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PERSPECTIVE

Risks Associated with Misuse of Ketamine as a Rapid-Acting Antidepressant

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Abstract Major depression is a serious psychiatric disorder and remains a leading cause of disability worldwide. Conventional antidepressants take at least several weeks to achieve a therapeutic response and this lag period has hindered their ability to attain beneficial effects in depressed individuals at high risk of suicide. The non-competitive *N*-methyl-*D*-aspartate glutamate receptor antagonist ketamine has been shown to have rapid antidepressant effects in both rodents and humans. The emergence of ketamine as a fast-acting antidepressant provides promising new insights into the development of a rapid treatment response in patients with clinical depression. However, its safety and toxicity remain a concern. In this review, we focus on the limitations of ketamine, including neurotoxicity, cognitive dysfunction, adverse events associated with mental status, psychotomimetic effects, cardiovascular events, and uropathic effects. Studies have shown that its safety and tolerability profiles are generally good at low doses and with short-term treatment in depressed patients. The adverse events associated with ketamine usually occur with very high doses that are administered for prolonged periods of time and can be relieved by cessation. The antidepressant actions of its two enantiomers, *S*-ketamine (esketamine) and *R*-ketamine, are also discussed. *R*-ketamine has greater antidepressant actions than *S*-ketamine, without ketamine-related side-effects. Future treatment strategies should consider using *R*-ketamine for the treatment of depressed patients to decrease the risk of adverse events associated with long-term ketamine use.

Keywords Antidepressant · Ketamine · Fast-acting · Depression · Safety

Introduction

Major depression is a serious psychiatric disorder and remains a leading cause of disability worldwide [1]. The conventional treatments over the past 50 years have targeted monoamine neurotransmitters, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. These antidepressants usually require at least several weeks to achieve significant therapeutic responses and this lag period has hindered their ability to attain beneficial effects in individuals with major depression who are at high risk of suicide. Therefore, it is critical to develop better antidepressants that have a rapid onset of efficacy, particularly for treatment-resistant patients who are at high risk of suicide. Ketamine is a noncompetitive *N*-methyl-*D*-aspartate glutamate receptor (NMDAR) antagonist that has antidepressant effects in many animal models of depression, such as the learned helplessness paradigm, forced swim test, passive avoidance test, and chronic unpredictable stress procedure [2–5]. Increasing clinical evidence shows that a single intravenous infusion of low-dose ketamine (0.5 mg/kg) has rapid antidepressant effects within 2 h and continues to remain effective for at least 1 week [6, 7]. Specifically, ketamine has been shown to have rapid antidepressant effects in patients with treatment-resistant depression

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following single or repeated intravenous infusions in two-site randomized controlled trials [6, 8, 9]. Depressed patients frequently present hopelessness, which is widely recognized as a major risk factor for suicidal behavior and influences their health and social functioning [10]. Several studies have shown that repeated doses of ketamine rapidly and persistently decrease suicidal ideation in patients with treatment-resistant depression who have suicidal thoughts [11, 12].

The emergence of ketamine as a fast-acting antidepressant provides promising new insights into the development of a rapid reversal response in patients with clinical depression. Significant clinical improvements in the symptoms of depression have been observed after ketamine administration, but its safety and toxicity remain a concern. However, the off-label use of ketamine as an antidepressant continues to be debated, and further research is needed to mitigate its potential harm [13]. In the present review, we summarize the limitations of ketamine that can influence its rapid antidepressant properties. A better understanding of its negative aspects may improve clinical outcomes, decrease adverse effects, and facilitate the discovery of novel fast-acting antidepressants with fewer side-effects and greater efficacy. Ketamine-induced adverse effects, such as neurotoxicity, cognitive dysfunction, adverse events associated with mental status, psychotomimetic effects, cardiovascular events, and uropathic effects, usually occur with high doses or prolonged treatment, which should be considered when developing ketamine as a rapid-acting antidepressant.

Neurotoxic Effects of Ketamine

A preclinical study using 7-day-old mice showed that a single dose of ketamine (5–40 mg/kg, subcutaneous) induced dose-dependent and permanent neuronal apoptosis in the sensorimotor cortex and cerebellum, suggesting that the use of ketamine in depressed pregnant women may promote an apoptotic process in the fetus and thus decrease the functional capacity of the brain [14]. In addition, in 7-day-old rat pups, seven repeated intraperitoneal doses of 20 mg/kg ketamine induced neurotoxicity, as reflected by significant increases in the number of degenerating neurons [15]. Early-life exposure to ketamine is toxic to the developing brain. One study found that maternal administration of ketamine during pregnancy caused widespread apoptosis in the fetal brain, neuronal loss, and disturbances in the maturation of pyramidal neurons in offspring [16]. In addition, maternal exposure to ketamine is associated with emotional disorders, such as anxiety and depression-like behavior, and cognitive impairment in offspring [17, 18]. Future studies are needed to evaluate the safety of ketamine in these specific types of patients, particularly in pregnant women.

Differences in the efficacy and side-effects of ketamine are thought to underlie the different neurotoxicity and behavioral profiles of high- *versus* low-dose ketamine. At low doses, it acts as a noncompetitive NMDAR antagonist that blocks the receptor by binding to a specific site at the NMDAR-gated ion channel [19, 20]. Doses of ketamine higher than low analgesic doses can interact with several other receptors and ion channels, including opioid receptors, monoamine transporters, and dopamine D_2 receptors [21, 22]. These interactions have been suggested to be responsible for such side-effects as learning and memory impairment, sedation, ataxia, and psychotomimetic effects that have been reported in humans [23]. Seven administrations of a low dose (10 mg/kg) or a single administration of 20 mg/kg did not produce neurotoxicity [15]. A significant, age-dependent neurotoxic reaction occurred in both male and female rats when they were exposed to increasing doses of ketamine (20, 40, 60, and 80 mg/kg) [24]. In aging animals (60 mg/kg at 18 months and 40 mg/kg at 24 months), the ketamine-induced neurotoxic reaction was very robust compared with younger animals (6 months old) [25].

Prolonged intravenous ketamine administration in patients with refractory status epilepticus produced acute and profound cerebellar deficits and worsened cerebral function [26], raising the possibility of ketamine-induced neurotoxicity. A previous study of 20 participants revealed that ketamine abusers exhibit a persistent deficit in source memory, suggesting that repeated ketamine use chronically impairs episodic memory [27]. A clinical study revealed dose-dependent abnormalities in white matter in the bilateral frontal and left temporoparietal regions after chronic ketamine use, providing evidence of the microstructural basis of changes in cognition and experience in prolonged ketamine users [28]. Repeated injections of ketamine, but not an acute injection, are sufficient to induce a loss of the γ-aminobutyric acid (GABA)ergic phenotype of parvalbumin interneurons [29]. Similarly, repeated exposure to ketamine in rats suppressed inhibitory synaptic transmission in the prefrontal cortex, producing biochemical changes in the GABAergic system that led to functional disinhibition [30]. Prolonged exposure to ketamine *in vitro* or repeated exposure *in vivo* increases interleukin-6 production in the brain, which is necessary and sufficient for the activation of NADPH oxidase and the subsequent loss of the GABAergic phenotype of parvalbumin interneurons [29]. Acute ketamine administration (30 mg/kg) produces a gradient of hippocampal hypermetabolism [31]. Moreover, repeated ketamine exposure (16 mg/kg) significantly decreases the parvalbumin-positive cell density relative to a saline-treated control group. This loss of parvalbumin-positive cell density is significantly associated with hippocampal volume loss, which in turn is closely associated with the pathophysiology of depression [31]. Considering

the potential risk of neurotoxicity that is generally associated with chronic ketamine use at higher doses, we propose that repeated infusions of low doses of ketamine are safe and effective in sustaining an antidepressant response [32–35]. Further investigations of the optimal dose and route of administration that are safe for chronic ketamine treatment are required.

Cognitive Effects of Ketamine

A double-blind, placebo-controlled, independent-group study of 54 healthy volunteers showed that infusions of two doses of ketamine (0.4 and 0.8 mg/kg) dose-dependently impaired episodic and working memory and slowed semantic processing, recognition memory, and procedural learning [36]. Another double-blind, placebo-controlled, randomized, within-subject study of 12 healthy volunteers showed that intravenous infusions of 50 and 100 ng/mL ketamine impaired episodic memory and recognition memory [37]. These findings indicate that ketamine induces robust episodic memory impairments, especially in the encoding of information into episodic memory [38]. In addition, neuroimaging data revealed that ketamine increased left frontal activity during a deep encoding task, providing indirect evidence that semantic memory impairments are induced by ketamine [39]. Furthermore, several studies have reported ketamine-induced deficits in sustained attention in a continuous performance task at different levels of information processing [40–42], suggesting attentional deficits following ketamine administration. However, double-blind, placebo-controlled, randomized, within-subject trials that evaluated sub-anesthetic doses of intravenous ketamine showed that it does not induce attentional difficulties [43, 44]. Moreover, a placebo-controlled, randomized, double-blind psychopharmacological trial found that intravenous ketamine (0.23 and 0.5 mg/kg) impaired performance on tasks that tested executive function in humans [45]. There is no evidence that repeated ketamine exposure increases psychotic, perceptual, euphoric, or anxiogenic responses [46]. Ketamine administration at sub-anesthetic doses has been consistently shown to present an acceptable level of risk in healthy individuals throughout their participation in a study [47].

Effects of Ketamine on Adverse Events Associated with Mental Status

Adverse events associated with mental status in response to ketamine have been generally mild and transient. Ten significant adverse events associated with mental status were documented in 833 healthy individuals who received sub-anesthetic doses of ketamine intravenously [47]. These events included self-reported sensations of "very unpleasant," "no control, not a good feeling," "weird," "panicky," and "too high, walls closing in," nightmares, insomnia, a lower ability to concentrate, tearfulness, and no response to verbal and painful stimuli [47]. Most of these events resolved within minutes after the cessation of ketamine administration, and they all improved within 4 days and were not present after 2 weeks.

Psychotomimetic Effects of Ketamine

A meta-analysis of eight randomized controlled trials showed that a single administration of ketamine was associated with transient psychotomimetic effects but not persistent psychosis or affective switches in the rapid treatment of unipolar and bipolar depression [48]. A double-blind, placebo-controlled, crossover study of 10 healthy individuals showed that an infusion of ketamine at a sub-anesthetic dose significantly augmented high-frequency oscillations that are associated with the psychotomimetic symptoms experienced during ketamine administration [49]. Similarly, spontaneously-occurring gamma oscillations were measured in rats after subcutaneous administration of a single dose of ketamine (10 mg/kg). Ketamine dose-dependently increases the power of wake-related gamma oscillations in the neocortex [50].

Cardiovascular Effects of Ketamine

Some cardiovascular events induced by ketamine have been described as being mostly transient elevations in blood pressure. In one study, 0.8 mg/kg ketamine was infused into 16 depressed patients who were undergoing electroconvulsive therapy. Five cardiovascular events were recorded, including severe hypertension and diastolic blood pressure >100 mmHg [51]. A double-blind, cross-over, placebo-controlled clinical trial was conducted over 2 weeks in 27 hospitalized depressive patients. The results showed that 0.54 mg/kg ketamine induced a mild increase in blood pressure, but this increase ceased within 30 min after the ketamine infusion [52]. These cardiovascular side-effects may be attributable to the systemic release of catecholamines and the inhibition of norepinephrine reuptake at peripheral nerves and in non-neuronal tissues, such as the myocardium [53]. Therefore, ketamine should be used cautiously in patients with preexisting cardiovascular disease, including ischemic heart disease and hypertension. In addition, blood pressure should be monitored during ketamine administration. Attention also needs to be paid to patients concerning the possible psychological effects of

ketamine. Such effects can be frightening to patients, but carefully preparing them for such eventualities can be very helpful [54].

Uropathic Effects of Ketamine

The first evidence of the uropathic effects of ketamine was reported in 2007, in which severe urinary tract damage was found in six young patients after chronic ketamine use [55]. The symptoms associated with the uropathic effects were mainly severe urgency, urinary frequency, intermittent hematuria, nocturia, dysuria, and bladder pain [56–59]. The duration and dosage of ketamine were proposed to be related to an increase in urinary tract dysfunction [58, 60]. Treatment usually occurs symptomatically because the pathophysiology of ketamine-induced damage to the urinary system remains unclear, and the symptoms are reversed by ketamine cessation.

Other Clinical Concerns

Several controlled studies of patients with depression, especially those with treatment-resistant forms, have shown that intravenous ketamine is safe and has a rapid effect on depressive symptoms. However, alternative routes of administration need to be considered for clinical practice. The first controlled randomized, double-blind, crossover study in 20 patients with major depression reported significant improvements in symptoms (based on the Montgomery–Åsberg Depression Rating Scale) 24 h after intranasal administration of ketamine hydrochloride (50 mg) [61]. The advantage of intranasal administration over intravenous administration is that the intranasal route produces rapid antidepressant effects (within 5–40 min) with fewer dissociative side-effects and no drug-induced euphoria [62]. Further investigations of the neural mechanisms that underlie intranasal ketamine-induced behavioral remission may shed light on the optimal route of administration for the treatment of depression.

Future Directions

Novel antidepressants are required with greater potency and longer-lasting effects than those currently in use. Such antidepressants should also have less severe side-effect profiles, including fewer psychotomimetic effects and a lower abuse potential. Ketamine (or *RS*-ketamine; $K_i = 0.53$ μmol/L for the NMDAR) is a racemic mixture that contains equal parts of *S*-ketamine (esketamine) and *R*-ketamine [63]. Esketamine has a ~3- to 4-fold greater anesthetic potency and more undesirable psychotomimetic side-effects than *R*-ketamine [64]. This is related to the fact that esketamine ($K_i = 0.30$ μmol/L for the NMDAR) has a ~4-fold greater affinity for the NMDAR relative to *R*-ketamine ($K_i = 1.4$ μmol/L for the NMDAR) [63]. Jansen Pharmaceuticals has been developing an intranasal formulation of esketamine as a novel antidepressant. Many researchers believe that NMDAR inhibition might play a role in ketamine's antidepressant actions [65]. Recently, Singh *et al*. [66] reported a rapid-onset antidepressant effect of esketamine in treatment-resistant patients with depression, although psychotic and dissociative symptoms were the highest 40 min after administration (0.20 or 0.40 mg/kg for 40 min). Unexpectedly, *R*-ketamine had greater potency and longer-lasting antidepressant effects than esketamine in animal models of depression [67, 68]. Therefore, it is unlikely that NMDARs play a major role in the long-lasting antidepressant effects of *R*-ketamine, although NMDAR antagonism may promote its rapid antidepressant action [67, 68]. Unlike esketamine, *R*-ketamine does not induce psychotomimetic-like side-effects or have abuse potential in rodents [67]. Furthermore, a single dose of esketamine (10 mg/kg), but not *R*-ketamine (10 mg/kg), resulted in the loss of parvalbumin immunoreactivity in mouse brain regions, including the prefrontal cortex [67]. A recent study using [^{11}C] raclopride and positron emission tomography showed a marked reduction of dopamine $D_{2/3}$ receptors in the striatum of monkeys after a single infusion of esketamine (0.5 mg/kg, 40 min) but not *R*-ketamine (0.5 mg/kg, 40 min) [69]. Considering the role of dopamine release in psychosis, the marked release of dopamine from presynaptic terminals in the striatum is likely associated with the psychotomimetic side-effects in humans after infusions of ketamine and esketamine. Psychosis is well known to be induced by NMDAR antagonists such as ketamine and phencyclidine, suggesting that the psychotomimetic effects of ketamine and esketamine are associated with NMDAR antagonism [70].

A recent study showed that a twice-weekly infusion of ketamine was sufficient as an initial repeated-dose strategy [71]. Acute transient psychotomimetic and dissociative symptoms were observed, but they usually resolved within 2 h after each infusion. The intensity of dissociative symptoms diminished with repeated dosing [71]. Recently, Yang *et al.* reported that repeated, intermittent administration of esketamine (10 mg/kg, once per week for 8 weeks) but not *R*-ketamine caused a loss of parvalbumin immunoreactivity in the prefrontal cortex of mice [72]. The loss of parvalbumin immunoreactivity in the prefrontal cortex may be associated with the psychosis and gamma-oscillation deficits in schizophrenia. Repeated esketamine or ketamine administration may have long-lasting detrimental side-effects that are manifested in the prefrontal cortex of humans [63]. Interestingly, esketamine has been

Table 1 Doses of ketamine used to treat depression and those that have toxic effects in humans

Dose (mg/kg)	Outcome measures
Doses of ketamine that have antidepressant effects	
0.5	21-item Hamilton Depression Rating Scale [6]
0.5	25-item Hamilton Depression Rating Scale [7]
0.5	Montgomery–Åsberg Depression Rating Scale [8, 9, 74, 75]
0.5	Response rate [34]
0.75	28-item Hamilton Depression Rating Scale [76]
1	Response rate [77]
0.2, 0.4	Montgomery–Åsberg Depression Rating Scale total score [71]
Dose	**Toxic actions**
Doses of ketamine that cause toxic effects	
2 mg/kg	Worsening of cerebral atrophy [26]
1.42 g	Chronic impairment of episodic memory [27]
0.4 and 0.8 mg/kg	Impairment of learning and memory [36]
50 and 100 ng/mL	Impairment of episodic memory and recognition memory [37]
0.23 and 0.5 mg/kg	Impairment of executive function [45]
0.54 mg/kg	Mild increases in blood pressure [52]
0.23 mg/kg	Adverse events related to mental status [47]
0.5 mg/kg	Psychotomimetic effects [40, 78]
0.3 and 0.5 mg/kg	Cardiovascular side-effects [8, 49]
18.5 g/week	Uropathy [56]

reported to induce more psychotic symptoms, loss of interest, and emotional withdrawal compared with *R*-ketamine in healthy individuals [73]. Altogether, the use of *R*-ketamine for the treatment of depressed patients may be a new therapeutic approach that reduces the detrimental side-effects of racemic ketamine. To date, no randomized, double-blind, controlled trials have been conducted with either *R*-ketamine or esketamine (or racemic ketamine) in depressed patients. Direct comparisons between *R*-ketamine and esketamine in depressed patients should be made in future studies.

Summary

Strong evidence has shown that ketamine is an effective and fast-acting antidepressant for a variety of depressed patients. Although few studies have investigated potential complications, its safety and tolerability profiles are generally good at low doses or with short-term treatment. Notably, adverse events associated with ketamine use in patients with mood disorders are usually associated with very high doses for prolonged periods of time and are relieved by discontinuation. Comparisons of ketamine doses that are used to treat depression and those that cause toxic effects in humans are listed in Table 1. Repeated ketamine administration at weekly intervals was found to be safe and effective in maintaining the treatment response. Considering the high abuse liability of ketamine, it should be administered only in clinical settings where patients can be continuously monitored. We suggest that it should only be used in emergency departments for suicidal patients if the patients are adequately monitored for subsequent transient actions. Future treatment strategies need to be developed to decrease the risk of adverse events associated with long-term ketamine treatment for depression.

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