Advances in the Therapeutic Effects of Ketamine on Cancer Pain Related Depression

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Abstract

Pain is a prevalent and significant adverse effect experienced by individuals diagnosed with cancer. Cancer patients with anxiety and depression can serve to exacerbate their pain. Cancer pain-related depression (CPD) is defined as a depressive state caused by the presence of ongoing cancer-related pain. CPD represents a significant physical and mental health burden for patients.

In clinical settings, ketamine has been shown to be an effective medication for cancer pain and depression. Ketamine has been shown to produce significant improvements in late-stage cancer pain and depression. This article reviews the development of ketamine in the treatment of cancer pain and depression, presents case reports of ketamine-assisted opioid therapy for CPD, and discusses related reports of adverse effects and immunoregulatory effects of ketamine, as well as its impact on tumor recurrence.

Keywords

Ketamine, Cancer pain, Depression, Ketamine infusion, Pain therapy

Introduction

About 19.3 million new cancer cases and almost 10.0 million deaths from cancer occurred in 2020 worldwide [1]. The growth of cancer is attributed to the aging population and the development of cancer screening technologies. Psychological factors such as depression play an important role in the development and prognosis of tumors. In clinical oncology, it is essential to diagnose and treat depression in cancer patients at an early stage [2,3].

Cancer-related depression (CRD) refers to a pathological depressive state or syndrome along with diagnosing and treating malignant tumors, making it one of the most common adverse emotions among cancer patients [4]. After diagnosis, cancer patients face the integration of multiple treatment modalities and bear greater psychological distress and anxiety during the transition between treatment approaches [5]. The psychological state of anxiety and depression, coupled with a negative attitude toward treatment, can lead to cancer progression or recurrence, which negatively affects treatment outcomes, prognosis, and overall quality of life [4].

Review of Research on the Comorbidities of Depression and Cancer

Tumors can cause patients to become depressed and subsequently develop depression. Conversely, depression can lead to the onset, development, recurrence, and metastasis of tumors. The two are interrelated and inseparable [5].

Increased incidence of depression in people with cancer

Cancer can increase the likelihood of depression in two ways. First, the occurrence of depression is associated with the abnormal immune dysfunction and disruption of the neuroendocrine system during the onset of cancer, which is accompanied by strong psychological reactions caused by severe diagnostic results and deteriorating physical conditions [5,6]. Second, cancer pain and toxic side effects caused by long-term radiotherapy, chemotherapy and immunotherapy can also lead to the onset and even worsening of depression in cancer patients [7].

Depression may increase cancer incidence

Depression-induced dysfunction of the HPA axis affects the immune status of cancer patients through neuroendocrine immune regulation [8,9].

Second, patients with depression have higher levels of inflammatory factors than the general population. Over time, these inflammatory factors can stimulate the body and damage cellular DNA, leading to mutations

and tumors [10,11]. The above evidence suggests that depression may affect tumor incidence and prognosis in cancer patients through neuroendocrine dysfunction and decreased immune function.

Third, research shows that breast cancer patients with depression are more prone to tumor recurrence [12]. Due to the interaction between depression and cancer, the treatment of CRD is crucial for the comprehensive management of malignant tumors.

Research on Cancer Pain and Depression

Comorbidity of cancer pain and depression

Hoos, et al. first reported that cancer patients suffer from pain-induced depression. The pain-induced depression will affect the effectiveness of analgesic treatment [13,14]. Kai hoi Sze, et al. found in a survey of 1721 cancer patients that 60% of them had pain symptoms, anxiety, depression, and a significant positive correlation with physical pain [15]. Zabora, et al. [16] found that CRD can shorten the survival time of cancer patients by 10% to 20%. Stommel, et al. [17] analyzed 871 cancer patients and found that patients with depression were more likely to die within 19 months compared to patients without depression. Therefore, it is believed that the prognosis of cancer patients can be assessed based on the degree of depression.

The above research suggests that depression is an adverse complication in cancer patients, and the reasons for its occurrence may include: (1) Cancer is a significant psychological stimulus for patients. When patients know the diagnosis of cancer, they immediately experience fear and sadness after initially denying it, and cannot accept the fact that they will give up their loved ones and leave this world forever; (2) Worry about the excessive economic burden caused by the disease; (3) Uncontrollable pain may also lead to anxiety and depression in patients; (4) When patients lack understanding of their own condition and hope for early diagnosis, they may also experience anxiety and depression; (5) Patients have more anxiety after learning that they have cancer, and the incidence of anxiety and depression is higher; (6) Some unbearable examinations and treatment procedures may also aggravate depression. Therefore, good pain relief and appropriate psychological or antidepressant treatment are of great importance for cancer patients [18].

A randomized controlled trial published in 2004 showed that pain levels might predict the onset of depression [19,20]. Depression is one of the most common mental illnesses caused by cancer and is often misdiagnosed [18]. Depression and pain typically co-occur in patients [21,22]. It is also reasonable to assume that the impact of cancer pain on quality of life and treatment outcomes is related to comorbid depression.

Given our understanding of the common central pathways and neuropharmacology of pain, depression, and anxiety, it seems reasonable to conclude that they are closely related [18].

Cancer pain related depression

The new concept of cancer pain related depression: Cancer pain-related depression (CPD) refers to a depressive state caused by persistent cancer-related pain. CPD not only imposes a great physical burden on patients, but also seriously affects their mental health. Persistent pain not only makes patients physically uncomfortable, but can also cause or exacerbate psychological symptoms such as depression, significantly reducing their quality of life. CPD not only interferes with patients' daily life and social activities, but can also interfere with the effectiveness of cancer treatment.

The diagnosis of CPD requires a combination of symptom presentation, medical history, assessment tools, and clinical examination. It must also be differentiated from common depressive disorders, medication side effects, and other mental and physical illnesses. Effective cancer pain management and psychological intervention are important to alleviate depression and improve patients' quality of life. Through interdisciplinary collaboration, clinicians can better identify and treat cancer-related depression and improve patients' overall health status.

Preliminary recommendations for the diagnostic basis of CPD

1) Symptoms of depression: Patients experience symptoms of depression such as low mood, loss of interest, worthlessness, fatigue, difficulty concentrating, and sleep disturbance during cancer pain [23,24]. These symptoms persist for at least two weeks and significantly interfere with the patient's daily life and functioning.

2) Medical history: Understand the patient's cancer type, course, level of pain, and impact on daily life. Cancer and its treatments (such as chemotherapy and radiation) are often associated with severe pain, which can be an important trigger for depressive symptoms [25,26].

3) Assessment tools: (1) Depression-related assessment tools include the use of standardized depression assessment scales, such as the Beck Depression Inventory (BDI), Hamilton Depression Scale (HAMD), etc., to objectively evaluate the degree of depression in patients. These scales can help clinicians quantify patients' depressive symptoms as a diagnostic reference [23,24]: Numerical Rating Scale (NRS), Visual Analog Scale (VAS), Faces Pain Scale (FPS), Brief Pain Inventory (BPI), McGill Pain Questionnaire (MPQ),

and Pain Relief Scale (PRS) [25,26]. Common assessment scales for tumor patients include: ECOG Performance Status (Eastern Cooperative Oncology Group), Karnofsky Performance Status (KPS), FACT-G (Functional Assessment of Cancer Therapy-General), QLQ-C30 (Quality of Life Questionnaire Core 30), MDASI (MD Anderson Symptom Inventory), Brief Pain Inventory (BPI), NCCN Distress Thermometer [25,26].

4) Clinical examination: Neuroimaging (such as MRI, CT, etc.) and laboratory tests may be necessary to rule out other physical diseases that may cause depressive symptoms. In particular, it is necessary to exclude depressive symptoms caused by brain metastases, metabolic abnormalities, etc. [25,26].

5) Expert consensus and guidelines: Diagnose depression based on international and national diagnostic guidelines [23,24], combined with the special circumstances of cancer patients [25,26].

Differential Diagnosis of CPD

The purpose of differential diagnosis is to distinguish CPD from other possible causes of depressive symptoms, including the following situations:

1) General depressive disorder: The core features of general depressive disorder are symptoms of low mood, loss of interest, and worthlessness that may be accompanied by physical pain, but the pain is not the primary cause of the symptoms [23,24]. The depressive symptoms of cancer-related depression are often accompanied by persistent cancer pain, and pain is an important trigger for their depressive symptoms [25,26].

2) Drug side effects: Some cancer treatment drugs (such as steroids [27], interferons [28], etc.) may cause depressive symptoms. A detailed medication history and the temporal relationship between symptoms can help distinguish between drug-induced depressive symptoms and cancer-related depression.

3) Other mental illnesses (anxiety disorders [29], post-traumatic stress disorder (PTSD) [30], etc), may present with similar depressive symptoms. A thorough psychiatric evaluation can help distinguish these conditions from cancer-related depression.

4) Physical illnesses such as hypothyroidism [31], brain tumors [32], infections [33], etc. may cause symptoms similar to depression. Clinical and laboratory tests can rule out depressive symptoms caused by these physical illnesses.

In conclusion, cancer pain may lead to or aggravate depression, and depressive states make cancer pain difficult to control and may promote tumor progression. Therefore, active and effective control of cancer pain can help improve patients' quality of life, treatment compliance, and even, to some extent, patient prognosis. Therefore, effectively treating CPD can help improve cancer treatment efficacy, treatment compliance, and even, to some extent, patient prognosis.

Research has confirmed that pain and depression share many common regulatory mechanisms, and exploring the optimal treatment approach and plan for CPD is an urgent issue that clinicians need to address.

Research on Ketamine Reducing Cancer Pain and Depression

Basic introduction to the pharmacological mechanism of ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist: Low doses ketamine can produce analgesic effects, while high doses can produce anesthetic and potent analgesic effects. As an anesthetic, ketamine also have some adverse effects including pseudopsychotic symptoms, gastrointestinal reactions visual impairment, and dizziness [34].

NMDA receptors consist of two subunits, GluN2A and GluN2B. S-ketamine acts primarily on the GluN2A subunit to induce hypnosis and primarily on the GluN2B subunit as part of the analgesic process [35].

Ketamine can non-competitively antagonize NMDARs. It reduces the activity of calcium channels and Ca^{2+} influx which regulate pain sensitivity [35]. With repeated stimulation of spinal C-fibers, NMDA receptors increase spontaneous fiber activity and receptive fields [36-38].

Effects of ketamine on other receptors: S-ketamine can also activate opioid receptors. S-ketamine also blocks sodium channels, inhibits NO release, suppresses muscarinic acetylcholine receptors, stimulates the sympathetic nervous system, induces NA release, promotes endogenous opioid release, and activates opioid receptors. After binding to the receptor, it produces further analgesic effects [39,40].

In the experimental model, ketamine dose-dependently inhibits the expression of monoamine ketone transporters in human embryonic kidney cells [36]. Ketamine inhibits the uptake of catecholamines by neurons and the extracellular space, leading to a high adrenergic state and an increase in circulating norepinephrine concentration [35].

In addition, the dexmedetomidine is more effective than the traditional use of the benzodiazepine midazolam in reducing the cardiac stimulatory effects of ketamine and post-anesthesia delirium [36].

Activation of glutamate-independent pathways leads to an inward flow of Ca^{2+} and mobilization into the calcium pool. The increase in Ca^{2+} is concentrated in the cytoplasm of brain neurons, leading to the upregulation of dopamine and causing the adverse effects of pleasure and psychotropic drugs [41,42]. Ketamine can also act on cholinergic, nicotinic, and muscarinic receptors, thereby affecting the function of these receptors [36,43].

Progress of ketamine in cancer pain

The content of cancer pain includes somatic pain, visceral pain, neuropathic pain, sympathetic maintenance pain, inflammatory pain, etc [44]. Currently, there are conflicting reports on the treatment of cancer pain with ketamine. One meta-analysis suggests that ketamine may be a viable option for the treatment of refractory cancer pain [45].

However, there are also reports suggesting that ketamine is recommended as an adjuvant therapy for cancer pain relief in adult patients, and the quality of the evidence needs to be further investigated [46]. Currently, the main limitations of research in this area include the small number of included studies, small sample size, or inability to quantify the effects of ketamine.

Research progress on ketamine improving depression:

(1) NMDAR inhibition and AMPAR activation are the main pathways and mechanisms by which ketamine, its isomers and metabolites exert their antidepressant effects.

Although ketamine has shown strong clinical efficacy in the treatment of refractory depression. However, the underlying mechanisms remain unclear. It is currently believed that inhibition of NMDARs and activation of AMPARs are involved in ketamine-induced antidepressant effects [47]. There are also studies showing that the antidepressant effects of ketamine are related to BDNF/TrkB, mTORC1, and others [48,49]. Meanwhile, previous studies on hydroxydemethylamine and demethylamine have shown that they have antidepressant effects in rodents, mainly through the combined action of BDNF/TrkB. Inhibition of NMDAR and subsequent activation of AMPAR are the main pathways and mechanisms by which ketamine, its isomers and metabolites exert antidepressant effects [49].

In terms of antidepressant effects, ketamine can achieve disinhibition of glutamatergic neurons by blocking the NMDAR of inhibitory gamma-aminobutyric acid (GABA) neurons, leading to glutamate bursts and ultimately promoting synaptic protein synthesis and BDNF/TrkB release, resulting in antidepressant effects [50].

(2) Changes in metabolites in individuals treated with ketamine

Metabolomic biomarkers include metabolites from tissues, cells, and various body fluids. Metabolomics in treatment-resistant depression (TRD) has been shown to identify potential metabolite-based biomarkers for understanding the pathophysiology of the disease [51].

Previous investigators have examined metabolite changes in patients receiving ketamine/s-ketamine treatment and explored their relationship to ketamine response. The diagnosis of major depressive disorder (MDD) with suicidal tendency is associated with several metabolomic abnormalities. For example, plasma or serum metabolites (such as acylcarnitine, ATP, histidine, arginine, citrulline, kynurenine, and ornithine) are associated with abnormal oxidation and may serve as potential biomarkers for MDD [51-54]. The excessive activity of the HPA axis in MDD patients induces neuroendocrine-immune dysfunction, resulting in the secretion of glucocorticoids, which are important for energy balance in the body [55].

(3) Ketamine intervention alters synaptic plasticity

Similarly, ketamine has been shown to be effective in inducing long-term synaptic plasticity depressive behavior in several models, including chronic corticosterone (corticosterone) and repetitive constraint stress, anxiety disorders and PTSD, chronic pain, middle cerebral artery occlusion, and mild stress from chronic accidents [56-58].

The ketamine (2R, 6R) metabolite hydroxydemethyl-amine (2R, 6R-HNK) exhibits antidepressant activity and downstream sustained synaptic plasticity. Studies in mice [59,60], rats [61], and *in vitro* [62] have shown that 2R, 6R-HNK can maintain antidepressant efficacy and alter sustained synaptic plasticity [57].

To date, neurophysiological studies of ketamine and other RAADs have suggested a transient increase in postsynaptic membrane activity in glutamatergic neurons in the prefrontal cortex as the main possible mechanism. Whether selective inhibition of non-synaptic NMDARs can fully induce substantial synaptic reconstruction and enhance the efficacy of RAADs is still unknown.

(4) Ketamine alters cortical relations

Before/after ketamine administration, FC between bilateral thalamus and right middle frontal cortex (BA46) and between left thalamus and left anterior cingulate gyrus (BA8) is increased in patients. The FC between the right thalamus and the bilateral frontal poles (BA9) as well as between the right thalamus and the left paranasal gyrus (BA10) is reduced. However, after multiple comparisons, the above changes did not

show statistical differences. Therefore, further research is needed to determine whether the changes in thalamic cortical connectivity induced by this drug are related to its antidepressant and anti-suicidal effects [63].

Knocking out STEP 61 in the medial prefrontal cortex (mPFC) can lead to abnormal expression of pTyr1472NR2B inside and outside of synapses and STEP 61 in the striatum of chronically stressed animals. Ketamine can correct these abnormalities while rapidly combating depression [64].

Resting state electroencephalography during baseline and 0.44 mg/kg dose of ketamine in 30 MDD patients. Use of a dynamic causal model to assess connectivity between the frontal and parietal lobes to fit the thalamic cortex model to the hierarchical connectivity nodes of the medial prefrontal cortex and superior parietal lobe.

Previous studies have shown that AMPA-mediated connectivity increases from the parietal lobe to the frontal lobe, while the GABA time constant is robustly decreased in the frontal lobe. These two parameters are relevant to the antidepressant properties of ketamine [65]. These results suggest that the antidepressant effect of ketamine is relevant to the acute frontal-parietal junction and GABA receptors.

(5) The antidepressant properties of ketamine and the TGF-β1/BDNF/TrkB pathway

Recently, hippocampal levels of TGF-β1 have been shown to parallel the depressive phenotype and cognitive impairment in animal models, and the clinical phenotype is low in response to "monoamine" antidepressants [66]. In the CSDS model, ketamine reduced the expression of TGF-β1 and its receptors in the prefrontal cortex and hippocampus of mice [67]. Similar results were confirmed in a mouse model of post-stroke depression [68].

Preservation of microglial function is particularly important for the antidepressant effect of ketamine [67]. In CSDS mice, intranasal administration of recombinant TGF-β1 activated BDNF/TrkB in microglia and produced antidepressant effects similar to those of ketamine [69]. Further research is needed to investigate the effects of regulating TGF-β1/BDNF/TrkB in microglia on the antidepressant effects of ketamine.

(6) Lateral habenular nucleus (LHb) involved in ketamine effects

1) Upregulation of β-CaMKII in the LHb is associated with clinical features of depression.

Quantitative proteomics shows that β-CaMKII is increased in the lateral tegmental nucleus of animal models, and antidepressants can downregulate its expression. In the lateral tegmental nucleus, increased β-CaMKII, but not α-CaMKII, significantly increased neuronal synaptic plasticity and resulted in severe depressive symptoms. Intervention with β-CaMKII-GluR1 can reverse these effects [70].

2) Ketamine has a selective inhibitory effect on NMDA receptors in specific brain regions in depression model mice [71].

Ketamine exhibits region-specific antidepressant effects by rapidly inhibiting NMDA receptor currents in LHb neurons of depression model mice. In depression model mice, LHb neurons showed high baseline activity and NMDA receptor open state, which made the effect of ketamine more significant in this area.

The study also found that the sensitivity of LHb neurons to ketamine can be exchanged by up-regulating CA1 neurons or down-regulating the activity of LHb neurons. This suggests that LHb is the primary brain target of ketamine's antidepressant effect, while other regions may be secondary targets. This distinction helps to design more precise and effective antidepressant treatments.

3) The fast-acting antidepressant ketamine rapidly alleviates depressive symptoms by blocking NMDA receptors in LHb [72].

In animal models of depression, LHb neurons showed significantly increased burst activity and theta wave synchronization, which were reversed by ketamine treatment. The burst activity of LHb neurons is dependent on NMDA receptors and T-type voltage-gated calcium channels (T-VSCCs), and blocking these channels can induce antidepressant effects in LHb. Ketamine reduces the burst activity of LHb neurons by blocking T-VSCC channels, thereby rapidly alleviating depressive symptoms. Systemic infusion of the T-VSCC blocker or local infusion of the T-VSCC antagonist mibefradil showed rapid antidepressant effects. The antidepressant properties of ketamine and T-VSCC blockers jointly block the activity of LHb neurons.

4) The role of LHb neuronal burst activity in depression, with Kir4.1 potassium channels in astrocytes is very important [73].

Research has shown that the activity of LHb neurons is significantly increased in depressed animals, driving depressive-like behavior that is the material basis of the rapid antidepressant ketamine.

The Kir4.1 potassium channel in LHb is significantly upregulated in a model of depression. Increased Kir4.1 current and protein levels are synchronized with the development of depressive-like symptoms, and this upregulation is associated with the membrane processes of astrocytes, which tightly surround neuronal cell bodies and synapses. By reducing extracellular

potassium concentration or increasing Kir4.1 expression, the phenomenon of neuronal membrane potential hyperpolarization and increased burst activity observed in depression models can be simulated. These results suggest that Kir4.1 in LHb neuronal membrane and burst activity is a novel target for the treatment of depression.

5) A single injection of ketamine has sustained antidepressant effects via NMDAR traps in the LHb [74].

Ketamine can continuously inhibit the explosive activity of LHb and block NMDAR for up to 24 hours after systemic injection. The long-term inhibition of NMDAR is not achieved by endocytosis, but depends on the application of ketamine to NMDAR-dependent traps. This mechanism demonstrates the dynamic equilibrium regulation of NMDAR by ketamine at different plasma concentrations.

6) The ketamine's antidepressant effect and the autonomic nervous system

Several studies have suggested that the autonomic nervous system plays a critical role in human cardiovascular health and depression, an emotional disorder [75,76]. Skin electrical activity (EDA) is a promising and non-invasive tool to measure sympathetic nervous system activity associated with emotional and cognitive states.

EDA parameters are significantly negatively correlated with several pre-treatment depressive symptoms [77], suggesting that the level of pre-treatment depression is negatively associated to the decrease in pre-treatment sympathetic tension. In the CSDS model, splenectomy attenuated the PFC OXPHOS pathway (such as COX11, UQCR11, and ATP5e), which may help reduce depression. In addition, SRI-01138 (TGF-β1 receptor agonist) and subphrenic vagotomy can attenuate the antidepressant response of CSDS-sensitive mice to ketamine after splenectomy [78].

Different administration routes of ketamine

(1) Intravenous administration

When administered intravenously, a single dose of ketamine has a rapid onset and relatively short duration of action, with onset within 30 seconds, a distribution half-life of 10 minutes, and an elimination half-life of 2.0-3.0 hours. Ketamine has the characteristics of high lipid solubility and wide distribution [79].

A patient with metastatic cancer pain was started on ketamine (0.4 mg/kg.hr) infusion, and the patient's pain was completely relieved without significant adverse reactions. The stable dose of ketamine reduced the need for opioid medication by 61.4% [80].

(2) Intrathecal administration

A 2010 case report showed that intrathecal self-guided injection of the right-handed optical isomer of ketamine (S-ketamine) (20 mg/d) in combination with morphine and bupivacaine improved symptoms of refractory cancer pain without other adverse effects (hypertension and neurological dysfunction) [81]. Spinal co-administration of ketamine and morphine enhanced visceral and somatic anti-injury effects [82]. Intrathecal injection of ketamine attenuated severe refractory pain unresponsive to opioid escalation [83].

(3) Intranasal administration

1) During dressing changes, ketamine nasal drops can significantly reduce patients' pain scores without any significant adverse reactions [84]. And there were no adverse reactions associated with the use of ketamine in adult patients, including hypertension, tachycardia, skeletal muscle hyperactivity, increased upper respiratory secretions, nystagmus, and diplopia [85,86].

In studies of acute traumatic pain [87], renal colic [88], and neuropathic pain [89], intranasal S-ketamine can achieve similar analgesic effects with fewer side effects compared to the morphine treatment group. Compared with the gel lubricant group alone, the pain score caused by nasogastric tube insertion decreased in the ketamine gel lubricant group (P = 0.026) [90].

2) Brain-targeted nasal drug delivery device and its prospects for use in the nasal administration of ketamine

Although nasal drops, sprays and other forms have been widely used, because existing drug delivery devices cannot penetrate deep into the nasal olfactory area, some drugs are absorbed into the bloodstream as they pass through the mucous membrane of the respiratory tract, which is rich in capillaries and blood flow. This method can only deliver some drugs to the nasal olfactory area, while the other part of the drugs that enter the bloodstream and cannot cross the blood-brain barrier cannot function in the brain, resulting in drug waste. On the other hand, improper use of nasal drops can cause them to enter the throat, resulting in drug waste and discomfort for patients, especially in special populations such as infants and young children, which can lead to serious consequences such as throat spasms and choking.

In response to the above problems, we offer a nasal, brain-targeted drug delivery device (patented, CN202320800855.7) [91]. It includes a nasal plug, guide wire, occlusion balloon, drug delivery connector, storage box, pressure measurement connector, supply fan, exhaust fan and fan controller. Occlusion of the balloon can block the lower nasal passage and throat, allowing the atomised drug to be delivered into the nasal

cavity by an air supply fan, remain in the nasal cavity for absorption by the olfactory area, and then enter the brain to play a targeted therapeutic role (Figure 1).

To date, there are no reports on the use of ketamine for nasal-brain targeted analgesia and antidepressant treatment. I believe that with the development of related research, targeted delivery of ketamine through the nose and brain will become a new drug delivery method for the treatment of cancer pain and depression.

(4) Other routes

In addition to the above routes of administration, ketamine can also be administered orally and rectally, but due to extensive hepatic first-pass elimination, the bioavailability of ketamine for treatment by these routes is low [79].

Ketamine and Tumor Recurrence

The perioperative procedures, including anesthesia, analgesia, surgical stress, blood transfusion, etc., may affect the proliferation and invasion ability of tumor cells, reduce the postoperative anti-tumor immune function of patients, and thus affect tumor metastasis and recurrence [92].

Immunoregulatory effects of ketamine

In clinical practice, balancing the relationship between immunosuppressive therapy and the risk of tumor recurrence is an important issue. Ketamine is a commonly used anesthetic and analgesic, and its immunomodulatory effects in the tumor environment have gradually attracted attention. Some studies indicated that it might affect immune responses in the tumor microenvironment through multiple mechanisms [92].

Studies have shown that NMDAR activation can induce lymphocyte activity, thereby affecting anti-tumor immune responses [91,92]. This suggests that ketamine may inhibit T cell proliferation and function, thereby affecting anti-tumor immune responses. NK cells are essential for innate immunity and are responsible for directly attacking tumor cells. Intraperitoneal injection
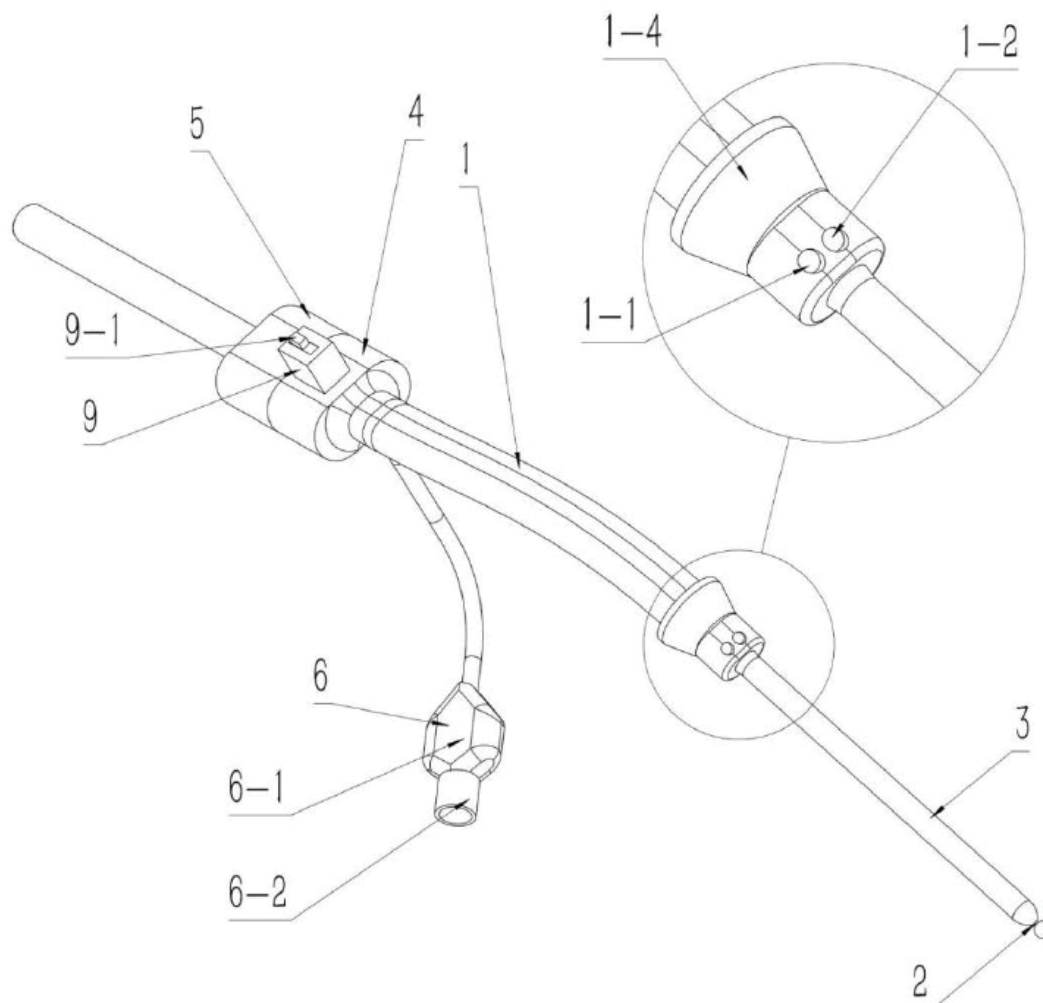

Figure 1: The nasal device for targeted drug delivery to the brain. The device comprises a nasal plug (1), a guide wire (2), a sealing air bag (3), a drug delivery connector (4), a storage box (5), a pressure measurement connector (6), an air supply fan (7), an exhaust fan (8) and a fan controller (9).

of ketamine can inhibit the activity of NK cells, reduce their ability to kill tumor cells, and induce metastasis of lung cancer cells [93]. These effects suggest that ketamine and the adrenergic system may regulate each other [94]. In animal models, Ford, et al. confirmed that ketamine (intraperitoneal injection) can reduce NK cell activity and inhibit lung metastasis of breast cancer cells [95]. Zhou, et al. confirmed that both ketamine and morphine could inhibit the levels of IL-2 and IFN-γ in T lymphocytes [93,96].

Low-dose ketamine appears to have immunosuppressive effects by inhibiting pro-inflammatory cytokines, reducing T and NK cell activity, and promoting anti-inflammatory pathways. These effects may be beneficial in treating harmful conditions caused by excessive inflammation, but they may also carry risks, such as reduced immune surveillance for infections and tumors. Therefore, further attention needs to be paid to the use of different doses of ketamine in different clinical settings, particularly in patients with compromised immune function or those at risk of cancer recurrence.

The effect of perioperative ketamine use on immune regulation

As a vital component of the immune system, NK cells can recognize and destroy cancer cells and virus-infected cells [97-99]. During the perioperative period (before and after surgery), factors such as surgical pressure, anesthesia, and pain can lead to immune suppression and reduce NK cell activity [100].

A human clinical trial has confirmed that a single dose of ketamine (0.15 mg/kg) reduces postoperative inflammation but does not affect NK cell activity [100].

However, there are also reports to the contrary. Ketamine (0.25 mg/kg administered preoperatively; 0.05 mg/kg/h maintained during surgery) did not alter immune function in rectal cancer patients during surgery [101].

The differences in the above research results may be closely related to the dosage, timing, and tumor type of ketamine administration, which also suggests that ketamine regulates the diversity of the body's immune system [102-104].

To further investigate the above experiment, Zhang, et al. used different doses of s-ketamine (intravenous infusion, respectively) to study the effect of ketamine on immune-inflammation. They confirm that s-ketamine (0.25-0.75 mg/kg) can reduce the opioid dosages during the perioperative period, lower postoperative inflammatory responses and immunosuppression in breast cancer patients [105]. Further research with large samples and multiple centers is needed to confirm and determine the optimal dosage for use.

Direct effects of NMDA antagonists on cancer cell biology

Activation of NMDARs induces influx of Ca^{2+} into cells, activating the CaMK II pathway, which can promote cellular processes that drive tumor proliferation [106]. Elevated intracellular calcium levels activate various signaling cascades, thereby promoting tumor growth, proliferation, death, and more [107,108].

Ketamine can downregulate key signaling molecules and reduce intracellular calcium levels, highlighting its potential anti-tumor effects. This inhibition of multiple pathways involved in cell survival, growth, angiogenesis and metastasis suggests that ketamine may be helpful for cancer treatment particularly in disrupting tumor growth and spread. Because of the critical role of calcium in cellular signaling, reducing intracellular calcium may impair many processes required for tumor cell survival, growth, and metastasis, including proliferation and migration [109,110].

Ketamine appears to promote lipid peroxidation and ferroptosis in cancer cells by regulating the lncPVT1/miR-214-3p/GPX4 axis. The accumulation of iron, lipid ROS and MDA, coupled with the decrease in GPX4 levels, weakens the cell's defense against oxidative stress, thereby inhibiting the survival ability of cancer cells. This mechanism highlights the potential pathway through which ketamine exerts its anticancer effects [110].

Some reports of perioperative ketamine promoting cancer recurrence

The immunomodulatory effect of ketamine in the tumor microenvironment may be twofold. Ketamine at anesthetic doses may inhibit the body's immune function, thereby promoting susceptibility to tumor metastasis [111-113]. Hofbauer, et al. confirmed that ketamine appears to inhibit LPS-induced granulocyte adhesion and migration and suppress inflammatory responses [111]. Ketamine has been shown to inhibit tissue damage induced by oxidative stress and to suppress macrophage activation and migration [112].

Compared with propofol, sodium thiopental, and halothane, inhibition of NK cell function by ketamine increases the susceptibility of tumors to metastasis because NK cells can recognize and destroy tumor cells. However, when beta-adrenergic blockers or low-dose immunostimulants are used as pretreatment, the effect of ketamine on promoting tumor metastasis can be significantly reduced [93,113].

Ketamine can enhance tumor growth by upregulating Bcl-2 in the MDA-MB-231 cell line [114]. High doses of S-ketamine and MK-801 promote the proliferation of pancreatic cancer cell lines, suggesting that further

clinical research is needed to explore the impact of ketamine on cancer treatment [115].

NFATc2 may influence tumor progression by regulating the activity of other transcription factors critical for cancer cell proliferation and survival [116]. Ketamine (5 μM) inhibited the expression of NFAT in PaTu8988t cells within 24 and 48 hours. However, after 72 hours of ketamine stimulation, the expression of NFATc2 increased significantly, suggesting that long-term use may have unexpected effects on cancer cell signaling and progression [117].

Diagnosis and Treatment Status of Adverse Effects of Ketamine

Urinary toxicity

The main clinical manifestations of ketamine cystitis are urinary retention, urinary incontinence, hematuria, bladder wall thickening, bladder volume reduction, and other lower urinary tract symptoms [118]. Long-term use of ketamine may cause damage to the urinary system [119-121]. Although there are studies confirming that ketamine may cause damage to the urinary system, the research is still in the exploratory stage and includes the following aspects: Ketamine and its metabolite, ketamine, damage bladder barrier dysfunction; ketamine may increase bladder oxidative stress through mitochondrial and endoplasmic reticulum-related pathways, leading to bladder cell apoptosis and disruption of the urinary epithelial barrier; and related inflammatory mediators, etc. [118].

Hepatotoxicity

Ketamine is potentially hepatotoxic. Research has shown that ketamine is extensively metabolized in the liver to metabolites that can damage hepatic parenchymal cells and other liver cells [122]. Ketamine abuse may increase lipid peroxidation reactions, oxidative stress, and hepatocyte pyroptosis [121-123].

The sphincter of Oddi is a part of the biliary system responsible for regulating the flow of bile from the bile duct into the duodenum. Previous studies have shown that ketamine can relax biliary smooth muscle, relax the biliary tract, and inhibit gallbladder movement through central mechanisms by blocking NMDA receptors [124,125].

Therefore, hepatotoxicity of ketamine is a concern, especially for developing individuals who require ketamine for anesthesia. Research is ongoing to elucidate its mechanism and identify potential protective measures.

Cognitive impairment

Long-term use of ketamine may impair working memory, mainly by impairing visual memory, verbal memory, and response inhibition, as well as by significantly impairing selection ability and sustained attention [126-129]. Ketamine participates in the regulation of brain signaling pathways by blocking NMDA receptors and may indirectly upregulate D1 receptors in the lateral prefrontal cortex. This phenomenon persists even after chronic dopamine depletion [130]. The above suggests that excessive use of ketamine may affect the function of the lateral prefrontal cortex, resulting in impaired memory and cognitive function. Unfortunately, research on the treatment of chronic pain and depression is limited.

Although ketamine is known to cause some acute cognitive side effects during and shortly after administration, such as dissociation, sedation, or memory impairment, studies typically indicate that these effects are short-lived. Six weeks after infusion, cognitive function usually returns to baseline levels, and most patients have no significant long-term residual effects [131-133].

Research has shown that even shortly after administration (e.g., 40 minutes after injection), ketamine has minimal acute neurocognitive effects in many patients [132,133]. However, it is still important to monitor any potential cognitive or psychological effects on an ongoing basis, especially given the dissociative properties of ketamine. Over time, short-term infusions have also been shown to maintain the benefits of antidepressants without significantly impairing cognitive function. However, the potential safety of ketamine in long-term treatment regimens remains to be investigated.

Hemodynamic effects

Ketamine has significant effects on hemodynamics, with major hemodynamic effects including hemodynamic disorders, and increased myocardial oxygen demand. Ketamine is contraindicated in individuals with cardiovascular diseases, pulmonary heart disease, pulmonary arterial hypertension, intracranial pressure, or high intraocular pressure [134]. When used at lower doses (e.g., in psychiatric applications such as depression), hemodynamic effects are usually milder than with higher anesthetic doses [135].

Tolerance and dependence

People who use ketamine frequently may experience rapid development of craving, compulsive behavior, and tolerance. With frequent use of ketamine, tolerance develops rapidly, meaning that users must gradually increase their dose to achieve the same dissociation or euphoric effect [136]. This escalation can increase the cognitive impairment, bladder toxicity (ketamine bladder syndrome), and mental health problems, et al. [137].

Ketamine's unique effect on NMDARs, combined with its effect on the dopamine system, has led to these patterns of addiction. It has also been found that long-term or frequent use can lead to psychological dependence and physical health complications.

The side effects and safety risks of ketamine should be carefully considered before making a choice. Which isomer (R- and S-ketamine) causes more adverse effects, particularly cognitive and dissociative symptoms, in recreational or therapeutic use? Is one isomer more risk effective than the other for certain indications (e.g., depression, chronic pain)? Answering these questions will help guide the safe use of ketamine, particularly in clinical settings where its use is of particular importance. The occurrence and side effects of the two isomers in racemic mixtures of ketamine, as well as the effects of their metabolites, are still new areas of research that need to be explored.

It is recommended that large-scale clinical trials, particularly in patients with depression, be conducted to adequately understand the therapeutic potential and safety of ketamine. The trials should address several key issues, including: Multiple doses and treatment regimens, long-term follow-up of clinical treatment outcomes, monitoring of potential side effects, different patient populations, and comparative studies between R- and S-ketamine. Conducting these rigorous long-term studies will provide key data to optimize the use of ketamine in clinical practice, maximizing its therapeutic potential while minimizing its risks.

Research on Combination Use of Ketamine and Opioids

Compared to ketamine, R-ketamine has stronger sedative and analgesic properties. A large number of clinical trials abroad are also focusing on its use in combination with opioid medications. Ketamine as an adjuvant drug can improve the analgesic effect of morphine and reduce side effects at low doses.

Mechanistic studies of ketamine in combination with opioids

Perioperative use of opioids has been shown to cause hyperalgesia and hypersensitivity in patients: Morphine cannot reverse central neuronal sensitization. In addition to acting on opioid receptors, morphine peptides also excite NMDA receptors. High doses of morphine can cause diffuse sensory hypersensitivity that can be reversed by excitatory amino acid receptor antagonists [138]. Experimental studies have shown that right-handed ketamine can attenuate central sensitization and hyperalgesia and reduce postoperative patient tolerance to opioid medications [139]. In patients who have not used opioids prior to surgery, intraoperative use of ketamine at an anesthetic dose

may reduce opioid consumption and pain [140].

Activated NMDARs participate in opioid tolerance: Opioid tolerance is an inevitable phenomenon involving activated NMDARs, nitric oxide and others [3,20]. Many neuronal factors are involved in the development of tolerance [141,142]: Reduced number of receptors, decoupling of receptor-effectors within cells, disruption of genome expression, adaptation of neuronal networks, etc.

In fact, it is the occupancy of opioid receptors that triggers tolerance, and as the number of occupied opioid receptors increases, tolerance becomes more likely. That is why tolerance is more likely to occur when opioid-resistant pain requires more morphine. NMDA receptor antagonists have antinociceptive properties in both neuropathic and nociceptive pain [143]. In addition, unlike morphine, these antagonists are effective even after administration. NMDA antagonists may attenuate morphine tolerance by modulating the effects of excitatory amino acids [143,144].

Neural regulation of periaqueductal gray (PAG) activity in the midbrain is the basis for the synergistic analgesic effect of morphine and ketamine: The periaqueductal gray (PAG) is critical in the integration of behavioral, somatic, and autonomic responses to threat, stress, and pain in animals [145,146]. Electroacupuncture can induce c-fos activation in the PAG [147], and the ventrolateral periaqueductal gray (vLPAG) is an important component mediating pain transmission [148,149]. The VLPAG is the basis of opioid analgesia. There is research confirming that neural regulation of VLPAG activity is the basis for the synergistic analgesic effect of morphine and ketamine.

The functional relationship between MOR and NMDAR is bidirectional. The functional cross-regulation between MOR and NMDAR in the PAG is regulated by protein kinase C (PKC)/PKA, and the postsynaptic association of these receptors is related to the transmission and regulation of nociceptive signals [149,150]. The bidirectional interaction between MOR and NMDAR in the PAG is related to the synaptic transmission of nociceptive signals by PKC/PKA [149,150]. Opioid drugs, including morphine, can disrupt the activity of MOR and NMDAR complexes that stimulate NMDAR, which can lead to abnormal regulation of the MOR pathway and opioid analgesic tolerance [151].

Perioperative combination with opioids to reduce perioperative opioid dose and prevent pain hypersensitivity

Many studies suggest that ketamine is best administered intravenously as an adjunct to opioids [152]. Although ketamine has the effect of sparing opioids, it has not been shown to reduce opioid-related

adverse effects such as PONV, pruritus, and respiratory depression [153,154].

Future studies should focus on high-risk populations with opioid tolerance for acute postoperative pain and on the effects of low-dose ketamine for acute postoperative pain on long-term pain syndromes (after mastectomy, thoracotomy, and phantom limb pain).

Morphine-ketamine for refractory cancer pain

Refractory cancer pain in patients: In patients with terminal cancer, long-term overuse of morphine can lead to opioid tolerance and sensitization, and the dose of morphine must be continuously increased to achieve its original effect. This inevitably leads to serious side effects such as nausea, vomiting, and dyspnea [151-154].

Research has shown that low-dose ketamine can inhibit or reverse morphine tolerance and pain sensitization, enhance the analgesic effect of opioid drugs, thereby reducing the dose of morphine and alleviating its adverse reactions [155]. When morphine is tolerated, ketamine can reduce the dose of the intrathecal analgesic morphine by 50% [138,156].

In a randomized, double-blind trial, 48 patients with advanced cancer received epidural pain management when systemic opioid and NSAID treatment was ineffective or intolerable [157]. The results showed that low-dose ketamine or neostigmine significantly prolonged the analgesic effect in patients, whereas mid-dose midazolam did not have this effect.

Two cancer patients [158] experienced decreased pain sensitivity and improved quality of life after receiving combined epidural ketamine, morphine, and bupivacaine. After receiving adjuvant ketamine, the patient had decreased pain sensitivity and no serious adverse events. Low-dose ketamine prolonged satisfactory analgesic effects and partially restored patients' quality of life when conventional treatment failed. The combination of ketamine with morphine and bupivacaine may prolong analgesia and reduce tolerance to morphine.

In one study [159], researchers evaluated the efficacy and safety of 5 days of continuous intravenous infusion (CIVI) and 5 days of stepwise titration of ketamine in the treatment of advanced cancer patients with refractory cancer pain. The results showed that ketamine CIVI may be a useful tool in the treatment of refractory cancer patients.

Researchers [160] evaluated the efficacy of different doses of intranasal ketamine (10, 30, and 50 milligrams) in treating refractory cancer pain. All doses of intranasal ketamine were well tolerated with short-term side effects, and no serious adverse events related to the

study drug were reported. Pain relief began within 15 minutes in most patients and continued throughout the study. The study showed that the exposure level of ketamine is consistent with the clearance rate, and the bioavailability of intranasal administration is approximately 50%.

Katzenschlager, et al. [161] confirmed that intrathecal injection of S (+)-ketamine is an effective method for treating chronic cancer-related neuropathic pain. However, its application to nerve axons carries potential risks in the absence of sufficient safety data. Current research findings has generated controversy regarding the neurotoxicity of the drug and further research is needed to comprehensively evaluate the long-term safety of intrathecal administration of S(+)-ketamine and its rationale in clinical practice.

***In vitro* study of the effect of the interaction between ketamine and morphine on T cells:** There is currently limited research on whether morphine and ketamine have an effect on the immune system in refractory cancer pain. Morphine, an exogenous opioid peptide, exerts potent analgesic effects by binding to opioid peptide receptors. Opioids can activate NMDA receptors and lead to tolerance. Ketamine has an affinity for opioid receptors that is only 1/10-1/20 of its affinity for NMDA receptors, but it can also promote the release of endogenous opioid peptides and stimulate opioid receptors, thereby exerting some analgesic effect [149-151]. Ketamine can also act on nicotinic and muscarinic acetylcholine receptors, block sodium channels, and interact with opioid receptors and calcium ion channels [162].

In addition, ketamine can inhibit the reabsorption of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin et al.). This activates or enhances the central pain inhibitory system, resulting in analgesic effects [163,164]. The sites of action of morphine and ketamine as two analgesics overlap, and their effects on the body's immunity may interact. Morphine and ketamine can simultaneously act on opioid receptors and exert immunosuppressive effects through multiple pathways. However, with respect to NMDA receptors, morphine exerts an excitatory effect while ketamine exerts an antagonistic effect. There are no relevant reports on which of the two has an advantage, either immunosuppression or immunopotentiation.

Although ketamine itself has immunosuppressive effects, it is currently the least immunosuppressive drug among general anesthetics. While morphine combined with low-dose ketamine provides adequate pain relief, it has been suggested that it may alleviate the immunosuppressive state of refractory cancer pain patients.

The combination of morphine and ketamine can

reduce the CD4+ percentage, and CD4+/CD8+ levels are detected through the JAK3/STAT5 pathway for IFN-Y, IL-2, and IL-17 [165]. This study confirms that this combination therapy can improve tumor pain and suppress the immune system. However, there are currently few studies on this topic, both nationally and internationally, and this conclusion still requires a large amount of experimental data to support.

Efficacy and safety of ketamine as adjuvant opioid therapy for cancer pain

As an analgesic adjunct to opioids, the quality of evidence for ketamine research is low, often resulting in small sample sizes and a high risk of bias [166]. The study by Hardy, et al. suggests that ketamine does not significantly improve analgesia compared with placebo, and the incidence of adverse events (including hallucinations and cognitive impairment) in the ketamine group is almost twice that of the placebo group [167].

The three studies used different routes and doses of ketamine, including intrathecal administration [168], intravenous injection [169], and subcutaneous injection [167]. Different routes and doses may affect the efficacy and safety of ketamine, but current studies are insufficient to determine the optimal route and dose.

The reasons for the inconsistent research results with ketamine in the past can be explained as follows. First, most studies have been conducted in heterogeneous patient populations, ranging from those undergoing anticancer treatment to patients with advanced cancer. Second, most studies lack a clear definition of pain in refractory cancer or include patients with low pain intensity. When high doses of opioids are required, opioid tolerance is evident and the likelihood of a neurologic component is high.

At this point, it may be more necessary to combine the use of ketamine for adjuvant analgesia. Third, many trials, including phase 3 trials, have used administration methods such as pill injection or continuous subcutaneous infusion (CSCI). The dose injection method is very convenient, but some people are concerned that it may cause serious adverse events (AEs) and AEs due to skin irritation, so the CSCI method is not recommended. The progressive dose titration method of continuous intravascular infusion (CIVI), although inconvenient for maintaining venous access, has the advantage of safely starting at a lower dose and increasing to an adequate dose as needed.

Current research data are insufficient to confirm that ketamine can be used as an opioid adjuvant in the treatment of cancer pain. Future research should pay particular attention to the interactions between ketamine and specific opioid drugs, as well

as the optimal dosage, therapeutic efficacy, and safety evaluation of ketamine in different cancer types and treatment stages.

Research Progress in the Discovery of Ketamine in Patients with CPD

The current research shows prospectively that ketamine can effectively treat refractory cancer pain and depression. The treatment of cancer pain in combination with depression is challenging. The comorbidity of depression and cancer pain remains a challenging issue. Ketamine's antidepressant effects may also be useful for CPD.

CPD, as an important factor affecting the condition and prognosis of cancer patients, is an urgent problem to be solved in cancer treatment. The incidence rate of depression in patients with advanced cancer is high, reaching 16.5%, and severely affects quality of life and survival [170]. Conventional antidepressants have limited efficacy and slow onset of action in advanced cancer patients and are not suitable for all patients.

A 39-year-old female patient with stage IVB cervical cancer, intractable pain, and suicidal ideation. After receiving an injection of ketamine (0.5 mg/kg, IV), her depressive symptoms rapidly improved, suicidal ideation disappeared, and pain was relieved. The patient continued to show significant improvement with subsequent treatment, demonstrating that ketamine can enhance the efficacy of conventional antidepressants [170]. This study highlights that ketamine may be an alternative for cancer pain patients who have poor efficacy or intolerance to conventional antidepressants.

A 64-year-old man with advanced thyroid cancer was hospitalized for severe neuropathic pain and major depression. After an intravenous injection of ketamine, the patient's pain, depression symptoms, and pain score decreased significantly [171].

A patient with metastatic ovarian cancer showed rapid and sustained improvement in depressive symptoms and pain reduction after treatment with ketamine (1 mg/kg, intramuscular injection, repeated doses at weekly intervals) [172].

A 50-year-old patient with metastatic prostate cancer was admitted for chronic nausea, vomiting, and severe orthostatic hypotension. The patient was diagnosed with major depression and had a poor response to existing medications such as venlafaxine. In the palliative care unit, the patient received ketamine "burst therapy" (0.5 mg/kg, intravenous drip over 60 minutes). After the first treatment, the patient's mood improved, but the effect was not sustained. The effect of the second treatment was more short-lived, although there was a mild side effect of hallucinations [173].

Figure 2: The therapeutic effects of ketamine on cancer pain related depression.
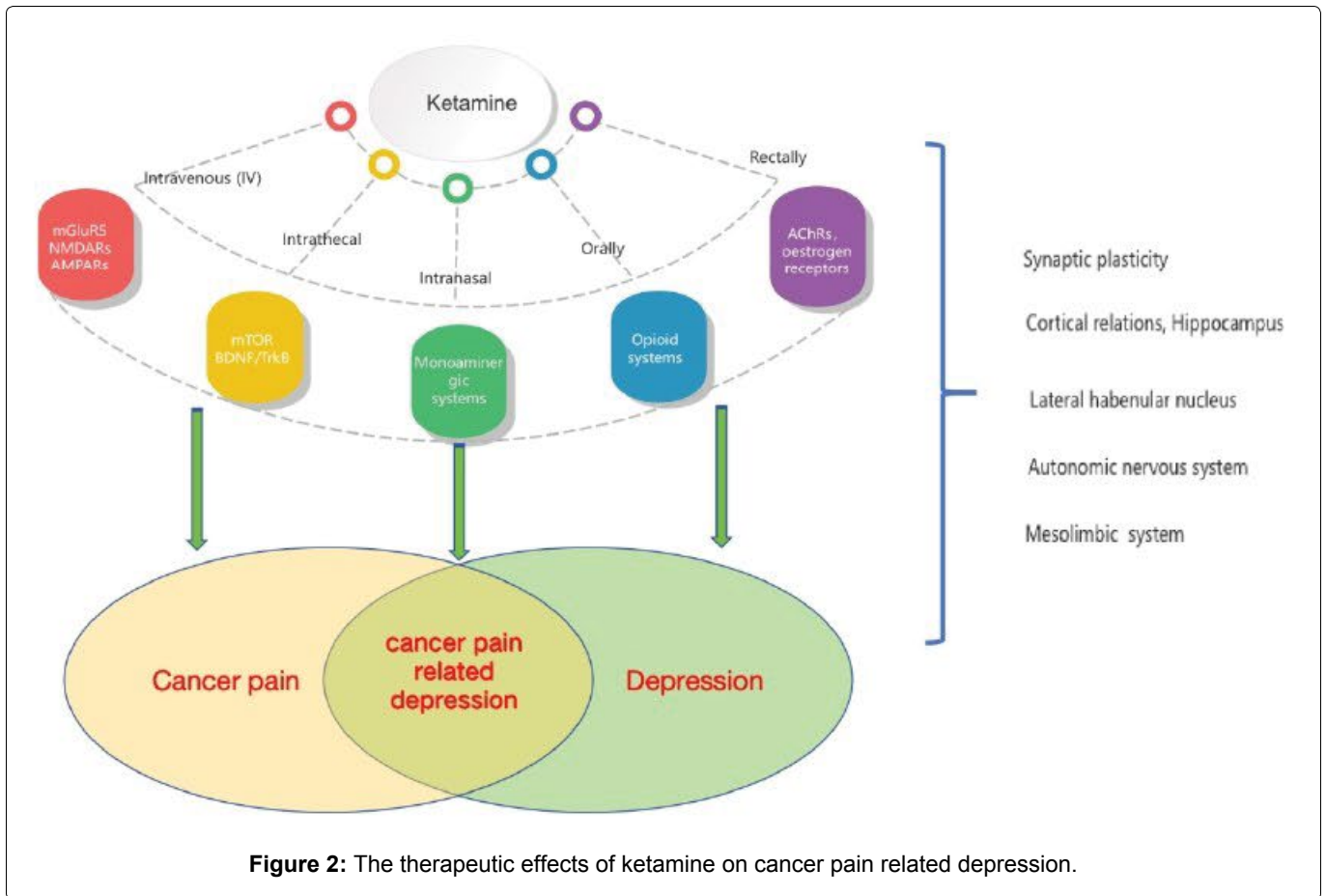
Conclusion

Currently, there is a lack of empirical evidence for the treatment of chronic pain-related depression with ketamine. Most of the available data are case reports, which may not be sufficient to draw definitive conclusions. The available literature suggests that ketamine may serve as an effective alternative for people with cancer pain who have poor efficacy or intolerance to conventional antidepressants. Nevertheless, further clinical trials are needed to determine the safety and long-term effects of ketamine, particularly in patients.

Ketamine may provide an initial antidepressant effect in patients with CPD (Figure 2). However, the sustainability of its therapeutic effects is limited, and the optimal dosage and administration regimen need further verification. Furthermore, it is of interest to assess its impact on patients' emotional state and suicide risk in the context of cancer pain management.

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Conflict of Interests Statement

The author is the inventor of the device mentioned in this review. (A brain-targeted nasal drug delivery device: CN202320800855.7).

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