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Research Article

REVOLUTIONIZING DEPRESSION TREATMENT: A PARADIGM SHIFT OF KETAMINE THERAPY – A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: Primary Objective : (1) The objectives of the study are as follows: assessment of the effectiveness of ketamine-based treatment in known patients of various subtypes of depression and (2) assessment of time of onset and duration along with routes of administration and safety of ketamine therapy. Secondary Objective : The objectives of the study are as follows: (1) evaluate changes in secondary outcomes in scales of depression and anxiety reporting improvement in overall mood and (2) emphasizing the need for extensive research and patient-based data collection for the future.

Methods: The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and the literature analysis included fourteen primary clinical studies including randomized controlled trials (RCTs), using electronic databases such as Google Scholar, MEDLINE, or PubMed for our search for relevant literature. RCTs and open-label case reports of adult patients with bipolar illness, major depressive disorder, or postpartum depression receiving ketamine through intravenous infusions or intranasal esketamine were included in the inclusion criteria. Potential review bias and data extraction were done independently by many reviewers with any discrepancies discussed by the team.

Results: MADRS was used as first-order outcomes and other depression and anxiety scales as second-order outcomes. Multiple studies revealed that ketamine therapy reduced the MADRS score, and this reduction occurred 40 min after the infusion and lasted up to 1 week. Moreover, the use of ketamine has proved helpful in addressing anxiety disorders and self-assessed depression, and some studies have demonstrated long-lasting effects of the drug. The safety findings indicated that ketamine was generally safe, as many of the side effects were reported on the same day of administration.

Discussion: This shows that ketamine therapy, especially for patients with treatment-resistant depression (TRD), can be a fast and effective biological treatment for depressive disorders. It could complement or even become a new treatment option due to its immediate onset and prolonged duration of action. Further studies should be conducted to determine the optimal administration intervals, side effects including cognitive impairment, and the frequency of relapses.

Conclusion: Ketamine has emerged as a new class of intervention for the management of depression due to its rapid and sustained antidepressant efficacy with lower risk of side effects. Although it is effective on its own for treating various conditions, there is a need for further research to determine how best to apply it clinically and to establish its side effects in the long run. However, given that ketamine holds the promise of filling the gaps for TRD patients, the substance plays a crucial role in changing the landscape of psychopharmacological management of depression.

Keywords: Ketamine, Treatment-resistant depression, Intranasal ketamine, Depression management.

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INTRODUCTION

Depression is a common mental health disorder that is estimated to affect about 264 million people worldwide [1]. It is associated with considerable human and social costs and is a common cause of disability in the world [2]. 17. 3 million persons, or 7% of the population, are affected by such disabilities. It was estimated that 1% of the adult population in the US will have experienced at least one major depressive episode in 2017 [3].

These days, managing depression involves a variety of therapeutic modalities that fall into three primary categories: psychosocial therapy, electroconvulsive therapy (ECT), and medications. Other therapies such as light therapy, transcranial direct current stimulation, vagal nerve stimulation, deep brain stimulation, repetitive transcranial magnetic stimulation, or sleep deprivation are employed in resistant or some rare circumstances. Furthermore, benzodiazepines can also be used in combination with other therapies, primarily as first-line treatments [4]. While there are several bipolar depression therapies currently in use, none of these therapies works to lessen depressive symptoms such as suicidal ideation in a few hours or days. Despite this, about one-third of patients do not respond to these drugs and exhibit insufficient improvement after two or more attempts with antidepressants [5,6]. When someone does respond in any way, the effects generally emerge after 2–4 weeks, and a significant percentage of patients will relapse over time.

Treatment-resistant depression (TRD) is described as a depressive episode that has not been remitted adequately with the use of at least two different antidepressants of adequate dose and duration [7]. Several approaches are applied for the management of TRD, such as ECT, psychotherapy, and switching between the therapies of different classes of antidepressants. Except for ECT, there is no treatment currently available that provides meaningful or rapid improvement to patients with severe depression. Recently, new treatments such as ketamine and other anti-inflammatory chemicals such as psilocybin have come into the picture. The efficacy of ketamine as an antidepressant and anti-suicidal agent in unipolar and bipolar depression has been confirmed in numerous studies, with up to 60–70% response rates in patients with TRD [8].

Therefore, we conducted a comprehensive search of ketamine trials and studies involving patients with severe depressive disorders, including

postpartum depression (PPD), bipolar disorder (BPD), and TRD, to compare the different pharmacokinetic effects, metabolites, and routes of administration of ketamine for its antidepressant effects (efficacy and safety) that may be used without adjunct oral antidepressant therapy and to determine the possibilities for replacing current treatment methods.

METHODS

Study selection

The current study is a systematic review of 14 primary clinical trials (Fig. 1) inclusive of randomized control trials done in adherence to the preferred reporting items for systematic reviews and meta-analysis checklist [9].

The titles and abstracts then went through a process of independent review by three blinded and unrelated reviewers according to the following criteria of inclusion. Any title that met these criteria or, if there was any doubt, was kept for the full article title, and the reviewers removed titles based on these criteria separately and recorded the reasons why. To find a resolution to these disputes, a third reviewer was enlisted.

Search strategy

Data were therefore obtained through the use of sources, including Google Scholar, PubMed, and the medical database known as MEDLINE. With the use of Medical Subject Heading terms and keywords, we investigated the PubMed database: intranasal ketamine treatment, ketamine, TRD, bipolar, depression, and PPD. A literature search was extensively and systematically performed including only full-text articles in the following databases also. To obtain further related manuscripts, the citations in the identified peer-reviewed articles and reviews were retrieved.

Inclusion and exclusion criteria

Inclusion criteria

a. Phase three clinical trials; additional research after trial conclusion; cohort studies; and narrative and systematic review in the English language only
b. Patients with major depressive disorder (MDD), between the ages of 18 and 64 years using both Montgomery–Åsberg Depression Rating Scale and DSM-V
c. Intervention: use of ketamine as intravenous infusions and intranasal esketamine
d. A pregnancy being free of complications whereby the woman is between the age of 18 and 35 years without any other chronic diseases that worsen an existing pregnancy
e. In the study, participants were 18–65 years of age with BPD-I or II, without psychotic traits, and currently meeting the DSM-IV criteria for a major depressive episode with duration of at least 4 weeks confirmed by the structured clinical interview for DSM-IV Axis I Disorders (SCID-P). At baseline and the initiation of each ketamine/placebo infusion cycle, participants had MADRS scores ≥20.

Exclusion criteria included DSM-V with other current psychotic disorders; any other current DSM-V Axis I or II disorder within the past 6 months; BPD, obsessive-compulsive disorder, or personality disorder. Other reasons for exclusion conformed to case reports and series, letters to the editor, articles published in languages other than English, animal studies, Phase 1 and 2 clinical trials, gray literature, and any reviewed studies in which adjunct medications were used.

Data extraction

Investigators used the PICOS framework, with input from two independent reviewers who extracted information on studies. The collected data were made more valid and consistent in an orderly manner through tape consideration. Before determining the final extraction criteria, the reviewers created and evaluated the standardized tables for the degree of ambiguity. Details such as study design, participant descriptors (mean age), nature of the intervention and control methods (dosage form and method of delivery), follow-up criteria including primary and secondary outcomes, and results in terms of scores on the assessment scales that were used formed part of the data that were abstracted.

Risk of bias (RoB) in individual studies

Employing the tools designed for RoB assessment, we evaluated the possible bias in each trial based on the Cochrane RoB tool that was developed for randomized controlled trials. Bias as a dimension of measurement, which is evaluated by this instrument, includes selection bias, performance bias, detection bias, attrition bias, and reporting bias. According to the matched-pair design, two different reviewers performed the RoB assessments, and whenever there was disagreement, the reviewers discussed with the third reviewer until they reached a consensus.

Data collection, analysis, and synthesis

Given that the majority of the included studies used clinician-rated outcome measures alone to measure the efficacy of ketamine, these measures rather than the self-report measures were a primary source of data in clinical trials. A report of every study included in the systematic review is done by the use of narrative and the result is presented in the form of a table. While studying the results, attention was paid to the number of infusions, their type, and time elapsed after the mentioned procedure. Other examined outcomes included clinical response and remission rates, time to relapse, and infusion of the study medication.

RESULTS

The main outcome measure was the score acquired using the MADRS. The results of the 17-item Hamilton Depression Rating Scale, the Visual Analog Scale, the Clinician-administered Dissociative States Scale, the Brief Psychiatric Rating Scale, the Hamilton Anxiety Rating Scale, the beck depression inventory, and the Young Mania Rating Scale were among the secondary outcome.

DISCUSSION

In this systematic review, the protocol performance of different forms of ketamine (and especially intranasal) for unipolar and bipolar depression has been reviewed. While searching for the data for this review, many articles were found regarding intranasal esketamine and intravenous racemic ketamine, but the comparisons between them at the level of subgroups were not significant. It needs to be understood here that while intravenous racemic ketamine is yielding better results having more long-term data and more subjects, the intranasal esketamine has received its FDA approval, indicating requirement of more intricate research for the same. The tabulated data for all experiments shown above clearly depicts the significant drug-by-time point interaction in MADRS scores for the studies 10, 11, 12, 14, 17, 19, 21, and 22. The study [12] also reported an effective use of intranasal ketamine in the subject of MDD patients where it produced fast relief on depressive symptoms with little side effects. Several studies, including 10, 21, 22, and 23, conducted using optimized study designs with TRD patients, noted the rapid onset of antidepressant response after a single ketamine infusion.

Furthermore, studies such as 11, 14, 17, and 19 have pointed out that ketamine works effectively for the treatment of acute suicidal ideation or suicidal behavior with rapid antidepressant and antisuicidal effects compared with control treatment, especially for suicidal patients who need specific treatment, especially suicidal patients who had one such episode at least once in the previous 12 months and are critically unwell and vulnerable patients. Furthermore, since the findings of the study [18] indicate that ketamine administration for candidates for cesarean section can be beneficial for better post-operative conditions, it can be suggested that a single dose of ketamine should be given to postpartum women after their cesarean section to prevent PPD.

S. No.	Study	Scale	Mean age	Dose (ketamine)	Primary outcome	Secondary outcome
1.	Murrough *et al*. 2013 [10]	MADRS	46.9; 42.7	0.5 mg/kg single infusion	With a Cohen's d of 0.81, the mean MADRS score for the ketamine group was 7.95 points (with a 95% confidence interval [CI] of 3.20–12.71) lower than that of the midazolam group. The findings of the analysis indicated that time and treatment had first-order effects on the Children's learning (time F=7. 62, df=1, 202, p≤0. In this case, the current analysis revealed that the ketamine group had significantly lower MADRS ratings (mean, 16.93; 95% CI, 14.03–19.82) than the midazolam group when scores were aggregated across time points.	On the Quick Inventory of Depressive Symptomatology, the ketamine group had a mean score 3.40 points lower than the midazolam group (p≤0.02 95% CI, 0.78–6.01), or 0.63 Cohen's d. Time had a significant impact (p≤0.006, df=1, 202, F=8.04), while therapy had a significant impact (p≤0.02, df=1, 202, F=6.61). Day 7 respondent status did not vary based on place (exact p=0.11). Neither the response rate nor the percentage of patients with CGI improvement scores of two or lower significantly differed across groups.
2.	Zarate *et al*. 2012 [11]	MADRS HDRS BDI VAS HAM-A BPRS CADSS YMRS	46.7	0.5 mg/kg infusion	Drug-by-time interaction was shown to be significant in MADRS (F10,187=5.94, p<0.001). The effects were moderate to large on Day 1 (d=0.70, 95% CI=0.42–0.98) and Day 2 (d=0.65, 95% CI=0.37–0.93) and the largest effect size (d=0.89, 95% CI=0.61–1.16) through 230 min (d=0.85, 95% CI=0.57–1.14). At baseline and on Days 7, 10, or 14, there was no discernible difference between the medicines (p=0.83, p=0.34, p=0.93, and p=0.19, respectively).	HDRS: p=0.001, F10,197=3.08 (significant from 40 min to Day 2). BDI: p=0.001, F10,140=3.08 VAS-Depression: p<0.001 (significant from 40 min to Day 14) and F10,168=4.02 Significant drug-by-time interactions between HAM-A and VAS-Anxiety start to indicate a decline at the 40-min mark. BPRS or YMRS: No noteworthy medication interactions or effects CADSS: noteworthy interplay exhibiting elevated values solely during the 40-min interval
3.	Lapidus *et al*. 2014 [12]	MADRS QIDS-SR BPRS+ CADSS	48.0±12.8	50 mg racemic ketamine hydrochloride	The MADRS score difference between ketamine and placebo was assessed to be 7.6±3.7 (95% CI: 3.9–11.3). Throughout the entire 7-day follow-up period, there was an improvement above the placebo (p<0.001 F1,18=28.10). There was also a significant time effect (F5,95=10.65, p<0.001). Apart from the main 24-h result, there were significant differences between ketamine and placebo at 40 min (p<0.001), 240 min (p=0.026), and 48 h (p=0.048). No discernible difference was seen after 72 h or 7 days.	As determined by the QIDS-SR at 24 h, ketamine was linked to a significant improvement in self-reports of depression [t17=3.30, p=0.004; mean difference of 3.0±2.4 (95% CI: 1.1–4.9)]. According to HAM-A scores, ketamine was more effective than a placebo at reducing anxiety symptoms 24 h later [t17=3.06, p=0.007; mean benefit of 4.5±3.2 (95% CI: 1.4–7.6)]. The CADSS and BPRS do not significantly correlate (p<0.05).
4.	Altinay *et al*. 2019 [13]	MADRS HAMD-17 CSSRS LIFE-RIFT YMRS CGI-I	38.5±18.5	0.5 mg/kg over 40 min infusion	HAMD, MADRS (p=0.72, SE=3.28, b=1.22): no significant difference	MOCA: not significant (b=0.98, SE=1.12, p=0.40). COWAT: not significant (p=0.34, SE=3.71, b=3.72).
5.	Fu *et al*. 2020 [14]	MADRS CGI-SS-r MOAA	40.8	Esketamine 84 mg (28 mg of esketamine base)	MADRS: At 24 h post-first dose, the treatment difference was 9.8% and 4 h post-doses, on day 25 was 16.1%. The total MADRS score at 24 h for	CGI-SS-r: (2-sided p=0.107). Insignificant MOAA/S: 11.5% had a score ≤3

S. No.	Study	Scale	Mean age	Dose (ketamine)	Primary outcome	Secondary outcome
					individuals who had attempted suicide before was (−5.53), and (−6.53) for those who had more severe depression symptoms.	
6.	Shiroma *et al*. 2020 [15]	MADRS BAI CGI CEQ Kaplan–Meier estimate, Long-rank test	54.4, 51.2	0.5 mg/kg	At T+24 after the conclusion of treatment (six infusions), there was no discernible difference between a single (MADRS mean change=21.0, 95% CI=17.2-24.8) and six ketamine treatments (MADRS mean change=17.2, 95% CI=13.2–21.2) (F1,52=2.41, p=0.13, ηp2=0.044). Comparing subjects receiving ketamine to those receiving midazolam, the mean MADRS score among the former was significantly lower by 8.07 (95% CI, 1.67–14.46) before infusion 5 (F1,95.7=6.28, p=0.014), 8.29 (95% CI, 1.87–14.70) at T+24 after infusion 5 (F1,96.7=6.58, p=0.012), and 6.40 (95% CI, 0.01–12.79) before infusion 6 (F1,95.7=3.94, p=0.050). Response and remission rates: After six infusions, there was no significant difference in the response rates (X21df=0.73, p=0.39), and there was also no significant difference in the remission rates (X21df=0.56, p=0.46). At T+24 following infusion 4, there was a significant difference in remission rates (six ketamine=54.2% against midazolam=17.9%; X21df=7.53, p=0.006), as well as in response rates (six ketamine=76% vs. midazolam=39.3%; X21df=7.25, p=0.007) at T+24 following infusion 5.	After 5 infusions (F4,182.28=1.74, p=0.14), and 6 (F5,234.50=1.53, p=0.18), BAI was minimal. Self-rated pain: p=0.27, F5,238.34=1.29, indicates no discernible difference. Midazolam plus single ketamine (baseline mean=5.14, 95% CI=4.75–5.53 to post-infusion mean=2.63, 95% CI=2.14–3.12) and six ketamine (baseline mean=5.32, 95% CI=4.90–5.74 to post-infusion mean=2.01, 95% CI=1.55–2.48) (t(48)=10.63, p<0.001) were found to have significant CGIs for subjects in both groups. After treatment ended, at T+24, there was no significant difference between the groups (F1,54.83=3.59, p=0.06). CEQ Score: There was no discernible difference between the groups in terms of expectancy (F1,52=0.03, p=0.86) or credibility (F1,52=0.19, p=0.66). Durability: For the midazolam plus single ketamine group, the Kaplan–Meier estimates of the 6-month recurrence rates following response were 75% (95% CI=54.2–95.8%) and 68.4% (95% CI=45.4–91.4%), respectively. A non-statistically significant difference in the relapse rates over time was found by the long-rank test (X21df=1.61; p=0.21).
7.	Zou *et al*. 2021 [16]	HAMD Mauchly's MMSE	65.76±3.98 65.62±3.92	0.3 mg/kg	Antidepressant effect: There was no confirmation of the hypothesis on Mauchly's test of sphericity (p=0.001). HAMD scores after the 4th and 6th sessions of ECT were lower in group KP than those in group P. Nevertheless, following the first sessions and at the end of the course, no discernible change was discovered.	Cognitive Impairment: On Mauchly's test of sphericity, the hypothesis was not confirmed (p=0.001). Tests of within-subjects effects revealed no significant interaction between treatment times and the anesthetic regimen (F=1.043, p=0.391). MMSE: A score <24 denoting cognitive function impairments was reported in 7 patients in group KP and 18 in group P.
8.	Ionescu *et al*. 2021 [17]	MADRS CGI-SS-r CADSS MOAA	41.4, 40.2	Esketamine 84 mg (28 mg of esketamine base)	Efficacy Results: Both the esketamine plus standard-of-care group (mean [SD]: −15.7 [11.56]) and the placebo plus standard-of-care group (−12.4 [10.43]) saw a decrease in MADRS from baseline to 24 h after the first	CADSS: Following the initial dosage, the group receiving esketamine plus standard care scored 15.9 overall, while the group receiving a placebo plus standard care scored 1.9. Compared to patients in the placebo plus standard-of-care

S. No.	Study	Scale	Mean age	Dose (ketamine)	Primary outcome	Secondary outcome
					dose (day 2). Esketamine significantly reduced depression symptoms (p=0.006 95% CI: −6.60, −1.11; LS mean difference [SE]: −3.9). The treatment groups clearly differed from one another by 4 h (95% CI: −6.38; −1.94 LS mean difference −4.2). CGI-SS-r: Not statistically significant (2-sided p=0.379), but a rapid reduction (median change from baseline at 24 h after the first dose: −1.0 point).	group (3/113 [2.7%]), a greater number of patients in the esketamine plus standard-of-care group (21/114 [18.4%]) had a MOAA/S score ≤3.
9.	Alipoor *et al.* 2021 [18]	APGAR EPDS	39.6, 40.5	Esketamine 84 mg (28 mg of esketamine base)	The Nesdonal group's mean APGAR score was 7.30±0.63 and the Ketamine-Nesdonal group's was 7.82±0.68, with a statistically significant difference (p>0.001) between the two groups.	EPDS: The mean score in the Ketamine-Nesdonal group decreased after 4 weeks of a cesarean section, compared to the score at 2 weeks, which was lower than the score recorded before the cesarean section (p>0.001).
10.	Canuso *et al.* 2021 [19]	MADRS CGI-SS-r	39.6, 40.5	Esketamine 84 mg (28 mg of esketamine base)	Efficacy Results : MADRS: The total score dropped in both groups 24 h after the first dosage, with the mean [SD] in the esketamine plus standard-of-care group being −16.1 [11.73] and in the placebo plus standard-of-care group being −12.6 [10.56]. Esketamine resulted in a reduction of depression symptoms.LS mean difference [SE], −3.8 [0.98]; 95% confidence interval [CI], −5.75−−1.89	CGI-SS-r: After 4 h of the first dose, the patients in the esketamine plus standard-of-care group had resolved their suicidality by 33.2%, while the patients in the placebo plus standard-of-care group had resolved their suicidality by 20.0%. After 24 h, the patient's levels of resolution improved to 34.5% and 32.9%, respectively. As of right now, the difference in mean (95% CI) between treatment groups at 4 h and 24 h was 1.6% and 13.2%, respectively. Safety Results: The days of intranasal dosage were when the majority of incidents happened. They were noted at 89.9% in the group receiving esketamine plus standard care, and 68.9% in the group receiving a placebo plus standard care. In the esketamine plus standard-of-care group, up to 94.4% of cases cleared on the same day, compared to 85.2% in the placebo plus standard-of-care group.
11.	Han *et al.* 2022 [20]	EPDS VAS RSS	31.85±4.16 31.64±3.93	S-ketamine 0.5 mg/kg	The rate of depression was 24.2 at 3 days which significantly decreased to 17.6 in the S group at 14 days after cesarean section. (p<0.05 as compared to the C group)	EPDS scores were almost the same before the delivery. A significant change was seen on Day 3 postpartum (7.65±3.14 vs. 6.00±2.47, p<0.001) At 4 hourly difference, after a cesarean section VAS scores were significantly lower in the S group. Similar to EPDS, RSS scores did not differ significantly between the groups until 24 h after delivery.

S. No.	Study	Scale	Mean age	Dose (ketamine)	Primary outcome	Secondary outcome
12.	Jones *et al*. 2022 [21]	MADRS SDS PHQ-9	46.1, 70.0	28 mg 56 mg 84 mg	The mean MADRS change (SD) was −20.3 (13.19) versus −15.8 (14.67) for the esketamine/antidepressant and antidepressant/placebo groups at day 28. Transform1/Transform-2 recorded a decreased response rate with esketamine/ antidepressant in the perimenopausal women as compared to premenopausal and postmenopausal women in a cohort study. In Transform-3, the remission rate was higher in older women than in males of the same age.	SDS and PHQ-9 analysis revealed no significant (p>0.20) sex impact or treatment-by interaction. Younger women reported a higher number of incidences of vertigo and dizziness as compared to younger men. On the other hand, the trend reversed in older patients.
13.	Ochs-Ross *et al*. 2022 [22]	MADRS GAD-7 PHQ-9 SDS	47.2, 69.7	28 mg [≥65 years only], 56 mg, or 84 mg	MADRS: −18.0 (7.19) −19.9 (7.03), respectively, in both age groups showing an overall reduction. However, when examined on day 28 of the induction phase (p=0.492, df=701, t=0.69), as well as day 28 of the maintenance phase (p=0.265, df=3470, t=−1.12,), there was no corresponding age difference with this reduction. The direct-entry patients (both age groups) showed improvement in their anxiety symptoms as measured by mean reductions in GAD-7 total scores during both the induction and maintenance phases (LS mean difference [95% CI]: 0.2 [−0.90; 1.33] and −0.4 [−1.54; 0.74]), in which order.	Improvements in both younger and older patients were seen on the SDS total score as mean reductions during the induction phase as well as the maintenance phase. The LS mean difference (with a 95% confidence interval) for the age groups is 0.4 [−0.64; 1.39] and −0.6 [−1.51; 0.39] correspondingly. Improvements in both younger and older patients were seen on the SDS total score as mean reductions during the induction phase as well as the maintenance. Phase (LS mean difference between age groups: −1.5 [−3.49; 0.47] and −0.4 [−2.14; 1.35]) at 95% confidence intervals.
14.	Niciu *et al*. 2014 [23]	MADRS HDRS HAM-A CADSS	45.4;48.5	0.5 mg/kg infusion	There was no significant interaction with the drug (MADRS: p=0.51; HDRS: p=0.29) or drug by the time [MADRS: p=0.83; HDRS: p=0.62], although the anxiety group did have a direct influence (p=0.04) and HDRS (p=0.04).	No evident difference was noted with the HAM-A or CADSS.

HDRS: Hamilton depression rating scale, VAS: Visual Analog Scale, CADSS: Clinician-administered Dissociative States Scale, BPRS: Brief Psychiatric Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, BDI: Beck depression inventory, YMRS: Young Mania Rating Scale, SDS: Sheehan Disability Scale, GAD-7: Generalized anxiety disorder 7-item, LS: Least squares, QIDS-SR: Quick inventory of depressive symptomatology-self report, CGI-SS-r: Clinical global impression-severity of suicidality-revised, BAI: Beck anxiety inventory, CEQ: Credibility and expectancy questionnaire, MMSE: Mini-mental state examination, EPDS: Edinburgh Postnatal Depression Scale, RSS: Ramsay Sedation Scale, and PHQ-9: Patient health questionnaire 9-item

Ketamine is a readily available inexpensive anesthetic that is an N-methyl-D-aspartate (NMDA) receptor antagonist. Due to experiments carried out on racemic substances and their enantiomers, S-ketamine (esketamine) and R-ketamine (arketamine), the FDA has at last approved the use of intranasal (IN) esketamine [24]. In the past 10 years, consistently many clinical, preclinical, and postmortem studies have identified the glutamatergic system as the target system for the development of the next generation of antidepressants. This is particularly noteworthy when it comes to the NMDA receptor complex [25]. Ketamine being a dissociative anesthetic [26] elicits certain psychomimetic effects that have been associated with the antidepressant properties. Several other processes have been described about the action of ketamine for the development of anti-depressive effects such as norepinephrine reuptake inhibition [27] and possible mu opioid receptor activation which can be of therapeutic use in the treatment of mood or anxiety disorders.

Body mass index (BMI) is another such aspect to consider, since in some studies, a higher BMI and an obese weight category are reflected in a greater increase in the immediate outcome achieved after receiving a single dosage of IV ketamine [28]. Several theories have been put forward to try and explain why depression is associated with obesity and it may be these factors that confound the preferential improvement in patients with a higher BMI when administered with ketamine. A more suitable hypothesis is the dysregulation of adipokine which is observed in obese patients with MDD and consequently affects ketamine as well as other antidepressants' responses [29].

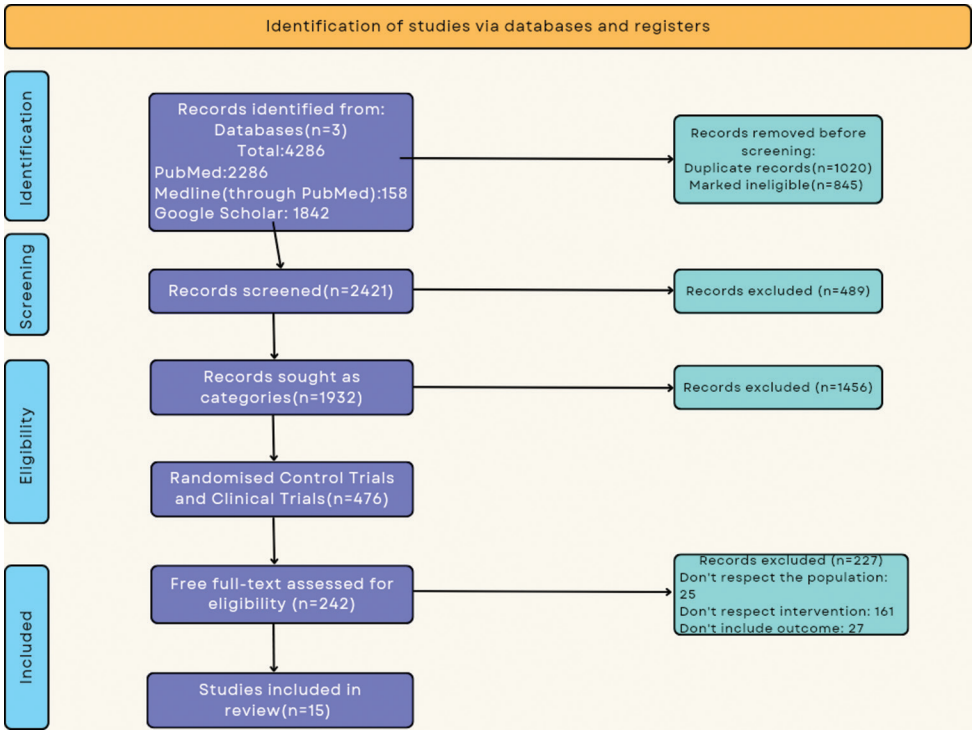

Fig. 1: PRISMA flowchart of study selection

Pretreatment activity in the pregenual anterior cingulate cortex (pgACC) has also been linked to the antidepressant response to ketamine injection in TRD patients [30]. This is consistent with earlier research that found that pgACC had higher pretreatment activity in selecting responders to pharmaceutical antidepressant therapies [31]. Studies (10, 21, 22, and 23) included in this review have clearly shown improvement in patients of TRD after a single infusion of ketamine.

Regarding tolerability, there appears to be no discernible gender difference in the frequency of adverse effects (AEs) recorded by ketamine prescribers; nevertheless, women tend to report greater headaches and nausea. A study that was part of this evaluation [23] also noted that TRD patients in groups based on their gender responded to ketamine similarly. Analysis shows that there are no appreciable differences in treatment response between men and women.

Xu *et al*. in their systematic review [32] reported a lower efficacy about lower doses of IV ketamine in a single administration of very low doses (e.g. 0.1 or 0.3 mg/kg IV). Moreover, the current cost is beyond average expenses as no insurance covers it. A more convenient option, as for now, is oral ketamine which is also widely available and also reports lower incidences of abuse [33].

ECT being a preferred mode of treatment for TRD has its own spectrum of disadvantages. One such is that it causes the patient to become aware of their loss of cognition. Cognitive assessment could employ the degree and extent to which learning and memory have been attained [34]. ECT affects glutamate receptors and disrupts the hippocampal plasticity that normally creates and retrieves memory; thus, memory loss has been accounted for by ECT [16]. It is argued that ketamine may potentially be used to fight these effects. Here, controversy arises from the fact that ketamine has been identified to prolong seizures during the earlier stages of treatment while other authors claim that it can accelerate the onset of ECT effects in addition to protecting against ECT-induced deficits in cognitive function [16]. A similar viewpoint has been put forward in an article that is incorporated into this review [16]. Low-dose ketamine did not enhance the outcomes of ECT but made the length of seizure in early ECT phases longer, which aids in setting the early course of ECT, and shields against detrimental cognitive effects. This finding however should be taken as a caution to the regular use of ketamine in low doses as an adjunctive to ECT since it normally has the theoretical capability to prolong seizure duration.

However, as the research [13] evidenced an intra-studies difference in early remission rates, it was also revealed that the use of ketamine along with ECT could lead to quicker recovery of the symptoms. The study recruited a comparatively small number of subjects, which would require further research to determine whether ECT + ketamine is more precise to induce early remission than the existing regular formulation of ECT + midazolam. No alteration in the hemodynamic variables of a patient undergoing ECT is observed when ketamine is administered in low doses. Hence, a more profound investigation and discussion are necessary in considering the impact of ketamine on depression in a patient who receives ECT, or for now, the reduced ketamine dose may be used possibly in some health-care facilities.

In most of the clinical trials underlying this analysis, patients with two or more severe medical/psychiatric conditions, a history of substance abuse, and/or MDD patients meeting the criteria for suicide risk were excluded. Moreover, there were constraints concerning the number of patients from non-white backgrounds that could be incorporated into the study. This has limited the generality of the results as the specifics of the situations under study have been made clear. In this regard, the same is crucial to note that in many studies, AEs such as drowsiness and dissociation stemming from esketamine could lead to unblinding. Furthermore, three *post hoc* studies were included in this review, thus, this type of study might be inherently biased. In addition, as indicated in the study, trials running for esketamine were not compiled due to a lack of collecting gray literature which could have yielded further conclusions.

It remains a fact that every drug has its set of side effects, and it would be remiss not to consider the most utilized intranasal (S)-ketamine, some of which include dizziness, dissociation, dysgeusia, vertigo, and nausea which were reported in several studies. These side effects can be mild to moderate depending on patient tolerance levels. The FDA adverse event reporting system has reported some serious side effects, which are important to distinguish because they require the researchers of a

controlled double-blinded study to investigate further [35], where some participants experienced syncope, headache, dissociation syndrome, and even ectopic pregnancy. Additional caution on its dependence and abuse characteristics ultimately places a constraint on its sale for commercial purposes in the market.

CONCLUSION

Using the information described in this review, it is agreed that ketamine exhibits an impressive response in the group that received it at different follow-ups after the first dose was administered. Analyzing the data that are presently available, it is safe to assume that ketamine has a potent antidepressant effect that could be used for the treatment of various groups of patients suffering from depression. However, regarding the long-term effects of the drug, the patients should be objectively assessed before definitive conclusions are made. Hence, there is evidence of the capacity of ketamine to be used as a therapeutic remedy for depression and will, therefore require further studies and consideration to know whether or not it will be suitable and effective in the future.

FUTURE DIRECTIONS

To investigate ketamine's antidepressant effects beyond a single injection and evaluate its long-term safety profile, more research is warranted. Studies that are especially designed to determine biomarkers of therapy response, identify relapse prevention strategies, and optimize dose are also required. Acquiring this vital information will help reduce any possible negative effects of ketamine medication while also optimizing the advantages for patients.

AUTHORS CONTRIBUTION

Yuvraj Kaushal, Pranav Goyal: Data curation, Conceptualization, Writing – original draft; Arshiya Sehgal: Writing – review and editing, Supervision, Resources, Project Administration; all authors commented on subsequent revisions and provided appropriate references.

CONFLICTS OF INTEREST

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