Rapidity of Symptom Improvement With Intranasal Esketamine for Major Depressive Disorder:
A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Rapid-acting treatment options are needed for major depressive disorder (MDD). The objective of this systematic review and meta-analysis was to estimate the magnitude of the treatment effect for intranasal esketamine over placebo at 24 hours after the first dose and at endpoint.

Data Sources: PubMed, abstracts of major psychiatric meetings, and ClinicalTrials.gov were searched up to November 2020 with no language constraints, cross-referencing the term *intranasal* with *esketamine* and *randomized*.

Study Selection: Of 27 studies reviewed, 8 articles, with a total of 1,437 patients with MDD, met study criteria and were included in the meta-analysis.

Data Extraction: Randomized, double-blind clinical trials comparing adjunctive treatment of standard antidepressants with intranasal esketamine for MDD, using intranasal placebo augmentation as a comparator, were selected.

Results: Estimates of the standardized mean difference (SMD) in change scores were pooled after examining for homogeneity using the test statistic proposed by DerSimonian and Laird. Findings of the random effects model were presented. Augmentation of standard antidepressants with intranasal esketamine resulted in greater Montgomery-Asberg Depression Rating Scale (MADRS) score reduction than adjunctive intranasal placebo at 24 hours. Across the trials, the SMD was 0.34 (95% CI = 0.11 to 0.46, $P < .0001$) with a 2.9-point greater mean MADRS score reduction following intranasal esketamine versus active control plus intranasal saline. A similar finding was evident at endpoint.

Conclusions: This updated systematic review and meta-analysis found that augmentation of antidepressants with intranasal esketamine was statistically and clinically more effective in reducing depression severity than augmentation with placebo, at both 24 hours and study endpoint. Future studies are needed to evaluate dose-response relationship for esketamine.

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Major depressive disorder (MDD) is a common clinical challenge for psychiatry services and is one of the 5 leading causes of years lived with disability globally.[1–6] Clinicians currently lack rapid-acting treatment options for patients presenting with MDD, as all US Food and Drug Administration (FDA)-approved oral antidepressants take weeks to months for maximal therapeutic effect.[7] In the past decade, significant progress has been made in understanding the potential of ketamine and its *S*-enantiomer, esketamine, as antidepressants. Controlled clinical trials have demonstrated the fast-acting benefits of intravenous (IV) ketamine or esketamine in the treatment of MDD.[8,9] In the United States and European Union, intranasal (IN) esketamine has been granted approval as an adjunctive medication for treatment-resistant unipolar depression (TRD).[10] However, individual phase 3 studies did not demonstrate a statistically significantly greater number of responders at day 2 (24 hours) who maintained their response throughout the study for esketamine compared to controls[11,12] (key secondary endpoint for demonstrating rapidity of action as agreed upon by FDA and sponsor). Therefore, the primary aim of this meta-analysis is to estimate the magnitude of the treatment effect for intranasal esketamine over placebo at 24 hours after the first dose. In addition, given that several studies focusing on the use of IN esketamine in MDD have been completed since our previous meta-analysis,[13] a secondary aim of this analysis is to include these additional studies to estimate the magnitude of effect for IN esketamine versus control at study endpoint.

METHODS

Data Sources and Search Strategy

Studies were first identified using searches of PubMed up to November 2020. Searches were conducted by cross-referencing the term *intranasal* with the terms *esketamine* and *randomized*. No language or year of publication

Clinical Points

- Rapid-acting treatment options are needed for major depressive disorder, but more information is needed on the effectiveness of newer treatments such as intranasal esketamine.
- In this updated systematic review and meta-analysis, augmentation of antidepressants with intranasal esketamine was found to be more effective in reducing depression severity than augmentation with placebo at 24 hours and study endpoint.

restrictions were used. We also obtained the program syllabi and searched the abstracts of major psychiatric meetings held since 2015 (American Psychiatric Association, American Society of Clinical Psychopharmacology, European College of Neuropsychopharmacology, Collegium Internationale Neuropsychopharmacologicum, Society of Biological Psychiatry, World Federation of Societies of Biological Psychiatry, World Psychiatric Association, and International Society for Affective Disorders). Authors or study sponsors were contacted to obtain a copy of the presentation as well as any pertinent study details. Finally, the ClinicalTrials.gov database was searched for any completed studies not identified by any of the above methods.

Study Selection

We selected randomized, double-blind clinical trials comparing adjunctive treatment of standard antidepressants with IN esketamine for MDD. Further, we selected studies that used IN placebo augmentation as a comparator. We then selected studies that also met the following inclusion criteria:

1. Studies that used either the Hamilton Depression Rating Scale (HDRS)[14] or the Montgomery-Asberg Depression Rating Scale (MADRS)[15] as their primary outcome measure.
2. Studies that exclusively focused on patients with MDD.

Reports were excluded if they exclusively focused on the treatment of patients with bipolar disorder, dysthymic disorder, psychotic MDD, minor depressive disorder, seasonal affective disorder, depression with a specific medical condition, or active alcohol or substance abuse disorders. Reports not describing original data (ie, containing data published elsewhere) and those that were not focused on the acute phase of treatment (ie, continuation, maintenance, relapse prevention) were excluded. For multiple poster presentations of a trial, the most recent presentation was used.

Data Extraction

Data were extracted with the use of a pre-coded form. The following data were extracted from studies included in the meta-analysis: the number of patients randomized to each treatment arm, the study population (TRD vs MDD with suicidal ideation [SI]), treatment setting (inpatient vs outpatient), geographic region in which the study was conducted, duration of the trial, dosing and frequency of administration of esketamine, type of control used, primary outcome measure used (HDRS or MADRS), and baseline and mean change in scores from baseline and their corresponding standard deviations for the primary outcome measure at 24 hours and study endpoint, as well as corresponding remission rates. Data were extracted independently by 2 of the authors (G.I.P., N.I.), and any discrepancies resolved in a joint meeting when the final dataset was compiled. A few missing datapoints were obtained from the Yale University Data Access (YODA) project (carried out under YODA Project #2021–4818), which has an agreement with Janssen Research & Development, L.L.C.

Quantitative Data Synthesis

The primary outcome of the meta-analysis was to compare the standardized mean difference in change in primary outcome scores between adjunctive esketamine and placebo. To accomplish this, we pooled the estimates of standardized mean difference (SMD) in change scores after examining for homogeneity using the test statistic proposed by DerSimonian and Laird,[16] We presented as our final estimate the findings of the random effects model; this model is more conservative than the fixed-effects model and incorporates both within-study and between-study variance. Exploratory analyses included evaluating TRD and SI studies separately and evaluating studies by dose separately. All exploratory analyses were conducted in an identical fashion as the primary and secondary analyses. All analyses utilized the meta package of meta-analytic tools as implemented in Stata 15.[17]

Role of the Funding Source

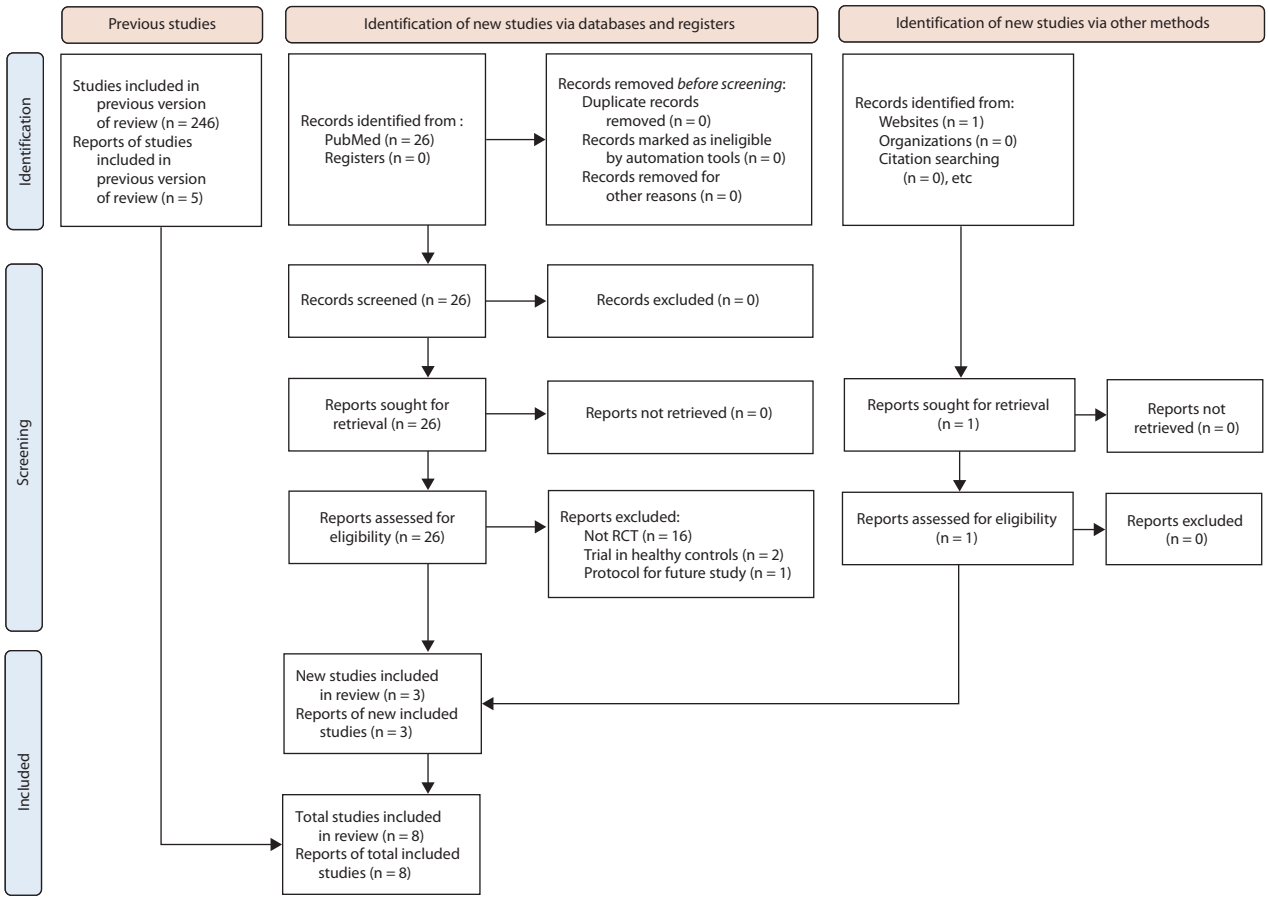
This was an unfunded study. The senior author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Initially, 26 abstracts were identified with the use of PubMed. Of these, 16 involved reviews of the use of ketamine or esketamine in MDD or other psychiatric disorders, 2 involved clinical trials in healthy controls, and 1 was a proposed protocol for a future study. The remaining 7 abstracts described double-blind, randomized studies in MDD. These 7 articles were obtained and reviewed thoroughly.[11,12,18–22] All were deemed eligible for inclusion. One additional study was identified with the use of ClinicalTrials.gov[23] (see Figure 1 for study flow information).

We were able to obtain efficacy data (SMD of change in scores) on each clinical trial's primary outcome measure for all 8 trials (see Table 1 for trials information). Thus, the meta-analysis was all-inclusive, with all existing studies pooled involving a total of 1,437 patients with MDD (928

Figure 1. PRISMA Diagram of Study Flow



Abbreviation: RCT = randomized controlled trial.

Table 1. Trials Information

Publication	Population	24 h MADRS	Duration (weeks)	Outcome (MADRS)	Setting	Location	Dose (mg)	Type of control	Δ MADRS[a] 24 h control	Δ MADRS[a] endpoint control
Daly et al, 2018[18]	TRD	Yes	1	Day 7	Outpatient	NA, Belgium, Japan	28, 56, 84	IN Pbo	−5.7	−4.9
Popova et al, 2019[12]	TRD	Yes	4	Day 28	Outpatient	NA, EU	56–84	New AD + IN Pbo	−5	−17
Fedgchin et al, 2019[11]	TRD	Yes	4	Day 28	Outpatient	NA, EU, LA	56, 84	New AD + IN Pbo	−6.4	−14.8
Ochs-Ross et al, 2020[19]	TRD	No	4	Day 28	Outpatient	NA, EU, LA, SA	28–84	New AD + IN Pbo	N/A	−6.3
NCT02918318[23]	TRD	Yes	4	Day 28	Outpatient	Japan	28, 56, 84	New AD + IN Pbo	−7.2	−15.3
Canuso et al, 2018[20]	SI	Yes	4	4 Hours	Inpatient	NA	84	SOC AD	−12.8	−23
Fu et al, 2020[21]	SI	Yes	4	24 Hours	Inpatient	NA, EU, AP, SA	84	SOC AD	−12.8	−25.8
Ionescu et al, 2019[22]	SI	Yes	4	24 Hours	Inpatient	NA, EU, LA	84	SOC AD	−12.4	−26.4

[a]Δ MADRS = mean MADRS score reduction.

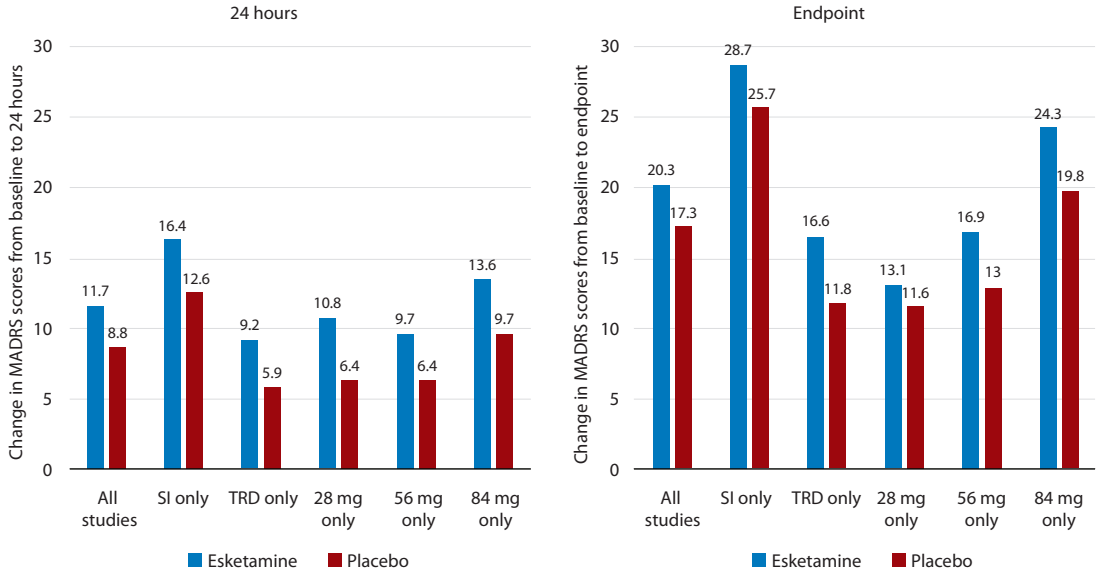
Abbreviations: AD = antidepressant, AP = Asia Pacific, EU = Europe, IN = intranasal, LA = Latin America, MADRS = Montgomery-Asberg Depression Rating Scale, NA = North America, N/A = not applicable, Pbo = placebo, SA = South Africa, SI = suicidal ideation, SOC AD = standard of inpatient care plus new antidepressant, TRD = treatment-resistant depression.

Table 2. Results of Exploratory Analyses

Group comparison	Timepoint	SMD	95% CI	*P* value	Heterogeneity *P* value	No. of comparisons
All studies	24 h	0.34	0.24 to 0.44	< .0001	.446	16
All studies	Endpoint	0.26	0.16 to 0.37	.004	.288	16
SI only	24 h	0.35	0.21 to 0.49	< .0001	.297	3
SI only	Endpoint	0.27	0.13 to 0.42	.0002	.147	3
TRD only	24 h	0.35	0.21 to 0.49	< .0001	.297	13
TRD only	Endpoint	0.27	0.13 to 0.42	< .0001	.147	13
28 mg only	2 4h	0.46	0.14 to 0.78	< .0001	.388	3
28 mg only	Endpoint	0.13	−0.17 to 0.45	.395	.379	3
56 mg only	24 h	0.38	0.11 to 0.65	.005	.263	4
56 mg only	Endpoint	0.27	−0.05 to 0.59	.103	.149	4
84 mg only	24 h	0.33	0.18 to 0.49	< .0001	.29	7
84 mg only	Endpoint	0.28	0.11 to 0.46	.01	.167	7

Abbreviations: SI = suicidal ideation, SMD = standardized mean difference, TRD = treatment-resistant depression.

Figure 2. Reduction in MADRS Score With Esketamine Versus Placebo



Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SI = suicidal ideation, TRD = treatment-resistant depression.

patients with TRD, 509 with MDD with SI) randomized to adjunctive treatment with either intranasal esketamine (802 patients) or placebo (635 patients). Outcome measure uniformity across studies was optimal, since all trials involved the use of MADRS as the study primary outcome measure. Augmentation of standard antidepressants with IN esketamine resulted in greater MADRS score reduction than adjunctive IN placebo at 24 hours. Specifically, across the trials, the SMD was 0.34 (95% CI = 0.11 to 0.46, $P < .0001$), with a 2.9-point greater mean MADRS score reduction following adjunctive IN esketamine versus active control plus IN saline. A similar finding was evident at endpoint also (SMD = 0.26, 95% CI = 0.16 to 0.37, $P = .004$), with a 3-point mean MADRS score reduction for adjunctive esketamine versus placebo. Augmentation of standard antidepressants with IN esketamine resulted in greater MADRS remission rate than adjunctive IN placebo at 24 hours. Specifically, across the trials, the risk ratio (RR) for remission at 24 hours was 2.31 ($P < .0001$) with no statistically significant heterogeneity ($P = .7$) and 1.37 at endpoint ($P < .0001$) with no statistically significant heterogeneity ($P = .7$). Mean remission rates at 24 hours and endpoint for esketamine and placebo, respectively, were 16.7% versus 7.3% at 24 hours (number needed to treat [NNT] = 10) and 27.9% versus 22.9% at endpoint (NNT = 20).

Exploratory analyses were conducted involving (1) grouping by dose and (2) subdividing studies into those examining pure TRD vs SI populations. Results of exploratory analyses are also outlined in Table 2 and Figure 2. Meta-regressions did not reveal dose to be a predictor of SMD at 24 hours ($P = .8$) or at endpoint ($P = .7$). Similarly, meta-regressions did not reveal dose to be a predictor of RR of remission at 24 hours ($P = .4$) or at endpoint ($P = .7$). In addition, meta-regressions did not reveal study population (acute suicidal ideation versus TRD) to be a predictor of SMD at 24 hours ($P = .8$) or at endpoint ($P = .9$). Similarly,

meta-regressions did not reveal study population (acute suicidal ideation versus TRD) to be a predictor of RR of remission at 24 hours ($P = .5$) or at endpoint ($P = .7$). Finally, meta-regressions did reveal greater baseline severity to serve as a predictor of lower RR of remission at 24 hours (coefficient = −0.2; $P = .04$) but not at endpoint (coefficient = −0.6; $P = .09$), while meta-regressions did not reveal greater baseline severity to serve as a predictor of lower SMD at 24 hours ($P = .05$) or at endpoint ($P = .08$).

DISCUSSION

In this systematic review and meta-analysis, 8 clinical trials of IN esketamine versus placebo were pooled, involving a total of 1,437 subjects—nearly double the sample size from a previous meta-analysis conducted by our group.[13] Due to the use of multiple doses in 2 trials, and the sequential-parallel comparison design in 1 trial,[18] these yielded a total of 16 esketamine vs placebo comparisons. Using a meta-analysis of these comparisons, we found that augmentation of antidepressants with IN esketamine was significantly more effective in reducing depression severity than augmentation with placebo. Specifically, the SMD in MADRS scores at 24 hours across all studies was 0.34, indicating a difference in change in MADRS scores between active treatment and placebo approximately equal in magnitude to one third of the pooled standard deviation (standard deviations across studies ranged from, approximately, 7 to 12 MADRS points). The SMD at study endpoint was 0.26, endpoint being 4 weeks in all studies except for one, which was 1 week in duration. A smaller SMD at endpoint than at 24 hours (despite a similar difference in change in MADRS scores between esketamine and placebo at endpoint than 24 hours) is explained by the larger measurement error at endpoint than 24 hours across studies. Consistent and vigorous predictors of outcome could not be identified by the use of subanalyses or meta-regressions.

Although the SMD for IN esketamine at 24 hours in our meta-analysis is numerically smaller than the SMD at 24 hours post ketamine or esketamine IV infusion reported in the literature,[8,9] several key elements of this dataset help put the present finding in clinical perspective. First, the derived effect sizes (SMD, NNT) for IN esketamine from our analysis at 24 hours are similar to the effect sizes reported for acute-phase treatments (median duration of 8 weeks) delivered by conventional antidepressants at study endpoint.[24] In addition, while the effect size derived for standard oral antidepressants corresponds to general patient populations with MDD, the present dataset exclusively involved patients with difficult to treat depression or severe suicidal ideation that required hospitalization. Furthermore, the effect size of conventional antidepressants is derived from studies comparing them to an oral placebo pill. Here, in all but 1 case,[17] the active comparator involved intranasal placebo that was added to either a newly initiated antidepressant (for TRD study) or comprehensive care provided to patients with MDD who were at an imminent risk of suicide and were admitted to an inpatient psychiatric facility. These factors support the assertion that IN esketamine possesses a rapid and clinically meaningful antidepressant effect.

Exploratory analyses we conducted further suggest that the SMD of esketamine versus placebo was similar when studies of patients with TRD were examined separately, as well as when studies of patients with MDD who were at an imminent risk of suicide were examined separately. In addition, secondary analyses that were stratified on the basis of dose found that the improvement with esketamine was significantly greater than placebo at 24 hours for all 3 doses (28 mg, 56 mg, and 84 mg). However, for the endpoint comparison, only the 84 mg dose was statistically significant versus placebo. Lower doses of esketamine (28 mg and 56 mg) did not significantly differ from placebo at endpoint—a caveat being the relatively fewer number of comparisons available for the 28 mg (n = 3) and the 56 mg (n = 4) than the 84 mg (n = 7) dose groups. These findings add to the limited literature on the dose-response relationship with ketamine/esketamine treatment. For instance, in the Rapidly Acting Treatments for Treatment-Resistant Depression (RAPID) ketamine study, the 0.5 mg/kg and 1 mg/kg dose groups demonstrated statistically greater reduction in depression severity as compared to the control condition (midazolam), whereas the 0.1 mg/kg group was statistically superior to the control condition only before adjusting for multiple comparisons (findings for the 0.2 mg/kg group were not significant).[8] In addition, a recent study of single infusion with either placebo or ketamine (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg) found a statistically significant correlation between ketamine dose and the degree of reduction in depression severity at 24 hours postinfusion.[25] Additional studies could help clarify whether doses higher than 84 mg of IN esketamine can be effective in subjects who do not respond to lower doses.

There are limitations to this report. While this is the largest meta-analysis of esketamine versus placebo to date, the sample size is relatively small to permit dose-response comparisons. Additionally, all studies involved treatment with an adjunctive antidepressant. The antidepressant effect of monotherapy with esketamine remains untested. Furthermore, participation in these trials was limited to adults with MDD. Therefore, the efficacy of esketamine in individuals with other mood disorders and in adolescents has not been reported.

In conclusion, this updated systematic review and meta-analysis of studies of intranasal esketamine found significantly greater improvement in depression severity at 24 hours as well as at the study endpoint. Furthermore, effect size of improvement was similar in studies of TRD only and SI only subjects. All studied esketamine doses (28 mg, 56 mg, and 84 mg) were significantly more effective than placebo at 24 hours. However, only the 84 mg dose was significantly more effective than placebo at study endpoint. Future studies are needed to evaluate dose-response relationship for esketamine.

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