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REVIEW

An update on ketamine and its two enantiomers as rapid-acting antidepressants

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ABSTRACT

Introduction: Depression is one of the most disabling diseases worldwide. Approximately one-third of depressed patients are treatment-resistant to the currently available antidepressants and there is a significant therapeutic time lag of weeks to months. There is a clear unmet need for rapid-acting and more efficacious treatments. (*R,S*)-ketamine, an old anesthetic drug, appears now to be going through a renaissance.

Areas covered: This paper reviews recent literature describing the antidepressant effects of ketamine and its enantiomer (*S*)-ketamine in patients with major depressive disorder (MDD) and bipolar disorder (BD). Furthermore, the authors discuss the therapeutic potential of (*R*)-ketamine, another enantiomer of (*R,S*)-ketamine, and (*S*)-norketamine.

Expert commentary: A number of clinical studies have demonstrated that (*R,S*)-ketamine has rapid-acting and sustained antidepressant activity in treatment-resistant patients with MDD, BD, and other psychiatric disorders. Off-label use of ketamine for mood disorders is proving popular in the United States. Meanwhile, preclinical data suggests that (*R*)-ketamine can exert longer-lasting antidepressant effects than (*S*)-ketamine in animal models of depression, and (*R*)-ketamine may have less detrimental side effects than (*R,S*)-ketamine and (*S*)-ketamine. Additionally, (*S*)-norketamine exhibits rapid and sustained antidepressant effects, with a potency similar to that of (*S*)-ketamine. Unlike (*S*)-ketamine, (*S*)-norketamine does not cause behavioral and biochemical abnormalities and could be a safer than (*S*)-ketamine too.

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1. Background

The *N*-methyl-D-aspartate receptor (NMDAR) antagonist ketamine (Figure 1) was first synthesized in 1962 at the company Park Davis with the aim of lessening the serious psychotomimetic/psychodysleptic side effects and abuse potential of phencyclidine (PCP) (Ki = 0.06 μM for NMDAR for rat cortical membranes) (Figure 1) [1]. Ketamine (Ki = 0.53 μM for NMDAR), also known as (*R,S*)-ketamine, is a racemic mixture, which contains equal parts of (*R*)-ketamine (or arketamine) (Ki = 1.4 μM for NMDAR) and (*S*)-ketamine (or esketamine) (Ki = 0.30 μM for NMDAR) (Figure 1) [1]. First human clinical study of ketamine was conducted in 1964 by Dr. Edward Domino and Dr. Guenter Corssen (University of Michigan). In 1970, ketamine was introduced into human use as an anesthetic drug. However, ketamine has some side effects, such as psychotomimetic and dissociative effects, and abuse potential. Ketamine has been used widely as a recreational drug [2,3].

Since Berman and colleagues reported antidepressant effects of ketamine in patients suffering from a major depressive disorder (MDD) [4], a lot of studies replicated its robust antidepressant effects in MDD and bipolar disorder (BD) patients. Since the monoaminergic antidepressants were developed in the 1950s, the discovery of ketamine's fast and robust antidepressant actions is the greatest advance in the depression research field in the last 60 years [5].

2. Antidepressant effects of (*R,S*)-ketamine in MDD

2.1. Single intravenous infusion

MDD is a severe mental illness that affects millions of people worldwide, and leading to severe health and serious socioeconomic consequences. There are some limitations (e.g. lower response rate and longer time lag) of the current antidepressants, like selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs). Therefore, there is an urgent medical need for rapid-acting antidepressants for patients who are refractory to the traditional antidepressants.

Berman et al. [4] first reported that a single intravenous (i.v) infusion of ketamine (0.5 mg/kg) produces an antidepressant response in MDD patients. Subsequently, several randomized, controlled single-infusion trials replicated ketamine's antidepressant actions in treatment-resistant depression (TRD) patients [6–9]. In all these studies, ketamine shows robust antidepressant effect after 24 h post-infusion compared with a saline-treated response. However, ketamine's antidepressant effects generally were abated by a few days to a few weeks following a single infusion. Dissociative and psychotomimetic effects were common after a single infusion in these studies. These adverse reactions gradually disappeared within 20-30 min after injection.

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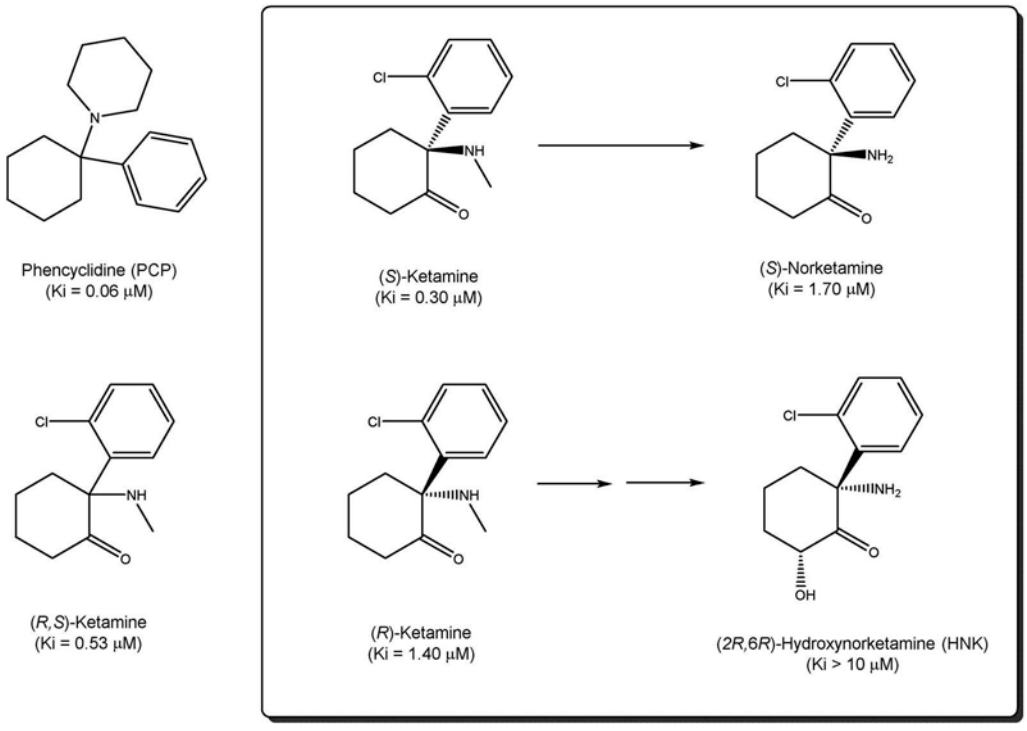

Figure 1. Chemical structure of phencyclidine (PCP), (*R,S*)-ketamine, enantiomers of ketamine and its metabolites norketamine and hydroxynorketamine (HNK). The values in the parenthesis are Ki values for NMDAR [1,72].

Given the dramatic side effects to ketamine and none with saline, early placebo-controlled ketamine trials are not truly blind. To avoid the limitation, Murrough et al. [10] used an active placebo, midazolam, because of its intravenously availability and ketamine-like pharmacokinetics. Ketamine (0.5 mg/kg, i.v.) treatment group's response rates (64%) were significantly greater than midazolam (0.045 mg/kg, i.v.) group's response rate (28%). Furthermore, Murrough et al. [11] demonstrated that suicide ideation score of ketamine (0.5 mg/kg, i.v.)-treated group was lower compared to midazolam (0.045 mg/kg, i.v.)-treated group, suggesting that ketamine is useful for the rapid treatment of suicide ideation. Subsequently, a recent study demonstrated that adjunctive ketamine (0.5 mg/kg, i.v.) significantly reduced depressed patients' suicidal ideation compared with midazolam (0.02 mg/kg, i.v.) [12]. It is noteworthy that the use of benzodiazepine is reported to interface ketamine's antidepressant actions in depressed patients [13,14].

2.2. Repeat intravenous infusion

In the previous open-label investigations and controlled trials, ketamine's response rates ranged from 25% to 85% at 24 h post-infusion and from 14% to 70% at 72 h post-infusion [15]. Consequently, the safety and efficacy of repeated ketamine infusion were studied. Ten medication-free TRD patients received six infusions over 12 days, and then assessed the safety and efficacy of repeated ketamine treatment [16]. Nine patients met the response criterion after the sixth infusions. After sixth infusion, the Montgomery–Åsberg Depression Rating Scale (MADRS) scores had a mean reduction rate of 85%. However, 19 days after the sixth infusion, most of the patients relapsed, just one patient remained minimal depressive symptoms for more than 3 months.

In an open-label study, Murrough and colleagues gave 24 TRD patients six times infusions of ketamine (0.5 mg/kg, i.v.) over a 12-day period [17]. They noted that 70.8% of patients responded to treatment, and that, among responders, the median time to relapse was 18 days after the last infusion. Four patients even remained relapse-free until 83 days later. More importantly, the treatments were well tolerated, without serious adverse events and sustained increase in psychotomimetic side effects.

Singh et al. [18] performed a double-blind, randomized, placebo-controlled study of ketamine (0.5 mg/kg, i.v., either two or three times weekly for up to 4 weeks) in TRD patients. In the twice-weekly dosing groups, the mean change of ketamine in MADRS score was −18.4. Meanwhile, in the thrice-weekly groups, it was −17.7 for ketamine. Both regimens were generally well tolerated. This study suggests that twice-weekly and thrice-weekly infusion of ketamine (0.5 mg/kg, i.v.) similarly maintained antidepressant efficacy [18].

2.3. Other administration routes

Besides intravenous infusion, ketamine also can be administered through other multiple routes, such as intramuscular, nasal, oral, rectal, and subcutaneous [19,20]. Intravenous administration is 100% bioavailable, and intramuscular ketamine has a slightly lower bioavailability (93%) (Table 1) [19]. Because of extensive first-pass metabolism of ketamine, oral's bioavailability is lower (17–29%). Bioavailability of intranasal and rectal administration is 8–45% and 11–25%, respectively (Table 1) [19].

Table 1. Pharmacokinetic profiles of (*R,S*)-ketamine in humans.

Route	Dose	Bioavailability	Tmax (min)
IV (intravenous)	1–4.5 mg/kg	100%	3
IM (intramuscular)	6.5–13 mg/kg	93%	5–10
Intranasal	0.5–1.0 mg/kg	8–45%	10–20
PO (oral)	0.25–0.5 mg/kg	17–29%	30
Rectal	9–10 mg/kg	11–25%	30–45

From Li et al. [19].

Loo and colleagues performed a small, placebo-controlled trial to compare the antidepressant response of subcutaneous, intramuscular, and intravenous ketamine administrations [21]. The results show that subcutaneous and intramuscular injections had a similar antidepressant response as intravenous ketamine administrations. However, subcutaneous injection was associated with fewest adverse effects.

A randomized control study showed that intranasal ketamine (50 mg) improved depressive symptoms within 24 h compared with placebo in MDD patients [22]. These patients had failed at least one prior antidepressant trial. Without serious psychotomimetic or dissociative effects and significant changes in hemodynamic parameters, intranasal ketamine was well tolerated for MDD patients. This study provides the first controlled evidence for the rapid antidepressant effects of intranasal ketamine.

In addition, over 28 days oral administration of ketamine (0.5 mg/kg/day) yielded positive results [23]. The patients' mood improved over the 28-day treatment period. Oral administration alleviated the level of symptom was the same as that achieved by intravenous infusion of ketamine. Interestingly, different with intravenous administrations, oral administrations of ketamine did not show significant antidepressant effects until day 14 of treatment, indicating that oral administration of ketamine does not have rapid-acting antidepressant action. Low bioavailability of oral administration may contribute to slow-acting antidepressant actions of ketamine.

As mentioned above, sublingual administration bioavailability is greater than orally. Lara and colleagues performed a clinical trial to evaluate the tolerability and efficacy of the sublingual formulation of ketamine (10 mg from a 100 mg/mL solution for 5 min, then swallowed) [24]. According to their findings, 20 of 26 (77%) patients with bipolar depression or MDD reported improved and stable mood, cognition. Sublingual administration patients had no euphoria, psychotic, or dissociative symptoms, just had a mild and transient lightheadedness.

3. Antidepressant effects of (*R,S*)-ketamine in bipolar depression

BD is a recurrent mood disorder. Depression, mania, and mixed states are the hallmark that distinguishes BD from MDD. However, BD patients experience depressive episodes three times more often than they do manic and hypomanic episodes. There is thus a great need for effective and safe antidepressant treatment for BD patients.

There are three randomized clinical trial (RCT) studies focus on ketamine antidepressant effect in depressed patients with BD. The work published by Diazgranados et al. [25] describes that ketamine (0.5 mg/kg, i.v.) showed robust and rapid antidepressant effects in TRD patients with BD. Subsequently, Zarate et al. [26] replicated ketamine's (0.5 mg/kg, i.v.) antidepressant efficacy in another bipolar depression RCT study. Nugent et al. [27] demonstrated cerebral metabolic correlates of antidepressant response to ketamine (0.5 mg/kg, i.v.) in depressed patients with BD. In this study, 21 depressed patients with BD underwent [^{18}F]-fluorodeoxyglucose (FDG) and positron emission tomography (PET) imaging after receiving a ketamine or placebo infusion. Compared to placebo, ketamine (0.5 mg/kg, i.v.) infusion improved patients' depression symptoms, and glucose metabolism activity in the right ventral striatum correlated with the change of MADRS scores. These alterations may partially underlie ketamine's mechanism of action [27].

Switch from depression to mania is a specific side effect when use antidepressant to treat depression in BD patients [28]. It is important to evaluate the switch mania risk when use ketamine in BD patients. Administration of subanesthetic dose of ketamine in BD patients may cause adverse effects, such as dissociative symptoms [29,30]. However, the risk of depression switch to mania has not yet been reported.

Taken together, a single infusion of ketamine may be considered to be a safe treatment in bipolar depression, although it has a short duration of action. More RCTs are needed to explore different administration routes of ketamine and to study how to sustaining antidepressant response in patients with BD.

4. Antidepressant effects of (*R,S*)-ketamine in other psychiatric disorders

Although the off-label use of ketamine in mood disorders such as MDD and BD is popular, several studies have examined ketamine to treat other psychiatric disorders, including post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), general anxiety disorder (GAD), social anxiety disorder (SAD) [31].

PTSD has a lifetime prevalence of approximately 10%, with women having a twofold greater risk than men [32]. McGhee et al. [33] reported that patients receiving perioperative ketamine had a lower prevalence of PTSD than soldiers receiving no ketamine during their surgeries in a military treatment center. This study suggests prophylactic effects of ketamine for stress-related psychiatric disorders, supporting from prophylactic effects of ketamine in rodents [34,35]. Furthermore, Feder et al. [36] reported that PTSD patients who received ketamine (0.5 mg/kg, i.v.) had a significant reduction in PTSD symptoms 24 h after infusion. These studies provide the evidence for a rapid reduction in symptom severity following ketamine infusion in PTSD patients. A retrospective study of long-term oral ketamine for TRD and PTSD demonstrated that inpatient hospital days and hospital admissions were reduced by 70% and 65% following treatment, respectively [37].

Rodriguez and colleagues published a series of research of ketamine in OCD patients. First, they reported a female patient with treatment-resistant OCD who demonstrated complete resolution of obsessions after a single ketamine infusion, and the anti-OCD effect sustained for 7 days [38]. Subsequently, the same group demonstrated that 50% of patients had a more than 35% reduction in Yale-Brown Obsessive-Compulsive Scale

scores in obsessions after intravenous ketamine (0.5 mg/kg) in 15 drug-free OCD patients [39]. Recently, combination with a brief course of exposure-based cognitive behavioral therapy (CBT) could help patients maintain ketamine's effects [40]. Collectively, ketamine has a rapid anti-obsessional effect in OCD patients with near-constant intrusive obsessions. However, it should be noted that previous researches focused on obsessions not compulsive symptoms. In contrast to depression symptoms, ketamine (0.5 mg/kg, i.v.) did not produce a significant improvement in OCD patients' compulsive symptoms [41]. Nonetheless, future RCT study using a large sample size will be helpful in examine whether both obsessions and compulsions are responded to ketamine.

At present, there are two reports on the safety and efficacy of ketamine in GAD and SAD. Glue et al. [42] recruited 15 GAD patients and 18 SAD patients. Patients received one or two weekly ketamine subcutaneously injection (1 mg/kg), and the whole treatment lasted 3 months. Besides transient dissociative symptoms, weekly ketamine dosing was safe and well tolerated. The patients showed improved social and/or work function during after 3 months of treatment. Furthermore, Taylor et al. [43] reported that a single infusion of ketamine (0.5 mg/kg) was effective in reducing anxiety symptoms in patients with SAD. Moreover, ketamine (0.25, 0.5, and 1.0 mg/kg, s.c., with 1 week between doses) dose-dependently improved Fear Questionnaire, increased EEG power most at high (gamma) frequency, and decreased it most at low (delta) frequency in treatment-resistant patients with GAD and SDA [44]. Collectively, it is likely that single or repeated ketamine infusions may be a therapeutic alternative for patients with GAD or SAD.

5. Biomarkers for ketamine's antidepressant actions

A single subanesthetic dose of ketamine produces a rapid antidepressant effect in about two-thirds of TRD patients, and the effects can last for over 1 week. However, the mechanism of ketamine's antidepressant effect is unclear. More importantly, predictable biomarkers that can distinguish patients with and without a response remain to be identified.

The Val66Met (rs6265) polymorphism in the brain-derived neurotrophic factor (*BDNF)* gene has been proposed as a potential obstacles to the antidepressant response to ketamine in patients with TRD [45]. The Val/Val carrier patients had a higher antidepressant response to ketamine than the Met carriers. The Met allele occurs at a 40–50% frequency within the Asian population, more than the frequency in Caucasian populations (20–30%) [46]. A recent study showed that the *BDNF* gene (rs6265) was not a significant predictor of ketamine's antidepressant response in TRD patients in a Taiwan population [9]. Nonetheless, further study on the *BDNF* gene (rs6265) using a large sample size with different ethnicity is needed.

Yang et al. [47] reported that serum levels of interleukin-6 (IL-6) at baseline in the ketamine responder group were significantly higher than those in the ketamine non-responder group, suggesting that serum IL-6 levels at baseline could be a useful predictive biomarker to select TRD patients with MDD or BD who would best benefit from ketamine's rapid antidepressant action. Furthermore, Kiraly et al. [48] reported that several cytokines showed significant changes in serum of TRD patients after ketamine (0.5 mg/kg, i.v.). Low levels of fibroblast growth factor 2 (FGF-2) at baseline were associated with treatment response for ketamine. In contrast, Park et al. [49] reported that changes in cytokines (IL-6 and TNF-α) levels post-ketamine were not related to antidepressant response. A recent study [50] reported that the decrease in TNF-α between baseline and 40 min post-infusion was positively correlated with a decrease in MADRS scores across time in the ketamine (0.5 mg/kg) group, suggesting that the rapid suppression of pro-inflammatory cytokines may contribute to the rapid-antidepressant effects of ketamine. Nonetheless, further studies using larger sample sizes are needed to assess the possibility of pro-inflammatory cytokines as predictable biomarkers.

Kadriu and colleagues demonstrated that ketamine significantly increased the osteoprotegerin (OPG)/receptor activator of nuclear factor kB Ligand (RANKL) ratio and plasma osteopontin (OPN) levels, significantly decreased RANKL levels [51]. The study suggests that the OPG/RANK/RANKL system may play a role in the antidepressant effects of ketamine in TRD patients. Recently, Zhang et al. [52] reported that (*R*)-ketamine, but not (*S*)-ketamine, significantly attenuated increased plasma levels of RANKL in susceptible mice after chronic social defeat stress. In addition, the authors reported a positive correlation between sucrose preference and the OPG/RANKL ratio. These findings suggest that inflammatory bone markers may play a role in the antidepressant effects of ketamine [or (*R*)-ketamine] [52].

A metabolomics study using blood samples from a double-blind, placebo-controlled crossover study of ketamine in medication-free TRD patients and healthy controls was reported [53]. After 4 h post-infusion, ketamine (0.5 mg/kg, i.v.) response resulted in more pronounced effects in the kynurenine pathway and the arginine pathway. Compared with non-responder, responders to ketamine treatment had a larger decrease in circulating kynurenine levels and a larger increase in the bioavailability of arginine [53].

The molecular mechanisms underlying the antidepressant effects of ketamine have been proposed from a number of preclinical studies [5]. For example, Li et al. [54] reported the mammalian target of the rapamycin (mTOR) signaling pathway is highly correlated with the rapid antidepressant effects of ketamine. mTOR is a ubiquitous protein kinase involved in protein synthesis and synaptic plasticity. Ketamine increased numbers of synaptic signaling proteins and increased numbers and functions of new spine synapses through activated the mTOR signaling pathway in the rat prefrontal cortex [54,55]. Interestingly, Denk et al. [56] reported for the first time evidence of increased mTOR phosphorylation in a depressed patient after (*S*)-ketamine infusion. The patient's depressive symptoms improved rapidly after an infusion of (*S*)-ketamine and did not return for 24 h. Subsequently, Yang et al. [57] also showed that ketamine ameliorates depression rapidly with acute increases in the expression of plasma mTOR in depressed patients. A recent preclinical study demonstrated that mTOR signaling in the prefrontal cortex plays a role in the antidepressant effects of (*S*)-ketamine, but not (*R*)-ketamine [58], supporting the clinical data [56]. It is, therefore, of great interest to study whether (*R*)-ketamine can affect mTOR signaling in the blood from depressed patients.

6. (*S*)-ketamine's antidepressant actions in depressed patients

Ketamine is a racemic mixture containing equal parts of (*R*)-ketamine (or arketamine) and (*S*)-ketamine (or esketamine). (*S*)-ketamine (Ki = 0.30 μM for NMDAR) has an approximately 4-fold greater affinity for the NMDAR than the (*R*)-ketamine (Ki = 1.4 μM for NMDAR) (Figure 1) [1]. Since the NMDAR inhibition was believed to play a key role in the antidepressant actions of ketamine, the Janssen Pharmaceutical Companies of Johnson & Johnson selected (*S*)-ketamine as the novel antidepressant.

A double-blind, placebo-controlled study showed that a single infusion of (*S*)-ketamine (0.20 or 0.40 mg/kg, i.v. for 40-min) showed a rapid (within 2 h) and robust antidepressant effects in TRD patients. Headache, nausea, and dissociation were the most common treatment-emergent adverse events. However, these side effects were transient and did not persist beyond 4 h from the start of the (S)-ketamine infusion (Table 2) [59]. Due to tolerability reasons, a retrospective study demonstrated that rapid infusion of (*S*)-ketamine (0.25 mg/kg, i.v., for 10-min) is possibly not the optimal choice to administer this drug for TRD (Table 2) [60]. A case report showed that (S)-ketamine (0.22 mg/kg, i.v., for 30-min) showed a robust and sustaining anti-suicidal and antidepressant response in a female schizophrenic patient accompany with severe post-psychotic depression. Importantly, during the whole augmentation treatment period, relevant psychotic or dissociative symptoms which may lead to a sustained remission of depressive symptoms and suicidality were not shown (Table 2) [61].

A double-blind, placebo-controlled crossover study showed that intranasal infusion of (*S*)-ketamine (84 mg) was associated with cognitive performance decline at 40 min post-infusion in healthy control subjects. In contrast, performance on these tests did not differ significantly between (*S*)-ketamine and placebo at 2, 4, or 6 h post-infusion [62]. Subsequently, a double-blind, placebo-controlled study showed no significant difference in driving performance 8 h after intranasal infusion of (*S*)-ketamine (84 mg) in healthy control subjects [63].

Furthermore, recently, two phase 2 RCTs assessing intranasal (*S*)-ketamine were reported. One study by Daly et al. [64] reported good efficacy with a rapid decline in the depressive symptoms and suicidality in patients that were given intranasal (S)-ketamine (28, 56, or 84 mg twice weekly) in TRD patients. Furthermore, a superior MADRS total score was reported in all 3 (S)-ketamine groups compared to the placebo, and correlating with intranasal dose (Table 2) [64]. Moreover, a published study from Canuso et al. [65] highlighted the efficacy and safety of intranasal (S)-ketamine with a rapid decline in the symptoms of depression and suicidality in patients at imminent suicide risk. Along with antidepressant therapy, (S)-ketamine (84 mg twice weekly for four weeks) reduced significantly the suicidal symptoms and depressive symptoms at both 4 and 24 h from the initial dose. However, it should be noted that after 4 weeks of treatment, these effects reported did not vary from those of the placebo (Table 2). Furthermore, the differences in suicide risk scores were not statistically significant at any time point between the groups [65]. Dissociative symptoms began shortly after each infusion with symptoms attenuating after the repeated dose. Compared with the placebo group, adult TRD patients who were prescribed (S)-ketamine had a significantly greater reduction in MADRS score from the baseline at day 28 (Table 2).

7. (*R*)-ketamine: a novel antidepressant candidate

Meta-analysis demonstrated that antidepressant effects of non-ketamine NMDAR antagonists are less potent than ketamine [66–69]. Preclinical studies demonstrated that (*R*)-ketamine showed greater potency and longer lasting antidepressant effects than (*S*)-ketamine in different animal models of depression [70–75]. Importantly, unlike (*S*)-ketamine, (*R*)-ketamine may not induce psychotomimetic side effects or exhibit abuse potential in rodents and monkeys [71,76,77].

Table 2. Use of (*S*)-ketamine in patients with major depressive disorder.

Study design	Sample size	Ketamine dosing	Outcome measures	Results	Limitations
Singh et al, 2016. [59] multi center, double blind, randomized, crossover, placebo controlled	30	IV: 0.20 mg/kg over 40 minutes	MADRS	Esketamine showed a rapid (within 2 hours) and robust antidepressant effect. Treatment-emergent adverse events were dose dependent.	Lack of CADSS assessment; Small sample size
Correia-Melo et al, 2017. [60] retrospective study	27	IV: 0.25 mg/kg over 10 minutes	MADRS; CGI	Thirteen patients (48.1%) showed therapeutic response within 1 week of intervention. Almost 11.1% of patients have a very disturbing experience.	Small sample size; Lack of control group
Bartova et al, 2018. [61] case report	1	IV: 0.22 mg/kg over 30 minutes	MADRS	Esketamine demonstrate a robust anti-suicidal and antidepressant effect after thrice weekly for 3 weeks in total.	A case report; Lack of control group
Daly et al, 2018. [64] multi center, double blind, randomized, placebo controlled	67	Intranasal: 28 mg, 56 mg or 84 mg twice weekly	MADRS	Change in MADRS total score in all 3 esketamine groups was superior to placebo, with a significant ascending dose-response relationship.	Small sample size
Canuso et al, 2018. [65] multi center, double blind, randomized, placebo controlled	68	Intranasal: 84 mg twice weekly for 4 weeks	MADRS	A significantly greater improvement in MADRS score was observed in the esketamine group compared with the placebo group at 4 hours and at 24 hours, but not at day 25.	Small sample size

Furthermore, Hashimoto et al. [77] reported a marked reduction of dopamine $D_{2/3}$ receptor binding in conscious monkey striatum after a single infusion of (*S*)-ketamine but not that of (*R*)-ketamine, suggesting that dopamine release by a single dose of (*S*)-ketamine may be associated with acute psychotomimetic and dissociative side effects in humans. Further study is needed to examine whether repeated infusions of (*R*)-ketamine can cause the dopamine release in the monkey and human brain. In addition, unlike (*R,S*)-ketamine and (*S*)-ketamine, (*R*)-ketamine had no effect to the expression of heat shock protein HSP-70 (a marker for neuronal injury) in the rat retrosplenial cortex [78]. Based on the above research results, (*R*)-ketamine could be a safer antidepressant effect in animal depression model than (*S*)-ketamine and (*R,S*)-ketamine [79–83].

Clinical study of (*R*)-ketamine in depressed patients is not yet reported although the use of (*R*)-ketamine in healthy control subjects was reported [84,85]. Further RCT studies will be required to study antidepressant effects of (*R*)-ketamine in depressed patients. Nonetheless, it is of great interest to perform direct comparisons between (*R*)-ketamine and (*S*)-ketamine in depressed patients.

8. (*S*)-norketamine: an alternative antidepressant for (*S*)-ketamine

Ketamine-induced side effects such as psychotomimetic effects and abuse liability are associated with the potent inhibition of the NMDAR in the brain. (*S*)-norketamine (Ki = 1.70 μM for NMDAR) is metabolized from (*S*)-ketamine by the microsomal cytochrome P450 system (Figure 1). Very recently, Yang et al. [86] reported that (*S*)-norketamine exhibits rapid and sustained antidepressant effects in rodent models of depression. These effects are similar to that of the antidepressant actions of (*S*)-ketamine. However, unlike (*S*)-ketamine, (*S*)-norketamine does not cause behavioral and biochemical abnormalities, such as abuse potential, prepulse inhibition deficits, increases in baseline γ-oscillations, and loss of parvalbumin immunoreactivity in the medial prefrontal cortex [86]. (*S*)-norketamine may have fewer detrimental side-effects in humans than (*S*)-ketamine because of the lower affinity of (*S*)-norketamine for NMDAR. Taken together, (*S*)-norketamine could be a safer alternative antidepressant than (*S*)-ketamine for use in humans [86,87].

9. Expert commentary

Antidepressant research of ketamine for 18 years suggests that ketamine is a prototype for the rapid-acting antidepressants. Ketamine is also being proved as a treatment choice for other psychiatric disorders such as OCD, PTSD, GAD, and SAD although ketamine has detrimental side effects including dopaminergic side effects (e.g. psychotomimetic effects, dissociative effects, addiction, dependence) [69] and others (e.g., risk of hepatotoxicity, cognitive deficits, ulcerative cystitis) [88,89]. Despite growing enthusiasm for rapid implementation, further research will be needed before it is appropriate to consider it a routine treatment for depression and other psychiatry disorders.

Meta-analysis demonstrated that antidepressant effects of non-ketamine NMDAR antagonists [e.g. traxoprodil (CP-101,606, rapastinel (GLYX-13), lanicemine (AZD6765), CERC (MK-0657)) are less potent than ketamine [66,67], suggesting that NMDAR inhibition may not play a key role in the antidepressant actions of ketamine. Preclinical data suggest that (*R*)-ketamine would be an alternative antidepressant for (*R,S*)-ketamine since (*R*)-ketamine may be free of side effects such as psychotomimetic and dissociative effects and abuse liability [79–83]. More importantly, (*R*)-ketamine exerted longer-lasting antidepressant effects than (*S*)-ketamine in animal models of depression. In the preclinical study, antidepressant effects of (*S*)-ketamine was less potent than (*R,S*)-ketamine and (*R*)-ketamine [73]. In addition, the order for neurotoxic effects (known as Olney's lesion) in rat retrosplenial cortex was (*S*)-ketamine > (*R,S*)-ketamine > (*R*)-ketamine [78]. However, there is a lack of clinical trial to compare the safety and efficacy of (*R,S*)-ketamine, (*R*)-ketamine and (*S*)-ketamine in depressed patients. Further understanding the precise mechanism(s) underlying ketamine's antidepressant using enantiomers of ketamine and its metabolites will prove to unlock novel insights into the neurobiology of depression and to develop the novel antidepressants.

The Janssen Pharmaceutical of Johnson & Johnson presented the five pivotal phase 3 trials of (*S*)-ketamine nasal spray in TRD patients: three short-term studies, one withdrawal maintenance-of-effect study, and one long-term safety study up to a year. The flexibly dosed (*S*)-ketamine nasal spray, plus a newly initiated oral antidepressant in adults with TRD showed a statistically significant and clinically meaningful rapid reduction of depressive symptoms, as compared with placebo nasal spray plus a new oral antidepressant. In contrast, the data from a second study in patients aged 65 and older with TRD with a similar design did not show statistical significance for its primary efficacy endpoint. Another study of (*S*)-ketamine (56 and 84 md for 4-weeks) in TRD patients did not demonstrate statistical significance for the primary endpoint, change in depression score from baseline to four weeks. Long-term (16-weeks) study showed that patients treated with (*S*)-ketamine nasal spray plus an oral antidepressant had a 51% lower risk of relapse than patients in the oral antidepressant plus placebo nasal spray group. Long-term (up to 52-weeks) open-label study showed that treatment with (*S*)-ketamine nasal spray plus an oral antidepressant appeared to be associated with sustained improvement in depressive symptoms at up to 52 weeks. Considering the mixed results of phase 3 trials for intranasal (*S*)-ketamine infusion, it seems that antidepressant actions of intranasal (*S*)-ketamine infusion in depressed patients are less potent than intravenous (*R,S*)-ketamine infusion. It is possible that mixed results of intranasal injection of (*S*)-ketamine in TRD patients may, in part, be due to lower bioavailability than intravenous administration of (*S*)-ketamine (Table 1).

In 2016, Zanos et al. [72] reported that metabolism of (*R,S*)-ketamine to (2*R*,6*R*)-hydroxynorketamine (HNK) was essential for (*R,S*)-ketamine-mediated antidepressant activity in rodents. However, recent studies reported that (2*R*,6*R*)-HNK is not essential for antidepressant effects of (*R*)-ketamine, although the conclusion needs to be replicated in future studies [90–97]. As mentioned above, it should be noted that intravenous infusion of (*S*)-ketamine has rapid-acting

antidepressant effects in TRD patients [59]. It is, therefore, unlikely that (2*R*,6*R*)-HNK is essential for (*R*,*S*)-ketamine-mediated antidepressant activity since (2*R*,6*R*)-HNK is not produced in the humans from (*S*)-ketamine. Validation for the clinical use of (2*R*,6*R*)-HNK in humans will be started at the National Institute of Mental Health, USA. Therefore, it is also of great interest to study direct comparisons between (*R*)-ketamine and its final metabolite (2*R*,6*R*)-HNK in depressed patients.

10. Five-year view

Clinical evaluation of (*R*)-ketamine in depressed patients has yet to be published although preclinical studies suggest that (*R*)-ketamine has greater potency and longer lasting antidepressant effects in comparison to (*S*)-ketamine in animal models of depression. Consequently, it would be of interest to directly compare (*R*)-ketamine and (*S*)-ketamine in depressed subjects, including those with TRD.

Lastly, it is important to note that ~30% of patients with depression are treatment-resistant to current antidepressant therapy having a therapeutic time lag from weeks to months. Indeed, there are currently no drugs for suicidal ideation in depressed patients. If (*R*)-ketamine demonstrated greater potency and increased the antidepressant effect, with decreased adverse effects in depressed patients compared to (*S*)-ketamine or (*R*,*S*)-ketamine, (*R*)-ketamine would be an innovative and valued antidepressant option. In a next 5-years, results of (*R*)-ketamine in depressed patients will be available and thereby give a clearer picture for future developments.

Key issues

- Depression affects nearly 20% of the population at some point during the life span. The currently available antidepressants are effective in only about two-thirds of depressed patients. There is a significant therapeutic time lag of weeks of months. The development of rapid-acting antidepressants which are effective in the TRD patients is the unmet medical need.
- (*R*,*S*)-ketamine caused rapid-acting and sustained antidepressant effects in depressed patients, including TRD. In addition, (*R*,*S*)-ketamine significantly reduced suicidal thoughts in depressed patients. Furthermore, (*R*,*S*)-ketamine showed antidepressant effects in patients with BD, PTSD, OCD, GAD, and SAD. Thus, the discovery of antidepressant actions of (*R*,*S*)-ketamine is the greatest breakthrough in the field of depression in over 60 years.
- (*R*,*S*)-ketamine is known to be the popular recreational drug. Because of the hallucinatory and dissociative effects of the drug, the recreational use of (*R*,*S*)-ketamine has been increasingly reported in recent years. Although the concerns about the safety of repeated (*R*,*S*)-ketamine infusions persist, it has been used as an off-label treatment for psychiatric disorders.
- (*R*,*S*)-ketamine is a racemic mixture containing equal parts of (*R*)-ketamine (or arketamine) and (*S*)-ketamine (or esketamine). (*S*)-ketamine shows an approximately 3–4 fold greater anesthetic potency and greater undesirable psychotomimetic side effects, compared with (*R*)-ketamine. The Janssen Pharmaceutical of Johnson & Johnson has been developing intranasal (*S*)-ketamine as antidepressant and anti-suicidal drug.
- Preclinical studies reported that (*R*)-ketamine showed greater potency and longer lasting antidepressant effects than (*S*)-ketamine in animal models of depression. Unlike (*S*)-ketamine, (*R*)-ketamine might not induce side effects (e.g., psychotomimetic and dissociative side effects, abuse liability). Collectively, (*R*)-ketamine could be a safer antidepressant in humans than (*R*,*S*)-ketamine and (*S*)-ketamine. Further RCTs of (*R*)-ketamine in depressed patients will be needed in a future.

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Declaration of interest

K Hashimoto is the inventor of filed patent applications on 'The use of *R*-ketamine in the treatment of psychiatric diseases' and '(*S*)-norketamine and salt thereof as pharmaceutical' by the Chiba University. K Hashimoto also declares that he has received research support from Dainippon Sumitomo, Otsuka, and Taisho. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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