American Journal of Therapeutics 31, e155–e177 (2024)

Psychedelic Therapy: A Primer for Primary Care Clinicians—Ketamine

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Background: Ketamine, an arylcyclohexylamine dissociative anesthetic agent, has evolved into a versatile therapeutic. It has a rapid-onset, well-understood cardiovascular effects and a favorable safety profile in clinical use. Its enantiomeric compound, esketamine, was approved by the Food and Drug Administration in 2019 for both treatment-resistant depression and major depressive disorder with suicidal ideation.

Areas of Uncertainty: Research indicates dose-dependent impacts on cognition, particularly affecting episodic and working memory following both acute administration and chronic use, albeit temporarily for the former and potentially persistent for the latter. Alongside acute risks to cardiovascular stability, ketamine use poses potential liver toxicity concerns, especially with prolonged or repeated exposure within short time frames. The drug's association with "ketamine cystitis," characterized by bladder inflammation, adds to its profile of physiological risks.

Therapeutic Advances: Data demonstrate a single intravenous infusion of ketamine exhibits antidepressant effects within hours (weighted effect size averages of depression scores (N = 518) following a single 0.5 mg/kg infusion of ketamine is $d = 0.96$ at 24 hours). Ketamine is also effective at reducing posttraumatic stress disorder (PTSD) symptom severity following repeated infusions (Clinician-Administered PTSD Scale scores: −11.88 points compared with midazolam control). Ketamine also decreased suicidal ideation in emergency settings (Scale for Suicidal Ideation scores: −4.96 compared with midazolam control). Through its opioid-sparing effect, ketamine has revolutionized postoperative pain management by reducing analgesic consumption and enhancing recovery.

Limitations: Many studies indicate that ketamine's therapeutic effects may subside within weeks. Repeated administrations, given multiple times per week, are often required to sustain decreases in suicidality and depressive symptoms.

Conclusions: Ketamine's comprehensive clinical profile, combined with its robust effects on depression, suicidal ideation, PTSD, chronic pain, and other psychiatric conditions, positions it as a substantial contender for transformative therapeutic application.

Keywords: ketamine, PTSD, chronic pain, depression, psychedelic, psychedelic assisted therapy, anesthetic

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CLINICAL CASE

An assigned female-at-birth 26 years old, who is receiving gender affirming treatment for gender dysphoria and is now living as a man, presents for the evaluation of acute suicidality in the primary care setting and is referred to a level 1 trauma center with dedicated psychiatric emergency services. On the initial evaluation, the patient has had an acute exacerbation of suicidality in the context of a traumatic incident 2 days prior—the individual was assaulted in a mugging attempt several blocks away from his home. He has a history of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), for which he has been in remission for the past 3 years. Prior medication trials for MDD and PTSD include desvenlafaxine (titrated up to 100 mg, daily), which had been the most effective medication for his depression but had been tapered off 1 year prior. Additional medication trials that led to partial response include fluoxetine (80 mg, daily) and sertraline (titrated up to 200 mg, daily). Quetiapine (50 mg, nightly) had been a successful treatment for insomnia but had been only marginally effective for the mitigation of MDD and PTSD symptoms. He had been psychiatrically stable until this recent traumatic event, which led to a relapse of symptoms. His only current medications include testosterone cypionate (100 mg/wk, intramuscularly [IM]) managed by a telehealth provider, as well as rosuvastatin (10 mg, daily) for hyperlipidemia. His weight is 215 lb, and his height is 5′6″. He is hesitant to consent to voluntary psychiatric admission due to 2 prior psychiatric admissions in his adolescence. Of note, on social history, the patient has been abstinent from alcohol for the past 3 years, until drinking in 2 binge episodes before presentation.

BACKGROUND

History

Ketamine is a dissociative anesthetic falling within the chemical class of drugs referred to as arylcyclohexylamines, which were developed by Parke-Davis and Co (now known as Pfizer) amidst its pursuit to find safe and effective anesthetics.[1] The first arylcyclohexylamine developed was phencyclidine (PCP) in 1956, which began being administered to patients undergoing surgery under the trade name "Sernyl" in 1957.[2–4] At the time, PCP was believed to be the most potent analgesic medication available, as powerful opioids, such as fentanyl, had yet to be discovered.[5] However, enduring postsurgical delirium was observed in patients upon their awakening.[6] PCP was quickly deemed an unattractive anesthetic for widespread use due to its psychotomimetic nature; thus, Parke-Davis initiated a new search for analogs of PCP that would mimic its anesthetic properties while unaccompanied by its associated psychotropic aftereffects.[5]

In 1962, Parke-Davis chemical consultant Calvin Stevens synthesized ketamine, then referred to as Cl-581.[7,8] Its chemical structure resembled that of PCP; yet, it had fewer adverse effects.[2,9,10] In 1964, Corssen and Domino conducted the first study testing ketamine as an anesthetic.[10] The study proved to be a great success, leading to ketamine's approval for use in children, adults, and the elderly by the US Food and Drug Administration (FDA) in 1970.[11] Due to its strong safety profile, as well as the fact that it does not cause clinically significant respiratory suppression, ketamine has been categorized by the World Health Organization as an essential medicine.[10,12] However, in the past several decades, a multitude of clinical uses for ketamine have begun to be explored, with applications ranging from treatment-resistant depression to chronic pain. This has resulted in a vast proliferation of research on ketamine. Thus, the purpose of this article is to provide an overview of the ever-expanding current clinical understandings of ketamine and its use in several contexts.

Chemistry and mechanism of action

The term "ketamine" was created to reflect the drug's chemical structure: ketone combined with an amine functional group. Chemically, ketamine is (±)2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone.[13] It is a combination of 2 optical stereoisomers: S(+) and (R)-ketamine which have different potencies and affinities for various receptors.[13,14] Because it is both water and lipid soluble, ketamine can be administered through diverse routes and can cross the blood–brain barrier.[13] Its primary metabolic pathway is *N*-demethylation by the cytochrome enzyme CYP3A4 to the active metabolite norketamine.[15,16] Because of its high lipophilicity and low protein binding, ketamine is metabolized rapidly, and its elimination half-life is 2 to 4 hours when administered intravenously.[15,17–19] Only 2% of ketamine is detected in urine unchanged.

Ketamine differs from other anesthetics (e.g., propofol, benzodiazepines, and barbiturates) in that it does not act on $GABA_A$ receptors.[20] Rather, ketamine's primary mechanism of action is mediated through antagonism of N-methyl-D-aspartate receptors (NMDARs)—ionotropic glutamate receptors that allow an influx of calcium upon synaptic depolarization.[11,21–23] It is

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a noncompetitive inhibitor, binding to the allosteric PCP binding site, which is localized within the receptors and is distinct from the glutamate-binding site.[3,22,24,25] Its binding creates a trapping open channel block, obstructing ion flow, and can remain in the channel postclosure.[26,27]

Although one might assume that this mechanism renders the brain hypoexcitable, ketamine's impact on cerebral activity is variable and regionally specific.[28] For instance, antagonism of NMDARs by subanesthetic doses of ketamine has been shown to be profoundly excitatory in the prefrontal cortex (PFC) due to a consequent rapid increase in glutamate release.[11,29] The seemingly contradictory nature of this finding was put to rest by Homayoun and Moghaddam,[30] who established that NMDARs primarily regulate the firing rate of cortical GABAergic interneurons, which are known to mediate the activity of cortical pyramidal neurons implicated in animal behavior.[31,32] It was concluded that the inhibition of NMDARs on GABAergic interneurons indirectly disinhibits downstream pyramidal neurons, thereby enabling an elevated release of glutamate.[30]

AREAS OF UNCERTAINTY

Risks and controversies

The hallmark of ketamine's psychological effects are changes in perception, involving out-of-body experiences, changes in color discrimination, and an altered sense of time.[33,34] Ketamine has also been reported to distort one's sense of body ownership—what is and is not part of our body.[35] These subjective effects have led ketamine ("K") to be sought out by recreational users. Ketamine is classified as a schedule III substance by the US Food and Drug Administration, and as a class B drug in the United Kingdom, with studies in rodents suggesting it can be addictive, as it increases dopamine in the nucleus accumbens (NAc).[36–38] It does so by inhibiting GABAergic neurons in the ventral tegmental area, resulting in the disinhibition of dopamine neurons within that same region.[39] Of note, a rise in dopamine levels in the NAc is an established mechanism evoked by drugs of abuse, such as cocaine.[40] Behavioral studies have inferred that ketamine is rewarding and reinforcing in rats as well,[41–43] yet another observed characteristic of drugs of abuse.

However, a recent study[39] found that, although ketamine does yield a robust dopamine increase in the NAc, it is highly transient and does not induce drug-adaptive synaptic plasticity in this region, as is thought to be necessary to engage the mesolimbic circuit reorganization that eventually underpins compulsive drug seeking[44] and drug taking.[45]In addition to an increase in dopamine, NMDAR agonism is also required for the potentiation of excitatory synapses onto ventral tegmental area dopamine neurons and type-1 dopamine receptor–expressing medium spiny neurons in the NAc[46]; thus, ketamine-induced NMDAR antagonism impedes the generation of synaptic plasticity in the ventral tegmental area and the NAc.[39] Indeed, although ketamine administration leads to initial dopamine-driven positive reinforcement, as is noted in previous studies,[41–43] its pharmacology lends itself to a low addiction liability.[39]

Preclinical studies suggest that ketamine produces neurotoxic effects.[47–49] One study showed that a single dose of ketamine (5–40 mg/kg, subcutaneous) in 7-day-old mice induced dose-dependent and permanent neuronal apoptosis in the sensorimotor cortex and cerebellum.[48] Another study in 7-day-old rat pups demonstrated that 7 repeated intraperitoneal doses of 20 mg/kg of ketamine resulted in significant neuronal degeneration.[49] Of note, these studies do not reflect dosages administered in a clinical setting. The most common subanesthetic infusion dose is 0.5 mg/kg, conventionally administered over the course of 40 minutes.[50] Recreational doses also fall far below those presented in preclinical studies. In a recreational context, ketamine is most commonly insufflated (consumed intranasally, or by "snorting") in single-dose increments typically falling in the range of 60–250 mg.[51] Thus, results from preclinical studies should be interpreted with caution.

NMDARs are thought to underpin synaptic plasticity, which is crucial for learning and memory.[52] Considering that the primary mechanism of ketamine is NMDAR antagonism, its effects on cognition have been widely studied. A double-blind, placebo-controlled, independent-group study of 54 healthy volunteers given 2 doses of ketamine (0.4 and 0.8 mg/kg intravenous [IV]) revealed dose-dependent decrements in episodic and working memory task performance[53]; however, there was no significant difference between the ketamine and control groups 3 days later. The study also noted slowed semantic processing, recognition memory, and procedural learning.[53] A later double-blind, placebo-controlled, randomized, within-subject study of 12 healthy volunteers showed that IV infusions of 50 and 100 ng/mL of ketamine caused disruptions in episodic memory encoding but not episodic memory retrieval.[54] Disruptions in executive function task performance have also been noted following ketamine administration (0.23 and 0.5 mg/kg IV).[55] After termination of these short ketamine

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infusions, memory formation returned to baseline, indicating that in naive ketamine users, ketamine-induced reductions in memory and executive function are transient.

Several studies have investigated cognitive function in frequent and infrequent ketamine users.[56–59] These studies suggest that infrequent or recreational ketamine use is not associated with long-term cognitive impairment.[60] By contrast, chronic ketamine use appears to induce similar but more marked effects on semantic and episodic memory, as have been observed following acute administration.[58] Cessation of chronic ketamine use in a group of 30 ex–ketamine users who had been abstinent for at least a year led to recovery of memory performance.[57]

Ketamine has long been viewed as a psychotomimetic or a drug that mimics psychosis; a meta-analysis recently found that ketamine significantly increases psychopathology in healthy participants.[61] Thus, ketamine is contraindicated for people who have schizophrenia because it may aggravate psychotic symptoms.[62]

Physiologically, ketamine has an indirect, stimulatory effect on the cardiovascular system, leading to increases in heart rate, cardiac output, myocardial oxygen consumption, and blood pressure.[63–65] Therefore, ketamine is contraindicated for people with cardiovascular conditions in which elevations of blood pressure may be detrimental, such as aortic dissection, myocardial infarction, uncontrolled hypertension, or aneurysms.[62] Acute cardiac risk is increased when ketamine is taken in conjunction with stimulant drugs.[52]

Studies have reported an elevated liver enzyme profile in patients following anesthetic and subanesthetic ketamine treatment.[66–68] A randomized controlled trial examined the efficacy of repeated 100-hour ketamine infusions (day 1 infusion started at 8 AM at 1.2 μg/kg/h; subsequent infusions occurred 3×/day at 8 AM, 12 PM, and 4 PM); infusion rate could be increased in steps of 0.6 μg/kg/h until a maximum infusion rate of 7.2 μg/kg/h was reached for complex regional pain syndrome-1, which reported the development of hepatotoxicity in 3 of 6 patients following a second ketamine exposure, occurring 3 weeks after the initial 100-hour treatment.[68] Alanine transaminase, alkaline phosphatase, aspartate transaminase, and g-glutamyl transferase levels increased to 3 times over the upper limit of normal. As a result, the trial was terminated. Following termination, enzyme levels returned to normal values within 3 months.[68] This suggests an increased risk for ketamine-induced liver injury with prolonged and/or repeated infusions within a short time frame. Single treatments seem to be less damaging to the liver. No liver enzyme elevations were detected in a study on 50 patients receiving a single 100-hour ketamine infusion.[69] Liver function should be regularly measured during such treatments, and cessation is required if liver injury occurs.

There is growing evidence confirming the emergence of "ketamine cystitis"—characterized by small contracted inflamed bladder with frequent urinary tract involvement.[33,70–74] This has been found to develop in 20%–30% of patients abusing ketamine.[33,73] Patients with ketamine cystitis present with bladder pain, dysuria, and severe urinary frequency and urgency. Some patients also present with gross hematuria. A consensus regarding the critical amount and duration of ketamine exposure that leads to symptoms has not yet been reached. Tsai et al found that patients sometimes developed symptoms within 1 month after starting the drug, but severe symptoms were obvious at the one-year mark.[74] A study observing adolescents using ketamine found that the usage of ketamine 3 or more times a week for at least 2 years yielded measurable symptoms.[72] Cessation is the key to successful treatment.

Unmasking effects

Over the past 50 years, interest in the therapeutic applications of ketamine has grown exponentially, largely in the context of psychiatric care.[3,75,76] However, ketamine, reported to produce salient psychoactive effects,[14,77] poses a challenge for pharmacological research, which heralds randomized controlled trials (RCTs) as the "gold standard" for gaining evidence on therapeutic efficacy. A key component of RCTs is the blinding (or "masking") of both the participants and the investigators to treatment conditions allocated for each participant. Such practice aims to limit confounding factors, such as the occurrence of bias in both the reporting and the subsequent interpretation of outcome measures. Unmasking can lead to expectation effects, that is, predictions and/or beliefs regarding the outcome of a specific treatment. Expectation effects has been found to mediate clinical outcomes and are associated with, and in some cases predictive of, better treatment results.[78–80]

Despite the established importance of blinding efficacy, it is rarely reported in psychotherapy or pharmacology studies.[81,82] In the case of ketamine and all other psychedelic drugs, inadvertent unmasking often occurs due to the psychoactive effect of the substances, which is typically obvious to the participant. For instance, a 2020 crossover RCT, assessing the antidepressant treatment efficacy of ketamine (0.43 mg/kg) versus the active placebo remifentanil (1.7 ng/mL),

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asked its participants at the end of the trial that which group they thought they were in before official unmasking.[83] Participants guessed correctly 88% (N = 24/27) of the time, with the most common reason being the psychoactive symptoms.[83]

Results from pharmacological research trials should be interpreted with caution, particularly those assessing treatment effects of psychedelic drugs known to elicit an array of subjective effects.

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THERAPEUTIC ADVANCES

Ketamine as a general anesthetic

Ketamine is an extremely versatile sedative and has found wide utility among medical professionals due to its unique pharmacodynamic profile. At the time of its inception, ketamine was a groundbreaking discovery in the field of general anesthesia. Its ability to effectively and rapidly induce anesthesia, combined with analgesia, without imparting marked cardiac or respiratory depression has enabled practitioners to avoid powerful opiates or volatile anesthetic gases, as are commonly needed for surgical procedures. With a rapid onset of action (20–30 seconds for IV and 3–5 minutes for IM injections), and a duration of action for surgical anesthesia ranging from 5 to 25 minutes, ketamine displays a pharmacokinetic profile similar to the most popular induction agent in today's operating room, propofol. Ketamine also displays a remarkable margin of safety, with a rather broad therapeutic index, as can be measured with an LD50/ED50 ratio 5 times that of pentobarbital.[84]

The unstable patient

Cardiovascular stability is a potentially beneficial effect of ketamine. Increases in mean arterial pressure, heart rate, and cardiac index/output enable ketamine to be used in patients who are hemodynamically compromised, such as in septic patients or those in hypovolemic shock due to excessive blood loss.[85,86] The more commonly used induction agent, propofol, can cause significant decreases in systemic blood pressure upon induction of anesthesia.[87] In healthy uncompromised patients, this effect is anticipated and of little consequence. It has been postulated that the cardiovascular stability induced by ketamine is a result of a direct sympathomimetic effect in patients with an intact autonomic nervous system and adrenergic system, as is deduced by its negative inotropic effect during isolated heart studies.[84,86,88]

Although cardiac contractility and heart rate may increase, ketamine improves coronary perfusion and may have utility in patients with severe or critical aortic stenosis when maintenance of aortic vascular resistance is paramount due to coronary perfusion pressures.[86]

Neurosurgery

The addition of ketamine permits lower doses of other IV anesthetics (e.g., propofol) to be used during total intravenous anesthetics, as are required to maintain the integrity of neurologic monitoring during neurosurgery of the brain or spine.[85,89,90] Of note, ketamine is the only anesthetic with analgesic properties that increases motor evoked potentials (MEPs) during neuromonitoring.[90]

In patients with traumatic brain injury, various benefits of ketamine include neuroprotection against cerebral ischemia, as well as its free radical scavenging and anticonvulsant properties.[85]

Ketamine and depression

Major depressive disorder (MDD) is a pervasive and debilitating mental illness that affects approximately 280 million people worldwide.[91] Not only does this produce a massive financial burden on both an individual and societal scale,[92] it is fatal as suicide is the fourth leading cause of death in 15–29-year-olds.[91] Despite MDD's devastating impact, current therapeutic interventions, particularly selective serotonin reuptake inhibitors (SSRIs), may take weeks to yield their antidepressant effects and only slightly more than one-third of individuals with MDD will enter remission after a first treatment.[93] Furthermore, one-third of MDD patients fail to remit, even after treatment with multiple antidepressants.[94] Thus, there is a massive unmet need for rapid-acting and effective antidepressants.

Recently, ketamine has garnered interest from researchers and clinicians alike due to its rapid, yet prolonged, antidepressant effects.[95] The antidepressant effects of ketamine were first demonstrated in 2000 by Berman et al,[96] who observed robust decreases in patient Hamilton Depression Rating Scale, 25-item scores following a single subanesthetic infusion of ketamine (0.5 mg/kg) in comparison to saline controls (mean difference: −14). These results have since been replicated in numerous clinical trials, extending to treatment-resistant depression as well.[97–102] A phase III trial in 174 participants indicated that when dosing is incremented based on the participant's response rather than fixed, ketamine is associated with a significantly higher remission rate (19.6%) than the anesthetic benzodiazepine midazolam (2.0%) in patients with treatment-resistant depression.[103]

Modes of administration other than IV infusion, such as IM, subcutaneous, oral, and intranasal (IN) routes, have also found success,[104–108] and in 2019,

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IN esketamine was approved by the US FDA under the name Spravato. The effects of a single dose of ketamine emerge within hours of administration (weighted effect size averages of depression scores (N = 518) following a single 0.5 mg/kg infusion of ketamine within 24 hours: $d = 1.012$; at 24 hours: $d = 0.96$) and can last up to approximately 2 weeks.[109]

The antidepressant potential of NMDAR antagonists other than ketamine, such as PCP, MK-801, and memantine, has been investigated; however, results from rodent studies are inconsistent, and clinical trials show little promise.[110–114] These findings suggest that NMDAR antagonism is not the sole mechanism underlying ketamine's antidepressant effects. Activation of ionotropic glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) by ketamine metabolite (2R,6R)-hydroxynorketamine ((2R,6R)-HNK), through either direct or indirect mechanisms, has become associated with ketamine's antidepressant effects.[114] Blockage of AMPARs using 2,3-hydroxy-6-nitro-7-sulfoamoylbenzo(f)quinoxaline (NBQX), an AMPAR antagonist, compromises ketamine's antidepressant effects in rodents.[115,116] However, there has yet to be evidence indicating that ketamine and/or its metabolites directly functionally act on or directly bind AMPARs.[117]

Postmortem and neuroimaging human studies have revealed impairments in connectivity in regions of the brain associated with depression, namely, the PFC and the hippocampus.[118–123] In MDD patients, ketamine has been found to normalize the PFC's global connectivity and the default mode network's global connectivity to that of non-MDD subjects.[124,125]

Rodent models have been used to extend these findings and have established that, like depression, exposure to chronic stress causes atrophy and impairs synapse and dendritic spine formation and function in the medial PFC and hippocampus.[119,126] A 2019 study found that chronic stress eliminated postsynaptic dendritic spines in the PFC and reduced correlated multicellular ensemble activity in PFC projection neurons.[126] Remarkably, of the spines lost during chronic stress, 48.3% were restored after intraperitoneal ketamine treatment (10 mg/kg) versus 3.3% in vehicle-treated controls.[126] Ketamine also restored coordinated multicellular ensemble activity. Furthermore, it has been found that ketamine reverses deficits in synaptic protein and spine number in layer V pyramidal neurons in the PFC.[127] This restoration appears to be dependent on the activation of the mammalian target of rapamycin (mTOR) pathway,[127] which has been functionally linked to the production of synaptic proteins required for the formation, maturation, and function of new spine synapses.[128] Infusion of rapamycin, an mTORC1 inhibitor, blocks ketamine-induced increases in levels of synaptic proteins in the PFC and its antidepressant behavioral effects in rodents.[128] Together, these studies suggest that ketamine-induced synaptogenesis directly reverses the deleterious effects of stress exposure and thus represents a mechanism for the rapid antidepressant actions of ketamine.

There has been increasing support for a neurotrophic hypothesis of depression. Brain-derived neurotrophic factor (BDNF), namely, is the most widely studied neurotrophic factor in the field of depression. Postmortem studies have shown decreased levels of BDNF and its receptor tropomyosin-related kinase B in the PFC of depressed subjects[129,130]; thus, BDNF is a major target of antidepressant medications. Postmortem studies have identified increased BDNF expression in psychiatric subjects prescribed antidepressant medication compared with unmedicated subjects in hilus ($t = 2.71$, $P = 0.009$), dentate gyrus ($t = 2.22$, $P = 0.031$), supragranular region 100-mm band outside the dentate gyrus (SG1) ($t = 2.88$, $P = 0.006$), and supragranular region starting at 100 mm from the dentate gyrus and extending a further 100 mm (SG2) ($t = 2.80$, $P = 0.007$).[131] In 2011, it was demonstrated that ketamine administration (3.0 mg/kg intraperitoneal) desuppresses BDNF translation in the hippocampus, thereby resulting in a marked increase in the expression (at 30 minutes, analysis of variance $F_{(2,12)} = 6.77$, $P = 0.0108$ for treatment, Bonferroni post hoc test, *, $P < 0.05$).[110] Ketamine failed to produce antidepressant-like effects in BDNF-knockout mice, indicating that its resultant increases in BDNF protein translation is a necessary mechanism.[110]

Ketamine and suicidal ideation

Suicidal ideation (SI) is a significant public health issue, as more than 700,000 people die of suicide every year.[132] Nevertheless, there is a dearth of evidence-based pharmacological treatment options for SI in patients with MDD and bipolar disorder.[133] In addition, pharmacotherapies that have been approved (e.g., lithium and clozapine) take several weeks to produce a clinical effect.[134] There are currently no pharmacological treatment options for acute and immediate relief of active SI. As such, there is an urgent need for novel and more effective treatments for SI, particularly for those who do not respond to conventional interventions.

Several studies have found success in testing ketamine's short-term antisuicidal effects.[135–142] In a 2016 double-blind, randomized, placebo-controlled trial, active-duty military patients with depression and acute suicidality awaiting inpatient psychiatric

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admission from the emergency department were given a single IV infusion of ketamine (0.2 mg/kg over 2 minutes) or saline (placebo).[136] In the treatment group, 67% showed significant improvements in the Beck Scale for Suicidal Ideation (BSS) and Beck Hopelessness Scale compared with placebo within 40 minutes of administration.[136] Although this study highlights ketamine's potential effectiveness in rapidly addressing SI within an emergency setting, it must be noted that these effects were transient because the differences between ketamine and placebo diminished following discharge. Two randomized, midazolam-controlled trials with identical dosages found significant decreases in SI at 24 and 48 hours postketamine infusion, determined by patient score reductions on the Scale for Suicidal Ideation (SSI); the mean difference between ketamine group and midazolam group was −4.96 points ($P < 0.001$) and −6.5 points ($d = 0.67$, $P = 0.047$), respectively.[137,138]

Positive results have been generated in numerous open-label trials assessing the efficacy of ketamine on longer-term scales.[142–145] In a 2019 trial by Zhan et al,[144] participants with SI at baseline were administered a single ketamine infusion (0.5 mg/kg over 40 minutes) 3 times weekly for 2 weeks. Of the 86 participants, 57% of participants had an antisuicidal response (defined as BSS, first 5 questions <2) at 24 hours postinfusion, and 65.1% after the sixth infusion. Remarkably, 70.6% of patients had a maintained antisuicidal effect at the 2-week, naturalistic follow-up.[144] A more recent open-label trial on 32 suicidal participants investigated the effects of 6 oral doses of ketamine (starting at 0.5 mg/kg, titrated to a maximum 3.0 mg/kg) over the course of 6 weeks.[143] Mean BSS scores decreased significantly from a high level of SI at the preketamine (week 0) time point to below the clinical threshold at the postketamine (week 6) time point (mean difference: −14.4 points, $d = 2.04$, $P < 0.001$; antisuicidal response defined by BSS ≤ score 6). Fifty percent of participants had achieved significant improvement by the follow-up time point (week 10), 4 weeks following the final dose.[143] These studies suggest that repeated administration of ketamine may be a feasible alternative treatment for chronic suicidality; however, they must be interpreted with caution because there are no control groups due to the open-label study design.

These positive results, as mentioned above, have not always been replicated, with various studies indicating that ketamine is not significantly more effective than placebo in reducing SI.[146,147]

IN esketamine has also been explored as a treatment option for SI. In a 2018 double-blind, randomized, placebo-controlled study, patients in either an emergency department setting or an inpatient psychiatric unit due to imminent suicide risk were given IN esketamine (84 mg, 2×/week for 4 weeks) or placebo along with standard-of-care antidepressant medication.[148] There were greater improvements on Montgomery-Åsberg Depression Rating Scale (MADRS) suicidal thoughts 4 hours after the initial dose ($d = 0.67$, $P = 0.002$); however, the effects were not present at 24 hours posttreatment or at the double-blind end point (day 25), suggesting a transient effect.[148] Other studies demonstrate that IN esketamine may not be a viable option because no differences were observed between treatment and placebo groups.[149,150]

The limited availability of evidence-based pharmacological treatments for SI in individuals with MDD and bipolar disorder underscores the urgent need for innovative interventions. Ketamine has shown promise in rapidly reducing SI, particularly in emergency settings, although its effects are often transient. Further research is needed to optimize ketamine administration protocols, explore combination therapies, and identify predictors of treatment response. Future directions should aim to enhance the sustained effectiveness of ketamine in addressing both acute and chronic SI, ultimately improving the lives of individuals at risk.

Ketamine and PTSD

PTSD is a debilitating and chronic psychiatric disorder characterized by the development of distressing symptoms following exposure to a traumatic event. Global prevalence rates range from 1.3% to 10.9%,[151] indicating a substantial public health concern. Despite the availability of various treatment approaches, such as cognitive behavioral therapy and pharmacotherapy, a significant proportion of individuals with PTSD fail to achieve full remission or experience delayed response to these interventions.[152,153] (However, as discussed in *Part VI* of this special edition, methylenedioxymethamphetamine has displayed promise as a novel treatment for PTSD.) Therefore, there is a growing interest in exploring novel treatment options, with emerging evidence suggesting the potential efficacy of ketamine in alleviating PTSD symptoms.

Results from studies investigating ketamine's mediating effect on PTSD onset have been mixed. A retrospective chart review of burn victims reported significantly lower prevalence of PTSD among patients who had received intraoperative ketamine (prevalence of PTSD was 27% (N = 32/119) in ketamine group versus 46% (N = 13/28) in no-ketamine group, $P = 0.044$), despite this group having larger

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burns, sustaining more severe injuries, undergoing more operations, and spending more time in the intensive care unit.[154] By contrast, a more recent study found ketamine to have no impact on PTSD prevalence.[155] Animal studies have observed no change depending on the timing of ketamine administration[156] or slightly adverse effects.[157] In 2 observational studies of accident victims, it was observed that patients who received ketamine had significantly higher acute stress symptoms and higher current PTSD symptoms, as reported in later assessment time points, in comparison to those administered opioids or nonopioid analgesics.[158,159] Methodological issues have been highlighted in these studies, though, such as a lack of adjustment for injury severity in the authors' statistical analysis. In addition, the authors' combining of midazolam with ketamine and the lack of information provided regarding dosages hampers confidence in the authors' interpretations.[160]

Clinical trials assessing ketamine's efficacy in attenuating chronic PTSD symptom severity have been more promising. A single ketamine infusion (0.5 mg/kg over 40 minutes) resulted in marked reductions in PTSD symptoms 24 hours postinfusion (mean difference in total Impact of Event Scale–Revised scores relative to midazolam: −12.7; $P = 0.02$) in unmedicated individuals diagnosed with chronic PTSD.[161], However, this effect was transient because differences between the ketamine group and placebo group were nonsignificant after 1 week.[161] Repeated ketamine infusions have been found to improve PTSD symptom severity for up to 2 weeks (mean difference in Clinician-Administered PTSD Scale for DSM-5 [CAPS-5] scores relative to midazolam: −11.88 points, $d = 1.13$, $P = 0.004$),[162, p. 202] with 1 open-label trial reporting median relapse time in remitters to be 41 days.[163] These findings were unable to be replicated in a 2022 double-blind, randomized, placebo-controlled trial[100]; however, of note, this study was in veterans and active-duty military personnel, a population that has been indicated to have low PTSD treatment response.[164]

Although investigations into ketamine's ability to occlude PTSD onset produced contradictory results, studies examining its effectiveness in reducing symptom severity have demonstrated significant positive outcomes. These findings suggest that ketamine holds promise as a potential therapeutic intervention for individuals with chronic PTSD, offering relief from the debilitating symptoms associated with the disorder. Moving forward, it is essential to further investigate and understand the underlying mechanisms by which ketamine exerts its therapeutic effects, as well as to explore optimal dosing strategies, treatment protocols, and long-term outcomes. In addition, future research endeavors should aim to identify potential biomarkers or patient characteristics that can predict individual responses to ketamine treatment, thus enabling more personalized and targeted interventions.

Ketamine and addiction

Substance use disorders (SUDs) are complex and pernicious conditions hallmarked by a pattern of symptoms caused by uncontrolled use of a substance despite its negative consequences. Some symptoms include experiencing cravings, being unable to terminate use, impaired ability to fulfill obligations at work, school, or home, using in risky settings, and increased tolerance.[165] SUDs create a substantial burden not only on an individual scale but also on a societal scale with 46.3 million people aged 12 years or older (16.5% of said population) reporting having a SUD in 2021.[166] Of those individuals, only 6.3% received any kind of substance use treatment that year.[166] A variety of treatments are available for different SUDs; however, results from trials report mixed efficacy and several barriers prevent individuals from receiving adequate care.[167–169] Thus, there is a great need for novel treatments that are fast-acting and widely accessible. Ketamine, both fast-acting and accessible, has yielded promising results in the context of a variety of SUDs.[170–177]

Cocaine use disorder is a substantial health problem; however, there are no FDA-approved pharmacotherapies currently available for those afflicted.[178] In 2014, a double-blind, 3-arm, crossover trial on 8 people with active cocaine dependence assessed the effects of subanesthetic infusions of ketamine on motivation to quit (University of Rhode Island Change Assessment [URICA]) and ratings of craving provided during cue exposure.[171] Three 52-minute IV infusions were administered: ketamine (0.41 mg/kg or 0.71 mg/kg) or active benzodiazepine control lorazepam (LZP; 2 mg). Compared with LZP, a single ketamine infusion (0.41 mg/kg) elicited a significant 60% increase in URICA scores over baseline scores ($P = 0.012$). Cue-induced cocaine craving, as quantified through visual analog scale scores, saw marked decreases in the ketamine treatment group in comparison to the LZP group. This decrease was augmented by the higher-dose infusion. Together, these results indicate that a single subanesthetic infusion of ketamine rapidly improves 2 drug dependence–related risk factors: low motivation to quit and cue-induced craving.

To expand on their previous findings, the same group later conducted a randomized, cross-over trial

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to evaluate cocaine use following either ketamine infusion (0.71 mg/kg) or midazolam (0.025 mg/kg).[170] During hospitalization, participants underwent choice sessions during which they were offered either 25 mg cocaine or $11. Following infusion, rates of cocaine self-administration were significantly lower in the ketamine group than in the midazolam group (mean difference in cocaine choices: −2.72, $P < 0.0001$).[170] Stress reactivity scores were measured using the Five Facet of Mindfulness Questionnaire because reactivity, associated with stress sensitivity and impulsivity, is thought to be a key impairment in SUDs.[170,179] Ketamine infusion led to a significantly higher nonreactivity score in comparison with midazolam (mean difference: 0.54, $P < 0.05$) up to 48 hours postinfusion.[170] To test the efficacy of a single infusion on cocaine use disorder, when paired with a mindfulness-based treatment program, Dakwar et al[173] administered either ketamine (0.5 mg/kg) or midazolam (0.025 mg/kg) to 55 participants while they began a 5-week course of mindfulness-based relapse prevention. In the last 2 weeks of the course, the ketamine group was found to have significantly higher odds of abstinence compared with the midazolam group (odds ratio: 5.7, $P = 0.02$). At the 6-month follow-up, rates of abstinence were significantly higher in the ketamine group (44%) than in the midazolam group (0%) ($P < 0.0001$). These collective findings offer compelling evidence for the promising role of ketamine in the management of cocaine use disorder.

In 2021, an estimated 2.5 million people aged 18 years and older had opioid use disorder (OUD) but only 36% of them received any treatment for substance use, and only 22% received pharmacological treatment for OUD, specifically.[180] Current pharmacological treatments for OUD and opioid withdrawal include naloxone, naltrexone, buprenorphine, and methadone, with buprenorphine and methadone showing the highest efficacy and being the most widely prescribed.[167,181] However, ketamine may be a more effective treatment option. In 2002, a randomized, controlled trial compared the efficacy of high-dose ketamine (2 mg/kg IM) versus a nonpsychoactive, control dose of ketamine (0.2 mg/kg IM) in 70 heroin-dependent participants also undergoing psychotherapy.[175] As confirmed by urine drug screens, the high-dose group exhibited a greater rate of abstinence at the 1-year mark than the low-dose group (24% vs. 6% abstinent subjects, $P < 0.05$). This effect was still significant at the 2-year mark as well (17% vs. 2% abstinent subjects, $P < 0.05$). Having established that a single, high dose of ketamine is effective, the same group conducted a later study comparing single versus repeated sessions of ketamine-assisted psychotherapy.[176] Fifty-nine participants with OUD underwent an initial session of psychotherapy in conjunction with a single ketamine infusion (2 mg/kg IM). They were then split into 2 groups: one group receiving 2 more psychotherapy sessions and the other receiving ketamine-guided psychotherapy sessions at a dose of 2 mg/kg IM per session. At 1 year, 50% of the multiple ketamine session group remained fully abstinent compared with 22.2% in the single ketamine session, demonstrating that the effect of multiple ketamine–guided psychotherapy sessions surpasses that of a single session. This study is limited by its lack of placebo; however, the authors argue that their previous study[175] had already delineated the effects of ketamine-assisted therapy versus placebo.

A number of factors can contribute to early opioid use, such as seeking pain relief, euphoria, and/or stress relief; however, after prolonged use, fear of withdrawal symptoms drives many to be unable to quit.[182,183] As such, mediating withdrawal symptoms may be a strong first step for treatment. In 1 randomized controlled trial, participants were given either placebo or a ketamine infusion (0.5 mg/kg IV for 1 hour) before undergoing rapid opiate antagonist induction while under general anesthesia.[174] The authors found that the ketamine group had significantly lower increases in blood pressure, heart rate, and cortisol levels during rapid opiate antagonist induction, showing that ketamine could dampen the physiological response to opiate withdrawal. Furthermore, ketamine reduced the amount of opiate antagonists that were required to maintain the same level of opiate withdrawal symptoms (MD: −3.1 mg, $P < 0.001$).

Worldwide, 5.3% of all deaths result from harmful use of alcohol.[184] In the United States alone, the prevalence of alcohol use disorder (AUD) in individuals aged 12 years and older has reached 10.6%, according to the 2021 National Survey on Drug Use and Health.[185] Beyond health consequences, AUD yields significant social and economic loss on both an individual and a societal scale.[184] Despite the devastating impact of AUD, few are in treatment, and available treatments do not find much success.[186]

Ketamine has exhibited promise in improving treatment outcomes for AUD, particularly when combined with motivational enhancement therapy, by reducing the likelihood of alcohol use, decreasing the risk of at-risk drinking, and delaying time to relapse.[172,177] In 2020, a randomized, midazolam-controlled, pilot trial observed alcohol use in 40 treatment-seeking adults with AUD receiving either IV ketamine (0.71 mg/kg) or the active control midazolam (0.025 mg/kg) while engaged in a 5-

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week outpatient regimen of motivational enhancement therapy.[172]Compared with midazolam, ketamine significantly lowered the likelihood of using alcohol during a 21-day period following infusion (47.1% vs. 59.1% abstinence rate). A 6-month follow-up reported higher rates of abstinence in the ketamine group (75%) in comparison to the midazolam group (27%). Building on these findings, Rothberg et al[177] used the same paradigm and found that ketamine significantly decreased the risk of risky drinking by approximately 5 times. Although further research is warranted to validate these results and determine long-term efficacy, ketamine may be a successful adjunct to AUD treatment, promoting both the initiation and maintenance of abstinence.

Although the transient psychoactive effects of subanesthetic doses of ketamine are a point of concern for some practitioners due to their contribution to abuse potential,[187] studies have found that these effects—particularly mystical-type experiences—may play an important role in mediating SUDs.[171,177,188] Psychedelic-induced mystical-type experiences involve a series of phenomena, such as feeling positive mood, peace, unity, sacredness, and a feeling of transcending time and space,[189] thus leading some to describe it as a subset of spiritual experience.[190] These mystical-type experiences have been described as "life changing," and they are shown to have enduring, positive psychological benefits.[191–193] In a secondary analysis of an aforementioned study on ketamine for treating cocaine addiction,[171] both high (0.71 mg/kg) and low (0.41 mg/kg) doses of ketamine led to significantly higher scores on the Hood's Mysticism Scale (HMS) compared with LZP (LZP vs. 0.41 mg/kg ketamine, median difference: 18; LZP vs. 0.71 mg/kg ketamine, median difference: 26; $P = 0.012$).[194] HMS scores, but not Clinician Administered Dissociative Symptoms Scale scores, were found to mediate ketamine's effects on motivation to quit cocaine (adjusted R^2 for total model = 0.775, $P < 0.005$). The same group conducted a later study that extended these findings, demonstrating that HMS scores mediated greater global improvement (decreased cocaine self-administration, cocaine use in natural ecology, and cocaine craving) from ketamine infusion relative to midazolam.[188] The decrease in odds of engaging in at-risk drinking observed in another aforementioned study[177] was also significantly mediated by HMS scores ($R^2 = -0.466$, $P < 0.05$).[177] Clinician Administered Dissociative Symptoms Scale score mediation did not achieve significance.

The data presented suggests a promising role for ketamine as a novel and potentially transformative treatment option for individuals grappling with SUDs. With SUDs representing a complex and pervasive public health challenge, these findings underscore the potential of ketamine in addressing multiple facets of these disorders, from enhancing motivation to quit and reducing cravings to mitigating the physiological response to withdrawal. Notably, the mediating role of mystical-type experiences induced by ketamine in improving treatment outcomes raises intriguing questions about the underlying mechanisms and enduring psychological benefits of such experiences. However, although the results presented in these studies are compelling, it is essential to further validate their long-term efficacy, potential side effects, and patient-specific considerations. Future research in this area should explore the optimal dosage and treatment protocols for various SUDs, evaluate the safety profile of ketamine, and assess the potential of combining ketamine with existing treatment modalities to maximize its therapeutic impact.

Chronic pain

The multimodal analgesia paradigm is now considered the standard of care among practitioners managing acute postoperative pain.[195] In this treatment modality, the use of multiple medications in relatively smaller doses is both more effective and less prone to side effects than treatments that use fewer or even a single medication which would require relatively larger doses. The addition of a single IV bolus of ketamine administered during surgery for patients with chronic pain resulted in reduced postoperative consumption of pain medications, as well as improved pain scores at rest and upon mobilization.[196]

Surgical patients are at an increased risk of pulmonary, cardiovascular, and thromboembolic complications in the postoperative period. Ketamine has shown a significant opioid-sparing effect; that is, the use of opioids can be unnecessary after ketamine has been administered. This property of ketamine is very desirable for achieving early ambulation, quick recovery, and maintenance of respiratory mechanics when included in the postoperative pain management regimen.[197]

Ketamine's unique polyreceptor affinity (NDMA, AMPA, and μ-opioid) enables it to treat chronic pain conditions while mitigating the hyperanalgesic effect of concomitant opioid therapy and the hyperanalgesia and allodynia that results from secondary to peripheral and central nociceptor sensitization.[85,196] Case reports and multicentric studies have shown significant efficacy in its use in phantom limb pain, chronic refractory or mixed neuropathic pain, and complex regional pain syndrome[196,198] (Table 1).

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Table 1. Selection of contemporary (21st-century) clinical trials on ketamine.

Study	Type	Dosing	Sample	Findings
Berman et al[96]	Double-blind, inactive placebo–controlled RCT with crossover	1 session of 0.5 mg/kg IV RK	7 MDD patients	At 72 h after crossover: significant decrease in HDRS-25 scores relative to placebo (MD: −14, $P < 0.001$)
Krupitsky et al[175]	Double-blind, active placebo–controlled RCT	1 session of 2 mg/kg IM RK or 1 session of 0.2 mg/kg (control dose) IM RK, both with psychotherapy	70 people with OUD	At 24 mo: significant increase in abstinence relative to control dose ($P < 0.05$)
Jovaisa et al[174]	Double-blind, inactive, placebo–controlled RCT	1 session of 0.5 mg/kg/h IV RK or 1 session of placebo, both with RAI under GA	58 patients with OUD	At 48 h: significantly less additional carbamazepine and clonazepam to maintain the same level of opiate withdrawal symptoms, relative to placebo group (MD: −3.1 mg, $P < 0.001$) At 4 mo: insignificant increase in the number of opiate-free weeks relative to placebo group (MD: +1.4 wks, $P > 0.05$)
Krupitsky et al[176]	Double-blind, dose–response RCT	2 mg/kg IM RK, 1×/month, 3 mo with psychotherapy or 1 session of 2 mg/kg IM RK with psychotherapy	59 people with OUD	At 14 mo after the final treatment: significant increase in abstinence for repeated-administration group (50%) relative to single-administration group (22.2%) ($P < 0.05$)
Feder et al[161]	Double-blind, active placebo–controlled RCT with crossover	1 session of 0.5 mg/kg IV RK and 1 session of 0.045 mg/kg MZ	41 chronic PTSD patients	At 24 h after crossover: significant decrease in IES-R scores relative to MZ (MD: −12.7, $P = 0.02$) At 7 d after crossover: insignificant difference in CAPS scores relative to MZ (MD: −8.7, $P = 0.20$)
Dakwar et al[171]	Double-blind, active placebo–controlled RCT with crossover	3 sessions of 0.41 mg/kg IV RK (K1), 0.71 mg/kg IV RK (K2), or 2 mg LZP	8 people with CUD	At 24 h after K1: significant increase in motivation to change cocaine use relative to LZP (URICA scores; MD: +3.45, $P = 0.012$); significant decrease in cue-induced cocaine craving (VAS ratings; MeD: −191, $P = 0.012$) At 24 h after K2: insignificant change in URICA scores ($P = 0.11$); significant decrease in cue-induced cocaine craving (VAS ratings; MeD: −71, $P = 0.11$) At 4 wks after the final treatment: significant decrease in cocaine use relative to baseline (MeD: −17 d use/28 d, $P = 0.012$)
Lapidus et al[107]	Double-blind, inactive placebo–controlled RCT with crossover	1 session of 50 mg IN RK and 1 session of inactive placebo	20 MDD patients	At 24 h after crossover: significant decrease in MADRS scores relative to placebo (MD: −7.6, $P < 0.001$); 44% response rate for RK versus 6% response rate for placebo At 72 h and 7 d after crossover: insignificant difference in MADRS scores relative to placebo ($P > 0.05$)

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Table 1. (*Continued*) Selection of contemporary (21st-century) clinical trials on ketamine.

Study	Type	Dosing	Sample	Findings
Murrough et al[138]	Double blind, active placebo–controlled RCT	1 session of 0.5 mg/kg IV RK and 1 session of 0.045 mg/kg MZ	Patients with score ≥4 on MADRS-SI	At 24 h: insignificant decrease in BSS relative to MZ (MD: −3.2, d = 0.34, P = 0.32)— At 48 h: significant decrease in BSS relative to MZ (MD: −6.5, d = 0.67, P = 0.047)— At 72 h and 7 d: insignificant decrease in BSS relative to MZ (P = 0.24, 0.56, respectively)
Loo et al[108]	Double-blind, dose–response, active placebo–controlled, non-randomized trial with crossover	5 sessions of 0.1, 0.2, 0.3, 0.4, 0.5 mg/kg RK versus 0.01 mg/kg MZ. Sequential cohorts of participants received IV (n = 4), IM (n = 5), SC (n = 6) RK	15 TRD patients	% of participants who achieved response and remission at least once, across all time points and doses: 75% (IV), 60% (IM), 100% (SC)— Significant decrease in MADRS scores relative to MZ at 24 h, but not at 7 d— Significant decrease in MADRS scores for 0.2 mg/kg relative to MZ (P = 0.001), but insignificant difference between 0.2 and 0.1 mg/kg (P = 0.095), and insignificant difference between 0.1 mg/kg and MZ
Burger et al[136]	Double-blind, inactive placebo–controlled RCT	1 session of 0.2 mg/kg IV RK or inactive placebo	10 active-duty members who presented to ED for depression or SI	At 4 h: significant decrease in BSS relative to placebo ($P < 0.05$)— At discharge and 2 wks after discharge: insignificant decrease in BSS relative to placebo
Dakwar et al[170]	Double-blind, active placebo–controlled RCT with crossover	3 six-day sessions: (1) an initial 2-d washout period; (2) a 28-min "sample session" on day 3 when 2 obligatory free-base cocaine doses (25 mg) were smoked; (3) a 52-min infusion on day 4 (session 1: placebo; session 2/3: 0.71 mg/kg IV RK or 0.025 mg/kg MZ); (4) a 70-min "choice session" of 5 choices (25 mg cocaine vs. $11) on day 5; and (v) discharge on day 6	20 people with CUD	At 28 h after crossover: significant decrease in cocaine choices (MD: −2.72 choices, $P < 0.0001$) At 3 d after crossover: significant decrease in cocaine use (MD: −$19.25/3 d, $P < 0.05$); significant decrease in cocaine cravings (MD: −44.3%, $P < 0.01$) At 15 d after crossover: insignificant decrease in cocaine use ($P > 0.05$); insignificant decrease in cocaine cravings ($P >$ 0.05)
Daly et al[105]	Double-blind, inactive placebo–controlled RCT with crossover	TP 1: IN SK given blinded 2×/week, 2 wks at 1 of 3 doses: 28, 56, or 84 mg. Participants in placebo group with QIDS-SR-16 ≥ 11 at end of week 1 were rerandomized to 1 of the SK groups or	67 TRD patients	End of TP 1: significant decrease in MADRS scores relative to placebo for 28 mg group (MD: −4.2, P = 0.02), 56 mg group (MD: −6.3, P = 0.001), and 84 mg group (MD: −9.0, $P < 0.001$); remission rate at the end of week 1 and week was 2 9% and 13% for 28-mg group, respectively, 9% and 0% for 56-mg

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Table 1. (*Continued*) Selection of contemporary (21st-century) clinical trials on ketamine.

Study	Type	Dosing	Sample	Findings
		placebo group again —		group, 25% and 20% for 84-mg group— End of TP 2: decrease in MADRS scores relative to start of phase 2 (MD: −7.2)
		TP 2: Optional open-label SK sessions (initial: 56 mg, subsequently adjusted based on clinic'an's judgment, 2×/week for 2 wks then 1×/week for 3 wks then 1×/2 wks)		
Grunebaum et al[137]	Double-blind, active placebo–controlled RCT with crossover	TP 1: 1 session of 0.5 mg/kg IV RK and 1 session of 0.02 mg/kg MZ— TP 2: Participants in MZ group with SSI >50% of baseline got 1 open-label session of IV RK. Participants continued with standard pharmacological treatment until 6-wk follow-up	80 MDD patients with SSI score ≥4	TP 1, at 24 h after crossover: significant decrease in SSI scores relative to MZ (MD: −4.96, d = 0.75, $P < 0.001$); 55% and 30% clinical response rate in RK group and MZ group, respectively— TP 2, at 24 h: significant decrease in SSI scores relative to start of phase 2 (MD: −7.85, $P < 0.001$)— Both phases, at 6 wks: significant decrease in SSI scores relative to baseline (MD: −8.52, $P < 0.0001$)
Sophia Albott et al[163]	Open-label	0.5 mg/kg IV RK, 3×/week, 2 wk	15 patients with comorbid PTSD and MDD	At 24 h after the final treatment: significant decrease in PCL-5 scores (MD: −33.27, d = 2.17, $P <$ 0.0005); 80% remission rate from PTSD according to CAPS-5 scores and 60% remission rate from depression according to MADRS scores At 2 wks after the final treatment: 80% remission rate from PTSD and 40% remission rate from depression
Canuso et al[148]	Double-blind, inactive placebo–controlled RCT	TP 1: Standard-of-care antidepressants + IN SK (84 mg, 2×/week) for 4 wks versus standard-of-care antidepressants + placebo for 4 wks TP 2: Standard-of-care antidepressants for 8 wks	68 patients in need of acute hospitalization due to imminent suicide risk, with MADRS score ≥22	TP 1, at 4 h after first dose: significant decrease in MADRS-SI scores relative to placebo group (d = 0.67, P = 0.002) TP 1, at 24 h after first dose and final treatment: insignificant decrease in MADRS-SI scores relative to placebo group (d = 0.35, P = 0.129; d = 0.29; P = 0.143, respectively) End of TP 2: insignificant decrease in BSS scores relative to placebo (MD: −2.3, P = 0.843)
Arabzadeh et al[104]	Double-blind, placebo-controlled RCT	Sertraline (initial: 25 mg/d, increased by 25 mg every 3 d) + oral RK (25 mg, 2×/day) for 6 wks, versus sertraline (same dose	81 MDD patients	At weeks 2, 4, and 6: significant decrease in HDRS scores relative to placebo group (week 2, MD: −3.47, $P < 0.001$; week 4, MD: −2.61, P = 0.001; week 6, MD: −1.91, P = 0.009)

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Table 1. (*Continued*) Selection of contemporary (21st-century) clinical trials on ketamine.

Study	Type	Dosing	Sample	Findings
		time course) + placebo for 6 wks		At week 6: insignificant increase in remission rate for RK group (22%) relative to placebo group (15%) ($P > 0.05$)
Popova et al[199]	Double-blind, placebo-controlled RCT (phase III)	Daily antidepressant + IN SK (initial: 56 mg; some increased to 84 mg on days 4, 8, 11, or 15; 2×/week) for 4 wks versus daily antidepressant + placebo for 4 wks	227 TRD patients	At 28 d: significant decrease in MADRS scores relative to placebo group (LSMD: −4.0, $d = 0.3$, $P = 0.02$); 53% remission rate in SK group and 31% remission rate in placebo group
Zhan et al[144]	Open-label	Up to 6 sessions of 0.5 mg/kg IV RK, 3×/week, 2 wk	86 patients either with MDD or bipolar depression (BDI or BDII), with (SSI)-part I ≥ 2	At 24 h after first session and sixth session: 57.0% and 65.1% antisuicidal response At 26 d after first session: 70.6% antisuicidal response At all time points (day 1–13, day 26): significant decrease in % of patients with SI ($P < 0.05$)
Daly et al[106]	Double-blind, placebo-controlled RCT (phase III). Aim was to test maintenance of response to IN SK	Maintenance phase (other phases reported in Popova et al[199], Fedgchin et al[200]): Daily antidepressant + IN SK (flexible dosing: 56 or 84 mg, either 1×/week or 1×/2 wks) for variable duration (median: 18.55 wks) versus daily antidepressant + placebo for variable duration (median: 10.15 wks)	297 TRD patients who already achieved stable remission or response from IN SK in studies[197,198]	End of maintenance phase: significant delay of relapse in SK group compared with placebo group in both stable remission group (HR: 0.49, $P = 0.003$) and stable response group (HR: 0.30, $P < 0.001$)
Dakwar et al[173]	Double-blind, active placebo–controlled RCT	1 session of 0.5 mg/kg IV RK or 1 session of 0.025 mg/kg MZ at the start of 5-wk mindfulness-based relapse prevention course	55 people with CUD	Last 2 wks of mindfulness course: significantly higher odds of abstinence in RK group relative to MZ group (OR: 5.7, $P = 0.02$) At 6 mo: significant increase in abstinence in RK group (44%) relative to MZ group (0%) ($P < 0.0001$)
Fedgchin et al[200]	Double-blind, placebo-controlled RCT (phase III)	Daily antidepressant + IN SK (either 56 or 84 mg, 2×/week) for 4 wks versus daily antidepressant + placebo for 4 wk	346 TRD patients	At 28 d after the final treatment: insignificant decrease in MADRS scores relative to placebo group for 84 mg (LSMD: −3.2, $P = 0.088$); 36%, 38.8%, and 30.6% remission rates in 56 mg, 84 mg, and placebo groups
Phillips et al[98]	Double-blind, active placebo–controlled RCT with crossover. Aim is to test single, repeated, and	TP 1: 1 session of 0.5 mg/kg IV RK and 1 session of 0.03 mg/kg MZ TP 2: If participants relapsed (≥80%	41 TRD patients	TP 1, at 24 h after crossover: significant decrease in MADRS scores relative to MZ (MD: −8.1, $P < 0.001$); 5% remission rate for RK versus 0% remission rate for MZ

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Table 1. (*Continued*) Selection of contemporary (21st-century) clinical trials on ketamine.

Study	Type	Dosing	Sample	Findings
	maintenance infusions of RK	baseline MADRS scores), RK given open-label (same dose) 3×/week, 2 wks TP 3: If participants responded (≥50% decrease in MADRS scores from baseline), RK given open-label (same dose) 1×/week, 4 wks		TP 2, at 24 h after the final treatment: significant cumulative decrease in MADRS scores relative to start of phase 2 (MD: −12, $P <$ 0.001); 23% remission rate TP 3, at 24 h after the final treatment: insignificant change in MADRS scores relative to start of phase 3 ($P = 0.49$)
Dakwar et al[172]	Double-blind, active placebo-controlled RCT	1 session of 0.71 mg/kg IV RK or 1 session of 0.025 mg/kg MZ, both in second week of 5-wk motivational enhancement therapy	40 people with AUD	At 21 d after treatment: significant increase in abstinence relative to MZ ($P < 0.05$) At 6 mo: 75% abstinence rate in RK group and 27% abstinence rate in MZ group
Feder et al[162]	Double-blind, active placebo–controlled RCT	0.5 mg/kg IV RK, 3×/week, 2 wks, or 0.045 mg/kg MZ (same time-course)	30 chronic PTSD patients	At 1 wk, 2 wks: significant decrease in CAPS-5 scores relative to MZ (MD: −8.80, $P = 0.03$; MD: −11.88, $P = 0.004$, respectively) At 2 wks: significantly higher clinical response rate in RK versus MZ group (67% vs. 20%, $P = 0.03$)
Can et al[143]	Open-label	Oral RK given 1×/week, 6 wks (initial: 0.5 mg/kg), titrated up 0.2–0.5 mg/kg or down 0.2–0.7 mg/kg, depending on patient tolerance, with a maximum dose of 3.0 mg/kg at treatment 6	32 patients with BSS score ≥6	At 1–7 d after the final treatment: significant decrease in BSS scores relative to baseline (MD: −14.4, $d = 2.04$, $P < 0.001$); 69% clinical response rate At 28–32 d after final treatment: significant decrease in BSS scores relative to baseline (MD: −10.9, $d = 1.54$, $P < 0.001$) but increase in BSS scores relative to 1–7 d after the final treatment (MD: −3.5, $d =$ 0.42, $P < 0.05$); 50% clinical response rate
Abdallah et al[100]	Double-blind, dose–response, inactive placebo–controlled RCT	0.2 mg/kg IV RK (low dose), 0.5 mg/kg IV RK (standard dose), or placebo, 2×/week, 4 wks	158 veterans and service members with PTSD	At 24 h after first treatment: insignificant increase in clinical response rate for standard dose and low dose (47% for both) relative to placebo (33%) ($P = 0.08$) At 24 h after the final treatment: insignificant decrease in PCL-5 scores relative to placebo for standard dose (MD: −5.0, $P = 0.28$) and low dose (MD: −6.4, $P = 0.16$); PCL-5 scores were insignificantly higher for standard dose than low dose ($P > 0.5$) At 4 wks after final treatment: significant decrease in PCL-5 scores relative to placebo for low dose (MD: −15.3, $P = 0.03$) but insignificant decrease for standard dose (MD: −9.8, $P = 0.34$)

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Table 1. (*Continued*) Selection of contemporary (21st-century) clinical trials on ketamine.

Study	Type	Dosing	Sample	Findings
Loo et al[103]	Double-blind, dose–response, active placebo–controlled RCT (Phase III)	SC RK given 2×/week, 4 wks Cohort 1: fixed dose of 0.5 mg/kg RK or 0.025 mg/kg MZ Cohort 2: dose escalation to 0.6, 0.75, 0.9 mg/kg RK or 0.03, 0.0375, 0.045 mg/kg MZ at sessions 2, 4, and 6 if <50% improvement from baseline in MADRS scores	Cohort 1: 68 TRD patients. Cohort 2: 106 TRD patients	Cohort 1, at 3–4 d after the final treatment: insignificant difference in remission rates (MADRS ≤10) between RK (6.3%) and MZ (8.8%) Cohort 2, at 3–4 d after the final treatment: significantly higher remission rates for RK (19.6%) than MZ (2.0%) ($P = 0.005$) Cohort 2, at 4 wks after the final treatment: insignificant difference in remission rates between RK (8.0%) and MZ (2.1%)

This is not a comprehensive list of all the clinical trials; we tried to select a subset of clinical trials that nonetheless represented all the different modes of administration (intramuscular, intranasal, and intravenous), types of ketamine (racemic and esketamine), study procedures (single administration, repeated administration, coadministration with antidepressants), and results (insignificant and significant outcomes). The psychiatric conditions included in this table are depression, suicidal ideation, posttraumatic stress disorder, and substance use disorders; however, there are other conditions that ketamine has been used to treat, including chronic pain. Ketamine was assumed to be racemic if not explicitly stated in study.

AUD, alcohol use disorder; BDI (BDII), bipolar I (II) disorder; BSS, Beck Scale for Suicide Ideation; CAPS(-5) , Clinician-Administered PTSD Scale (for DSM-5); CUD, cocaine use disorder; ED, emergency department; GA, general anesthesia; HDRS(-25), Hamilton Depression Rating Scale (25-item); HR, hazard ratio; IES-R, Impact of Event Scale-Revised; IM, intramuscular; IN, intranasal; IV, intravenous; LSMD, least-squares mean difference; LZP, lorazepam; MADRS(-SI), Montgomery–Åsberg Depression Rating Scale (suicidal ideation subscale); MD, mean difference; MDD, Major Depressive Disorder; MeD, median difference; MZ, midazolam; OR, odds ratio; OUD, opioid use disorder; PCL-5, PTSD Checklist for DSM-5; QIDS-SR-16, Quick Inventory of Depressive Symptomatology, self-reported, 16-item; RAI, rapid opioid antagonist induction; RK, racemic ketamine; SC, subcutaneous; SI, suicidal ideation; SK, esketamine; SSI, Scale for Suicidal Ideation; TP, treatment phase; TRD, treatment-resistant depression; VAS, visual analogue scale.

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CONCLUSIONS

The multifaceted exploration of ketamine's clinical applications across various medical domains presented in this review underscores its profound potential and the nuanced complexities associated with its therapeutic use. The extensive investigation into ketamine's pharmacological profile, particularly its efficacy as an anesthetic agent, its unique impact on unstable patients, its role in neurosurgery, and its evolving applications in addressing a swath of psychiatric disorders and chronic pain, signals a paradigm shift in therapeutic approaches within medicine. However, the comprehensive understanding of ketamine's benefits is accompanied by a consideration of the risks, such as psychotomimetic effects and potential for abuse, thereby necessitating a cautious approach toward its clinical implementation.

The implications of the data presented in this review highlight the imperative for further robust research endeavors to elucidate and optimize ketamine's therapeutic mechanisms and potential applications. As ketamine continues to emerge as a promising treatment modality, it becomes crucial to conduct rigorous RCTs with stringent blinding measures, especially in the context of psychotherapy and pharmacology studies, to provide robust evidence of its therapeutic efficacy. Moreover, although the rapid and pronounced effects of ketamine in addressing various conditions, such as MDD and SI, are noteworthy, the transient nature of its benefits underscores the need for sustained effectiveness and optimized treatment protocols. Continued exploration of ideal dosing, administration routes, and long-term outcomes is imperative to maximize its therapeutic impact and mitigate potential adverse effects.

Furthermore, the integration of ketamine into clinical practice demands a cautious approach, necessitating close monitoring of patients for adverse reactions, such as hepatotoxicity, cystitis, and cognitive impairment, and careful consideration of individual patient characteristics that might influence treatment response. Future research directions should focus on enhancing sustained effectiveness across diverse patient populations, exploring combination therapies, and identifying predictive markers for treatment response. This holistic approach to research and clinical implementation is pivotal in shaping the future

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landscape of medicine and advancing the development of more effective and personalized pharmacological interventions. By pursuing these research avenues and acknowledging the complexities involved, the medical community can pave the way for a more nuanced and refined application of ketamine in therapeutic contexts, ultimately offering improved treatment options and enhanced patient care.

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