

Review

Pharmacological management of cancer pain: Novel therapeutics

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ABSTRACT

Patients diagnosed with cancer often experience pain during their treatment course, making it difficult to care for themselves and continue with their activities of daily living. When cancer is found at later stages, the pain can become severe and constant; reducing their quality of life and significantly affecting mental and physical well-being. Despite opioids being known to provide adequate analgesia for higher pain levels, they are often the reason for under-dosing because of their adverse effects and concern for addiction. There are also patients who do not respond well to opioids because of genetic anomalies or personal preference. Therefore, there is a need for novel non-opioid cancer pain treatments. There are many new cancer pain treatments that are emerging. This manuscript discusses cancer pain, risk factors, epidemiology, guidelines for the treatment of cancer pain, personalization of cancer pain therapy, breakthrough pain, cancer-induced peripheral neuropathy, established cancer pain treatment options, and novel emerging cancer pain treatment options.

1. Introduction

Patients diagnosed with cancer often experience pain during their treatment course, making it difficult to care for themselves and continue with their activities of daily living. When cancer is found at later stages, the pain can become severe and constant; reducing their quality of life and significantly affecting mental and physical well-being [1,2]. It is not unusual for pain to persist even after completion of chemotherapy or radiation. It is estimated that 50% of cancer survivors will live with long-term chronic pain [3]. The pain experienced is created by cancer itself, affecting surrounding nerve fibers or from chemotherapy and radiation damaging these fibers, producing a heightened sensation of pain [4]. Using a scale to assess the level of pain can help determine its

intensity and allow for better treatment options creating a tolerable level of pain [5]. The World Health Organization (WHO) published guidelines for healthcare providers to assist with pain management upon assessing the level of severity [5,6]. While cancer patients and survivors may experience moderate to severe pain, they are often managed inadequately, affecting their daily lives and relationships [4]. Despite opioids being known to provide adequate analgesia for higher pain levels, they are often the reason for under-dosing because of their adverse effects and concern for addiction [7]. For patients in which opioids are not the initial option, nonopioid management is an alternative. As better treatments are developed against cancer and more is known about various cancer types, patients are given a greater chance of survival. Providing patients with optimal pain control can lessen the burden

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carried throughout their cancer treatment and post-cancer pain, giving them the opportunity for a better quality of life [8]. This manuscript will discuss cancer pain, risk factors, epidemiology, guidelines for the treatment of cancer pain, personalization of cancer pain therapy, breakthrough pain, cancer-induced peripheral neuropathy, established cancer pain treatment options, and novel emerging cancer pain treatment options.

2. Epidemiology and risk factors for cancer pain

The highest incidence of cancer types and leading causes of mortality worldwide for many years have been lung cancer, breast cancer, and colorectal cancers [9]. Males are reported to have a 20% higher incidence than females overall [9]. While 50% of patients continue on to have chronic cancer pain-causing significant distress, various barriers affecting the patient or the healthcare provider can add to ineffective management [3,10]. Factors that may limit a patient's ability to seek pain medication are influenced by their insurance coverage, a limited number of refills, or having lower health literacy [11,12]. Health providers have inclusively reported that limitations on electronic prescriptions and needing prior authorization places a delay in managing pain [10]. Families with low socioeconomic status, including children, report a greater prevalence of pain and distress compared to higher socio-economic status families [13]. The lack of access and knowledge of resources contributes to longer suffering and disability. Many of these patients experience frequent or constant pain, further affecting their daily life [14]. The severity of the pain felt by the patient contributes to having greater levels of fatigue, poor sleep, aggression, and socially isolating [15].

Several factors can influence a patient's perception of pain when creating an individual treatment plan. A lack of understanding of a patient's cultural background, spiritual beliefs, and perception of pain can place the patient at risk of being undertreated [16]. A patient's personal beliefs can result in underreporting as they can see suffering as a part of human life or have fears of becoming dependent on the medication [17]. The health providers must address all patient questions and concerns to limit miscommunications affecting treatment. Knowing the type of cancer also assists in proper management as cancer pain varies among the different types, the stage during diagnosis, and the location [18]. Those diagnosed with sarcomas or advanced cancer have a higher incidence of chronic pain [19]. Some cancer pain is more difficult to suppress, such as head and neck cancer, as the tumor makes likely damage on surrounding nerves [20]. Other associations with higher rates of chronic cancer pain are smoking, low physical activity, and being female (two X chromosomes (XX)) [19] (Fig. 1). A thorough medical history can identify these risk factors to address them while receiving treatment. Patients unsatisfied with their current medications should be aware that switching is an option [21]. As 50% of patients who switch can optimize their treatment plan and, in some cases, reduce adverse effects [21].

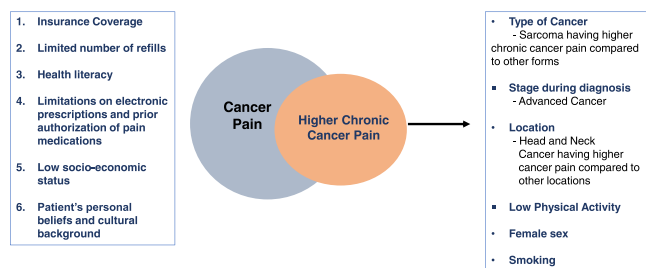


Fig. 1. Risk Factors for Cancer Pain. Several factors influence perception of pain. These factors are important to consider when creating individual treatment plans.

3. Guidelines for treatment of cancer pain

In 1986, the World Health Organization (WHO) released guidelines for the management of cancer pain. The development of these guidelines was meant to provide evidence-based treatment options for healthcare providers and assist in policy decision-making on opioids regulation [22]. Since then, the WHO has continued to release updates for the use of analgesics and adjuvants. These recommendations target adolescents as young as ten years old to adults greater than 60 years of age. The guidelines serve as a multi-step process, giving patients a variety of treatment options depending on the severity of their pain without immediately initiating opiates. Before beginning the first step of the WHO ladder, health providers need to assess the patient's pain level. A poor assessment can lead to inadequate pain control and unnecessary treatment [16]. Obtaining a comprehensive history and focused assessment of pain includes location, quality, and intensity. Regular screenings are recommended to address changes and create a better quality of life for cancer patients [16]. Once a proper assessment has been achieved, health providers can begin with the WHO treatment guidelines.

Step 1 begins with nonopioid drugs for patients with mild pain. Depending on patient presentation, adjuvants during step 1 may be recommended for better pain control, especially neuropathic pain [22, 23]. Addition of adjuvants include anticonvulsants, antidepressants, and NMDA antagonists. Patients that continue to have persistent pain or increase in severity can continue to step 2 of the ladder. Step 2 addresses moderate pain by initiating opioids at this point [22]. Healthcare providers may decide to add nonopioids or adjuvants when appropriate. Step 3 is for patients with severe pain that require stronger doses for greater pain control. Some patients may benefit from counseling when pain is exacerbated by symptoms of depression and anxiety [22].

Patients that have previously undergone treatment using WHO indicated a 57–81% decrease in pain, and 75% of them reported good or excellent pain control [24]. Overall, studies have found WHO guidelines to be an effective method in providing pain relief even in severe cases [24]. An important discussion for healthcare providers to have with patients is the possibility to not be completely free of pain but instead manage pain to a tolerable level [22]. All possible adverse effects should also be discussed to ensure patient safety and decrease the risk of misuse or abuse [22]. It is important for healthcare providers to initially identify any risk factors that may influence patient care, such as comorbidities, barriers to access medication, or previous history of opioid abuse [22]. Early identification of any risk factors can assist in creating a plan to better manage their pain.

4. Personalization of therapy

The management of cancer pain is very complex because there is a wide variability of responses among patients to different treatments and medications [25]. For example, one patient could experience excellent relief with one analgesic, while a different patient may have better results with a different medication. Furthermore, expression of pain is dependent not just on nociceptive input, but also on the patient's ability to cope, distress levels, cancer-related suffering, family support, presence of delirium, and behavioral attitudes toward opioids [26]. In addition to assessing pain, it is essential to evaluate underlying modifiers of pain expression, such as the existence of additional physical and psychological distress, delirium, or somatization, and risk factors and barriers to effective pain management.

Research shows that genetics can influence opioid sensitivity, thus doses of a specific opioid can also vary markedly among patients [25]. Therefore, it is necessary to individualize therapy, taking into account the differing pharmacology of mu opioids and various sensitivity of patients to the drugs. It is not possible to predict which patient will respond best to which drug or dose, so recognizing the need to try different options and increase doses is vital in improving patient care

[25].

Systematic screening is the first step in personalized pain treatment, followed by a full pain evaluation. A precise categorization of pain defines its etiology and mechanism, which in turn directs therapy options. Identifying modulators of pain expression, such as psychological distress, alcoholism, drug abuse, and delirium, allows doctors to adapt therapy recommendations more precisely. The documentation of a tailored pain objective gives a customized response criterion. Then, a multifaceted treatment strategy addressing the pain mechanism, etiology variables, and modulators can be developed. Lastly, longitudinal monitoring tailored to the requirements of the person allows doctors to enhance adherence and, eventually, maximize pain management over time [27].

5. Breakthrough Pain

Breakthrough cancer pain (BTCP) is a specific subset of cancer pain defined as a transient exacerbation of pain in a patient who has otherwise stable baseline background pain [28]. A recent systematic review indicated that cancer pain is present in approximately 75% of advanced cancer patients with BTCP, specifically affecting over half of all cancer patients – an overall prevalence of 59.2%. The lowest prevalence of BTCP was noted in outpatient clinics at 39.9% and the highest prevalence in hospice care settings at 80.5% [29]. The general diagnostic algorithm for BTCP first assesses if the patient has background pain (pain for ≥ 12 h/day or persistent pain when not on analgesics), then whether background pain is controlled properly, and lastly, if the patient has transient exacerbations of their pain, respectively. If these conditions are met, a diagnosis of BTCP can be made [30].

BTCP is formally characterized as a rapid onset (within minutes), high intensity, increase in pain lasting upwards of approximately 30 min. The pain is typically superimposed on the persistent baseline pain – often maintaining the same location as the original pain. BTCP is paroxysmal. It can occur several times a day and can trend upwards of ten or more episodes per day. The intensity of BTCP has been noted on average to be a 7 when assessed on a 10-point VAS scale and is thus often severe [28]. BTCP is generally categorized as incidental or idiopathic. Incidental pain can be volitional (walking, getting dressed, intentionally moving, etc.), non-volitional (coughing, voiding, defecation, swallowing, etc.), or procedural (due to diagnostic or therapeutic intervention). Conversely, idiopathic BTCP arises spontaneously and is thus much less predictable. Additionally, end-of-dose failure pain references onset of pain at the end of the duration of an analgesic dose – it is thus not considered a subset of BTCP. The etiology of BTCP can be due to the primary disease, adverse treatment effects, or other comorbidities [28].

Given the heterogeneous nature of BTCP, it has been a challenging pain syndrome to treat. Treatment is highly individualized and relies on understanding both pain-related factors and patient-related factors. Traditionally, the infrastructure of most cancer pain treatment plans includes treating the underlying cause, avoiding factors that provoke the pain episodes, background pain control, and rescue medications for acute BTCP. Non-pharmacologic and interventional methods are used in some cases as well [31]. The hallmark of addressing BTCP pharmacologically is rescue medications which primarily consist of rapid-onset opioids (ROO). The dosing is determined as a proportion of the long-acting opioids used to control persistent background pain. Traditionally, oral morphine was the standard ROO used for BTCP, at an average of approximately 10–16% (full-range 5–20%) of the daily dose of background pain medications. Given this proportional dosing pattern, the ROOs must be adjusted if the background does happen to need modification according to pain levels and medication tolerance [32].

In more recent years, evidence suggests the onset and lasting duration of orally administered morphine are not optimal for treating acute episodes of BTCP. Various reviews and control trials have illustrated improved efficacy in treating BTCP when using a variety of Fentanyl preparations. These formulations include consist of transmucosal

fentanyl - fentanyl buccal soluble film (FBSF), intranasal fentanyl spray (INFS), and sublingual fentanyl tablets. Evidence from these reviews and control trials demonstrated improved pain scores overall with more rapid relief of BTCP when compared to standard morphine control. The fentanyl preparations were seen to be particularly useful for rapid resolution of pain when administered at the time of onset of BTCP episodes [33]. Randomized control trials examining the pharmacokinetic properties further supported fentanyl formulations to be much more rapid-acting than the standard oral morphine treatments with peak plasma concentrations in 9–15 min, with intranasal formulations being the most rapid, versus approximately 25–30 min in rapid release morphine. Additionally, the pain intensity difference was greater in nearly all preparations of fentanyl, with intranasal administration being nearly double that of morphine [34]. However, since BTCP is so heterogeneous and treatment plans are so individualized, there are still indications noted for standard oral opioids. They still serve as effective prophylaxis of anticipated BTCP episodes – usually administered 30 min prior to predictable episodes – and for longer duration episodes of BTCP [32]. Further comparative studies have examined a cost-effective analysis of transmucosal fentanyl preparations versus standard oral morphine for BTCP. When analyzing for cost-adjustments and quality of life improvement metrics, the fentanyl formulations were generally determined to be more economically sustainable over time for patients (5,8). Though other data has suggested, the economic and financial impact may be more variable and should be assessed on a case-to-case basis [35]. (Fig. 3).

6. Cancer Induced Peripheral Neuropathy (CIPN)

The International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) defines neuropathic pain as "pain resulting directly from a lesion or disease affecting the sensorimotor system [36]." There are numerous causes of neuropathic pain, including peripheral nerve lesions and lesions of the brain and spinal cord. The most prevalent pathophysiological feature of pain caused by neurological lesions is that the lesion affects the somatosensory pathways, notably the nociceptive fibers and their peripheral and central connections. Neuropathic pain in oncology patients may be induced by either the nerve damage produced by the cancer's mass impact or by treatments such as chemotherapy, radiation, and surgery [23]. Pain, numbness, and tingling are the symptoms of peripheral neuropathy, which is caused by damage to the nerves in the fingers and toes. Cancer treatments including surgery and radiation, and the disease itself, may cause peripheral neuropathy in cancer patients and survivors. CIPN is the most prevalent reason why patients must reduce their chemotherapy dosage. Due to the severe and upsetting nature of CIPN, some cancer patients may even discontinue treatment. Drugs that inhibit the activity of histone deacetylase (HDAC), are currently being evaluated in clinical trials for their potential to boost the efficacy of chemotherapy. Animal studies demonstrate that certain HDAC inhibitors can prevent and reverse CIPN [37].

7. Established pharmacological cancer pain treatments

7.1. Opioids

Almost all opioids bind to the mu receptor, a GPCR. Binding to the receptor reduces adenylyl cyclase activity, calcium channel opening, and neurotransmitter release. [25]. Opioids may work centrally, inhibiting the release of GABA from the periaqueductal grey area or inhibiting afferent nerves at the spinal cord level [25]. Analgesic effects of opioids depend on the mu-receptor saturation and are affected by a variety of factors. Factors include the distribution of receptors, severity of pain, type of pain, and prior exposure to opioids [38] (Fig. 2). Although almost all clinically used opioids act through the mu receptors, not all patients respond equally to each opioid, therefore the specific drug

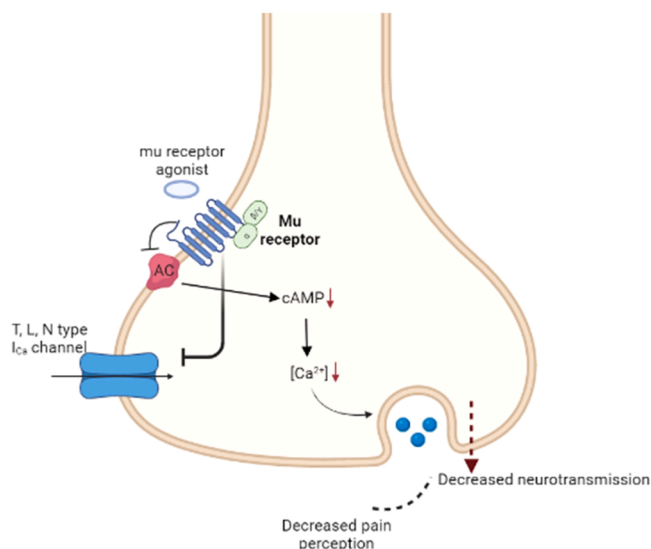


Fig. 2. Mechanism of action of opioids.

choice for each patient is empirically chosen [25]. The variability in responses among patients are thought to have a biologic basis and involve biased agonism and the many mu opioid receptor subtypes [25]. Opioids differ in their chemical make-up [38]. As a result, the properties affect the equianalgesic dosages of each opioid. Morphine is the standard opioid to which others are compared [39]. Medications are decided on better-side effects, lipophilicity, longer half-life, and management compared to others [39]. The ceiling for opioid medications is the inability of a drug to relieve the pain beyond a certain point despite increased dose or based on the side-effects due to increased dosages [25, 39]. For example, patients who are poor liver enzyme CYP2D6 metabolizers will not likely receive adequate pain control from prodrugs that require metabolism (Codeine, hydrocodone, and oxycodone). In contrast, ultra-rapid metabolizers are at risk for opioid toxicity [38].

Common side effects of opioid administration include dizziness, constipation, tolerance, sedation, physical dependence, respiratory depression, and vomiting [40]. Addiction and physical dependence are clinical concerns that may cause a physician to be hesitant when prescribing opioids. Less common side effects include hyperalgesia, muscle rigidity, myoclonus, delayed gastric emptying, and immunologic and hormonal dysfunction [40]. The side effects with the most incidences are constipation and nausea. These side effects have a great impact on patient quality of life as they can be very difficult to manage and tolerance to them does not develop, especially for constipation. Switching opioids

or routes of administration may provide some relief of side effects [40]. See Table 1.

7.2. Non-opioids

7.2.1. NSAIDs

The analgesic effects of non-steroidal anti-inflammatory drugs (NSAIDs) have been related to inhibition of cyclooxygenase (COX), which is responsible for the synthesis of peripheral prostaglandins [38, 41]. NSAIDs are especially beneficial for mild pain that is caused by inflammation, which reduces the pain to a level pre-inflammation [38, 42]. For this reason, NSAIDs are commonly paired with opioid therapies to allow for pain control. NSAIDs were able to be continued for longer periods and avoided increases in opioid dosage [41]. Unlike opioids that can be titrated for pain relief, NSAIDs have ceiling effects, and no therapeutic gain is achieved in increasing doses beyond recommended dosages [41]. Raising the dosage above recommended amounts increases the likelihood of adverse effects [41].

Several risks are associated with NSAIDs, especially in patients including elderly patients and patients with renal impairment or gastrointestinal disease. Other side effects include GI bleed or perforation, cardiac or renal compromise, and thrombocytopenia [38,41]. Caution for NSAIDs should be considered for patients who are receiving medications that could increase NSAID toxicity, such as steroids [41]. Patients at risk should have their dose started low and slowly increased to prevent adverse effects [38,43]. Celecoxib, a specific COX-2 NSAID, should be considered for certain high-risk patients due to a lower risk of GI adverse effects [38]. No clear preference for specific NSAIDs can be suggested [41]. Aspirin is an irreversible COX inhibitor that has been known to reduce the risk of colorectal cancer and prostate cancer [44]. Studies show the benefit of taking aspirin for mild cancer pain when compared to a placebo [45].

7.2.2. Acetaminophen

Acetaminophen (oral paracetamol) is a reversible COX inhibitor with very weak anti-inflammatory properties. However, it does not have the same side-effect profile that is associated with NSAIDs [38]. Acetaminophen can lead to the creation of N-acetyl-p-benzoquinone imine (NAPQI). Although this is normally in small amounts, if the dose of Acetaminophen is large enough, a large amount of this hepatotoxic metabolite is created [38]. Similar to NSAIDs, acetaminophen is combined with opioids for analgesic effects. Patients should not exceed 4000 mg daily, and those with liver dysfunction should not exceed the maximum of 2000–3000 mg daily dose [38]. The efficacy of acetaminophen has some debate, as the evidence does not support or disprove the use of paracetamol for cancer pain management [46].

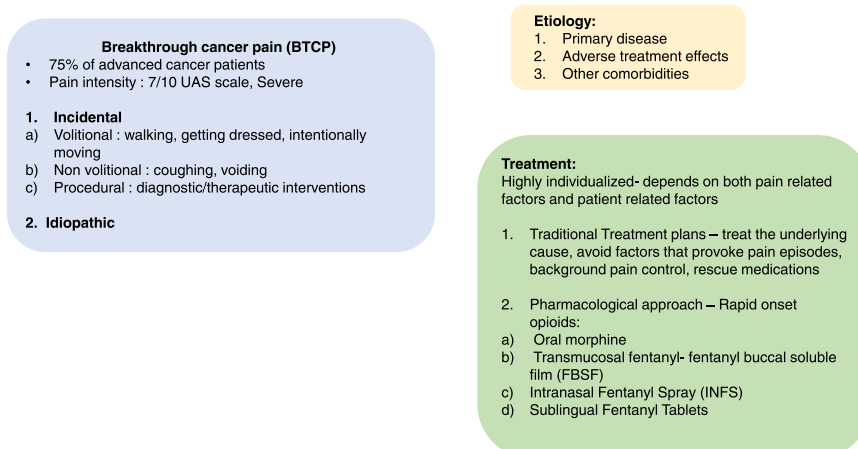


Fig. 3. Breakthrough Cancer Pain and Treatment.

Table 1

Side Effects Associated with Established and Novel Pharmacological Cancer Pain Treatments.

Established Pharmacological Cancer Pain Treatments	Effects
Opioids	Sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression
NSAIDs	Indigestion, stomach ulcer, headaches, drowsiness, dizziness, gas, bloating, heartburn, nausea, vomiting
Acetaminophen	Nausea, stomach pain, loss of appetite, itching rash, headache, dark urine, clay-colored stools
Antidepressants	Headache, nausea, dry mouth, insomnia, dizziness, diarrhea or constipation, sexual problems, fatigue
Anticonvulsants	Dizziness, drowsiness, fatigue, nausea, tremor, rash, weight gain
N-methyl-D-aspartate (NMDA) Antagonists	Hallucinations, lightheadedness, dizziness, fatigue, headache, out-of-body sensation, nightmares, sensory changes
Alpha-2 agonists	Depression, bradycardia, orthostatic hypotension, constipation, nausea, gastric upset, dry mouth
Novel Pharmacological Cancer Pain Treatments	Effects
Tapentadol	Headache, heartburn, stomach pain, dry mouth, excessive tiredness, anxiety, drowsiness, difficulty falling or staying asleep
Celecoxib/Parecoxib	Stomach pain, heartburn, gas, diarrhea, constipation, nausea, vomiting, swelling in your hands or feet, dizziness; or, cold symptoms such as stuffy nose, sneezing, sore throat
Duloxetine	Difficulty sleeping, headaches, dizziness, blurred vision, constipation, diarrhea, nausea, dry mouth
Cannabis	Headaches, dry mouth, dry eyes, lightheadedness, dizziness, drowsiness, fatigue
Tetrodotoxin (TTX)	Headache, diaphoresis, body numbness, dysarthria, dysphagia, nausea, vomiting, abdominal pain, Generalized malaise, weakness, and lack of coordination and, in more severe cases, hypotension, Cardiac arrhythmias, muscle paralysis, and cranial nerve dysfunction may develop
Botulinum Toxin Type A (BTX)	Muscle weakness, vision problems, trouble speaking or swallowing, breathing problems, loss of bladder control
TRPM8 Activator Menthol	Menthol, through activation of TRPM8, may have effects similar to tissue cooling that reduces pain in some injury states. Side effects of Menthol Topical may include: Hypersensitivity reactions. Stinging/burning/tingling sensation of skin.
Growth Factors Inhibitors	The most common skin manifestations are papulopustular lesions in the seborrheic areas (upper torso, face, neck, and scalp). Other cutaneous side effects include xerosis and hair and nail changes
Lemairamin (agonist of $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChRs))	Tachycardia, increased arterial pressure and reduction of gastrointestinal motility
Denosumab (Prolia)	Back pain, blistering, crusting, irritation, itching, or reddening of the skin, cracked, dry, or scaly skin, muscle or bone pain, pain in the arms or legs, skin rash, encrusted, scaly, and oozing, Swelling
Tanezumab	Arthralgia, headache, hyperesthesia, and myalgia
Protease-activated receptor 2 (PAR2) antagonist	Mediates some of the inflammatory and pain responses associated with immune-

Table 1 (continued)

mediated inflammatory diseases (PAR2 activation results in the release of inflammatory cytokine and chemokine from keratinocytes, endothelial, and epithelial cell).
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7.2.3. Antidepressants

Antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCAs) can be used for neuropathic pain [38,47]. However, studies question the efficacy of anti-depressant efficacy over opioid monotherapy [47]. Studies assessing SNRI and TCAs for cancer neuropathic pain are extrapolated from non-cancer data [47]. It is thought that norepinephrine reuptake is necessary for the treatment of neuropathic pain, as such selective serotonin reuptake inhibitors (SSRI) have worse results on treating neuropathic pain when compared to SNRI [48]. The use of TCAs in the critically ill or the elderly might be limited due to a similar side-effect profile of that of opioid toxicity (i.e., drowsiness, constipation, urinary retention, and other adverse effects) [48,49]. Patients tolerate secondary amines (desipramine and nortriptyline) better than tertiary amines, especially elderly patients [48,50]. Trazadone has also shown some efficacy in cancer neuropathic pain management [48,51].

7.2.4. Anticonvulsants

Anticonvulsant medication may be beneficial for patients with neuropathic pain, whereas NSAIDs are better at treating nociceptive pain [38]. Gabapentin and pregabalin are two anticonvulsants that have shown reduced opioid dosage requirements and decreased opioid side-effects [38,48,52]. As increased dosages cause drowsiness, a slow titration, especially in elderly patients, is recommended. It is recommended that doses be increased by 50%–100% every three days if required [38,49,53]. A randomized trial of 605 patients compared the utilization of opioid monotherapies to that of a combined gabapentinoid and opioid therapies, finding no significant difference between the two. However, due to the heterogeneity of patients, benefits for those with definite neuropathic cancer pain cannot be excluded [47].

7.2.5. N-methyl-D-aspartate (NMDA) Antagonists

Ketamine, an NMDA antagonist that binds all opioid receptors, is another pharmacological agent that might be useful for neuropathic pain for end-of-life cancer patients [38]. Side-effects for ketamine therapy include somnolence, hallucinations, depersonalization, and nausea but occur in reduced incidence when given in a low dose for analgesia [38,54]. A retrospective study supported the effectiveness of ketamine for treatment for neoplastic pain that does not respond to opioid treatment but stressed that patients be monitored for developing side effects. However, some studies testing this therapy had too few patients to be conclusive, and one study did not find a clear benefit for ketamine utilization [54]. Amantadine, another NMDA antagonist, has also shown some reduction in cancer neuropathic pain [48].

7.2.6. Alpha-2 agonists

Alpha-2 adrenergic agonists, such as Clonidine, have an established role in acute pain management, and studies are showing the efficacy of its use in chronic pain conditions [55]. One study examined the efficacy of intrathecal clonidine in 31 patients. Of these, 13 patients (42%) had long-term success with this therapy [56]. Patients are usually given alpha-2 adrenergic agonists intraspinal to avoid systemic side effects [48]. Dexmedetomidine is another alpha-2 agonist similar to Clonidine, but it is 8 times more specific for alpha-2 receptors. [57].

8. Novel pharmacological cancer pain treatments

8.1. Tapentadol

Tapentadol is a centrally acting analgesic with two synergistic modes of action, as it binds to the μ -opioid receptor (MOR) and inhibits noradrenaline reuptake (NRI). Therefore, tapentadol is considered the first member of a new pharmacological class, MOR-NRI [58].

According to the evidence available, tapentadol extended release was well tolerated and effective in cancer patients with chronic pain. In randomized, double-blind, active-controlled trials, it was demonstrated to be non-inferior to typical opioids such as morphine or oxycodone in the treatment of moderate-to-severe cancer pain in both opioid-naïve and opioid-pretreated patients. The good analgesic efficacy may be partially attributable to tapentadol's effect on neuropathy-related pain components. In conjunction with the low incidence of gastrointestinal side effects and the overall acceptable safety profile, tapentadol can be regarded a suitable option for cancer pain patients who commonly experience nausea, vomiting, constipation, and other occurrences that further diminish their quality of life [58].

In a prospective observational study, 88% ($n = 80$) of the participants were classified as responders and maintained a numerical rating scale (NRS) score of 3 or less, with significant improvements in pain intensity and neuropathic pain [59]. A 2020 retrospective single-center investigation of moderate-to-severe cancer pain ($n = 84$) indicated clinically significant pain alleviation (a 50% reduction in NRS) in opioid-tolerant and opioid-naïve patients (94.5% and 89.7%, respectively) within a median of 3 days [58].

A recent network meta-analysis of tapentadol in cancer and non-cancer pain found 29 RCTs and 19 withdrawal trials. RCT results showed that tapentadol caused less nausea and constipation than other strong opioids, but withdrawal trial evidence was limited and conflicting [60]. A confidence assessment of an earlier network meta-analysis [20] found that tapentadol is associated with a lower incidence of constipation than oxycodone, but not with other strong opioids [61].

According to a retrospective study evaluating the safety and factors affecting the discontinuation of tapentadol, of the 685 patients who did so, 17.4% did so because of side effects (most commonly nausea and drowsiness). Those who switched to another strong opioid after experiencing negative side effects were more likely to stop taking it, as were those who were not given the peripherally acting MOR antagonist naldemedine and those who received tapentadol from a palliative medicine specialist [62].

Mazzola et al. evaluated the efficacy and safety profile of tapentadol PR in a cohort study of 30 opioid-naïve head and neck cancer patients with background pain due to painful mucositis during intensity-modulated radiation therapy with or without cisplatin for either definitive or adjuvant purposes. At the onset of pain, 50 mg of Tapentadol PR twice daily was administered; this dose may well be increased based on clinical need. The observation period was 90 days from the onset of antineoplastic therapy; 25% of patients were administered tapentadol PR 22 days after the initiation of antineoplastic therapy. After 39 days, this percentage grew to 50%, and after 43 days, it reached 75%. In 26 patients (86.7%), pain intensity was reduced by 30%, and in 23 patients (76.7%), it was reduced by 50% [63].

Galiè et al. performed a prospective, open-label study to investigate the efficacy and safety of tapentadol PR in patients with CIPN after taxane-and/or platinum-based chemotherapy regimens. After three months of treatment with tapentadol, 19 (86%) of 22 patients had a response (NRS reduction 3 vs. baseline). Tapentadol decreased NRS and DN4 readings from baseline to the most recent visit, and their health status improved as determined by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC-QLQ-C30) [64].

8.2. Celecoxib/parecoxib

Celecoxib, a selective COX-2 inhibitor, is used to treat cancer pain and has less gastrointestinal side effects than nonselective NSAIDs [65]. Celecoxib has been studied as a cancer adjuvant, however there is insufficient data to recommend it consistently [66].

The short-term usage of parecoxib, a parenteral COX-2 inhibitor and prodrug of valdecoxib, has been tested for the treatment of cancer pain. It might be less likely to cause stomach problems than the preferred COX-1 inhibitor ketorolac. A 3-day burst of daily subcutaneous injections of parecoxib was administered to 19 patients with malignant bone pain who were already taking opioids in an open label pilot study, and the results showed a significant decrease in the median pain score across all patients at 24 h with no serious side effects [67].

A retrospective chart review of 80 patients in a specialized palliative care unit who received continuous subcutaneous infusions of parecoxib for at least seven days for cancer pain reported a significant decline in pain scores on the NRS and the need for opioid rescue doses. This treatment was generally well tolerated, which suggests that it could be a good choice for people with cancer pain. Local site reactions, a drop in renal function, and dyspepsia were some reported side effects. There was also one case of gastrointestinal perforation and hematemesis [68].

8.2.1. Duloxetine

Duloxetine is a serotonin and norepinephrine reuptake inhibitor authorized for multiple indications, including severe diabetic neuropathy, and plays a role in the management of neuropathic pain due in part to its suppression of P2X receptors that are activated on microglia [69]. In a 2014 Cochrane analysis of over 600 patients, duloxetine was found to be beneficial for central and peripheral neuropathic pain, fibromyalgia, and depression-related pain, but not for cancer pain [70]. It is recommended as a first-line treatment for all neuropathic pain excluding trigeminal neuralgia by NICE [71].

In a multicenter, randomized, double-blind, placebo-controlled trial, duloxetine added to a combination of opioid and pregabalin was effective to treat cancer-related neuropathic pain, with a significantly higher proportion of patients using duloxetine experiencing pain relief by day 10 [72]. In an open, prospective RCT, either pregabalin or duloxetine was administered to patients with lung cancer and with neuropathic pain. Both medications significantly decreased pain scores within three months, however duloxetine was more effective than pregabalin [73]. Finally, A retrospective chart review of 43 patients with cancer-related mixed pain indicated that the combination of methadone and duloxetine reduced the total Edmonton Symptom Assessment System (ESAS) score. ESAS is a patient-reported outcome measure used for screening and reassessment of nine prevalent cancer-related symptoms using an NRS. In the combo group, the total ESAS score decreased by 5.6 points. In addition, it significantly decreased pain subscores on the ESAS by 0.9 and emotional symptom burden by 1.8 when compared to either drug alone [74].

8.2.2. Cannabis

Cannabinoids are gaining popularity as a treatment for chronic cancer and noncancer pain, with some evidence suggesting that they can help reduce hyperalgesia and allodynia in inflammatory and neuropathic pain. Cannabis sativa has been found to have more than 100 compounds, but most of the attention has been on 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [75,76]. Cannabinoids induce analgesia by activating CB1 receptors found in the CNS and nerve terminals. Additionally, peripheral CB2 receptors assist analgesia by inhibiting the generation of pain and inflammatory mediators, which is essential for cancer pain management [77].

The American Society of Clinical Oncology clinical practice guidelines for chronic pain in adult cancer survivors recommended medical cannabis after balancing risks and benefits [78].

Cannabinoids can effectively modulate tumor growth, both in vitro

and in vivo cancer models, however, the anticancer effects seem to be dependent on the type of cancer and drug dose. Understanding how cannabinoids can modulate essential cellular processes involved in tumorigenesis (progression through the cell cycle, cell proliferation and cell death) and the interactions between cannabinoids and the immune system are crucial for improving existing medications and developing new therapeutic approaches [79].

Cannabinoids are particularly successful at suppressing the pain symptoms of chemotherapy-induced and other peripheral neuropathies, but their broad usage is constrained by central nervous system (CNS)-mediated adverse effects. In a rat model of cisplatin-induced peripheral neuropathy, one molecule from a class of recently produced synthetic peripherally restricted cannabinoids (PRCBs) was evaluated. Results indicate that local or systemic delivery of 4-2-[(1E)-1[(4-propylnaphthalen-1-yl)methylidene] - 1 H-inden-3-yl]ethylmorpholine (PrNMI) inhibited CIPN mechanical and cold allodynia in a dose-dependent manner. Orally administered PrNMI decreased CIPN allodynia symptoms dose-dependently in both male and female rats without CNS adverse effects [80].

8.2.3. Tetrodotoxin (TTX)

Tetrodotoxin (TTX) is a powerful neurotoxin that is mostly present in pufferfish. It inhibits sodium channels that play a crucial role in pain signaling. One article evaluated the role of TTX in bone cancer pain. Using an in vivo behavioral test, the researchers discovered that blocking dorsal root ganglion (DRG) neuron activity with intrathecal injections of TTX (10 g/kg, once a day) reduced tumor-induced thermal hyperalgesia and mechanical allodynia in rats with bone cancer [81]. Multiple clinical trials, including phase II and phase III trials, have evaluated TTX. In terms of the safety and efficacy of TTX in reducing cancer-related pain, the outcomes of these studies have been positive [82]. A Phase IIa open-label research indicated that the 30 g b.i.d. dose of TTX administered intramuscularly for 4 days to cancer patients whose pain was not alleviated by usual therapy appeared to be safe and effective [83]. Subsequently, the role of TTX in cancer-related pain was evaluated in a larger Phase II randomized, multicenter, double-blind, placebo-controlled trial, which revealed a statistically insignificant trend toward a greater number of 234 responders in the active treatment arm based on pain intensity difference. A recent multicenter, randomized, double-blind, placebo-controlled, parallel-design trial on TTX (30 g) administered subcutaneously twice daily for four days indicated a favorable benefit-risk profile and clinically significant analgesic effect (Number Needed to Treat of approximately 4–6) in the treatment of uncontrolled moderate to severe cancer-related pain [84]. However, this trial was underpowered, and additional research is required to reproduce and confirm the results.

8.2.4. Botulinum Toxin Type A (BTX)

BoNT-A is a strong neurotoxin generated by *Clostridium botulinum* that prevents the release of acetylcholine at presynaptic levels in muscle tissue, hence blocking the action potential in the neuromuscular junction [85]. The potential of BoNT-A as an analgesic medication for both nociceptive and neuropathic cancer pain has been investigated in numerous animal models and human subjects during the past few years. BoNT-A reduces the release of pain mediators from nerve endings and dorsal root ganglion, disrupting the nociceptive transmission directly through the anterolateral and trigeminothalamic systems, however its mechanism is not well known [86].

8.2.5. TRPM8 activator menthol

The activation of receptors for cooling in models of neuropathic pain suggested a unique intervention target for cooling-induced analgesia [87]. Evidence from preclinical studies indicates that activation of the transient receptor potential melastatin 8 (TRPM8) ion channel by topical medications produces significant analgesia [88, p. 8], [89].

Furthermore, clinical evidence suggests that the TRPM8 activator, topical menthol, offers potential as a new analgesic therapy for localized cancer-related neuropathic pain, enhancing patient-reported outcomes [90].

8.2.6. Growth factors inhibitors

Recent clinical and preclinical research has linked the epidermal growth factor receptor signaling pathway to chronic pain conditions. EGFR belongs to the ErbB family of receptor tyrosine kinases (one of four) that play crucial roles in the progression and development of numerous malignancies. Following the binding of different ligands to the EGFR, the receptor activates numerous intracellular signaling pathways. Several of these signaling pathways, including phosphatidylinositol 3-kinase, are recognized pain mediators. Recent data from pilot clinical and preclinical studies suggests that EGFR inhibitors may have clinical utility for the treatment of chronic pain. EGFR inhibitors are well-known for their usage as cancer treatments [91].

8.2.7. Lemairamin

Lemairamin (wgx-50) is extracted from the plant pericarps of *Zanthoxylum*. It can reduce neuroinflammation in Alzheimer's disease as an agonist of 7 nicotinic acetylcholine receptors (7nAChRs) [92,93]. A recent study examined its antinociceptive effects on pain hypersensitivity and investigated the underlying mechanisms, revealing that lemairamin might generate antinociception in pain hypersensitivity via the spinal IL-10/-endorphin pathway after 7nAChR activation [92].

8.2.8. Denosumab (Prolia)

Denosumab is a type of targeted therapy called a monoclonal antibody. This is the first drug approved to treat bone pain caused by metastatic cancer, and of bisphosphonates like alendronate (Fosamax), and is regarded as a first-line therapy for cancer-induced bone pain [94]. According to the recommendations of the European Society for Medical Oncology (ESMO), cancer patients with non-metastatic illness and osteoporosis may be treated with bone-modifying drugs (BMAs) to lower the risk of fractures. Denosumab provides various benefits over other bone-modifying drugs, including subcutaneous self-administration by the patient, no need for hospitalization, no dosage adjustments in renal impairment, and a low incidence of acute phase anaphylaxis. Furthermore, lifestyle therapies such as exercise, optimal dietary vitamin D and calcium consumption, and additional medication interventions are advised.

8.2.9. Tanezumab

Tanezumab is another potential new treatment for bone pain due to metastatic cancer. Tanezumab is an antibody, which blocks the activity of a pain-signaling molecule called nerve growth factor (NGF). A 2022 randomized, placebo-controlled, phase 2 study evaluated the safety and efficacy of tanezumab for treatment of schwannomatosis-related pain. Schwannomatosis, a rare tumor suppressor syndrome, predisposes people to the development of numerous schwannomas and meningiomas. The most common symptom is chronic, severe pain. This study's main purpose is to evaluate the analgesic effectiveness of subcutaneous tanezumab 10 mg in patients with SWN who continue pre-existing pain medication, and is currently being investigated [95]. Another 2022 study investigated the impact of tanezumab on health status, non-work activities and work productivity in adults with moderate-to-severe osteoarthritis. Subcutaneous tanezumab (2.5 mg and 5 mg) was tested in double-blind, placebo-controlled clinical trials. In comparison to placebo, treatment of tanezumab dramatically enhanced health status, non-work activities, and work productivity [96].

8.2.10. Protease-activated receptor 2 (PAR2) antagonists

PAR2 antagonists are being studied to treat oral cancer pain [97]. Proteases are enzymes that degrade proteins and contribute to the spread of cancer by damaging surrounding tissues. Proteases can also

bind to and activate the PAR2 receptor molecule on neurons. When proteases activate PAR2 on neurons, PAR2 can increase the sensitivity of other pain receptors on neurons [98]. Cancer-induced chemosensitivity is poorly understood. TRPV1 is increased on sensory neurons that innervate oral malignancies, according to numerous cancer pain models spanning many species. Furthermore, TRPV1 modulates pain from oral cancer [97]. TRPV1 might be activated by agonists in the tumor microenvironment, such as an increased proton concentration. In one of the most promising experiments to date, intrathecal resiniferatoxin ablation of TRPV1 fibers cured cancer pain and restored function in a canine bone cancer model [99]. Understanding the mechanism and second messengers that underlie TRPV1 sensitization in response to PAR2 activation may reveal a technique for pharmacological antagonism and therapy of oral cancer pain.

9. Interventional treatments

Neuraxial analgesia involves the epidural or intrathecal (spinal) administration of local anesthetics, opioids, or coanalgesics. A combination of morphine and additional analgesics, such as bupivacaine or clonidine, administered intrathecally may provide superior pain relief. Clonidine, an alpha2-adrenergic agonist, has been authorized for the treatment of neuropathic cancer pain. In non-cancer and cancer pain sufferers, intrathecal ziconotide, a neuron-specific calcium channel blocker, is also an authorized analgesic that has been demonstrated to reduce pain intensity in RCTs. Nonetheless, these procedures require specialized equipment and a pain specialist, and despite being generally safe, they can have significant adverse effects. Poor documentation exists regarding the role of nerve blocks and neurolytic procedures in NCP [58].

10. Conclusion

Cancer-related discomfort affects the majority of all diagnosed individuals. Some people are even impacted chronically beyond therapy completion. Effective pain management is essential for preserving the quality of life of cancer patients and requires an accurate diagnosis.

The management of cancer pain is very challenging due to the vast variation in patient reactions to various therapies and drugs. Research indicates that heredity might impact opioid sensitivity; hence, dosages of a given opioid can vary significantly across people. Consequently, it is vital to individualize treatment, taking into consideration the diverse pharmacology of mu opioids and the varying medication susceptibility of individuals. A accurate classification of pain identifies its origin and mechanism, so directing treatment choices. Identifying modulators of pain expression, such as psychological distress, alcoholism, drug misuse, and delirium, enables physicians to tailor therapeutic recommendations more accurately.

Breakthrough cancer pain (BTCP) is a subtype of cancer pain characterized as a brief aggravation of pain in patients with stable baseline background pain. Formally, BTCP is defined by a quick start (within minutes), high intensity, pain increase that lasts for more than 30 min. Given the heterogeneity of BTCP, it has proven to be a difficult pain condition to treat. Understanding both pain-related and patient-related aspects is crucial to the treatment, which is highly customized. The characteristic of pharmacological treatment for BTCP is the use of opioids with quick onset as rescue medicines (ROO).

Neuropathic pain in oncology patients may be caused by either the nerve damage caused by the cancer's mass effect or by therapies like chemotherapy, radiation therapy, and surgery. Inhibitors of histone deacetylase (HDAC) are being studied in clinical studies for their potential to enhance the effectiveness of chemotherapy. Studies on animals indicate that certain HDAC inhibitors may prevent and reverse CIPN.

Opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antidepressants, anticonvulsants, NMDA antagonists, and alpha 2 agonists are established pharmacological cancer pain therapies.

Tapentadol, Celecoxib/Parecoxib, Duloxetine, cannabis, Tetrodotoxin (TTX), Botulinum Toxin Type A (BTX), TRPM8 Activator Menthol, Growth Factors Inhibitors, Lemairamin, Denosumab (Prolia), Tanezumab, Protease-activated receptor 2 (PAR2) antagonists, and Interventional Therapies, such as Nonopioid drugs are often the initial therapeutic option offered for individuals with new or modest pain, and in certain instances they have shown to be effective. However, opioids are the cornerstone of effective pharmacologic therapy of cancer pain, particularly in more severe patients. However, not all patients react well to opioids, necessitating other therapy alternatives. There are several interesting new alternatives for treating cancer pain, but greater investigation of the potential of non-opioid therapies is required. Overall, effective pain management is essential for cancer patients and is most successful when preceded by an accurate evaluation and organized, evidence-based pharmaceutical regimen.

CRediT authorship contribution statement

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Data Availability

No data was used for the research described in the article.

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