Emerging Use of Ketamine for the Treatment of Migraine and Other Headache Disorders

An increasing body of research is proving ketamine to be an effective treatment option for migraine and other headache disorders.

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According to the World Health Organization (WHO),[1] 3.1 billion people or 40% of the global population experience headaches, the majority of which meet criteria for tension-type headache with mild to moderate severity associated with limited functional disability, and which generally respond to simple over-the-counter analgesics. However, an estimated 1.1 billion persons worldwide experience migraine, a chronic, moderate to severe, painful disorder that the WHO ranks among the most functionally disabling medical conditions in terms of years lived with disability. Other less common headache disorders, such as cluster headache and other trigeminal autonomic cephalalgias (TACs), new daily persistent headache (NDPH), the indomethacin-responsive hemicranias, and chronic post-traumatic headache are also painful and disabling.

Preventive pharmacotherapy for migraine has evolved considerably with the introduction of calcitonin gene-related peptide (CGRP) receptor or ligand blockers, which include the anti-CGRP monoclonal antibodies and the gepants. However, a substantial number of people with migraine do not respond to available preventives, and many of the less common chronic headache disorders have no Food and Drug Administration (FDA)–approved treatment. Thus, there exists an unmet need for safe and effective treatment options for people with refractory headache disorders.

What Is Ketamine?

Ketamine was first synthesized in 1962 by scientists at Park-Davis as a safer alternative to phencyclidine. By adding a ketone and amine side chains to phencyclidine (hence the name ketamine), a compound was developed that does not induce respiratory depression and has little effect on blood pressure and heart rate. Approved as a schedule 3 analgesic/anesthetic in 1970, ketamine was used on the battlefield in the Vietnam War because of its rapid onset, safety, and efficacy as a dissociative anesthetic.[2] Today, ketamine is widely used in emergency departments, operating rooms, and intensive care units as a dissociative anesthetic/analgesic. Its common use in veterinary medicine, primarily because of its safety profile for equine and other veterinary surgeries, has earned it the nickname "horse tranquilizer."

Mechanism of Action

The primary mechanism of action of ketamine lies in its antagonism of the NMDA receptor (NMDAR), which causes glutamate release onto the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor. This stimulates brain-derived neurotrophic factor–tropomyosin receptor kinase B, mammalian target of rapamycin, and eukaryotic elongation factor 2, all of which promote synaptic plasticity.[3] In addition, ketamine acts on all opioid receptors, with a high affinity for the μ opioid receptor; potentiates the presynaptic inhibitory effects of γ-aminobutyric acid by binding to the γ-aminobutyric acid–A receptor; and blocks the hyperpolarization-activated cyclic nucleotide-gated channel

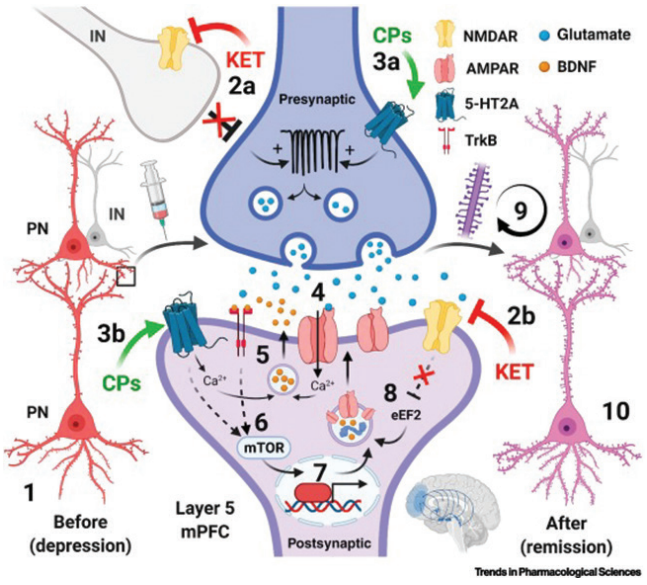

Figure 1. Mechanism of action of ketamine.
Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; CPs, classical psychedelics; eEF2, eukaryotic elongation factor 2; IN, inhibitory neuron; KET, ketamine; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NMDAR, NMDA receptor; PN, pyramidal neuron.
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1 receptor (Figures 1 and 2).[2,3] Ketamine is excreted renally, and has a plasma half-life of 3 hours.

How Ketamine Works in Headache Treatment

Ketamine has become increasingly popular in treating depression and has more recently been studied for its potential efficacy in the treatment of refractory migraine and other headache disorders.[2] Migraine pathophysiology is complex. One pathway involves increased glutamate signaling, leading to dysregulation of brainstem activation, particularly in the periaqueductal gray, dorsal raphe nucleus, and locus coeruleus, which leads to a phenomenon known as cortical spreading depolarization or depression (CSD). CSD stimulates afferent nociceptors in the trigeminal vasculature, which in turn is hypothesized to be involved in precipitating migraine. Animal and in vitro studies have suggested that ketamine reduces CSD.[4]

In addition, NMDAR activation transmits nociceptive signals in the trigeminal nucleus caudalis and stimulates structures that cause a release of glutamate and CGRP, which play prominent roles in the pathophysiology of

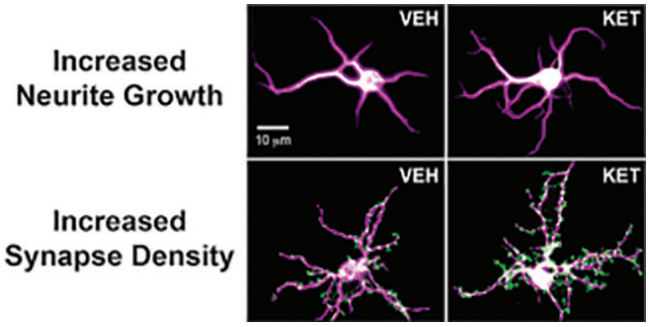

Figure 2. Increase in neurite growth and synaptic density in ketamine-treated neuron compared with vehicle.
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migraine. Thus, antagonizing NMDAR decreases transmission of nociceptive signals that lead to headache.[5] Glutamate and NMDAR also play roles in central sensitization, which can lead to hyperalgesia in chronic pain syndromes. NMDAR antagonism by ketamine may help alleviate this hyperalgesia, and its opioid agonist activity may provide acute pain relief.[6]

Evidence for Ketamine in Headache Disorders

Migraine

There is evidence that intravenous (IV) ketamine may be effective for acute treatment of migraine. In a systematic review, Podkowa et al[4] found that 100% of participants with migraine without aura experienced acute pain relief at a mean time of 44 minutes after IV infusion.[7] A study on individuals with refractory migraine found that pain scores decreased from an average of 6.6 to 3.4 points (on a 0- to 10-point visual analog scale [VAS]) at 142 minutes after IV ketamine infusion.[8] Moreover, a randomized controlled trial found that 34.4% of participants had a >50% reduction in pain levels over 5.1 days, on average.[9] However, the acute effects of ketamine remain unclear, as another study found no significant change in pain severity 30 minutes after infusion compared with a control group.[10] Further research is needed to elucidate the potential of ketamine as an acute migraine treatment.

In terms of sustained effects from ketamine, another study in a systematic review[4] found that 77% of participants responded to ketamine, with effects peaking at 4.6 days on average. Forty percent of participants had sustained effects from ketamine, measured as a >2-point reduction in VAS pain scale ratings, lasting until their first follow-up at an average of 38.1 days. A total of 39% of participants had sustained effects at their second follow-up, at an average of 101.3 days after treatment.[11] Another study found

that 74.6% of people with chronic migraine were acute responders and 23.4% were sustained responders. Pain levels decreased by an average of 4.6 points on the VAS from the time of admission to discharge. The sustained responders had an average pain score reduction of 2.1 points on the VAS at follow-up compared with initial admission.[12]

These results indicate substantial clinical benefit of ketamine use for individuals experiencing chronic migraine, as there is evidence that ketamine treatment may provide both acute and lasting benefit. However, more research is needed to confirm how long the effects of ketamine last, because conflicting evidence exists. Another study found that ketamine acutely reduced numeric rating scale pain levels from 7.4 to 3.7, but that the pain levels returned to 7.2 at discharge and after 6 weeks.[13]

Cluster Headache

In terms of use of ketamine to treat cluster headache, a systematic review[14] found that 54% of participants with chronic cluster headache were pain-free within 2 weeks of their ketamine infusion, and 100% of participants with episodic cluster headache were pain-free at the 2-week mark.[15] Another report described 2 individuals with cluster headache: 1 became pain-free, and the other had a >50% reduction in cluster attacks, with effects lasting for 6 weeks.[16] In another study of 17 individuals with chronic cluster headache, 76% of participants responded to IV ketamine, and there was a significant reduction in the number of cluster headache attacks, decreasing on average by 3.1 attacks per day.[17]

New Daily Persistent Headache

In a small inpatient NDPH trial, 14 participants responded acutely to IV ketamine treatment, with a reduction in VAS pain score of 4.24 points on average from infusion to discharge. Of the 6 participants who followed up, 4 had sustained effects from ketamine, as defined by a 2-point reduction in VAS pain score, compared with before infusion.[12] However, another report comparing lidocaine and ketamine infusions found that 2 individuals who received lidocaine infusions had a >50% reduction in pain level, whereas those who received ketamine did not achieve significant pain relief.[9]

Short-Lasting Unilateral Neuralgiform Headache

In a systematic review[18] including a case series of short-lasting unilateral neuralgiform headache with conjunctival injection and tearing, a trigeminal autonomic cephalalgia that is a form of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms, individuals remained attack-free for 3 months after treatment. Minor recurrences were managed successfully with sublingual ketamine.[19] Another case series found that participants were attack-free for 6 months after treatment.[20]

Posttraumatic Headache

In a systematic review of individuals with traumatic brain injury, 3 studies showed a dose-dependent decrease in spreading depolarizations after ketamine infusion.[21] In addition, many properties of ketamine, including its analgesic, sedative, antiseizure, hemodynamic, and airway resistance effects (it activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction), make it ideal for sedation and analgesia in people with traumatic brain injury.[22]

Familial Hemiplegic Migraine

In familial hemiplegic migraine, the evidence has been limited to intranasal administration of ketamine. A systematic review[5] found that 5 of 11 individuals benefited from intranasal ketamine treatment in both pain level and duration of episodes when treating acute attacks, whereas 6 individuals had no benefit.[23] In addition, ketamine provided short-term effects in 14 attacks and was able to decrease aura symptoms in 5 out of 11 individuals. Two of these 11 participants reported reduced subsequent headache pain levels.[23]

This effect on aura symptoms is of particular interest in that aura is linked to NMDA activation and glutamate release, so there has been considerable interest in NMDA antagonists in the treatment of migraine with aura. Multiple forms of familial hemiplegic migraine (types 1, 2, and 3) involve genetics associated with excess synaptic glutamate.

Medication Overuse Headache

In a study of 12 individuals with medication overuse headache, 41.7% benefited from IV ketamine treatment, with 25% of individuals experiencing >50% pain reduction and 25% achieving pain freedom. However, these individuals were compared with a group that received lidocaine infusions, in which a >50% reduction in pain level in 50% of individuals and pain freedom in 22.2% was reported.[9] Therefore, whether ketamine is superior to lidocaine in the treatment of medication overuse headache is unclear, and more research is needed to confirm.

Practical Considerations

There is no established, evidence-based protocol for IV ketamine infusion. Our center—the New England Institute for Neurology and Headache, in Stamford, CT—ran a study evaluating every other day (3 days per week) infusions for 2 weeks vs 4 days in a row and found no difference in outcomes. Therefore, our standard protocol is the latter,

TABLE. KETAMINE THERAPY OUTCOMES TRACKED OVER 3 MONTHS

	Before infusion	1 Day after infusion	1 Week after infusion	1 Month after infusion	3 Months after infusion
MIDAS	78				20
PHQ-9	15	6	5	3	3
GAD-7	12	12	11	11	8
VAS	7	5	5	3	4
PGIC		+1	+2	+3	+3

Abbreviations: GAD-7, Generalized Anxiety Disorder–7; MIDAS, Migraine Disability Assessment Scale; PGIC, Patient Global Impression of Change; PHQ-9, Patient Health Questionnaire–9; VAS, visual analog scale.

which requires less of a time commitment. Our individual darkened infusion suites are equipped with reclining chairs, blankets, and pillows. People are given noise-cancelling headphones, and some choose to listen to curated music, whereas others prefer silence. Vital signs are monitored continuously during infusion, and a nurse or advanced practice provider is present at all times. Because nausea is a common side effect of ketamine treatment, IV ondansetron is administered before ketamine. Total duration of the infusion is 60 to 90 minutes. The goal is to increase the dose each day, on average from .25 to >2 mg/kg, depending on a number of variables including patient response, degree of sedation, vital signs, and adverse events. Data, which vary by diagnosis, are collected on all individuals before infusion and 1 day, 1 week, 1 month, and 3 months after infusion.

Case Report

JV, age mid-50s, presented with a 42-year history of migraine (the first 30 years episodic migraine, the next 12 years chronic migraine), along with anxiety, depression, and posttraumatic stress disorder (PTSD). JV had tried >15 migraine preventive medications, including several beta-blockers, topiramate, onabotulinumtoxinA, tricyclic antidepressants, anti-CGRP monoclonal antibodies, and atogepant, with either limited efficacy or intolerable side effects. JV was taking duloxetine 120 mg/d for depression and prazosin 3 mg/d at bedtime for PTSD-related sleep disorder.

Before infusion, JV's Migraine Disability Assessment Scale score was 78 (grade IVB, indicating very severe disability), average daily pain score was 7/10, Patient Health Questionnaire–9 score was 15 (indicating major depression), and Generalized Anxiety Disorder–7 score was 12 (indicating moderate anxiety). JV received a starting dose of .35 mg/kg of ketamine on day 1, which was increased daily, reaching 2.25 mg/kg by day 4. JV tolerated the infusions well and said, *"I feel undepressed for the first time since I was 5."* Outcomes were tracked over 3 months and are shown in the Table. JV had sustained improvement in migraine, PTSD, anxiety, and depression symptoms, and Patient Global Impression of Change score indicated *"very much improved."* By 1 month, the duloxetine dose was reduced to 60 mg, and duloxetine was discontinued by month 2. Prazosin use decreased to 1 mg several times per week.

Not all individuals respond to ketamine therapy. In data collected so far at our center in 2024, 15% of individuals report no improvement, 19% report a 25% to 49% improvement, 33% report a 50% to 74% improvement, and 33% report a 75% to 100% improvement in their primary symptoms. Of all responders, approximately one third have a sustained response, and in two thirds the effect will wane over 3 to 6 months, requiring a booster ketamine session, or the use of compounded intranasal ketamine, which can be instilled at home.

Summary

Ketamine is a relatively safe, easy to administer dissociative anesthetic/analgesic with ability to induce neuroplasticity, mainly through antagonism of the NMDA glutamate receptor. Small studies and case series attest to its ability to ameliorate head pain of diverse etiology. At our center, ~85% of people with headache have reported some response, which is sustained for at least 3 months. Further studies are needed to validate its efficacy, but ketamine has proven highly effective in our most refractory cases and offers a treatment option when multiple therapies from different classes are poorly tolerated or provide inadequate relief. ■

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Disclosures

The authors report no disclosures.