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Ketamine as a therapeutic agent for depression and pain: mechanisms and evidence

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ABSTRACT:

Ketamine is an anesthetic drug which is now used to treat chronic pain conditions and psychiatric disorders, especially depression. It is an N-methyl-D-aspartate (NMDA) receptor antagonist with additional effects on α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, opioid receptors, and monoaminergic receptors. This article focuses on ketamine's role in treating depression and pain, two commonly comorbid challenging conditions with potentially shared neurobiologic circuitry. Many clinical trials have utilized intravenous or intranasal ketamine for treating depression and pain. Intravenous ketamine is more bioavailable than intranasal ketamine and both are effective for acute depressive episodes. Intravenous ketamine is advantageous for post-operative analgesia and is associated with a reduction in total opioid requirements. Few studies have treated chronic pain or concurrent depression and pain with ketamine. Larger, randomized control trials are needed to examine the safety and efficacy of intravenous vs. intranasal ketamine, ideal target populations, and optimal dosing to treat both depression and pain.

1. Introduction

Ketamine's history dates back to 1956, when Dr. Harrold Maddox synthesized phencyclidine (PCP). Early studies demonstrated that PCP led either to hyperactivity, central depression, general anesthesia, or a cataleptic state based on dosage (1). The pharmaceutical company Parke Davis invested in multiple research studies describing PCP's pharmacological properties. PCP was an effective surgical anesthetic agent; however, a significant proportion of patients were "unmanageable" with "several degrees of manic behavior" in the postoperative period (2).

The severe psychotomimetic manifestations associated with PCP motivated Parke Davis to develop analogues with less severe adverse effects. In 1964, a short-acting anesthetic compound CI-581 was introduced; it later was named ketamine. The US Food and Drug Administration approved the use of ketamine as a general anesthetic in 1970 for adults, children, and the elderly. Ketamine has since been utilized as an analgesic and an anti-depressant with widespread clinical applications traversing psychiatry, anesthesiology, and neurology.

While ketamine is generally known as a noncompetitive, high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist, it also interacts with α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), opioid, cholinergic, catecholaminergic, and hyperpolarization-activated cyclic nucleotide-gated (HCN) receptors (3–7). Understanding ketamine's downstream signaling mechanisms may provide insight into its potential clinical applications and side effects. An assessment of ketamine as a treatment option for individuals with concomitant depression and acute and chronic pain is essential, given that mood disorders and pain are frequently co-morbid, share neurobiological mechanisms, and are often difficult to treat (8–10).

Currently, tricyclic anti-depressants (TCAs, e.g., amitriptyline and nortriptyline) and serotonin and norepinephrine reuptake inhibitors (SNRIs, i.e., duloxetine and venlafaxine) are commonly used to treat individuals with coexisting depression, anxiety and chronic pain. However, TCAs and SNRIs confer cardiac side effects, orthostatic hypotension, and hypertension (11–12) and take several weeks to ameliorate affective symptoms. Moreover, many patients with pain have treatment-resistant depression (13). Ketamine in its intravenous and intranasal forms has been widely studied in pain and depression and may be an alternative to TCAs and SNRIs in the treatment of co-occurring symptoms (14). We thus performed a qualitative review

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evaluating ketamine's pharmacologic mechanisms and efficacy in these conditions.

2. Pharmacokinetics and pharmacodynamics

Ketamine is available in intravenous, intramuscular, intranasal, and oral forms which have bioavailabilities of about 100%, 93%, 50%, and 17% respectively (15–16). Oral ketamine's bioavailability is low; therefore, higher amounts of oral ketamine must be administered to reach higher blood levels. Oral ketamine is less commonly utilized in analgesia or depression, in part because of high absorption variability across the population, as well fear of potential mis-use if self-administered without medical supervision (17–20). The higher and more consistent bioavailability of intranasal and intravenous (IV) administration has led to greater focus on these two routes. Intravenous ketamine is available as a racemic mixture of (R)- and (S)-enantiomers. For intravenous dosing, subanesthetic doses of 0.5mg/kg IV ketamine are typically used in research studies for depression, and 1.5-2mg/kg are typically administered for induction of general anesthesia.

Intranasal ketamine contains the (S)-enantiomer (esketamine). When ketamine is provided intranasally, about half of the dose is swallowed and the rest is absorbed through the nasal cavity. It is estimated that 0.5mg/kg of intravenous ketamine has similar bioavailability to 56mg of intranasal esketamine (21). To adjust for this, the intranasal ketamine has been optimized by: 1) aerosolization to allow rapid absorption into the systemic circulation (22–23); 2) dispensing higher doses to account for lower bioavailability of the intransasal form; and 3) including only the (S)-enantiomer, which has a higher binding affinity to the NMDA receptor compared to the (R)-enantiomer ([S]-ketamine has an inhibitory constant [K_i] of 0.30-0.69uM, compared to [R]-ketamine with K_i of 1.4-2.57uM) (24–25). (R)-ketamine (arketamine) has been studied as an anti-depressant agent in pre-clinical models and associated with less psychotomimetic effects; however, compared to the S-enantiomer, it offers less analgesia and anesthesia, so arketamine has not been highly focused on (26).

Ketamine has a relatively low (~47%) plasma protein binding ability and is rapidly distributed to highly perfused tissues such as the lungs and heart, with a distribution half-life of seven to 11 minutes and volume of distribution ranging from one to three L/kg (27–28). Both enantiomers undergo oxidative metabolism via hepatic cytochrome P450 enzymes. *CYP2B6* and *CYP3A4* enzymes demethylate ketamine to norketamine. CYP3A4 mediates N-demethylation of (S)-ketamine at a quicker rate than the (R)-enantiomer (29). Norketamine is the major, active metabolite and retains anti-depressant and anesthetic effects – albeit with lower potency than its parent compound - and is associated with less cognitive impairment compared to (S)-ketamine (30). Hydroxylated ketamine metabolites with glucuronic acid are excreted via urine and bile.

3. How does ketamine work?

This section briefly summarizes decades of ketamine investigations and offers a framework in which to conceptualize the potential utility of IV and intranasal ketamine in depression and pain.

a. NMDA receptors

Glutamate is the key excitatory amino acid in the central nervous system. Glutamatergic synaptic transmission is thought to regulate emotion and cognition (31), and individuals with mood disorders have elevated glutamate levels in their spinal fluid and brain tissue (32–35).

Glutamate acts on two types of receptors: ionotropic and metabotropic. Ionotropic receptors include NMDA, AMPA, and kainate receptors that are formed by multiple protein subunits. The NMDA receptor is a tetrameric transmembrane cation channel formed by GluN1, GluN2A, and GluN2B subunits. Metabotropic receptors include mGlu receptors, which are seven-transmembrane domain G-protein coupled receptors. While ketamine primarily acts on ionotropic receptors, it is important to emphasize that antagonism of metabotropic receptors (i.e., mGlu2 and mGlu3) has been shown to improve depressive symptoms (36–37).

Magnesium ions block the NMDA receptor under resting conditions. To activate the receptor, membrane depolarization is required to displace the magnesium ion, in addition to a requirement for the binding of glutamate and glycine and/or serine. Ketamine is an antagonist of the NMDA receptor and binds within the channel. In order for ketamine to block the NMDA channel, the channel must be open (thus ketamine is called an "open channel blocker"). Ketamine blocks the flow of ions through the channel and can remain in the channel when the channel closes. This "trapping effect" may explain ketamine's prolonged block time. When ketamine and magnesium, both acting as NMDA receptor antagonists, are administered together, there may be synergistic reductions in acute pain (38–40).

Ketamine targets NMDA receptors located on the 1) post-synaptic neuronal terminals, 2) gamma-aminobutyric acid- (GABA)ergic interneurons, and 3) extra-synaptic space such as glial cells (41–42). Inhibition of GABAergic interneurons leads to disinhibition and enhancement of excitatory glutaminergic neurotransmission in areas like the medial prefrontal cortex (43). It is thought that GABAergic inhibition is preferential, as anesthetic doses of intravenous ketamine decrease extracellular levels of prefrontal glutamate while subanesthetic doses of intravenous ketamine increase glutamate prefrontal levels and disinhibit pyramidal cells (43–45).

Ketamine blocks NMDA receptors on post-synaptic neurons, which inhibits eukaryotic elongation factor-2 (eEF2) kinase that then increases brain-derived neurotropic factor (*BDNF*) translation (46). BDNF proteins are released from the postsynaptic neuron and activate the tyrosine-related kinase (Trk B) receptor. Downstream of the Trk B receptor is the signaling cascade of extracellular signaling related kinases (ERKs) and protein kinase-B (Akt/PKB) that suppress glycogen synthase kinase-3 (GSK-3). Inactivation of GSK-3 induces mammalian target of rapamycin (mTOR). mTOR activation is fundamental in synaptogenesis and spine formation in the prefrontal cortex processes, phenomena that have been linked to anti-depressant activity in rodent models (47–49). The Trk B/BDNF pathway was once thought to be unique to ketamine and NMDA agents; however, new research suggests that ketamine may be more similar to the other typical anti-depressants, which also directly bind to and activate Trk B (50). This new finding requires replication. Ketamine selectively blocks extra-synaptic NMDA receptors with GluN2B subunits, and glutamate transporter-1 on astrocytes regulates these GluN2B- NMDA receptors(51–52). When activated, the GluN2B-NMDA activates mTOR1, which stimulates protein synthesis (53).

NMDA receptors are implicated in the development of opioid dependence and tolerance, phenomena that are important for chronic pain management. As briefly mentioned above, NMDA receptors may regulate behavioral and neural plasticity processes like long-term potentiation and learning (54). In the 1990s, scientists hypothesized that NMDA receptor antagonists could inhibit the development of opioid tolerance and dependence. MK-801 was the first NMDA antagonist that was shown to inhibit the development of tolerance to and physical dependence on morphine without interfering with analgesia (55–57). Trujillo et al then sought to see if these effects were specific to MK-801 or NMDA receptor antagonists; therefore, they examined the effects of intravenous ketamine and PCP on the development of tolerance to morphine. The authors reported that ketamine infusion inhibited tolerance to morphine antinociception at subanesthetic doses (58). These results demonstrated that ketamine could decrease opioid tolerance and dependence at subanesthetic doses with a lower likelihood of psychotomimetic effects.

Glutamate also plays a key role in central sensitization and opioid-induced hyperalgesia. In chronic pain syndromes, individuals often have an exaggerated and prolonged response to noxious (hyperalgesia) or innocuous (allodynia) stimuli. One mechanism contributing to these phenomena is central sensitization – i.e., increased responsiveness of

nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. NMDA receptors in the spinal cord are significant regulators of central sensitization; unmyelinated afferent C-fibers transmit glutamate to the second order sensory neurons in the superficial laminae of spinal cord dorsal horn, where NMDA and AMPA receptors are expressed in the post-synaptic membrane (59–60). As such, ketamine's ability to target NMDA receptors and modulate central sensitization may decrease analgesic responses.

In rodent behavioral studies, repetitive activation of NMDA receptors leads to hyperalgesia and allodynia; NMDA antagonists such as dextromethorphan, MK-801, and ketamine have been shown to attenuate these outcomes (61–62). Pre-procedural ketamine may persistently decrease pain-related behavior, as administration of intrathecal ketamine prior to ligation of spinal nerves was associated with up to two weeks of decreased allodynia and pain behaviors (63). Additionally, pre-incisional intrathecal administration of ketamine decreased mechanical hypersensitivity after nerve injury in a dose-dependent fashion (64).

b. AMPA receptors

AMPA receptors are homomeric or heteromeric channels formed by a combination of four subunits GluA1-4 or GluRA-D which form a hetero-tetrameric receptor via dimers-of-dimers. These cation-permeable ionotropic glutamate receptors are located at postsynaptic membranes and facilitate synaptic plasticity underlying memory and learning (65).

A growing body of literature suggests that ketamine's main effects on depression and pain rely heavily on indirect activation of AMPA receptors. This indirect effect may be via ketamine's metabolites, (2R, 6R) –hydroxynorketamine ([2R, 6R] -HNK) or (2S, 6S) – HNK (similar to the parent compound, the (R,R)-HNK enantiomer) has stronger affinity to the AMPA receptor than the (S,S) enantiomer (66). Preclinical models demonstrated that pre-or post-treatment with AMPA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX) blocks the anti-depressant effect of ketamine injections (67–68). Similarly, when rats were treated with the AMPA receptor agonist CX546, the effects of ketamine were potentiated, as rats had decreased swim test immobility time and increased levels of *mTOR* and *BDNF* in the hippocampus and medial prefrontal cortex. NBQX pretreatment attenuated ketamine's effects by demonstrating findings opposite to CX546 - increased immobility time and decreased *mTOR* and *BDNF* levels (69). These findings imply that ketamine leads to indirect AMPA receptor agonism and upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex.

Interestingly, the tricyclic anti-depressant imipramine and selective serotonin reuptake inhibitor fluoxetine were associated with AMPA receptor upregulation in the medial prefrontal cortex or hippocampus, and anti-depressant effects were diminished by NBQX, suggesting that AMPA may be implicated in the downstream pathways of both classical and rapid anti-depressants (70).

AMPA receptors are expressed in neural structures implicated in pain processing and synergistically work with NMDA receptors (71). Pre-synaptic AMPA receptors expressed on primary afferent nerves and GABAergic inhibitory interneurons assist with nociceptive processing (72). In chronic pain syndromes, the density of AMPA receptors increases in the hippocampus (73). Descending pathways from the amygdala provide AMPA-mediated synaptic input to the periaqueductal grey and rostral ventral medial medulla. AMPA injections within the rostral ventral medial medulla of rodents with hyperalgesia diminish paw withdrawal to noxious stimuli, suggesting a key role for AMPA in descending pain modulatory pathways.

AMPA receptor antagonists may be useful in treating chronic pain. In one study led by Cumberbatch, rats were given intravenous NBQX and GYKI 53655 (an AMPA antagonist that also binds to the NMDA receptor at a lower affinity). Investigators found that both agents reduced responses to peripheral stimuli; furthermore, GYKI 53655 decreased tap and heat responses. These data suggest that AMPA receptors are fundamental in nociceptive transmission and work in concert with other receptors like NMDA (74).

Similarly, systemic administration of AMPA receptor antagonists reduced formalin-induced and thermally-induced pain in rats (75). Intrathecal NBQX and CNQX (another AMPA antagonist) blocked hyperalgesia in first degree burn and incisional models (76–77). Taken altogether, AMPA receptor agonism in the prefrontal cortex and hippocampus contributes to anti-depressant response; though, AMPA receptor antagonism (at the level of subcortical pain processing structures, the spinal cord structures, and dorsal root ganglia) may alleviate acute and chronic pain.

c. Hyperpolarization-activated cyclic nucleotide-gated channels (HCN)

HCN channels regulate neuronal excitability and activity, as well as synaptic plasticity and dendritic processing (78). HCN channels also regulate sleep and arousal and pacemaker rhythm in the heart (79). Such channels are located in the brain, retina, and heart, and the activity of sodium and potassium ions regulates the channel's hyperpolarization-activated current (known as the h current, I_h). HCN channels exist in activated or hyperpolarized states (80), but not inactivated conformations. There are four HCN subtypes: HCN1 is the most common isoform and located in the cerebellar cortex, dorsal root ganglia, hippocampus and neocortex; HCN2 isoforms are more common in the thalamus and midbrain; and HCN4 is predominant in basal ganglia and thalamic nuclei (81).

Chen et al published one of the first studies reporting that ketamine antagonizes HCN1 channels. In *in vitro* models with recombinant HCN1 channels, the authors demonstrated that ketamine selectively inhibited I_h channels. In wild-type mice, ketamine led to membrane hyperpolarization improvement in dendrite synaptic formation (such phenomena are thought to regulate slow cortical rhythms and thus a hypnotic-like state); however, in *HCN1* knockout models, there was a reduction in the loss-of-righting reflex. Thus, both NMDA antagonism and HCN1 agonism may contribute to the hypnotic properties of ketamine. In addition, the investigators found that anti-depressant effects of ketamine were diminished in HCN1 knockout models (82–83). Later, Zhang et al demonstrated that application of the HCN1 inhibitor zatebradine to rodent hippocampal slices blocked ketamine's effects via a presynaptic mechanism (84). The authors postulated that presynaptic NMDA receptor inhibition decreases presynaptic HCN channel function, thereby leading to glutamate release and promotion of AMPA activity in post-synaptic membranes.

As mentioned above, BDNF is a marker positively correlated with anti-depressant effects. Ketamine augments BDNF and HCN1 expression in the prefrontal cortex of mice exposed to prolonged stress, suggesting that ketamine-induced regulation of HCN1 may be implicated in depression (85). Both NMDA receptor and HCN channel inhibition converge downstream in the mTOR pathway, a pathway that mediates enhancement of synaptic proteins and synaptic transmission in depression (86).

Regarding peripheral pain, HCN channel blockers, such as ZD-7288, attenuate hypersensitivity in neuropathic pain models and in rodent models of peripheral nerve injury (87). At the supraspinal level, HCN expression level increased in rat amygdala after chronic compression of the sciatic nerve; when ZD-7288 was applied, there was an anti-nociceptive response (88). Similarly, chronic sciatic nerve compression leads to an increase HCN protein levels and I_h currents in the periaqueductal gray area of rat models, and infusion of ZD-7288 into the area diminished neuropathic pain (89–90). Altogether, the evidence suggests that ketamine acts as a direct and indirect antagonist (via NMDA receptors) of HCN channels, which are implicated in depression and pain.

d. Opioid receptors

Opioid receptors are G-protein coupled receptors that regulate intracellular cyclic AMP levels by affecting adenylyl cyclase activity. These receptors are expressed within central and peripheral neurons and are stimulated by endogenous peptides (such as endorphins, enkephalins, and dynorphins) in response to noxious stimuli. The analgesic

effects of opioids have been noted for thousands of years (in fact, opium as an analgesic agent was documented on Ebers Papyrus in 1500 BC) (91–92). Following their identification in the 1970's (93), opioid receptors and their function have been characterized extensively. The three main types of receptors mu, kappa, and delta are expressed throughout the central and peripheral nervous system. The specific locations and signaling of the opioid receptors determine analgesic effects or explain unwanted side effects of opioid receptor agonists. Mu receptors are abundantly expressed in the medial thalamus and brainstem; their activation is associated with analgesia, respiratory depression, sedation, euphoria, and physical dependence. Kappa receptors are expressed in the limbic system, brainstem, and spinal cord and regulate analgesia, dependence, dysphoria, and respiratory depression. Delta receptors are expressed in the dorsal root ganglia and spinal cord and primarily regulate analgesia (94–95).

There is a long-standing history implicating opioid receptors in depression. Mouse knockout models for mu, delta, and kappa receptors have been characterized and show hedonistic behaviors (96). Similarly, peripheral injection of enkephalins and endorphins lead to antidepressant effects in mice and regulate despair-like behaviors (97–98). Clinical trials of buprenorphine, a kappa-opioid receptor antagonist, demonstrate a rapid but transient anti-depressant effect (99).

The analgesic effect of ketamine can be blocked by naloxone, an opioid receptor antagonist (100). Further *in vitro* studies found that ketamine bound to opioid receptors and displaced a radioactively labeled opioid receptor agonist (101). At high doses, ketamine has affinity for the mu opioid receptor and lower affinity to the kappa and delta receptors (102). (S)-ketamine binds to mu and kappa receptors at a two- to four- fold higher affinity than the (R)-enantiomer. Analgesic effects of ketamine may be due to its preferential mu receptor binding.

It remains unclear whether ketamine induces analgesia directly or indirectly. Direct murine brain exposure via intracerebroventricular injection of mu and delta receptor antagonists demonstrated inhibition of ketamine's analgesic effects (103); however, this observation was not replicated in humans when a global opioid inhibitor, naloxone, was co-administered with ketamine (104).

Recently, Williams et al conducted two double-blind crossover clinical studies that demonstrated a potential link between ketamine's interaction with opioid receptors and depression. The authors showed that 50 mg of oral naltrexone (an antagonist of mu and kappa opioid receptors) administered prior to ketamine administration attenuated anti-depressant and anti-suicidality effects (105–106). Two preclinical studies closely examined these findings in mice, but their conclusions are incongruent with the human data. In one study, naltrexone prior to ketamine administration did not negate ketamine's anti-depressant effects in the chronic social defeats stress and lipopolysaccharide inflammation mouse model (107). Another study reported that naltrexone treatment did not inhibit ketamine's anti-depressant effects in rodents with learned helplessness (108). The difference in the results of human and rodent studies may be due to 1) naltrexone's mechanism of action via the toll-like receptor, which is also linked to opioid dependence, suggesting that there are non-opioid mechanisms associated with naltrexone administration (109) and 2) various and incongruent rodent models of depression are often utilized.

e. Monoaminergic receptors

There are five subtypes of dopamine receptors and seven subtypes of 5-HT receptors expressed within the central nervous system. Dopamine and serotonin receptors are metabotropic receptors except for the ionotropic 5-HT_3 receptor. Dopamine and serotonin modulate reward, motivation, memory and attention functions (110). During acute pain, serotonin is released from spinal neurons and inhibits dorsal horn responses to noxious stimuli (111).

Ketamine acts as a partial agonist on D2 dopamine receptors and binds to 5-HT_2 serotonin receptors (112). Several human positron emission tomography reports indicate that subanesthetic ketamine doses decrease striatal D2 receptor binding of radiolabeled raclopride, an indicator of dopamine release (113–114). However, these findings were not replicated in other studies using similar infusion doses and time intervals (115) Rodent models demonstrate that with subanesthetic administration of ketamine, dopamine levels increase in the frontal cortex, striatum, and nucleus accumbens (116). Dopamine activation in these areas may contribute to the ketamine's association with psychotic symptoms. In fact, ketamine can exacerbate psychosis if given to individuals at risk of developing schizophrenia (117–118); given this, it is speculated that dopamine receptors may mediate ketamine's psychotomimetic side effects.

With regard to serotonin, ketamine administration increases serotonin levels in the prefrontal cortex in mice (119) and increases ventral pallidum and accumbal 5-HT_{1B} receptor binding in nonhuman primates. The AMPA antagonist NBQX blocks this effect, suggesting that AMPA receptor activation may be convergent in the serotonin pathway as well (120). Tiger et al designed a placebo-controlled double-blind controlled trial in which IV ketamine was provided to individuals resistant to SSRIs. PET imaging demonstrated an increase in 5-HT_{1B} binding in the hippocampus after one dose of ketamine, and baseline 5-HT_{1B} binding in the ventral striatum inversely correlated with depressive symptoms (121).

Ketamine's activation of 5-HT receptors appears to play an important role in depression and pain. Serotonin receptor antagonist pretreatment to rodents reduced ketamine's anti-depressant effects in the forced swim test and novelty-suppressed feeding test (119,122). Ketamine's affinity to 5-HT_2 receptors is also relevant in analgesia. Crisp et al reported that methysergide, a 5-HT_2 antagonist, attenuated the analgesic effect of ketamine in rats (123).

f. Inflammatory pathways

Depression and pain often co-occur, often in chronic disabling conditions such as rheumatoid arthritis and fibromyalgia. Neuroinflammatory processes may link these conditions, as chronic inflammation alters neural signaling involved in pain processing and regulation of mood and cognition (124–125). A series of rodent-based studies have found that increases in interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), and interleukin -1beta (IL-1B) in brain regions like the hippocampus, anterior cingulate, amygdala, and frontal cortex result in concurrent depression and pain. In these studies, rodents with a nerve injury developed behavioral endpoints related to depression, in a time-dependent manner (126–127). Dellarole et al showed that in TNF-receptor knockout mice, inducing nerve injury did not lead to depressive behaviors, suggesting that pro-inflammatory cytokine TNF-alpha may regulate depressive symptoms in in mouse models of neuropathic pain (127). In human studies, meta-analyses show that higher serum concentrations of pro-inflammatory markers such as IL-6, TNF-alpha, and IFN-gamma are present in depressed adults (128–131). IFN-alpha is cytokine that has demonstrated a causal role linking depression and inflammation, as when IFN-alpha therapy is provided to persons with hepatitis C, there is a high increase in depressive symptoms (132–133).

Early clinical studies observed that ketamine compared to other anesthetic agents improved outcomes in high inflammatory states such as septic shock (134). Ketamine provided prior to surgical procedures for anesthesia can reduce the production of excess proinflammatory cytokines, and this occurs even at subanesthetic doses of 0.15-0.25mg/kg in a single bolus (135–136). IL-6 is cytokine associated with poor postoperative outcomes (137), and ketamine has been shown to decrease IL-6, along with C-reactive protein (CRP) and tumor necrosis factor alpha (TNFa) (138–149).

In depression, ketamine has an overall anti-inflammatory effect. In rat models, ketamine reduces IL-6 and IL-1b expression levels in the prefrontal cortex and hippocampus (140). Likewise, in a human population of treatment resistant depressed individuals and their age-, sex-, and body mass index-matched controls, out of 41 inflammatory markers, IL-6 and IL-1a decreased 4 hours after ketamine infusion (141). IL-6 has been studied as a biomarker that could predict response to ketamine treatment; as depressed individuals with higher IL-6 levels responded

better to ketamine compared to controls in one study(142). However, a larger study led by Park et al disproved this previous finding and found that ketamine increased IL-6 levels about 4 hours after infusion and did not predict depressive symptom changes (143).

A key mechanism contributing to sensory symptoms such as allodynia and hyperalgesia in neuropathic pain conditions is the activation of microglia in the spinal cord (144–145). Activated microglia release inflammatory mediators leading to a decrease in activation thresholds of nociceptors. This then contributes to pain and mechanical and thermal hypersensitivity observed in neuropathic pain (146). In addition to its NMDA-mediated effects, ketamine has shown to suppress microglia via toll-like receptor 3 (TLR3) inhibition, and via interference with Ca^{2+} and K^{+} signaling (147). Intrathecal ketamine administration also down-regulates c-Jun N-terminal kinase (a member of the mitogen-activated protein kinase family that mediates inflammation in nerve injury) and was shown to attenuate rodent pain behavior in a dose -dependent fashion (148). Despite these preclinical data, there are limited clinical studies that investigate the interaction among inflammation, analgesia, and ketamine.

g. Summary

In this section, we described the several overlapping mechanistic pathways that implicate a possible dual-therapeutic role of ketamine for depression and pain. The overall view is that while ketamine is primarily a strong NMDA antagonist, it also acts as an indirect and direct AMPA agonist; HCN antagonist; mu-, kappa-, delta-opioid receptor agonist; serotonin receptor 5-HT_2 agonist, dopamine 2 receptor agonist, and anti-inflammatory agent.

4. What are ketamine's clinical effects?

a. Adverse effects

The scientific and clinical community hesitated to test ketamine as a treatment option for psychiatric disorders and pain for three reasons: first, ketamine (like PCP) had abuse potential (149–150); second, it was thought that NMDA antagonism would exacerbate underlying psychiatric illness; third, PCP or ketamine – especially at higher doses- can lead to psychotomimetic effects like catatonia, hallucinations, delusions, and maniacal excitation (151–154).

Ketamine became a recreational drug of abuse beginning around the 1970s, with peak misuse in the United States in the 1980s as a "club drug" (155). While ketamine was initially abused in the injectable form, it is currently abused in capsule, tablet, powder, and crystal forms. To minimize misuse, the FDA established a Risk Evaluation and Management (REMS) strategy for intranasal esketamine's appropriate drug storage, handling, dispensing, and monitoring. Intranasal ketamine was FDA- approved for TRD in 2019 and currently listed as a Class III scheduled drug (moderate-low potential for physical and psychological abuse).

Psychotomimetic side effects emerge within 10 minutes of ketamine infusion and may subside within 40 minutes of administration (156–159). The ketamine S-enantiomer has been associated with greater psychotomimetic effects than the R-enantiomer. Vollenweider et al reported administration of (S)-ketamine caused acute psychotic reactions at a mean plasma ketamine concentration of 539ng/ml, while administration of (R)-ketamine at a comparable plasma concentration was not associated with reports of acute psychotic reaction. Rather, subjects reported experiencing a feeling of "well-being" at this concentration of (R)- ketamine administration (160). Studies have shown that co-administering oral clonidine decreases psychotomimetic effects and nightmares (161–162) and nightmares (163). The logic in utilizing clonidine, an alpha-2-adrenergic agonist, stems from the hypothesis that ketamine hyperactivates the cholinergic pathway from the basal forebrain and the glutamatergic pathway from the thalamus. The hyperactivity and convergence of these two pathways on corticolimbic neurons may lead to stimulated behavioral effects; thus, blocking the cholinergic pathway may decrease stimulation of downstream corticolimbic neurons (164–166).

Transient cognitive impairment can occur with subanesthetic doses of ketamine given over 40 minutes to 120 minutes at doses of 0.4 to 0.8mg/kg in healthy volunteers. Effects include impairment in concentration, recall and recognition, as well as implicit (procedural) and explicit (episodic and semantic) memory impairment during or after administration (153–154,166–167).

Hemodynamic perturbations often occur during ketamine infusion. A transient increase in heart rate and blood pressure reverts to baseline after 10-30 minutes (158,168). Similar hemodynamic changes also occur during administration of intranasal ketamine, peak at 40 minutes and return to baseline between one to two hours (169–171). In addition, subanesthetic doses of ketamine can also lead to dizziness and nausea/vomiting (172–173).

Chronic ketamine use at high doses over extended periods of time has not been extensively studied in clinical trials. With chronic recreational ketamine use, neurotoxicity as well urinary urgency, dysuria, and hematuria have been noted (174–175). In fact, studies employing computer tomography show that recreational ketamine use is associated with bladder wall thickening and peri-vesical inflammation (176). Ketamine withdrawal symptoms documented in a case series of 30 daily ketamine users included: palpitations, tremors, sweating, anxiety, depression and insomnia (177).

b. Anti-depressant effects

In 2000, a landmark study led by Berman et al showed that intravenous ketamine could produce robust and rapid anti-depressant effects. Berman's group recruited nine participants who met DSM IV criteria for major depressive episode. They then provided a single 40-minute ketamine infusion at a subanesthetic dose of 0.5mg/kg. After 240 minutes, there was a noticeable anti-depressant effect that lasted for several days. This pilot study showed that a *single* dose of ketamine could lead to *rapid* anti-depressant responses *within hours* compared to weeks or months of typical anti-depressant agents (156).

After the single-infusion case series by Berman et al., multiple randomized control trials have confirmed ketamine's efficacy for treatment resistant depression (157–158,178–179). A single dose of IV ketamine (racemic mixture, dosed at 0.5mg/kg) produces anti-depressant effects that begin within hours, peak in one or three days, and last up to a week or more in 30% to 50% of patients (180). In a recent meta-analysis, a single dose of ketamine with or without psychotropic augmentation therapy 24 hours post infusion rapidly improved depressive scores (181). One study compared a 96-hour continuous infusion to a 40-minute infusion and found that those who received the prolonged infusion were more likely to have sustained improvement in depressive symptoms eight weeks after infusion compared to the 40-minute infusion (161). With the prolonged infusion, there was a response-dependent decrease in hyperconnectivity of the subgenual anterior cingulate cortex to the default mode network, and a treatment-dependent decrease in limbic system hyperconnectivity (162), providing a potential locus for effects that should be followed up with randomized, placebo-controlled trials.

First-line anti-depressant therapies like monoaminergic agents have a 40-47% response rate and it may take weeks to months before depressive symptoms improve (182). In contrast, IV ketamine have been shown to have a 65-70% response rate in patients with depression and can rapidly reduce suicidal ideation (156–157). These anti-depressant and anti-suicidality effects are noticeable within a day (183). Likewise, ketamine given as single or repeated doses produces remission rates that are comparable to or better than typical four-to-six-week monoaminergic anti-depressant regimens (182,184). Weekly maintenance ketamine doses may sustain anti-depressant effects (185), and ketamine used twice vs. thrice weekly have equal efficacy for treatment resistant depression (186). A randomized controlled trial led by Phillips et al. found that a median number of three infusions was required to achieve an anti-depressant response, and a weekly administration of one ketamine dose decreased depressive symptoms during maintenance

treatment (168). McMullen et al recently reviewed strategies to prolong the effect of ketamine in treatment resistant depression. The authors note that repeat IV ketamine compared to typical psychotropic medications and procedural therapies for depression was more advantageous in prolonging anti-depressant efficacy (187).

In adults, doses of 0.5mg/kg over 40 minutes or 1mg/kg are more efficacious for depression; though, there are often dose-dependent dissociative effects and concern for abuse potential of the racemic mixture. Doses lower than 0.5mg/kg (ie., 0.1 and 0.2 mg/kg) have not been reported to produce substantial improvement in depression scores (188–189).

Depressive symptoms can be a post-surgical complication. Mashour et al report that about 50% of patients who had depressive symptoms three or 30 days after major surgery had no prior history of depression (190). Given this, randomized controlled trials have been conducted to determine if intraoperative ketamine at a subanesthetic dose would lead to a reduction in depression. Several studies have demonstrated that subanesthetic dosing of ketamine can reduce depression in depressed and healthy individuals when symptoms were measured after day one of surgery (191–192). However, this finding has not been replicated in larger studies or meta-analyses (193). For example, in an international study by Mashour et al., 670 individuals above the age of 60 years were enrolled. The investigators randomized participants into three groups: intraoperative ketamine at a dose of 0.5mg/kg, ketamine at 1mg/kg, or saline placebo. They found that new onset depressive symptoms were common outcomes, and that ketamine administration did not improve or prevent depression (190). Similarly, the use of ketamine during electroconvulsive therapy (a rapid procedure with high efficacy for treatment resistant depression) as an augmentation or prophylactic strategy to reduce depressive has not proven to be advantageous (194–195). Altogether, the evidence is not strong for the use of subanesthetic ketamine during general anesthesia for major procedures or for electroconvulsive therapy.

Other delivery methods such as intranasal ketamine for depression represent active areas of research. As mentioned above, S-ketamine (esketamine) has a four-fold greater affinity for the NMDA receptor compared to the R-enantiomer. It was therefore hypothesized that a lower dose of esketamine could adequately treat depressive symptoms via NMDA blockade while decreasing the risk of dose-dependent dissociative effects. Because intravenous formulations have limited applicability in the outpatient setting, esketamine was developed into an intranasal formulation. Two initial phase 2 trials demonstrated that intranasal esketamine was highly efficacious in treating depressive symptoms and suicidality (196–197). In the first trial, Canuso et al provided a fixed dose of 84mg intranasal esketamine twice a week for four weeks to individuals with major depressive disorder. They monitored depressive symptoms and suicidal thought items at 4 and 24 hours after esketamine was administered and found that compared to the placebo group, the intranasal esketamine group had significant improvement in depressive scores and suicidal thought items (196). In the second trial, Daly et al enrolled individuals with treatment resistant depression and randomized participants into four groups (placebo and esketamine at doses of 28mg, 56mg, and 84mg, [197]). Efficacy of intranasal esketamine has also been tested in older adults ($\geq$65 years) with treatment resistant depression. In a recent study, older adults either received flexible esketamine dosing (28, 56, 84mg) and oral anti-depressant or intranasal placebo and oral anti-depressant. Authors found no statistical difference in depressive scores between the two treatment groups (199). One limitation to this study was that older adults received lower doses of esketamine compared to other studies including 18-64 year old individuals (56 and 84 mg). Also, older adults may have needed a longer time to get up to an adequate dose and therefore failed to receive an adequate trial of esketamine by the primary endpoint time of 4 weeks. There are only very limited data on IV ketamine in older adults with depression. Therefore, the utility of ketamine and esketamine in older aged-adults is unclear and requires further investigation.

Four phase 3 studies have been performed focusing on relapse prevention, dosing and the elderly population (170,197–199). These studies were submitted to the U.S. Food and Drug Administration, and intranasal esketamine was approved for treatment-resistant depression in 2019. Intranasal esketamine has potential liability for adverse effects to occur, as described below; though, the results from pivotal clinical trials discussed above and reviewed by the FDA indicate that the risk of medically concerning adverse events is very low.

How do intravenous racemic mixture and intranasal esketamine compare? At this time, there is not enough evidence available to compare the two formulations. Bahji et al conducted a recent systematic review and meta-analysis in which they compared the efficacy of racemic (IV) and S-ketamine (intranasal, esketamine) formulations in depression. They found that racemic ketamine compared to esketamine had greater overall response, remission rates, and lower dropout rates. However, the authors did not find significant differences when comparing depressive sub-groups (i.e., MDD vs. bipolar depression) (200). To date, there has not been a randomized control trial comparing IV racemic ketamine to intranasal esketamine. Additionally, long-term relapse prevention data for IV ketamine is not available.

c. Analgesic effects

Ketamine's analgesic effects were first documented in pediatric patients undergoing ophthalmologic procedures (201) and in adults and children undergoing wound dressing changes, such as burn patients. Ketamine has been chosen in these situations because it preserves airway and respiratory function while providing sedation and local anesthesia (202–203). Over several decades, ketamine has been evaluated for treating acute and chronic post-operative pain, neuropathic pain, and cancer pain at a subanesthetic IV dose of 0.5 mg/kg.

Typically, opioids are used in the treatment of acute post-operative pain, but they are associated with side effects such as nausea and respiratory depression. Opioids may paradoxically also lead to hyperalgesia and increased analgesic requirements. The addition of ketamine can help minimize opioid-related side effects and reduce opioid analgesic requirements. In pre-clinical studies, IV ketamine improved the analgesic effect of fentanyl and diminished immediate hyperalgesia (204). Similarly, in meta-analyses of randomized controlled trials of low dose ketamine, administration was associated with decreased total opioid use and pain scores over two days (205–206). Ketamine may also reduce post-operative nausea and vomiting (207–208). This benefit has been attributed to reductions in total opioid administration, leading to decreased opioid-associated nausea and vomiting rather than ketamine's direct anti-emetic effect on 5-HT receptors. Another meta-analysis demonstrated that perioperative intravenous ketamine reduced postoperative opioid consumption by eight milligram morphine equivalents a day (209). However, multiple clinical trials have reported a lack of benefit associated with the addition of ketamine to standard analgesia treatment (210).

Like the IV racemic mixture, S-ketamine may confer advantages in acute pain at a lower dose. Randomized controlled trials suggest that IV S-ketamine may reduce post-operative opioid consumption (211–212). Data comparing intranasal ketamine to opioids for pain are inconclusive. When utilized in emergency room settings for pediatric patients, intranasal ketamine was associated with reduced pain scores and decreased opioid requirements. Side effects such as dizziness and dissociation were transiently were also observed (213–214). Other studies have reported that there is no statistical difference in pain scores when intranasal fentanyl versus intranasal ketamine is administered, and that intranasal ketamine is associated with more non-severe adverse events such as unpleasant taste, dizziness, dysphoria, or hallucinations (215).

Acute pain can transition to a chronic pain state. This circumstance has been reported to lead to functional impairment in about ten percent of all surgical cases (216–217), necessitating the need for alternative strategies in preventing pain chronicity. The mechanisms regulating the

transition from acute to chronic pain are complex, and often include ongoing afferent input from the injured peripheral tissues, sensitization of spinal cord neurons to afferent input, and maladaptive cognitive and emotional control contributing to impaired descending inhibition (218). Synaptic strengthening in the spinal cord dorsal horn to glutamatergic transmission, which includes overexpression of NMDA and AMPA receptors, has been identified as an important contributor to central sensitization and pain chronicity (218–219). These findings have provided the rationale for testing NMDA and AMPA blocking strategies to prevent the transition from acute to chronic pain (220).

Ketamine may be useful in reducing the onset and severity of chronic pain, as shown in a meta-analysis demonstrating that perioperative ketamine may lead to a small but statistically significant reduction in chronic post-surgical pain (221). However, another meta-analysis found no significant relationship between perioperative ketamine administration and chronic pain reduction beyond one month (222).

Sustained chronic pain relief may require more frequent or longer time periods of ketamine administration. In a randomized control trial that enrolled individuals with fibromyalgia, those who received 0.5mg/kg of S-ketamine over 30 minutes had an analgesic effect that peaked at 45 minutes (223). A meta-analysis of IV ketamine used for treating pain syndromes showed a small improvement in pain for up to two weeks (224). Schwartzman et al conducted a randomized double-blind placebo-controlled trial in which ketamine infusions of 20-30 mg/hour lasting 100 hours were administered to patients with complex regional pain syndrome. The investigators reported statistically significant reductions in multiple pain parameters and analgesia lasted up to three months (225), To date, no general consensus has been established with respect to intravenous ketamine dosage or duration. Few randomized controlled trials that have tested multiple doses over longer durations for treating pain. One reason for such mixed findings may be that placebo effects with invasive treatments such as intravenous infusions are quite large. Therefore, such a placebo effect may mask true effects of ketamine. Carr et al conducted a randomized, double-blind, placebo-controlled cross-over trial in which up to five doses of intranasal ketamine were provided to 20 individuals with breakthrough pain. Intranasal ketamine, 10-50 mg, offered pain relief within 10 minutes that lasted up to an hour. There were no serious side effects, though 20% experienced changes in taste and 10% had transient blood pressure elevation (226).

In cancer-related pain, intravenous ketamine has been tested as adjuvant therapy in individuals with poor response to opioids and was shown to reduce morphine requirements, especially in patients experiencing cancer pain with a neuropathic element (227). When oral ketamine dosed from 40 to 400 mg per day was compared to placebo in a double-blind randomized controlled trial in adults with cancer-related neuropathic pain, there was no analgesic benefit associated with oral ketamine administration as compared to responses observed in the placebo group (228). The findings in the literature have been inconsistent, with an overall low quality of evidence. Currently, ketamine has only been recommended for certain patients with refractory cancer pain, particularly with a neuropathic component or manifestations such as wind-up (temporal summation), suggesting the presence of central sensitization or neuropathic pain that no longer responds to high doses of opioids or in patients who experience predictable breakthrough pain (229).

d. Combined anti-depressant and analgesic effects

There are few clinical studies which examine the efficacy of ketamine as a dual-agent for depression and analgesia, and thus far, studies have utilized IV ketamine vs. intranasal ketamine. In a case report published by Sexton et al, a palliative medical team from the University of San Diego utilized a trial of continuous IV ketamine at 0.2 mg/kg/hour in an older adult with thyroid cancer who experienced severe depression, suicidal ideation, and severe pain. Within 5 hours of infusion, the patient's pain score decreased from 8 to 3 points on a 10 point scale; 26 hours into ketamine infusion, the patient's pain score was a 0, and he was observed to have euthymic affect and no suicidal ideation. The individual was discharged home with a central catheter and continuous ketamine infusion. Continuous ketamine administration occurred until he passed away, two weeks later (230). Similarly, ketamine infusion was shown to be effective in treating acute suicidal ideation and chronic pain in a 14-year-old female and 46-year old male in two other case reports (231–232).

One of the first clinical trials to address the effectiveness of IV ketamine as an agent in depression and pain was published this year (233). In this study, Zhou et al recruited 66 participants with treatment resistant depression and split the group into those who had current pain or no pain. They found that 50% of the population recruited endorsed at least one pain symptom. The investigators provided all treatment resistant depressed individuals a total of six subanesthetic IV ketamine infusions over 2 weeks and found that individuals with pain and depression had higher response and remission rates compared to those who did not begin the study with a pain symptom. To note, headache occurred in about 19% of total ketamine infusions; however, headaches resolved after ketamine dose was administered. As a secondary aim, the authors measured serum inflammatory marker levels in the same 66 individuals with depression and their age-and-sex matched controls. They found that several pro-inflammatory cytokines were increased in the depressive group. The individuals with depression had serum markers measured after IV ketamine treatment. In the depressed group with pain, IL-6 significantly decreased after ketamine infusions. This study has several limitations, in that it was not a randomized control trial, many subjects had missing cytokine data, and depressed patients were not body mass index matched to controls (i.e., body mass index is high in depressed individuals and could confound results). Nonetheless, despite these limitations, Zhou et al's findings highlight the advantage of utilizing IV ketamine in a population with depressive and pain symptoms.

5. Conclusion

a. Key points

Ketamine has had a long-standing history as an anesthetic agent and recently has been receiving attention due to its usage in treating both depression and acute or chronic pain. The evidence demonstrates that intravenous and intranasal ketamine are rapid, effective treatment options for depression and that intravenous ketamine may have a role in treating acute post-operative pain and preventing pain chronicity. However, data are inconclusive regarding whether ketamine is a safe and effective therapeutic option for chronic pain. Furthermore, the current literature on ketamine is limited to individuals between the ages of 18 to 64 years of age. Currently, the efficacy of IV and intranasal ketamine for adults greater than 65 years of age with depression or acute or chronic pain is not well established.

b. Current practice guidelines

The American Psychiatric Association (APA) Council guidelines for managing depression, published in 2017, were based on IV ketamine, with recommendations to provide 0.5mg/kg over 40 minutes for up to two to three times a week for two to three weeks, followed by a taper course (234). After esketamine was approved by the FDA in 2019, an international group of mood disorder specialists composed a new set of guidelines. The expert panel has made recommendations for IV and intranasal ketamine. In addition to the 2017 guidelines, the authors recommended that if an individual does not respond to four to six intravenous ketamine treatments (less than 20% improvement from baseline depressive symptoms), then subsequent ketamine treatments should not be provided. They recommend that treatment resistant depressed adults can start intranasal esketamine at 56mg on day one and increase to up to 84 mg twice weekly from weeks one to four. After the fourth week, treatment resistant patients can receive esketamine 56-84mg once a week every one to two weeks. If esketamine is ineffective in substantially improving depressive symptoms after the fourth week, esketamine should be discontinued (235). In the United States,

esketamine can only be provided by sites that have been approved and established by Jansen Pharmaceuticals, which the FDA oversees. To mitigate misuse or adverse events, conditions of the risk evaluation and mitigation strategy (REMS) have to be met, and healthcare providers are required to supervise patients receiving esketamine for two hours after self-administration. Side effects such as dizziness, dissociation, changes in blood pressure, and sedation are monitored (236).

Guidelines published by American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists currently indicate that the level of evidence for usage of ketamine in chronic pain syndromes such as neuropathic pain, cancer pain, and fibromyalgia is Grade C, with low certainty (237). Ketamine was not identified as a safe and effective treatment for neuropathic pain in the guidelines of Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association of the Study of Pain (238).

c. Future directions

While ketamine can affect multiple neurobiological pathways shared between depression and pain, there is limited evidence on which particular mechanisms contribute most to analgesic and anti-depressant effects, and what the ideal dose is to treat each of these two clinical conditions. At high ketamine doses, greater anesthetic and analgesic properties can be achieved, but the likelihood of psychotomimetic effects increases. On the other hand, doses above 0.5mg/kg do not seem to result in a greater acute anti-depressant effect (239).

Many topics in ketamine research require further investigation, including questions such as: how do the long-term effects of IV vs. intranasal ketamine compare? What are the clinical characteristics of good versus poor responders to ketamine? How does IV ketamine vs. intranasal ketamine efficacy compare in older adults? And, if mechanistically, ketamine can act as a dual-purpose agent in depression and pain, what is the ideal dosage and formulation? More research studies, including well-done clinical trials, are needed to answer these pressing issues about the optimal use of ketamine for its anti-depressant and analgesic properties.

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