid receptor (MOR) and hence have actions that are similar although the pharmacokinetic profiles of different drugs are not the same. There are much positive data on opioids in the animal models[41,54–57] although some studies found a reduced efficacy of acute systemic morphine than in inflammatory models.[54] Furthermore, as in the clinic where incident pain needs high doses of opioids, acute opioid administration required elevated doses to modulate pain behaviour.[58,59] However, the guidelines suggest the use of prolonged release opioids and so a caveat with the above animal studies was the use of acute dosing.

We have, therefore, employed the chronic dosing of morphine over time,[55] and here the drug was effective. Cancer-induced bone pain prior to the final morphine injection was still significantly lower than in cancer animals receiving saline injections. As with GBP, the superficial dorsal horn neurons in morphine chronically treated animals had a reduced hyperexcitability although the altered phenotype of NS:WDR persisted.

Opioid-induced hyperalgesia

In the United Kingdom alone, 300,000 people are diagnosed with cancer every year and two-thirds of those will experience pain that requires a strong opioid. While morphine remains the 'gold-standard' analgesic, the chronic consumption of opioids does not only produce analgesia but can be associated with worsening paradoxical pain sensations; this is the so-called phenomenon of opioid-induced hyperalgesia (OIH). The clinical reality of OIH continues to prompt debate, but as early as the 19th century, it was recognized that the potency of opioid treatment could be limited according to the time required for use. Defined as the need for increasingly high levels of opioids to maintain pain inhibition after repeated drug exposure, clinicians face an ongoing problem when arguing in favour of a dichotomy between OIH and opioid tolerance, although the preclinical and clinical evidence dissociating these two distinct phenomena is mounting.[60]

Animal studies demonstrating neuroadaptive alterations in the pain modulatory circuitry following chronic opioid treatment are plentiful and reliable. Data detailing changes in the central glutaminergic system, spinal dynorphin content and descending facilitations provide a compelling dossier of changes to neuronal mechanisms that underlie this particular pain state. There is an enhanced response of spinal neurons to nociceptive neurotransmitters in rodent models of OIH and evidence of increased neuronal excitability in the deep dorsal horn of the spinal cord extends to colonic distension.[61] While the endogenous opioid system is not believed to modulate at least high-dose OIH, the involvement of the NMDA receptor system is indisputable. Previously, morphine-evoked nociceptive behavioural responses in mice were not reversed by pretreatment with naloxone. Instead, dose-dependent inhibition was achieved using intrathecal administration of NMDA receptor antagonist or NMDA ion channel blocker.[62]

Translating research from bench to clinic, and corroborating animal model and patient case data regarding OIH, is crucial. Reassuringly, a recent study showed that naloxone did not reverse the hyperalgesia experienced by healthy human volunteers who were briefly exposed to remifentanil.[63] Although it is true that these findings can only be related to high-dose acute opioid exposure, it is pertinent to note that the human study substantiated the findings of the earlier animal study mentioned. Similarly, perioperative administration of NMDA receptor antagonist ketamine is associated with lower post-operative pain scores and less opioid requirement in patients undergoing major lumbar spine surgery.[64] This ties in neatly with studies that highlight the therapeutic potential of methadone, an opioid receptor agonist and NMDA receptor antagonist, against the problem of OIH. A single intraoperative bolus of methadone, as opposed to continuous sufentanil infusion, reduced post-operative opioid requirement in patients by almost 50% both 48 hours and 72 hours after complex spinal surgery. Pain scores were also significantly lowered in this patient group who, by the very definition of their chronic pain problem, were controlling preoperative pain with opioid analgesics. The authors of the study recognized that their chances of developing hyperalgesia were thus enhanced and so the use of methadone offered a unique alternative treatment.[65]

Methadone is a key player in emerging therapies being offered to reverse or reduce the risk of patients developing the paradoxical pain sensations associated with chronic morphine exposure, and opioid switching is becoming an increasingly accepted practice. Previously, a study outlined details of patients admitted to an acute pain and palliative care unit on an emergency basis who underwent immediate and rapid titration with intravenous morphine. After a subset of patients developed OIH, switching and re-titrating to intravenous methadone was shown to achieve a stable analgesic response in those susceptible individuals.[66] Interestingly, in this study, patient pain was only scored using the numerical scale, and this is relevant for those patients who did not report worsening pain with intravenous morphine. Opioid addicts have an altered sensitivity to pain which is modality dependent, and in particular, their threshold for thermal pain is lowered. The percentage of patients with severe pain who developed OIH in the Mercadante study could have been higher simply because this modality was not tested.

Prospective clinical studies have reported increased post-operative pain in patients following increased perioperative opioid use. But whether or not acute intraoperative opioid exposure contributes to the development of OIH remains a debatable topic since Cortinez and colleagues reported no increased post-operative pain or post-operative opioid consumption in patients receiving intraoperative remifentanil during elective gynaecological surgery.[67] These contradictory reports could be to do with dosing, however, because patients in the latter study had lower total intraoperative opioid exposure.[61]

By combining the findings of animal studies investigating the central changes that must occur in order for hyperalgesia to manifest following chronic opioid treatment and the findings of patient studies investigating the prevalence of OIH and its characteristics, the use of morphine and other strong opioids in the clinic can be optimized. Combination therapies are believed to be an efficient way to tackle OIH. Following spinal infusion of opioid agonist and chronic opioid

exposure, the characteristics most commonly associated with neuropathy including spinal cord hypersensitivity, thermal hyperalgesia, increased spinal dynorphin content and opioid tolerance are observed in rats in the absence of peripheral pathology. Pregabalin, indicated for neuropathic pain, reduces neuronal hyperexcitability and visceral hypersensitivity following chronic morphine exposure in rats. Theoretically, pregabalin could offer a viable combination-therapy for patients suffering from OIH. This links to a very recent clinical study that showed a single preoperative dose of pregabalin in patients undergoing urological surgery attenuated the increased hyperalgesia, increased pain intensity and increased area of hyperalgesia otherwise experienced in these patients following high-dose remifentanil.[68]

The premise that enhanced functionality at 5-HT_3 receptors may be a contributory underlying mechanism in OIH is supported by many publications. Descending serotonergic circuits play a key role at spinal levels in regulating the therapeutic actions of pregabalin, and there is a reciprocity between the monoamines, 5-HT and noradrenaline. Dexmedetomidine, an alpha-2 adrenoceptor agonist, is shown to have an anti-hyperalgesic effect in patients undergoing laparoscopic surgery with high-dose remifentanil anesthesia.[68]

Ultimately, an ever-increasing number of studies published on those drugs that modify the OIH phenotype in animal models, as well as clinical data detailing the positive effects of combination therapies alongside opioid treatment, not only lend weight to those clinicians who recognize OIH as a real and debilitating pain state but also have great clinical implications. Indeed, the use of combinations has recently been reviewed,[69] and the issue is attempting to increase the pain control by targeting of two mechanisms. Alternatively, better tolerability might be achieved by allowing lower doses of two drugs. In patients and in animals, here is a positive action between morphine and GBP when combined.[70,71] There may be further benefits if, as suggested above, gabapentinoids are able to mitigate against OIH. Much further research is needed. Interestingly, tapentadol is a novel drug with a combination of pharmacological effects within a single molecule. The drug has been demonstrated to treat effectively both acute and chronic pain, both in animal models and in patients and is also effective on mixed pains, namely, low-back pain and, importantly, in cancer pain patients.[72,73] The drug acts by stimulating inhibitory MOR and mediating noradrenaline reuptake inhibition (NRI) leading to activation of the inhibitory alpha-2 adrenoceptor at spinal levels. These dual actions produce effective analgesia but with a reduced opioid load tolerability. We have demonstrated efficacy in a model of cancer-induced bone pain.[74]

Finally, reducing the tumour load will decrease the peripheral drives to the central pain signalling systems and there clearly is a place for interventional approaches, either by nerve block or by spinal delivery of agents. In the latter case, the ability to deliver high local doses of suitable agents could reduce pain while reducing side-effects. Based on targeted selective pharmacological ablation of key spinal cord pain transmitting neurons,[50] a recent proof of concept in dogs with cancer-induced bone pain[75] has led to a current trial NCT02036281 in terminal cancer pain patients.

The future looks hopeful since the animal models are providing mechanistic insights into the unique events that underlie cancer pain. They appear to translate to the patient and hence back- and forward-translation will help the patient. A number of novel targets have been identified that could lead to better therapies. The important issue that bedevils all pain states is how to find mechanisms in patients to guide therapy that could address the mechanisms? In other pains, the sensory phenotype of the patient is being addressed by sensory testing, questionnaires and descriptors,[71,76] and these approaches could be applied in cancer pain.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. World Health Organization. Cancer 2014, http://www.who.int/mediacentre/factsheets/fs297/en/ (accessed February 2014).
2. Falk S and Dickenson AH. Pain and nociception: mechanisms of cancer-induced bone pain. *J Clin Oncol*. Epub ahead of print 5 May 2014. DOI: 10.1200/JCO.2013.51.7219.
3. Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. *Eur J Pain* 2005; 9(2): 195–206.
4. Zeppetella G. Impact and management of breakthrough pain in cancer. *Curr Opin Support Palliat Care* 2009; 3(1): 1–6.
5. Caraceni A and Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain* 1999; 82(3): 263–274.
6. Deandrea S, Montanari M, Moja L, et al. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 2008; 19(12): 1985–1991.

7. Schwei MJ, Honore P, Rogers SD, et al. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. *J Neurosci* 1999; 19(24): 10886–10897.
8. Urch CE, Donovan-Rodriguez T and Dickenson AH. Alterations in dorsal horn neurones in a rat model of cancer-induced bone pain. *Pain* 2003; 106(3): 347–356.
9. Jimenez-Andrade JM, Mantyh WG, Bloom AP, et al. Bone cancer pain. *Ann NY Acad Sci* 2010; 1198: 173–181.
10. Mach DB, Rogers SD, Sabino MC, et al. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience* 2002; 113(1): 155–166.
11. Serre CM, Farlay D, Delmas PD, et al. Evidence for a dense and intimate innervation of the bone tissue, including glutamate-containing fibers. *Bone* 1999; 25(6): 623–629.
12. Jimenez-Andrade JM, Mantyh WG, Bloom AP, et al. A phenotypically restricted set of primary afferent nerve fibers innervate the bone versus skin: therapeutic opportunity for treating skeletal pain. *Bone* 2010; 46(2): 306–313.
13. Ivanusic JJ. Size, neurochemistry, and segmental distribution of sensory neurons innervating the rat tibia. *J Comp Neurol* 2009; 517(3): 276–283.
14. Blair HC. How the osteoclast degrades bone. *Bioessays* 1998; 20(10): 837–846.
15. Halvorson KG, Sevcik MA, Ghilardi JR, et al. Similarities and differences in tumor growth, skeletal remodeling and pain in an osteolytic and osteoblastic model of bone cancer. *Clin J Pain* 2006; 22(7): 587–600.
16. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006; 12(20 Pt 2): 6243s–6249s.
17. Urch C. The pathophysiology of cancer-induced bone pain: current understanding. *Palliat Med* 2004; 18(4): 267–274.
18. Clohisy DR, Perkins SL and Ramnaraine ML. Review of cellular mechanisms of tumor osteolysis. *Clin Orthop Relat Res* 2000; (373): 104–114.
19. Julius D and Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001; 413(6852): 203–210.
20. Drake MT, Clarke BL and Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; 83(9): 1032–1045.
21. Honore P, Luger NM, Sabino MA, et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. *Nat Med* 2000; 6(5): 521–528.
22. Schwarz EM and Ritchlin CT. Clinical development of anti-RANKL therapy. *Arthritis Res Ther* 2007; 9(Suppl. 1): S7.
23. Lipton A and Goessl C. Clinical development of anti-RANKL therapies for treatment and prevention of bone metastasis. *Bone* 2011; 48(1): 96–99.
24. Joyce JA and Pollard JW. Microenvironmental regulation of metastasis. *Nat Rev Cancer* 2009; 9(4): 239–252.
25. Patel S and Dickenson AH. An updates review: refresher course syllabus. In: Mogil JS (ed.) *Pain*. Washington, DC: IASP Press, 2010, pp. 27–35.
26. Chen EP and Smyth EM. COX-2 and PGE2-dependent immunomodulation in breast cancer. *Prostaglandins Other Lipid Mediat* 2011; 96(1–4): 14–20.
27. Vasko MR. Prostaglandin-induced neuropeptide release from spinal cord. *Prog Brain Res* 1995; 104: 367–380.
28. Mantyh WG, Jimenez-Andrade JM, Stake JI, et al. Blockade of nerve sprouting and neuroma formation markedly attenuates the development of late stage cancer pain. *Neuroscience* 2010; 171(2): 588–598.
29. Janig W and Baron R. Complex regional pain syndrome: mystery explained? *Lancet Neurol* 2003; 2(11): 687–697.
30. Jimenez-Andrade JM, Ghilardi JR, Castaneda-Corral G, et al. Preventive or late administration of anti-NGF therapy attenuates tumor-induced nerve sprouting, neuroma formation, and cancer pain. *Pain* 2011; 152(11): 2564–2574.
31. Zhang X, Huang J and McNaughton PA. NGF rapidly increases membrane expression of TRPV1 heat-gated ion channels. *EMBO J* 2005; 24(24): 4211–4223.
32. Pezet S and McMahon SB. Neurotrophins: mediators and modulators of pain. *Annu Rev Neurosci* 2006; 29: 507–538.
33. Gould HJ 3rd, Gould TN, England JD, et al. A possible role for nerve growth factor in the augmentation of sodium channels in models of chronic pain. *Brain Res* 2000; 854(1–2): 19–29.
34. Ji RR, Samad TA, Jin SX, et al. Woolf CJ. p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. *Neuron* 2002; 36(1): 57–68.
35. Spierings EL, Fidelholtz J, Wolfram G, et al. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. *Pain* 2013; 154(9): 1603–1612.
36. Hill R. Blocking the effects of NGF as a route to safe and effective pain relief–fact or fancy? *Pain* 2011; 152(10): 2200–2201.
37. Kaan TK, Yip PK, Patel S, et al. Systemic blockade of P2X3 and P2X2/3 receptors attenuates bone cancer pain behaviour in rats. *Brain* 2010; 133(9): 2549–2564.
38. Hansen RR, Nasser A, Falk S, et al. Chronic administration of the selective P2X3, P2X2/3 receptor antagonist, A-317491, transiently attenuates cancer-induced bone pain in mice. *Eur J Pharmacol* 2012; 688(1–3): 27–34.
39. Ghilardi JR, Rohrich H, Lindsay TH, et al. Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. *J Neurosci* 2005; 25(12): 3126–3131.
40. Minett MS, Falk S, Santana-Varela S, et al. Pain without nociceptors? Nav1.7-independent pain mechanisms. *Cell Rep* 2014; 6(2): 301–312.
41. Medhurst SJ, Walker K, Bowes M, et al. A rat model of bone cancer pain. *Pain* 2002; 96(1–2): 129–140.
42. Clohisy DR and Mantyh PW. Bone cancer pain. *Clin Orthop Relat Res* 2003; (Suppl. 415): S279–S288.
43. Mantyh PW and Hunt SP. Setting the tone: superficial dorsal horn projection neurons regulate pain sensitivity. *Trends Neurosci* 2004; 27(10): 582–584.
44. Sikandar S, Ronga I, Iannetti GD, et al. Neural coding of nociceptive stimuli-from rat spinal neurones to human perception. *Pain* 2013; 154(8): 1263–1273.
45. Bannister K, Bee LA and Dickenson AH. Preclinical and early clinical investigations related to monoaminergic pain modulation. *Neurotherapeutics* 2009; 6(4): 703–712.

46. Khasabov SG, Biorn C and Simone DA. Sensitization of spinal dorsal horn neurons in a murine model of cancer pain. In: *Society for Neuroscience 34th annual meeting* (Online abstract viewer/itinerary planner), San Diego, CA, 23–27 October 2004. Washington, DC: Society for Neuroscience.
47. Donovan-Rodriguez T, Dickenson AH and Urch CE. Gabapentin normalizes spinal neuronal responses that correlate with behavior in a rat model of cancer-induced bone pain. *Anesthesiology* 2005; 102(1): 132–140.
48. Bauer CS, Nieto-Rostro M, Rahman W, et al. The increased trafficking of the calcium channel subunit alpha2delta-1 to presynaptic terminals in neuropathic pain is inhibited by the alpha2delta ligand pregabalin. *J Neurosci* 2009; 29(13): 4076–4088.
49. Peters CM, Ghilardi JR, Keyser CP, et al. Tumor-induced injury of primary afferent sensory nerve fibers in bone cancer pain. *Exp Neurol* 2005; 193(1): 85–100.
50. Suzuki R, Morcuende S, Webber M, et al. Superficial NK1-expressing neurons control spinal excitability through activation of descending pathways. *Nat Neurosci* 2002; 5(12): 1319–1326.
51. Donovan-Rodriguez T, Urch CE and Dickenson AH. Evidence of a role for descending serotonergic facilitation in a rat model of cancer-induced bone pain. *Neurosci Lett* 2006; 393(2–3): 237–242.
52. Burgess SE, Gardell LR, Ossipov MH, et al. Time-dependent descending facilitation from the rostral ventromedial medulla maintains, but does not initiate, neuropathic pain. *J Neurosci* 2002; 22(12): 5129–5136.
53. Bannister K, Sikandar S, Bauer CS, et al. Pregabalin suppresses spinal neuronal hyperexcitability and visceral hypersensitivity in the absence of peripheral pathophysiology. *Anesthesiology* 2011; 115(1): 144–152.
54. Luger NM, Sabino MA, Schwei MJ, et al. Efficacy of systemic morphine suggests a fundamental difference in the mechanisms that generate bone cancer vs inflammatory pain. *Pain* 2002; 99(3): 397–406.
55. Wacnik PW, Kehl LJ, Trempe TM, et al. Tumor implantation in mouse humerus evokes movement-related hyperalgesia exceeding that evoked by intramuscular carrageenan. *Pain* 2003; 101(1–2): 175–186.
56. Urch CE, Donovan-Rodriguez T, Gordon-Williams R, et al. Efficacy of chronic morphine in a rat model of cancer-induced bone pain: behavior and in dorsal horn pathophysiology. *J Pain* 2005; 6(12): 837–845.
57. Baamonde A, Lastra A, Juarez L, et al. Effects of the local administration of selective mu-, delta-and kappa-opioid receptor agonists on osteosarcoma-induced hyperalgesia. *Naunyn Schmiedebergs Arch Pharmacol* 2005; 372(3): 213–219.
58. Menendez L, Lastra A, Fresno MF, et al. Initial thermal heat hypoalgesia and delayed hyperalgesia in a murine model of bone cancer pain. *Brain Res* 2003; 969(1–2): 102–109.
59. Vermeirsch H, Nuydens RM, Salmon PL, et al. Bone cancer pain model in mice: evaluation of pain behavior, bone destruction and morphine sensitivity. *Pharmacol Biochem Behav* 2004; 79: 243–251.
60. Richebe P, Cahana A and Rivat C. Tolerance and opioid-induced hyperalgesia. Is a divorce imminent? *Pain* 2012; 153(8): 1547–1548.
61. Bannister K and Dickenson AH. Opioid hyperalgesia. *Curr Opin Support Palliat Care* 2010; 4(1): 1–5.
62. Sakurada T, Watanabe C, Okuda K, et al. Intrathecal high-dose morphine induces spinally-mediated behavioral responses through NMDA receptors. *Brain Res Mol Brain Res* 2002; 98(1–2): 111–118.
63. Chu LF, Dairmont J, Zamora AK, et al. The endogenous opioid system is not involved in modulation of opioid-induced hyperalgesia. *J Pain* 2011; 12(1): 108–115.
64. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 2010; 113(3): 639–646.
65. Gottschalk A, Brodner G, Van Aken HK, et al. Can regional anaesthesia for lymph-node dissection improve the prognosis in malignant melanoma? *Br J Anaesth* 2012; 109(2): 253–259.
66. Mercadante S. Switching methadone: a 10-year experience of 345 patients in an acute palliative care unit. *Pain Med* 2012; 13(3): 399–404.
67. Cortínez LI, Brandes V, Muñoz HR, et al. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. *Br J Anaesth* 2001; 87(6): 866–869.
68. Lee C, Lee HW and Kim JN. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J Anesthesiol* 2013; 64(1): 19–24.
69. Gilron I, Jensen TS and Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. *Lancet Neurol* 2013; 12(11): 1084–1095.
70. Matthews EA and Dickenson AH. A combination of gabapentin and morphine mediates enhanced inhibitory effects on dorsal horn neuronal responses in a rat model of neuropathy. *Anesthesiology* 2002; 96(3): 633–640.
71. Gilron I, Tu D and Holden RR. Sensory and affective pain descriptors respond differentially to pharmacological interventions in neuropathic conditions. *Clin J Pain* 2013; 29(2): 124–131.
72. Imanaka K, Tominaga Y, Etropolski M, et al. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. *Curr Med Res Opin* 2013; 29(10): 1399–1409.
73. Mercadante S, Porzio G, Ferrera P, et al. Tapentadol in cancer pain management: a prospective open-label study. *Curr Med Res Opin* 2012; 28(11): 1775–1779.
74. Falk S, Patel R, Heegaard AM, et al. Spinal neuronal correlates of tapentadol analgesia in cancer pain: a back-translational approach. *Eur J Pain*. Epub ahead of print 11 June 2014. DOI: 10.1002/ejp.530.
75. Brown DC and Agnello K. Intrathecal substance P-saporin in the dog: efficacy in bone cancer pain. *Anesthesiology* 2013; 119(5): 1178–1185.
76. Freeman R, Baron R, Bouhassira D, et al. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. *Pain* 2014; 155(2): 367–376.