The Multifaceted Role of IV Ketamine Infusions to Control Depression, Post-Traumatic Stress Disorder, Chronic Regional Pain Syndrome, and Chronic Headaches

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Abstract:

Ketamine has been around since the 1960s, providing analgesia, amnesia, hypnosis and has been used to treat acute pain, chronic pain, acute on chronic pain, neuropathic pain, refractory head pain, depression, and post-traumatic stress disorder (PTSD).

Depression, posttraumatic-stress disorder, and chronic regional pain syndrome (CRPS), can all be extremely debilitating pathologies from a functional, emotional, and spiritual perspective. The mind, body, and spirit are all interconnected, and play a crucial role in the management of these medical conditions. Though oral medications have been used as a mainstay therapy, there can be some limitations with achieving therapeutic effects.

Ketamine is a mixture of R-ketamine and S-ketamine, each demonstrating unique qualities in aiding treatment. Additional metabolism of R-ketamine and S-ketamine has resulted in distinctive metabolites providing treatment for depression, suicidal ideations, and complex regional pain syndrome. Intravenous ketamine administration has provided therapeutic effects for headaches refractory to standard therapy.

The utilization of ketamine continues to evolve and continues to provide beneficial clinical treatments, with limited side effects.

Keywords: Ketamine, Depression, Post-Traumatic Stress Disorder, Complex Regional Pain Syndrome, Chronic Headaches, Migraines

Introduction:

Ketamine is a unique anesthetic agent providing analgesia, amnesia, and hypnosis, while having minimal respiratory depressant effects. It belongs to an exclusive drug class with extensive pharmacodynamic effects and there are no agents possessing all of those desirable properties. Ketamine was first produced in the 1960s as an alternative to phencyclidine and subsequently approved by the FDA in 1970. Ketamine use has continued to evolve over the last few decades with increasing off label use outside of the operating room. Ketamine has shown effectiveness in individuals suffering from acute, chronic, or acute on chronic pain with its anti-hyperalgesic and anti-inflammatory response (1).

Ketamine can be used to treat acute pain, chronic pain, acute on chronic pain, complex regional pain syndrome (CRPS), phantom limb pain, along with other neuropathic pain syndromes (2). There continues to be ongoing research on the usage of ketamine in treating depression, post traumatic stress disorder (PTSD), respiratory and neurological pathologies, and refractory headaches (3,4). Additionally, ketamine has been used as an adjunct in psychotherapy and as a procedural sedative (2).

Ketamine is a mixture of R-Ketamine and S-Ketamine:

Ketamine is a non-competitive antagonist to the phencyclidine site of the N-methyl-d-aspartate (NMDA) receptor for glutamate (5). Ketamine is primarily utilized as a racemic (50:50) mixture of its two enantiomers R-ketamine and S-ketamine. The binding affinity of the S-ketamine for the NMDA receptor is approximately 4-fold greater than the R-ketamine, translating to nearly 4 times greater analgesic and anesthetic effect compared to R-ketamine. However, with a greater binding affinity, S-ketamine has more undesirable psychomimetic effects (6). These undesirable effects consist of blurred vision, altered hearing, dizziness, proprioceptive disturbances, and illusions or hallucinations (7). It has been demonstrated that S-ketamine is the primary enantiomer responsible for the psychomimetic effects of illusions, alterations in hearing, vision, and proprioception (8). Additionally, administration of identical doses of each enantiomer have demonstrated S-ketamine produces psychotic reactions, including depersonalization and hallucinations, while R-ketamine produced more of a state of relaxation (9).

In animal models, R-ketamine has produced more antidepressant properties compared to S-ketamine. R-ketamine has shown longer-lasting antidepressant effects as opposed to S-ketamine (10).

Some randomized controlled trials, case series, along with case reports, demonstrate that single or repeated intravenous or intranasal administration of the S-ketamine enantiomer has antidepressant effects in individuals suffering from refractory depression (11).

Most recently (March 2019), the United States Food Drug Administration (FDA) approved S-ketamine intranasal formulation

for the treatment of refractory depression, however this medication may only be prescribed through a restricted distribution system. The R-ketamine formulation is still in the trial phase at this time (12), thus both R-ketamine and S-ketamine have therapeutic effects depending on the pathology and chronic disease process.

Ketamine is rapidly and extensively metabolized

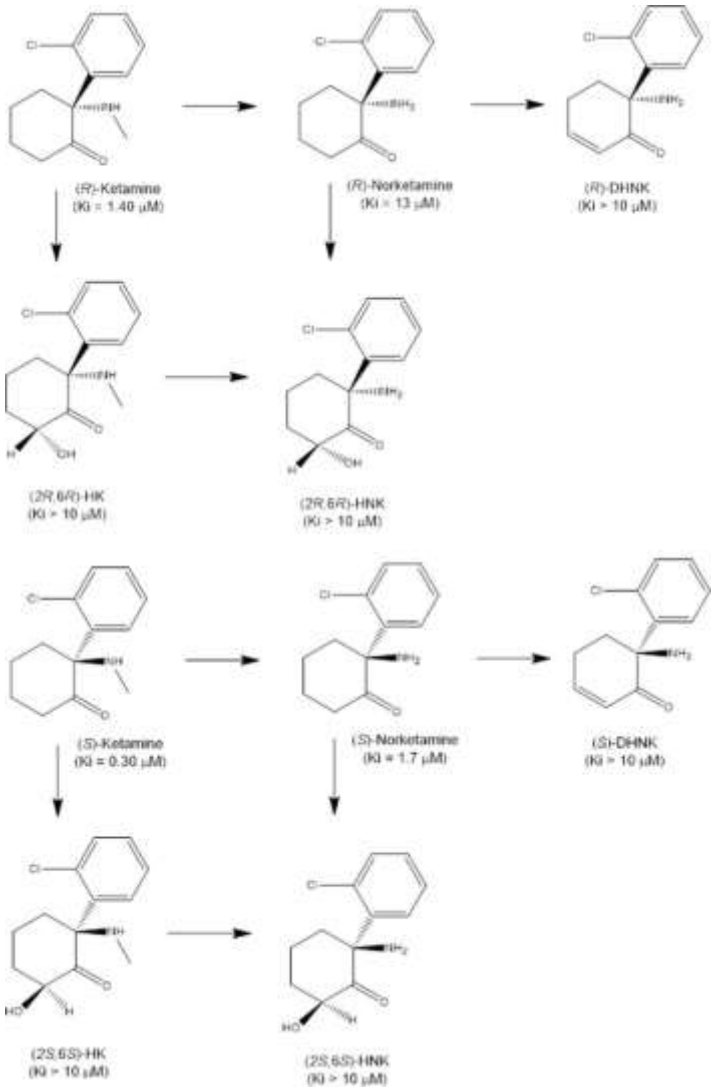
After administration, R-ketamine and S-ketamine are rapidly metabolized by CYP2B6 and CYP3A4 to R-norketamine and S-norketamine, which appear within 10 minutes. R-norketamine and S-norketamine are then further metabolized to R-dehydronorketamine (DHNK) or S-dehydronorketamine (DHNK) or hydroxylated in the C6 position by CYP2A6 producing (2R, 6R)-hydroxynorketamine (HNK) and (2S, 6S)-HNK. The transformation of ketamine to HNK may be a key aspect of Ketamine's therapeutic effects as animal models have shown that (2R,6R)-HNK and (2S,6S)-HNK produce antidepressant responses (13) and that (2R,6R)-HNK is effective in multiple animal models of neuropathic pain (HNK pain). Additionally, R-ketamine or S-ketamine may also be first metabolized to (2R, 6R)-hydroxyketamine (HK) or (2S, 6S)-hydroxyketamine (HK) and then later metabolized to (2R, 6R)-hydroxynorketamine (HNK) or (2S, 6S)-hydroxynorketamine (HNK), respectively (6). Please see Figure 1.

Utilization of Ketamine Outside of the Operating Room:

Although ketamine is best described as a dissociative anesthetic, its additional properties such as analgesia, amnesia, anti-inflammatory, and antidepressant characteristics, allow it to be administered outside of the operating room (13).

Ketamine appears effective as an adjuvant treatment for suicidal behavior. A systematic review showed ketamine to be an immediate treatment option for suicidal ideation with nominal short-term side effects (14). Several research studies (both uncontrolled and controlled randomized trials) advocate the use of intravenous Ketamine to produce a reduction in suicidal ideation in patients who have been diagnosed with major depression or bipolar depression.

Maintained improvement in suicidal ideation time ranged from 230 minutes up to 10 days post infusion from a 40 minute infusion. Price et al conducted a randomized controlled trial in treatment-resistant depression which indicated that intravenous ketamine rapidly reduces suicidal ideation over and above an active placebo (15). Although Ketamine has the potential to be the standard of care for rapid treatment for depression in patients with suicidal ideation, further studies are needed to investigate the mechanism of action, adverse effects, benefits and long- term outcomes.



Chemical Structure of Enantiomers of ketamine and its metabolites (6)

Ketamine appears to promote reduction of inflammation without delaying the healing process in both animal experiments and human observation. Ketamine prevents the prevalent anti-pro-inflammatory influences (16). In a meta-analysis and systematic review of intraoperative Ketamine, the authors found that ketamine exerts anti-inflammatory effects (17). Studies reveal that ketamine, through it is NMDA antagonistic activity suppresses T-cell differentiation and thus, the production of ensuing cytokine production in vitro (18). Ketamine also has an opioid sparing effect in patients after a total hip arthroplasty even when the drug morphine is combined with a multimodal analgesia. Utilization of Ketamine and the proposed anti-inflammatory effect of ketamine were found to improve pain after rehabilitation at 1 month and decreased postoperative chronic pain for up to 6 months after the hip replacement (19). Another study demonstrated that ketamine utilization

during elective coronary artery bypass graft surgery exerts anti-inflammatory effects during and after cardiopulmonary bypass (20). The majority of these studies are based on inflammatory markers before and after ketamine utilization and larger prospective human studies are needed for the anti-inflammatory effects for both in and out of the operating room.

Depression:

Depression or Major Depressive Disorder (MDD) is one of the most common mental illnesses worldwide. MDD consists of 5 or more out of the 9 symptoms: "depressed mood, loss of interest or pleasure, change in weight or appetite, insomnia or hypersomnia, psychomotor retardation or agitation, loss of energy or fatigue, worthlessness or guilt, impaired concentration or indecisiveness, thoughts of death or suicidal ideation or attempt," (including at least depressed mood and loss of interest or pleasure) in the same 2 week period (21).

According to the National Institute of Mental Health (NIMH), MDD affects nearly 16% of people in the United States and almost 7% of the U.S. population every year (22). Globally, nearly 300 million individuals suffer from depression and it is the world's leading cause of disability. There are multiple treatment options for depression, but according to the World Health Organization (WHO), less than 50% of individuals receive treatment (23). 60% of patients suffering from MDD respond to antidepressant agents, but the remainder unfortunately do not and are classified as treatment-resistant depression (22). Most typical and atypical antidepressant agents increase the levels of norepinephrine, serotonin, or dopamine in the central synaptic cleft in order to reduce the symptoms of depression. Although pharmacologic therapy has advanced and evolved over the decades, there still continues to be treatment-resistant depression. Subanesthetic ketamine intravenous administration may decrease depressive symptoms as quickly as within 24 hours in patients suffering from treatment-resistant depression. However, in order to achieve a sustained antidepressant state, repeat infusions are often necessary (22). Additionally, ketamine increases brain derived neurotrophic factor (BDNF) protein expression in the hippocampus, which contributes to enhanced synaptic responses, resulting in antidepressive effects (24). Recent studies in rodents have demonstrated that ketamine rapidly increases BDNF and vascular endothelial growth factor (VEGF) release in the prefrontal cortex and hippocampus. BDNF and VEGF lead to enhanced central and spinal synapses, resulting in neurogenesis and antidepressive effects (25).

Ketamine has also demonstrated anti-depressant effects in those suffering from bipolar depression. The S-ketamine enantiomer administered intravenously or intramuscularly has been an effective antidepressant by reducing suicidal ideation and anhedonia. S-ketamine administered intranasally has also decreased suicidal ideations in depressed patients (13).

Post-Traumatic Stress Disorder:

Post-Traumatic Stress Disorder (PTSD) is a neuropsychological condition in which there "is the presence of recurrent, intrusive distressing memories, dreams, dissociative reactions such as flashbacks, and reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event experienced by an individual" (26). This "traumatic event can be an actual or threatened case of death, serious injury, or sexual assault that affected an individual, close friend, or family member" (American Psychiatric Association). Individuals will avoid "people, places, conversations, and situations," which can trigger their memories of the traumatic event (American Psychiatric Association). Symptoms may be similar to major depressive disorder "including negative beliefs and expectations, negative emotional states, anhedonia, and social withdrawal" (26).

In the United States, PTSD has an approximate prevalence of 8.7% with a "higher prevalence in military veterans, firefighters, police officers, and emergency medical personnel" (26). In the rest of the world, PTSD has a higher prevalence amongst "survivors of rape, military combat and captivity, and genocide" (26). PTSD can be extremely disabling to an individual leading to a lower socioeconomic status and 80% of those individuals are more likely to be diagnosed with another mental disorder (26).

Antidepressants consisting of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), and cognitive behavioral therapy (CBT) have proven to be effective modalities in reducing the symptoms of PTSD, but many still continue to suffer. (27)

Several investigations have demonstrated that symptoms of PTSD are brought on by a "loss of synaptic connectivity," primarily due to glutamate (28). It is postulated that glutamate plays an essential role in neuronal plasticity and synapses, which is why Ketamine may be used as an alternative agent to enhance neuronal connectivity (29).

Activation of the NMDA receptor has been shown to increase the creation of depressive and anxious memories, which is why high NMDA receptor activity may actually lead to PTSD (30). Since ketamine functions as an NMDA receptor antagonist, it may decrease the formation of these memories and theoretically reduce the symptoms of PTSD. Additionally, there is some evidence that antagonizing NMDA receptors in the hippocampus can "stop the consolidation of fear conditioning," which could as well reduce PTSD symptomology (31).

Though ketamine has demonstrated therapeutic effects against treatment resistant depression, its effects seem to be short lasting. Nonconventional treatments such as yoga, meditation, and mindfulness cognitive therapy, have proven to be efficacious in the treatment of refractory depression and could be possible longer lasting therapies. Yoga and mindfulness therapies are safe and effective not only for

depression, but also for other psychiatric disorders in children and adults (53,54). Yoga and meditation originate from over thousands of years ago from the East and are used to reconnect or realign the mind and body as one entity. These low costing and safe interventions can be used to target specific symptoms of depression while empowering the individual to treat him or herself (54).

Mindfulness cognitive behavioral therapy (MCBT) is used to disrupt the autonomic process associated with a depressive episode. The goal is to teach the individual to "focus less on the incoming stimuli and instead focus more on accepting and observing them without judgment" (55). A meta-analysis consisting of 6 randomized controlled trials with a total of 593 participants comparing the use of MCBT for depression to standard conventional treatment and placebo. MCBT decreased the risk of relapse or recurrence with a risk ratio of 0.66, which represents a relative risk reduction of 34% when compared to treatment or placebo groups (56). Therefore, yoga, meditation, and mindfulness cognitive behavioral therapies can all beneficial to patients who suffer from treatment resistant depression.

Clinical Presentation of CRPS:

Complex Regional Pain Syndrome (CRPS) is a debilitating condition involving an imbalance in the sympathetic nervous system. CRPS consists of severe unbearable pain presenting in a regional distribution of the body. This pain usually presents with abnormal sensory, motor, sudomotor, vasomotor, and/or trophic changes (51). CRPS can be further subdivided into two categories depending on if there is an injury to a nerve. CRPS Type I (formerly known as reflex sympathetic dystrophy) does not involve injury to a nerve while CRPS Type II (formerly known as causalgia) does involve injury to a nerve (32).

In order to fulfill the diagnosis of CRPS, the following criteria must be met:

Budapest Criteria
• Continuing pain, which is disproportionate to any inciting event.

• Must report at least **one** symptom in all four of the following categories:
  • **sensory** – reports of hyperaesthesia and/or allodynia
  • **vasomotor** – reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
  • **sudomotor/edema** – reports of edema and/or sweating changes and/or sweating asymmetry
  • **motor/trophic** – reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

• Must display at least **one** sign at time of evaluation in **two or more** of the following

categories:

- **sensory** – evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
- **vasomotor** – evidence of temperature asymmetry (> 1 °C) and/or skin colour changes and/or asymmetry
- **sudomotor/edema** – evidence of edema and/or sweating changes and/or sweating asymmetry
- **motor/trophic** – evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

- There is no other diagnosis that better explains the signs and symptoms.

Once ketamine is administered, it is metabolized to a spectrum of metabolites via the cytochrome P450 system (13, 52). Intravenous administration of ketamine in humans results in higher plasma concentrations of its metabolite, 2S,6S;2R,6R-hydroxynorketamine, than ketamine (33). Administration of 2R,6R-hydroxynorketamine in mice via intraperitoneal injection has demonstrated therapeutic effects for depression, while limiting the anesthetic or sedative side effects (34). Currently there are no published studies on the administration of 2R,6R-hydroxynorketamine in humans for chronic or postoperative pain. Pain is not only primarily physical, but may consist of an emotional or spiritual component as well. For this reason, there continues to be some overlap between depression and pain. Therefore, treating one component may indirectly provide relief to the other.

Ketamine administration in mice has demonstrated short-term therapeutic effects in treating complex regional pain syndrome type-1 (35), which is why ketamine infusions continue to be used clinically for CRPS-1 (36). In a mice study consisting of CRPS-1 secondary to tibia fracture, reduced allodynia effects were seen as long as 4 days after the last injection of 2R,6R-hydroxynorketamine. The half life of 2R,6R-hydroxynorketamine is less than 1 hour, which suggests 2R,6R-hydroxynorketamine may decrease central sensitization in CRPS (13). Interestingly, a similar study was done on CRPS-2 mice with 2R,6R-hydroxynorketamine, but the antiallodynic effects lasted less than 24 hours (37).

Intravenous Ketamine for Refractory Migraine Headache

Migraine is described as a common primary headache disorder with high socio-economic and personal impacts (38). It is commonly disabling, occurring for no obvious reason, and not necessarily the result of any other underlying disease (39). In the 2010 Global Burden of Disease Study (40), it was ranked

as the third most prevalent disorder in the world. A few years later, it was ranked the third-highest cause of disability worldwide in both males and females under the age of 50 years (41).

Migraines are characterized by pulsing head pain, nausea, and sensitivity to light and sound and should not be confused with tension-type headaches which present with non-pulsing "band-like" pressure on both sides of the head, and not accompanied by other symptoms (42). Because headeaches are so prevalent in the US, and the difficulty in finding effective treatments, the Headache Society recommends that health care professionals use the classification system to help make a more specific diagnosis as to the type of headache a patient has, and allow better and more effective options for treatment (43). A comprehensive and complete review by Siberstein et al. (44) provides an operational diagnostic criteria for chronic migraine. With such a broad range of symptoms and lack of definitive treatments, it would appear that these conditions have a complex interplay of genetic, developmental, and environmental risk factors.

Once it is established that a patient is refractory to standard available drug treatments, a specialist may suggest intravenous ketamine as a preventive treatment. The terms "intractable" and "refractory" have been used interchangeably implying that the headache is frequent and untreatable, and the patient is usually classified as disabled by standard scales, such as MIDAS or HIT-6. Experts in this field have criticized the interchangeable use of the terms claiming the need for more specific criteria. Silberstein et al. (45) proposed a graded classification scheme for defining intractability to acute and preventive treatments based on the patient's previous response/failure to proven acute or preventive therapies. Their classification tables were carefully constructed based on the extensive clinical experience of experts in the field. Moreover, this classification system should be useful to clinicians and researchers wishing to abide by some consistent criteria for selecting patient candidates for ketamine infusion treatment.

Similarily to treatment resistant depression, CRPS, and PTSD, administration of subanesthetic (≤1.0 mg/kg/hr) multiday intravenous ketamine infusion has shown promise in the treatment of refractory migraine headaches. Several of routes of administration have also been successfully used for treatment of primary headaches. It is of interest that the first published (46) use of ketamine for treatment of severe and frequent migraines was from subcutaneous administration using an 80 microgram/kg dose. In their randomized double-blind crossover study, the authors reported marked relief of pain as an acute treatment and also as a prophylactic therapy, compared to placebo. A few years later Kaube et al. (47) used intranasal ketamine (25 mg) for the treatment of migraine aura with limited success. A German study by Granata et al. (48) in patients with cluster headaches demonstrated efficacy with a 40 min-1 hr low dose ketamine infusion at approximately 2-week intervals with a

maximum of 4 treatments per patient. The attacks were completely aborted in 100% of the patients with episodic headaches and in 54% of patients with chronic cluster headaches. The duration of pain relief was 3-18 months. It was not until 2016 that Pomeroy et al. (49) reported on their 10 year experience using intravenous, in-patient multi-day low dose ketamine for the treatment of refractory headache. Their retrospective study included patients with chronic migraine (82%), and new daily persistent headaches (18%) treated using an incremental dosing protocol starting at 0.1 mg/kg/hr up to a maximum dose of 1.0 mg/kg/hr. Their results show that 71% of patients were classified as acute responders and 27% had a sustained response. In 2018 Schwenk et al. (50) reported similar findings as Pomeroy et al.'s study in patients diagnosed with intractable migraine. 77% of their patients were classified as immediate responders and 39% as sustained responders with a mean of 101 days post treatment. It should be noted that 97% of their patients had a diagnosis of refractory migraine and 3% had cluster headache.

The use of in-patient intravenous ketamine for the treatment of refractory migraine has increased over the past few years however only a few studies have demonstrated encouraging clinical benefit in this select patient population. The pain relief is time limited, typically lasting between one week and 3 months in responders. Future research will need to determine if dosing strategy could improve efficacy, while a better understanding of ketamine's mechanisms and pathways could lead to development of new therapies. In light of its increasing use in hospitalized patients, monitoring considerations are also important to ensure its safe administration. Unfortunately, the monitoring practices for ketamine infusions in the literature vary considerably and may also be institution dependent and not necessarily consistent with ASA recommendations for moderate sedation. (51) Appropriate monitoring is therefore important during administration of ketamine and the level of monitoring should depend on the likelihood of deleterious signs and symptoms (eg, elevated blood pressure and heart rate, ECG changes, loss of consciousness, psychotomimetic), as well as the potential for adverse events (eg, chest pain, airway obstruction, hallucinations). Finally, the need for large well-designed clinical trials is needed as current evidence is based on a few observational retrospective studies and ketamine's use for the treatment of other chronic conditions.

Conclusions:

Ketamine continues to be a unique and exclusive pharmacologic agent with a multitude of therapeutic effects. Though most often used in the operating room environment by anesthesiologists, the exceptional characteristics nearly allow it to be administered by all practitioners. The beneficial effects of ketamine continue to evolve as more studies are now focused on the metabolites of ketamine. As the fields of pain and behavioral medicine continue to cultivate over the next decade, the uses of ketamine will continue to advance.

References:

1. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. *Acta Pharmacologica Sinica*. 2016;37(7):865-872. doi:10.1038/aps.2016.5.

2. Radvansky BM, Puri S, Sifonios AN, Eloy JD, Le V. Ketamine—A Narrative Review of Its Uses in Medicine. *American Journal of Therapeutics*. 2016;23(6). doi:10.1097/mjt.0000000000000257.

3. Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine Infusions for Treatment Refractory Headache. *Headache: The Journal of Head and Face Pain*. 2016;57(2):276-282. doi:10.1111/head.13013.

4. Schwenk ES, Dayan AC, Rangavajjula A, et al. Ketamine for Refractory Headache. *Regional Anesthesia and Pain Medicine*. 2018:1. doi:10.1097/aap.0000000000000827.

5. Ketamine Mechanism of Action. *Anesthesia General*. November 2017. anesthesiageneral.com/ketamine-mechanism-of-action.

6. Yang C, Yang J, Luo A, Hashimoto K. Molecular and cellular mechanisms underlying the antidepressant effects of ketamine enantiomers and its metabolites. *Translational Psychiatry*. 2019;9(1). doi:10.1038/s41398-019-0624-1.

7. Mathisen LC, Skjelbred P, Skoglund LA, Øye I. Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. *Pain*. 1995;61(2):215-220. doi:10.1016/0304-3959(94)00170-j.

8. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. *Journal of Pharmacology and Experimental Therapeutics* . 1992;260(3).

9. Vollenweider F, Leenders K, Øye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *European Neuropsychopharmacology*. 1997;7(1):25-38. doi:10.1016/s0924-977x(96)00042-9.

10. Zhang J-C, Li S-X, Hashimoto K. R (−)-ketamine shows greater potency and longer lasting antidepressant effects than S ( )-ketamine. *Pharmacology Biochemistry and Behavior*. 2014;116:137-141. doi:10.1016/j.pbb.2013.11.033.

11. Andrade, Chittaranjan. “Ketamine for Depression, 3: Does Chirality Matter?” The Journal of Clinical Psychiatry, vol. 78, no. 06, 28 June 2017, doi:10.4088/jcp.17f11681.

12. Hashimoto K. Rapid- acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. *Psychiatry and Clinical Neurosciences*. 2019;73(10):613-627. doi:10.1111/pcn.12902.

13. Zanos P. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *European Neuropsychopharmacology*. 2017;27. doi:10.1016/s0924-977x(17)30999-9.

14. Reinstatler L, Youssef NA. Ketamine as a Potential Treatment for Suicidal Ideation: A Systematic Review of the Literature. *Drugs in R&D*. 2015;15(1):37-43. doi:10.1007/s40268-015-0081-0.

15. Price RB, Iosifescu DV, Murrough JW, et al. Effects Of Ketamine On Explicit And Implicit Suicidal Cognition: A Randomized Controlled Trial In Treatment-Resistant Depression. *Depression and Anxiety*. 2014;31(4):335-343. doi:10.1002/da.22253.

16. Jahangiri L, Kesmati M, Najafzadeh H. Evaluation of analgesic and anti-inflammatory effect of nanoparticles of magnesium oxide in mice with and without ketamine. *European Review for Medical and Pharmacological Sciences* . 2013;17(20).

17. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does Intraoperative Ketamine Attenuate Inflammatory Reactivity Following Surgery? A Systematic Review and Meta-Analysis. *Anesthesia & Analgesia*. 2012;115(4):934-943. doi:10.1213/ane.0b013e3182662e30.

18. Gao M, Jin W, Qian Y, Ji L, Feng G, Sun J. Effect of N-methyl-D-aspartate receptor antagonist on T helper cell differentiation induced by phorbol-myristate-acetate and ionomycin. *Cytokine*. 2011;56(2):458-465. doi:10.1016/j.cyto.2011.06.022.

19. Remérand F, Tendre CL, Baud A, et al. The Early and Delayed Analgesic Effects of Ketamine After Total Hip Arthroplasty: A Prospective, Randomized, Controlled, Double-Blind Study. *Anesthesia & Analgesia*. 2009;109(6):1963-1971. doi:10.1213/ane.0b013e3181bdc8a0.

20. Welters I, Feurer M-K, Preiss V, et al. Continuous S -( )-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass. *British Journal of Anaesthesia*. 2011;106(2):172-179. doi:10.1093/bja/aeq341.

21. Uher R, Payne JL, Pavlova B, Perlis RH. Major Depressive Disorder In Dsm-5: Implications For Clinical Practice And Research Of Changes From Dsm-Iv. *Depression and Anxiety*. 2013;31(6):459-471. doi:10.1002/da.22217.

22. Coccaro EF. New Hope for Patients with Major Depressive Disorder? *New England Journal of Medicine*. 2019;381(10):980-981. doi:10.1056/nejme1907638.

23. Koskie, Brandi. "Depression: Facts, Statistics, and You." *Healthline*, Healthline Media, 14 May 2019, www.healthline.com/health/depression/facts-statistics-infographic#1.

24. Kim J-W, Monteggia LM. Increasing doses of ketamine curtail antidepressant responses and suppress associated synaptic signaling pathways. *Behavioural Brain Research*. 2020;380:112378. doi:10.1016/j.bbr.2019.112378.

25. Deyama S, Duman RS. Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine. *Pharmacology Biochemistry and Behavior*. 2020;188:172837. doi:10.1016/j.pbb.2019.172837.

26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.

27. Liriano F, Hatten C, Schwartz TL. Ketamine as treatment for post-traumatic stress disorder: a review. *Drugs in Context*. 2019;8:1-7. doi:10.7573/dic.212305.

28. Rasmussen KG. Ketamine for Posttraumatic Stress Disorder. *JAMA*

Psychiatry. 2015;72(1):94. doi:10.1001/jamapsychiatry.2014.1621.

29. Krystal JH, Abdallah CG, Averill LA, et al. Synaptic Loss and the Pathophysiology of PTSD: Implications for Ketamine as a Prototype Novel Therapeutic. *Current Psychiatry Reports*. 2017;19(10). doi:10.1007/s11920-017-0829-z.

30. Mcghee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The Correlation Between Ketamine and Posttraumatic Stress Disorder in Burned Service Members. *The Journal of Trauma: Injury, Infection, and Critical Care*. 2008;64(Supplement). doi:10.1097/ta.0b013e318160ba1d.

31. Zimmerman JM, Maren S. NMDA receptor antagonism in the basolateral but not central amygdala blocks the extinction of Pavlovian fear conditioning in rats. *European Journal of Neuroscience*. 2010. doi:10.1111/j.1460-9568.2010.07223.x.

32. Goebel A, Bisla J, Carganillo R, et al. A randomised placebo-controlled Phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial). *Efficacy and Mechanism Evaluation*. 2017;4(5):1-82. doi:10.3310/eme04050.

33. Zarate CA, Brutsche N, Laje G, et al. Relationship of Ketamines Plasma Metabolites with Response, Diagnosis, and Side Effects in Major Depression. *Biological Psychiatry*. 2012;72(4):331-338. doi:10.1016/j.biopsych.2012.03.004.

34. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological Reviews*. 2018;70(3):621-660. doi:10.1124/pr.117.015198.

35. Das V, Kroin JS, Moric M, Buvanendran A. Biochemical and Pharmacological Characterization of a Mice Model of Complex Regional Pain Syndrome. *Regional Anesthesia and Pain Medicine*. 2017;42(4):507-516. doi:10.1097/aap.0000000000000622.

36. Tajerian M, Clark JD. New Concepts in Complex Regional Pain Syndrome. *Hand Clinics*. 2016;32(1):41-49. doi:10.1016/j.hcl.2015.08.003.

37. Xu Q, Yaksh TL. A brief comparison of the pathophysiology of inflammatory versus neuropathic pain. *Current Opinion in Anaesthesiology*. 2011;24(4):400-407. doi:10.1097/aco.0b013e32834871df.

38. Borsook D, Dodick DW. Taking the headache out of migraine. *Neurology: Clinical Practice*. 2015;5(4):317-325. doi:10.1212/cpj.0000000000000171.

39. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202.

40. GBD 2010 The Global Burden of Disease Study 2010. Lancet 2012;380:2053–260.

41. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545–1602.

42. Clinch C (2011) Chapter 28. Evaluation & Management of headache - CURRENT Diagnosis & Treatment in family medicine. In: South-Paul JE, Matheny SC, Lewis EL (eds) Lange Current Series, Third edn. McGraw-Hill. isbn:9780071624367

43. Silberstein SD, Lipton RB, Dodick DW. Operational Diagnostic Criteria for Chronic Migraine: Expert Opinion. *Headache: The Journal of Head and Face Pain*. 2014;54(7):1258-1266. doi:10.1111/head.12407.

44. Silberstein SD, Dodick DW, Pearlman S. Defining the Pharmacologically Intractable Headache for Clinical Trials and Clinical Practice. *Headache: The Journal of Head and Face Pain*. 2010;50(9):1499-1506. doi:10.1111/j.1526-4610.2010.01764.x.

45. Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: therapeutic and theoretic implications. Int J Clin Pharmacol Res. 1995;15(5-6):181-9. PubMed PMID: 8835616.

46. Kaube H, Herzog J, Kaufer T, Dichgans M, Diener HC. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. *Neurology*. 2000;55(1):139-141. doi:10.1212/wnl.55.1.139.

47. Granata L, Niebergall H, Langner R, Agosti R, Sakellaris L. Ketamin i. v. zur Behandlung von Clusterkopfschmerz. *Der Schmerz*. 2016;30(3):286-288. doi:10.1007/s00482-016-0111-z.

48. Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine Infusions for Treatment Refractory Headache. *Headache: The Journal of Head and Face Pain*. 2016;57(2):276-282. doi:10.1111/head.13013.

49. Schwenk ES, Dayan AC, Rangavajjula A, et al. Ketamine for Refractory Headache. *Regional Anesthesia and Pain Medicine*. 2018:1. doi:10.1097/aap.0000000000000827.

50. Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology*. 2002;96(4):1004-1017. doi:10.1097/00000542-200204000-00031.

51. Harden RN, Oaklander AL, Burton AW, et al. Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines, 4th Edition. *Pain Medicine*. 2013;14(2):180-229. doi:10.1111/pme.12033.

52. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Molecular Psychiatry*. 2018;23(4):801-811. doi:10.1038/mp.2017.255.

53. Pradhan B, Parikh T, Makani R, Sahoo M. Ketamine, Transcranial Magnetic Stimulation, and Depression Specific Yoga and Mindfulness Based Cognitive Therapy in Management of Treatment Resistant Depression: Review and Some Data on Efficacy. *Depression Research and Treatment*. 2015;2015:1-14. doi:10.1155/2015/842817.

54. Pradhan B, Sharma A. Editorial (Thematic Issue: The Time has Come for Integrating Complementary Medicine into Psychiatry). *Adolescent Psychiatry*. 2015;5(2):71-72. doi:10.2174/2210676605021504301543 42.

55. Felder JN, Dimidjian S, Segal Z. Collaboration in Mindfulness-Based Cognitive Therapy. *Journal of Clinical*

Psychology. 2012;68(2):179-186. doi:10.1002/jclp.21832.

56. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis. Clinical Psychology Review. 2011;31(6):1032-1040. doi:10.1016/j.cpr.2011.05.002.