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Multidisciplinary Pain Management in Oncology: Balancing Opioid Use and Alternative Therapies

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Abstract:

Introduction and purpose:

Pain management in cancer patients remains a critical aspect of oncology care, significantly impacting quality of life and treatment outcomes. Despite advancements in cancer therapy, pain continues to be a prevalent and debilitating symptom, affecting up to 80% of patients with advanced cancer. This article aims to synthesize the latest evidence on the role of opioids in cancer pain management, focusing on their efficacy, safety, and factors influencing their use. It also explores the potential of multidisciplinary interventions and the contributions of nursing care in optimizing pain management.

Materials and methods:

A literature review was conducted, encompassing clinical trials, meta-analyses, and guidelines on cancer pain management. The review analyzed the mechanisms of cancer pain, opioid classification, pharmacokinetics and pharmacodynamics, as well as alternative pain management strategies, including non-opioid therapies and non-pharmacological interventions.

Results:

Opioids remain the cornerstone of cancer pain management, particularly for moderate to severe pain. However, their use is associated with risks such as constipation, nausea, respiratory depression, and potential immunosuppressive effects. Alternative therapies, including adjuvants and non-pharmacological interventions, play a crucial role in managing pain, especially in patients with neuropathic pain. Multidisciplinary team approaches have shown promise in improving pain control and patient QOL.

Conclusion:

Effective cancer pain management requires an individualized approach, integrating both pharmacological and non-pharmacological strategies. Further research is needed to optimize opioid use, develop novel therapies, and integrate digital technologies into pain management. Multidisciplinary collaboration and a holistic approach to patient care are essential for improving treatment outcomes.

Keywords:

Cancer pain, opioids, adjuvant therapies, multidisciplinary teams, non-pharmacological pain management, quality of life, opioid pharmacokinetics, neuropathic pain, digital health technologies in pain management

Introduction

Pain management in cancer patients remains a critical aspect of oncology care, significantly impacting patients' quality of life (QOL) and overall treatment outcomes. Despite advancements in cancer therapy, pain continues to be a prevalent and debilitating symptom, affecting up to 80% of patients with advanced cancer, with more than one-third reporting moderate to severe pain and up to 10% experiencing chronic severe pain [6].

The complexity of cancer pain arises from various factors, including direct tissue injury, metastatic disease, inflammatory processes, and treatment-related adverse effects such as post-surgical pain and chemotherapy-induced peripheral neuropathy [3, 6]. Effective pain management is essential not only for alleviating suffering but also for improving functional status and psychological well-being.

Pain in cancer patients is multifaceted, often described as "total pain," encompassing physical, psychological, spiritual, and social dimensions [4]. This complexity necessitates a comprehensive approach to pain assessment and management. Standardized tools such as the 0–10 numeric rating scale, visual analog scale, and the Edmonton Symptom Assessment Scale (ESAS) are commonly used to evaluate pain severity and its associated symptoms, such as depression, anxiety, and drowsiness [4]. Recent advancements in digital health, including mobile applications, have shown promise in facilitating regular pain assessments, patient education, and timely medication adjustments. However, barriers such as socioeconomic status, data protection concerns, and the need for evidence-based validation limit their widespread adoption [4].

Opioids are the cornerstone of cancer pain management, particularly for moderate to severe pain, as recommended by the World Health Organization (WHO) analgesic ladder [1]. However, the efficacy and safety of opioids vary widely due to differences in pharmacodynamics, pharmacokinetics, and individual patient factors such as pharmacogenetics and organ function [1]. While morphine is often considered the first-line opioid, other options like methadone, fentanyl, and tapentadol offer unique pharmacological profiles that may be better suited for certain patients [1]. Despite the availability of various opioids, there is no consensus on which opioid is most effective, and undertreatment remains a significant issue, often due to systemic barriers and suboptimal dosing [2].

Emerging evidence suggests that opioids may have immunosuppressive effects, potentially influencing tumor growth and reducing the efficacy of immunotherapy, particularly immune checkpoint inhibitors (ICIs) [5]. Experimental studies indicate that opioids, via the hypothalamic-pituitary-adrenal axis, may increase tumor growth, risk of infection, and potentially shorten survival [5]. However, robust clinical data are lacking, and the current evidence is primarily based on animal models. Until more definitive clinical studies are conducted, the use of opioids remains essential for managing cancer pain, particularly in patients undergoing immunotherapy, where withholding opioids could expose patients to unbearable pain and psychological distress [5]. To mitigate potential risks, it is recommended to use the lowest effective opioid dose, combined with non-opioid analgesics and adjuvant therapies, to minimize opioid-related adverse effects [5].

The WHO analgesic ladder, introduced in 1985, has been a foundational framework for cancer pain management, advocating a stepwise approach starting with non-opioid medications and progressing to weak and then strong opioids [6]. However, the opioid crisis and the phenomenon of opioid unresponsiveness in some patients have necessitated a re-evaluation of this approach. Vargas-Schaffer proposed a modified version of the analgesic ladder, incorporating a fourth step that includes invasive techniques such as interventional pain management procedures [6].

Advances in imaging technology, including CT scans and real-time three-dimensional visualization, have enhanced the precision and safety of these interventional techniques, allowing for better targeting of pain sources, even in patients with complex anatomies due to prior surgeries or tumor distortions [6].

Breakthrough pain, characterized by transient exacerbations of pain despite controlled background pain, affects approximately 50% of cancer patients and is associated with significant anxiety, depression, and reduced QOL [4]. Effective management of breakthrough pain involves the use of both scheduled long-acting opioids for background pain and short-acting immediate-release opioids for breakthrough episodes. The recommended dosage for breakthrough opioids typically ranges from 5–20% of the total daily opioid dose, adjusted based on patient age and specific needs [4]. However, the optimal ratio of scheduled to breakthrough opioids and their use in clinical practice, particularly in inpatient settings, remains unclear and warrants further investigation [4].

Multidisciplinary team (MDT) interventions have emerged as a promising approach to improving cancer pain management. MDTs, which include nurses, physicians, pharmacists, and other specialists, provide comprehensive and coordinated care, leading to better symptom control and enhanced QOL [2]. Nurses, in particular, play a pivotal role in MDTs, offering holistic care and facilitating dynamic, patient-centered pain management strategies [2]. However, challenges remain, as a significant proportion of patients do not respond adequately to initial MDT interventions, and pain often escalates over time [2].

The concept of "total pain," introduced by Cecily Saunders, underscores the importance of addressing not only physical pain but also psychological, social, spiritual, and financial distress in cancer patients [5]. A holistic approach to pain management that incorporates these dimensions can reduce the reliance on high-dose opioids and improve overall patient outcomes. Proper evaluation of total pain, including the use of validated instruments to assess psychological distress, social isolation, and spiritual pain, is crucial for developing individualized pain management plans [5].

This review paper aims to synthesize the latest evidence on the role of opioids in cancer pain management, focusing on their efficacy, safety, and the factors influencing their use. We will also explore the potential of MDT interventions and the contributions of nursing care in optimizing pain management. By addressing gaps in current research and highlighting future directions, this review seeks to contribute to the ongoing efforts to improve cancer pain management globally.

Mechanisms of cancer pain

Cancer pain is a complex phenomenon resulting from various pathophysiological mechanisms, including nociceptive, neuropathic, and nociplastic (central sensitization) processes [8]. In most cases, cancer pain presents as a mixed-pain syndrome, rarely occurring as purely nociceptive or neuropathic [8]. Up to 80% of patients with advanced cancer experience pain, with more than one-third reporting moderate to severe pain and up to 10% suffering from chronic severe pain [6].

Nociceptive pain arises from direct tissue damage caused by tumor growth or metastasis. It can result from the compression of internal organs (visceral pain), bones (bone pain), or soft tissues (somatic pain) [8]. Inflammatory processes associated with tumor growth lead to the release of mediators such as prostaglandins, cytokines, and substance P, which activate pain receptors (nociceptors) in the peripheral nervous system [7]. In the case of bone pain, osteolysis and the stimulation of pain receptors by growth factors and cytokines play a key role [7].

Neuropathic pain results from damage or dysfunction of the nervous system caused by direct tumor invasion of nerves, compression of neural structures, or the toxic effects of chemotherapy and radiotherapy [8]. It is characterized by burning, tingling, or "electric shock" sensations and is challenging to treat due to complex pathophysiological mechanisms, including peripheral and central sensitization [8]. Neuropathic cancer pain (NCP) affects approximately 40% of patients with cancer pain and is associated with poorer treatment outcomes and reduced quality of life [8].

Central sensitization is a process in which neurons in the central nervous system become overly sensitive to normal or subthreshold stimuli, leading to chronic pain and phenomena such as allodynia (pain caused by stimuli that are not normally painful) and hyperalgesia (increased pain sensitivity) [7]. In cancer pain, central sensitization may result from continuous stimulation of nociceptors by inflammatory mediators released by the tumor or its microenvironment [7]. The underlying pathogenesis of cancer pain involves not only nociceptive mechanisms due to ongoing tissue damage but also atypical somatosensory processing in the peripheral or central nervous systems, contributing to neuropathic and sensitization processes [6].

At the molecular level, cancer pain is associated with the activation of signaling pathways such as protein kinase C (PKC) and nuclear factor kappa B (NF-κB), which regulate the expression of genes related to inflammation and pain [7]. Additionally, changes in the expression of opioid receptors and ion channels in sensory neurons can lead to resistance to analgesic treatments [7].

Impact of Anticancer Therapies

Chemotherapy and radiotherapy can cause pain as a side effect, for example, by inducing peripheral neuropathy or damaging soft tissues [8]. Postoperative pain is another significant issue, particularly in patients undergoing extensive surgical procedures [7]. Cancer pain can also be attributed to treatment-related complications, such as post-surgical pain and chemotherapy-induced peripheral neuropathy [6].

Opioids in cancer pain management

Classification of opioids

Opioids are classified based on their interaction with opioid receptors into three main categories: **agonists**, **partial agonists**, and **antagonists**.

- **Agonists** (e.g., morphine, fentanyl, oxycodone, hydromorphone) fully activate opioid receptors, providing strong analgesic effects.
- **Partial agonists** (e.g., buprenorphine) activate receptors but produce a limited response, even at high doses.
- **Antagonists** (e.g., naloxone) block opioid receptors and are used to reverse opioid effects in cases of overdose or respiratory depression [3, 8].

Opioids can also be categorized as **weak opioids** (e.g., codeine, tramadol) and **strong opioids** (e.g., morphine, fentanyl, oxycodone, methadone). Weak opioids are typically used for moderate pain, while strong opioids are reserved for moderate to severe cancer pain [8].

Pharmacokinetics and pharmacodynamics

Opioids vary significantly in their pharmacokinetic (absorption, distribution, metabolism, excretion) and pharmacodynamic (mechanism of action) properties, which influence their efficacy, safety, and suitability for different types of cancer pain.

- **Morphine**: A hydrophilic opioid with a slower onset but longer duration of action. It is metabolized in the liver to active metabolites (morphine-6-glucuronide) and inactive metabolites (morphine-3-glucuronide). Morphine is widely used for chronic cancer pain but may require dose adjustments in patients with renal impairment due to metabolite accumulation [3, 8].
- **Fentanyl**: A lipophilic opioid with rapid onset and short duration, making it ideal for breakthrough pain. It is available in transdermal patches for stable pain management, but titration requires careful monitoring due to its potency (100 times stronger than morphine) [8].
- **Methadone**: A synthetic opioid with a long half-life and dual mechanisms of action (mu-opioid receptor agonism and NMDA receptor antagonism). It is particularly effective for neuropathic pain but requires cautious dosing due to its unpredictable pharmacokinetics and risk of toxicity (e.g., QT prolongation, respiratory depression) [8, 9].
- **Tapentadol**: A newer opioid with dual mechanisms of action (mu-opioid receptor agonism and norepinephrine reuptake inhibition). It is effective for both nociceptive and neuropathic pain and has a lower risk of gastrointestinal side effects compared to traditional opioids [8].
- **Buprenorphine**: A partial agonist with a ceiling effect for respiratory depression, making it safer in some patients. It is available in transdermal patches and sublingual formulations, offering long-lasting pain relief with fewer side effects [9].

Dosing and titration

Opioid dosing requires careful titration to achieve effective pain relief while minimizing side effects. The **World Health Organization (WHO) analgesic ladder** recommends starting with low doses and gradually increasing based on patient response and pain severity [3, 8].

- **Breakthrough Pain**: Short-acting opioids (e.g., immediate-release morphine, fentanyl lozenges) are used at 5–20% of the total daily opioid dose. For example, a patient on 100 mg of oral morphine daily might receive 5–20 mg of immediate-release morphine for breakthrough pain [8].
- **Elderly Patients or Organ Dysfunction**: Lower doses and longer intervals between administrations are recommended to minimize toxicity. For instance, methadone dosing must be carefully individualized due to its long and variable half-life [8, 9].
- **Opioid Rotation**: In cases of inadequate pain relief or intolerable side effects, switching to an alternative opioid (e.g., from morphine to methadone) may be necessary. Equianalgesic dosing tables are used to ensure safe and effective transitions [8, 21].

Side effects of opioids

Opioids are associated with a range of side effects, which vary depending on the specific drug, dose, and patient factors. Common side effects include:

- **Constipation**: The most prevalent side effect, often requiring prophylactic laxative therapy (e.g., stimulant laxatives like senna or osmotic laxatives like polyethylene glycol) [3, 8, 20].
- **Nausea and Vomiting**: Typically transient but may require antiemetic treatment (e.g., metoclopramide, ondansetron) [8].
- **Sedation and Respiratory Depression**: Rare but potentially life-threatening, particularly in opioid-naïve patients or those with comorbidities. Risk is higher with lipophilic opioids like fentanyl [8].
- **Tolerance and Dependence**: Long-term opioid use can lead to tolerance (requiring higher doses for the same effect) and physical dependence. Careful monitoring and patient education are essential to minimize the risk of addiction [8].

Weak opioids in cancer pain management

Weak opioids, such as **codeine** and **tramadol**, are used for moderate cancer pain. Tramadol has additional monoaminergic properties (norepinephrine and serotonin reuptake inhibition), making it useful for neuropathic pain. However, weak opioids have a **therapeutic ceiling effect**, limiting their efficacy in severe pain. The **European Association for Palliative Care (EAPC)** recommends using low-dose strong opioids instead of weak opioids for moderate cancer pain, as they provide better pain relief with fewer side effects [8].

Strong opioids in cancer pain management

Strong opioids are the cornerstone of cancer pain management, particularly for moderate to severe pain.

- **Morphine**: The gold standard for cancer pain, available in immediate-release (IR) and controlled-release (CR) formulations. CR morphine is preferred for chronic pain, while IR morphine is used for breakthrough pain [3, 8].
- **Oxycodone**: A semi-synthetic opioid available in IR and CR formulations. It is equally effective as morphine but may cause fewer side effects like sedation and hallucinations [8].
- **Hydromorphone**: A potent opioid used as an alternative to morphine, particularly in patients with renal impairment. It is available in oral and parenteral formulations [8].
- **Fentanyl**: Available in transdermal patches, lozenges, and intravenous formulations. It is ideal for stable pain but requires careful titration due to its potency [8].
- **Methadone**: Effective for neuropathic pain due to its NMDA receptor antagonism. However, its long half-life and risk of QT prolongation necessitate cautious dosing and monitoring [8, 9, 21].
- **Tapentadol**: A newer opioid with dual mechanisms of action, offering effective pain relief with a lower risk of gastrointestinal side effects. It is increasingly used for neuropathic cancer pain (NCP) [8].

Special considerations

- **Buprenorphine**: A partial agonist with a lower risk of respiratory depression, making it safer for patients with respiratory comorbidities. It is available in transdermal patches, providing long-lasting pain relief [9].
- **Drug-Drug Interactions**: Opioids metabolized by CYP3A4 (e.g., fentanyl, methadone, buprenorphine) are at risk of interactions with CYP3A4 inhibitors (e.g., ketoconazole) or inducers (e.g., rifampin). For example, coadministration of fentanyl with CYP3A4 inducers can lead to reduced analgesia, while CYP3A4 inhibitors can increase opioid toxicity [9].
- **Opioid Rotation**: Switching from one opioid to another (e.g., from morphine to methadone) may be necessary in cases of inadequate pain relief or intolerable side effects. Equianalgesic dosing tables are used to ensure safe transitions [8, 21].

Opioid therapy in metastatic cancer: benefits, harms, and stakeholder perspectives

Opioids are a key component of pain management in metastatic cancer, but the evidence on their long-term benefits and harms is limited. The BEST Study (Benefits, Harms, and Stakeholder Perspectives) aims to address this gap by examining pain experiences, opioid side effects, and decision-making among patients, care partners, and clinicians [11]. Approximately 66% of advanced cancer patients receive long-term opioid therapy (≥90 consecutive days), compared to 40% with limited-stage disease. While opioids effectively reduce pain, patients with advanced cancer are at risk of opioid-related harms, including side effects (e.g., nausea, constipation) and the potential for misuse or addiction. Polypharmacy and high-dose opioid use further complicate this balance [11, 20].

The BEST Study uses a behavioral decision research (BDR) framework to explore how stakeholders make opioid-related decisions. By comparing expert guidelines ("normative model") with real-world decision-making ("lay model"), the study aims to inform future interventions and improve opioid prescribing practices in metastatic cancer [11]. Preliminary findings suggest that co-prescribed medications (e.g., benzodiazepines) and patient factors (e.g., history of substance use) influence opioid-related risks. The study's results are expected to guide personalized, patient-centered pain management strategies [11].

Emerging research on the epigenetic modulation of opioid and cannabinoid receptors offers new insights into pain management. Epigenetic changes, such as DNA methylation and histone modifications, can influence the expression of opioid receptors (e.g., MOR, DOR, KOR) and cannabinoid receptors (e.g., CB1, CB2), potentially affecting the efficacy of opioid- and cannabinoid-based therapies [13]. For example, studies have shown that histone deacetylase (HDAC) inhibitors can upregulate the expression of delta-opioid receptors (DOR) in the brainstem, enhancing their analgesic effects [13]. Similarly, DNA methyltransferase (DNMT) inhibitors have been found to increase the expression of mu-opioid receptors (MOR), potentially improving the response to opioid therapy in patients with chronic pain [13]. These findings suggest that targeting epigenetic mechanisms could enhance the efficacy of opioids and cannabinoids in cancer pain management, offering new avenues for personalized treatment strategies [13].

Alternatives to opioids in cancer pain management

While opioids are a cornerstone in the management of cancer pain, their use is often limited by side effects such as constipation, nausea, respiratory depression, and the risk of tolerance, dependence, and addiction. For this reason, non-opioid analgesics and adjuvant therapies play a crucial role in providing effective pain relief, particularly for patients with neuropathic cancer pain (NCP) or those who cannot tolerate opioids. These alternatives include pharmacological adjuvants, interventional procedures, and non-pharmacological therapies, often used in combination to target multiple pain pathways and enhance overall pain control [1, 8].

Non-pharmacological interventions, such as cognitive-behavioral therapy (CBT), mindfulness, acupuncture, and physical therapies, have gained attention for their potential to alleviate cancer pain without the adverse effects associated with pharmacological treatments. A recent systematic review and network meta-analysis (NMA) protocol aims to evaluate the efficacy of various non-pharmacological interventions for cancer pain management, providing a comprehensive comparison of their effectiveness [12]. This study will rank interventions based on their efficacy, offering evidence-based guidance for clinicians and patients. The findings are expected to highlight the potential of non-pharmacological methods, such as relaxation techniques, music therapy, and yoga, in improving pain management and overall quality of life in cancer patients [12].

Adjuvant pharmacological treatments are medications originally developed for other indications but found to have analgesic properties, particularly in neuropathic and mixed pain syndromes. Among these, anticonvulsants such as gabapentin and pregabalin are first-line options for NCP. These gabapentinoids modulate calcium channels in the central nervous system, reducing neuronal excitability and pain transmission. Pregabalin, in particular, has shown statistically significant reductions in cancer-related neuropathic pain compared to placebo in some studies, while gabapentin is often used for chemotherapy-induced peripheral neuropathy (CIPN), although the evidence for its efficacy remains limited [8]. For patients who do not respond to gabapentinoids, third-line options such as carbamazepine, oxcarbazepine, and sodium valproate may be considered, though their use is less common due to potential side effects and limited evidence in cancer pain [8].

Antidepressants are another important class of adjuvants, particularly for neuropathic pain. Tricyclic antidepressants (TCAs) like amitriptyline and nortriptyline inhibit the reuptake of serotonin and norepinephrine, enhancing descending pain inhibitory pathways. However, their use is often limited by anticholinergic side effects such as dry mouth, sedation, and cognitive impairment, especially in elderly patients [8]. Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, are better tolerated and have demonstrated efficacy in managing CIPN. Duloxetine, in particular, is recommended as a first-line treatment for neuropathic pain related to cancer treatment, offering a favorable balance between efficacy and tolerability [8].

Cannabinoids, including medical cannabis containing tetrahydrocannabinol (THC) and cannabidiol (CBD), have been explored as potential alternatives for cancer pain. However, the evidence for their efficacy remains inconclusive. A systematic review found no significant benefit of cannabinoids over placebo in reducing chronic cancer pain, highlighting the need for further research in this area [8].

Recent studies have shown that CBD, a non-psychoactive cannabinoid, may offer analgesic, anti-inflammatory, and neuroprotective effects, making it a promising option for managing cancer-related pain [13]. CBD interacts with the endocannabinoid system (ECS), which plays a crucial role in pain modulation, and its epigenetic regulation may enhance the efficacy of cannabinoid-based therapies [13].

Recent clinical trials have investigated the use of cannabinoids, particularly THC and CBD, in cancer pain management. For instance, a study by Johnson et al. demonstrated that a combination of THC and CBD extracts significantly reduced pain in patients with cancer-related pain who were unresponsive to opioid treatment [14][15]. Another study by Portenoy et al. found that lower doses of nabiximols (a THC:CBD extract) provided significant pain relief with fewer adverse effects compared to higher doses [14][15]. Despite these promising findings, the overall evidence remains mixed, with some studies showing no significant difference between cannabinoids and placebo in pain relief [14][15]. The side effects of cannabinoids, such as cognitive impairments, are generally mild compared to opioids, but the risk of addiction and other long-term effects warrants further investigation [14][15].

For patients with inadequate pain relief or intolerable side effects from systemic therapies, interventional procedures offer targeted pain management options. Spinal analgesia, including intrathecal or epidural administration of local anesthetics, opioids, or clonidine, can provide effective pain relief with fewer systemic side effects. Spinal cord stimulation is another option, though its efficacy in cancer pain is less established compared to non-malignant pain [8]. Radiotherapy is particularly effective for localized cancer-related bone pain, which often has neuropathic and inflammatory components. By reducing tumor size and inflammation, radiotherapy alleviates pain caused by nerve compression or bone destruction, providing significant relief for many patients [8]. Percutaneous ablation techniques, such as cryoablation, radiofrequency ablation, and microwave ablation, target tumor tissue or nerve structures involved in pain transmission. These minimally invasive procedures reduce tumor size and inflammation, offering significant pain relief and reducing opioid requirements [8].

Non-pharmacological therapies, such as transcutaneous electrical nerve stimulation (TENS) and acupuncture, can complement pharmacological treatments, particularly for patients with chronic or refractory pain. TENS is a non-invasive, low-cost therapy that uses electrical impulses to modulate pain signals. While evidence for its use in cancer pain is limited, it has shown efficacy in reducing acute and chronic pain in other contexts [8]. Acupuncture, which may activate descending pain control systems and modulate pain-related ion channels, has been explored for cancer pain, particularly chemotherapy-induced neuropathy. However, the evidence remains weak, with studies often limited by methodological shortcomings and heterogeneity [8].

A multimodal approach, combining pharmacological and non-pharmacological therapies, is often the most effective strategy for managing cancer pain. This approach targets multiple pain pathways, enhances analgesia, and minimizes side effects. For example, combining gabapentinoids with antidepressants or opioids can provide synergistic pain relief while reducing the required dose of each medication, thereby lowering the risk of side effects [1, 8]. Additionally, patient education plays a critical role in cancer pain management.

Educating patients about the risks of opioid overdose and the use of naloxone can improve safety and empower patients to manage their pain more effectively. Studies show that patients who receive education about naloxone are more likely to perceive it as beneficial and feel confident in its use during emergencies, highlighting the importance of comprehensive patient-centered care [10].

Future research directions

The management of cancer-related pain remains a complex and evolving field, necessitating ongoing research to optimize therapeutic strategies and improve patient outcomes. This chapter outlines key areas for future investigation, focusing on the comparative efficacy of opioids, the development of novel therapies, the optimization of multidisciplinary team (MDT) approaches, and the integration of digital technologies in pain management.

Despite the widespread use of opioids in cancer pain management, the evidence base for their comparative efficacy remains limited. Large-scale, randomized controlled trials (RCTs) are urgently needed to evaluate the effectiveness of different opioids, such as morphine, oxycodone, and fentanyl, in controlling cancer-related pain. These studies should assess not only short-term analgesic efficacy but also long-term outcomes, including the risk of tolerance, dependence, and potential effects on cancer progression [17, 18]. Additionally, research should explore the differential effects of full agonists versus partial agonists and their respective side effect profiles. Such data would inform evidence-based guidelines and help tailor opioid therapy to individual patient needs.

The adverse effects associated with opioid use, such as constipation, nausea, and respiratory depression, remain significant barriers to effective pain management. Future research should focus on the development of novel analgesics with improved safety profiles. Promising approaches include the use of liposomal formulations and advanced drug delivery systems, which allow for controlled release and targeted action, thereby minimizing systemic side effects [16, 20]. Furthermore, the exploration of adjuvants, such as NMDA receptor antagonists and serotonin-norepinephrine reuptake inhibitors, may enhance the efficacy of opioids while reducing required doses [16]. Another innovative avenue is the development of selective μ-opioid receptor agonists, which may provide potent analgesia with fewer off-target effects [19].

Multidisciplinary teams (MDTs) play a critical role in the comprehensive management of cancer pain, integrating expertise from oncology, anesthesiology, psychology, and physical therapy. However, further research is needed to evaluate the long-term impact of MDTs on patient outcomes, including pain control, quality of life, and healthcare utilization [16]. Studies should also investigate the most effective models of collaboration among healthcare professionals and the role of patient-centered care in optimizing pain management strategies. Additionally, the integration of palliative care specialists into MDTs may further enhance the holistic management of cancer pain.

The advent of digital health technologies, such as mobile applications, telemedicine platforms, and real-time pain monitoring systems, offers new opportunities for improving cancer pain management. However, the long-term efficacy and safety of these tools remain understudied. Future research should evaluate the impact of digital interventions on pain control, patient adherence to treatment, and overall quality of life [16].

Specific areas of interest include the use of wearable devices for continuous pain monitoring, the role of artificial intelligence in personalized pain management, and the ethical implications of data collection and privacy in digital health. Additionally, studies should explore the integration of digital tools into existing healthcare workflows to ensure seamless implementation and maximize patient benefits.

Breakthrough pain, characterized by sudden and severe episodes of pain, poses a significant challenge in cancer pain management. Oral transmucosal fentanyl citrate (OTFC) has emerged as a promising option for the rapid relief of breakthrough pain due to its unique pharmacokinetic properties. OTFC is a potent, short-acting opioid that is rapidly absorbed through the buccal mucosa, providing analgesia within minutes of administration [19]. Clinical studies have demonstrated its superiority over immediate-release morphine in terms of onset of action and patient satisfaction [19].

Future research should focus on optimizing dosing strategies, evaluating long-term safety, and exploring the role of OTFC in specific patient populations, such as those with opioid tolerance or complex pain syndromes. Additionally, the integration of OTFC into multimodal pain management protocols warrants further investigation.

Summary and conclusions

Cancer pain presents a significant clinical challenge due to its complex nature, involving nociceptive, neuropathic, and nociplastic mechanisms. Often manifesting as mixed-pain syndromes, it requires a nuanced approach to both diagnosis and treatment.

Although opioids remain central to managing moderate to severe cancer pain, their use is associated with considerable adverse effects, such as constipation, nausea, and respiratory depression. Additionally, emerging evidence suggests they may exert immunosuppressive effects, potentially influencing cancer progression and the efficacy of immunotherapy. Despite the availability of various opioids, undertreatment remains a persistent issue due to systemic barriers, suboptimal dosing strategies, and the lack of a universally accepted consensus on the most appropriate opioid selection for specific patient populations.

Breakthrough pain, affecting nearly half of cancer patients, continues to be challenging to manage due to inconsistencies in guidelines regarding the appropriate balance between scheduled and breakthrough opioid administration. Multidisciplinary team (MDT) approaches have shown promise in improving cancer pain management. However, significant obstacles remain in ensuring effective collaboration among healthcare professionals and addressing the holistic needs of patients, including psychological, social, and spiritual distress.

A personalized approach to cancer pain management is essential, taking into account the specific pain type, patient comorbidities, and pharmacogenetic factors. Optimizing opioid selection, titration, and rotation can enhance efficacy while minimizing adverse effects. A multimodal strategy that integrates pharmacological treatments, such as opioids and adjuvant medications like gabapentinoids and antidepressants, with non-pharmacological interventions, including cognitive-behavioral therapy, acupuncture, and transcutaneous electrical nerve stimulation (TENS), allows for a comprehensive approach that targets multiple pain pathways and reduces reliance on high-dose opioids.

For patients with refractory pain, interventional procedures like spinal analgesia, radiotherapy, and percutaneous ablation provide targeted relief while reducing systemic opioid requirements. Digital tools, such as mobile applications and wearable devices, can enhance real-time pain monitoring, improve patient education, and facilitate timely adjustments to treatment plans.

Continuous medical education is essential for healthcare professionals to bridge existing knowledge gaps in opioid pharmacology, multimodal pain management, and interventional pain techniques. Training programs should emphasize the importance of MDT collaboration and holistic care. Similarly, educating patients and caregivers on pain management strategies, opioid-related risks, and the appropriate use of naloxone can enhance treatment adherence and safety. Addressing the psychological and social dimensions of "total pain" is also crucial in optimizing overall well-being. Raising public awareness of the complexities of cancer pain and the significance of early intervention can help reduce stigma and improve access to effective pain management solutions.

In conclusion, effectively managing cancer pain requires an individualized and comprehensive approach that integrates pharmacological and non-pharmacological therapies, interventional techniques, and digital health solutions. Multidisciplinary collaboration and ongoing education for healthcare professionals, patients, and the public are fundamental to improving patient outcomes and enhancing quality of life.

Disclosure

Author's contribution

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