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Review

Opioids in Cancer Pain Management: A Double-Edged Sword of Relief and Risk

*Olutomiwa Ayoola Omokore[1], Ibrahim Olalekan Quadri[1], Perelade Jojo Kingdom[1], Ifeanyichukwu Chidubem Ogbuiyi-Chima[1], Somtochukwu Emmanuel Meribole [1], Temiloluwa Oluwatimilehin Olayinka[1], Samuel Ogunnoiki[1], Samuel-Ogunnoiki Precious[1], Adeyoola Olaitan MBBS[1], Nkechi Chima-Ogbuiyi[2], Ogeoma Chidinma Ifeanyichukwu[3], Richard Chigozirim Ikpegbu[1], Funmilayo Grace Adelakun[1], Peace Oluwaferanmi Aderinboye[3], Patrick Okpanachi[1], Omolola Oladeji[4], Hinda Baah[5], Promise Edochie[1], Dennis Tsegah[6].

[1]Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, NIgeria
[2]Department of Nursing, Herzing University, Wisconsin, USA
[3]Benjamin S. Carson Snr, School of Medicine, and Allied Health. Ilishan-Remo, Ogun State, Nigeria
[4]Afe Babalola University, Ado- Ekiti, Ekiti State, Nigeria
[5]University of Ghana, Accra, Ghana.
[6]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Abstract

Opioids are indispensable for managing cancer-related pain but carry risks such as immunosuppression, increased susceptibility to infections, and potential tumour progression. Balancing effective pain relief with these risks remains a critical challenge. This review examines the dual role of opioids in cancer pain management, highlighting their benefits, risks, and ethical implications while exploring strategies to mitigate adverse effects. Through a comprehensive literature review, we analysed mechanisms of opioid-induced immunosuppression, infection risks, tumour progression, and ethical prescribing practices. Additionally, strategies such as multimodal analgesia, opioid rotation, and personalised medicine were evaluated. Findings indicate that while opioids effectively alleviate cancer pain, they may suppress immune function, elevate infection risks, and potentially promote tumour progression. Mitigation strategies, including multimodal approaches, immunomodulatory interventions, and adherence to ethical principles (beneficence, non-maleficence, autonomy, and justice), are essential for safe opioid use. In conclusion, opioids remain vital for cancer pain management but require judicious application to minimise risks. Future research should prioritise non-opioid alternatives and immunomodulatory therapies to enhance patient outcomes.

Keywords: Opioids, Cancer Pain, Immunosuppression, Infection Susceptibility, Tumour Progression, Ethical Prescribing, Multimodal Analgesia, Personalised Medicine.

***Correspondence:** Olutomiwa Ayoola Omokore, Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, Nigeria. **Email:** omokoreolutomiwa@gmail.com

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Introduction

Over the past 30 years, oncology has transformed cancer from a terminal to a chronic condition, necessitating long-term management. While improved prognosis is beneficial, it brings physical, social, and psychological challenges, particularly chronic pain. [1] Opioids, guided by the WHO analgesic ladder, remain central to cancer pain management, with potent opioids like morphine used for severe pain. [2] However, long-term opioid use raises concerns about dependence, abuse, and side effects, highlighting the need for more research. [3] Alternative therapies, such as cannabinoids and neuromodulation, are being explored but are best used alongside opioids to reduce reliance.[1] A multidimensional approach is essential for effective chronic pain management. [1]

This paper aims to provide a comprehensive overview of the role of opioids in cancer pain management, focusing on their benefits, risks, and ethical implications. The study seeks to consolidate knowledge on opioid use by synthesising information from reputable sources and scientific literature, with the goal of enhancing understanding and awareness among healthcare professionals, patients, and policymakers.

Specifically, the study aims to: Examine the mechanisms of opioid action in pain relief, including their interaction with opioid receptors in the central and peripheral nervous systems; Explore the benefits of opioids in improving quality of life for cancer patients, particularly in managing moderate to severe pain; Investigate the risks associated with opioid use, including immunosuppression, increased susceptibility to infections, and potential tumour progression; Assess strategies to mitigate opioid-related risks, such as multimodal analgesia, opioid rotation, and personalised medicine approaches; Discuss ethical considerations in opioid prescribing, emphasising the principles of beneficence, non-maleficence, autonomy, and justice to guide clinical practice and Highlight emerging research and future directions, including non-opioid alternatives and immunomodulatory therapies, to improve cancer pain management outcomes.

By addressing these objectives, this study aims to contribute to the knowledge surrounding opioid use in cancer care, inform clinical practice, and promote safer, more effective pain management strategies for patients.

Methodology

This study systematically gathered and analysed information on the role of opioids in cancer pain management, focusing on their benefits, risks, and ethical implications. The methodology involved a comprehensive review of reputable sources, including scientific literature, peer-reviewed journals, and authoritative medical websites. The following steps were undertaken:

Literature Search

A thorough search was conducted using online databases, such as PubMed, Google Scholar, and Medline, to identify relevant articles, reviews, and studies related to opioid use in cancer pain management. Keywords used in the search included “opioids,” “cancer pain”, “immunosuppression”, “infection susceptibility”, “tumour progression”, “ethical prescribing”, and “multimodal analgesia”.

Inclusion and Exclusion Criteria

The search results were screened based on predefined inclusion and exclusion criteria. Only articles written in English and with full text availability were considered. Studies on human and animal subjects, clinical trials, and reviews providing comprehensive insights into opioid mechanisms, risks, benefits, and ethical considerations in cancer pain management were included. Articles in other languages or without full texts were excluded.

Data Extraction
Pertinent data and information were extracted from the selected articles. This included details on the mechanisms of opioid action, their impact on immune function, risks such as infection susceptibility and tumour progression, and strategies for mitigating these risks. Key findings, statistics, and clinical recommendations were recorded.

Data Analysis
The extracted data was analysed and organised thematically. Similarities and patterns in the findings were identified, and key concepts related to opioid use in cancer pain management were synthesised. Data were categorised into subtopics, such as mechanisms of action, risks, ethical considerations, and emerging alternatives, for a coherent presentation.

Citation and Referencing
All sources used in the study were adequately cited and referenced. The references were formatted according to the appropriate citation style (Vancouver) to ensure accuracy and consistency.

Manuscript Composition
The findings and insights from the analysis were synthesised and used to construct the study sections. By employing this methodology, this study ensured a rigorous and systematic approach to gathering and analysing relevant information on opioid use in cancer pain management. The utilisation of reputable sources and adherence to inclusion and exclusion criteria enhanced the validity and reliability of the findings.

Importance of balancing efficacy and safety in opioid use
Although the nature of cancer-related pain is more than enough indication for the prescription and use of opioids, their numerous side effects encourage a high level of scrutiny before clinical use. [4] The problems do not only lie in the side effect profile of the medication, as there are methods of improving patient response to opioids, but in the way the drugs are used, misused, and prescribed in large proportions, needing careful stewardship before use.[4] However, this does not warrant a distorted outlook on the issue, where patients experience inadequate pain relief in the bid to scrutinise the amount or level of opioids prescribed. [5] The safe and effective use of opioids in the management of pain in an oncology setting requires knowledge of their mechanism of action, pharmacodynamics, and pharmacokinetics, leading to appropriate selection, dosing, and titration of these medications. [5] It also requires in-depth knowledge of adverse effects to expect and how to manage said complications. [5] Some of the principles currently being used by oncologists to balance the safe and effective use of these medications include titration, used to establish a starting dose and response due to interpersonal variation in analgesic response; rotation, from one opioid or route of administration to another to prevent opioid-induced neurotoxicity (which occurs before mortality in 85% of patients) and a lack of pain control after titration has been achieved; and regular assessment of side effects in each patient to enable swift management. [5] Additionally, the interpersonal relationship between the physician and patient needs to be established to determine if the patient has risk factors for overuse, as well as agreements between both parties and strategies for adherence. Achieving this balance begins with the awareness of problems associated with opioid use, as well as interdisciplinary care from oncologists and addiction specialists. [5]

Mechanism of opioid action in pain relief
Opioid medications replicate the effects of endogenous opioid peptides by binding to specific opioid receptors, resulting in a range of pharmacological responses. There are four distinct opioid receptor types: μ, δ, κ, and the 'opioid-like orphan receptor.' [6] Opioids primarily exert inhibitory effects by closing N-type voltage-gated calcium channels and opening calcium-dependent inwardly rectifying potassium channels. This leads to neuronal hyperpolarisation and decreased excitability. Endogenous opioids and

their receptors are strategically positioned within pathways responsible for pain transmission, modulation, and perception. While the μ-opioid receptor is primarily linked to analgesia, δ- and κ-opioid receptor agonists also contribute to antinociception at both spinal and supraspinal levels. Opioids specifically influence the sensation of "second pain", transmitted by slowly conducting, unmyelinated C fibres, but have minimal impact on "first pain", which is carried by small, myelinated Aδ fibres. [6] In the dorsal horn, peripheral nociceptive signals transmitted via C fibres involve the presynaptic release of neuropeptides such as tachykinins (substance P and neurokinin A) and glutamate. Tachykinins bind to postsynaptic neurokinin receptors (NK1 and NK2), while glutamate interacts with AMPA and NMDA receptors, triggering depolarisation and intracellular signalling changes. The activation of presynaptic μ, δ, and κ opioid receptors inhibits the release of these neurotransmitters from the sensory fibre terminals, thereby reducing pain signalling.[6]

The Role of Opioids in Cancer pain management and types of opioids used.

Pain is a serious consequence of cancer and its treatment. Cancer pain is broadly categorised into nociceptive and neuropathic pain. Nociceptive pain, which includes somatic and visceral types, arises from the activation of nociceptors due to actual or potential tissue damage. Somatic nociceptive pain can be superficial or deep, is well localised, and commonly results from bone metastases or malignant ulcers. Chronic pain in cancer patients can result from various factors, including peripheral neuropathies caused by radiation, chemotherapy (such as platinum-based agents, paclitaxel, and vincristine), or tumour invasion. Radiation-induced fibrosis and chronic postsurgical incisional pain are also common contributors. Some patients experience phantom limb pain, while others develop arthropathies and musculoskeletal pain due to changes in posture or mobility. Additionally, visceral pain may occur as a result of organ damage or obstruction related to tumours or cancer treatments. [7,8]

The WHO Analgesic Ladder outlines a stepwise approach to pain management, including the use of opioids based on the severity of pain. For moderate pain, Step 2 introduces "weak" opioids such as codeine, often in combination with non-opioid analgesics. As pain intensity increases, Step 3 recommends the use of stronger opioids to provide adequate relief. This structured framework has been widely adopted for cancer pain management and has proven effective for many patients. However, there is ongoing debate about its adaptability to all pain conditions, as individualised treatment approaches may sometimes be necessary. [9]

Awareness of the proper and effective use of opioids in oncology is crucial for ensuring adequate pain management. A thorough understanding of their mechanism of action, pharmacokinetics, and pharmacodynamics aids in selecting, dosing, and adjusting these medications appropriately. Since adverse effects are common, the oncology team must be proficient in preventing and managing complications such as constipation, nausea, sedation, and neurotoxicity. [5]

Building on the structured approach of the WHO analgesic ladder, cancer pain management follows the three-step WHO analgesic ladder, with treatment based on pain severity. Mild pain Visual Analogue Score (VAS < 3/10) is non-opioid analgesics such as paracetamol and NSAIDs for mild pain.

However, moderate pain (VAS 3–6/10) requires Step 2 treatment, which includes a combination of non-opioids and weak opioids such as codeine, tramadol, or dihydrocodeine. Tramadol (1.5 mg/kg every 6 hours) is a common option, and its analgesic effect is comparable to codeine. Combining weak opioids with non-opioid analgesics remains a standard recommendation, though their effectiveness remains a subject of debate. [8,9,10]

Tramadol is widely used in palliative care; however, evidence supporting its efficacy remains limited, and its adverse effects can be significant. It is considered a step 2 opioid in the WHO analgesic ladder,

particularly when other weak opioids, such as codeine or dihydrocodeine, are not well tolerated. Tramadol is associated with notable side effects, including dizziness, nausea, vomiting, and constipation. Additionally, its influence on serotonin metabolism raises concerns about serotonin toxicity, particularly in elderly patients. It can also lower the seizure threshold and exhibit reduced analgesic efficacy in individuals with poor cytochrome P450 2D6 (CYP2D6) metabolism. Adverse drug interactions with tramadol often result from overdose or the sudden combination of medications that may interact negatively. It is essential to assess potential interactions before prescribing tramadol to prevent harmful effects. Tramadol is known to interact with various drugs, including MAO inhibitors, antidepressants, carbamazepine (Tegretol), blood thinners, digoxin, ketoconazole, rifampin, erythromycin, quinidine, and other medications that induce drowsiness. [10,11]

Dihydrocodeine (DHC), a codeine derivative, has an analgesic potency ratio of 5:1 compared to oral morphine. It is usually better tolerated than codeine. [14] Unlike codeine and tramadol, its effectiveness is independent of CYP2D6 enzyme activity, reducing variability in patient response. Metabolised primarily into DHC-6-glucuronide and dihydromorphine, it has milder side effects than codeine. Available only in controlled-release form, DHC is administered every 12 hours, with a maximum daily dose of 240 mg. It is commonly used for moderate pain, particularly in patients with coexisting cough and dyspnoea. [10,13]

Codeine remains a widely used weak opioid, though its analgesic activity is dependent on its conversion to morphine via CYP2D6. In poor metabolisers, this conversion is inefficient, rendering the drug ineffective, whereas ultrarapid metabolisers may be at risk of toxicity. [10]

Despite the historical use of weak opioids in cancer pain management, there is ongoing debate about their effectiveness. Studies have questioned whether weak opioids provide significant benefits over non-opioid analgesics, and meta-analyses have found no straightforward evidence supporting their superiority. A 2014 Cochrane review of weak opioids in cancer pain management similarly failed to provide definitive recommendations. Moreover, research suggests that the efficacy of Step 2 opioids is often limited to 30–40 days, after which most patients require escalation to stronger opioids due to inadequate pain relief rather than adverse effects. [10]

For moderate to severe cancer pain (VAS >6/10), step 3 of the WHO analgesic ladder recommends strong opioids as the mainstay of treatment. Common opioids used include morphine, methadone, oxycodone, fentanyl, hydromorphone, and buprenorphine, with oral morphine being the first-line choice. In cases where gastrointestinal issues or haemodialysis complicate oral administration, transdermal fentanyl and buprenorphine serve as alternatives. Opioid switching, particularly to methadone, can improve pain relief and tolerability. Individual dose titration with normal-release morphine every 4 hours, along with rescue doses for breakthrough pain (BTP), is standard practice. [14]
Morphine, a widely used opioid analgesic, primarily exerts its effects through mu-opioid receptor activation in the central and peripheral nervous systems. It modulates pain perception via descending inhibitory pathways and inhibits nociceptive transmission, leading to effective pain relief. Morphine can be administered through multiple routes, including oral, intravenous, epidural, intrathecal, intramuscular, and rectal formulations, allowing for flexible pain management. While its effectiveness makes it a key analgesic, its potential for misuse and abuse necessitates careful monitoring. [15]

Methadone is often considered an alternative opioid for cancer pain management, especially when other opioids lose efficacy. However, its use is limited by concerns such as accumulation leading to delayed toxicity, unpredictable pharmacokinetics, potential drug interactions, QT prolongation, and challenges with dosing and opioid conversion. Despite these drawbacks, methadone's dual action as a μ-opioid receptor agonist and NMDA receptor antagonist may offer benefits in managing neuropathic pain and

hyperalgesia. Its high oral bioavailability, long half-life, and affordability make it a potential first-line opioid, particularly in resource-limited settings. [16]

Benefits of opioids for improving quality of life in cancer patients.

Opioids serve as essential and, in many cases, indispensable analgesics for managing acute pain in cancer patients. However, their use in chronic cancer pain management is more complex, requiring both healthcare providers and patients to carefully assess the potential risks associated with treatment. Existing guidelines recommend several strategies to enhance the safe use of opioids in cancer pain management. These include implementing a signed treatment agreement, conducting periodic urine drug screenings, educating both patients and carers, and referring individuals to palliative care or pain specialists when necessary. Additionally, guidelines advise against high-risk opioid formulations and emphasise minimising the total daily dose for patients who are more vulnerable to opioid-related complications. [16] Meske et al. conducted a meta-analysis evaluating the efficacy of opioids for chronic pain management, demonstrating that most patients (63%) experienced clinically meaningful pain relief. Their findings support the role of opioids in improving not only pain severity but also overall patient-reported outcomes, including physical function and perceived well-being. While concerns over opioid misuse and dependence have led to stricter prescribing guidelines, this analysis highlights that opioids remain a valuable option, particularly for cancer patients who suffer from debilitating pain. Meske et al. argue that, when used appropriately, opioids can enhance comfort, reduce distress, and improve the quality of life for individuals facing advanced disease. However, they emphasise the need for further research to refine long-term safety protocols and ensure that opioid therapy is administered responsibly within a framework that prioritises patient well-being and minimises potential harm. [17]

Pain, opioids, and the immune system

Opioid receptors are ubiquitous in both the central nervous system (CNS) and peripheral tissues, including the gastrointestinal tract and the heart, across neuronal and non-neuronal structures. While analgesia is primarily mediated by opioid receptors in the CNS, evidence suggests that receptors in the peripheral nervous system also contribute to pain relief. Additionally, opioid receptors within the enteric nervous system regulate gastrointestinal motility, secretion, and electrolyte balance. [18].

More importantly, opioid receptors are found in the immune system. There is an established relationship between the immune system and pain; these distinct entities intersect during inflammation. In inflammatory responses, white cells contain opioid peptides as they transmigrate into tissue. These peptides are released on peripheral nerves at the site of inflammation to counter inflammatory pain. The migration of opioid peptide-containing leukocytes is regulated by chemokines and adhesion molecules. Neurokinins, such as substance P, also play a role in recruiting these cells. The release of opioid peptides from granulocytes can be triggered by chemokines like CXCR2 ligands. This process relies on intracellular calcium levels and the activation of phosphoinositide 3-kinase (PI3K) and p38 mitogen-activated protein kinase (MAPK). [19]

In the central nervous system (CNS) immunocompetent cells, such as glia, possess a diverse range of receptors that enable them to directly respond to various stimuli, including opioids. Additionally, both microglia and astrocytes can be indirectly influenced by opioids through downstream effects on neurons. For instance, although the specific extracellular mediator remains unknown, knockout of neuronal PKCγ has been shown to reduce morphine-induced upregulation of GFAP. Moreover, neuronal peptides like CGRP and chemokines such as CCL2 and CX3CL1 enhance glial reactivity following repeated morphine exposure. Notably, immune cells within the CNS also express opioid receptors and toll-like receptors, facilitating direct interactions with opioids. [20]

The paradox of pain relief vs. immunosuppression

The effects of exogenous opioids on immune function in patients are a significant cause for concern in the clinical setting, as patients on long-term therapy with opioids like morphine routinely report an increase in bacterial and viral infections. [18] This rise in the rate of infections comes from the effect opioid-induced analgesia has on the immune system as a whole, as opioids bind to and activate mu-opioid receptors (MORs), which are expressed in several areas and cell types. [18] When activated, the MORs in the central and peripheral nervous systems work to mediate analgesia, which is the sought-after function. [5] However, when those expressed in immune cells like macrophages, neutrophils, T cells, and B cells are activated, the result is an impaired immune response, leading to a higher incidence of infections. [20] This impaired immune response is due to direct and indirect pathways that affect innate and adaptive immunity mechanisms. Direct pathways are through interaction with receptors on immune cells, while indirect pathways are through activation of receptors within the CNS and the hypothalamic-pituitary-adrenal axis, releasing corticosteroids and immunosuppressive hormones. [20] Opioids act on the innate immune system by activating MORs on immune cells, causing several effects, which include reduced proliferative capacity and impaired phagocytosis in macrophages, impairment of interleukin-8 (IL-8) activity leading to decreased migration, and reduced neutrophil superoxide production in neutrophils, all leading to impaired bactericidal activity. [20] In the adaptive immune system, morphine reduces T cell proliferation, T helper cell response, and CD4/CD8 population, while in B cells, it reduces proliferation and antibody production. [20] It is equally important to note that the immunomodulatory effects of opioids depend on the type of opioid used, independent of its potency and duration of action. [18] These immune effects depend instead on the structural attributes of the opioid in particular, as the presence of a carboxyl group at C6 and a hydroxyl group within the molecule would indicate immunosuppressive effects, as seen in morphine and oxycodone but not in hydromorphone, which is equally as potent. [18]

Mechanisms of opioid-induced immunosuppression

Opioids and Innate immune system

Opioids have been shown to activate mu-opioid receptors (MORs) on various innate immune cells. In macrophages, this activation leads to reduced proliferative capacity, impaired recruitment, inhibited phagocytosis, and diminished bactericidal activity. While the precise mechanisms remain unclear, these immunomodulatory effects are thought to involve crosstalk with Toll-like receptors (TLRs) and altered nuclear factor-kappa B (NF-κB) signalling. Opioids also inhibit neutrophil migration by disrupting interleukin (IL)-8 signalling and reducing neutrophil superoxide production, thereby compromising bactericidal function. Additionally, opioids impair antigen presentation by dendritic cells by suppressing IL-23 production. Natural killer (NK) cell cytotoxicity is also reduced, primarily due to MOR activation in the central nervous system. Furthermore, opioids decrease mast cell activation, leading to increased intestinal permeability and a heightened risk of infection. [20,21,22] The activation of the μ-opioid receptor induces phosphorylation and desensitisation of chemokine receptors (e.g., CCR1, CCR2, CXCR1, and CXCR2) on macrophages, resulting in reduced receptor sensitivity. [18]

It is worth noting that the effect of opioids on the innate immune system is dose dependent. For instance, in vitro experiments, it was noticed that at lower to moderate doses, opioids impair macrophage phagocytic function, while higher doses induce apoptosis through the Toll-like receptor 9 (TLR9) and p38 MAPK pathway. This apoptotic response is further influenced by the suppression of microRNA miR-873, which is significantly downregulated in peritoneal macrophages of mice exposed to opioid doses ranging from 20 to 140 mg/kg. MicroRNAs (miRNAs) are short, single-stranded RNA molecules (20–40 base pairs) that regulate intracellular protein expression. Notably, macrophages transfected with miR-873 mimics exhibit a substantial reduction in apoptosis following opioid exposure. Although the precise mechanism is not yet fully elucidated, miR-873 is believed to exert its effects through modulation of the TLR signalling pathway. [18]

Additional effects of opioid treatment include the suppression of NF-κB, a reduction in the release of the chemokine CXCL2 (a CXCR2 ligand), and decreased NF-κB-dependent gene transcription in response to Streptococcus pneumoniae infection in animal studies. As a result, opioid users may have an increased susceptibility to infections caused by gram-negative bacteria. However, clinical evidence supporting this association remains limited. [18,23]

Opioids and the adaptive immune system

Prolonged opioid treatment has been shown to compromise the adaptive immune response in a manner like its effects on the innate immune system. Specifically, opioids impair T-cell function, alter cytokine expression, suppress T-cell apoptosis, and modify T-cell differentiation and T-helper cell function and reduce CD4/CD8 population, while also reducing B-cell function through activation of the μ-opioid receptor. In antigen-presenting cells (APCs), opioid exposure leads to a downregulation of major histocompatibility complex class II (MHC-II) expression, particularly on B cells. This reduction in MHC-II levels consequently diminishes the APCs' ability to activate T cells, further impairing immune function. Additionally, lower MHC-II expression negatively impacts T-cell proliferation. [18,20, 21].

Opioids also bind to μ-opioid receptors on T cells, promoting differentiation towards the T-helper cell type 2 (TH2) phenotype, [4,5] This activation results in the superactivation of adenylyl cyclase, increased intracellular cAMP levels, activation of the p38 MAPK pathway, and phosphorylation of CREB. These molecular changes subsequently stimulate the T-cell-specific transcription factor GATA3, leading to a shift toward the TH2 phenotype. TH2 cells secrete IL-4, IL-5, and IL-10, cytokines associated with immune responses against helminth infections rather than the robust antiviral and antibacterial immunity typically mediated by TH1 cells. This intracellular shift toward a TH2-dominant response is believed to weaken overall immune function. However, given the complexity of T-cell immunology, further research is necessary to fully elucidate the functional consequences of opioid-induced immune modulation. [18,21]

Literature on the effects of opioids on the B-lineage of lymphocytes remains scanty; it is known that they are reduced by cell proliferation and secretion of antibodies. This is believed to happen as a result of lack of stimulation from T cells and macrophages rather than direct activity of opioids on B cells [24]

Impact on Gut Barrier and Sepsis

A key opioid side effect is slowed gastrointestinal (GI) transit, which can contribute to bacterial translocation. Hilburger et al. reported that morphine-induced sepsis in mice resulted from gut flora entering systemic circulation, identifying Proteus mirabilis, Enterococcus faecalis, and Escherichia coli in mesenteric lymph nodes, peritoneal cavity, spleen, and liver. Morphine-treated mice were also sensitised to endotoxin-induced shock, a major complication of Gram-negative sepsis. Holaday's earlier research showed naloxone protected against endotoxin-induced hypotensive shock, implicating endogenous opioids in sepsis pathology. [26] Additionally, opioid treatment alters gut microbiota composition, promoting the expansion of gram-positive pathogens. These changes facilitate the translocation of harmful microbes, increasing the risk of systemic infection. [22]

Opioids may compromise the integrity of the intestinal barrier and cause gut dysbiosis, thereby facilitating systemic infections. This occurs by increasing the sensitivity of gut epithelial cells to Toll-like receptor (TLR) activation, which permits the translocation of bacteria from the intestinal lumen, causing systemic infections. [26]

Roy's laboratory found that morphine disrupted tight junctions in the ileal mucosa, causing bacterial translocation. This effect depended on TLR4, as TLR4 k/o mice did not experience increased gut permeability. Ampicillin-resistant E. coli introduced via gavage also translocated systemically in

morphine-treated mice, confirming gut barrier compromise. Moreover, morphine withdrawal led to recurrent sepsis, emphasising the cyclical nature of opioid-induced immune dysfunction. [27]

Opioid use and specific infections

Opioids adversely affect the immune system in the aforementioned ways; there are a couple of other ways that opioid use predisposes patients to infections.

Early studies, such as Tubaro et al., found that morphine sensitised mice to infections like Candida albicans and Klebsiella pneumoniae. Morphine decreased survival rates and reduced the mean time to death, linked to suppressed phagocyte activity. [28] Additional research showed that morphine enhanced HIV replication in monocytic cells and increased HIV Tat cytotoxicity via upregulated inflammatory cytokines. [29,30]

Morphine dramatically sensitised mice to Salmonella typhimurium, reducing survival from 28 days to five days. Morphine-treated mice harbored bacterial burdens of 10^6 per tissue analysed, while naltrexone-treated mice showed no detectable organisms. MOR knockout (MOR k/o) mice displayed resistance, confirming the role of the mu-opioid receptor (MOR) in morphine-mediated Salmonella susceptibility. Interestingly, animals developed tolerance to opioid-induced Salmonella sensitivity after 96 hours of morphine exposure, but withdrawal reinstated susceptibility. [31]

Studies showed morphine increased susceptibility to Streptococcus pneumoniae, correlated with delayed neutrophil recruitment, and reduced levels of CXCL1, CXCL2, TNF-α, IL-1, IL-6, and IL-17/IL-23 in bronchoalveolar lavage fluid. MOR k/o mice were not sensitised, confirming opioid mediation. Morphine also suppressed the alveolar macrophage response to pneumococcal infection, downregulating NF-κB and key cytokines, compromising innate immunity.[32,33]

Breslow et al. found that morphine increased mortality from Acinetobacter baumannii infections, with higher bacterial burdens in vital organs. Increased pro-inflammatory cytokines were observed systemically, but IL-17A and CXCL1 were depressed locally, leading to impaired immune response. Similarly, morphine dramatically increased mortality from Listeria monocytogenes despite sublethal infection doses in control animals. [34]

Peterson's research indicated morphine addiction sensitised mice to Toxoplasma gondii, causing 86% mortality compared to 0% in controls. [35] Naloxone reversed this effect. In parasitic infections, Singh et al. found that low morphine doses suppressed Plasmodium berghei and Leishmania donovani, but high doses increased susceptibility. [36,37]

Opioids and tumour progression

Opioids are increasingly utilised by anaesthesiologists not only during the perioperative period but also for the management of chronic cancer pain. However, recent studies have raised significant concerns regarding their potential role in cancer progression. Opioids have been implicated in promoting tumour growth through multiple mechanisms. By stimulating μ-opioid receptors (MOR) expressed in vascular endothelium, opioids activate vascular endothelial growth factor (VEGF)-mediated angiogenesis, thereby facilitating tumor vascularization Additionally, they contribute to immunosuppression, further compromising the body's ability to counteract malignant cell proliferation .[38–40]

Morphine, once regarded as an essential analgesic for cancer patients, has emerged as a particularly potent agent within this class. Beyond its analgesic properties, morphine has been shown to enhance angiogenesis, increase vascular permeability, and create a microenvironment conducive to tumour dissemination when administered in low doses. Research has demonstrated that morphine, when

administered at therapeutic doses in a human breast cancer xenograft model in mice, promotes tumour neovascularisation. [38–40]

Other opioids have also demonstrated immunomodulatory and tumour-promoting effects. Tramadol, which possesses serotonergic and noradrenergic activity, has been shown to suppress surgery-induced lung metastasis in vitro. Fentanyl has been reported to inhibit natural killer (NK) cell cytotoxicity in the postoperative setting. Similarly, sufentanil and alfentanil have been found to impair leukocyte function, inhibit NK cell activity, and suppress mitogen-triggered lymphocyte proliferation. [38–40]

The challenge of balancing analgesia with immune resilience

As recent studies have shown that certain opioids can negatively impact the immune response through the downregulation of innate and acquired immune pathways, the physician and surgeon are now at a crossroads. The patient with cancer who already has a compromised immunity, is faced with potential infections and depends on their already weakened immune system. [41,42] That same patient with cancer also battles pain. The immune system plays a crucial role in combating cancer, and any factors that affect the body's natural anti-tumour defences can significantly influence the progression and outcome of malignant disease. [42]

According to the World Health Organisation (WHO) cancer pain ladder, cancer pain treatment begins with nonopioids, followed by mild and severe opioids until the patient is pain free. [43] Opioids are highly effective analgesics that are supported as first-line treatment for moderate-to-severe pain, which oftentimes is the type of pain cancer patients have. [41]

What do you then do when the solution to one problem can exacerbate another problem?

The current justification for ongoing opioid analgesic treatment is rooted in findings from animal studies, which indicate that treatment of physical pain may not only potentially promote cancer progression but also compromise the immune system, leading to immunosuppressive effects. [44]

The long-term immunological effects of opioid treatment in patients with chronic cancer pain have been found to differ significantly from those observed in healthy individuals or post-surgical patients receiving short-term opioid treatment due to distinct immunological profiles among these populations. Opioids, via immune (and non-immune) effects, can influence cancer progression in animal studies and other patient groups. The effect of opioids on prognosis in patients with cancer not undergoing surgery has been systematically reviewed. [42,45]

There seems to be a relationship between the duration of opioid treatment and the impact of immunosuppression A study by Borland et al. found the impact of morphine on immune function to be influenced by various factors, including the duration of administration (acute vs. chronic), the route of administration, and the specific immune parameters being evaluated. [42]

To balance analgesia with immune resilience, clinicians can consider the following strategies: multimodal analgesia, opioid sparing strategies, immunomodulatory therapies, and personalised medicine. Using a combination of non-opioid analgesics, such as NSAIDs and acetaminophen, can reduce the need for opioids and minimise immunosuppression. A multicenter randomised double-blind trial, known as the OCTOPUS study, conducted by Beloeil and colleagues, investigated the efficacy of morphine alone and in combination with paracetamol, nepafenac, and ketoprofen. [46] The study revealed that combining these three non-opioid analgesics with morphine significantly reduced morphine consumption within the first 48 hours following surgery. This finding has important implications, as decreased postoperative opioid use may contribute to a lower risk of long-term opioid misuse. Furthermore, gabapentinoids have emerged as effective alternative analgesics, demonstrating efficacy across a broad range of clinical indications. [46] Also, techniques like pain reprocessing therapy and cognitive-behavioural therapy can

help reduce pain intensity and opioid requirements. Agents like interferons and interleukins can enhance immune function, potentially mitigating the immunosuppressive effects of opioids. [47]

A personalised approach to cancer pain management, considering individual patient factors and cancer types, can help optimise analgesia while minimising immunosuppression. A personalised approach to cancer pain management is increasingly recognised as crucial, as individuals exhibit significant variability in their response to opioids, including differences in pain relief, side effects, and impacts on immune cell function. [48]

Ethical considerations in opioid prescribing for cancer patients

Prescribing opioids for cancer patients is a complex issue that raises several ethical concerns. While opioids are effective in managing cancer pain, their use can also lead to addiction, overdose, and compromised immunity. [41] With the opioid epidemic, there is a need for responsible opioid prescribing practices. Patients taking opioids for cancer-related pain could be on opioids for a long time; thus, tolerance could develop. Given that they might also be on opioids intermittently, it is important to know if regular or intermittent opioids are more immune protective and how this influences clinical outcomes and prescriptions. There are situations in which large quantities of prescription opioids end up on the black market, fuelling non-therapeutic use of these drugs. Clinicians have ownership of the prescribing cycle and need to carefully oversee opioid prescribing; postoperative opioid use should be measured in days. Use of controlled-release formulations should be reduced in naive patients. Systems need to be tightened to blunt the spread of this epidemic. When prescribing opioids, the clinician needs to make decisions based on the ethical principles of autonomy, beneficence, non-maleficence, and justice. [48]

The principle of justice, which requires healthcare providers to distribute benefits and risks fairly and equitably, is also relevant in opioid prescribing for cancer patients. Opioid therapy should be accessible to all patients who require it, regardless of their socioeconomic status, age, or other factors. Furthermore, healthcare providers must ensure that opioid therapy is not inappropriately withheld from patients who require it. [48] However, in the principle of non-maleficence, healthcare providers should avoid causing harm to patients. [49] Physicians also need to respect the autonomy of patients. As many patients with cancer experience intense perioperative pain during disease, withholding opioids would be unethical because of exposing these patients to unbearable pain. Moreover, opioids relieve dyspnea and psychological distress, thus improving patients' quality of life Patients have the right to be fully informed about the benefits and risks of opioid therapy and to participate in decision-making about their care. [49] Healthcare providers must ensure that patients are able to provide informed consent and that their autonomy is respected throughout the treatment process. Patients must be fully informed about the benefits and risks of opioid therapy and provide informed consent before initiating treatment. [48].

While opioids can be improved in terms of their effectiveness and reduced side effects, it is essential to recognise that these valuable medications are not the primary problem. Rather, the issue lies with us, the healthcare providers, prescribers, and users, and the alarming rates at which these drugs are being misused and overprescribed, fuelling a devastating epidemic. [42].

In the absence of definitive evidence regarding the effects of opioids on tumour growth and survival in patients undergoing immunotherapy, there is currently no justification for withholding opioid therapy. Instead, a comprehensive and patient-centred approach is essential, involving attentive listening, thorough clinical evaluation, and regular assessment of patient-reported outcomes, including pain intensity, physical symptoms, and psychological distress. This comprehensive approach enables healthcare providers to accurately diagnose and manage pain, considering its type (neuropathic or somatic), severity, underlying causes, location, and triggering factors. [42]

Strategies for Mitigating Risks in Opioid Use for Cancer Pain Management

Managing cancer-related pain often requires the use of opioids, which, although practical, can be associated with risks such as immunosuppression and other adverse effects. To enhance analgesia while minimising these risks, several strategies may be implemented:

Opioid Rotation

Opioid rotation, the practice of switching from one opioid to another, is a promising strategy in the management of cancer pain. Its primary aim is to improve pain control while reducing adverse effects. This approach takes advantage of the concept of incomplete cross-tolerance among opioids; a patient who has developed tolerance to one opioid may respond more favourably to a different opioid at a lower dose. [50] Incomplete cross-tolerance implies that the tolerance built up to one opioid does not wholly transfer to another, allowing for a reduction in dosage and potentially fewer side effects. [50] This possibility of decreased immunosuppressive impact is encouraging. Research has demonstrated that opioid rotation can enhance analgesia and decrease opioid-related toxicity, offering a more favourable outlook for cancer pain management. [51]

Multimodal Pain Management

Employing a multimodal pain management approach is a reassuring strategy. It involves combining opioids with non-opioid analgesics and interventional techniques to achieve superior pain control with lower opioid dosages. Non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids can address inflammatory components of cancer pain, while nerve blocks can target specific pain pathways. This comprehensive strategy not only enhances analgesia but also reduces the cumulative opioid dose, thereby potentially mitigating immunosuppression and providing a sense of security about minimising opioid-related toxicity. [50]

Immunomodulatory Interventions

Integrating immunomodulatory interventions into the treatment plan is advisable to counteract opioid-induced immunosuppression. This may include using agents that bolster immune function, such as immunostimulants or immune system enhancers, or adopting therapies that have a neutral or positive effect on the immune system, such as stress management or sleep optimisation. [50] While specific pharmacological agents are under investigation, maintaining optimal nutrition, managing stress, and ensuring adequate sleep are practical measures that support immune health and can be part of a comprehensive immunomodulatory strategy. [51]

Personalized Medicine Approaches

Personalising opioid therapy based on individual patient factors is an empowering approach. Genetic profiles, comorbidities, and previous responses to analgesics can be considered. This personalised approach, often facilitated by pharmacogenetic testing, can identify patients at higher risk for adverse effects, allowing clinicians to tailor opioid selection and dose accordingly. This personalised approach maximises analgesic benefits while reducing risks, including immunosuppression, and enables healthcare professionals to deliver more effective and safer treatment. [52]

In conclusion, mitigating the risks associated with opioid use in cancer pain management requires a multifaceted approach. Implementing opioid rotation, adopting multimodal pain management strategies, incorporating immunomodulatory interventions, and personalising treatment plans are essential steps toward achieving adequate analgesia while preserving immune function. [52]

Future Directions and Research Needs in Non-Opioid Alternatives and Novel Analgesics

The exploration of non-opioid alternatives and novel analgesics represents a crucial area of research in pain management, particularly for individuals experiencing chronic pain related to cancer. Traditionally, opioids have been the primary pharmacological intervention for managing severe pain related to malignancy, but the increasing reliance on these medications has contributed to the ongoing global opioid crisis. [53] The rising incidence of opioid misuse and associated mortality has necessitated a reassessment of pain management strategies, with a growing emphasis on alternative approaches that are both effective and safer. [54] Therefore, further research into non-opioid pain management strategies is imperative to mitigate the economic and public health burden associated with opioid dependence while ensuring adequate pain relief for patients.

One promising area of research involves the evaluation of non-steroidal anti-inflammatory drugs (NSAIDs) as potential alternatives to opioids. A study comparing the efficacy of ketorolac, an NSAID, with pentazocine, an opioid, for cancer pain management demonstrated similar levels of analgesic potency between the two drugs. [43] Notably, patients in the ketorolac group did not experience significant adverse effects, suggesting that this NSAID could serve as a viable alternative to opioid-based treatment. However, further large-scale clinical trials are necessary to confirm these findings and determine the long-term safety and efficacy of NSAIDs in chronic pain management. [55]

Beyond conventional pharmacological approaches, novel analgesic strategies are being explored, including targeted toxin therapies, gene-based interventions, and receptor-specific approaches. [56] Targeted toxin therapies leverage the ability of toxins, such as saporin, to selectively bind to pain-related receptors, such as mu-opioid and neurokinin-1 receptors, leading to the destruction of nociceptive neurones and prolonged analgesia. [57] However, the irreversible nature of these toxins limits their applicability in non-terminal conditions. To address this limitation, alternative agents such as botulinum toxins have been investigated for their ability to temporarily inhibit pain signalling, offering a reversible and potentially safer method of pain relief. [58] Despite promising preclinical results, more research is needed to determine the safety, specificity, and long-term effects of these treatments in human subjects. [59]

Gene-based approaches have also emerged as a potential frontier in pain management. Strategies such as antisense oligonucleotide therapy and viral vector-mediated gene transfection have been explored for their ability to modulate the expression of key nociceptive proteins, including substance P, NMDA receptor subunits, and TRPV1 receptors. [60] Preclinical studies have demonstrated that inhibiting these pain-associated proteins can result in significant analgesia. [61]. Additionally, gene therapy techniques have been used to enhance the expression of analgesic molecules, such as GABA and endogenous opioid peptides, which could provide long-term pain relief with fewer side effects than traditional opioid medications. [61] Despite these promising findings, extensive clinical trials are required to evaluate the safety, efficacy, and ethical implications of gene-based pain therapies before they can be widely implemented in clinical practice. [62]

In addition to pharmacological and gene-based interventions, alternative pain management strategies such as transcutaneous electrical nerve stimulation (TENS) and neuroablative procedures are gaining attention. [63] TENS, which involves the application of low-voltage electrical currents to modulate pain perception, has shown potential benefits in some cases. [64] However, a recent Cochrane review found insufficient evidence to support its efficacy in cancer pain management, highlighting the need for more rigorous studies to assess its effectiveness. [65]

Neuroablative techniques, including coeliac plexus block, superior hypogastric plexus block, and percutaneous cordotomy, have demonstrated promise in alleviating pain in cancer patients, particularly

those in advanced stages of the disease. [66] For instance, coeliac plexus neurolysis has been shown to provide significant pain relief in patients with pancreatic cancer, enabling a reduction in opioid consumption. [67] However, despite these benefits, neuroablative procedures are often considered a last resort due to their invasive nature and potential complications. [68] Additional research is needed to refine these techniques, improve patient selection criteria, and evaluate their long-term impact on quality of life. [69]

Similarly, percutaneous vertebroplasty and kyphoplasty, which involve the injection of bone cement into fractured vertebrae, have been utilised as palliative measures for cancer-related bone pain. [70] While these procedures offer significant pain relief and improved mobility, further studies are required to assess their comparative effectiveness against other non-opioid interventions and their long-term outcomes.[71]

While considerable progress has been made in the development of non-opioid pain management strategies, there remains a critical need for further research to optimise their efficacy, safety, and clinical applicability. [72] Advancements in targeted toxin therapy, gene-based approaches, neuromodulation techniques, and minimally invasive procedures hold great potential for transforming pain management. [73] However, extensive preclinical and clinical investigations are necessary to address existing limitations and ensure that these novel interventions provide sustainable and equitable solutions for patients suffering from chronic pain. As the medical community continues to confront the challenges posed by opioid dependency, prioritising research into non-opioid analgesics will be essential for advancing pain management practices and improving patient outcomes. [18]

Conclusion

The use of opioids in cancer pain management presents a complex balance between providing effective analgesia and mitigating significant risks, including immunosuppression, increased infection susceptibility, and potential tumour progression. While opioids are indispensable for alleviating severe pain and improving quality of life, their long-term use necessitates careful consideration of their immunomodulatory effects. Ethical prescribing practices must prioritise patient autonomy, beneficence, and justice, ensuring that pain relief is achieved without compromising immune resilience or cancer outcomes. Multimodal approaches, opioid-sparing strategies, and personalised medicine offer promising avenues to reduce reliance on opioids while maintaining effective pain control. Future research should focus on developing non-opioid alternatives and immunomodulatory therapies to address the limitations of current opioid-based regimens. A patient-centred approach, guided by robust evidence and ethical principles, is essential to navigate the challenges of opioid use in cancer care and to optimise outcomes for patients living with chronic pain.

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