Exploration of Immunology

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Open Access Review

Balancing analgesia and immunity: revisiting the immune consequences of opioid therapy

Lucia Daiana Voiculescu[1*], Thomas Li[1], Franzes Anne Liongson[1], Sanjay Menghani[2]

[1]Department of Anesthesiology, Perioperative Care and Pain Medicine, NYU Grossman School of Medicine, New York, NY 10016, USA

[2]Department of Medicine, NYU Grossman School of Medicine, New York, NY 10016, USA

***Correspondence:** Lucia Daiana Voiculescu, Department of Anesthesiology, Perioperative Care and Pain Medicine, NYU Grossman School of Medicine, New York, NY 10016, USA. lucia.voiculescu@nyulangone.org

Academic Editor: Calogero Caruso, University of Palermo, Italy

Received: July 1, 2025 **Accepted:** March 19, 2026 **Published:** April 28, 2026

Cite this article: Voiculescu LD, Li T, Liongson FA, Menghani S. Balancing analgesia and immunity: revisiting the immune consequences of opioid therapy. Explor Immunol. 2026;6:1003251. https://doi.org/10.37349/ei.2026.1003251

Abstract

Opioids remain central to managing moderate to severe pain, yet they also produce significant and often under-recognized effects on the immune system. In this narrative review, we synthesize evidence from 1994 to 2025 across preclinical, translational, observational, and limited interventional studies in adults to examine how different opioid classes modulate immunity and the clinical relevance of these effects. Opioids act directly on immune cells via mu-opioid receptors (MORs), nociceptin/orphanin FQ receptors (NOR), and Toll-like receptor 4 (TLR4), and indirectly through neuroendocrine, autonomic, neuroinflammatory, and gut microbiota-mediated pathways. Immunologic consequences are drug specific: Morphine, fentanyl, and to a lesser extent methadone exhibit pronounced immunosuppressive profiles; oxycodone appears comparatively less suppressive; and buprenorphine and tramadol generally preserve, and may in some contexts enhance, immune function. Clinically, chronic or intensive opioid exposure is associated with increased risk of infection and sepsis-related mortality, potential facilitation of tumor progression or recurrence, impaired perioperative and transplant outcomes, and contributions to tolerance and opioid-induced hyperalgesia, with convergent data indicating these immune effects are intrinsic to opioid pharmacology. Framing opioid-induced immunomodulation as a clinically meaningful, agent-specific phenomenon argues for incorporating immunologic risk into analgesic selection—prioritizing less immunosuppressive opioids where appropriate, considering rotation and tapering strategies, using peripherally acting antagonists, and implementing multimodal analgesia—while underscoring the need for standardized immunologic endpoints, rigorously controlled clinical studies, and development of next-generation analgesics that maintain effective pain relief while minimizing detrimental immune effects.

Keywords

opioids, immunomodulation/immunosuppression, immune system, morphine, opioid receptors, infection/sepsis, cancer, transplant

Introduction

Opioids are a class of compounds commonly used in the treatment of moderate to severe acute and chronic pain arising from both malignant and non-malignant conditions. While their analgesic efficacy is well-established, accumulating evidence indicates that opioids exert significant effects on other physiological systems, including the immune system [1, 2].

The conceptual link between opioids and immune suppression can be traced to the pioneering work of Dr. Ioan Cantacuzino (often referred to as Jean Cantacuzène) [3] in the late 19th century. His landmark research demonstrated that administering morphine, in the form of tincture of opium, to guinea pigs, either before or during infection, impaired the immune process in several ways. Specifically, morphine delayed the process of chemotaxis, migration of phagocytes in response to chemical signals, and effectively paralyzed their mobility and their ability to engulf pathogens. Even in animals treated with a protective serum, the presence of opium rendered the immune defense ineffective by disabling the phagocytic mechanisms needed to clear transformed bacteria. In essence, opium abolishes both natural and acquired immunity by functionally paralyzing immune cells. These early observations were instrumental in raising awareness of a potential association between opioid use and immune suppression.

Since Dr. Ioan Cantacuzino's seminal work in the 19th century, the understanding of opioid-immune interactions has significantly advanced [4]. The clinical relevance of opioid-induced immunomodulation has become increasingly evident in the context of the HIV (Human Immunodeficiency Virus)/ AIDS (Acquired Immunodeficiency Syndrome) epidemic, the global rise in opioid use and misuse, and the expanding population of immunocompromised patients. Contemporary research efforts focus on delineating receptor-specific mechanisms, identifying opioids with more favorable immunological profiles, and developing analgesic strategies that preserve immune integrity while maintaining effective pain control.

This review aims to synthesize current evidence on the molecular, cellular, and clinical dimensions of opioid-induced immunomodulation. By integrating mechanistic insights from preclinical studies with clinical and epidemiological data, we examine how distinct opioid agents differentially influence immune pathways and clinical outcomes, including infection risk, cancer progression, perioperative recovery, and opioid tolerance.

The review underscores the need for methodological standardization and more translational research to enhance understanding and clinical recognition of these frequently underdiagnosed effects.

To ensure a comprehensive and clinically relevant synthesis, we conducted a structured, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)-guided search of PubMed/MEDLINE, Embase, Web of Science, and Google Scholar (Sept 1994–Mar 2025), supplemented by hand-searching key reviews and citation snowballing. Searches combined opioid terms (e.g., morphine, fentanyl, methadone, and buprenorphine) with immune-related keywords [e.g., immunomodulation, Toll-like receptor 4 (TLR4), cytokines, and microbiome] and clinical areas (e.g., infection, cancer, transplant, and opioid tolerance). English- and French-language records were included without species restrictions. Adult human studies were prioritized, with animal, in vitro, preclinical, and pediatric data retained when mechanistically informative or otherwise relevant. Eligible evidence ranged from rodent and in vitro studies to observational cohorts and limited clinical trials. Data extraction focused on opioid type, exposure details (dose, duration), immune outcomes [e.g., natural killer (NK) cell activity and glial signaling], and clinical impacts (e.g., infection rates and cancer recurrence). Historical and emerging research on opioids, including biased agonists, was included to provide a comprehensive synthesis. Due to the heterogeneity of studies, results were narratively synthesized by mechanism, opioid class, and clinical relevance.

Opioid pharmacology and interaction with the immune system

Opioid-induced immunomodulation refers to the alteration of immune responses caused by opioid exposure. These effects can be immunosuppressive or, in some contexts, immunostimulatory [5]. Immunomodulation remains an under-recognized and under-studied side effect, particularly in clinical

settings. Understanding these effects is critical, especially for patients requiring long-term opioid therapy, individuals with compromised immunity, and those at risk for infections or malignancies.

Opioid receptors: structure, subtypes, and function

Opioid receptors belong to the G protein-coupled receptor (GPCR) family, a class of transmembrane proteins that initiate intracellular signaling cascades upon activation. When an opioid receptor is engaged by a ligand, it triggers a signaling pathway involving increased cyclic adenosine monophosphate (cAMP) production and activation of protein kinase A (PKA). This leads to downstream modulation—either activation or inhibition—of various proteins, enzymes, and ion channels.

Opioid receptors are widely distributed throughout the central and peripheral nervous systems. They are also expressed on non-neuronal tissues, including immune cells.

Five major opioid receptor subtypes have been described: the mu-opioid receptor (MOR), kappa-opioid receptor (KOR), delta-opioid receptor (DOR), nociceptin/orphanin FQ receptor (NOR), and the more recently identified zeta-opioid receptor (ZOR).

The best-characterized receptors—MOR, KOR, and DOR—are naloxone-sensitive and mediate classical opioid effects such as analgesia, respiratory depression, euphoria, and dependence. Among these, MOR plays a central role in both analgesic and immunomodulatory actions. Evidence from MOR knockout (MORKO) mouse models demonstrates that morphine fails to suppress immune pathways in the absence of MOR, establishing its necessity for opioid-induced immunosuppression [1, 6, 7].

NOR, a naloxone-insensitive opioid receptor, is found in the limbic system and appears to be involved in the regulation of opioid tolerance. NOR and its endogenous ligand, nociceptin/orphanin FQ (N/OFQ), are expressed in both the central nervous system (CNS) and peripheral immune cells at comparable levels, suggesting a potential role for NOR as a key mediator in neuroimmune interaction and brain-immune axis regulation.

Clinically elevated NOR-related messenger ribonucleic acid (mRNA) expression has been observed in intensive care unit (ICU) patients with advanced cancer, sepsis, and major surgery, correlating with increased mortality [8].

ZOR, the zeta-opioid receptor, has been implicated in tissue growth and repair [6, 9, 10], though no definitive role in immune modulation has yet been established.

Opioid receptor expression in immune cells

Opioid receptors are expressed on a wide range of immune cells, including macrophages, lymphocytes, and dendritic cells. Activation of these receptors by exogenous opioids modulates key immune functions—altering cell proliferation, cytokine secretion, chemotaxis, and phagocytic activity [1, 6]. Endogenous opioid peptides, such as endorphins and enkephalins, also interact with these receptors and contribute to immune regulation [11].

Mechanisms of opioid-induced immunomodulation

Opioids modulate both innate and adaptive immunity through direct and indirect mechanisms. Direct effects involve receptor-mediated signaling on peripheral immune cells, whereas indirect effects arise from central activation of the hypothalamic-pituitary-adrenal axis (HPA axis) and modulation of autonomic nervous system activity [6, 9, 12, 13].

Direct cellular and cytokine-mediated effects

Direct opioid signaling in immune cells suppresses key effector functions. Morphine has been shown to suppress NK cell activity, impair macrophage phagocytic function, and inhibit lymphocyte proliferation, thereby weakening the host's initial immune defense mechanisms [1, 6, 13].

Upon activation, opioid receptors modulate intracellular signaling cascades involving adenylate cyclase, cAMP, mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF-κB), which are pivotal in regulating immune gene expression. Additionally, opioids influence cytokine production, typically downregulating pro-inflammatory cytokines such as interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ), while promoting anti-inflammatory mediators such as transforming growth factor-beta (TGF-β) and IL-10 [5, 13, 14]. This shift in cytokine profiles compromises pathogen clearance and may promote immune dysregulation [1, 5].

Indirect neuroendocrine and autonomic pathways

Opioids influence immune function indirectly through their actions on the CNS. By binding to opioid receptors expressed in the CNS, morphine activates the HPA axis, leading to the release of glucocorticoids and catecholamines, stress hormones with potent immunosuppressive properties [7, 13, 15, 16].

Glucocorticoid effects on immunity are complex: They suppress T helper type 1 (Th1)-mediated cellular immunity, promote T helper type 2 (Th2) responses, impair dendritic cell maturation, and expand IL-10-producing regulatory T cells [7, 17].

Morphine-induced activation of the sympathetic nervous system further suppresses immune function via catecholamines and various neuropeptides. Catecholamines inhibit NK cell activity and alter lymphocyte function [7]. Neuropeptides—such as substance P, somatostatin, and vasoactive intestinal peptide—bind to high-affinity receptors on lymphocytes, eliciting distinct immunomodulatory effects [18].

Although specific pathways remain under debate [6], the convergence of direct and indirect mechanisms accounts for the immunosuppressive phenotype observed with many opioids.

Opioid-mediated dysregulation of innate host defense

Innate immunity provides a rapid, non-specific barrier against invading pathogens. Opioids disrupt several key components of this first line of defense by engaging MORs expressed on various immune cells, including neutrophils, macrophages, mast cells, NK cells, and dendritic cells [1, 2, 4]. In macrophages, morphine has been shown to impair proliferation, reduce phagocytic capacity and migration, and diminish bactericidal activity, while neutrophil recruitment to the sites of bacterial infection is similarly inhibited [4, 12, 19].

Additionally, morphine reduces mast cell activation, leading to increased intestinal permeability and thereby facilitating microbial translocation and infection [4, 12, 19].

The impact of opioids on macrophages appears to be dose-dependent: At low to moderate doses, morphine impairs phagocytic capacity, whereas higher doses can trigger macrophage apoptosis via TLR9 signaling and activation of the p38-MAPK pathway [4].

Collectively, these disruptions weaken the innate immune competence and heighten susceptibility to a broad spectrum of pathogens, including HIV, hepatitis C, and influenza [6, 20]. The cumulative effect is a compromised first-line defense that leaves the opioid-exposed host more vulnerable to both acute and chronic infections.

Opioid modulation of adaptive immunity

The adaptive immune system orchestrates highly specific responses and immunological memory through coordinated interactions among T cells, B cells, and antigen-presenting cells (APCs) such as macrophages and dendritic cells. Within this network, opioids exert complex and predominantly suppressive effects.

Chronic opioid use has been associated with impaired T- and B-cell function, including reduced T helper cell proliferation and diminished antibody production by B cells [1, 6]. Opioid exposure has also been shown to alter T-cell differentiation and to impair memory T-cell formation, further weakening adaptive defense mechanisms [2, 4, 20].

Morphine, in particular, has been found to decrease the expression of major histocompatibility complex class II (MHC-II) molecules on B cells by approximately 33%. This reduction constrains antigen

presentation, thereby impairing T-cell activation and the coordination of the adaptive immune response [19]. These effects are believed to be partly mediated through activation of the HPA axis and the sympathetic nervous system, which elevate corticosteroid levels—known potent mediators of immunosuppression [21, 22].

At the cytokine level, morphine promotes an anti-inflammatory milieu characterized by increased TGF-β and IL-10 and reduced IL-2, IL-1β, TNF-α, and IFN-γ [23].

Concurrently, it skews T helper differentiation toward a Th2 phenotype, favoring humoral immunity while attenuating Th1-mediated cellular immune responses [24].

Although advantageous in certain contexts (e.g., parasitic defense and allergy), this Th2 bias compromises host resistance to intracellular pathogens, including viruses and many bacteria [24].

Together, these effects illustrate how opioids, particularly when used chronically, can undermine the adaptive immune system's capacity to respond effectively to infections, vaccines, and other immunological challenges.

Variability in the immunomodulatory profiles of opioids

Opioids display significant heterogeneity in their immunological effects, raising important clinical considerations. Their net impact reflects a balance between direct, intrinsic immunomodulatory properties and indirect effects via analgesia and attenuation of neuroendocrine stress responses. Morphine, widely regarded as the "reference molecule" in opioid-immune and pain management research, consistently demonstrates potent immunosuppressive effects [25], a profile not uniformly shared across the class.

The degree of immunosuppression correlates closely with MOR activity, a central mediator of opioid-induced immune suppression.

Potent MOR agonists—such as morphine, fentanyl, and methadone—tend to exhibit more pronounced immunosuppressive effects. In contrast, agents like oxycodone, buprenorphine, tramadol, and oxymorphone show minimal immunosuppressive activity, and in some cases, may even exert immunostimulatory effects [7, 25, 26]. Enhanced penetration across the blood-brain barrier by morphine, fentanyl, and methadone may further amplify centrally mediated immunosuppressive pathways [27].

Biased (functionally selective) signaling at the MOR offers additional mechanistic insight. Different opioids, while binding the same receptor, differentially favor G-protein- versus β-arrestin-dominated pathways, leading to distinct downstream signaling programs and immune outcomes [28].

Overall, opioids exhibit agent-specific immunomodulatory signatures shaped by MOR activity, CNS penetration, and biased signaling, spanning a continuum from immunosuppression to relative immune preservation or, in some cases, immunostimulation (Table 1).

Morphine

Morphine is a prototypical immunosuppressive opioid, affecting both innate and adaptive arms of immunity [1, 6, 12, 25]. It promotes microbial translocation and inflammatory injury within the gastrointestinal tract, further exacerbating systemic immune dysfunction [13].

In a retrospective study on patients with cancer receiving either morphine or oxycodone, infections occurred significantly more often in the morphine-treated group. Acknowledging the study limitations, the authors proposed that morphine's immunosuppressive profile may contribute to heightened infection risk in this population [29]. These findings align with broader evidence that morphine suppresses key cellular components of innate and adaptive immunity and is associated with increased risk of postoperative complications [12, 13, 27].

The effect of morphine on tumor biology is complex and context-dependent. In some preclinical models, morphine can enhance tumor proliferation, invasiveness, and angiogenesis, potentially facilitating tumor progression under certain conditions. Conversely, other studies show that morphine can induce

Table 1. Differential immunomodulatory effects of commonly used opioids in humans and translational models.

Opioid	Predominant immune profile*	Relative direction/magnitude	Reported immune effects (human/translational)	Mechanistic considerations
Morphine	Immunosuppressive	Moderate–strong	↓ NK cell activity; ↓ T-cell proliferation; Impaired macrophage function	Strong MOR agonism; HPA axis activation; High CNS penetration
Fentanyl	Immunosuppressive	Moderate	↓ NK cell cytotoxicity; Reduced lymphocyte responsiveness	Potent MOR agonist; Central pathways
Methadone	Immunosuppressive	Mild–moderate	Modest reduction in NK cell activity	Long-acting MOR agonist; Central effects
Oxycodone	Minimally immunosuppressive	Mild and transient	Limited or transient suppression of cellular immunity	MOR agonist with lower immunosuppressive profile
Tramadol	Immune-preserving/potentially immunostimulatory	Mild enhancement	↑ NK cell activity; ↑ IL-2; Preserved T-cell responses	Weak MOR agonist; SNRI activity
Buprenorphine	Immune-preserving	Neutral	Preserved NK and T-cell function	Partial MOR agonist; κ-antagonism; Biased signaling

↓: decrease; ↑: increase; NK: natural killer; MOR: mu-opioid receptor; HPA axis: hypothalamic-pituitary-adrenal axis; CNS: central nervous system; IL-2: interleukin-2; SNRI: serotonin-norepinephrine reuptake inhibitor. *: Immune effect profiles are derived primarily from human observational and perioperative studies, supported by translational and mechanistic data. The magnitude and causality of opioid-induced immune modulation in humans remain incompletely defined. Key references [7, 25, 26, 27].

apoptosis and inhibit angiogenesis, indicating possible tumor-inhibitory effects. These divergent outcomes, shaped by cancer type, dose, timing, and experimental conditions, preclude a unified conclusion regarding morphine's net impact on tumor growth [27].

Fentanyl

Fentanyl appears to share many of morphine's immunosuppressive properties, though its profile is less extensively studied. Available data support dose-dependent suppression of NK cell activity, lymphocyte multiplication, and cytokine release [6, 25]. In animal models, chronic fentanyl administration is associated with the development of tolerance not only to analgesia but also to its immunosuppressive effects. Notably, tolerance to immunosuppression may emerge earlier than tolerance to analgesia, both outcomes being influenced by the dose and duration of exposure.

Human studies, largely in perioperative cohorts or healthy volunteers, similarly report reductions in NK cell activity and levels, diminished $CD8^+$ cytotoxic T cells, and decreased cytokine production [25, 30].

By contrast, patients with cancer pain or individuals using fentanyl illicitly remain underrepresented in current research. Robust, long-term studies in these populations are needed to clarify fentanyl's sustained immunological consequences.

Oxycodone

Oxycodone is a semi-synthetic opioid and a relatively selective full MOR agonist, with moderate-to-high MOR affinity—though lower than that of morphine and fentanyl—and weaker binding to DORs and KORs. Oxycodone and its active metabolite, oxymorphone, readily cross the blood-brain barrier, exerting direct effects on CNS. Despite extensive clinical use, the immunological profile of oxycodone is not fully delineated.

Animal studies suggest that oxycodone is less immunosuppressive than morphine [25]. In male mice, repeated oxycodone administration has been reported to suppress immune function while upregulating TLR4 and NF-κB mRNA expression in T cells, suggesting potential pro-inflammatory and/or

immunosuppressive effects that may depend on dose and exposure duration [31].

In human studies, oxycodone has been associated with milder and more transient immunosuppressive effects compared with morphine and fentanyl [25, 29].

Overall, current evidence suggests that oxycodone may have a comparatively favorable immunomodulatory profile among commonly used MOR agonists, although further research is needed to fully define its immune effects.

Methadone

Methadone is a synthetic opioid with a multifaceted pharmacology: It functions primarily as a MOR agonist, with weaker activity at KOR and DOR, and additionally acts as a weak N-methyl-D-aspartate (NMDA) receptor antagonist. This NMDA component may influence both analgesia and tolerance development.

Animal and human studies indicate that methadone exerts mild immunosuppressive effects, including reduced NK cell activity, impaired macrophage function, and diminished antibody production—generally less pronounced than with morphine or fentanyl. Much of the clinical immunomodulatory effects of methadone have been examined in the context of opioid use disorder (OUD) maintenance therapy.

In heroin-dependent individuals, methadone-assisted detoxification has been shown to restore aspects of cellular immunity compromised by chronic heroin use. Dendritic cell populations (myeloid and plasmacytoid subsets) and Human leukocyte antigen-DR isotype (HLA-DR) expression, which are significantly reduced in these individuals, partially recover following methadone treatment [32].

Overall, multiple studies report improvements in immune function among individuals on methadone maintenance therapy. However, it remains uncertain to what extent these benefits are attributable to direct pharmacologic effects of methadone versus broader health gains associated with cessation of illicit opioid use [25].

Buprenorphine

Buprenorphine displays a unique and complex receptor profile, acting as a high-affinity partial MOR agonist, a partial agonist/antagonist at KOR, an antagonist at DOR, and a weak partial NOR agonist. This receptor diversity likely underpins its distinct pharmacological and immunological effects.

Buprenorphine generally exhibits minimal immunosuppressive activity.

Several studies report neutral or even protective, immunostimulatory effects, suggesting potential advantages in immunocompromised settings. In animal studies, buprenorphine—unlike morphine and fentanyl—did not impair NK cell, T cell, or macrophage function [25].

In clinical settings, individuals with OUD maintained on buprenorphine show significant improvements in immune markers following the initiation of treatment. Existing research suggests that opioid-induced peripheral immune suppression may be reversible with buprenorphine therapy [33]. These observations raise the possibility that buprenorphine not only avoids further immune compromise but may contribute to restoration of immune homeostasis.

To date, converging preclinical and clinical evidence suggests that buprenorphine has little to no detrimental impact on immune function, positioning it as a particularly attractive option for analgesia and maintenance therapy when immune preservation is a priority [25, 34, 35]

Tramadol

Tramadol is a centrally acting analgesic with a dual mechanism of action: weak MOR agonism and inhibition of serotonin and norepinephrine reuptake. Its main active metabolite, O-desmethyltramadol (M1), displays higher MOR affinity than the parent compound. This combined opioid and monoaminergic activity shapes a distinct immunomodulatory profile compared with conventional MOR agonists.

Animal and human studies indicate that tramadol and M1 exert minimal immunosuppressive effects—significantly less than those observed with morphine [26]. In fact, data suggest that tramadol may enhance

certain immune functions under specific conditions, including increased NK cell cytotoxicity, augmented phagocytosis, enhanced lymphocyte proliferation, and elevated IL-2 production. These immunostimulatory actions are largely attributed to tramadol's serotonergic properties, consistent with broader evidence that serotonin and norepinephrine play important roles in immune regulation [14, 25, 26, 36].

Multiple preclinical and clinical comparisons demonstrate that tramadol preserves immune function, often in direct contrast to other opioids, particularly morphine [26]. In perioperative settings, tramadol has been shown to counteract surgery-induced suppression of NK cell activity and lymphocyte proliferation, suggesting a protective role during acute physiological stress [37].

Tramadol's minimal or absent immunosuppressive effects likely reflect its low MOR affinity. Its capacity to preserve—or even stimulate—immune responses makes it a compelling analgesic choice in clinical scenarios where maintaining immune competence is critical.

Clinical implications of opioid-induced immunosuppression

The clinical significance of opioid-induced immunosuppression remains frequently under-recognized and incompletely understood, despite growing evidence of its relevance across a range of medical settings. In immunocompetent individuals, opioid-associated immune alterations may be transient and clinically negligible; however, in patients with pre-existing immune dysfunction, these effects can contribute to substantial morbidity.

In routine practice, potential immunologic consequences of opioid therapy are seldom integrated into clinical decision-making. Pain management protocols typically prioritize analgesic efficacy and tolerability, with limited consideration of baseline immune status or the comparative immunosuppressive properties of specific opioids. This gap in clinical awareness likely reflects the lack of definitive high-quality human studies, as much of the existing data is derived from preclinical models or observational studies with inherent confounding factors. Nevertheless, the cumulative evidence supports a more nuanced approach to opioid prescribing, particularly in immunocompromised or critically ill populations, where opioid choice, dose, and duration may meaningfully influence outcomes.

Susceptibility to infections

The interaction between opioid use, immune dysregulation, and infection gained heightened attention in the 1980s, when the concurrent epidemics of heroin use and HIV/AIDS were accompanied by high rates of opportunistic infections. In this setting, overlapping drivers of immune impairment—including HIV infection, chronic opioid use, and recurrent infections—created a synergistic vulnerability associated with worse clinical outcomes and increased mortality.

In humans, prolonged opioid use has been linked to an increased incidence of a wide range of infections, including bacterial skin and soft tissue infections, respiratory and urinary tract infections, as well as endovascular and musculoskeletal infections [1, 4, 6, 11, 38]. The risk is particularly elevated among intravenous opioid users, where both pharmacologically induced immunosuppression and non-sterile injection practices contribute to heightened vulnerability. In the context of HIV-1 (Human Immunodeficiency Virus type 1) infection, opioids appear to further potentiate immune dysfunction, exacerbating HIV-1 pathogenesis and increasing susceptibility to additional opportunistic viral and bacterial infections [39].

Studies in hospitalized patients with sepsis have shown that chronic opioid use is associated with increased mortality compared to opioid-naive individuals [40, 41]. Premorbid opioid therapy has been independently associated with reduced survival following ICU admission [40]. Consistent with experimental and clinical data on opioid-associated immunosuppression, patients receiving long-term opioid therapy demonstrate a higher incidence of positive microbiological cultures across gram-positive, gram-negative, and fungal pathogens. Additionally, chronic opioid use is known to compromise intestinal barrier function, promoting bacterial translocation and systemic infection [41].

Collectively, these findings suggest that chronic opioid use prior to critical illness may weaken host defenses and increase susceptibility to infection, thereby worsening clinical outcomes.

A retrospective ten-year cohort analysis demonstrated that initiation of long-acting opioids with known immunosuppressive properties (e.g., morphine, fentanyl, and methadone) was associated with higher infection rates among hospitalized patients, with the greatest risk observed within the first 30 days of therapy [42].

Additional insight into opioid-induced immune disruption comes from patients with inflammatory bowel disease (IBD). In this population, prolonged opioid administration has been associated with gut microbiome dysbiosis, characterized by pathogenic bacterial overgrowth and enhanced microbial translocation. These changes disrupt immune homeostasis, propagate chronic inflammation, and may contribute to systemic infectious complications [13, 43].

In conclusion, these observations underscore the need to systematically assess infection risk when considering long-term opioid therapy, especially in patients with pre-existing immune compromise, gastrointestinal pathology, or critical illness, where even modest immune perturbations can precipitate serious—and potentially fatal—infectious events.

Cancer progression

Patients with malignancy represent a particularly vulnerable group in whom opioid-induced immunosuppression may influence disease trajectory. Although opioids remain essential for the management of cancer-related pain, their potential to impair anti-tumor immunity has become a growing concern, especially as immunotherapies become increasingly important in cancer treatment.

In addition to immunomodulation via the MOR, opioids can activate TLR4 and trigger pro-inflammatory signaling cascades. These dual and sometimes opposing actions highlight the complex, bidirectional nature of opioid-immune interactions.

In vitro data indicate that exposure of human NK cells to various opioids can suppress their cytotoxic activity against leukemia cell targets, though the magnitude of this effect differs across agents [12]. Notably, fentanyl, M1, and [D-Pen^2, D-Pen^5] enkephalin did not impair NK cell function in these models. Beyond sparing NK function in vitro, fentanyl has been reported to inhibit invasion and progression of human colorectal cancer cells, likely via downregulation of miR-182 and MMP-9 expression through β-catenin signaling pathways [44, 45].

The suppression of NK cell function observed with other opioids appears to be mediated primarily through MOR and KOR. Buprenorphine, methadone, and tramadol have all been implicated in NK cell inhibition [30]. This direct suppression of NK activity, in conjunction with additional indirect mechanisms, may contribute to the association between perioperative opioid exposure and increased cancer recurrence [30, 44].

Preclinical models further support the potential for opioids to influence tumor biology. Animal studies have shown that morphine can promote tumor neovascularization, growth, and metastasis [6, 13, 27]. In a transgenic mouse model of breast cancer, Nguyen et al. [46] reported that opioids enhanced tumor progression when administered after tumor establishment, whereas pre-tumor exposure did not have the same effect, suggesting that timing and disease stage may modulate opioid-tumor interactions.

Human data regarding opioid use and cancer risk or progression remain mixed and are confounded by underlying indications for opioid therapy.

A 2022 cohort study using propensity score matching and multivariate Cox regression analysis found that long-term opioid use was associated with an increased risk of several malignancies, including gastric, breast, colorectal, prostate, ovarian, pancreatic, lung, head and neck, esophageal, and liver cancers [47]. The authors proposed several potential mechanisms—immune dysregulation, post-opioid chromosomal damage, enhanced neovascularization and angiogenesis, pharmacologic interactions with carcinogens, and organ dysfunction leading to prolonged carcinogen exposure—but emphasized the need for confirmatory studies.

Emerging evidence suggests that opioids may facilitate cancer progression less through direct oncogenic effects and more by suppressing immune surveillance and promoting angiogenesis [12, 13, 20]. Through MOR- and TLR4-mediated pathways, opioids modulate immune and inflammatory responses, suppress NK cell activity, alter T- and B- cell function, reduce antibody production, and dampen cytokine release. This broad immunosuppression may compromise the host's capacity to mount an effective anti-tumor response and reduce micrometastatic expansion, potentially impacting disease progression and the effectiveness of immunotherapies [2, 15, 25, 30]. Ultimately, opioid-associated effects on cancer outcomes may be driven predominantly by alterations in host immunity rather than direct tumor cell targeting [15].

Cancer patients often exist in a state of fragile immune equilibrium. Opioid therapy is only one of many factors that influence this balance. The malignancy itself, cancer treatments, organ dysfunction, malnutrition, pain, and psychological stress all contribute to immune compromise. Uncontrolled pain and suffering can independently impair immune function and overall health, and may in some cases be more detrimental than the immunologic effects of appropriately used opioids [48].

These considerations underscore the importance of carefully balancing effective pain control with the potential risks of opioid-induced immune modulation, particularly in patients receiving immunotherapies or undergoing curative-intent treatment. Striking this balance should remain a central focus in comprehensive oncologic care.

Impact on surgical outcomes

In patients undergoing major surgery, immune competence is challenged by both the underlying disease process and the physiological stress of the operative procedure. Pain itself, together with immune-modulating mediators released at the site of tissue injury, further destabilizes this fragile immunologic balance [11, 35]. Opioids are routinely administered for perioperative analgesia; however, their immunosuppressive effects may exacerbate immune dysfunction during this critical period.

Data from animal and human investigations indicate that both acute and chronic opioid administration can suppress NK cell activity, inhibit lymphocyte proliferation, and attenuate cytokine production—effects that may impair wound healing and increase the risk of postoperative infection [2, 11, 35]. Observational clinical studies further associate chronic preoperative opioid use with higher rates of postoperative infections, including pneumonia and serious surgical site or deep organ/space infections [4].

These concerns are amplified in oncologic surgery, where immune competence plays a pivotal role in controlling residual disease and limiting metastatic dissemination. Patients with preexisting immune compromise—such as those with chronic systemic illnesses, malnutrition, or concurrent immunosuppressive therapies—may be particularly susceptible to complications, prolonged recovery, and worsening of overall prognosis when exposed to immunosuppressive doses of opioids.

Given the converging immunosuppressive effects of surgery, pain, and opioid administration, careful evaluation of analgesic strategies is essential in high-risk surgical populations. Multimodal analgesia, incorporating non-opioid pharmacologic agents, regional anesthesia techniques, and non-pharmacologic modalities, can reduce systemic opioid requirements and may help preserve perioperative immune function.

Implications for transplant recipients

Transplant recipients, who rely on a tightly calibrated immunosuppression to maintain graft function while preserving host defense, represent a population in whom additional opioid-induced immune modulation may be particularly consequential. Direct data in this group remain limited, but insights can be extrapolated from perioperative, oncology, and critical care literature.

Preclinical and clinical studies show that morphine can markedly depress NK cell activity and inhibit T-cell proliferation—processes that are central to both immune surveillance and graft tolerance. Opioid-induced suppression of NK cells, macrophages, and T cells, along with inhibition of key cytokines, has been implicated in delayed graft acceptance, diminished graft survival, and increased infection risk, ultimately contributing to higher morbidity and mortality [49, 50].

These effects are especially concerning in solid organ transplant (SOT) recipients, where any additional immune perturbation can shift the balance toward either rejection or uncontrolled infection.

A systematic review of opioid use in SOT recipients and living donors identified chronic pre-transplant opioid use as an independent predictor of adverse post-transplant outcomes, including increased risk of graft loss and death [49]. Although mechanistic pathways were not delineated in that review, other studies suggest that opioid-induced reductions in NK cell numbers and activity may predispose to infections and post-transplant malignancies [50]. Infection remains a leading cause of death among SOT patients [51], and a recent study by Søborg et al. [52] reported that infectious complications were the most frequent cause of death during the first year after transplantation. Opioid-associated impairment of gut barrier integrity, neutrophil dysfunction, and cytokine suppression further heighten vulnerability to opportunistic infections in this context.

For transplant recipients, whose management depends on maintaining an optimal equilibrium between immunosuppression and host defense, opioid therapy has the potential to shift this balance toward harmful immune suppression. Judicious opioid use, preference for agents with more favorable immunologic profiles when feasible, and integration of multimodal analgesic strategies may help mitigate these risks.

Implications for opioid tolerance

Opioid tolerance arises from interconnected processes within the CNS and the peripheral immune system. Although the mechanistic landscape is complex and not yet fully understood, opioid-induced neuroinflammation—shaped by dynamic crosstalk between central and peripheral immune signals—has emerged as a key contributor [9].

Within the CNS, opioids activate glial cells, particularly microglia and astrocytes, via MOR as well as pattern recognition receptors such as TLR4. TLRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). TLR4, in particular, detects endotoxins like lipopolysaccharide (LPS) and activates pro-inflammatory signaling cascades that overlap with IL-1β pathways [53, 54].

Opioid-mediated MOR activation can potentiate glial responses to LPS, amplifying neuroinflammation. The resulting release of inflammatory mediators sensitizes nociceptive neurons, increases their excitability, diminishes opioid analgesic efficacy, accelerates tolerance, and may promote opioid-induced hyperalgesia. In a self-augmentation pattern, injured or sensitized neurons release signals that further activate glial cells and perpetuate neuroinflammatory cascades [9]. At the receptor level, tolerance is driven by MOR desensitization and downregulation, engagement of β-arrestins and regulators of G-protein signaling (RGS) proteins, and compensatory upregulation of excitatory neurotransmission, including NMDA/glutamate pathways.

While CNS glial cells are central to these processes, the role of the peripheral immune system in initiating and sustaining central immune signaling is increasingly recognized. Peripheral inflammatory signals can access the CNS via circulating cytokines and immune-derived mediators, including blood-borne IL-1β-containing vesicles and neutrophil-derived microparticles, which in turn activate microglia and reinforce neuroinflammation [9, 55, 56].

Peripherally, opioid-induced immunosuppression predominates; however, the net immune effect can differ by drug, dose, and exposure duration, and pro-inflammatory actions have been observed under specific conditions.

Given this intricate bidirectional communication, strategies to mitigate opioid tolerance may benefit from targeting both central and peripheral immune mechanisms. Potential approaches include inhibition of TLR4 signaling, blockade of pro-inflammatory cytokines such as TNF-α and IL-1β, and modulation of peripheral immune pathways that drive CNS glial activation.

Strategies to mitigate opioid-induced immunosuppression

The mechanistic basis of opioid-induced immunosuppression in humans remains incompletely understood. Both short-term and prolonged opioid exposure have been shown to impair immune function in healthy individuals and in those with underlying immune compromise. Reducing opioid-related immunologic impact is particularly critical in patients with heightened baseline vulnerability, such as those with malignancy, critical illness, or post-transplant immunosuppression. Several established pain-management strategies may confer immunologic benefits by minimizing opioid exposure or shifting toward agents with more favorable immune profiles.

Opioid rotation and tapering are core components of contemporary analgesic practice. Transitioning from strongly immunosuppressive opioids to agents with comparatively lower immunomodulatory potential, such as buprenorphine or tramadol, may help attenuate immune impairment while maintaining acceptable analgesia. Gradual dose reduction, where clinically feasible, may further limit immune disruption.

Peripherally acting opioid antagonists represent another, less commonly employed strategy. Agents such as methylnaltrexone and alvimopan selectively block peripheral opioid receptors without compromising central analgesia. Although these drugs were originally developed to treat opioid-induced bowel dysfunction and postoperative ileus, emerging evidence suggests that they may also mitigate peripheral immunosuppressive signaling by blocking opioid actions on immune cells and gut-associated lymphoid tissues [6, 13].

Multimodal analgesia—integrating non-opioid medications, regional anesthesia, physical therapy, and non-pharmacologic approaches—has become standard in many perioperative and chronic pain settings and can substantially decrease opioid requirements. In immunocompromised patients, additional supportive measures such as prophylactic vaccinations, immunostimulatory therapies, optimized nutritional support, and probiotic supplementation may further reinforce host defense and partially counterbalance opioid-related immune effects [13, 20].

Collectively, these approaches emphasize the importance of individualized, integrative pain management strategies that seek to preserve immune function while maintaining adequate analgesia, particularly in high-risk patient populations.

Future directions and research needs

Further research is needed to delineate the dose-, duration-, and agent-specific immunologic effects of opioids, to identify high-risk patient populations, and to establish evidence-based prescribing guidelines that incorporate immune considerations. Characterizing genetic and environmental determinants of opioid responsiveness—spanning both analgesic efficacy and immunologic impact—will be central to developing more personalized and effective treatment strategies.

Emerging data highlights the potential of artificial intelligence (AI) as an adjunct to clinical judgment in predicting individualized opioid requirements based on patient-specific factors such as age, weight, medical history, and type of surgery [57]. Such tools may help optimize dosing, minimize unnecessary exposure, and indirectly mitigate immune consequences. Large-scale epidemiological studies and prospective clinical trials are also needed to translate experimental findings into real-world clinical practice [6].

Another emerging area of interest involves the interaction among opioid use, gut microbiome alterations, and systemic immune function [13]. Opioid-induced dysbiosis may represent a key intermediary between pharmacologic exposure and immune outcomes, with implications for infection risk, inflammatory disease, and possibly cancer progression.

Significant efforts are underway to design novel opioid molecules that retain robust analgesic efficacy while minimizing immunosuppressive and other adverse effects. Two promising avenues are biased ligands and peripherally restricted opioids. Biased ligands, particularly G protein-biased MOR agonists, selectively activate analgesic signaling while limiting β-arrestin-mediated pathways, which have been implicated in

respiratory depression and may contribute to immune suppression. Peripherally restricted opioids are engineered to act predominantly on peripheral MORs without crossing the blood-brain barrier, thereby reducing central side effects and potentially limiting systemic immunomodulation [58, 59].

Ultimately, integrating immunologic considerations into analgesic research and clinical practice has the potential to improve patient outcomes and accelerate the development of safer, more targeted opioid and non-opioid analgesic therapies.

Conclusions

Opioid-induced immunomodulation is multifaceted, clinically relevant, and heterogeneous across different agents and clinical contexts. While opioids remain essential for pain management, an expanding body of evidence underscores the importance of recognizing and addressing their potential to impair immune function.

Individualized opioid prescribing that explicitly considers immunologic status—particularly in patients with chronic disease, those undergoing major surgery, or individuals receiving immunosuppressive therapies—may help mitigate adverse outcomes. Incorporating multimodal analgesia, selecting agents with more favorable immune profiles when appropriate, and closely monitoring high-risk patients are key components of this approach.

Ongoing translational research, rigorously designed clinical studies, and sustained clinical vigilance will be essential to refine therapeutic strategies, guide rational opioid use, and improve outcomes for patients whose immune function is already compromised or at risk.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

cAMP: cyclic adenosine monophosphate

CNS: central nervous system

DOR: delta-opioid receptor

HIV: Human Immunodeficiency Virus

HIV-1: Human Immunodeficiency Virus type 1

HPA axis: hypothalamic-pituitary-adrenal axis

ICU: intensive care unit

IFN-γ: interferon gamma

IL: interleukin

KOR: kappa-opioid receptor

LPS: lipopolysaccharide

M1: O-desmethyltramadol

MAPK: mitogen-activated protein kinase

MOR: mu-opioid receptor

MORKO: mu-opioid receptor knockout

mRNA: messenger ribonucleic acid

NF-κB: nuclear factor kappa B

NK: natural killer

NMDA: N-methyl-D-aspartate

NOR: nociceptin/orphanin FQ receptors

OUD: opioid use disorder

SOT: solid organ transplant

TGF-β: transforming growth factor-beta

Th1: T helper type 1

Th2: T helper type 2

TLR4: Toll-like receptor 4

TNF-α: tumor necrosis factor alpha

ZOR: zeta-opioid receptor

Declarations

Author contributions

LDV: Conceptualization, Writing—original draft, Writing—review & editing, Visualization, Supervision. TL: Writing—original draft, Writing—review & editing, Visualization. FAL: Writing—original draft. SM: Writing—original draft. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

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