Review

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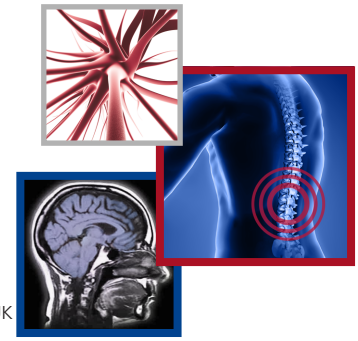
Pain Management



Cancer pain: where are we now?

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Increasing numbers of those living with and beyond cancer presents a clinical challenge for pain specialists. A large proportion of these patients experience pain secondary to their disease or its treatment, impeding rehabilitation and significantly impacting upon their quality of life. The successful management of this pain presents a considerable challenge. This review aims to outline current concepts and treatment options, while considering nuances within pain assessment and the use of large-scale data to help guide further advances.

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The *World Cancer Report 2014* highlights the increasing global prevalence of cancer [1]. In 2003, 10 million people developed malignancies with 6.2 million dying from the disease [2]. In 2015, there were 17.5 million new cancer cases and 8.7 million related deaths [3]. Proportionally, fewer cancer-related deaths have led to an increase in cancer survivors. In 2018, there are an estimated 43.8 million people living with cancer (within 5 years of diagnosis) worldwide [4].

The prevalence of cancer-related pain (33–64%) is closely associated with the stage of disease [5]. Pain has a marked impact on cancer patients; a pan-European survey of patients with all stages of cancer identified that 69% had activities of daily living impeded by pain [6]. The psychosocial consequences of cancer pain (particularly anxiety and depression) are well documented [7]. Despite the impact that pain has on quality of life, half of those undergoing cancer treatment report that their quality of life is not a priority in the overall care that they receive [6].

Van den Beuken-van Everdingen *et al.* have delineated the prevalence of pain in the cancer population [5]. Their most recent work highlights an increase in published research on pain in this population but despite this focus, its prevalence has not decreased [8].

Considerable improvements in identification and treatment of malignancies have led to the increased survival rates, with unintended negative impact upon wellbeing and quality of life [9,10]. Managing pain in the cancer population remains a clinical challenge; we will outline current concepts and treatment options while considering pain assessment and the use of large-scale data to help guide further advances.

Mechanisms of pain in cancer

Tumor & microenvironment

Figure 1 categorises the mechanisms of pain in cancer.

Exact physiological mechanisms for cancer pain are not yet fully established. It is likely that varying mechanisms are responsible depending upon tumor type and location [11]. A complex relationship exists between a malignant lesion and its microenvironment; a tumor does not exist in isolation but has a dynamic relationship with host cells [12]. Both secrete numerous mediators (Figure 2) that are implicated in pain, peripheral sensitization and angiogenesis.

Angiogenesis is integral to both tumor growth and metastatic spread. This process is initiated following basement membrane injury, subsequent tissue hypoxia and release of angiogenic factors. These factors activate endothelial cells to proliferate and stabilize, resulting in angiogenesis. Mediators promoting this process include IL-6, IL-8, TNF-α, VEGF, endothelin and prostaglandin E. Conversely, IL-10, IL-12 and angiotensin have inhibitory effects [13].

Mediators implicated in cancer pain include protons, endothelin, adenosine triphosphate, neurotrophic factors and cytokines [11,14,15]. NGF, neuturin and BDNF are examples of the neurotrophic factors implicated [11,16–18].

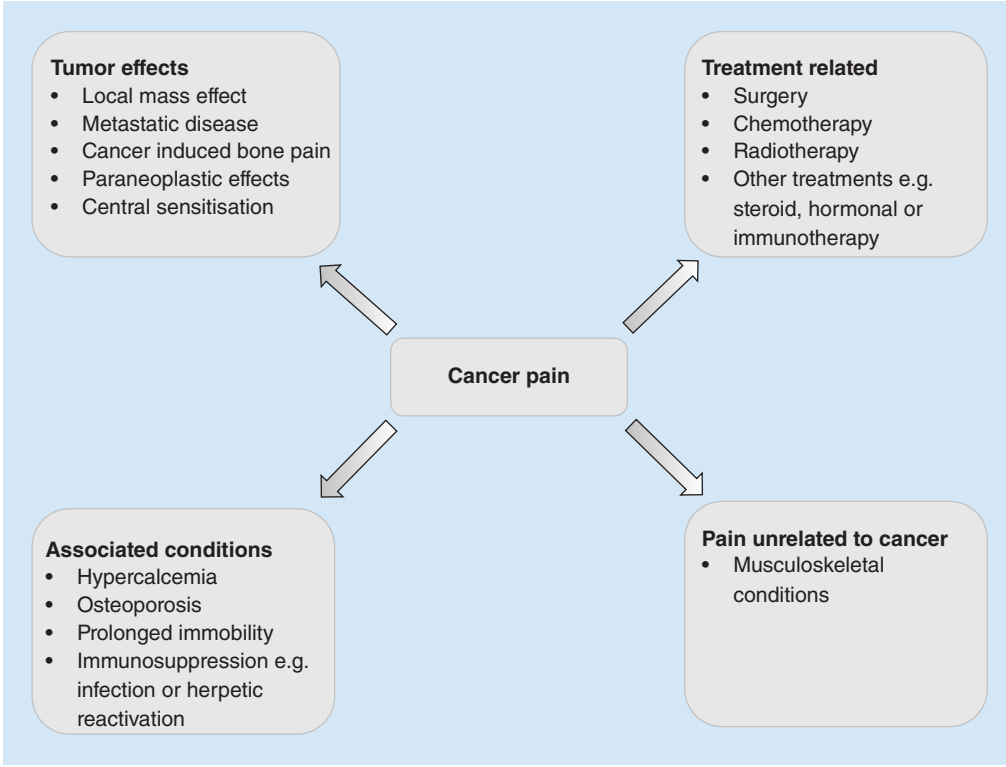

Figure 1. Summary of mechanisms of cancer pain.

Other integral physiological processes

Nociceptive stimuli are transduced into sensory neurone action potentials, however, the precise mechanisms by which this occurs subsequent to mechanical nociceptor stimulation remain poorly understood [19]. The transduction of chemical mediators is better described and can involve both the transient receptor potential vanilloid and acid-sensing ion channel families [20,21]. Cationic (Na^+ and Ca^{2+}) flux triggers depolarization once threshold potentials are reached.

Peripheral sensitization results in transcriptional and translational modification to receptors and ion channels, producing a lower threshold for neuronal activation and increased magnitude of response observed [22]. Mediators and processes implicated in the development appear to be similar in cancer and non-cancer pain states [11,23–26]. The mechanisms by which central sensitization occurs, include increased membrane excitability and synaptic transmission, or decreased descending inhibition, resulting in states of facilitation, potentiation or amplification [27]. The *N*-methyl-D-aspartate (NMDA) receptor has been implicated in the initiation and persistence of central sensitization [27]. The receptor is blocked by a Mg^{2+} ion, under normal physiological conditions, and following sustained afferent input this is ejected allowing Ca^{2+} passage [20]. The neurochemical changes that occur within the dorsal horn and spinal cord, and which mediate central sensitization in persistent pain states, differ depending upon the underlying pain state [28]. Electrophysiological studies in cancer pain have demonstrated a higher percentage of wide dynamic range (WDR) neurones, when compared with nociceptive specific (NS) neurones, implying that NS cells have been sensitized and behave functionally as WDR cells [14]. WDR neurones demonstrate increased spontaneous activity in addition to increased responsiveness to thermal and mechanical stimuli [29].

Cancer-induced bone pain

Tumor deposits within bone (primary or secondary) result in pain through disparate mechanisms, namely structural disruption, increased local osteoclastic activity, inflammatory mediator release and changes in sensory innervation. These pain mechanisms are often intertwined, for instance, local inflammatory mediator release increases osteoclast activity and subsequent bone destruction. IL-1, IL-6, TGF-β and RANKL are examples of such molecules [30,31]. The resulting net bone resorption allows room for further tumor expansion [32]. Disruption to periosteum, marrow or

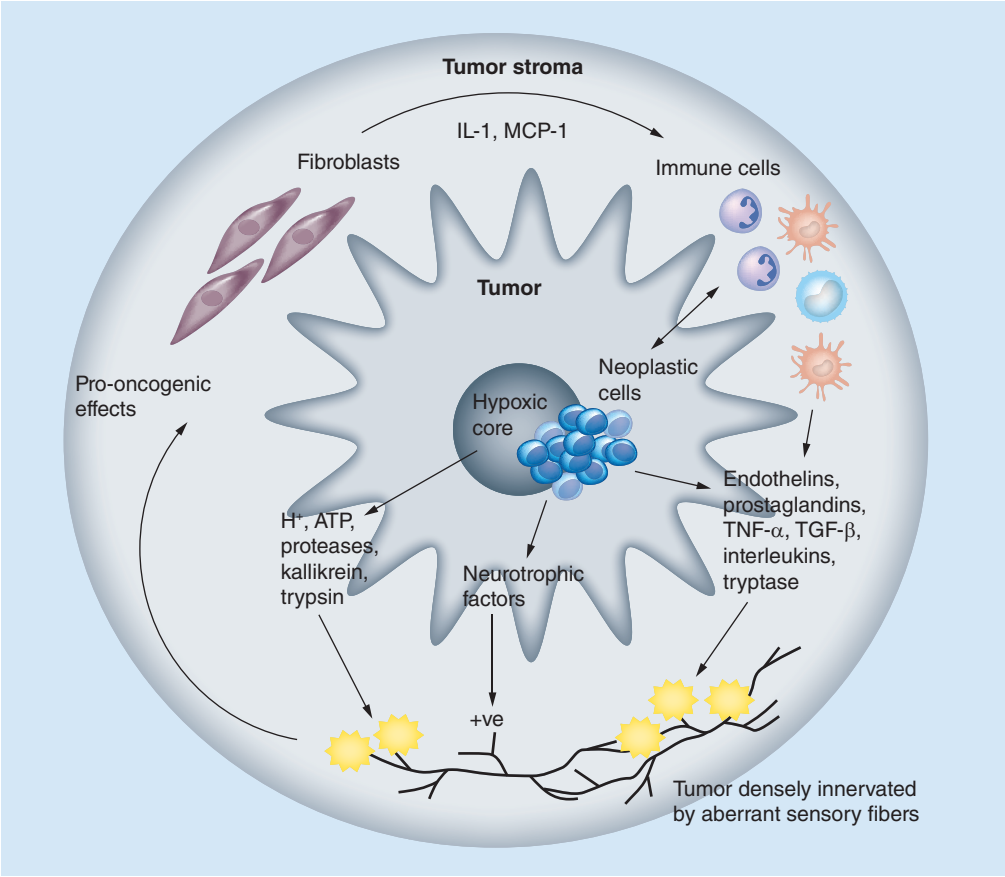

Figure 2. Tumor and its microenvironment.

cortex can result in pain. Malignant bone pain has a neuropathic component [33,34]. NGF is implicated in significant sprouting of aberrant sensory and sympathetic nerve fibers, in periosteum, mineralized bone and marrow [34].

Treatment-related pain

Persistent post-surgical pain

Surgery represents an integral component of the management of many cancers. Persistent post-surgical pain (PPSP) is prevalent throughout the post-surgical population and is particularly pertinent to cancer patients. A formal definition of PPSP does not exist, but Werner and Kongsgaard have proposed it is pain that develops or increases intensity following a surgical procedure, either as a continuation of acute postoperative pain or developing after an asymptomatic period. It must be isolated to the surgical field, the territory of a nerve or dermatome associated with the surgical field. The pain must have been present for at least 3–6 months, and significantly impact upon quality of life. Additionally, any other causes (e.g., infection or recurrence of malignancy) must have been excluded [35].

PPSP is more frequently observed following certain procedures including thoracotomy, breast surgery and limb amputation, although it may occur after any surgery even if relatively limited [36,37]. A significant proportion of patients with PPSP have neuropathic features; although variable, these features have been identified in up to 68% of patients [38,39]. The presence of neuropathic features has a greater impact upon quality of life [40]. Despite peripheral nerve injury being a clear risk factor for the development of PPSP, the relationship is complex. 100% of patients undergoing rib retraction as part of thoracotomy procedures have been demonstrated to have intercostal nerve injuries in the immediate postoperative period [41]. Although this cohort was not observed beyond the intraoperative period to determine the incidence of persistent pain nor its phenotype, PPSP following thoracotomy and rib retraction is not uniformly reported [42]. Attempts to define the association between intercostal nerve damage during surgery and PPSP have failed to ascertain a link [43].

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Table 1. Risk factors for the development of persistent post-surgical pain.

Patient factors	Surgical factors	Other factors
Anxiety	Longer duration of procedure	Surgery in low-volume centers
Depression	Open procedure	Postoperative pain
Raised BMI	Retraction/destruction nerves	Chemotherapy
Preexisting pain	Use of drains	Radiotherapy
Pain catastrophizing		
Genetic factors		
Young age†		

†Older age risk for phantom limb pain.

PPSP is a significant problem after breast cancer surgery and contributes adversely to patients' quality of life [44]. It may involve the scar site, chest wall, axilla or ipsilateral arm [45]. Attempts to preserve the intercostobrachial nerve have not been demonstrated to significantly reduce its incidence [46].

There are a number of risk factors for PPSP development and these are detailed in Table 1.

Although certain risk factors are more remediable than others, for example, effective control of postoperative acute pain, no single risk factor has been identified that can be targeted by an intervention to prevent PPSP [47]. It is clear, however, that the transition from acute pain to PPSP is a critical process, which is an area of considerable interest and research [48]. The identification of risk factors has led to the development of risk stratification tools. Some centers have active transitional pain services, aiming to address PPSP preoperatively, postoperatively as an inpatient and subsequent to discharge [49].

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) occurs following chemotherapy, typically affecting longer, sensory nerve fibers. The risk of development and severity depend on a number of factors including drug type and cumulative dose of treatment. Overall, prevalence rates as high as two thirds have been reported during the first month of chemotherapy [50]. Platinum compounds (cisplatin, carboplatin and oxaliplatin), vinca alkaloids (vincristine) and taxanes (paclitaxel) are commonly implicated. The pathophysiology of CIPN is not fully understood, although multiple contributory processes have been identified [51–53]. Different agents may result in alternative pathophysiological mechanisms and therefore result in a constellation of signs and symptoms.

The development of newer targeted therapeutic agents has highlighted their role in peripheral neuropathies. Proteasome inhibitors, including bortezomib, utilized for the treatment of refractory or relapsed myeloma, are associated with a high incidence of peripheral neuropathy [54]. Thalidomide analogs including lenalidomide and pomalidomide have also both been implicated in the development of peripheral neuropathies but with a lower incidence than bortezomib [31]. Bevacizumab, a monoclonal antibody, increases the incidence of peripheral neuropathy when administered in combination with paclitaxel, compared with those who take paclitaxel alone [55]. Neurotoxic effects of other monoclonal antibodies, including brentuximab and ipilimumab, have also been demonstrated [56,57]. With increased use of such agents, more clarity about the incidence and natural history of associated neuropathies is likely to ensue.

Radiotherapy

Radiotherapy utilizes the application of ionizing radiation to cause cellular DNA changes, resulting in cell death. The effects of radiotherapy depend on numerous factors, but ultimately, non-malignant tissues can also be vulnerable to injury. Toxicities including mucositis and nerve plexopathies are among the most commonly encountered following radiotherapy.

Radiotherapy-induced damage can result in either early or late toxicities, depending on the time taken for development of injury subsequent to exposure to ionizing radiation. Early reactions involve cell loss from tissues possessing high cellular turnover, such as mucosa or epidermis-causing mucositis and epidermal desquamation, respectively [58]. Conversely, late tissue reactions occur secondary to injury to slower-renewing tissues such as nerve or muscle, manifesting as fibrosis, necrosis and atrophy. Cytocidal effects of ionizing radiation result in direct cellular and tissue damage. Indirect effects describe the reactive effects that take place in other cells or tissues as a consequence of radiation-related injury, which includes bystander effects [59], a phenomenon in which nonirradiated cells, in close proximity to those irradiated, display genetic damage themselves [60].

Nervous tissue is particularly susceptible to radiotherapy damage both through direct damage from ionizing radiation and the fibrosis that can result. Radiation-induced brachial plexopathy presents with variable onset and timing [31]. Prevalence is under 2% when a total dose of less than 55Gy is utilized [61]. It can present as a temporary pathology, in such cases, the onset is typically rapid and resolution of symptoms usually occurs within 1 year [62]. Otherwise, classical presentation is with initial paraesthesia, subsequent numbness and delayed progressive motor weakness [31].

Radiation-induced oral mucositis is an expected tissue injury that results from acute inflammation of oral mucosa, tongue and pharynx [63,64]. The typical course is one of four phases [65]. There is an initial inflammatory phase with release of free radicals, proinflammatory cytokines, prostaglandins and TNF. The subsequent epithelial phase results in reduced epithelial cell turnover, ultimately resulting in its breakdown. This is followed by an ulcerative phase and later the healing phase [65]. The duration of this process varies widely from 7 to 98 days [66]. Radiation-induced oral mucositis can be a significant barrier to adequate nutrition and as a consequence may interrupt or limit desired cancer treatment, thus proving a major challenge in the treatment of head and neck cancers [67].

Aromatase inhibitor-induced arthralgia

This is a particularly challenging condition to treat and patients should be informed that joint pains are a common side effect of such medications. Aromatase inhibitors (AIs) are more effective than tamoxifen in postmenopausal women with breast cancer, with improved disease-free survival and decreased contralateral breast cancer [68,69]. Patients may, therefore, decide to persist with this medication despite developing associated arthralgia. The pathophysiology has yet to be fully established, although oestrogen depletion [70], cytokine activity [71] and vitamin D deficiency [72] have all been implicated.

Pain assessment

Assessment is integral to the management of pain [73]. Often assessments utilized are unidimensional, focusing upon pain intensity, which may not be the most important parameter to the patient. The multifactorial and complex biopsychosocial nature of pain should be reflected within the assessment.

To what extent is cancer pain similar to other non-cancer pain conditions, and therefore are different assessment tools required for cancer pain assessment? A diagnosis of cancer impacts the way patients feel and communicate pain [74]. Not only do those with progressive or recurrent disease report lower perceived health-related quality of life [75] but survivors have also been demonstrated to have worse mental health than a reference population [76]. Pain assessment tools, therefore, developed for non-cancer-based populations may not be transferable to the cancer population.

Many of the tools used in clinical practice utilize a Likert-type system for a severity assessment. These can be verbal, numerical or visually presented with a minimum (no pain at all) and a maximum (worst pain ever experienced). There is often variation in reporting of symptoms between individual patients, which may hamper comparison.

Assessment tools developed to consider other elements of pain include the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI) that have been validated in several languages and are applicable in cancer pain [77,78]. The MPQ, and its shortened version (MPQ-SF), include pain intensity, visual analogue scale (VAS) assessment, pain descriptors, while considering 'affective' and 'evaluative' elements. More recently, the MPQ-SF has been enhanced, at least in part, to make it more effective at detecting neuropathic pain [79]. The BPI assessment is partitioned into a sensory (e.g., severity) dimension and a reactive dimension (interference) [80]. The BPI also has an abbreviated version (BPI-SF) often favored for brevity and only relying on 24-h pain recall rather than 1 week required by the traditional BPI [81].

The number and heterogeneity of evaluation measures for cancer pain mean there is no single-accepted method for assessment. de Wit *et al.* [82] studied 313 cancer patients with pain, investigating four outcome measures to determine the adequacy of pain treatment. They identified that inadequately treated pain varied significantly (16–91%) depending upon the tool being used to perform this assessment. They concluded that the choice of measure, rather than the treatment itself was more influential on proportion of patients identified with inadequate pain relief. This highlights the need for a valid and applicable tool to evaluate cancer pain.

Ultimately, one must acknowledge and consider the multifactorial aspects of cancer pain. Any discussion about assessment must seek to identify and justify meaningful and pragmatic outcomes that not only are patient-centered but also are valid for quality assurance and service development (e.g., patient-related outcome measures).

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Treatment of pain

Cancer pain affects numerous components of human function, including personality, mood, behavior, social relations and ability to work. Dame Cicely Saunders, the founder of the modern hospice movement, coined the term 'total pain' to characterize this multidimensional nature of the palliative patient's pain experience to embrace the physical, psychological, social and spiritual domains. The impact upon each of these areas will vary for individual patients [83], highlighting the importance of a biopsychosocial approach to assessment and management. This requires multidisciplinary team management, comprising physicians, nurses, medical social workers, physiotherapists, pharmacists and psychologists [83].

Pharmacological treatments

WHO analgesic ladder

Guidelines published by the WHO in 1986 (Cancer Pain Relief) were developed to address the poor management of cancer pain, a situation thought to stem principally from clinicians' reluctance to use strong opioids due to fears of addiction/tolerance/misuse. The guidelines aimed to achieve 'freedom from cancer pain', and introduced five fundamental principles: 'by mouth', 'by the clock', 'by the ladder', 'for the individual' and 'attention to detail'. Using this approach and administering the right drug in the right dose at the right time is claimed to be 80–90% effective in providing adequate pain relief [84,85].

The WHO ladder has been the subject of debate; patients with advanced cancer have reported significantly better pain relief and greater improvement in general condition following treatment with strong opioids (third step on the ladder and more correctly referred to as 'opioids for moderate to severe pain') when compared with those treated rigidly as per the WHO analgesic ladder [86], promoting discussions proposing removal of second step opioids. Moreover, there are few if any data from randomised controlled trials (RCTs) that support the use of the WHO ladder. Criticisms regarding the lack of incorporation of multidisciplinary approaches to pain in cancer patients indicate that an update may be required.

Nonsteroidal anti-inflammatory drugs

Although nonsteroidal anti-inflammatory drugs may be effective in the treatment of inflammatory pain states, a recent systematic review concluded that, due to the low quality of the evidence available, it was not possible to prove or disprove their utility in the treatment of cancer pain [87].

Opioids

Concerns exist regarding the potential detrimental effects of opioids. Opioid side effects can be debilitating with both the incidence and impact increasing when larger doses are administered. These effects include, but are not limited to sedation, nausea and vomiting, constipation, respiratory depression and endocrine dysfunction. Although opioids may be initially effective in reducing or alleviating pain, opioid tolerance, increasing pain severity and opioid-induced hyperalgesia can result in reduced efficacy. Opioid tolerance, a neurophysiological mechanism, results in higher doses required to achieve the same perceived level of analgesia. Opioid-induced hyperalgesia is a paradoxical increase in pain perception and is thought to be due to sensitization of pronociceptive mechanisms [88]. Both opioid tolerance and opioid-induced hyperalgesia may result in dose escalation, with varying results. Another key concern is the impact of opioids on immune function, thereby potentially affecting cancer recurrence. However, a prospective cohort study of 34,188 patients provided no clinically relevant evidence of an association between opioid prescriptions and breast cancer recurrence [89].

The use of opioids in cancer survivors who have completed treatment remains a topic of significant debate [90]. The recent opioid crisis, which has received widespread media attention (especially in the USA), has heightened apprehensions surrounding this subject. In the absence of any evidence pertaining to a benefit of opioids in the management of pain in cancer survivors, managing persistent pain in this population with the same principles as those applied to other persistent pain states would constitute a precautious and pragmatic approach.

A relatively newer agent, tapentadol, has a dual mechanism of action (mu-opioid agonist and noradrenaline reuptake inhibition). It has the potential to be a better tolerated and efficacious agent in the treatment of moderate–severe cancer pain in patients who do not tolerate classical opioids. However, a recent Cochrane review concluded that, for cancer pain, pain relief and adverse events were comparable between tapentadol, morphine and oxycodone groups [91].

Table 2. Recommendations from Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated Special Interest Group on Neuropathic Pain recommendations.

Pharmacotherapy	NNT (95% CI)	NNH (95% CI)
First-line drugs		
Gabapentin	6.3 (5.0–8.3)	25.6 (15.3–78.6)
Gabapentin-extended release/enacarbil	8.3 (6.2–13)	31.9 (17.1–230)
Pregabalin	7.7 (6.5–9.4)	13.9 (11.6–17.4)
SNRIs	6.4 (5.2–8.4)	11.8 (9.5–15.2)
TCAs	3.6 (3.0–4.4)	13.4 (9.3–24.4)
Second-line drugs		
Capsaicin 8% patches	10.6 (7.4–19)	Inconsistent
Lidocaine patches	Undetermined	Safety – excellent
Tramadol	4.7 (3.6–6.7)	12.6 (8.4–25.3)
Third-line drugs		
Strong opioids	4.3 (3.4–5.8)	11.7 (8.4–19.3)
Botulinum toxin A	1.9 (1.5–2.4)	Safety – excellent

NNH: Numbers needed to harm; NNT: Numbers needed to treat; SNRI: Serotonin and noradrenaline reuptake inhibitor; TCA: Tricyclic antidepressant.
Data taken from [98].

'Adjuvants' & the mechanism-based approach

Additional drugs – 'adjuvants' – are added at any stage of the WHO ladder, aiming to treat adverse effects of analgesics, enhance pain relief, treat specific types of pain or treat concomitant psychological disturbances, such as insomnia, anxiety and depression. However, the term 'adjuvant' is vague and potentially confusing, therefore nonopioids should be referred to by their mechanism of action (e.g., anti-inflammatory, etc).

Pain medicine is moving toward a more mechanism-based approach whereby identification of processes contributing to the pain can aid appropriate treatment selection [92]. A recent randomized, double-blind, placebo-controlled phenotype-stratified study, demonstrated that oxcarbazepine is more efficacious in the treatment of peripheral neuropathic pain associated with an 'irritable nociceptor' phenotype (preserved thermal sensation and some gain of sensory function) [93]. Any reworking of the WHO ladder approach should attempt to encompass this tenet.

Neuropathic pain in cancer patients

Numerous studies have tried to identify the proportion of cancer patients that experience neuropathic pain. The estimated prevalence has been reported to be anywhere from 15.3 to 44% [94,95], which is higher than in non-cancer pain states [96].

The International Association for the Study of Pain (IASP) has worked toward achieving a consensus on phenotyping neuropathic pain for genetic studies in humans [97]. For cases of 'possible' neuropathic pain to be included in genetic studies, the following criteria must be met:

- Pain with neuropathic characteristics (assessed using a screening tool: Douleur Neuropathique; DN4, painDETECT or self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale; S-LANSS)
- Distribution or location of this pain that is anatomically consistent with an underlying somatosensory lesions or disease
- Further characterization in the form of a clinical history.

The latest recommendations from the Special Interest Group on Neuropathic Pain of IASP [98] suggest the following approach to treating neuropathic pain. This meta-analysis used numbers needed to treat to achieve 50% reduction in pain intensity as the primary effect measure. Numbers needed to harm were calculated, using the number of patients required to be treated for one patient to drop out due to adverse effects. Tables 2 and 3 summarize their findings.

Although opioids have a low numbers needed to treat of 4.3 (3.4–5.8), they are recommended as third-line treatment due to potential risk of abuse and concerns related to the recently observed increase in mortality associated with opioid use.

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Table 3. Recommendations for other drugs based on the GRADE classification, with some selected numbers needed to harm from Pharmacotherapy for neuropathic pain in adults: systematic review, meta-anlaysis and updated Special Interest Group on Neuropathic Pain recommendations.

Inconclusive evidence	Weak against	Strong against
Capsaicin cream	Cannabinoids	Levetiracetam
Carbamazepine	Sodium Valporate	Mexiletine
Clonidine (topical)		
Lamotragine		
NMDA antagonists		
Oxycarbazepine		
SSRI antidepressants		
Tapentadol		
Topiramate – NNH 6.3 (5.1–8.0)		
Zonisamide – NNH 2.0 (1.3–4.6)		

NMDA: *N*-methyl-D-aspartate; NNH: Numbers needed to harm; SSRI: Selective serotonin reuptake inhibitor.
Data taken from [98].

Botulinum toxin suppresses the release of neurotransmitters involved in nociceptive transmission, including endothelin-1, substance P, calcitonin gene-related peptide and neuropeptide Y [99].

Topical agents are useful for localized peripheral neuropathic pain, with a presumed local pain generator [98]. The use of 2% menthol in aqueous cream, clonidine, ketamine, topical tricyclic antidepressants, capsaicin 0.075% cream and lidocaine patches have all been reported [100], generally in small studies. Despite the relative lack of evidence, as these agents are well tolerated, with minimal side effects, their use is attractive in cancer patients who are often physically frail.

Other agents

Ketamine may be used as an adjuvant to opioids, however, a Cochrane systematic review from 2015 concluded that the evidence is insufficient to support its use [101].

Alongside bisphosphonates, the use of denosumab (a human monoclonal antibody that inhibits RANKL) can be effective when treating cancer-induced bone pain [102]. Rarely, gastrointestinal toxicity, renal toxicity and osteonecrosis of the jaw occur with bisphosphonates. Tanezumab (an NGF sequestering agent) has efficacy in treating cancer-induced bone pain, however, the exact role and its long-term safety profile are less well-established [103].

Oncological treatments

Treatment of the underlying cancer offers a potential pain management approach. Identifying molecular targets that have a role in both pain and cancer, such as the numerous cytokines implicated in cancer pain, is an intriguing strategy for future drug development.

Chemotherapy

Understanding tumor biology and the hallmarks for cancer has led to the development of new drugs in oncology, including immunomodulatory agents and drugs that target proliferation, angiogenesis or growth-signaling pathways. Targeted therapies can be used alone or in combination with chemotherapeutic agents or radiotherapy.

Hormone therapy

Antiandrogen therapies can have dramatic analgesic effects in the treatment of prostate cancer. Response rates of over 90% following initial exposure with a median duration of between 18 and 24 months have been reported [104].

Various hormonal treatment therapies are successfully used in the management of breast cancer. Antioestrogens (tamoxifen or toremifene), aromatase inhibitors (anastrozole and letrozole) as well as progestins (megestrol and medroxyprogesterone) may all have roles in management [105]. These therapies can result in various types of pain; for instance, aromatase inhibitors are commonly associated with the development arthralgia [70].

The inflammatory and immune system response to cancer plays an important role in pain. Cytokines are key mediators for this process and can be responsible for nociceptor sensitization. Although some agents that target such cytokines are used for rheumatological conditions, their efficacy in cancer pain has yet to be demonstrated. These include anti-TNF agents (etanercept, infliximab, adalimumab), agents blocking IFN-γ, IL-6, IL-8 or endothelin-1 [14,15]. Additional consideration should be placed on potential effect in oncogenesis of these agents.

Radiotherapy

Radiotherapy can be an effective local treatment modality for patients with painful bone metastases. The analgesic benefits may not be immediately apparent, frequently taking between several days and a few weeks to be experienced [106]. A systematic review of palliative radiotherapy trials in bone metastases demonstrated that single and multiple fraction regimens provided equal pain relief; however, significantly higher retreatment rates were required in those receiving single fractions [107].

High-intensity-focused ultrasound

High-intensity-focused ultrasound (HIFU) utilizes MRI guidance to enable precise tissue thermal ablation and has been demonstrated to be effective in reducing pain from bone metastases that are nonresponsive to radiotherapy or conventional analgesia [108]. HIFU has also been used to reduce pain from primary tumors such as inoperable pancreatic cancers [109]. Its mechanism of action is poorly understood but it is thought that thermal effects result in localized denervation of the target. This technique is of interest as it does not expose the patient to ionizing radiation and it has been shown to produce pain relief within a day from the treatment episode. However, the majority of patients treated have required sedation or other forms of anesthesia (general or regional) in order to tolerate the treatment [108].

Nuclear medicine

Radioisotopes such as samarium and strontium can be used to treat painful bony metastases. The uptake depends upon osteoblastic activity and therefore higher turnover of bone leads to enhanced incorporation and targeted local dosing [110]. These are typically reserved for patients with bony metastases that are not responsive to established treatments, as they carry a risk of myelotoxicity [111].

Surgical treatments

For many malignancies, surgery is a principal element of the treatment. Frequently, this involves primary tumor resection or debulking. Excision of some cancers, for example oral cancers, relieves pain in most, if not all patients; supporting the hypothesis that oral cancer pain stems from mediators within the cancer environment [11]. There are, however, multiple other surgical interventions which may help with pain including but not limited to defunctioning procedures, internal fixation or stabilization of bone fractures as well as vertebroplasty or kyphoplasty for vertebral fractures.

Interventional pain management

A variety of regional analgesic techniques may be appropriate for pain treatment in cancer patients. Numerous interventional techniques exist, and the appropriateness of each will depend upon patient, oncological and institutional factors. The importance of appropriate patient selection and delivery of these methods in the context of full biopsychosocial support cannot be overemphasized.

Neuraxial (intrathecal or epidural) drug delivery

Neuraxial drug delivery is considered in patients with intractable pain in whom pharmacological therapies have failed to achieve analgesia or have caused unacceptable side effects. Recent guidelines from the European Association for Palliative Care have detailed the use of central neuraxial opioid administration [112].

The advantage of this method of drug delivery is that equianalgesic doses are only a fraction of the systemic doses, hence limiting the side effect profile while providing analgesia. Important considerations when planning neuraxial drug delivery include postinsertion management depending on type of device used (fully implantable or external pump). The risks of infection, catheter tip granulomas (potentially leading to compression of neurological structures), possible androgen deficiency in men and opioid side effects must be taken into account prior to insertion [113].

In patients with infusions lasting more than a few days, the observation that pain does not recur immediately or soon after catheter removal has led to the hypothesis that some degree of reversal of central sensitization and wind-up can occur [114].

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Neurolysis & neuromodulation

Coeliac plexus & splanchnic neurolysis

The coeliac plexus is the largest sympathetic plexus formed by the union of the greater, lesser and least splanchnic nerves. This is the site of one of the few remaining neurolytic blocks commonly used. Computer tomography-guided and endoscopic ultrasound-guided approaches have improved success rates, when compared with fluoroscopic approaches of coeliac plexus blockade [115]. For unresectable pancreatic tumors, thorascopic splanchnic neurolysis has been described [116] and small studies report reduction in pain scores and improved quality of life [117].

Cordotomy

Cordotomy is performed percutaneously at the cervical level and it involves the disruption of the lateral spinothalamic tract in the treatment of severe, opioid-resistant cancer pain. It is most frequently performed for patients with mesotheliomas where life expectancy is less than 1 year. Although the technique has been described since the late 1960s, there has been recent interest in newer techniques using computer tomography/MRI and endoscopic guidance [115]. Because of the nature of the pathology and life expectancy, it is difficult to perform studies involving large numbers of patients and evaluate long-term complication rates.

Radiofrequency procedures

Conventional radiofrequency or pulsed radiofrequency of the lumbar dorsal root ganglia and the sacral sensory roots can offer pain relief from tumor infiltration of the lumbosacral plexus and painful lower limb tumors [115]. Additionally, pulsed radiofrequency to the dorsal root ganglion can be used therapeutically for persistent post-surgical thoracic pain and has been shown to be superior to pharmacotherapy and pulsed radiofrequency of the intercostal nerves [118].

Cryoablation

A recent systematic review concluded that cryoablation can both improve pain scores and quality of life for subsequent months [119]. Its use in combination with radiotherapy, vertebroplasty or bisphosphonates resulted in greater improvements than when cryotherapy was used alone [119].

Neuromodulation techniques

Although a developing evidence base exists for numerous other complex pain states, a Cochrane review in 2015 concluded that there was insufficient evidence to advocate the role of spinal cord stimulation in cancer pain and that ultimately more studies were needed [120].

Percutaneous electrical nerve stimulation therapy aims to modulate the activity of peripheral nerves; it has been used successfully in patients with postirradiation allodynia and for post-thoracotomy and post-breast surgery (PPSP) [115].

Psychological interventions

Psychological distress has been reported to be greater as the intensity of cancer pain increases [104,112]. Approximately, a third of all the patients diagnosed with cancer will develop psychological disorders such as depression and generalized anxiety disorder [121]. Appreciation of the psychological consequences and influences on pain are fundamental to considering effective pain management strategies. Acceptance and commitment therapy represents the third wave of behavioral and cognitive therapies and is an approach that emphasizes the importance of flexibility within the psychological processes and responses when faced with a difficult or distressing situation, for example, living with cancer. One of the primary aims of acceptance and commitment therapy is to support people's willingness to accept what is out of their personal control (such as the inability to eradicate pain), as well as commit to taking action that enriches and brings meaning to their life [122].

Physiotherapy

Therapeutic exercise plus graded and purposeful activity remain important in the care of patients with cancer pain. General musculoskeletal deconditioning throughout the course of their disease and treatment is a frequent occurrence. The use of massage, soft tissue mobilization, TENS, heat and cold therapy plus lifestyle adjustments remain options in the care of these patients [123].

Complementary therapies

Acupuncture produces analgesic effects that can be attributed to a range of mechanisms, such as polymodal receptor discharge, increase in circulatory levels of opioid peptides and improved blood flow. Persistent pain has been demonstrated to respond well to acupuncture [124]. Furthermore, it has been reported to significantly reduce joint pain associated with aromatase inhibitors [71]. A Cochrane systematic review evaluating five randomized controlled studies comparing acupuncture with sham acupuncture or analgesics acknowledged that there were studies showing benefit in cancer pain, but the heterogeneity of methodologies prevented pooling of data for meta-analysis and therefore subsequently concluded that there was insufficient evidence to determine its effectiveness [125].

Perceptions & barriers

The relationship between clinicians and their patients is complex. Shared perceptions and goals of treatment are frequently reported as factors that derive success within this field [126,127].

With particular reference to this patient group, numerous perceptions require consideration, with many factors pertinent to both patients and clinicians. Clinicians' perceptions that patients are reluctant to report pain [128,129], are reinforced by patient hesitance [130], secondary to desire to be a 'good patient' or concerns about distracting from cancer care or treatment [131]. Similarly, patients and clinicians report fear of addiction and fear of side effects [128,129,132] that can act as barriers to treatment compliance.

Inadequate cancer pain management is consistently reported [129,133]. Clinicians' perceptions with regard to causative factors include inadequate assessment of pain and lack of knowledge of healthcare professionals [129,131,134]. In certain parts of the World, limitation of opioid availability prevents effective cancer pain management [128,131]. From patients' perspectives, there is frequently an underlying fear that pain represents disease progression or indeed recurrence, yet relationships between changes in pain and variability in disease are not well established [135].

Analgesic therapies may lead to side effects that interfere with quality of life. This is not unique to analgesic side effects, as pain itself can significantly impact upon one's quality of life. Xia's study reported that 88.8% of those surveyed reported that pain affected multiple aspects of daily life, namely sleeping, concentration and activities of daily living [128]. Patients frequently feel that in the management of their cancer-related pain, their quality of life is not considered [6].

Any mismatch between perceptions will not only impact upon the doctor–patient relationship but can also lead to inadequate pain management. Regular reviews to assess adherence, side effects and concerns facilitate achieving good pain management [136]. Adam *et al.* reviewed eight systematic reviews and 34 randomized controlled trials that assessed interventions to potentially overcome these barriers and improve cancer pain [137]. All interventions included at least one of the following seven fundamental constituents: improving pain assessment, increasing knowledge about cancer pain, enhancing communication regarding cancer pain, educating about pain management strategies, refining analgesic prescribing, tackling nonadherence and encouraging reassessment.

A systematic review and meta-analysis examining patient-based education interventions in the management of cancer pain reported that with comparison to usual care or control, a variety of educational interventions did improve patient attitude and knowledge, without significant changes to medication adherence. Reduction in average pain intensity by over one point and reduction in worst pain intensity by just under one point on 0–10 rating scales resulted in conclusions that patient-based educational interventions are probably underused [138].

Future perspective, recent development & advent of big data

The population with cancer pain is increasing [8] and binary assessment of the presence of pain and focus on intensity may be outdated. Pain intensity is not always the parameter that reflects what is most important to the patient. Meaningful and pragmatic outcomes that are patient-centered, valid for quality assurance and effective for service development are key.

It is important to consider how we document and record assessment data, which may prove integral to using real data to justify the utility of our services. Patient-related outcome measures lend themselves well to large-scale data collection. Our institution currently collects patient-reported measures on every patient that consents when attending outpatient pain management clinics. Data collected can be refined depending on the reason for presentation but typically will include assessments regarding pain (BPI) as well as psychosocial factors (Hospital Anxiety and Depression Scale) and reported changes (Patient's Global Impression of Change). Data can be analyzed to consider audit, look at specific pain phenotypes and also assess responses to treatments. Increasing data will provide insight into specific patient groups and allow refinement of care. The Quebec pain registry [139], is another

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example, which states that its database provides standardized data for a large cohort of patients based upon validated measurement tools. They currently report nearly 1000 patients enrolled within this registry and by the end of 2016, had published eight related studies.

Given the barriers identified previously, a personalized, patient-centered approach to pain management has been advocated [54]. Some would argue that this is the approach we have been using in pain medicine for many years. Integrating pain education as part of consultations has been demonstrated to decrease current and average pain intensities, reducing the consequential interference on daily living and increasing adherence [140]. A systematic review and meta-analysis concluded that current evidence suggests that cancer pain services ought to provide patient-based education in order to improve knowledge on analgesia and managing pain [138].

Recent developments in the knowledge of and identification of risk factors for the development of PPSP have led to validated risk-stratification tools to potentially identify those at high risk and facilitate targeted interventions [141]. The use of transitional pain services may offer promising results in reducing the transition from acute to chronic pain [49]. This constitutes the use of a multidisciplinary team to provide optimization of preexisting pain, pain education, psychological interventions as well as acute pain management postoperatively and patient reviews postdischarge [49].

Numerous studies have investigated the benefit of early provision of palliative care. Improved quality of life, fewer depressive symptoms, greater patient satisfaction and indeed longer survival have all been reported [142,143]. Although early integration of palliative care has numerous reported benefits, resource implications would mean that patient selection is paramount. At what point should this integrated care model be applied, and to whom, remains essential to further developing this strategy.

Executive summary

Incidence

- The overall incidence of cancer is increasing.
- Developments in available therapies have led to increased survivors.
- Unfortunately, the incidence of pain in the cancer population does not appear to be decreasing.
- The anticipated continued progression along this course means that our services need to be dynamic and innovative.

Consultations

- Assessments need to consider the multifactorial aspects of cancer pain.
- Consultations should integrate patient education.

The future

- Ultimately, utilizing large standardized datasets of patient-reported outcome measures could be integral to allowing assessment, research and development of the care we offer.

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