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REVIEW ARTICLE

Comparative antidepressant effects and safety of intravenous racemic ketamine, psilocybin and theta burst stimulation for major depressive disorder: A systematic review and network meta-analyses of randomized controlled trials

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Abstract

The individual efficacy and safety of intravenous racemic (IV) ketamine, psilocybin, and theta burst stimulation (TBS) for major depressive disorder have been demonstrated through meta-analyses of randomized controlled trials (RCTs), but the comparative usefulness of these novel treatments has not yet been fully examined. We systematically searched the CENTRAL, Medline, CINHAL, and ClinicalTrials.gov databases for randomized controlled trials up to July 4, 2024. Random-effects network meta-analyses were conducted to compare the Comparative antidepressant effects and safety of intravenous racemic ketamine, psilocybin and theta burst stimulation for major depressive disorderantidepressant efficacy, tolerability, and acceptability of IV ketamine, psilocybin, and TBS. Twenty-eight RCTs were included. All treatments were superior to placebo, with IV ketamine and psilocybin showing significantly greater antidepressant efficacy than TBS. No significant differences were detected between all treatments and placebo in tolerability and acceptability. In a subgroup analysis focusing on short periods of 1 week or less, only IV ketamine was significantly more effective than placebo. In another subgroup analysis focusing on periods of 4 weeks or longer, IV ketamine and psilocybin showed significantly better antidepressant effects than placebo. The confidence in the evidence ranged from very low to moderate. Specifically, there is a scarcity of studies on psilocybin and a lack of direct comparison trials. The findings suggest that IV ketamine and psilocybin may be more effective treatments compared to TBS. Additionally, IV ketamine may have an advantage in terms of rapid onset of action. The number of included studies is limited, especially for psilocybin, and therefore the current findings are preliminary, necessitating further accumulation of direct-comparison RCTs.

KEYWORDS
ketamine, meta-analysis, psilocybin, theta burst stimulation, transcranial magnetic stimulation

INTRODUCTION

Approximately 185 million people worldwide suffer from major depressive disorder (MDD), making it a significant global disease burden.[1] The gold standard antidepressant treatment faces challenges such as inadequate efficacy and high dropout rates due to the burden of side-effects.[2] In particular, the delay onset of antidepressant effect is a pressing issue, for example, in patients with imminent suicidal ideation and in those who have difficulty continuing treatment. Therefore, novel treatments have emerged that focus on the rapid onset of antidepressant effects while seeking higher antidepressant efficacy and safety: theta burst stimulation (TBS), ketamine, and psilocybin.

The efficacy and safety of TBS for MDD have been demonstrated in a meta-analysis of randomized controlled trials (RCTs).[3] TBS reduces treatment time compared to standard repetitive transcranial magnetic stimulation (rTMS), thereby lessening patient burden while maintaining comparable antidepressant efficacy.[4] Advances in TBS protocols have been particularly noteworthy; for instance, Stanford Neuromodulation Therapy (SNT) demonstrated rapid and impressive antidepressant effects immediately following a 5-day intervention in a small-scale, double-blind RCT with 29 participants (TBS group: remission rate 57.1%, response rate 71.4%; sham group: 0%, 13.3%).[5]

The rapid antidepressant effect and safety of intravenous racemic (IV) ketamine for MDD were also verified in a previous meta-analysis of RCTs.[6] Although the US Food and Drug Administration (FDA) approved intranasal esketamine for treatment-resistant depression, IV ketamine has shown superior antidepressant efficacy and acceptability compared to intranasal esketamine.[6,7] The time course of antidepressant efficacy for IV ketamine in treatment-resistant depression has been shown to emerge at 4 h, peak at 24 h, and diminish by 7 days after a single infusion, according to a previous meta-analysis.[8]

Psilocybin has also demonstrated rapid antidepressant efficacy and safety for MDD[9,10] and has recently been designated as a breakthrough therapy by the FDA.[11] Although current evidence primarily supports its use in combination with psychotherapy, two high oral doses of psilocybin may sustain antidepressant effects for 3 to 6 months.[12,13]

Assessing the relative rapidity of antidepressant effect, magnitude of antidepressant effect, and safety of these novel treatments at the present time would be useful for designing future RCTs. Therefore, we conducted a systematic review and random-effects network meta-analyses of these treatments.

METHODS

The protocol was registered in advance with PROSPERO (CRD42024562855). The study adhered to the PRISMA guidelines for network meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-analysis).[14]

Inclusion criteria for articles in the review

Type of studies

We included RCTs that evaluated the relative antidepressant efficacy of TBS, IV ketamine, and psilocybin using either placebo/sham controls or direct comparisons between these three active interventions for the treatment of MDD.

Study participants

Participants were primarily diagnosed with MDD according to standard diagnostic criteria. To account for heterogeneity, studies were excluded if they included more than 20% of participants with bipolar disorder or focused on patients with other psychiatric or physical conditions, and studies with fewer than 20 participants were excluded.

Intervention

In addition to monotherapy, TBS, IV ketamine, and psilocybin were also included in combination with other psychotropic drugs or psychotherapies, provided there was no significant difference in allocation between the treatment and control groups. Controls were placebo and sham stimulation. Anesthetics, such as midazolam, were not considered eligible as placebo. In psilocybin research, very low doses of the active drug are often considered placebos. In this study, we included very low doses of psilocybin in the placebo group, based on the determination that such low doses are unlikely to exhibit antidepressant effects.[15]

Type of outcomes

Primary outcomes

Continuous changes in depressive symptoms between pre- and post-intervention were measured. We avoided converting continuous variables into arbitrary binary variables to prevent drawing incorrect conclusions that could arise from setting arbitrary cut-off points, which would reduce information and decrease statistical power.[16] For outcome measurement scales, we used the following predefined hierarchy: first, the Montgomery–Åsberg Depression Rating Scale (MADRS), followed by the Hamilton Rating Scale for Depression (HRSD), and finally the Beck Depression Inventory (BDI). For post-intervention time points, we used values as close to the end of the intervention as possible in trials with repeated dosing, and for single-dose trials, we used the point showing the most pronounced antidepressant effect in the active intervention group. This approach was taken because, while the effects of ketamine are known to wane after a single dose,[8] it is expected that the time point immediately

following the intervention in repeated dosing trials will show the maximum antidepressant effect for all drugs. However, recognizing the importance of comparing antidepressant effects after some time has passed, we included the comparison of antidepressant effects at 4 weeks or later as a secondary outcome. Additionally, safety outcomes were defined as tolerability, measured by the discontinuation rate due to adverse events, and acceptability, measured by the discontinuation rate due to any reason.

Secondary outcomes

We compared the antidepressant effects for rapid efficacy within a time point of 1 week. For repeated dosing trials, we used the closest reported time point within the 1-week period, and for single-dose trials, we selected the point where the antidepressant effect was most pronounced. Additionally, mid-term antidepressant effects were evaluated using the time point closest to 4 weeks, with a minimum duration of 4 weeks.

Measures of treatment effects

For binary variables, we calculated pooled odds ratios, whereas for continuous variables, we calculated pooled standardized mean difference (SMD).

Search strategies

We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and ClinicalTrials.gov databases up to June 27, 2024, without any language or country restrictions (Table S1). Additionally, we reviewed the reference lists of relevant studies. Two reviewers (Itsuki Terao and Wakako Kodama) screened the titles and abstracts and then conducted full-text reviews.

Data extraction and quality assessment

Itsuki Terao initially performed the data extraction and quality assessment, which was then verified by Wakako Kodama Quality assessment, which was conducted using the Risk of Bias 2 tool for evaluating antidepressant efficacy in the primary analysis.[17] The data extraction form included information on demographic and clinical characteristics, primary or secondary outcomes, and potential effect modifiers. Values not disclosed in tables or text were extracted from the figures using WebPlot Digitizer Version 4.6,[18] which has been shown to have good validity and reliability.[19] Authors were contacted to obtain any missing data needed for the analysis.

Network meta-analyses

The transitivity assumption was evaluated by examining the clinical and methodological characteristics gathered during data extraction. Frequentist random-effects network meta-analyses was conducted using R software Version 4.2.1[20] with the "netmeta" package.[21]

Assessment of the confidence of the evidence

The confidence of the evidence regarding changes in depressive symptoms for the primary analysis was assessed using the Confidence in Network Meta-Analysis (CINeMA) framework.[22] This assessment focused on six domains: "within-study bias," "reporting bias," "indirectness," "imprecision," "heterogeneity," and "incoherence."[22,23]

RESULTS

Identification of relevant studies

The literature search identified 5080 candidate records, and 28 studies were included after screening and full-text review (Figures S1 and S2 & Table S2).[5,24–50] Details of the trials excluded from the full-text review are described in Table S3. There are nine studies (226 participants) investigating IV ketamine, 16 studies (416 participants) on TBS, and three studies (231 participants) on psilocybin. IV ketamine was evaluated in seven single-administration trials and psilocybin in three, whereas all TBS studies involved repeated administrations. The mean ages of participants in the included studies range from 14.6 to 52.7 years. The proportion of male participants in the included studies ranges from 0.0% to 92.3%. In almost all included studies, the subjects were blinded. Baseline depression severity scores indicate moderate to severe depression. Most participants in the studies were diagnosed with treatment-resistant depression. As potential effect modifiers, there were inevitably differences in intervention methods, although there were no obvious differences in patients' medical conditions, such as treatment resistance and depression severity.

Risk of bias assessment

The risk of bias was "low" for most studies (Figure S3). The main issues were the lack of protocol details in the manuscript, preventing assessment of protocol deviations, and the absence of descriptions of randomization methods. Substantial imbalances in dropouts were observed in one study each for IV ketamine and psilocybin.[40,41]

Results of network meta-analyses

Primary outcomes

Efficacy

The primary outcomes are shown in Table 1a. All interventions demonstrated significantly superior antidepressant effects compared to placebo. IV ketamine and psilocybin showed significantly greater antidepressant effects than TBS. There were no significant differences in the other comparisons.

Tolerability and acceptability

No significant differences in tolerability or acceptability were detected between any of the interventions and placebo (Tables 1b and 1c).

Secondary outcomes

The secondary outcomes are presented in Table 2. For antidepressant effects within one week, IV ketamine showed significantly greater effects compared to placebo, while neither TBS nor psilocybin demonstrated a significant difference from placebo (Table 2a). No significant differences in antidepressant effects were detected between the interventions. For antidepressant effects at 4 weeks or longer, both IV ketamine and psilocybin demonstrated significantly superior effects compared to placebo, while TBS did not show a significant difference from placebo (Table 2b). IV ketamine showed significantly greater antidepressant effects than TBS. Even when analysis was limited to a single IV ketamine infusion, post hoc analysis confirmed that IV ketamine remained significantly superior to placebo at time points beyond 4 weeks. Specifically, we confirmed that a single dose of IV ketamine had an antidepressant effect significantly superior to placebo at a time point of 4 weeks or longer (SMD = 12.86, 95% confidence interval [4.67; 21.05]). Furthermore, due to concerns that age might influence the results of the analysis as an effect modifier, we performed a post-hoc network meta-analysis of antidepressant effects restricted to studies where the mean age of participants was ≥18 years; no studies were excluded for IV ketamine or psilocybin, and two studies were excluded for TBS.[48,49] The results of the analyses were generally similar to those for all ages, but TBS was significantly superior to placebo for antidepressant effects over 4 weeks (Table S4).

TABLE 1a Network meta-analysis results for antidepressant efficacy.

IV ketamine			
4.7503 [1.1983; 8.3023]	TBS		
−2.0956 [−7.8412; 3.6499]	**−6.8459 [−12.2867; −1.4052]**	Psilocybin	
8.2905 [5.4597; 11.1212]	**3.5402 [1.3946; 5.6857]**	**10.3861 [5.3862; 15.3860]**	Placebo

Note: Bold text indicates statistical significance. Values above 0 suggest the superior efficacy of drugs in columns over those in rows.
Abbreviations: IV, intravenous racemic; TBS, theta burst stimulation.

TABLE 1b Network meta-analysis results for tolerability.

IV ketamine			
2.0992 [0.4701; 9.3731]	TBS		
0.8449 [0.0837; 8.5337]	0.4025 [0.0423; 3.8282]	Psilocybin	
1.7905 [0.5836; 5.4930]	0.8529 [0.3166; 2.2980]	2.1192 [0.2804; 16.0182]	Placebo

Note: Bold text indicates statistical significance. Values above 1 suggest the inferior tolerability of drugs in columns over those in rows.
Abbreviations: IV, intravenous racemic; TBS, theta burst stimulation.

TABLE 1c Network meta-analysis results for acceptability.

IV ketamine			
0.7608 [0.2354; 2.4583]	TBS		
1.2076 [0.2863; 5.0944]	1.5874 [0.4395; 5.7331]	Psilocybin	
0.6235 [0.2415; 1.6096]	0.8196 [0.4110; 1.6343]	0.5163 [0.1748; 1.5248]	Placebo

Note: Bold text indicates statistical significance. Values above 1 suggest the inferior acceptability of drugs in columns over those in rows.
Abbreviations: IV, intravenous racemic; TBS, theta burst stimulation.

TABLE 2a Network meta-analysis results for antidepressant efficacy within 1 week.

IV ketamine			
4.3579 [−1.0579; 9.7736]	TBS		
1.4024 [−5.7341; 8.5389]	−2.9555 [−10.1646; 4.2536]	Psilocybin	
7.1625 [3.4016; 10.9234]	2.8047 [−1.0922; 6.7016]	5.7602 [−0.3049; 11.8252]	Placebo

Note: Bold text indicates statistical significance. Values above 0 suggest the superior efficacy of drugs in columns over those in rows.
Abbreviations: IV, intravenous racemic; TBS, theta burst stimulation.

TABLE 2b Network meta-analysis results for antidepressant efficacy at 4 weeks or more.

IV ketamine			
9.8568 [1.8627; 17.8509]	TBS		
6.7154 [−3.1520; 16.5828]	−3.1414 [−12.0906; 5.8077]	Psilocybin	
14.4160 [8.0448; 20.7872]	4.5592 [−0.2692; 9.3876]	**7.7006 [0.1658; 15.2354]**	Placebo

Note: Bold text indicates statistical significance. Values above 0 suggest the superior efficacy of drugs in columns over those in rows.
Abbreviations: IV, intravenous racemic; TBS, theta burst stimulation.

The confidence of the evidence

The confidence of the evidence for each outcome ranged from very low to moderate (Table S5). The most common factor leading to the downgrading of confidence of the evidence was heterogeneity. In IV ketamine studies, heterogeneity might be attributed to differences in administration frequency and varying time points, while the use of different protocols could be the cause for TBS. However, excluding these heterogeneous studies would result in an insufficient number of studies for a valid analysis.

DISCUSSION

This study is the first systematic review and network meta-analyses to compare the antidepressant effects, tolerability, and acceptability of IV ketamine, psilocybin, and TBS for MDD. The primary outcomes reaffirmed that all interventions have significantly superior antidepressant effects compared to placebo[3,6,7,9] and, importantly, showed for the first time that IV ketamine and psilocybin may be more effective than TBS.

In terms of tolerability and acceptability, no significant differences were observed between any of the interventions and placebo, or among the interventions themselves, which aligns with previous studies.[3,7,9] Regarding the secondary outcome, IV ketamine demonstrated significant rapid antidepressant effects within 1 week, whereas TBS and psilocybin did not. Additionally, IV ketamine and psilocybin showed significant antidepressant effects at 4 weeks or longer, whereas TBS did not. Therefore, IV ketamine, psilocybin, and TBS are suggested to be all effective and safe treatments for MDD, with IV ketamine and psilocybin potentially being more effective than TBS, and IV ketamine possibly being the most superior due to its robust and rapid onset of action.

IV ketamine demonstrated significant antidepressant effects in seven out of nine studies,[25,26,34,42,44,47,50] and psilocybin showed significant effects in all three studies,[30,40,45] despite being single-dose studies. Because single doses have the advantage of reducing patient burden, IV ketamine and psilocybin administration is clinically useful. Furthermore, as mentioned in the introduction,[7] the attenuation of the effects of single-dose ketamine administration has been a problem, but we confirmed post hoc that the significant antidepressant effects of a single dose of IV ketamine are sustained for 4 weeks or longer. This also highlights the usefulness of IV ketamine.

Focusing on the 95% confidence intervals, which are close to 0, the antidepressant effects of psilocybin for less than 1 week are likely to become statistically significant as the number of RCTs increases (Table 2). Therefore, direct comparative studies focusing on the rapid antidepressant effects of psilocybin and IV ketamine are to be expected. On the other hand, TBS treatment seems to be at the stage of exploring effective protocols rather than comparing them with other interventions, as there is a wide variation in effectiveness across protocols and it does not appear to have a greater or more rapid antidepressant effect than IV ketamine or psilocybin when taken together as a whole. For example, the SNT protocol has been shown to have a rapid and high antidepressant effect, and a series of RCTs on SNT in the future could show comparable efficacy to IV ketamine and psilocybin.[5]

In a meta-analysis restricted to participants with a mean age of 18 years or older, the antidepressant effect of TBS was significantly superior to placebo at 4 weeks or more, underlining the usefulness of TBS in patients in this age group. Only two studies of TBS alone were conducted in inclusion studies in which participants were under 18 years of age,[48,49] requiring further accumulation of IV ketamine, psilocybin, and TBS studies in adolescents with depression. In particular, the antidepressant effect was non-significant compared to

placebo in the study involving adolescents and young adults with major depressive disorder by Zhang et al. ($N = 90$).[48] They attributed this to the high placebo effects and to the fact that the participants had a lower pulse rate of 600–1200 pulses/day (considering that the brain is still developing), whereas a previous meta-analysis showed that antidepressant effects are superior at 1800 pulses/day or more,[51] suggesting that the number of pulses in the study by Zhang et al. was inadequate. As the significant antidepressant effect of rTMS on adolescent depression has been demonstrated in a previous meta-analysis,[52] it is expected that further protocol refinements will demonstrate the antidepressant effect of TBS on adolescent depression.

In treatment-resistant depression, IV ketamine showed significantly better antidepressant effects than aripiprazole and lithium.[7] In addition, a recent network meta-analysis reported that there was no significant difference in antidepressant efficacy between ECT and IV ketamine in severe depression, and rather side-effects such as headache and memory impairment were significantly less with IV ketamine.[53] These support the clinical benefit of IV ketamine over conventional treatments. Psilocybin did not differ significantly from IV ketamine in its antidepressant effect in the present study, leading to a speculation that psilocybin may also be superior to conventional treatments. As mentioned in the Introduction section, the efficacy of TBS treatment is comparable to that of rTMS,[4] and furthermore, rTMS did not significantly differ from aripiprazole in antidepressant efficacy,[54] implying that TBS treatment may be comparable to conventional treatment in antidepressant efficacy. The relative effectiveness of these treatments is expected to be determined in head-to-head trials.

LIMITATIONS

This study has several limitations. (1) The transitivity assumption may have been violated by the following potential effect modifiers: patient characteristics, such as age, gender, depression severity, and comorbid conditions; treatment-related factors, like the type, intensity, and adherence to therapy; and biological variables, including genetic polymorphisms, neuroinflammation markers, and metabolic differences. The IV ketamine and TBS studies had small sample sizes, which may have biased the small-study effect to produce an apparently higher antidepressant effect. In addition, variation in placebo response rates per intervention suggests imbalance of the effect modifiers. Furthermore, the interventions were not directly compared in head-to-head RCTs, resulting in their relative effectiveness being assessed solely through indirect comparisons. Therefore, the current findings are preliminary and direct comparative RCTs need to be conducted on these interventions. (2) The RCTs involving IV ketamine and psilocybin largely consisted of single-dose studies, introducing a degree of heterogeneity. This reliance on single-dose studies presents a drawback for IV ketamine, particularly since repeated-dose trials have demonstrated that its antidepressant effects tend to increase with the number of doses.[35,41,55] Even so, it is noteworthy that both IV ketamine and psilocybin have shown antidepressant efficacy for periods extending beyond 4 weeks. (3) There are concerns regarding whether blinding was maintained for all interventions, as the side-effects specific to each intervention would not occur with placebo or sham stimulation. However, although this is a partial assessment, clearly disproportionate dropout rates occurred in only two studies. Direct comparison trials are needed. (4) The common side-effects of ketamine, such as headaches, nausea, dissociation, psychotomimetic effects, and increased blood pressure,[56] as well as the common side-effects of psilocybin, such as "bad trips" and risky behavior, have not been comprehensively evaluated across all RCTs, making a relative risk assessment infeasible. Additionally, the risks of misuse and abuse need to be evaluated over the long term.[57] Furthermore, psilocybin treatment requires psychotherapy, which can pose limitations on clinical feasibility.[58] (5) There are various protocols in the research on TBS, resulting in varying effects. (6) The confidence in the evidence, which ranges from moderate to very low, indicates that the results could potentially shift in direction. (7) The number of studies included in this analysis is extremely small, with only three studies for psilocybin, which is particularly notable. Therefore, the results are preliminary, and further accumulation of RCTs is necessary. (8) The current review focused on three interventions that were expected to have an earlier onset of antidepressant effect, and clinical treatment choice should be based on more comprehensive evidence. (9) We were not able to search important databases, such as Embase or PsycINFO.

CONCLUSION

This study suggests that IV ketamine and psilocybin may be superior to TBS in the treatment of MDD, with IV ketamine alone demonstrating a significant antidepressant effect within the first week. However, due to various limitations, particularly the small number of included studies, especially for psilocybin, and the absence of direct comparative trials, these findings should be interpreted as preliminary. Future head-to-head RCTs should be designed to confirm these findings.

AUTHOR CONTRIBUTIONS

Itsuki Terao contributed to the conception and design of the study, acquisition and analysis of data, and drafting the manuscript and figures. Wakako Kodama contributed to the conception and design of the study, acquisition and analysis of data, and drafting the manuscript and figures.

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N/A.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

N/A.

PATIENT CONSENT STATEMENT

N/A.

CLINICAL TRIAL REGISTRATION

N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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