Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

# Lidocaine for Depressive Symptoms and Comorbid Pain: A Narrative Review of Mechanisms, Evidence, and Safety

Min Xia[1,2,*], Jinnian Duan[3,*], Nan Chen[1], Wanru Zhou[1], Na Zhang[1], Miao Feng[1], Yang Sun[4], Yong Luan[1]

[1]Department of Anesthesiology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, People's Republic of China; [2]Department of Anesthesiology, General Hospital of the Yangtze River Shipping, Wuhan Brain Hospital, Wuhan, Hubei, People's Republic of China; [3]Liaoning Provincial Key Laboratory of Cerebral Diseases, Department of Physiology, College of Basic Medical Sciences, Dalian Medical University, Dalian, Liaoning, People's Republic of China; [4]Department of Anesthesiology, The General Hospital of Benxi Iron and Steel Group, Benxi, Liaoning, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yong Luan, Email luanyong@dmu.edu.cn



**Abstract:** Depression, a globally prevalent mental health disorder, poses significant treatment challenges, particularly in treatment-resistant cases. Increasing evidence suggests a strong bidirectional relationship between chronic pain and depression, underpinned by shared neurobiological mechanisms, including dysregulation of glutamatergic signaling and neuroinflammatory processes. In this narrative review, we synthesize preclinical and clinical findings on lidocaine, a local anesthetic that has attracted interest for its potential neuropsychiatric effects. Proposed pharmacological mechanisms of lidocaine, including sodium channel blockade, N-methyl-D-aspartate (NMDA) receptor antagonism, and anti-inflammatory properties, which together may contribute to its putative mood-modulating properties. Clinical evidence to date remains limited and heterogenous, consisting largely of small-sample controlled trials, observational studies, and investigations primarily conducted in pain populations rather than in primary depressive disorders. Despite some studies suggest rapid but transient improvements in depressive symptoms, challenges such as transient effects, dosing optimization, and safety considerations remain. Addressing these gaps through robust clinical trials and exploring biomarkers for personalized treatment could unlock the full potential of lidocaine in bridging pain management and psychiatry, offering a novel avenue for treating complex cases of depression.

**Keywords:** lidocaine, pain management, depression, comorbidity

## Introduction

Depression as a widespread global concern affects more than 300 million people worldwide.[1] It was responsible for a global total of more than 50 million people living with a disability in 2015, ranking it as the single largest contributor to non-fatal impairments.[2] On top of that, depression is one of the leading causes of death by suicide, regardless of major or subthreshold depression.[3] The humanistic and economic burden that depression brings to the patients is not negligible, including lower work productivity and higher healthcare utilization than those without depression.[4–6] The estimated economic burden due to depression is in the hundreds of millions of dollars, accounting for 4–8% of GDP and diverting resources that could be allocated to other critical areas.[5] Despite advancements in pharmacological and psychotherapeutic treatments, depression remains a complex and challenging disorder to treat, especially for individuals with treatment-resistant depression (TRD). A universally accepted definition of TRD is currently lacking. Based on widely accepted research criteria, TRD is generally defined as failure to achieve remission after two or more adequate antidepressant trials of at least 6–8 weeks' duration.[7,8] TRD, characterized by a lack of response to multiple antidepressant treatments, affects a substantial portion of those diagnosed and underscores the need for novel therapeutic strategies. A study from Thailand noted 19.6% of TRD among depressed patients receiving antidepressant treatment. And the aggregated economic costs associated with TRD were nearly twice as high as non-TRD.[9]

https://doi.org/10.2147/DDDT.S580802
Received: 11 November 2025
Accepted: 21 March 2026
Published: 7 April 2026

A significant portion of individuals with depression disorder suffer from chronic pain. Nearly 1 in 20 adults in the U.S. deal with chronic pain while experiencing anxiety or depression and 55.6% of the adults with unremitted anxiety or depression also have chronic pain, according to the new research from Rosa et al.[10] Chronic pain is a heterogeneous condition that can be broadly categorized into nociceptive, neuropathic, and nociplastic phenotypes, each involving distinct underlying mechanisms and potentially differing responses to treatment.[11] Depression often affects and is affected by pain, especially chronic pain.[12–16] A cross-section study enrolling 15,213 populations in China confirmed a partial mediating effect of chronic pain on chronic disease and depression. It found that patients with more chronic diseases had more severe pain (OR = 3.697, P < 0.001, CI = 2.919–4.681) and were more likely to develop depression (OR = 2.777, P < 0.001, CI = 2.497–3.090)[13] and that treatments for pain are just as important to consider when treating depression.[13,14] Among adolescents, researchers even more radically stated that pain presence was associated with lifetime depression (OR[95% CI]: 1.76 [1.45, 2.13], p < 0.001).[15] Depression likewise affects patients' perception and nociceptive threshold thereby altering their perception of pain.[16] This comorbidity complicates diagnosis and treatment, as pain can exacerbate depressive symptoms and vice versa.[13,16] Both conditions share common neurobiological pathways, including neurogenesis,[12] excitatory/inhibitory imbalance,[17,18] and neuroinflammation,[19] etc, suggesting that targeting these pathways could provide therapeutic benefits for both conditions. Importantly, the expected clinical benefit and underlying mechanisms of analgesic interventions, such as lidocaine, are likely to vary across pain phenotypes, with stronger mechanistic rationale in neuropathic and mixed pain states due to their greater involvement of peripheral and central sensitization processes. Understanding the shared mechanisms between pain and depression is essential for developing more effective treatments that target both conditions simultaneously.

Lidocaine was first synthesized in 1942 and approved for use in clinical in 1948. It is well known to the public as a classic local anesthetic for its ability to block nerve conduction by inhibiting sodium channels. Besides perioperative use for pain management, lidocaine is commonly used in clinical settings for anti-ventricular arrhythmias. Expanding on these effects based on the ion channel blocking properties, lidocaine garnered growing attention for its potential role in treating psychiatric disorders, particularly depression with comorbid pain. Current interpretations of its antidepressant potential generally distinguish between a possible direct mood-modulating effect mediated through central neurobiological mechanisms and a secondary improvement in depressive symptoms resulting from interpreting existing clinical evidence. Within current treatment algorithms for depression, lidocaine is not considered a first-line therapy but has been explored primary as a potential adjunctive or investigational option for TRD. Recent studies have suggested the effects of lidocaine on the central nervous system may extend beyond local anesthesia, making it a candidate for treating more conditions such as TRD.[20–23] The researchers also found anti-inflammation,[20,21] neuroprotective,[22] and attenuating mitochondrial damage properties[23] of lidocaine. Given the shared neurobiological pathways between chronic pain and depression, lidocaine's ability to modulate these pathways has sparked interest in its repurposing as an antidepressant, particularly in clinical contexts characterized by comorbid chronic pain, heightened inflammatory activity, or central sensitization. Reversible temporary silencing of basolateral amygdala using lidocaine significantly alleviates depression in mice exposed to chronic stress.[24] Recent research has shown that lidocaine may provide relief from depressive symptoms in patients with comorbid pain conditions.[25,26] However, available clinical evidence remains limited and largely derived from small-scale trials and heterogeneous populations, and ongoing investigations are continuing to evaluate its efficacy, durability of response, and safety profile in TRD, positioning lidocaine as a potential but still experimental adjunctive treatment approach.

## Literature Retrieval

A comprehensive literature search was conducted to identify relevant studies on the use of lidocaine in the treatment of depression, particularly in individuals with TRD and comorbid chronic pain. The search covered databases including PubMed, Embase, and Web of Science from January 2000 to September 2025, using search terms such as "lidocaine," "depression," "treatment-resistant depression," "chronic pain," "neurological mechanisms," and "antidepressant effects". Studies were included if they were clinical trials, observational studies, or meta-analyses that assessed the effect of lidocaine on depression or related conditions, particularly those investigating lidocaine administered intravenously or locally for depression with or without comorbid pain in adult populations diagnosed with depression (major depressive disorder or treatment-resistant depression). Articles had to be published in peer-reviewed journals. In addition, selected preclinical studies were included when relevant to elucidate the potential neurobiological mechanisms underlying lidocaine's antidepressant effects and to provide mechanistic context for the clinical findings. Studies were excluded if they did not provide relevant clinical or

mechanistic evidence regarding lidocaine's effects on depression, lacked a clearly defined methodology or outcome measures, or were published in languages other than English. Case reports, abstracts, and conference proceedings were also excluded. Two dependent reviewers conducted the literature search and screened studies for eligibility. Title and abstract were first screened for relevance, followed by full-text review of potentially eligible articles. Inter-reviewer agreement during the screening process was assessed using Cohen's kappa coefficient ($\kappa = 0.82$), indicating strong agreement. Any discrepancies in study inclusion were resolved through discussion and consensus among the review team.

# Pharmacological Mechanism of Lidocaine

## Effects on Ion Channels

Lidocaine primarily works by blocking voltage-gated sodium channels (VGSCs, Nav), thereby inhibiting the conduction of nerve impulses.[27] Its blockade of VGSCs constitutes the molecular basis for its local anesthetic effect. Beyond this classical action, growing evidence suggests that lidocaine's modulation of specific ion channel subtypes may underlie its potential in treating the pain-depression comorbidity.[28]

VGSCs can be classified into 9 isoforms (Nav1.1–1.9) enriched in different tissues and organs of the organisms. Among then, Nav1.7, Nav 1.8, and Nav1.9 are strongly linked to the pain perception.[29,30] Chronic pain, in turn, is a major driver of depressive symptoms.[10,12,31] For instance, in a chronic social defeat stress model, mice exhibited depressive-like behavior and displayed hyperalgesia, concomitant with altered Nav1.8 expression.[32] Conversely, dysfunction of Nav1.1 in the prefrontal cortex (PFC) has been directly linked to depressive-like behavior, and reduced expression of SCN1A (encoding Nav1.1) was found in post-mortem PFC samples from depressed individuals.[33] Genetic studies also identified SCN2A (Nav1.2) mutations might contribute to depression susceptibility.[34] Recent research further indicates that lidocaine can modulate Nav1.6, an isoform implicated in mood regulation.[35,36] Additionally, some specialized types of sodium channels, such as the Loss of sodium leak channel (NALCN) was found decreased in the dentate gyrus (DG) of the depressed male mice, and NALCN knockdown in DG evokes depression-like behavior in controls.[37] Thus, lidocaine's simultaneous blockade of pain-associated Nav isoforms (eg, 1.7, 1.8) and mood-regulation-associated isoforms (eg, 1.1, 1.2) provides a plausible dual mechanism for alleviating the pain-depression cycle.

Lidocaine also acts on potassium channels, including inward rectifier $K^+$ channels (Kir) family[38] and voltage-gated potassium channel (Kv).[39,40] Overexpression of Kir channels (eg, Kir1.1, Kir2.1) in the nucleus accumbens is relevant to depressive phenotypes,[41] and Kir3[42] and Kir6.2[43] are implicated in the mechanisms of antidepressants and pain modulation. Kv channels, like Kv1.1 and Kv3.1 are also modulated by lidocaine[39,40] and their dysfunction has been linked to depressive-like behaviors.[44,45] Furthermore, lidocaine can mediate Transient receptor potential (TRP) ion channels,[46,47] which is involved in the regulation of pain and the detection of environmental stimuli.[7,48] Genetic polymorphisms in TRPV1 rs222741 [ORadj (95% CI): 1.97 (1.02–3.85), p=0.046], TRPV4 rs3742037 [ORadj (95% CI): 2.03 (1.06–3.96), p=0.035], and TRPM8 rs17862920 [ORadj (95% CI): 0.48 (0.23–0.96), p=0.042] are associated with the comorbidity of migraine and depression,[49] with their roles in depressive-like behavior confirmed in animal models.[50–52]

In summary, lidocaine's multi-target action on ion channels underpins its potential in treating pain-depression comorbidity. By inhibiting pain-transmitting sodium channels (eg, Nav1.7, Nav1.8), it can alleviate a key driver of depression. Concurrently, by modulating potassium and TRP channels involved in mood circuit regulation (eg, in PFC, nucleus accumbens), it may directly correct the neuronal excitability imbalances underlying depressive states.[33] This coordinated action on peripheral and central nervous system (CNS) channels allows lidocaine to target multiple nodes within the shared pathophysiology of chronic pain and depression.

## Glutamatergic Modulation

In addition to its effects on sodium channels, lidocaine has been shown to interact with glutamate receptors, particularly the NMDA receptor.[53–55] Lidocaine concentration-dependently inhibits the NMDA receptor thus reducing the NMDA-induced currents.[53] In oocytes with human NMDA receptor expressed, lidocaine mediates the inhibition of NMDA via the PKC pathway intracellularly.[54] NMDA receptors are involved in synaptic plasticity and the transmission of excitatory signals in the brain. Dysregulation of NMDA receptor function has been implicated in a range of psychiatric disorders, including

depression[56–59] besides pain modulation.[54,59,60] Upregulation of NMDA receptors in the dorsal raphe nucleus significantly improves depressive-like behavior in chronic unpredictable mild stress (CUMS) models.[57] Subsequent research confirmed that blockade of NMDA at rest deactivates CaMKIII and suppresses the translation of neurotrophic factors like brain-derived neurotrophic factor (BDNF), resulting in fast-acting behavioral antidepressant-like effects.[58] Another study demonstrates knockdown of Glutamate Ionotropic Receptor NMDA Type Subunit 2B (GluN2B) subunits of NMDA receptors in mice in γ-aminobutyric acid (GABAergic) interneurons specifically reversed antidepressant-like behaviors.[61] A key role of GluN2B in pain management was also identified in the establishment of a chronic pain model by intraperitoneal injection of cerulein in mice. Glutamatergic neurons in the lateral parabrachial nucleus are activated, leading to excessive glutamate release which binds to the GluN2B subunit of NMDA receptors, ultimately resulting in the development of chronic pain.[60] Independently, Tian et al showed GluN2B-containing-NMDA receptors mediated synaptic plasticity alterations might be a potentially important mechanism for chronic stress-exacerbated neuropathic pain.[59] It has also shown that the process of NMDA receptors involves α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Microinjection of AMPA receptor antagonist in the midbrain ventrolateral periaqueductal gray could abolish the mitigated foot shock stress-induced depression-like behavior in rats.[62] This as well suggests that as targets for glutamate binding, not only the NMDA receptors, but also the AMPA receptors bridge the development of depression and pain.

AMAP receptors consist of four subunits (GluA1-GluA4) that are involved in mediating the onset of various pain processes, including neuropathic pain,[63] inflammatory pain,[64] and pain hypersensitivity.[65] As opposed to NMDA receptors, AMPAR receptors are highly mobile, eliciting transport from (to) synapse and migration along the plasma membrane, an underlying mechanism by which it may regulate synaptic plasticity.[66] Enhancement of APMA receptors ameliorated the synaptic plasticity impairments and depressive-like behaviors caused by sleep deprivation,[67] which also occurs similarly in spatial restraint stress mice.[68] Even the APMA receptors are found to modulate the onset of depression and pain through similar molecular mechanisms such as AMPA receptor trafficking.[63,69] Injection of lidocaine in vivo triggers synaptic scaling in motoneurons to block spontaneous neural network activity, an effect that may be mediated by reducing GluA2-containing AMPA receptors.[70] It has also been suggested that lidocaine may affect GluA1-containing AMPA receptor trafficking via inhibiting the postoperative inflammatory response.[71] Aside from the direct effects on postsynaptic glutamate receptors, lidocaine accomplishes glutamatergic regulation by affecting the glutamate transport system. Lidocaine enhances Excitatory Amino Acid Transporters 3 (EAAT3) activity at certain concentrations, with this action possibly mediated by PKC and PI3K.[72] Whereas in a model of a genetic rat model of depression, researchers identified upregulation of EAAT3 mRNA and protein expression.[73] Intrathecal injection of siRNA of EAAT3 reduces mechanical pain sensitivity and thermal pain sensitivity,[74] presumably by modulating glutamate-mediated pain transmission. These elucidate the role of lidocaine in glutamatergic regulation, a process that plays an integral role both in the modulation of pain and the development of depression. It might open the possibility of a novel concept for the antidepressant effects or treatment of pain co-morbid depression with lidocaine.

## Anti-Inflammatory Effects

Depression has been increasingly recognized as a disorder with inflammatory components. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are often elevated in individuals with depression and are thought to contribute to the pathophysiology of the disorder.[71] These inflammatory markers can affect brain function and neurotransmitter systems, leading to mood disturbances. Liang et al enrolled 67 depressed patients and 67 healthy controls, and found that inflammation by measuring high-sensitivity C-reactive protein (hsCRP) levels in peripheral blood was markedly higher in the depressed population than in healthy controls. And the level of hsCRP is expressed at different levels in different types of depression.[75] Although hsCRP is not a direct reflection of the true level of inflammation, these results also give relatively reliable evidence in humans. Schmitz et al found that peripheral blood IL-6 concentrations were significantly higher in depressed patients than in healthy controls.[76] This alteration was closely related to abnormal functional connectivity of the default mode network,[76] which is highly correlated with the development of depression.[77] When the depression symptoms improved, peripheral blood levels of IL-1α, IL-1β, IL-7, and IL-12p70 were also remarkably reduced in rats.[78] An increase of TNF-α mediates astrocyte activation by binding to its receptor exacerbated depressive-like behavior in CUMS mice.[79] IL-6 improves depressive-like behavior by mediating the SATA/Acp5 pathway in mice with neuropathic pain.[80]

Lidocaine has demonstrated anti-inflammatory properties by reducing the levels of these pro-inflammatory cytokines.[20,21,81] It inhibits inflammation-related pathophysiologic changes, including increased levels of IL-4, IL-5, IL-13, eotaxin-1, and TNF-α.[82,83] Besides, lidocaine could attenuate local inflammation via blocking peripheral neuronal vesicular exocytosis.[81] Continuous systemic administration of lidocaine significantly reduced accumulation and p38 phosphorylation of microglial cells, thus alleviating the tactile allodynia.[84] These effects are particularly relevant for individuals with depression comorbid pain, as chronic pain is often associated with elevated inflammatory markers. IL-6 and IL-8 mediated inflammation in humans or rats elicits pain as well as depressive symptomatology.[80,85] Lopes et al discovered that inflammation, even when well controlled, causes chronic pain and depression in the later stage of the disease Analgesic therapy alone did not alleviate the depressive-like behavior, and intracerebroventricular infusion of anti-TNF antibodies blocked the depressive-like behavior and alleviated the persistent pain.[86] The anti-inflammatory properties, in addition to its analgesic properties, may allow lidocaine to be a better choice for the treatment of chronic pain combined with depression secondary to inflammatory response. It also promises the lidocaine as a potential antidepressant in some way.

## Neuroplasticity and Synaptic Remodeling

Neuroplasticity, the brain's ability to reorganize itself by forming new neural connections to various stimuli and experiences, is a fundamental mechanism underlying learning, memory, and mood regulation.[87–89] This adaptability is particularly significant in the context of mood disorders such as depression, where alterations in neural circuits and synaptic connections can lead to persistent changes in mood and behavior. The concept of neuroplasticity encompasses a range of processes, including synaptogenesis, dendritic remodeling, and changes in neurotransmitter systems, all of which contribute to the brain's capacity to maintain emotional homeostasis.[90] Targeting neuroplasticity has therefore become a promising approach in the development of novel antidepressant therapies, including the exploration of lidocaine's effects on synaptic remodeling.

Recent research has highlighted the potential of targeting neuroplasticity as a therapeutic strategy for mood disorders. For instance, modulating the NMDA receptor has been shown to induce rapid synaptogenesis and reverse synaptic deficits caused by chronic stress, offering a promising avenue for the treatment of depression.[56,59,91] Depression is associated with structural and functional changes in the brain, including reduced synaptic density, diminished dendritic complexity, and decreased levels of BDNF. BDNF is essential for synaptic plasticity and neuronal survival, and its dysregulation is implicated in the pathophysiology of depression.[92] Studies have shown that individuals with depression often exhibit lower levels of BDNF in the hippocampus and prefrontal cortex, regions critical for mood regulation. Moreover, along with the upregulation of BDNF using a drug, the mice exhibited significant improvements in synaptic reversibility and neuronal survival.[93] In the social defeat stress model, overexpression of constitutively active RAS-related C3 botulinum substrate 1 (Rac1) in nucleus accumbens abolished prunes stubby spines to accomplish synaptic remodeling and ameliorate depressive-like behavior in mice.[94] Transitions in synaptic plasticity are also involved in the development of chronic pain. Kiritoshi et al propose a progressive loss of synaptic plasticity during the transition of pain from acute to chronic.[95] Another study identified altered genes related to synaptic plasticity based on transcriptomic profiling as well as neurotransmitter imbalances indicated by altered glutamate and GABA in the Cerebrospinal Fluid in chronic pain model mice. It is believed that changed synaptic plasticity contributes to the persistence of chronic pain and associated emotional disturbances including depression.[96] Synaptic remodeling or modulation is likely to be a breakthrough in the treatment of depression, especially TRD combined with chronic pain.

In the functional dyspepsia model, abnormal signals transmitted by the vagus nerve may alter the reduction of BDNF in the central amygdala, affecting synaptic plasticity, leading to gastroparesis hypersensitivity, and inducing depressive-like behavior. Blockade of this signaling by lidocaine ventrolateral periaqueductal gray local injection reversed pain- and depressive-related behaviors in model mice.[97] An in vitro experiment demonstrates that administration of lidocaine blocks embryo spontaneous neuronal network activity triggering synaptic scaling, thus affecting synaptic plasticity.[70] Lidocaine can also suppress glycine transporter 1,[98] which in turn enhances hippocampal theta network connectivity and synaptic plasticity.[99] The rapid onset of lidocaine's effects suggests that it may induce neuroplastic changes more quickly than traditional antidepressants, making it a potentially valuable option for patients with acute depressive episodes. Moreover, lidocaine's dual action on pain and depression could be especially beneficial for individuals with comorbid conditions, as chronic pain itself is associated with disruptions in neuroplasticity. Overall, lidocaine's multifaceted pharmacological profile, including its sodium channel

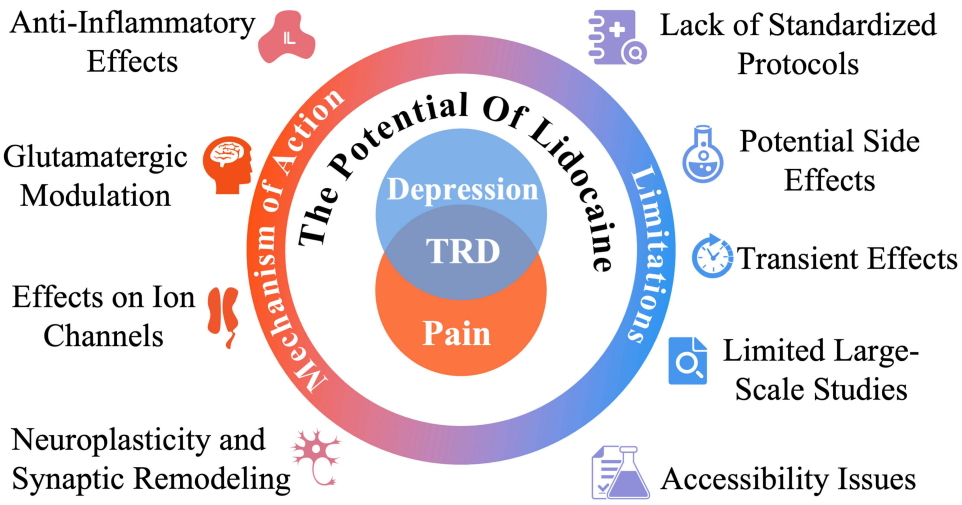


**Figure 1** A schematic overview of potential mechanism and limitation of lidocaine's antidepressant properties. The left hemisphere summarizes a hypothesis-generating neurobiological mechanisms of lidocaine treatment of TRD comorbid pain. The right hemisphere outlines the key limitations and challenges associated with its clinical application.

blockade, modulation of glutamatergic neurotransmission, anti-inflammatory effects, and promotion of neuroplasticity (Figure 1), suggests a promising role in the treatment of depression, particularly in cases resistant to conventional therapies.

## Clinical Evidence for Lidocaine in Depression

Emerging evidence suggests intravenous lidocaine may offer potential rapid antidepressant effects in depression. Recent randomized controlled trials demonstrate that patients receiving lidocaine infusions (a 1.5 mg/kg bolus of intravenous (IV) followed by continuous IV infusion of 1.5 mg/kg/h) often report rapid improvements in mood, with effects emerging within hours and lasting for several days.[100] Although this conclusion is based on a randomized controlled trial (RCT) with a high level of evidence, its interpretation is limited by the small sample size and the reliance on secondary outcomes. It was observed that lidocaine has a fast onset of action, while a single IV injection of 50 or 100 mg has a short duration of 10–20 minutes.[101] In the same period, another study also confirmed a half-life of about 10–20 minutes 1 hour after a bonus intravenous of lidocaine.[102] Whereas without a bonus dose, patients on continuous IV infusion of lidocaine reached acceptable blood levels within 30–60 minutes, and half-life was also 10–20 minutes.[103] Previous studies have established that lidocaine possesses a rapid onset of action and metabolism after IV which sets the pharmacokinetic basis for the rapid onset of action of lidocaine and also brings concerns about the duration of action. Another RCT identified pulsed radiofrequency combined with continuous postoperative intravenous infusion of lidocaine effectively alleviates subacute postherpetic neuralgia and concurrently reduced patient's anxiety and depression symptoms. However, in contrast to the sustained improvement in pain and anxiety, the antidepressant effect was observed only during the period of lidocaine administration.[104] Local use of lidocaine also had been implicated to regulate mood including alleviating depression scores while treating pain. A randomized, double blinded, placebo-controlled trial found local use of lidocaine relief depression status at 6-month follow-up [(95% CI): 2.2 (1.83–2.56), p=0.001, 4 weeks; (95% CI): 4.4 (4.03–4.76), p=0.001, 6 months].[105] Another randomized controlled trial also suggested local injection of lidocaine improves depression scores while reducing pain.[106] Therefore, the observed depressive symptom reduction may partly reflect indirect benefits related to pain relief, improved physical functioning, overall recovery rather than a direct antidepressant pharmacological effect of lidocaine. Additionally, nonspecific factors such as anxiolysis associated with procedural care, improved patient–clinical interaction, or expectancy effects cannot be fully excluded.[107,108]

This pharmacokinetic-independent long-term effect also suggests that lidocaine may accomplish these effects beyond classical sodium channel blockade. It is worth noting that these studies primarily targeted pain outcomes, it remains difficult to distinguish direct antidepressant effects from secondary depressive symptom reduction related to analgesia, functional recovery, or reduced symptom burden. A meta-analysis of 14 RCTs investigating the association between perioperative

intravenous lidocaine and subjective quality of recovery demonstrated that the lidocaine group had significantly higher emotional status scores compared with the placebo group.[109] This finding was based on data from 9 of the 14 RCTs, encompassing 769 patients. However, it is important to note that emotional status was assessed as a secondary outcome in these trials, and a substantial proportion of cases were not evaluated using standardized depression scales.

The limited clinical and animal experimental evidence supporting lidocaine as a treatment for simple depression may stem from the strong public perception of its local anesthetic effects. Consequently, numerous studies have explored lidocaine for treating depression associated with chronic pain or comorbid pain, a prevalent and significant subtype of TRD. Lidocaine has a well-established molecular mechanism for depression comorbid with pain. Beyond its rapid-acting analgesic properties, whether administered locally or intravenously, also targets the pathogenesis of depression, such as anti-inflammatory, synaptic remodeling, and glutamatergic modulation.[55,70,81,110] Further research on lidocaine as a potential treatment for depression, especially TRD, could expand clinical options and enhance decision-making in depression management.

Despite the promising findings outlined above, it is crucial to acknowledge that clinical evidence supporting lidocaine's antidepressant efficacy remains preliminary. As shown in Table 1, the existing body of research is characterized by small sample sizes, heterogeneous study designs, and often, the assessment of depressive symptoms as a secondary outcome in trials primarily focused on pain relief. Furthermore, not all studies report positive mood outcomes; some trials have found no significant difference between lidocaine and placebo on depression. A multicenter randomized controlled trial suggested that perioperative lidocaine IV failed to improve postoperative depressive states.[111] Although these findings were derived from secondary outcomes and were not assessed using standardized depression rating scales, they nonetheless suggest that the therapeutic efficacy of lidocaine for pain-associated depression remains questionable.

# Potential Benefits, Limitations, and Challenges

## Potential Benefits and Comparative Perspective

Lidocaine presents a unique profile of potential benefits that warrants its investigation as an antidepressant, particularly when viewed in the context of existing therapies and the limitations of current evidence.

One of the most compelling potential advantages is its capacity for rapid symptom alleviation. Traditional antidepressants, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, often require weeks to achieve therapeutic effects due to the time needed for synaptic and neuroplastic adaptations. In contrast, intravenous lidocaine administration can lead to significant pain relief within hours,[112] which may indirectly improve mood in patients suffering from chronic pain.[31] This rapid pharmacological action, primarily attributed to its fast blockade of voltage-gated sodium

**Table 1** Summary of Clinical Studies for Lidocaine in Depression

| Study | Study Design | Population | Age/ Sample Size | Dosage Regimen | Primary Outcome | Depression Measures | Depression Improve/ Duration | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| Li, et al[100] | DB RCT | Patients with Thyroidectomy | 18–65/117 | IV 1.5 mg/kg bolus+1.5 mg/kg/h perioperative | QoR-40 | SDS Score | Yes/2 d[a] | NR |
| Zhang, et al[104] | RCT | Patients with SHN | 50–75/64 | IV 3 mg/kg at a rate of 25 mL/h for 2 h | VAS | SDS Score | Yes/5 d | Dizziness and Vomiting[b] |
| Nambi, et al[105] | DB RCT | Patients with frozen shoulder | 18–60/60 | 50mg Local Injection | VAS | HADS | Yes/6 m | No |
| Karadaş, et al[106] | DB RCT | Patients with TTH | 18–65/48 | Multiple localized injections | VAS | HDS | Yes/3 m | Injection pain and Dizziness[c] |
| Hung, et al[109] | Meta-analysis | Patients undergo surgeries | 18–65/769 | IV 1.5 or 2 mg/kg bolus +1–3 mg/kg/h perioperative | QoR-40 | QoR-40 | Yes/NR | Not Reported |
| Paterson, et al[111] | DB RCT[d] | Patients undergo MIC | ≥18/495 | IV 1.5-mg/kg bolus+1.5 mg/kg/h for 6 or 12 h | GI-3 | QoR-15 | No/NR | No |

**Notes**: [a]The SDS assessments were only conducted up to second day postoperative. [b]3 patients experienced injections site and injection pain; 2 experienced dizziness; [c]1 patient experienced dizziness, 3 patients experienced vomiting; [d]This research was a multicentral DB RCT.

**Abbreviations**: DB, Double Blind; RCT, Randomized Controlled Trial; IV, intravenous; QoR-40, Quality of Recovery 40; SDS, Self-Rating Depression Scale; SHN, Subacute Herpe Zoster Neuralgia; NR, Not Reported; VAS, visual analog scale; HADS, Hospital Anxiety and Depression Scale; TTH, Tension-type headache; HDS, Hamilton depression scores; MIC, Minimally Invasive Colectomy; GI-3, The time point at which the patient first tolerates solid food and has their first bowel movement or passes wind.

channels,[113] could be particularly advantageous for individuals with severe depression or suicidal ideation who require immediate relief. Moreover, some reported depressive symptom reduction could arise from broader nonspecific therapeutic effects, including reduced anxiety related to pain control, improved sleep following analgesia, or placebo responses associated with interventional treatments.[114,115] These possibilities highlight the importance of interpreting current findings cautiously, particularly in studies where depressive symptoms were measured as secondary outcomes rather than primary endpoints. However, it is crucial to note that current evidence remains insufficient to substantiate a direct and independent rapid antidepressant effect of lidocaine, highlighting a key area for further research.

Emerging evidence suggests that lidocaine's effects extend beyond acute symptom relief and may contribute to long-term neuroprotection.[116] Depression is associated with neuroinflammation, oxidative stress, and impaired neuroplasticity, all of which can lead to structural and functional brain changes. Lidocaine has been found to reduce neuroinflammatory markers,[117] decrease excitotoxicity through NMDA receptor modulation, and enhance synaptic plasticity[118] mechanisms that are crucial for sustained mood stabilization. A comparative perspective with ketamine, the established rapid-acting antidepressant,[119] helps define lidocaine's potential niche. Both agents modulate the NMDA receptor, contributing to rapid onset. However, ketamine is a high-affinity NMDA antagonist with known dissociative side effects and abuse potential, whereas lidocaine offers a broader mechanism (including sodium channel blockade) and lacks these psychiatric side effects, though it carries risks of dose-dependent cardiovascular and CNS toxicity. This profile suggests lidocaine might suit specific subpopulations, such as patient with TRD and significant pain comorbidity or those intolerant to ketamine's dissociative effects.

The dual targeting of pain and depression is another significant benefit. Depression and chronic pain share overlapping neurobiological mechanisms. Lidocaine's broad pharmacological profile-encompassing sodium channel blockade, NMDA receptor modulation, anti-inflammatory effects, and promotion of neuroplasticity-allows it to address multiple pathways simultaneously.[55,70,81,118] Research indicates that lidocaine's analgesic properties may confer benefits in mood regulation,[26] as chronic pain itself is a major risk factor for the development and persistence of depression.[120–122] By blocking voltage-gated sodium channels and modulating NMDA receptor activity, lidocaine reduces neuronal hyperexcitability, thereby alleviating both physical pain and emotional distress.[113,118] This makes it an attractive option for substantial subpopulation of individuals with comorbid chronic pain and depression, where conventional mono-mechanistic treatments often fall short.

From a practical standpoint, lidocaine a well-established safety and accessibility profile in its traditional uses. Its pharmacokinetics, dosing strategies, and potential side effects are well-documented, allowing for controlled administration in medical settings. When used under controlled conditions, it has demonstrated a favorable safety profile, with transient and manageable side effects (eg, dizziness, nausea).[123] Furthermore, it is a relatively affordable and widely available medication, potentially lowering the barrier to treatment for some patients.

However, this proposition is tempered by the significant limitations of the current evidence base. The clinical findings supporting lidocaine's antidepressant efficacy, as discussed in Pharmacological Mechanism of Lidocaine, are preliminary. The existing body of research is characterized by small sizes, heterogeneous study designs, and often, the assessment of depressive symptoms as a secondary outcome in pain trials. This introduces potential bias and limits generalizability. Furthermore, not all studies report positive mood outcomes, underscoring the need to identify predictors of response. Therefore, while the potential benefits are theoretically sound and supported by early data, they must be considered hypothetical until by large-scale, well-controlled trials that directly compare lidocaine to both placebo and established rapid-acting therapies like ketamine.

## Safety and Limitations

Despite lidocaine's safety profile in anesthesia, the systemic use of lidocaine for psychiatric indications, particularly at higher doses or with repeated administration, necessitates a rigorous evaluation of its potential risks.

Lidocaine's adverse effects are markedly dose dependent. CNS toxicity is the most common concern, presenting initially as dizziness, perioral numbness, and tinnitus, which can progress to tremors, drowsiness, and even seizures at higher plasma concentrations.[124] Animal studies have shown that systemic administration of high-dose lidocaine can induce neurotoxicity in emotion-related brain regions such as the hippocampus and amygdala,[125] raising important safety concerns for its long-term use in depression. Cardiovascular toxicity typically occurs at even higher doses, manifesting as negative inotropy,

hypotension, and arrhythmias. Furthermore, lidocaine is primarily metabolized by the liver, posing a risk of prolonged half-life and accumulation in patients with hepatic impairment or the elderly.[126]

Studies suggest that the antidepressant effects of lidocaine are short-lived. For example, one study found that lidocaine infusion significantly improved anxiety and depression symptoms, but these effects were observed only two weeks post-infusion, indicating that the duration may be limited.[26] Another study reported that lidocaine was effective in reducing anxiety and depression in patients with chronic tension-type headaches, though it did not specify the duration of these effects.[106]

To mitigate these risks and limitations, the implementation of lidocaine for depression treatment must be accompanied by strict clinical protocols. This involves employing standardized, weight-based infusion protocols that initiate with lower doses and are titrated slowly. Continuous monitoring of cardiovascular and neurological status during infusion is commonly recommended in clinical practice because lidocaine can affect cardiac conduction and central nervous system activity, particularly at higher doses or in vulnerable populations.[127–129] Such monitoring requirements may increase the logistical complexity of administering lidocaine in routine psychiatric settings. Administration must be confined to a medical setting equipped with resuscitation facilities and personnel, ensuring continuous monitoring of Electrocardiography, blood pressure, and oxygen saturation throughout the procedure. If feasible, therapeutic drug monitoring is also essential. Healthcare staff should be specifically trained to recognize the early premonitory signs of CNS toxicity. Furthermore, careful patient selection is paramount, avoiding use in individuals with severe cardiac conduction blocks, significant hepatic impairment, or a history of epilepsy. Currently, safety data regarding repeated or long-term intravenous lidocaine infusions for depression are scarce, representing a critical area for focus in future clinical trials.

## Challenges in Clinical Implementation

One of the challenges in clinical implementation is the need to position lidocaine relative to existing treatments. Ketamine has garnered substantial clinical evidence and regulatory acceptance as a rapid-acting antidepressant, particularly for TRD.[130,131] Its well-documented efficacy and safety profile set a high standard. While lidocaine shows promise due to its dual action on pain and mood regulation, it must demonstrate clear, distinct benefits over ketamine to justify its adoption, especially in a competitive therapeutic landscape.[26] Clinicians may be more inclined to use treatments with robust data and established protocols. Shifting the paradigm to include lidocaine requires overcoming skepticism and inertia within the medical community.

There is currently no consensus on the optimal dosing regimen, infusion duration, or frequency for achieving antidepressant effects. This lack of standardization can lead to variability in outcomes and increased risk of adverse effects. The anesthetic effects of lidocaine are typically transient, necessitating repeated administrations.[132] Lidocaine has a relatively narrow therapeutic window, and systemic toxicity-including neurological symptoms (eg, dizziness, seizures) and cardiovascular complications such as arrhythmias-may occur when plasma concentrations exceed safe thresholds.[129,133] For individuals with special constitutions such as obesity or debility, medication administration differs from that for ordinary individuals and requires even greater caution.[111,128,129] Moreover, unlike oral antidepressants, intravenous administration requires infusion facilities, monitoring equipment, and trained personnel, which may not be routinely available in psychiatric clinics.[134] These logistical constraints could limit widespread clinical adoption unless simplified protocols, clear safety guidelines, and integrated care pathways are developed. Frequent treatments may burden patients, potentially affecting adherence and overall satisfaction with the treatment regimen. The need for continual infusions implies higher cumulative costs, not only in terms of direct treatment expenses but also in terms of time and healthcare personnel.

Using lidocaine off-label in psychiatry brings additional risks and uncertainties. Although lidocaine has a well-established safety profile in its traditional uses, its effects and side-effect profile in the context of depression require rigorous monitoring. This includes managing potential cardiovascular effects, central nervous system toxicity, and other adverse reactions.

Many psychiatric practitioners lack familiarity with lidocaine administration, as it traditionally falls within the domain of anesthesiology or pain management. Training is particularly important for lidocaine administration involves intravenous delivery and carries a risk of systemic toxicity if dosing or monitoring procedures are not correctly followed.[129,135,136] Without sufficient clinical training, there may be an increased risk of dosing errors, delayed identification of neurological or

cardiovascular adverse effects, or inadequate patient monitoring during infusion. Implementing this treatment would likely necessitate cross-disciplinary collaboration, additional training, and the development of specialized treatment protocols to ensure safe and effective administration. In practice, this may include structured training programs for psychiatric clinicians and nursing staff, the development of standardized clinical guidelines for lidocaine infusion, and collaboration with anesthesiology or pain medicine specialists to provide oversight and technical support during early stages of clinical implementation. Without formal approval for depression, using lidocaine remains off-label, which may deter many clinicians from adopting this treatment due to legal and institutional constraints.[137] Hospitals and clinics may have strict policies regarding off-label use, necessitating additional oversight, documentation, and justification, all of which add to the complexity of integrating lidocaine into psychiatric treatment protocols.

The transition of lidocaine from a traditional anesthetic to a potential treatment for depression faces multifaceted challenges. Regulatory hurdles, the need for repeated infusions, comparisons with established rapid-acting antidepressants like ketamine, and the inherent risks of off-label use all contribute to a complex clinical landscape. Mitigating these challenges necessitates rigorous clinical trials, the establishment of standardized treatment protocols, and strengthened interdisciplinary collaboration to facilitate the successful integration of lidocaine into psychiatric practice.

## Future Research Directions

To fully understand lidocaine's role in depression treatment, several key areas require further exploration. The most important and desirable is clinical trials and long-term efficacy of lidocaine in treating depression. One of the most pressing research needs is the execution of large-scale, randomized controlled trials assessing lidocaine's effectiveness in depression. Importantly, some reported improvements in depressive symptoms may be secondary to analgesic effects, anxiolytic responses, or nonspecific treatment-related factors, underscoring the need for future trials specifically designed to isolate direct antidepressant effects. Future RCTs should use standardized depression endpoints (eg, Montgomery-Åsberg Depression Rating Scale or Hamilton Depression Rating Scale) as primary outcomes, include placebo-controlled or active comparator arms, and apply clearly defined TRD criteria with stratification by pain phenotype or inflammatory status. Specifically, studies should: (a) compare lidocaine's effects with placebo and standard antidepressant treatments; (b) define IV dosing protocols (bolus versus continuous infusion), frequency, and treatment duration to determine the optimal regimen for sustained antidepressant effects; (c) investigate lidocaine's long-term safety profile, particularly in patients requiring repeated infusions; (d) determine whether specific subgroups (eg, those with comorbid pain, inflammation, or neurochemical imbalances) experience greater benefits. Additionally, studies should assess how lidocaine compares to ketamine, another rapidly acting antidepressant that also modulates glutamatergic pathways. Determining whether lidocaine offers similar benefits with fewer side effects could influence its adoption in psychiatric practice.

Given that lidocaine's antidepressant effects appear transient, it may be most effective when used as part of a multimodal treatment strategy. Research might be anchored in the synergistic effects of lidocaine with other antidepressants or anti-depressive treatments. Investigating whether lidocaine enhances the efficacy of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants. Exploring whether combining lidocaine with transcranial magnetic stimulation or electroconvulsive therapy yields synergistic benefits. Combination therapies may improve outcomes by addressing both the neurochemical and psychological components of depression, offering a more comprehensive treatment approach.

## Conclusion

Lidocaine, a widely used local anesthetic, has emerged as a candidate adjunctive intervention for depression, particularly in individuals with TRD and comorbid chronic pain. Its pharmacological actions—such as sodium channel blockade, glutamatergic modulation, anti-inflammatory effects, and promotion of neuroplasticity—provide a mechanistic and hypothesis-generating neurobiological rationale for potential antidepressant properties (Table 2), although much of this support remains preclinical or hypothesis-generating. Clinical studies suggest that lidocaine may produce rapid depressive symptom reduction in some patients, especially those with comorbid depression and pain; however, the evidence specifically from trials designed with depressant outcomes as primary endpoints in limited. The evidence remains inconsistent due to small sample sizes, heterogeneous study designs, and methodological differences, including short follow-up durations and differences in dosing and monitoring protocols,

**Table 2** Potential Molecular Targets Involved in Lidocaine Treatment for TRD Comorbid Pain

| Category | Targets |
|---|---|
| Effects on Ion Channel | Block VGSCs, Kir family, Kv1.1, Kv3.1, and TRP |
| Glutamatergic Modulation | NMDA receptors, AMPA receptors, glutamate transport system, EAAT3 activity |
| Anti-Inflammatory | Pro-inflammatory cytokines (eg. IL-3, IL-6, TNF-α) microglial cell, p38 phosphorylation |
| Neuroplasticity and Synaptic Remodeling | Synaptic plasticity, BDNF and synaptic plasticity related signaling |

**Abbreviations**: TRD, Treatment-Resistant Depression; VGSCs, Voltage-Gated Sodium Channels; Kir, Inwardly Rectifying Potassium channel; Kv, Voltage-Gated Potassium channel; TRP, Transient Receptor Potential channel; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT3, Excitatory Amino Acid Transporter 3; IL, Interleukin; TNF, Tumor Necrosis Factor; BDNF, Brain-Derived Neurotrophic Factor.

which undermine the reliability and generalizability. Many studies lack blinding, use inadequate control groups, or assess depression as a secondary endpoint, complicating the direct evaluation of lidocaine's antidepressant effects. Additionally, publication and selection biases, along with variability in outcome measures, dosing protocols, and treatment settings, further hinder definitive conclusions about its efficacy and safety. Overall, the current clinical evidence is preliminary and of variable quality. Several critical questions remain unanswered, including the long-term safety with repeated use, optimal dosing for sustained antidepressant effects, and identification of reliable biomarkers or clinical predictors of response. Further studies should prioritize well-powered, double-blind randomized controlled trials with depression severity as a primary endpoint, standardized intravenous protocols, appropriate safety monitoring, and stratification by TRD definition and pain phenotype. Addressing these gaps is essential to determine whether lidocaine can be meaningfully incorporate into depression treatment algorithms. Until such data are available, its role should be considered investigational rather than established.

## Acknowledgments

The technical support provided by the research staff at the First Affiliated Hospital of Dalian Medical University. Financial support from the [Scientific Research Projects from Wuhan Municipal Health Commission (WX23Z26)], the [Key R&D Projects in Liaoning Province (2024JH2/102500060)], the [Natural Science Foundation of Liaoning Province (2024-MS-154)], and the [2025 Chronic Disease Management Research Project (GWJJMB202510042014)], which facilitated the execution of this research. Any other individuals or organizations who contributed but did not meet the criteria for authorship. Co-first authors: Min Xia and Jinnian Duan.

## Disclosure

The authors declare that they have no conflicts of interest related to the publication of this manuscript. No financial relationships with any organizations, government entities, or companies influenced this work.

## References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9
2. World Health Organization. Depression and other common mental disorders: global health estimates; 2017. Available from: https://iris.who.int/handle/10665/254610. Accessed March 31, 2026.
3. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. *Br J Psychiatry*. 2013;202(1):22–27. doi:10.1192/bjp.bp.112.112169
4. Jain S, Gupta S, Li VW, Suthoff E, Arnaud A. Humanistic and economic burden associated with depression in the United States: a cross-sectional survey analysis. *BMC Psychiatry*. 2022;22(1):542. doi:10.1186/s12888-022-04165-x
5. Arias D, Saxena S, Verguet S. Quantifying the global burden of mental disorders and their economic value. *EClinicalMedicine*. 2022;54:101675. doi:10.1016/j.eclinm.2022.101675
6. Baik SY, Shin KE, Fitzsimmons-Craft EE, et al. The relationship of race, ethnicity, gender identity, sex assigned at birth, sexual orientation, parental education, financial hardship and comorbid mental disorders with quality of life in college students with anxiety, depression or eating disorders. *J Affect Disord*. 2024;366:335–344. doi:10.1016/j.jad.2024.08.098
7. Sakaguchi R, Mori Y. Transient receptor potential (TRP) channels: biosensors for redox environmental stimuli and cellular status. *Free Radic Biol Med*. 2020;146:36–44. doi:10.1016/j.freeradbiomed.2019.10.415
8. Kudlow PA, Cha DS, McIntyre RS. Predicting treatment response in major depressive disorder: the impact of early symptomatic improvement. *Can J Psychiatry*. 2012;57(12):782–788. doi:10.1177/070674371205701211
9. Prasartpornsirichoke J, Pityaratstian N, Poolvoralaks C, et al. The prevalence and economic burden of treatment-resistant depression in Thailand. *BMC Public Health*. 2023;23(1):1541. doi:10.1186/s12889-023-16477-y

10. De La Rosa JS, Brady BR, Ibrahim MM, et al. Co-occurrence of chronic pain and anxiety/depression symptoms in U.S. adults: prevalence, functional impacts, and opportunities. *Pain*. 2024;165(3):666–673. doi:10.1097/j.pain.0000000000003056
11. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976–1982. doi:10.1097/j.pain.0000000000001939
12. Li XJ, Wu S, Liu ZH, et al. CXCR2 modulates chronic pain comorbid depression in mice by regulating adult neurogenesis in the ventral dentate gyrus. *Acta Pharmacol Sin*. 2025. doi:10.1038/s41401-025-01496-9
13. Ma Y, Xiang Q, Yan C, Liao H, Wang J. Relationship between chronic diseases and depression: the mediating effect of pain. *BMC Psychiatry*. 2021;21(1):436. doi:10.1186/s12888-021-03428-3
14. Sun M, Wang X, Lu Z, et al. Chronic postsurgical pain increases postoperative depression risk. *J Epidemiol Community Health*. 2025: jech–2024–222761. doi:10.1136/jech-2024-222761
15. Tagliaferri SD, Nguyen J, Han LKM, et al. Exploring the associations between the presence, characteristics, and biopsychosocial covariates of pain and lifetime depression in adolescents: a cross-sectional ABCD study analysis. *J Affect Disord*. 2025;372:106–116. doi:10.1016/j.jad.2024.12.025
16. Scaini S, Davies S, De Francesco S, Pelucchi A, Rubino S, Battaglia M. Altered pain perception and nociceptive thresholds in major depression and anxiety disorders: a meta-analysis. *Neurosci Biobehav Rev*. 2025;169:106014. doi:10.1016/j.neubiorev.2025.106014
17. Liu X, Hou Z, Han M, et al. Salvianolic acid B alleviates comorbid pain in depression induced by chronic restraint stress through inhibiting GABAergic neuron excitation via an ERK-CREB-BDNF axis-dependent mechanism. *J Psychiatr Res*. 2022;151:205–216. doi:10.1016/j.jpsychires.2022.04.014
18. Wang X, Wu S, Zuo J, et al. Selective activation of SIGMAR1 in anterior cingulate cortex glutamatergic neurons facilitates comorbid pain in depression in male mice. *Commun Biol*. 2025;8(1):150. doi:10.1038/s42003-025-07590-2
19. Liu Y, Jin F, Chen Q, et al. PDGFR-α mediated the neuroinflammation and autophagy via the JAK2/STAT3 signaling pathway contributing to depression-like behaviors in myofascial pain syndrome rats. *Mol Neurobiol*. 2024. doi:10.1007/s12035-024-04616-4
20. Klinger RY, Cooter M, Berger M, et al. Effect of intravenous lidocaine on the transcerebral inflammatory response during cardiac surgery: a randomized-controlled trial. *Can J Anaesth*. 2016;63(11):1223–1232. doi:10.1007/s12630-016-0704-0
21. Su D, Gu Y, Wang Z, Wang X. Lidocaine attenuates proinflammatory cytokine production induced by extracellular adenosine triphosphate in cultured rat microglia. *Anesth Analg*. 2010;111(3):768–774. doi:10.1213/ANE.0b013e3181e9e897
22. Popp SS, Lei B, Kelemen E, Fenton AA, Cottrell JE, Kass IS. Intravenous antiarrhythmic doses of lidocaine increase the survival rate of CA1 neurons and improve cognitive outcome after transient global cerebral ischemia in rats. *Neuroscience*. 2011;192:537–549. doi:10.1016/j.neuroscience.2011.06.086
23. Li J, Zhu X, Yang S, et al. Lidocaine attenuates cognitive impairment after isoflurane anesthesia by reducing mitochondrial damage. *Neurochem Res*. 2019;44(7):1703–1714. doi:10.1007/s11064-019-02799-0
24. Tripathi SJ, Chakraborty S, Rao BSS. Remediation of chronic immobilization stress-induced negative affective behaviors and altered metabolism of monoamines in the prefrontal cortex by inactivation of basolateral amygdala. *Neurochem Int*. 2020;141:104858. doi:10.1016/j.neuint.2020.104858
25. de Oliveira Rocha R, Teixeira MJ, Yeng LT, et al. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study. *Pain*. 2014;155(11):2274–2281. doi:10.1016/j.pain.2014.08.015
26. Liu H, Lu F, Zhou D, et al. The analgesic and emotional response to intravenous lidocaine infusion in the treatment of postherpetic neuralgia: a randomized, double-blinded, placebo-controlled study. *Clin J Pain*. 2018;34(11):1025–1031. doi:10.1097/AJP.0000000000000623
27. Bant JS, Aman TK, Raman IM. Antagonism of lidocaine inhibition by open-channel blockers that generate resurgent Na current. *J Neurosci*. 2013;33(11):4976–4987. doi:10.1523/JNEUROSCI.3026-12.2013
28. Prica C, Hascoet M, Bourin M. Antidepressant-like effect of lamotrigine is reversed by veratrine: a possible role of sodium channels in bipolar depression. *Behav Brain Res*. 2008;191(1):49–54. doi:10.1016/j.bbr.2008.03.007
29. Zhang B, Shi X, Liu X, et al. Discovery ofE0199: a novel compound targeting both peripheral NaV and KV7 channels to alleviate neuropathic pain. *J Pharm Anal*. 2025;15(1):101132. doi:10.1016/j.jpha.2024.101132
30. Middleton SJ, Perini I, Themistocleous AC, et al. Nav1.7 is required for normal C-low threshold mechanoreceptor function in humans and mice. *Brain*. 2022;145(10):3637–3653. doi:10.1093/brain/awab482
31. Aaron RV, Ravyts SG, Carnahan ND, et al. Prevalence of depression and anxiety among adults with chronic pain: a systematic review and meta-analysis. *JAMA Network Open*. 2025;8(3):e250268. doi:10.1001/jamanetworkopen.2025.0268
32. Pagliusi M, Bonet IJM, Lemes JBP, et al. Social defeat stress-induced hyperalgesia is mediated by nav 1.8+ nociceptive fibers. *Neurosci Lett*. 2020;729:135006. doi:10.1016/j.neulet.2020.135006
33. Riga MS, Pérez-Fernández M, Miquel-Rio L, et al. Scn1a haploinsufficiency in the prefrontal cortex leads to cognitive impairment and depressive phenotype. *Brain*. 2024;147(12):4169–4184. doi:10.1093/brain/awae167
34. Zhang T, Rao QM, He YY, Cai JT, Liu HY, Lin YL. [Association of SCN2A, ABCB1 and CYP2C19*3 with genetic susceptibility to major depressive disorder]. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2022;56(3):287–294. Chinese. doi:10.3760/cma.j.cn112150-20211021-00973
35. Xia M, Wang B, Lu J, et al. Sodium channel Nav1.6 involved in modulating isoflurane-induced perioperative cognitive disorder of mice. *Eur J Pharmacol*. 2026;1015:178545. doi:10.1016/j.ejphar.2026.178545
36. Iqbal MK, Supratik K, Khan B, et al. Protective effect of scorpion-venom heat-resistant peptide (SVHRSP) against depression associated with Parkinson's disease via suppression of CREB-Akt pathway-mediated inflammation. *Br J Pharmacol*. 2026. doi:10.1111/bph.70364
37. Wang J, Yang Y, Liu J, et al. Loss of sodium leak channel (NALCN) in the ventral dentate gyrus impairs neuronal activity of the glutamatergic neurons for inflammation-induced depression in male mice. *Brain Behav Immun*. 2023;110:13–29. doi:10.1016/j.bbi.2023.02.013
38. Nakahira K, Oshita K, Itoh M, Takano M, Sakaguchi Y, Ishihara K. Clinical concentrations of local anesthetics bupivacaine and lidocaine differentially inhibit human Kir2.x inward rectifier K+ channels. *Anesth Analg*. 2016;122(4):1038–1047. doi:10.1213/ANE.0000000000001137
39. Olschewski A, Hempelmann G, Vogel W, Safronov BV. Blockade of Na+ and K+ currents by local anesthetics in the dorsal horn neurons of the spinal cord. *Anesthesiology*. 1998;88(1):172–179. doi:10.1097/00000542-199801000-00025
40. Trellakis S, Benzenberg D, Urban BW, Friederich P. Differential lidocaine sensitivity of human voltage-gated potassium channels relevant to the auditory system. *Otol Neurotol*. 2006;27(1):117–123. doi:10.1097/01.mao.0000186443.11832.8a

41. Kobayashi T, Washiyama K, Ikeda K. Inhibition of G protein-activated inwardly rectifying K+ channels by the antidepressant paroxetine. *J Pharmacol Sci*. 2006;102(3):278–287. doi:10.1254/jphs.fp0060708
42. Kim S, Shou J, Abera S, Ziff EB. Sucrose withdrawal induces depression and anxiety-like behavior by Kir2.1 upregulation in the nucleus accumbens. *Neuropharmacology*. 2018;130:10–17. doi:10.1016/j.neuropharm.2017.11.041
43. Fan Y, Kong H, Ye X, Ding J, Hu G. ATP-sensitive potassium channels: uncovering novel targets for treating depression. *Brain Struct Funct*. 2016;221(6):3111–3122. doi:10.1007/s00429-015-1090-z
44. Miyata S, Taniguchi M, Koyama Y, et al. Association between chronic stress-induced structural abnormalities in Ranvier nodes and reduced oligodendrocyte activity in major depression. *Sci Rep*. 2016;6:23084. doi:10.1038/srep23084
45. Chen J, Winston JH, Fu Y, et al. Genesis of anxiety, depression, and ongoing abdominal discomfort in ulcerative colitis-like colon inflammation. *Am J Physiol Regul Integr Comp Physiol*. 2015;308(1):R18–R27. doi:10.1152/ajpregu.00298.2014
46. Leffler A, Fischer MJ, Rehner D, et al. The vanilloid receptor TRPV1 is activated and sensitized by local anesthetics in rodent sensory neurons. *J Clin Invest*. 2008;118(2):763–776. doi:10.1172/JCI32751
47. Piao LH, Fujita T, Jiang CY, et al. TRPA1 activation by lidocaine in nerve terminals results in glutamate release increase. *Biochem Biophys Res Commun*. 2009;379(4):980–984. doi:10.1016/j.bbrc.2008.12.183
48. Dai Y. TRPs and pain. *Semin Immunopathol*. 2016;38(3):277–291. doi:10.1007/s00281-015-0526-0
49. Wang M, Gu Y, Meng S, et al. Association between TRP channels and glutamatergic synapse gene polymorphisms and migraine and the comorbidities anxiety and depression in a Chinese population. *Front Genet*. 2023;14:1158028. doi:10.3389/fgene.2023.1158028
50. Lin YW, Cheng SW, Liu WC, et al. Chemogenetic targeting TRPV1 in obesity-induced depression: unveiling therapeutic potential of eicosapentaenoic acid and acupuncture. *Brain Behav Immun*. 2025;123:771–783. doi:10.1016/j.bbi.2024.10.028
51. Li W, Xu Y, Liu Z, et al. TRPV4 inhibitor HC067047 produces antidepressant-like effect in LPS-induced depression mouse model. *Neuropharmacology*. 2021;201:108834. doi:10.1016/j.neuropharm.2021.108834
52. Ulrich M, Wissenbach U, Thiel G. The super-cooling compound icilin stimulates c-Fos and Egr-1 expression and activity involving TRPM8 channel activation, Ca2+ ion influx and activation of the ternary complex factor Elk-1. *Biochem Pharmacol*. 2020;177:113936. doi:10.1016/j.bcp.2020.113936
53. Sugimoto M, Uchida I, Mashimo T. Local anaesthetics have different mechanisms and sites of action at the recombinant N-methyl-D-aspartate (NMDA) receptors. *Br J Pharmacol*. 2003;138(5):876–882. doi:10.1038/sj.bjp.0705107
54. Hahnenkamp K, Durieux ME, Hahnenkamp A, et al. Local anaesthetics inhibit signalling of human NMDA receptors recombinantly expressed in Xenopus laevis oocytes: role of protein kinase C. *Br J Anaesth*. 2006;96(1):77–87. doi:10.1093/bja/aei271
55. Zhang L, Tanabe K, Yanagidate F, et al. Different effects of local anesthetics on extracellular signal-regulated kinase phosphorylation in rat dorsal horn neurons. *Eur J Pharmacol*. 2014;734:132–136. doi:10.1016/j.ejphar.2014.03.048
56. Zhang J, Duan J, Li W, et al. An antidepressant mechanism underlying the allosteric inhibition of GluN2D-incorporated NMDA receptors at GABAergic interneurons. *Sci Adv*. 2025;11(10):eadq0444. doi:10.1126/sciadv.adq0444
57. Cao K, Zhong J, Wang S, et al. SiNiSan exerts antidepressant effects by modulating serotonergic/GABAergic neuron activity in the dorsal raphe nucleus region through NMDA receptor in the adolescent depression mouse model. *J Ethnopharmacol*. 2024;328:118040. doi:10.1016/j.jep.2024.118040
58. Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011;475(7354):91–95. doi:10.1038/nature10130
59. Tian Y, Yang XW, Chen L, et al. Activation of CRF/CRFR1 signaling in the central nucleus of the amygdala contributes to chronic stress-induced exacerbation of neuropathic pain by enhancing GluN2B-NMDA receptor-mediated synaptic plasticity in adult male rats. *J Pain*. 2024;25(8):104495. doi:10.1016/j.jpain.2024.02.009
60. Wu JL, Kuang WQ, Zhu ZY, et al. Upregulation of NR2B subunits of NMDA receptors in the lateral parabrachial nucleus contributes to chronic pancreatitis pain. *CNS Neurosci Ther*. 2025;31(3):e70313. doi:10.1111/cns.70313
61. Gerhard DM, Pothula S, Liu RJ, et al. GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *J Clin Invest*. 2020;130(3):1336–1349. doi:10.1172/JCI130808
62. Yang PS, Peng HY, Lin TB, et al. NMDA receptor partial agonist GLYX-13 alleviates chronic stress-induced depression-like behavior through enhancement of AMPA receptor function in the periaqueductal gray. *Neuropharmacology*. 2020;178:108269. doi:10.1016/j.neuropharm.2020.108269
63. Liang Z, Li L, Bai L, et al. Spinal nerve transection-induced upregulation of SAP97 via promoting membrane trafficking of GluA1-containing AMPA receptors in the dorsal horn contributes to the pathogenesis of neuropathic pain. *Neurobiol Dis*. 2024;194:106471. doi:10.1016/j.nbd.2024.106471
64. Kopach O, Dobropolska Y, Belan P, Voitenko N. Ca2+-permeable AMPA receptors contribute to changed dorsal horn neuronal firing and inflammatory pain. *Int J Mol Sci*. 2023;24(3):2341. doi:10.3390/ijms24032341
65. Li Y, Bai X, Gao M, et al. AKAP150 and its palmitoylation contributed to pain hypersensitivity via facilitating synaptic incorporation of GluA1-containing AMPA receptor in spinal dorsal horn. *Mol Neurobiol*. 2021;58(12):6505–6519. doi:10.1007/s12035-021-02570-z
66. Guntupalli S, Park P, Han DH, et al. Ubiquitination of the GluA1 subunit of AMPA receptors is required for synaptic plasticity, memory, and cognitive flexibility. *J Neurosci*. 2023;43(30):5448–5457. doi:10.1523/JNEUROSCI.1542-22.2023
67. Zheng Y, Yu X, Wei L, et al. LT-102, an AMPA receptor potentiator, alleviates depression-like behavior and synaptic plasticity impairments in prefrontal cortex induced by sleep deprivation. *J Affect Disord*. 2024;367:18–30. doi:10.1016/j.jad.2024.08.176
68. Xia B, Huang X, Sun G, Tao W. Iridoids from Gardeniae fructus ameliorates depression by enhancing synaptic plasticity via AMPA receptor-mTOR signaling. *J Ethnopharmacol*. 2021;268:113665. doi:10.1016/j.jep.2020.113665
69. He JG, Zhou HY, Wang F, Chen JG. Dysfunction of glutamatergic synaptic transmission in depression: focus on AMPA receptor trafficking. *Biol Psychiatry Glob Open Sci*. 2023;3(2):187–196. doi:10.1016/j.bpsgos.2022.02.007
70. Garcia-Bereguiain MA, Gonzalez-Islas C, Lindsly C, Butler E, Hill AW, Wenner P. In vivo synaptic scaling is mediated by GluA2-lacking AMPA receptors in the embryonic spinal cord. *J Neurosci*. 2013;33(16):6791–6799. doi:10.1523/JNEUROSCI.4025-12.2013
71. Tan H, Cao J, Zhang J, Zuo Z. Critical role of inflammatory cytokines in impairing biochemical processes for learning and memory after surgery in rats. *J Neuroinflammation*. 2014;11:93. doi:10.1186/1742-2094-11-93

72. Do SH, Fang HY, Ham BM, Zuo Z. The effects of lidocaine on the activity of glutamate transporter EAAT3: the role of protein kinase C and phosphatidylinositol 3-kinase. *Anesth Analg*. 2002;95(5):1263–1268, table of contents. doi:10.1097/00000539-200211000-00030
73. Wei YB, Melas PA, Villaescusa JC, et al. MicroRNA 101b is downregulated in the prefrontal cortex of a genetic model of depression and targets the glutamate transporter SLC1A1 (EAAT3) in vitro. *Int J Neuropsychopharmacol*. 2016;19(12):pyw069. doi:10.1093/ijnp/pyw069
74. Li X, Yang H, Qian M, et al. Intracellular metabotropic glutamate receptor 5 in spinal dorsal horn neurons contributes to pain in a mouse model of vincristine-induced neuropathic pain. *Neurosci Lett*. 2025;852:138193. doi:10.1016/j.neulet.2025.138193
75. Liu H, Wu X, Wang Y, et al. TNF-α, IL-6 and hsCRP in patients with melancholic, atypical and anxious depression: an antibody array analysis related to somatic symptoms. *Gen Psychiatr*. 2022;35(4):e100844. doi:10.1136/gpsych-2022-100844
76. Schmitz CN, Sammer G, Neumann E, et al. Functional resting state connectivity is differentially associated with IL-6 and TNF-α in depression and in healthy controls. *Sci Rep*. 2025;15(1):1769. doi:10.1038/s41598-025-85514-0
77. Tozzi L, Zhang X, Chesnut M, Holt-Gosselin B, Ramirez CA, Williams LM. Reduced functional connectivity of default mode network subsystems in depression: meta-analytic evidence and relationship with trait rumination. *Neuroimage Clin*. 2021;30:102570. doi:10.1016/j.nicl.2021.102570
78. Clunas H, Walpole S, Babic I, et al. Improved recognition memory and reduced inflammation following β-caryophyllene treatment in the Wistar-Kyoto rodent model of treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2025;138:111312. doi:10.1016/j.pnpbp.2025.111312
79. Gao M, Song Y, Liu Y, Miao Y, Guo Y, Chai H. TNF-α/TNFR1 activated astrocytes exacerbate depression-like behavior in CUMS mice. *Cell Death Discov*. 2024;10(1):220. doi:10.1038/s41420-024-01987-4
80. Zhao YT, Deng J, Liu HM, et al. Adaptation of prelimbic cortex mediated by IL-6/STAT3/Acp5 pathway contributes to the comorbidity of neuropathic pain and depression in rats. *J Neuroinflammation*. 2022;19(1):144. doi:10.1186/s12974-022-02503-0
81. Sun PY, Li HG, Xu QY, et al. Lidocaine alleviates inflammation and pruritus in atopic dermatitis by blocking different population of sensory neurons. *Br J Pharmacol*. 2023;180(10):1339–1361. doi:10.1111/bph.16012
82. Serra MF, Anjos-Valotta EA, Olsen PC, et al. Nebulized lidocaine prevents airway inflammation, peribronchial fibrosis, and mucus production in a murine model of asthma. *Anesthesiology*. 2012;117(3):580–591. doi:10.1097/ALN.0b013e31826687d5
83. Xu S, Hu S, Ju X, Li Y, Li Q, Wang S. Effects of intravenous lidocaine, dexmedetomidine, and their combination on IL-1, IL-6 and TNF-α in patients undergoing laparoscopic hysterectomy: a prospective, randomized controlled trial. *BMC Anesthesiol*. 2021;21(1):3. doi:10.1186/s12871-020-01219-z
84. Suzuki N, Hasegawa-Moriyama M, Takahashi Y, Kamikubo Y, Sakurai T, Inada E. Lidocaine attenuates the development of diabetic-induced tactile allodynia by inhibiting microglial activation. *Anesth Analg*. 2011;113(4):941–946. doi:10.1213/ANE.0b013e31822827a2
85. Barry A, O'Halloran KD, McKenna JP, McCreary C, Downer EJ. Plasma IL-8 signature correlates with pain and depressive symptomatology in patients with burning mouth syndrome: results from a pilot study. *J Oral Pathol Med*. 2018;47(2):158–165. doi:10.1111/jop.12666
86. Lopes F, Vicentini FA, Cluny NL, et al. Brain TNF drives post-inflammation depression-like behavior and persistent pain in experimental arthritis. *Brain Behav Immun*. 2020;89:224–232. doi:10.1016/j.bbi.2020.06.023
87. Egger K, Aicher HD, Cumming P, Scheidegger M. Neurobiological research on N,N-dimethyltryptamine (DMT) and its potentiation by monoamine oxidase (MAO) inhibition: from ayahuasca to synthetic combinations of DMT and MAO inhibitors. *Cell Mol Life Sci*. 2024;81(1):395. doi:10.1007/s00018-024-05353-6
88. Uhlig M, Reinelt JD, Lauckner ME, et al. Rapid volumetric brain changes after acute psychosocial stress. *Neuroimage*. 2023;265:119760. doi:10.1016/j.neuroimage.2022.119760
89. Luo X, Che X, Li H. Concurrent TMS-EEG and EEG reveal neuroplastic and oscillatory changes associated with self-compassion and negative emotions. *Int J Clin Health Psychol*. 2023;23(1):100343. doi:10.1016/j.ijchp.2022.100343
90. Zhang B, Chen X, Lv Y, et al. Cdh1 overexpression improves emotion and cognitive-related behaviors via regulating hippocampal neuroplasticity in global cerebral ischemia rats. *Neurochem Int*. 2019;124:225–237. doi:10.1016/j.neuint.2019.01.015
91. Wang CC, Held RG, Chang SC, et al. A critical role for GluN2B-containing NMDA receptors in cortical development and function. *Neuron*. 2011;72(5):789–805. doi:10.1016/j.neuron.2011.09.023
92. Wu Y, Zhu Z, Lan T, et al. Levomilnacipran improves lipopolysaccharide-induced dysregulation of synaptic plasticity and depression-like behaviors via activating BDNF/TrkB mediated PI3K/Akt/mTOR signaling pathway. *Mol Neurobiol*. 2024;61(7):4102–4115. doi:10.1007/s12035-023-03832-8
93. Yao C, Jiang N, Sun X, et al. Effects of inulin-type oligosaccharides (JSO) from Cichorium intybus L. on behavioral deficits induced by chronic restraint stress in mice and associated molecular alterations. *Front Pharmacol*. 2024;15:1484337. doi:10.3389/fphar.2024.1484337
94. Golden SA, Christoffel DJ, Heshmati M, et al. Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. *Nat Med*. 2013;19(3):337–344. doi:10.1038/nm.3090
95. Kiritoshi T, Yakhnitsa V, Singh S, et al. Cells and circuits for amygdala neuroplasticity in the transition to chronic pain. *Cell Rep*. 2024;43(9):114669. doi:10.1016/j.celrep.2024.114669
96. Huang Z, Tan H, Fu Y, et al. Neurotransmitter imbalance and amygdala synaptic plasticity in lumbar disc herniation-induced chronic pain and related emotional disturbances: a multi-omics analysis. *Neuropharmacology*. 2025;271:110405. doi:10.1016/j.neuropharm.2025.110405
97. Cordner ZA, Li Q, Liu L, et al. Vagal gut-brain signaling mediates amygdaloid plasticity, affect, and pain in a functional dyspepsia model. *JCI Insight*. 2021;6(6):e144046, 144046. doi:10.1172/jci.insight.144046
98. Werdehausen R, Kremer D, Brandenburger T, et al. Lidocaine metabolites inhibit glycine transporter 1: a novel mechanism for the analgesic action of systemic lidocaine? *Anesthesiology*. 2012;116(1):147–158. doi:10.1097/ALN.0b013e31823cf233
99. Ahnaou A, Broadbelt T, Biermans R, Huysmans H, Manyakov NV, Drinkenburg WHIM. The phosphodiesterase-4 and glycine transporter-1 inhibitors enhance in vivo hippocampal theta network connectivity and synaptic plasticity, whereas D-serine does not. *Transl Psychiatry*. 2020;10(1):197. doi:10.1038/s41398-020-00875-6
100. Li M, Yang X, Zhu K, Shen L, Xie C. Effects of perioperative intravenous lidocaine and esketamine on the quality of recovery and emotional state of patients after thyroidectomy: a randomised, double-blind, controlled trial. *Indian J Anaesth*. 2024;68(4):340–347. doi:10.4103/ija.ija_1010_23

101. Frieden J. Antiarrhythmic drugs. Part VII. Lidocaine as an antiarrhythmic agent. *Am Heart J*. 1965;70(5):713–715. doi:10.1016/0002-8703(65)90399-6
102. Beckett AH, Boyes RN, Parker JBR. Determination of lignocaine in blood and urine in human subjects undergoing local analgesic procedures. *Anaesthesia*. 1965;20(3):294–298. doi:10.1111/j.1365-2044.1965.tb02533.x
103. Gianelly R, Von Der Groeben JO, Spivack AP, Harrison DC. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *N Engl J Med*. 1967;277(23):1215–1219. doi:10.1056/NEJM196712072772301
104. Zhang W, He C. Clinical efficacy of pulsed radiofrequency combined with intravenous lidocaine infusion in the treatment of subacute herpes zoster neuralgia. *Pain Res Manag*. 2022;2022:5299753. doi:10.1155/2022/5299753
105. Nambi G, Alghadier M, Eltayeb MM, et al. Additional effect of extracorporeal shockwave therapy with lidocaine injection on clinical and MRI findings in frozen shoulder: a prospective, randomized, double-blinded, placebo-controlled trial. *Pain Ther*. 2024;13(2):251–268. doi:10.1007/s40122-024-00575-9
106. Karadaş Ö, Inan LE, Ulaş ÜH, Odabaşi Z. Efficacy of local lidocaine application on anxiety and depression and its curative effect on patients with chronic tension-type headache. *Eur Neurol*. 2013;70(1–2):95–101. doi:10.1159/000350619
107. Xiang Y, He J, Li R. Appropriateness of sham or placebo acupuncture for randomized controlled trials of acupuncture for nonspecific low back pain: a systematic review and meta-analysis. *J Pain Res*. 2018;11:83–94. doi:10.2147/JPR.S152743
108. Davies JN, Colagiuri B, Sharpe L, Day MA. Placebo effects contribute to brief online mindfulness interventions for chronic pain: results from an online randomized sham-controlled trial. *Pain*. 2023;164(10):2273–2284. doi:10.1097/j.pain.0000000000002928
109. Hung KC, Chu CC, Hsing CH, et al. Association between perioperative intravenous lidocaine and subjective quality of recovery: a meta-analysis of randomized controlled trials. *J Clin Anesth*. 2021;75:110521. doi:10.1016/j.jclinane.2021.110521
110. Hermanns H, Hollmann MW, Stevens MF, et al. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. *Br J Anaesth*. 2019;123(3):335–349. doi:10.1016/j.bja.2019.06.014
111. Paterson H, Vadiveloo T, Innes K, et al. Intravenous lidocaine for gut function recovery in colonic surgery: a randomized clinical trial. *JAMA*. 2024:e2423898. doi:10.1001/jama.2024.23898
112. Silvinato A, Floriano I, Bernardo WM. Multiple lidocaine infusions for relief of neuropathic pain: systematic review and meta-analysis. *Rev Assoc Med Bras*. 2020;66(7):889. doi:10.1590/1806-9282.66.7.889
113. Vedantham V, Cannon SC. The position of the fast-inactivation gate during lidocaine block of voltage-gated Na+ channels. *J General Physiol*. 1999;113(1):7–16. doi:10.1085/jgp.113.1.7
114. Zhang B, Zhou Q. Esketamine for postoperative analgesia after cesarean section: effects on pain, mood, sleep quality, and safety. *Medicine*. 2025;104(37):e44432. doi:10.1097/MD.0000000000044432
115. Huneke NTM, Amin J, Baldwin DS, et al. Placebo effects in randomized trials of pharmacological and neurostimulation interventions for mental disorders: an umbrella review. *Mol Psychiatry*. 2024;29(12):3915–3925. doi:10.1038/s41380-024-02638-x
116. Sisti MS, Nishida F, Zanuzzi CN, Laurella SL, Cantet RJC, Portiansky EL. Lidocaine protects neurons of the spinal cord in an excitotoxicity model. *Neurosci Lett*. 2019;698:105–112. doi:10.1016/j.neulet.2019.01.019
117. Chen K, Wei P, Zheng Q, Zhou J, Li J. Neuroprotective effects of intravenous lidocaine on early postoperative cognitive dysfunction in elderly patients following spine surgery. *Med Sci Monit*. 2015;21:1402–1407. doi:10.12659/MSM.894384
118. Biella G, Lacerenza M, Marchettini P, Sotgiu ML. Diverse modulation by systemic lidocaine of iontophoretic NMDA and quisqualic acid induced excitations on rat dorsal horn neurons. *Neurosci lett*. 1993;157(2):207–210. doi:10.1016/0304-3940(93)90738-7
119. DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2010;71(12):1605–1611. doi:10.4088/JCP.09m05327blu
120. Agüera-Ortiz L, Failde I, Mico JA, Cervilla J, López-Ibor JJ. Pain as a symptom of depression: prevalence and clinical correlates in patients attending psychiatric clinics. *J Affect Disord*. 2011;130(1–2):106–112. doi:10.1016/j.jad.2010.10.022
121. Von Knorring L, Perris C, Eisemann M, Eriksson U, Perris H. Pain as a symptom in depressive disorders. II. Relationship to personality traits as assessed by means of KSP. *Pain*. 1983;17(4):377–384. doi:10.1016/0304-3959(83)90169-0
122. Lee P, Zhang M, Hong JP, et al. Frequency of painful physical symptoms with major depressive disorder in Asia: relationship with disease severity and quality of life. *J Clin Psychiatry*. 2009;70(1):83–91. doi:10.4088/JCP.08m04114
123. Kundra P, Vinayagam S. Perioperative intravenous lidocaine: crossing local boundaries and reaching systemic horizons. *Indian J Anaesth*. 2020;64(5):363–365. doi:10.4103/ija.IJA_431_20
124. Foong KW, Chaw SH, Lo YL, Loh PS. Population pharmacokinetics of intravenous lidocaine in adults: a systematic review. *Clin Pharmacokinet*. 2024;63(5):623–643. doi:10.1007/s40262-024-01373-4
125. Blas-Valdivia V, Cano-Europa E, Hernández-García A, Ortiz-Butrón R. Hippocampus and amygdala neurotoxicity produced by systemic lidocaine in adult rats. *Life Sci*. 2007;81(8):691–694. doi:10.1016/j.lfs.2007.07.007
126. Weinberg L. Pharmacokinetics and pharmacodynamics of lignocaine: a review. *WJA*. 2015;4(2):17. doi:10.5313/wja.v4.i2.17
127. Daykin H. The efficacy and safety of intravenous lidocaine for analgesia in the older adult: a literature review. *Br J Pain*. 2017;11(1):23–31. doi:10.1177/2049463716676205
128. Tognolini AR, Liu X, Pandey S, et al. Dosing optimisation of intravenous lidocaine in patients with class 1–3 obesity by population pharmacokinetic analysis. *Anaesthesia*. 2025;80(5):511–521. doi:10.1111/anae.16531
129. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia*. 2021;76(2):238–250. doi:10.1111/anae.15270
130. Jelen LA, Stone JM. Ketamine for depression. *Int Rev Psychiatry*. 2021;33(3):207–228. doi:10.1080/09540261.2020.1854194
131. Kim JW, Suzuki K, Kavalali ET, Monteggia LM. Ketamine: mechanisms and relevance to treatment of depression. *Annu Rev Med*. 2024;75:129–143. doi:10.1146/annurev-med-051322-120608
132. Berk T, Silberstein SD. The use and method of action of intravenous lidocaine and its metabolite in headache disorders. *Headache*. 2018;58(5):783–789. doi:10.1111/head.13298
133. Martin RD, Scanlon M, McCabe K. Lidocaine-associated CNS toxicity at therapeutic dosage: a case report and literature review. *Cureus*. 2024;16(6):e62231. doi:10.7759/cureus.62231

134. Thornton NL, Wright DJ, Glozier N. Implementation of a ketamine programme for treatment-resistant depression in the public health system: lessons from the first Australian public hospital clinic. *Aust N Z J Psychiatry*. 2024;58(7):549–554. doi:10.1177/00048674241237094
135. Egan D, Ragland V, Jha M. Building competency in administering intravenous racemic ketamine: a single site experience of expanding residency education in interventional psychiatry. *Acad Psychiatry*. 2025;49(6):580–581. doi:10.1007/s40596-025-02167-x
136. Lee IWS, Schraag S. The use of intravenous lidocaine in perioperative medicine: anaesthetic, analgesic and immune-modulatory aspects. *JCM*. 2022;11(12):3543. doi:10.3390/jcm11123543
137. Lenk C, Duttge G. Ethical and legal framework and regulation for off-label use: european perspective. *Ther Clin Risk Manag*. 2014;10:537–546. doi:10.2147/TCRM.S40232