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REVIEW ARTICLE

Pharmacologic Management of Persistent Pain in Cancer Survivors

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Abstract

Improvements in screening, diagnosis and treatment of cancer has seen cancer mortality substantially diminish in the past three decades. It is estimated there are almost 20 million cancer survivors in the USA alone, but some 40% live with chronic pain after completing treatment. While a broad definition of survivorship that includes all people living with, through and beyond a cancer diagnosis—including those with active cancer—is often used, this narrative review primarily focuses on the management of pain in people who are disease-free after completing primary cancer treatment as adults. Chronic pain in this population needs a different approach to that used for people with a limited prognosis. After describing the common chronic pain syndromes caused by cancer treatment, and the pathophysiologic mechanisms involved, the pharmacologic management of entities such as post-surgical pain, chemotherapy-induced neuropathy, aromatase inhibitor musculoskeletal syndrome and checkpoint inhibitor-related pain are described. The challenges associated with opioid prescribing in this population are given special attention. Expert guidelines on pain management in cancer survivors now recommend a combination of pharmacologic and non-pharmacologic modalities, and these are also briefly covered.

Key Points

Chronic pain following cancer treatment is common. In survivors with an excellent prognosis, a biopsychosocial approach to pain management is recommended.

The use of long-term opioid therapy in this population raises the same concerns as it does in chronic non-malignant pain.

Adjuvant analgesics have an important role, as neuropathic pain is common in cancer survivors.

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1 Introduction

Advances in cancer management (earlier detection and better treatment) in the past 30 years have seen cancer change from a terminal illness to a chronic one. In the United States, the National Cancer Institute (NCI) estimates there was a 31% decrease in cancer mortality between 1990 and 2018, with approximately two-thirds people with cancer now living 5 years beyond diagnosis [1]. According to Cancer Research UK, half the people diagnosed with cancer in Britain will live at least 10 years (https://www.cancerresearchuk.org/health-professional/cancer-statistics/survival, accessed 22 November 2021). As a result of the decrease in cancer mortality, the number of cancer survivors has increased, in the case of the United States from approximately 3 million in 1971 to more than 15 million in 2016 [2]. These numbers are predicted to exceed 20 million by 2026 and 26 million by 2040.

Unfortunately, improved cancer survival comes at a cost as patients may experience adverse physical and psychosocial effects from the diagnosis and its treatment. These adverse effects can be severe, debilitating and persistent, sometimes permanent. Pain is one such adverse effect and all modalities of cancer treatment—surgery, chemotherapy, radiation therapy (RT), transplants and immunotherapy—can be painful. Acute pain becomes chronic in

approximately 10–20% cases [3], causing distress and disability that reduces the quality of life long term.

Twenty years ago, when the outlook of a cancer diagnosis was less optimistic, cancer treatment-related pain was classified as a subset of cancer pain and was mainly treated with opioids [4]. Nowadays, the use of opioids in cancer survivors with chronic pain is raising the same concerns as it does in patients with chronic non-malignant pain. This is especially so when the patient has completed definitive treatment for early-stage disease and the prognosis is good [5]. Furthermore, there is increasing recognition that chronic non-malignant pain is a common comorbidity in cancer survivors [6] and opioids are no longer recommended for this condition [7]. Consequently, the American Society of Clinical Oncology (ASCO) guideline on the management of pain in cancer survivors ranks opioids as third-line treatment [8].

Numerous reviews of the broad topic of pain in cancer survivors have been published. Some are comprehensive [9], while others focus on specific issues. Subsequent to the ASCO guideline being published in 2016, there have been a small number of broad reviews of survivor pain treatment [10, 11]. The aim of this narrative review is to provide an update of the etiology and management of chronic pain in cancer survivors, with the emphasis of management being on pharmacological treatments. However, because pharmacological approaches are not effective in all cases, some non-pharmacological approaches are also presented. This review is restricted to pain in survivors of adult cancers; pain in survivors of paediatric cancer has been reviewed recently by others [12].

2 Definition of Pain in Cancer Survivors

Before reviewing the pharmacological management of pain in cancer survivors, consideration needs to be given to who is included under the 'cancer survivor' label and what kind of pain is being referred to. According to the NCI's Office of Cancer Survivorship, an individual is considered a cancer survivor "from the time of diagnosis throughout the balance of his or her life" https://cancercontrol.cancer.gov/ocs/statistics#definitions. Furthermore, family, friends and voluntary caregivers who are affected by the diagnosis in any way are included as 'survivors'. Accordingly, survivors are not only those free of disease but also those living with cancer. A broad survivorship definition has benefits, for example including people with treatable, slow-growing tumours who may be on treatment intermittently, as well as those who have incurable disease that is controlled with systemic therapy, some of whom live with incurable cancer for 10–20 years while fully functional [2]. However, this broad definition implies that cancer-related pain, for which unlimited amounts of opioids are generally considered appropriate, would be within the scope of a review on cancer survivor pain. Furthermore, patients living with cancer have different psychosocial issues to disease-free survivors as they cope with living with an eventually terminal diagnosis. This situation may impact on pain management (e.g. uncertainty about the durability of the response to cancer treatment; how to handle comorbid conditions and disease prevention, screening and treatment in the setting of limited life expectancy; and managing discussions regarding new drugs and early-stage clinical trials) [2].

The Survivorship Taskforce of the European Organization for Research and Treatment of Cancer takes a narrower approach to defining survivors, limiting it to those who have completed primary treatment (with the exception of maintenance therapy) and have no active disease [13]. Pain arising from the diagnosis and treatment of premalignant conditions (e.g. ductal carcinoma in situ, cervical intraepithelial neoplasia, non-invasive skin cancers, myelodysplasia and benign central nervous system tumours) would also be included using this definition.

However, even accepting a narrow definition of survivorship, further clarification of the type of pain is needed. Most cancer treatment-related pain is short-lived and not persistent, procedural pain being especially problematic in paediatric oncology [14]. Cancer survivors may also have concomitant chronic pain that is not directly attributable to cancer or its treatment; given that cancer is usually a disease of middle/older age, comorbid non-malignant pain syndromes are common in the oncology population [6]. Both treatment-related pain and comorbid non-malignant pain may occur concurrently, the latter often aggravated by the physical and emotional effects of the cancer diagnosis and treatment.

In summary, this narrative review assumes a narrow definition of survivorship and focuses on chronic pain directly attributable to cancer treatment. The scope of the article is as follows:

- Adults who have had cancer or pre-malignant tumour diagnosed and treated after the age of 18 years.
- They have completed primary/first-line treatment (typically for early-stage disease and given with curative intent).
- They do not currently have evidence of active disease.
- Their pain is attributed to the administration of anti-cancer treatment.
- The pain has persisted beyond the usual time expected for the tissue damaged by the treatment to recover.

Many adult cancer survivors have chronic pain after treatment. With the prevalence estimated to be up to 40% [15], this equates to 8 million individuals in the USA alone. This number is expected to continue to grow as the population

ages, more cancer is diagnosed and cancer treatments and supportive care continue to improve.

3 Common Cancer Treatment-Related Pain Syndromes

All modalities of cancer treatment may cause acute pain that persists beyond the time for healing in approximately 20% of patients [16]. Some patients develop persistent pain on maintenance treatments that are continued long-term after initial treatment was completed, such as breast cancer survivors with aromatase inhibitor-related musculoskeletal syndrome (AIMSS) [17]. In a few cases, chronic pain can occur as a late effect, remote in time from the administration of treatment such as radiation plexopathy [18]. Some of the most common chronic pain syndromes related to cancer treatment, their prevalence and established risk factors are shown in Table 1. Clearly, disease recurrence, paraneoplastic syndromes and unrelated rheumatic or neurologic diseases should be considered as potential differential diagnoses of cancer treatment-related pain, and the comprehensive patient assessment should be focused on ruling out evidence of disease based on history, clinical features, laboratory tests, imaging and/or biopsy.

3.1 Neuropathic Pain After Cancer Treatment

Although many different types of normal tissue may be damaged by cancer treatment, nerve damage is common. It can follow the conventional cancer treatment modalities of surgery, chemotherapy and/or RT.

3.1.1 Persistent Pain Post-cancer Surgery

Chronic pain has been reported after almost all types of surgery, with a higher prevalence (> 20%) reported in sites that are common surgical fields in oncology, such as breast, thorax and spine [19]. While the high prevalence of persistent pain post-cancer surgery is often attributed to iatrogenic nerve injury, there are other contributors including central sensitization and comorbid pre-existing pain in the operated area [19].

Persistent pain post-breast cancer surgery (PPPBCS, also known as post-mastectomy syndrome) is perhaps the most well documented cancer treatment pain syndrome, with many studies and reviews of the topic being published in the past two decades. PPPBCS has been estimated to affect as many as two women in three, and is moderate to severe in 15–20% of cases 1-year post-surgery [20]. The exact mechanism of PPPBCS is unknown, but is usually attributed to damage of nerves such as in the chest wall or axilla (e.g. intercostobrachial nerve) during surgery. Consequently, it is often reported with typical neuropathic descriptors, such as burning, shooting, as well as mechanical allodynia and deep blunt pain. PPPBCS can begin shortly after surgery but may not come on for several months and can go on for years. In fact, pain is more common after minimally invasive surgery (lumpectomy) than mastectomy. It may be located in the axilla, the shoulder, arm or chest wall. Risk factors include young age, axillary dissection and sectioning of the intercostobrachial nerve. Introduction of sentinel node biopsy has reduced but not eliminated the prevalence of PPPBCS [21].

Validated prediction models have been developed to screen for patients at high risk of developing PPPBCS. In one model, preoperative pain in the operative area ($p < 0.001$), high body mass index ($p = 0.039$), axillary lymph node dissection ($p = 0.008$) and more severe acute postoperative pain intensity at the seventh postoperative day ($p = 0.003$) were included in the final prediction model [20]. An online risk calculator has been developed to operationalize the model. Machine learning has also been utilized in predicting PPPBCS, with 21 single or aggregated parameters being identified including demographic features, pain-related variables and psychological characteristics. This method had a cross-validated accuracy of 86% and a negative predictive value of approximately 95% [22].

Post-thoracotomy pain syndrome (PTPS) occurs with a prevalence ranging from 25 to 57%, although severe in < 10% [23]. Post-thoracotomy pain is predominantly neuropathic in nature, and as with PPPBCS, the etiology is usually attributed to surgical nerve damage, being less common after minimally invasive surgery (e.g. videoscopic-assisted surgery) than open thoracotomy. Unlike PPPBCS, preoperative risk stratification of susceptible individuals for PTPS is not well established [23]. Adjuvant radiation and chemotherapy appear to predispose patients to developing chronic PTPS. Poor postoperative pain management (first 24 hours after surgery) was the sole factor that predicted the development and severity of long-term pain. Psychologic factors are also important, including preoperative anxiety, somatization and pain catastrophizing [23].

Other major cancer surgeries commonly associated with chronic pain afterwards include neck dissection [24], colorectal surgery [25], and post-nephrectomy pain [26].

3.1.2 Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Neuropathy is one of the most common complications of chemotherapy. Several classes of chemotherapeutic agents are neurotoxic, including the platinum-based compounds, taxanes, vinca alkaloids, thalidomide derivatives and proteasome inhibitors. Newer classes of chemotherapeutic agents including molecular-targeted agents like ado-trastuzumab

Table 1 Common chronic pain syndromes related to cancer treatment [23]

Pain syndrome	Treatment modality	Incidence/prevalence	Risk factors
Neuropathic pain			
Persistent pain post-cancer surgery	Breast cancer surgery [20–22]	20–68% 15–20% moderate-severe at 1 year	Young age High BMI ALND Acute post-operative pain Psychological characteristics
	Thoracotomy	25–57% Severe: < 10%	Adjuvant chemotherapy/RT Acute post-operative pain Psychological characteristics
	Neck dissection [24]	0–100%	Not yet identified
	Colorectal surgery [25]	22% at 6 months	Young age Peoperative abdominal pain Preoperative anxiety Longer duration of surgery High pain intensity on movement within 24 h after surgery
	Nephrectomy [26]	4% at 6 months	Not yet identified
Chemotherapy-induced peripheral neuropathy [27–30]		60% at completion 30% at 6 months	Older age Type of chemotherapy (platinum > taxane) Number of cycles PN, diabetes, statins Smoking, alcohol
Chronic pain post-RT [18]	Gynecologic Head and neck Lung apex Breast	39% 15% 12% 2%	Type of cancer Total dose Large dose per fraction Surgery, chemotherapy
Nociceptive pain			
Musculoskeletal pain post-surgery or RT		Variable	Not identified
Aromatase inhibitor-associated musculoskeletal syndrome [17]		Up to 50% 28% discontinue treatment	Younger age BMI > 30 Prior taxane chemotherapy
Rheumatic and musculoskeletal pain associated with checkpoint inhibitors [43]		Up to 22%	Not yet identified
Joint and fascia manifestations of chronic graft vs host disease [45]		29%	Not yet identified

ALND axillary lymph node dissection, *BMI* body mass index, *PN* peripheral neuropathy, *RT* radiation therapy

emtansine, brentuximab vedotin and the checkpoint inhibitors have also been associated with the development of neuropathic pain [27]. Although these agents are neurotoxic due to various pathological mechanisms (see Sect. 3.1.3), clinically they tend to all present as a symmetrical sensory-predominant peripheral neuropathy that may be associated with significant pain. Some 60% of individuals exposed to neurotoxic chemotherapy agents develop CIPN [28]. In one recent study, the type of chemotherapy (most common after platinum-based chemotherapy) and number of cycles received was associated with a higher incidence of CIPN [29]. A number of non-chemotherapy-related risk factors have also been identified. Older age, history of pre-existing neuropathy, symptom burden and alcohol intake were independent risk factors on multivariate analysis. Statins and diabetes mellitus were implicated on univariate analysis [29]. Smoking, abnormal creatinine clearance and specific sensory changes during chemotherapy have also been implicated. Although the prevalence of CIPN decreases with time, 30% of patients report it 6 months post-treatment [28]. Those surviving > 5 years often continue to have substantial impairments [30].

3.1.3 Chronic Pain Post-radiation Therapy

While RT plays an important role in palliation of painful cancer deposits, it may also be the source of treatment-related pain, albeit rarely. Its occurrence is better recognized

with improved long-term cancer survival. Onset can be within a few months of the end of RT or up to several years later. Chronic enteritis, cystitis, proctitis, osteoradionecrosis, pelvic fractures and chest wall pain are all described, along with various neuropathic pains (plexopathies, peripheral nerve entrapments and myelopathy) [18]. Risk factors include large overall treatment dose, large dose per RT fraction and combined treatment with surgery or chemotherapy.

Although overall the incidence of post-RT pain is falling, nevertheless, it occurs in 2% of breast cancer survivors and up to 15% of head and neck cancer survivors [31].

The most widely recognized form of post-RT pain is chronic neuropathic pain after breast cancer treatment [32]. Chronic painful radiation-induced neuropathies usually occur several years after RT and are often progressive and irreversible. Brachial plexopathy is more common after treatment of apical lung cancer (incidence 12% at 3 years) [33] than breast cancer [32]. Symptoms of post-RT brachial plexopathy begin any time from 6 months to 20 years (median time 1.5 years) after treatment and progressive weakness is common. In the past, pain has been documented as severe enough to need opioids in 50% of cases.

Chronic pain is also described after RT for head and neck cancer [34], gynaecological cancer [35] and prostate cancer [36]. Despite advances in RT techniques, patients with head and neck cancer may experience oral complications up to 6 months later, with resulting negative impacts on oral function and quality of life. In a prospective, multi-centre, longitudinal cohort study of 372 patients with head and neck cancer who received high-dose RT with curative intent, mean overall pain score was unchanged from baseline at 6 months in 216 evaluable patients, although it was mild on average (score only 9.2 ± 17.7 on a 0–100 score) [34]. Patients also complained of other persisting symptoms impairing oral health-related quality of life at 6 months including dry mouth, sticky saliva, difficulty swallowing solid foods and dysgeusia. Gynaecological cancer survivors can develop lumbosacral plexopathy after pelvic RT and axial neuropathy of the spinal cord after cervical RT. Women previously treated with pelvic radiation report a higher occurrence of symptoms from the urinary and gastrointestinal tract as well as lymphedema, sexual dysfunction and pelvic pain. In a Scandinavian study that compared women who had been treated for various gynaecological malignancies (> 80% of whom had endometrial or cervical cancer) and were on average 6 years out from completing RT with age-matched controls who had not been treated for cancer, the most prevalent problems were pelvic bone pain (39%), dyspareunia (17%), abdominal pain (12%), dysuria (10%) and genital pain (5%) [35]. While erectile dysfunction is the most well-known side effect of RT for prostate cancer, other changes in sexual function may occur, including orgasm-associated pain (15%) and painful erections (6%) [36]. Penile paraesthesias or cold sensations occurred in 2%. Increasing time since final treatment increased the risk of penile sensory disturbances.

3.2 Nociceptive Pain

Some of the more common examples include

1. Musculoskeletal pain following surgery [37] and/or RT. While the main pain syndromes following surgery and or RT are neuropathic, somatic tissues such as skin, muscle, fascia and bone can also be damaged by these modalities. Scarring and fibrosis of soft tissues results in misalignment and pain. For example, rotator cuff syndrome is common following breast cancer surgery due to misalignment of the subacromial space [38].
2. AIMSS. Joint and muscular symptoms occur in up to half of breast cancer survivors receiving long-term adjuvant treatment with third-generation aromatase inhibitors (AI) such as anastrozole, letrozole and exemestane. These symptoms are bad enough to cause > 25% of patients to discontinue treatment, adversely impacting survival [17]. They typically report pain or soreness in the hands, knees, hips, lower back, shoulders and feet beginning during the first few months of treatment. Difficulty sleeping and early-morning stiffness are commonly reported. Extra-articular manifestations include myalgia, fibromyalgia, neuropathy and carpal tunnel syndrome. While AI are generally used in post-menopausal women, younger age, higher BMI and taxane chemotherapy have been identified as risk factors for AIMSS [39]. In patients with AIMSS, switching AI therapy to a different agent is often effective [39–41].
3. Immunotherapy-related pain. Checkpoint inhibitors (monoclonal antibodies targeting immunological checkpoints) such as ipilimumab, nivolumab, and pembrolizumab have become available during the past 10 years and are being used increasingly in oncology. These agents work by activating T cells, so they produce a variety of inflammatory, autoimmune-like effects. They are unlike other cancer toxicities, affecting almost any organ system, but most often the skin, gastrointestinal tract, endocrine system glands and lungs [42]. Painful rheumatological syndromes are also common, occurring in 1.5–22% of patients [43]. These can include arthralgia, arthritis, myalgia, myositis, dry mouth, musculoskeletal pain and back pain.
4. Chronic graft versus host disease (cGVHD) following transplantation. cGVHD can occur after bone marrow or stem cell transplantation for adult haematological malignancies. It is a complex systemic disease with a wide spectrum of clinical features. cGVHD may be active for years, or even decades, requiring potentially years of immunosuppressive therapies and placing patients at

risk for a number of late complications. Painful manifestations may include scleroderma, myositis, fasciitis, joint stiffness and sicca syndrome of eyes and mouth [44], and joint and fascia complications occurred in 29% in one series [45]. The gastrointestinal tract can also be involved, including the liver and pancreas.

4 Pathophysiology of Cancer Treatment-Related Pain Syndromes

Painful stimuli are sensed by nociceptors in the peripheral nervous system (PNS) and nociceptive information is then passed to the central nervous system (CNS) at the level of the spinal cord and then sent to higher brain regions via several ascending pathways [46, 47]. Integration of these sensory signals with cognitive and emotional states in the brain leads to activation of descending pain pathways that can directly modulate incoming nociceptive information. Dysfunction in any part of this pathway, including the non-sensory components, can contribute to the development of chronic pain [3, 48–50].

In animal models, chronic pain is induced by sustained peripheral inflammation or nerve injury [51]. These prolonged injuries cause diverse neuronal adaptations that increase the responsiveness of both PNS and CNS nociceptive circuits, referred to as peripheral and central sensitization, respectively [52]. The two most frequent types of prolonged injury caused by cancer treatments occur due to surgery [19, 53] or treatment with chemotherapy agents [37, 54–56]. The pathophysiological changes that can result from surgery and chemotherapy may be targets for novel treatment approaches and are summarized in Table 2.

Table 2 Pathophysiological changes caused by cancer treatment, which may be targets for novel treatment options in chronic treatment-related pain

Cancer surgery	Glutamate release, NMDA receptor changes, and calcium ion influx in dorsal horn of spinal cord
	mRNA-mediated protein synthesis in spinal cord
Chemotherapy	Axonal degeneration
	Mitochondrial damage
	Increased reactive oxygen species
	Altered calcium homeostasis
	Altered ion channel expression
	Increased inflammatory cytokines
	Increased TLR4 receptor expression on glial cells

4.1 Post-surgical Pain Mechanisms

Surgery can lead to prolonged inflammation (e.g. due to wound infection or dysregulated inflammatory response) and/or directly damage peripheral nerves. In this context, it is unsurprising that cancer treatments with surgery as a modality are often associated with the development of chronic pain. The mechanisms include glutamate release, changes in n-methyl d-aspartate receptors, and calcium influx leading to neuronal death [19]. mRNA-mediated protein synthesis leading to centralization is another post-surgical mechanism [19].

4.2 Post-chemotherapy Pain Mechanisms

Chemotherapy is not perfectly targeted to cancer cells, so is cytotoxic in normal tissues, including those of the nervous system. Peripheral nerves originating from neurons in the dorsal root ganglion (DRG) are particularly susceptible to damage as the blood–brain barrier does not protect them. In addition, DRGs are intensely vascularized and maintained by a complicated nerve repair and regeneration process, which is altered by chemotherapy agents [37, 56–58]. Understanding the mechanisms that generate peripheral neuropathy is essential to help to identify and develop effective treatment options and guide the selection of appropriate analgesic therapies.

Paclitaxel and oxaliplatin are commonly used chemotherapeutic agents that are neurotoxic. They are cytotoxic to cancer cells via different mechanisms. Paclitaxel and other taxanes (e.g. docetaxel, cabazitaxel) are microtubule-stabilizing agents that impair cell division [59, 60], while platinum-based chemotherapies such as oxaliplatin are alkylating agents that binds to cellular DNA to inhibit cell RNA transcription and replication [61, 62]. Paclitaxel and oxaliplatin produce a plethora of changes in the PNS that lead to CIPN. Both cause axonal degeneration [63], mitochondrial damage, increased reactive oxygen species, altered calcium homeostasis, changes in ion channel expression [54–57] and modulation of the inflammatory and immune systems [37, 64]. However, it is still unclear which molecular changes occur first, which mechanisms are shared by both drug types and how each change contributes to nerve damage.

Although both paclitaxel and oxaliplatin neurotoxicity manifests as ‘glove and stocking’ neuropathies, the acute effects of these drugs trigger neuropathic symptoms that are distinct with respect to sensation, timing, severity and recovery [61]. Paclitaxel usually leads to painful sensations in both the hands and feet, often described as an aching sensation, which does not become worse after repeat treatments. By contrast, oxaliplatin affects the hands more strongly than the feet, gets progressively worse with each subsequent treatment, and produces a cold-induced neuropathy (attributed to a metabolite of oxaliplatin [65, 66]). These data suggest that the mechanisms by which paclitaxel and oxaliplatin initiate nerve damage are distinct. Understanding these mechanisms

may help identify medications that can protect peripheral neurons from the cytotoxic effects before they occur.

One example of a neuroprotective strategy that is currently undergoing clinical trials is based on the observation that both taxanes and platins accumulate in DRGs [67]. The level of the cytotoxic drug held in DRGs can remain elevated for a prolonged period, and higher intracellular levels correlate with more severe CIPN [68, 69]. Building on previous work [55, 70, 71], some recent pre-clinical studies have systematically applied knock-out strategies to assess which transporters are required for concentrating paclitaxel and oxaliplatin in sensory neurons [72, 73]. This work showed that the organic anion transporting polypeptide (OATP1B2) is necessary for paclitaxel accumulation in DRGs and triggers acute and tonic pain behaviours [72]. In contrast, knock-out of OATP1B2 did not interfere with oxaliplatin-induced pain behaviours [73]. Instead, these were dependent on the organic cation transporter 2 (OCT2). Thus, compounds that prevent OATP1B2- [72] and OCT2-dependent [73, 74] uptake of paclitaxel and oxaliplatin, respectively, may have the potential to protect against CIPN. The ability of dasatinib inhibition of OCT2 to prevent oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer [74, 75] is currently being evaluated in a clinical trial (ClinicalTrial.gov identifier: NCT04164069; open to recruitment at the time of writing).

The impact of PNS and CNS neuroinflammatory and neuroimmune processors on CIPN are being increasingly considered [37, 57, 76]. Many chemotherapeutic compounds, including paclitaxel, increase the serum levels of cytokines and monocytes in patients [77, 78] and pre-clinical CIPN models. Evidence suggests that chemotherapeutic agents alter both the innate and adaptive immune responses. This results in increased proinflammatory immune cells, dysregulation of Schwann cells [63, 79] and activation of DRG satellite glial cells, which release cytokines and further unbalance inflammation [37]. Modulation of many immune and inflammatory processors reduces pain behaviours in pre-clinical CIPN models. Toll-like receptors (TLR), which are expressed on immune cells and play a critical role in the innate immune system, are also expressed on DRG neurons, where they are thought to regulate sensory functions [80, 81]. TLR-4 expression in DRGs is increased as paclitaxel-induced CIPN develops [82] and is thought to promote macrophage infiltration. Interestingly, TLR4 antagonists can prevent the development of paclitaxel-induced pain behaviours [81]. The pre-clinical evidence supports the theory that the inflammatory and immune systems are involved in CIPN development. The role of these systems in other chronic pain conditions [83], together with the immunomodulatory effects that chemotherapies engage to destroy tumours [37], suggests that normalizing chemotherapy-induced immune changes may reduce CIPN and have broad-spectrum therapeutic benefits. In summary, research on the mechanisms underlying CIPN has been robust but there is a need for a more systematic comparison of mechanistic factors contributing to CIPN stimulated by different chemotherapy drugs, administered individually and in combinations commonly used in the clinic [84]. As inflammatory processes and the pain experience are different in males and females [85–88], this work needs to be done in both sexes and validated across various model systems and patient populations. In particular, this should include pre-clinical cancer models, as tumours themselves have immunomodulatory properties that are likely to be relevant [37, 89]. Current evidence suggests that although divergent mechanisms underlie the development of CIPN, the degenerative pathways they trigger are comparable. Thus, understanding how specific chemotherapy treatments damage peripheral nerves may help identify chemotherapy-specific early interventions that prevent CIPN. Conversely, a clear understanding of the shared degenerative pathways that establish and maintain CIPN could result in effective broad-spectrum therapies that are effective for CIPN, as well as other neuropathies. More research is needed to understand the pathophysiology of cancer treatment-related pain which will likely lead to improved pharmacotherapy.

5 Current Approaches to the Pharmacotherapy of Chronic Pain in Cancer Survivors

Choosing the best pain management strategy for a cancer survivor is complex. It is important to take into consideration the potential impact of pain medications on health, physical and mental states, health behaviours, professional and personal identity, sexuality and financial standing.

5.1 Opioids

Cancer patients often require initiation of opioid treatment for relief of moderate-severe pain arising during their diagnostic work-up and treatment. However, the role of long-term opioid therapy (LTOT) in cancer survivors, especially those who are disease-free after completing definitive treatment, is unclear. According to some, it raises the same concerns as it does in people with chronic non-malignant pain [5]. Chronic opioid use is also associated with chronic constipation, mental clouding, hypogonadism, effects on sexual desire and fertility, sleep disorders, hyperalgesia, and tolerance, misuse and abuse. Chronic use of opioids by long-term survivors may interfere with employment, family dynamics and personal identity. Possible personal

implications of chronic opioid use include fear of substance abuse, substance abuse relapse, and the social cost of accepting pain medications during treatment if in a recovery community, especially for survivors who require opioid replacement therapy with buprenorphine or methadone for opioid use disorder (OUD). Key points for using long-term opioid therapy in cancer survivors are summarized in Table 3.

LTOT would not be recommended in cancer survivors who have chronic pain from pre-existing non-malignant comorbidities such as osteoarthritis, spondylosis or migraine because they are considered ineffective for this purpose [7]. Concomitant non-cancer pain is common in cancer survivors [6] and it can be exacerbated by the deconditioning that follows cancer treatment. These patients need a full diagnostic workup using a biopsychosocial approach and should be treated congruent with the etiology of pain. Opioids would only be recommended in patients with moderate-severe pain that has not responded to maximum tolerated doses of non-opioid therapies [90, 91].

A recent review of persistent opioid use in cancer survivors has found a relationship between LTOT and various clinical factors including cancer type, socioeconomic factors and comorbidities [92, 93]. A national survey in the US found that 5% of opioid prescriptions were for cancer survivors [94]. They were more likely to receive opioids than patients without a cancer history, but they did not have an increased incidence of opioid misuse, which was uncommon, occurring in only 3–4% of both groups. Risk factors for misuse by cancer survivors included younger age (aged 18–34 years vs ≥ 65 years) (OR 7.06; 95% CI 3.03–16.41; $p < 0.001$), alcohol use disorder (OR 3.22; 95% CI 1.45–7.14; $p = 0.005$) and non-opioid drug use disorder (OR 14.76; 95% CI 7.40–29.44; $p < 0.001$) [94]. It is somewhat controversial whether opioid misuse in chronic pain patients, including cancer survivors, is the same entity as OUD in people who use opioids for non-medical purposes. An alternative term, complex persistent opioid dependence (CPOD), is preferred by some to describe this diagnostic entity, which is hard to diagnose by the DSM-V criteria for OUD [95]. CPOD has the same underlying mechanism and responds to the same treatment, with opioid replacement therapy [95]. When opioid misuse does occur in a cancer survivor, it can present a very challenging management problem [96].

Overdose is the most feared consequence of opioid use. It has been increasing not only in the general population but also among cancer patients [97]. Furthermore, co-involvement of alcohol and/or benzodiazepines in these deaths is common and increasing, reaching 14.7% for alcohol and 21.0% for benzodiazepines in one recent study [98]. Reducing the concomitant use of these agents provides a potential target for policy and practice efforts to reduce opioid-related harms.

Opioid diversion (defined as unlawful channelling of opioids from the patient for whom they were prescribed to others) is also a risk with long-term opioid use, even in cancer survivors. Unused prescription opioids are the primary source of misuse among family members, as well as the community at large [93]. Among family members with OUD, 70% began taking opioids prescribed to a relative and only 30% obtained their drugs of addiction from other sources [99]. However, prescribers do need to take ownership of opioid diversion: the study also showed that for those at the highest risk of overdose—people who use prescription opioids nonmedically 200 or more days a year—the most common way they get opioids is through their own prescriptions (27% of the time), as often as they get the drugs from friends or family for free (26%) or buy them from friends (23%).

Given all these problems, the decision to continue or restart opioids after completing cancer treatment should not be made lightly. When opioids are necessary, the lowest effective dose should be prescribed and as the painful condition resolves, opioids should be tapered down or discontinued in a safe manner.

5.1.1 Reducing or Discontinuing Opioids

In cancer survivors who have been taking opioids for years, tapering may need to be done over a prolonged

Table 3 Long-term opioid therapy (LTOT) in disease-free cancer survivors: key points

The role of LTOT is unclear
The main indication is moderate-severe treatment-related pain not responding to maximally tolerated therapy with non-opioid approaches
Opioids that were initiated during cancer treatment should be tapered off in survivors. This should be done gradually to avoid pain exacerbation and other adverse events (depression, suicide, illicit drug use, accidental overdose)
LTOT is not normally recommended for comorbid chronic non-malignant pain, which is common in cancer survivors
If LTOT is indicated in cancer survivors, it needs the same close monitoring as for patients with chronic non-malignant pain
Although opioid misuse by people with chronic pain may be distinguished from opioid use disorder seen with recreational drug use, the pathophysiologic mechanisms are similar and the treatment the same, with opioid replacement therapy
Risk factors for misuse are young age (under 35 years) and personal history of substance abuse
Risk factors for opioid overdose include prolonged use and concomitant alcohol and benzodiazepine use

period—weeks to months or longer. If withdrawal symptoms prevent further dose decrease, the taper should be temporarily halted and resumed when the withdrawal symptoms decrease, and with close monitoring. Observational data suggests that serious harms such as opioid overdose and suicidal ideation can occur following opioid dose reduction or discontinuation, but the incidence of these harms at the population level is unknown [100]. Referral to an addiction specialist, primary care provider or clinic who can prescribe opioid replacement therapy may be helpful for long-term management of OUD or CPOD in a cancer survivor, and new approaches to the transitioning of treatment are being developed [101].

5.1.2 Monitoring of Long-Term Opioid Therapy

Realistic goals, agreement about safe usage, storage and disposal and frequent reassessment are paramount if opioid therapy is considered for a cancer survivor. Realistic goals include functional pain management outcomes and creation of a strategy to avoid/ minimize the risks related to opioids. Treatment needs to be re-evaluated if treatment goals or safety goals are not met.

- Establish and document desirable functional outcomes.
- Re-evaluate the effectiveness and necessity of opioids on a regular basis.
- If the expected outcome is not achieved, other treatment alternatives should be considered. If opioids are no longer appropriate, recommend gradual tapering of opioids to help avoid symptoms of withdrawal.
- Consider establishing pain treatment agreements.
- Adjuvant medications and non-pharmacological interventions should be considered.
- Use a multimodality approach to pain management if warranted, and if those resources are available. Consider referral to a specialist in interventional pain, physical medicine and rehabilitation, or other appropriate consultants.
- It is important to be aware that pain experience in a cancer survivor can be influenced by both medical and psychosocial events during and after cancer treatment. Psychological support of the survivor with chronic pain is necessary, and referral to psychosocial services should be considered.

5.1.3 Overcoming Barriers to Long-Term Opioid Therapy When It is Clinically Appropriate

Cancer patients are generally excluded from various guidelines suggesting limiting chronic opioid prescribing (https://www.cdc.gov/drugoverdose/pdf/prescribing/Guidelines_Factsheet-a.pdf (last accessed May 22, 2021). In the US, however, 92% of US oncology practices are concerned that restrictions on opioid prescribing to non-cancer pain patients will result in undertreating cancer pain (American Society of Clinical Oncology. 2017 Oncology Practice Census [102]). About 40% of the oncology practices in the US report new barriers to patients receiving opioids in the pharmacy [102]. If chronic opioids are indicated, the prescriber should provide administrative support to the cancer survivor to ensure appropriate access to opioids.

5.1.4 Opioids and Pregnancy

If a survivor on LTOT is pregnant or wants to become pregnant, opioids should not be stopped abruptly. Safe pain management should be coordinated with the obstetrician. If the pregnant survivor has OUD and takes buprenorphine for addiction and/or pain, the opioid prescriber should provide access to addiction services without stopping buprenorphine.

5.2 Adjuvant Analgesics

Adjuvant analgesics are defined as medications with other primary indications that possess analgesic properties under certain circumstances. They are integral components in all three steps of the WHO analgesic ladder for treatment of cancer pain, and utilization of adjuvant agents in cancer patients has been demonstrated to correlate with improvement in cancer-related pain, anxiety and depression, and lower opioid doses [103]. They are now often prescribed as first-line or monotherapy, rather than as an add-on to opioid therapy, and they are recommended before opioids in the management of cancer treatment-related pain [8].

Common adjuvant analgesics include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), selected antidepressants, anticonvulsants, N-methyl-D-aspartate (NMDA) receptor antagonists and steroids. Other agents such as local anaesthetics, benzodiazepines, α2-agonists (e.g. clonidine or tizanidine), bisphosphonates, monoclonal antibodies or topical agents also play a role in treating specific pain conditions. The evidence base for the systemic administration of these agents in cancer survivors is summarized in Table 4.

5.2.1 Anti-inflammatory Agents

The ASCO Guideline on pain in cancer survivors recommends prescribing non-opioid analgesics such as paracetamol (acetaminophen) and NSAIDs for chronic treatment-related pain [8]. These agents will be expected to be most effective for the nociceptive pain syndromes (see Table 1) as well as comorbid chronic non-malignant pain such as spondylosis or osteoarthritis, which are often aggravated by cancer treatment. A recent systematic review of randomized

controlled trials (RCTs) on NSAIDs in cancer pain included one RCT where 73% of participants were breast cancer survivors. They were randomized to receive celecoxib 200 mg twice daily or diclofenac 50 mg twice daily for 6 weeks. While the primary outcome was mood (celecoxib was more of an antidepressant), both groups experienced an approximately 25% reduction in pain, from a baseline of around 6/10 to around 4.5/10 [104].

Given the inflammatory basis of checkpoint inhibitor toxicity, a stepwise escalation of rheumatological therapy has been recommended for patients with painful complications not responding to NSAIDs. The first step is local or systemic glucocorticoids (e.g. prednisone) followed by disease-modifying antirheumatic drugs. Severe myositis can be life-threatening and requires a high dose of glucocorticoids and close monitoring. In the case of patients with pre-existing rheumatic disease on immunosuppressive treatment who need to be treated with checkpoint inhibitors for cancer, it is recommended to maintain their baseline treatment at the lowest effective dose before starting immunotherapy [43].

5.2.2 Antidepressants

Antidepressants are used for cancer treatment-related neuropathic pain, most commonly tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRI). Their use is largely guided by studies on non-selective neuropathic pain conditions. A highly cited systematic review of pharmacotherapy for neuropathic pain in adults from a few years ago recommended antidepressants as first-line agents for neuropathic pain in adults [105]. The primary outcome measure in the review was a 50% reduction in pain score (when this was not available, a 30% reduction or at least moderate pain relief were used as surrogates). The quality of the evidence using the GRADE criteria was high for SNRI and moderate for TCA. SNRI had a number-needed-to-treat (NNT) of 6.4 (95% CI 5.2–8.4) while TCA had an NNT of 3.6 (95% CI 3.0–4.4). For both SNRI and TCA, the NNT was lower than the number-needed-to-harm (11.8 and 13.4, respectively), indicating a favourable risk–benefit profile [105].

In terms of cancer survivor pain specifically, there have been specific studies of antidepressants for painful CIPN, with only the SNRI agent duloxetine being specifically recommended by the American Society of Clinical Oncology [8]. This is based on results of two RCTs of duloxetine at doses of up to 60 mg daily [106, 107]. At least 30% reduction in baseline pain score was achieved in 38% and 73% of patients in the duloxetine arms of the two studies, and 11% and 18% in the two control arms, leading to NNTs of 3.7 and 1.6, respectively. Fatigue (7%), insomnia (5%) and nausea (5%) were the most common adverse effects reported by

Table 4 Summary of evidence from controlled clinical trials for systemic adjuvant analgesics in cancer survivors[a]

Drug class [references]	Drugs, daily dose (mg/day), duration	Pain syndrome	Number in study	Mean pre-post reduction in pain score/10	Percentage with reduced pain score	NNT
Non-steroidal anti-inflammatory drugs [104]	Celecoxib 400 mg vs diclofenac 100 mg, 6 weeks	Breast cancer survivors, post-chemotherapy or radiation therapy	53	1.4 vs 1.5		
Tricyclic antidepressants [110, 111]	Amitriptyline 10–50 mg vs placebo, 7 weeks	CIPN	44	3.4 vs 1.9		
	Nortriptyline 100 mg vs placebo, 4 weeks	CIPN	51	0.7 vs 0.3	69 vs 27%	2.4
Serotonin-norepinephrine reuptake inhibitors [106, 109, 113]	Duloxetine 60 mg vs placebo, 5 weeks	CIPN	231	0.7 vs 0.3	59 vs 38%	4.8
	Duloxetine 60 mg vs placebo, 12 weeks	AIMSS	255	2.8 vs 2.0	68 vs 59%	11
	Venlafaxine 75 mg vs placebo, 10 weeks	Post-mastectomy pain	13	4.9 vs 4.8		
Gabapentinoids [117]	Gabapentin up to 2700 mg vs placebo, 6 weeks	CIPN	115	1.0 vs 0.6		
Medicinal cannabis products [139]	Nabiximols, up to 32.4 mg THC vs placebo, 4 weeks	CIPN	16	0.75 vs 0.37	31 vs 0%	

AIMSS aromatase inhibitor musculoskeletal syndrome, *CIPN* chemotherapy-induced peripheral neuropathy, *NNT* number needed to treat, *THC* tetrahydrocannabinol

[a]No controlled studies identified for pregabalin or ketamine

patients treated with duloxetine, but was no different to the placebo arm [106]. There has not been a study of venlafaxine for established CIPN, although it has been shown to be effective for acute neurotoxicity from oxaliplatin [108]; however, there is small, older RCT of low-dose venlafaxine (18.75 mg daily) versus placebo for persistent pain after breast cancer surgery [109]. The study found no difference in the average daily pain score (primary outcome) but average pain relief and maximum pain intensity were significantly lower in the intervention group. Anxiety and depression were not affected, and adverse effects did not show significant differences between treatments. The evidence for tricyclic antidepressants in CIPN is considered inconclusive, based on two old studies showing no benefit for amitriptyline up to 50 mg per day in one RCT [110] and limited evidence in favour of nortriptyline up to 100 mg per day in the other [111], although these doses were generally well tolerated.

Duloxetine has also been evaluated in AIMSS, and showed decreases in AIMSS symptoms in two patients out of three, although some patients experienced intolerable adverse effects [112]. Specifically, a large multi-site RCT compared duloxetine 60 mg for 12 weeks versus placebo in 255 patients [113]. By the primary endpoint at 12 weeks, more patients (68 vs 59%) receiving duloxetine had a reduction in pain score of ≥ 2 points but the difference was not significant. Again, the most common any-grade adverse events in the duloxetine arm were fatigue (32%) and nausea (30%), with dry mouth (25%) and headache (21%) also common [118].

5.2.3 Anticonvulsants

Anticonvulsants are also frequently used against cancer treatment-related neuropathic pain, again extrapolating significant evidence from treatment of non-malignant conditions [105]. Gabapentin and pregabalin exert their effect through modulation of calcium channels [114], while phenytoin, lamotrigine and carbamazepine suppress ectopic discharge by inhibiting sodium channels [115]. In a systematic review of CIPN [116], it was concluded that the evidence does not support the use of gabapentinoids or lamotrigine for this indication. One older, well designed but negative RCT was included, with gabapentin given for 6 weeks to a target dose of 2700 mg/day [117]. There were no studies of pregabalin. Drowsiness, headache and somnolence are common limitations for this class of adjuvant analgesics in the cancer population [118].

5.2.4 NMDA Receptor Antagonists

Ketamine has been increasingly used for refractory cancer pain and is considered 'third line' for other chronic pain [119]. Infusions of ketamine have been shown to be effective in pre-clinical CIPN models [120], but has not been evaluated for clinical neuropathic pain in cancer survivor pain in humans [121]. Limitations to using ketamine include concerns for hypertension and neuropsychiatric side effects [122], and its limited modes of delivery, and high heterogeneity from existing studies that resulted in insufficient evidence for its efficacy have precluded its widespread routine use [119, 123]. More recently, there has been renewed interest in investigating its sublingual/oral route for improved accessibility and a study addressing its role in cancer-related breakthrough pain is currently underway (ANZCTR ID: ACTRN12621000328875).

Magnesium is a nutrient with NMDA receptor antagonist activity and additional effects on muscle relaxation and anti-inflammatory mechanisms that has gained popularity due to its relative inexpensiveness and safety profile, despite inconclusive evidence on efficacy to date [124, 125]. Studies are also underway for its wider application in managing cancer-related pain, including in the prevention of post-mastectomy syndrome [126].

In summary, the ASCO expert panel on cancer survivor pain acknowledged that "NMDA antagonists are taken by some cancer survivors with chronic pain and may benefit some of those who receive them. However, the efficacy of these agents and their long-term effectiveness have not been established" (Recommendation 2.5, Qualifying Statement) [8].

5.2.5 Topical Analgesics

Several RCTs have demonstrated variable benefits with topical agents in various acute and chronic pain syndromes in cancer survivors. These include doxepin mouthwash for acute radiation-induced mucositis [127], high-dose capsaicin 8% patch [128] or amitriptyline cream for CIPN neuropathy [129, 130] and capsaicin cream [131] or lignocaine transdermal patches for post-surgical pain [132–134]. However, heterogeneity of the studies warrants clinical discretion when making treatment decisions in individual patients.

5.3 Cannabinoids

Cannabis sativa contains a multitude of phytocannabinoids, such as the psychoactive constituent Δ9-tetrahydrocannabinol (THC), plus other constituents such as cannabidiol (CBD) that do not produce THC-like psychotropic side effects. Agonism at CB1 and CB2 receptors by cannabis-based medicines have shown analgesia in rodent models of neuropathic pain [135]. Cancer patients have reported favourable outcomes for managing chemotherapy-induced nausea and vomiting as well as symptoms

due to cancer such as pain [136], but there are differing views as to their clinical efficacy and safety in light of the limited number of high-quality clinical trials evaluating these benefits being currently available [137, 138]. We located one study specifically addressing the safety and efficacy of cannabinoids in cancer survivors, a small ($n = 16$) placebo-controlled RCT of nabixomols—an oromucosal spray with a plant-derived combination of THC and CBD—at a maximum dose of 12 sprays (32.4 mg THC) per day for chemotherapy-induced polyneuropathy [139]. There was a small positive effect size for achieving a 50% reduction in pain (0.11) in favour of cannabis over placebo, but it was not statistically significant (95% CI − 0.06 to 0.28). Five (31%) of the nabixomols group were considered 'responders', with an average reduction of numeric rating scale for pain of 2.6. This study is included in a Cochrane review of the efficacy, tolerability and safety of cannabis for neuropathic pain [140]. The review included 16 studies with 1750 participants. It showed that cannabis-based medicines may increase the number of people achieving pain relief of 30% or greater compared with placebo (39 vs 33%; NNT 11 [95% CI 7–33]; moderate quality evidence). However, any potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms, as they increased nervous system adverse events with a number needed to harm (NNTH) of only 3 (95% CI 2–6) and psychiatric disorders with a NNTH of 10, occurring in 17 vs 5%.

We also found one systematic review on the opioid-sparing effects of cannabis in non-cancer chronic pain [141]. Nine studies involving 7222 participants were included, but all were observational studies and only one had a control group [142]. This study evaluated the magnitude of associations between enrolment in the New Mexico Medical Cannabis Program (MCP), opioid prescription use and pain-related outcomes, when compared with an historical control before the program started. They found clinically and statistically significant evidence of an association between MCP enrolment and opioid prescription cessation, opioid dose reduction and improved quality of life [142]. The study design does not, however, allow for any causal inferences about MCP enrolment and the observed outcomes to be made.

We did find a qualitative study analysing interviews in 33 Canadian cancer survivors using the broad definition of survivorship (from diagnosis until the end of their life) [143]. All 33 survivors believed that cannabis would relieve their symptoms, but only 17 (approximately half) were currently using it. Reasons given for using it were that it was a "more natural alternative" to prescription medications; it helped reduce polypharmacy because it was effective for multiple symptoms; and that the legalization of recreational use implied that 'safer products' must now be available. Those who chose not to use it were deterred by the lack of evidence and the risk of dependency. The attitudes of their physician, family and friends towards medicinal cannabis was also a factor in their decision making.

5.4 New Drugs

While new formulations of old drugs have been approved, very few truly novel analgesics have been approved by the US Food and Drug Administration or other regulatory agencies in recent decades. The opioid epidemic is leading to renewed interest in finding new targets [144]. Novel opioids, α-adrenergic agonists and oxytocin have been identified as potential candidates, along with target toxins and gene-based approaches such as protein synthesis blockade and transfection [144, 145]. With regard to cancer treatment-related pain specifically, novel agents are being evaluated for CIPN. MR309, an oral sigma 1 antagonist (sigma-1 is a mitochondrial endoplasmic reticulum receptor), has been shown to reduce chemotherapy-induced mitochondrial structural changes and pain behaviours in lab animals [146]. A randomized phase II clinical trial of MR309 was shown to improve short-term outcomes (decreased cold hypersensitivity) in patients receiving oxaliplatin-based chemotherapy, reducing treatment dropouts and allowed a higher cumulative dose of oxaliplatin to be given [147]. However, its effect on chronic pain outcomes is unknown.

6 Nonpharmacological Approaches

Various organizations including ASCO and National Comprehensive Cancer Network (NCCN) recommend a combination of pharmacologic and non-pharmacologic modalities for managing chronic pain in cancer survivors [2, 8]. Non-pharmacological strategies include neuromodulation, complementary and alternative medicine, and psychosocial interventions.

6.1 Neuromodulation

Transcutaneous electrical nerve stimulation (TENS) uses electrical fields to active motor or sensory fibres, which in turn inhibit the spinothalamic system and minimize pain sensation (the gate control theory) [148]. TENS is a reasonable

option for patients who have focal pain. It has been shown to improve pain control for breast cancer patients and function for various cancer patients as a goal-directed therapy [149, 150]. Specialized devices have shown efficacy in CIPN [151]. Limitations to broad adoption of TENS units (cumbersome, decreased usage over time and transient effects) have led to development of more precise and implanted systems [149] such as peripheral nerve stimulation (PNS) and spinal cord stimulation (SCS).

By implanting a stimulator closer to a nerve, the skin is bypassed as a resistor, and thus PNS can preferentially activate fast-acting sensory fibres, creating comfortable sensations that indirectly inhibit pain signals [152]. PNS devices have been shown to be helpful in treating post-mastectomy pain syndrome and chronic radiation- and surgical resection-related neuropathies [152]. SCS primarily works by stimulating the dorsal columns to inhibit transmission of pain signals [153]. Patients with focal pain and an intact epidural space may benefit from these devices. SCS has been used for cancer treatment pain such as radiation neuritis and chemotherapy-induced peripheral neuropathy [154].

6.2 Psychological Therapy for Chronic Pain in Cancer Survivors

Chronic pain, whether related to cancer treatment or otherwise, is a multidimensional phenomenon that benefits from being assessed and managed within a biopsychosocial framework [155–158]. For example, high levels of preoperative anxiety, depression, distress and catastrophizing were predictive of post-operative pain at all time points up to 12 months and beyond in women with early-stage breast cancer [158]. In cancer survivors, there is strong evidence that depression and anxiety are associated with increased pain and higher levels of physical activity are associated with lower levels of pain [156]. Likewise, loneliness, fatigue and sleep problems are all associated with greater pain in this group.

Psychological interventions to address these feelings could in turn influence levels of pain and pain's interference with function by reducing distress, improving sleep and increasing activity levels and function. Although they are not aimed at pain reduction per se, all of these outcomes can serve to reduce pain levels. Unfortunately, because of limited access to and/or reimbursement of psychological treatments in many countries, treatment for pain in cancer survivors still tends to be primarily biomedical, and assessment is not routinely conducted within a biopsychosocial framework. This situation persists despite mounting evidence that a range of psychological and behavioural interventions can reduce pain severity and pain interference in patients with cancer, as they do in patients with chronic pain from the wider population.

Psychological and behavioural approaches have been shown to reduce cancer pain at diagnosis and during treatment [156]. However, there is far less research available on the psychological and behavioural aspects of survivor pain and related interventions. Strategies that have been evaluated include exercise programmes with group and cognitive behavioural therapy (CBT) elements. CBT in this context refers to a range of skills and behaviours including cognitive training to reframe pain-related catastrophic cognitions, using adaptive behaviours such as engaging in distraction, pacing and planning activities, relaxation, imagery, exercise and yoga [156]. Education may include CBT elements that address barriers to engagement in treatment and that assist in effective communication with healthcare providers, particularly about pain. All of the above can also be useful in assisting partners and caregivers to respond to pain and pain-related distress in a manner that will help reduce these [156].

6.3 Complementary and Alternative Medicine

Once carefully incorporated into standard care, complementary and alternative medicine (also known as integrative medicine) therapies can complement other treatments and enhance the quality of care that survivors with chronic pain are receiving. Most of the current research data comes from studies of mind–body practice, acupuncture, massage therapy and music therapy, and data from RCTs support the effect of hypnosis, acupuncture and music therapy in reduction of pain [159]. Mindfulness meditation, yoga, qigong and massage therapy have not been shown to reduce pain per se but can relieve the emotional distress that is commonly associated with pain. One expert in the field recommends considering the burdens and risks to patients, patient preference and the presence or absence of better alternatives when making decisions on whether an integrative medicine therapy is of clinical value [159].

7 Conclusion

Millions of people are living with chronic pain after completing cancer treatment and the number continues to grow as improvements in cancer treatment continue to be developed. While opioids are the mainstay of pain due to cancer, their use is problematic in disease-free cancer survivors who have been treated with curative intent and have a normal prognosis. If these people have chronic pain, other treatment options should be tried first. While we have summarized here the latest information on non-opioid drugs that can be prescribed, including adjuvant analgesics, medicinal cannabis products, and investigational agents, it must be recognized that a multidimensional approach is needed for the optimal

management of chronic pain, with non-pharmacologic interventions being provided alongside pharmacologic ones.

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