Exploring the Role of Ketamine in Maintaining the Antidepressant Response

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ABSTRACT

A large body of research indicates that ketamine is safe and well tolerated at sub-anesthetic doses and shows potential as a novel antidepressant. However, the effect of single infusions of ketamine, although reliably replicated and effective in relieving depressive symptoms, is transient, with relapse occurring within 2 weeks of treatment. Recent studies have focused on identifying a safe and effective ketamine administration protocol for the rapid and sustained relief of depressive symptoms. A comprehensive literature search was conducted (for studies from January 2010 to April 2018 that administered intravenous ketamine in multiple infusions) and a total of 17 studies meeting criteria were included in this review. We enumerate principle points of studies that administered multiple infusions of ketamine and followed patients over a longer period of time. We also identify the pressing need for additional research to fill in the gaps that exist around appropriate dosage regimens and an effective maintenance strategy. **[*Psychiatr Ann*. 2018;48(9):437-446.]**

Depressive disorders, including bipolar and unipolar depression, represent a significant health care burden in the United States and cost the labor force an estimated $24 billion annually in lost productivity.[1] Patients with medical conditions and comorbid depression have health care costs 5 times higher than those of nondepressed patients with the same medical issues.[2] Additionally, the devastating outcome of suicide, which results from untreated and under-treated mental illness, adds to the public health and economic burden.[3] Worldwide, suicide now ranks as the third most common cause of mortality in people age 15 to 44 years, the age group that is considered to be the most economically productive.[3] There were 42,773 deaths by suicide reported in the US 2014,[4] and the World Health Organization estimates that 1.5 million people worldwide will die by suicide in 2020.[5] Approximately 90% of people who die by suicide have a history of mental illness.[6] Unfortunately, there are few evidence-based approaches to prevent suicide and even fewer potential treatments focused on rapid amelioration of depressive symptoms, which can further acutely increase risk of suicide.

Traditional antidepressant medications target neurotransmitters like serotonin, norepinephrine, and dopamine by modifying the monoamine transporter system. Delayed therapeutic responses, suboptimal efficacy, and tolerance in the context of chronic use have been the most commonly documented limitations on the effectiveness of conventional antidepressant medications.[7,8] The interest in N-methyl-D-aspartate (NMDA) receptors as a promising target for treatment-resistant depression is more than a decade old. Several studies have explored the role of ketamine and other NMDA receptor antagonists in an

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Disclosure: The authors have no relevant financial relationships to disclose.
doi:10.3928/00485713-20180816-03

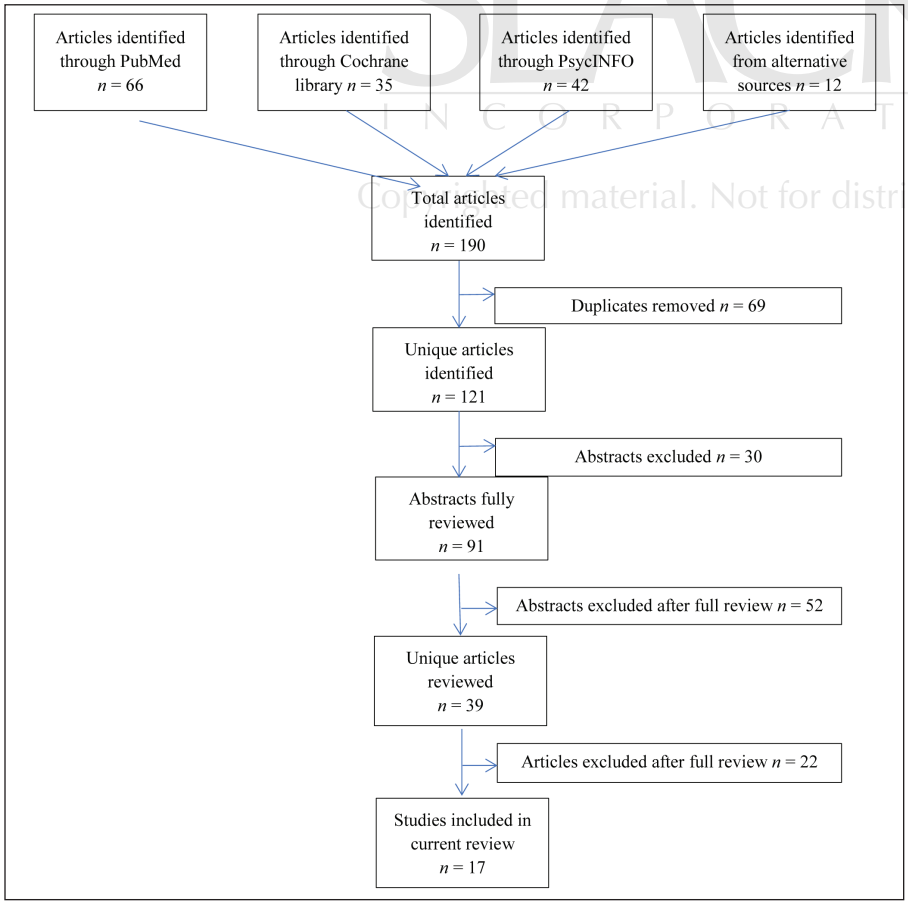

Figure 1. Flowchart demonstrating selection of review articles.

attempt to elucidate their mechanisms of action and explain the advantages of using them instead of traditional antidepressants.[8-10] Although the literature is replete with evidence that ketamine is efficacious in rapidly alleviating depressive symptoms and suicidal tendencies,[11-15] significant gaps continue to exist in our knowledge with regard to an optimal dosage regimen for maintenance of this effect and the potential for adverse effects over long-term administration. Ketamine has several significant advantages over current antidepressants because it is available in oral, subcutaneous, intranasal, intramuscular, and intravenous formulations. Substantial concerns exist about the side effect profile of ketamine, particularly its ability to cause cognitive impairment when used over long periods of time.

Current research on ketamine is focused on identifying a safe and effective administration protocol for the rapid and sustained relief of depressive symptoms. One focus of these studies is the examination of side effects of ketamine and identification of potential long-term side effects of repeated administration. This article aims to provide a brief overview on what is known to date about how ketamine has fared as a novel drug to maintain the antidepressant response through repeated administrations.

METHODS

A comprehensive literature search was conducted on PubMed, PsycINFO, the Cochrane database and alternate sources like Google Scholar and MEDLINE through April 2018 for peer-reviewed articles published in English, using a combination of two subsets of keywords: "ketamine," "trials," "intravenous infusions," "multiple infusions," "serial infusions" AND "depression," "major depressive disorder," or "bipolar depression." The search was narrowed to include only those articles that specifically addressed the treatment of depression with multiple intravenous infusions of ketamine. Articles studying the effects of single infusions, or articles published in languages other than English, were excluded. **Figure 1** shows the step-by-step process of article selection.

Data Extraction and Outcomes

All data were extracted by the same reviewer. The primary outcome measures were treatment response rate, maintenance of the response, and the time to relapse. All contributing studies used the Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), or the Hamilton Depression Rating Scale (HAM-D). The frequency and/or severity of dissociative, psychotomimetic, and hemodynamic effects were evaluated as secondary outcomes when mentioned in the studies included.

RESULTS

A total of 17 articles that met the criteria were identified and are included for discussion in this review. These articles comprise four double-blind, placebo-controlled trials,[16-19] six open-label studies,[11,20-24] one naturalistic observational study,[25] one case series,[26] and five case reports.[27-31] **Table 1** summarizes the key points of each study.

Broadly speaking, all of the studies included in the review reported that most of the 214 total participants showed dramatic improvement in depressive symptoms with ketamine infusions based on BDI, MADRS, and HAM-D scores. In one report, a greater reduction in depression was seen

Table 1.

Salient Features of Studies Reviewed

Author (Year)	Patients, *N* (Age)	Participant(s)	Study Design/Methods/Dosing (Total Number of Infusions)	Results	Most Commonly Reported Adverse Events
Stefanczyk-Sapieha et al.[27] (2008)	1 M = 1 (50 years)	With hormone-refractory prostate cancer, metastatic to the bone, lymph nodes, and chest, admitted to a tertiary palliative care unit, also with severe treatment-resistant depression	Case report Patient chose to receive infusions (0.5 mg/kg) that were administered over 60 minutes (2 infusions)	Duration of follow-up: not mentioned • Rapid euphoric effect after first infusion that wore off after 72 hours, although not entirely • After second infusion, a limited euphoric effect compared to the first dose was observed and recurrence of depressive symptoms occurred within 24 hours • On the days of the ketamine infusions, the patient's pain scores were lower and less breakthrough analgesia was required	Only a single mild side effect—visual hallucinations during second infusion
Liebrenz et al.[28] (2009)	1 M = 1 (55 years)	With severe treatment-resistant depression, nicotine and alcohol co-dependence, and failure of multiple medication trials	Case report First infusion of 0.5 mg/kg over 50 minutes followed by clinical assessment of depression severity. Second infusion of same dose administered after complete fading of effects (2 infusions)	Duration of follow-up: 6 weeks • Rapid resolution of depressive symptoms after first infusion showing about a 60% decrease in HAM-D and BDI scores. Complete fading of antidepressant effects on day 35 • Similar rapid alleviation in symptoms after second infusion but also less pronounced and faster fading of the effects of the infusion	Dizziness, nausea, and dissociative symptoms that resolved 2 hours after infusions
Aan Het Rot et al.[11] (2010)	10 M = 5, F = 5 (mean ± SD: 51.4 ± 14.6 years)	With chronic or recurrent MDD, having failed ≥2 antidepressant trials in the current episode; participated in open-label, single-dose IV ketamine study; had 50% reduction in severity of symptoms for at least 24 hours; scored ≥32 on Clinician-Administered Inventory for Depressive Symptoms	Open-label study Day 1: 40 minutes of IV infusion in inpatient settings with continuous vital signs monitoring If ≥50% reduction in MADRS score on day 2, five additional infusions on days 3, 5, 8, 10, and 12 on outpatient basis (1-5 infusions)	Duration of follow-up: 45 days • 9 of 10 participants showed response within 24 hours of first infusion and maintained it for as long as they received additional infusions, for at least 6 days after the last one • 8 of 9 relapsed within a mean of 30 days from first infusion or 19 days after sixth infusion • Individually, 3 of 8 patients remained depression-free for more than 4 weeks, almost 7 weeks, and 3 months, respectively, after ketamine infusions	Abnormal sensations, weakness or fatigue, headache, "hearing or seeing things" All side effects were transient and resolved at completion of infusions

Table 1. (continued)

Salient Features of Studies Reviewed

Author (Year)	Patients, *N* (Age)	Participant(s)	Study Design/Methods/Dosing (Total Number of Infusions)	Results	Most Commonly Reported Adverse Events
Messer et al.[26] (2010)	2 M = 2 (45, 50 years)	With MDD without psychotic features per *DSM-IV* who had received multiple ECT treatments and had persistent symptoms of depression; HAM-D score ≥18	Case series 2 patients randomized to receive one of the following: • A series of 6 ketamine infusions (0.5 mg/kg) every other day • Ketamine infusions on days 1 and 7, and 4 saline infusions on every other day in the interim	Duration of follow-up: 42 days • Lower dose of ketamine produced the desired antidepressant effect and also allowed patients a quicker recovery than they had with ECT • Both participants had marked changes in depression but return of symptoms was observed on day 29 after the last treatment for first patient and on day 18 for second patient	No cognitive impairment, difficulties with memory, or problems with concentration. Mild "intoxicating" effect with talkativeness and decreased inhibition that dissipated within 2 hours of cessation
Messer and Haller[29] (2010)	1 F = 1 (46 years)	With MDD, hospitalized for course of ECT	Case report After first infusion, 3 additional infusions over 5 days, 3 series of 6 ketamine infusions given every day over next 16 weeks (22 infusions)	Duration of follow-up: >15 months • BDI score reduced from 22 to 6 after first infusion • Patient in remission for >15 months with maintenance infusions	No psychotic or dissociative symptoms, no tachyphylaxis or tolerance
Blier et al.[30] (2012)	1 (F = 1 (44 years)	Unipolar depression, failed ECT and multiple medication trials	Case report Infusions over 40 minutes given to single patient (41infusions)	Duration of follow-up: unclear (a few weeks) • 50% decrease in dysphoria and anxiety lasting only 36 hours, benefits lasting a few hours • Remains symptomatic with repeated infusions but was able to do chores at home instead of staying in bed	Metallic taste, mild derealization
Ghasemi et al.[16] (2013)	18 M = 8, F = 10 (Mean ± SD: Group A = 35.2 ± 13.6 years Group B = 40 ± 16.4 years)	With MDD per *DSM-IV*, currently in major depressive episode without psychotic features	Randomized, blinded study Group A: 3 ketamine infusions (0.5 mg/kg) every 48 hours Group B: 3 ECT sessions every 48 hours (3 infusions)	Duration of follow-up: 4 weeks or until relapse[a] • 90% patients met response criteria after first infusion and all continued maintained response throughout the 2-week period • Significant difference for HDRS scores throughout all 6 sessions • Significantly lower BDI and HDRS scores in patients who received ketamine versus ECT at first and second treatment and 72 hours after treatment • Less depression reduction after first ECT compared with ketamine group	Increase in systolic blood pressure and heart rate in 3 patients after second and third infusion of ketamine, which was temporary and not clinically significant

Table 1. (continued)

Salient Features of Studies Reviewed

Author (Year)	Patients, *N* (Age)	Participant(s)	Study Design/Methods/Dosing (Total Number of Infusions)	Results	Most Commonly Reported Adverse Events
Murrough et al.[20] (2013)	24 M = 15, F = 9 (Mean ± SD = 48.1 ± 13 years	With chronic or recurrent MDD per *DSM-IV;* score ≥32 on IDS-C; recruited from academic outpatient psychiatric clinic and failed at least two FDA-approved antidepressant medications in current episode	Open-label study Antidepressant washout of ≥2 weeks (or 4 weeks for fluoxetine) Phase I: infusions (0.5 mg/kg) to all participants (3 per week over a 12-day period Phase II: Outpatient follow-up (Up to 6 infusions)	Duration of follow-up: 83 days since last infusion • Overall response rate = 70.8% • Large significant mean decrease in MADRS score at 2 hours after first ketamine infusion; effect largely sustained for duration of infusion period. The largest difference seen between responders and nonresponders was for lassitude • Response at study end strongly predicted by response at hour 4 (94% sensitive, 71% specific). Conversely, lack of rapid response was a poor prognostic indicator for future infusions • Among responders, median time to relapse after the last ketamine infusion was 18 days. Four participants did not relapse through the entire 12-week study period	Strange or unreal sensations, blurred vision, drowsiness; one-third experienced elevated blood pressure and heart rate at least once; small but significant increase in psychotomimetic and dissociative symptoms
Rasmussen et al.[21] (2013)	10 M = 4, F = 6 (Mean ± SD = 47.2 ± 14.9 years)	With a major depressive episode as part of either MDD (recurrent or single episode) or bipolar II disorder; recruited from adult inpatient units or outpatient clinics	Open-label study Infusions (0.5 mg/kg) over 100 minutes (2 per week) in recovery room of ECT suite (Up to 4 infusions)	Duration of follow-up: 4 weeks • 8 of 10 patients completed and responded to the infusions, showing at least a 50% reduction in the MADRS scores at some point; remission defined as a score ≤9 • A total of 5 patients remitted, and of these patients, 1 required 1 infusion, 3 required 2 infusions, and 1 required 4 infusions	Headache, dizziness, vertigo
Shiroma et al.[22] (2013)	14 M = 14 (Mean ± SD = 52.1 ± 15.2 years)	With recurrent MDD without psychotic features per *DSM-IV*; HDRS score ≥14; failure to achieve remission from ≥2 antidepressant trials of different pharmacological classes; recruited by referrals from mental health and primary care clinics	Open-label study Infusions on alternate days over a 12-day period and weekly follow-up (6 infusions)	Duration of follow-up: 4 weeks or until relapse • 12 of 14 recruited patients completed the infusion schedule and 11 of those achieved response and 8 remitted, showing significant decrease in MADRS scores over infusion period • 5 of 11 patients maintained their response status throughout the 4 weeks of follow-up but 6 relapsed over a range of 7-28 days, the mean being 6 days	Transient and tolerant psychoactive and hemodynamic changes, mild increase in blood pressure and pulse

Table 1. (continued)

Salient Features of Studies Reviewed

Author (Year)	Patients, *N* (Age)	Participant(s)	Study Design/Methods/Dosing (Total Number of Infusions)	Results	Most Commonly Reported Adverse Events
Szymkowicz et al.[25] (2013)	3 Ages and genders not disclosed	With a current major depressive episode without psychotic features, who had in common a history of failing several antidepressants, augmentation regimens, and ECT treatments	Naturalistic observational study with no antidepressant washout Patient 1: 16 infusions (total dose, 21 mg) Patient 2: 34 infusions (total dose, >160 mg) Patient 3: Acute series of 7 ketamine infusions followed by maintenance regimen, for total of 32 infusions (total dose, 35 mg)	Duration of follow-up: 12 months • Patient 1: Resolution of depressive symptoms reported after third infusion, moderate relapse 8 months later and then remitted with an acute series of 3 more infusions • Patient 2: Response reported with 7 infusions; suicidal relapse after treatment termination, then another 7 infusions received with good effect but also experienced exacerbation of cognitive difficulties and was started on MAO inhibitor that allowed 5-month period free of ketamine. Subsequently hospitalized for a suicidal attempt at ninth month and infusions reinitiated followed by antidepressant maintenance after 12-month period • Patient 3: Hypomanic state ensued after the twelfth infusion, and a suicidal attempt via polydrug overdose was recorded at thirteenth. When infusions were resumed, improvement in functionality was recorded although depression had not abated. Significant improvement in depression noted at 27th infusion in the ninth month	Patient 2 experienced exacerbation of cognitive difficulties and insomnia
Diamond et al.[23] (2014)	28 M = 16, F = 12 (Mean ± SD = 47 ± 15 years)	With treatment-resistant bipolar or unipolar depression (current or past history of lack of response to two adequate antidepressant trials), recruited via secondary care referrals and self-referrals through advertisements in media and a study website	Open-label study Group A: 15 participants received infusions (0.5 mg/kg) once a week for 3 weeks Group B: 13 participants received infusions twice a week for 3 weeks in the ECT clinic (3-6 infusions)	Duration of follow-up: 26 weeks • 8% of the 15 and 62% of the 13 participants completed all the planned infusions, and a total of 8 participants did not do so mainly because of adverse effects or failure to benefit • Large average decrease in BDI scores from baseline noted; 61% of participants also showed reduction in suicidal ideation that persisted in responders to the 3-week mark but was not seen in nonresponders	Panic attack (1), vasovagal episode (1), worsening of suicidal ideation and mood symptoms (1) leading to drop-outs; transient perceptual distortions, detachment, anxiety, nausea, and confusion

Table 1. (continued)

Salient Features of Studies Reviewed

Author (Year)	Patients, *N* (Age)	Participant(s)	Study Design/Methods/Dosing (Total Number of Infusions)	Results	Most Commonly Reported Adverse Events
Lai et al.[17] (2014)	4 M = 2 (29, 62 years) F = 2 (45, 66 years)	With MDE ≥4 weeks; MADRS ≥20, failed at least one antidepressant trial	Double-blind, placebo-controlled crossover study Infusions (0.1-0.4 mg/kg) over 2-5 minutes 1 week apart and one randomly inserted placebo treatment (Up to 4 infusions)	Duration of follow-up: 7 days • 3 of 4 patients showed ≥50% decrease in MADRS score, 2 at a minimum 0.1 mg/kg and other 2 at 0.4 mg/kg, and all relapsed within 1 week	Tachycardia and hypertension with dosing of 0.4 mg/kg, resolved within 15 minutes of infusion; one patient became sedated after every infusion
Hassamal et al.[31] (2015)	1 F = 1 (65 years)	With unipolar depression, after having failed multiple antidepressant trials and becoming intolerant to the side effects of ECT	Case report (12 infusions [0.5 mg/kg])	Duration of follow-up: 18 months • Initially, patient experienced remission after augmentation with 6 infusions • With re-emergence of symptoms at 4 and 12 months, 3 additional infusions were administered over 1 week, which resulted in remission for the next 6 months	Mild perceptual experiences such as feeling light and untethered after first infusion, but none reported at subsequent infusions
Singh et al.[18] (2016)	67 M = 22, F = 45 (Mean ± SD = 43.9 ± 11 years)	Recurrent treatment-resistant MDD without psychotic features IDS-C Scale score ≥34	Multicenter placebo-controlled, double-blinded study Group A: Twice weekly dosing, Group B: Thrice weekly dosing 0.5 mg/kg for up to 4 weeks Patients discontinuing due to lack of efficacy had option to receive infusions at same frequency in open phase (8-12 infusions)	Duration of follow-up: 4-6 weeks • Significant improvement in mean MADRS score but greater decrease in twice-weekly compared to thrice-weekly groups • Proportion of responders and remitters higher in both groups compared with placebo group • Similar improvement in open-label phase • Antidepressant response/efficacy in both groups maintained over 15 days	Headache, anxiety, dissociation, nausea, and dizziness
Cusin et al.[24] (2016)	14 M = 3, F = 11 (Mean ± SD = 50 ± 7.78 years)	With MDD, HAM-D28 score ≥20, with history of three or more failed antidepressant trials, suicidal ideation >3 months (measured by C-SSRS), HAM-D28 suicide item ≥2	Open-label study 0.5 mg/kg for first 3 infusions then 0.75 mg/kg for final 3 infusions (6 infusions over 3 weeks [2/wk])	Duration of follow-up: 3 months • 12 of 14 participants completed all 6 infusions • Statistically significant decrease in HAM-D28 scores with medium and large effect sizes for the first and next 3 infusions • 1 of the 5 responders experienced a sustained response after the final infusions, whereas the other 4 responders relapsed by 2 weeks	Physical side effects: tiredness, headache, dizziness Dissociative side effects: derealization, depersonalization, amnesia

Table 1. (continued)

Salient Features of Studies Reviewed					
Author (Year)	Patients, *N* (Age)	Participant(s)	Study Design/Methods/Dosing (Total Number of Infusions)	Results	Most Commonly Reported Adverse Events
Loo et al.[19] (2016)	15 (IV = 4, IM = 5, SC = 6) M = 4, F = 11 (Mean ± SD = 48.5 ± 11 years	With diagnosis of MDD per *DSM-IV* and a depressive episode of ≥4 weeks; recruited through advertisement to general public and to health professionals	Placebo-controlled, multiple crossover, double-blind study Five increasing doses of 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg bolus doses (IV injected over 5 minutes) tested in ascending order given at least 1 week apart with one placebo-controlled treatment randomly inserted (2-6 injections)	Duration of follow-up: 6 months until relapse • Overall response/remission rates = 75% (IV), 60% (IM), 100% (SC), with mean time to relapse of 23.2 days • 12 of 15 participants met criteria for both response and remission at least once during the trial • Greater antidepressant response at higher dosage (ie, proportion of sample that met response/remission criteria increased as dose increased from 0 to 0.4 mg/kg) • Improvement in MADRS scores followed by attenuation as doses increased	Mild depersonalization, derealization, altered body and time perception that resolved within 40 minutes after injection at all doses and with all routes Transient increases in systolic and diastolic blood pressure and heart rate within 5-10 minutes after IV and 10-15 minutes after IM and SC injections

[a] *Antidepressant effects of ketamine remained 72 hours and 1 week after 3rd infusion.*

Abbreviations: BDI, Back Depression Inventory; C-SSRS, Columbia-Suicide Severity Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, *fourth edition; ECT, electroconvulsive therapy; F, female; FDA, US Food and Drug Administration; HAM-D28, 28-item Hamilton Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; IDS-C, Inventory for Depressive Symptomatology–Clinician; IM, intramuscular; IV, intravenous; M, male; MAO, monoamine oxidase; MDD, major depressive disorder; MDE, major depressive episode; MdDRS, Montgomery-Åsberg Depression Rating Scale; SC, subcutaneous; SD, standard deviation.*

when compared with those receiving electroconvulsive therapy.[15] Two case reports noted, however, that subsequent infusions were not as efficacious or long lasting[26,27] as the first one. Murrough et al.[19] additionally reported that response at the end of their study was also seen to be predicted by response to first infusion at the 4-hour point of recording depression scale scores. Almost all studies observed participants over an extended period of time, ranging from 7 days to 18 months, to observe how long the antidepressant effect could be maintained. Most studies showed that participants relapsed even after multiple infusions, albeit with variable times to relapse.

All of the studies covered in this review except three[16,18,23] administered ketamine via intravenous infusions at uniform sub-anesthetic doses of 0.5 mg/kg over a period of 40 to 100 minutes with the notable exception of one placebo-controlled, multiple crossover, double-blind study[18] that administered five doses of gradually increasing ketamine as bolus via intravenous, intramuscular, and subcutaneous routes.

The most commonly reported adverse events in all the studies included mild dissociative symptoms like depersonalization, derealization, anxiety, panic attacks, and transient elevations in blood pressure and heart rate, all of which resolved almost instantaneously after cessation of infusions. Cognitive side effects were reported with repeated infusions amounting to administration of >160 mg of ketamine over 34 infusions.[24]

DISCUSSION

The studies included in this review show a few common themes, the most important of which include long-term follow-up to observe the supposed lasting effects of multiple infusions of ketamine. Importantly, these studies repeatedly demonstrated the safety of intravenous ketamine when administered in sub-anesthetic doses in controlled

settings with ongoing monitoring. With the marked and rapid alleviation of depressive symptoms, significant improvement in the functionality of some participants was also noted, and a certain number remained in remission. Serial infusions in most of these studies were conducted in outpatient or similar settings, offering a more clinically practical and applicable dosing strategy that is easy to replicate and cost-effective for administration of ketamine to patients. The case reports even went a step further to describe cases of people with serious comorbidities or concomitant substance use issues, steering this research on ketamine in the direction of applicability in clinical practice.

One study administered ketamine after washout of antidepressant regimens, however,[19] and most others continued or altered the patients' medications while giving ketamine infusions. This brings up the prospect of ketamine to be used as an adjunct rather than as the primary antidepressant. However, discontinuation of antidepressants could potentially result in clinical decompensation, which in turn could bring up ethical challenges of increasing the risk of suicidality.

The major limitations were the small sample sizes and variability in the inclusion criteria for participants, primary outcome measures, scales of measurement, follow-up intervals, and overall methodological rigor.

Although this review highlights the promise that ketamine shows as a novel antidepressant, especially when infused serially at regular intervals, it also identifies the pressing need for additional research to determine appropriate dosage regimens for effective maintenance.

Present and future research will elucidate the logistics of dosing and administration, but the variability in the patient population in case reports and trials reviewed in this article raises questions about defining the particular patient subset that should be offered ketamine infusions and is most likely to benefit from them. It calls for certain factors like age, severity of depression, presence of comorbidities, willingness and ability to follow up regularly, and the plausibility of individual variabilities in response and relapses to be taken into consideration.

CONCLUSION

This review illustrates the effectiveness, favorable safety profile, and practical feasibility of the use of repeated infusions of ketamine at sub-anesthetic doses in patients with treatment-resistant depression. Further studies are needed to establish protocols for appropriate dosing strategies of ketamine by conducting robust trials with a fairly large sample sizes to allow for generalizability of findings.

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