Efficacy of Esketamine Augmentation in Major Depressive Disorder: A Meta-Analysis

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ABSTRACT

Objective: Esketamine, the *S*-enantiomer of ketamine, was recently approved as a rapid-acting intranasal therapy for depression and is currently under development for suicidality. The authors sought to determine the efficacy of adjunctive intranasal esketamine in major depressive disorder (MDD).

Data Sources: A systematic search of PubMed/MEDLINE was conducted up to January 2019, in addition to abstracts of major psychiatric meetings held since 2010. Searches were conducted by cross-referencing the term *intranasal* with the term *esketamine*. Where necessary, authors and/or study sponsors were contacted in order to obtain a copy of the presentation as well as any pertinent study details.

Study Selection: 241 study abstracts were initially identified and reviewed. Selected studies were randomized, double-blind clinical trials comparing adjunctive intranasal esketamine to adjunctive placebo for MDD.

Data Extraction: Data were extracted independently by two of the authors. A random effects model was used to calculate the standardized mean difference (SMD) between esketamine and placebo (intranasal saline) in the Montgomery-Asberg Depression Rating Scale (MADRS) score change from baseline to endpoint, serving as the primary outcome of the study.

Results: Five trials with 774 patients were pooled. Adjunctive esketamine was significantly more effective than placebo for MADRS score change, response, and remission (N = 774, SMD = 0.36, 95% CI = 0.24–0.49, $P < .0001$; response: risk ratio [RR] = 1.40, 95% CI = 1.22–1.61, $P < .0001$; remission: RR = 1.45, 95% CI = 1.20–1.75, $P < .0001$). Results remained statistically significant regardless of differences in the study sample, fixed vs new/optimized baseline antidepressants.

Conclusions: Adjunctive intranasal esketamine for patients with MDD who are either treatment-resistant or acutely suicidal appears to be an effective treatment strategy.

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Major depressive disorder (MDD) is a common medical disorder with a lifetime prevalence of 16.2% for adults in the United States. The pathophysiology and drug development of MDD has mostly been dominated by the monoamine hypothesis.[1] However, in the past two decades, there has been a considerable effort to uncover novel molecular targets and brain circuitry abnormalities underlying the neurobiology of depression.[2–4]

The glutamatergic neurotransmission has garnered the most attention, with ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist and glutamatergic modulator, showing considerable promise as a breakthrough rapid-acting antidepressant therapy in treatment-resistant depression (TRD).[5,6] Randomized controlled trials have demonstrated intravenous ketamine's robust and consistent antidepressant effects.[7–9] With ketamine's very poor oral bioavailability due to extensive first-pass metabolism,[10,11] the intravenous (IV) route has been the preferred and most studied mode of administration, although not without its logistical pitfalls; the requirement of twice- or thrice-weekly infusion visits, along with the repeated insertion of IV lines, represent significant patient burden and inconvenience. This has led to the consideration of more convenient routes, such as the intranasal formulation. The latter was shown to have a bioavailability of approximately 45%–50% across different racial and age groups, surpassing the bioavailability of oral, sublingual, and rectal formulations.[10,11]

Esketamine, the *S*-enantiomer of ketamine, was recently approved by the US Food and Drug Administration as an intranasal augmentation therapy to a newly started antidepressant for TRD (2 or more failed treatment trials).[12] It has a high affinity for the NMDA receptor, resulting in a significantly higher potency than the *R*-enantiomer.[13,14] Published studies investigating esketamine's antidepressant efficacy have been encouraging.[15,16] In a phase 2 randomized, placebo-controlled trial, repeated administration of intranasal esketamine 56 mg and 84 mg in patients with TRD demonstrated a rapid and robust antidepressant response.[15] Since then, a number of clinical trials have examined the role of intranasal esketamine in MDD. The goal of this work is to review these trials and provide an overall estimate of the efficacy of intranasal esketamine in MDD.

METHODS

Data Sources and Search Strategy

Studies were first identified using searches of PubMed/MEDLINE up to January 2019. Searches were conducted by cross-referencing the term *intranasal* with the term *esketamine*.

Clinical Points

- Intranasal esketamine is a recently approved drug for the treatment of depression.
- Augmentation of antidepressants with intranasal esketamine is an efficacious treatment strategy in major depressive disorder.

No language or year of publication restrictions were used. We also obtained the program syllabi and searched the abstracts of major psychiatric meetings held since 2010 (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, International Society for Affective Disorders). Authors or study sponsors were contacted in order to obtain a copy of the presentation as well as any pertinent study details.

Study Selection

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

1. Studies that used either the Hamilton Depression Rating Scale (HDRS)[17] or the Montgomery-Asberg Depression Rating Scale (MADRS)[18] 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, or seasonal affective disorder or depressed patients 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 criteria used to establish the diagnosis of MDD, the number of patients randomized to each treatment arm, the design of the trial (ie, parallel, parallel-sequential, crossover), the duration of the trial, medication and dosing, the primary outcome measure used (HDRS or MADRS), response rates, remission rates, and mean change in scores from baseline and their corresponding standard deviations for the primary outcome measure. Data were extracted independently by two of the authors (G.I.P., N.C.S.), and any discrepancies were resolved in a joint meeting when compiling the final dataset. To evaluate the quality of clinical trials, a Jadad score[19] was calculated for each trial (Table 1). Additionally, a funnel plot and Egger test were conducted for assessment of publication bias (Supplementary Figure 1).

Quantitative Data Synthesis

The primary outcome of the meta-analysis was to compare the standardized mean difference (SMD) in change in primary outcome scores between adjunctive esketamine and placebo. The secondary outcome was to compare the risk ratio (RR) for response and remission between these two groups. Time point of interest was study endpoint. To accomplish this, we pooled the estimates of SMD in change scores and response and remission rates among studies after examining for homogeneity using the test statistic proposed by DerSimonian and Laird.[20] To calculate estimates, where response or remission rates were 0, 0.5 was added to rates in both treatment groups. 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 studies separately, evaluating trials in which the augmented antidepressant is newly introduced and/or optimized. 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 (College Station, Texas; StataCorp LP).

RESULTS

Initially, 241 abstracts were identified with the use of PubMed/MEDLINE. Of these, 233 involved trials in different medical conditions or healthy volunteers, reviews, opinions, surveys, chart reviews, case studies/series, or uncontrolled biomarker studies that did not meet the inclusion criteria. The remaining 8 abstracts described double-blind, randomized studies in depression. These 8 articles were obtained and reviewed thoroughly. Six of these articles were excluded, because 2 focused on the administration of esketamine to healthy volunteers[21,22]; 3 employed an intravenous,[9,16,23] intramuscular,[23] or subcutaneous[23] formulation of either esketamine[16] or ketamine[9,23]; and 1 employed an intranasal formulation of ketamine.[24] The remaining 2 articles[15,25] were included in the meta-analysis.

Five additional clinical trials were identified as recently completed, unpublished poster presentations at scientific meetings.[26–30] Two of these were excluded because they focused on continuation and maintenance therapy,[26,30] while the remaining 3[27,28,30] were included in the meta-analysis, for a total of 5 included trials (Supplementary Figure 2). One of the trials employed a sequential-parallel comparison design (SPCD),[15] resulting in separate meta-analytic entries for stages I and II.

Table 1. Study Descriptions and Characteristics

Study	% Women	Age (y), Mean ± SD	Patient Population	Design	Sample Size per Treatment Arm	Duration to Primary Endpoint (MADRS)	Total Study Duration	Intranasal Esketamine Dose	Frequency	Remission Definition	Adjunctive or Monotherapy	Jadad Score
Daly et al, 2018[15]	57	44.7 ± 10	MDD and 2 or more failed trials	Phase 2, 2-panel, double-blind, doubly randomized, delayed-start, placebo-controlled study (a variant of sequential-parallel comparison design)	Placebo (n = 33); esketamine 28 mg (n = 11), 56 mg (n = 11), or 84 mg (n = 12)	Baseline (pretreatment) to day 8, in each study period (total of 2 periods)	Days 1–15, then open-label phase days 15–74, then 8 weeks posttreatment f/u period	28 mg, 56 mg, or 84 mg[a]	Twice weekly in each period (total of 2 periods of 1 week each)	MADRS total score ≤ 10	Adjunctive to patient's stable AD regimen	5
Canuso et al, 2018[25]	65	35.8 ± 13	MDD with imminent risk of suicide	Double-blind, randomized, placebo-controlled	Esketamine: 35; placebo: 31	4 Hours postdose	4 Weeks of double-blind treatment (days 1 to 25) and then 8 weeks of posttreatment follow-up (days 26 to 81)	84 mg[b]	Twice weekly for 4 weeks	MADRS total score ≤ 12	Adjunctive to patient's stable AD regimen or initiated regimen by study physician	5
Fedgchin et al, 2018[30]	71	46.3 ± 11.2	MDD with at least 2 failed AD trial and 1 of which observed prospectively	Phase 3, randomized, double-blind, active-controlled	Placebo (n = 33); esketamine 28 mg (n = 11), 56 mg (n = 11), or 84 mg (n = 12)	Baseline to day 28	4 Weeks AD lead-in → 4 weeks randomization + 24 weeks f/u	56 mg, 84 mg[c]	Twice weekly for 4 weeks	MADRS total score ≤ 12	Adjunctive to a new oral AD initiated by study physician	5
Popova et al, 2018[27]	62	Esketamine: 44.9 ± 12.6; placebo: 46.4 ± 11.1	MDD with at least 2 failed AD trial and 1 of which observed prospectively	Phase 3, randomized, double-blind, active-controlled	Esketamine: 114; placebo: 109	Baseline to day 28	4 Weeks AD lead-in → 4 weeks randomization + 24 weeks f/u	56 mg or 84 mg (flexible dosing)[c]	Twice weekly for 4 weeks	MADRS total score ≤ 12	Adjunctive to a new oral AD initiated by study physician	5
Ochs-Ross et al, 2018[28]	62	70 ± 4.5	MDD with at least 2 failed AD trial and 1 of which observed prospectively	Randomized, double-blind, active-controlled	Esketamine: 72; placebo: 65	Baseline to day 28	4 Weeks AD lead-in → 4 weeks randomization + 2 weeks f/u	28 mg or 56 mg or 84 mg (flexible dosing)[c]	Twice weekly for 4 weeks	MADRS total score ≤ 12	Adjunctive to a new oral AD initiated by study physician	5

[a]Adjunctive to patient's stable AD regimen.
[b]Adjunctive to patient's stable AD regimen or initiated regimen by study physician.
[c]Adjunctive to a new oral AD initiated by study physician.
Abbreviations: AD = antidepressant, f/u = follow-up, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

Figure 1. Forest Plot of Standardized Mean Difference (SMD) in Change in Primary Outcome Scores Between Adjunctive Esketamine (EK) and Placebo

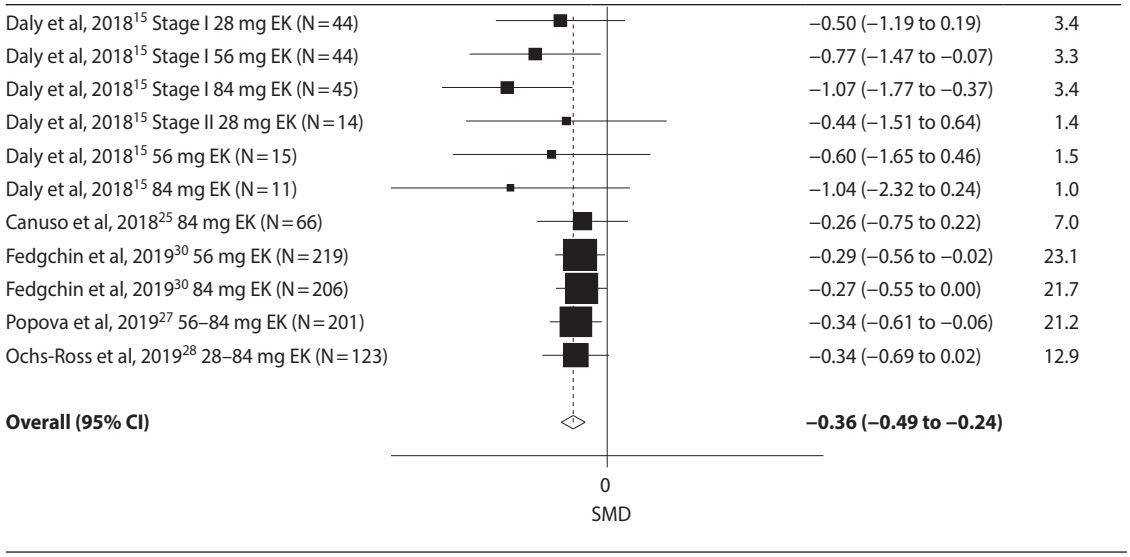


Table 2. Primary and Exploratory Meta-Analyses

	Intranasal Esketamine Augmentation	Intranasal Placebo Augmentation	Estimate (SMD or RR)	*P* Value
Total pooled sample				
Sample size	442	332		
SMD			0.36	<.0001
Response (%)	53.2	36.4	1.4	<.0001
Remission (%)	38.5	24.7	1.45	<.0001
TRD subjects only (without Canuso et al[25])				
Sample size	407	301		
SMD			0.37	<.0001
Response (%)	50.2	31.3	1.41	<.0001
Remission (%)	35.8	22.2	1.45	<.0001
New/optimized antidepressant sample (without Daly et al[15])				
Sample size	408	299		
SMD, day 28			0.30	<.0001
Response (%), day 28	55.1	39.8	1.38	<.0001
Remission (%), day 28	40	27	1.42	<.0001

Abbreviations: RR = risk ratio, SMD = standardized mean difference, TRD = treatment-resistant depression.

We were able to obtain efficacy data (standardized mean difference of change in scores and response and remission rates) on each clinical trial's primary outcome measure for all 5 trials (Table 1 for trials information). Thus, the meta-analysis was all-inclusive, with all existing studies pooled involving a total of 774 MDD outpatients randomized to adjunctive treatment with either intranasal esketamine or placebo. Outcome measure uniformity across studies was optimal, since all trials involved the use of MADRS as the study primary outcome measure.

Analysis of Primary and Secondary Outcome Measures

Augmentation of standard antidepressants with intranasal esketamine resulted in greater MADRS score reduction than adjunctive intranasal placebo. Specifically, across the trials, the SMD was 0.36 (95% CI = 0.24–0.49, $P < .0001$) (Figure 1; Table 2). Accordingly, RRs for response and remission were 1.40 (95% CI = 1.22–1.61, $P < .0001$) and 1.45 (95% CI = 1.20–1.75, $P < .0001$) (Figures 2 and 3; Table 2). Exploratory analyses were conducted involving (1) subdividing studies into those examining pure TRD populations (thus, excluding Canuso et al[25]) and (2) examining studies in which augmented antidepressants were initiated upon randomization and/or optimized during the double-blind phase[25,27,28,30]—incidentally, these were of 4 weeks' duration. Results of exploratory analyses are also outlined in Table 2.

DISCUSSION

In this systematic review and meta-analysis, 5 clinical trials involving intranasal esketamine were pooled, involving a total of 774 subjects. Due to the use of multiple doses in 2 trials, and the SPCD design in 1, these yielded a total of 11 esketamine-placebo comparator arms. Augmentation of antidepressants with intranasal esketamine was significantly more effective than placebo augmentation for MADRS score change and response as well as remission. Specifically, the SMD in MADRS scores across studies was 0.36, indicating a difference in change in MADRS scores between active treatment and placebo equal in magnitude, approximately, to one third of a pooled standard deviation (standard deviations across studies ranged from, approximately, 6 to 14 MADRS points). In addition, the pooled risk ratios for response and remission were 1.4 and 1.45, respectively, indicating a 40% and 45% higher chance of response and remission for intranasal esketamine than placebo. In terms of raw pooled response and remission rates at study endpoint, these figures were 53.2% versus 36.4% and 38.5% versus 24.7% for intranasal esketamine versus placebo, yielding numbers needed to treat (NNTs) of, approximately, 6 and 7.

Figure 2. Forest Plot of Risk Ratio (RR) of Response Rate Between Adjunctive Esketamine (EK) and Placebo

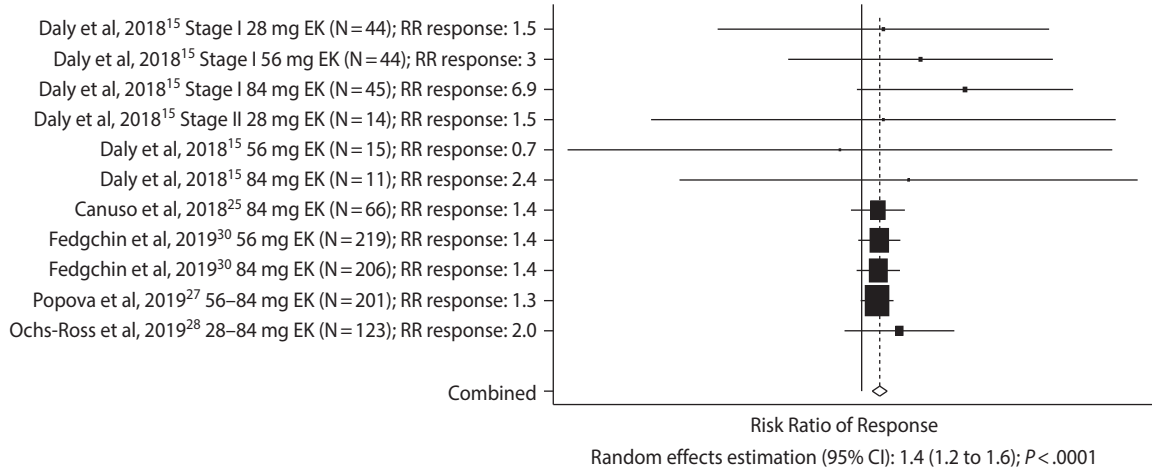
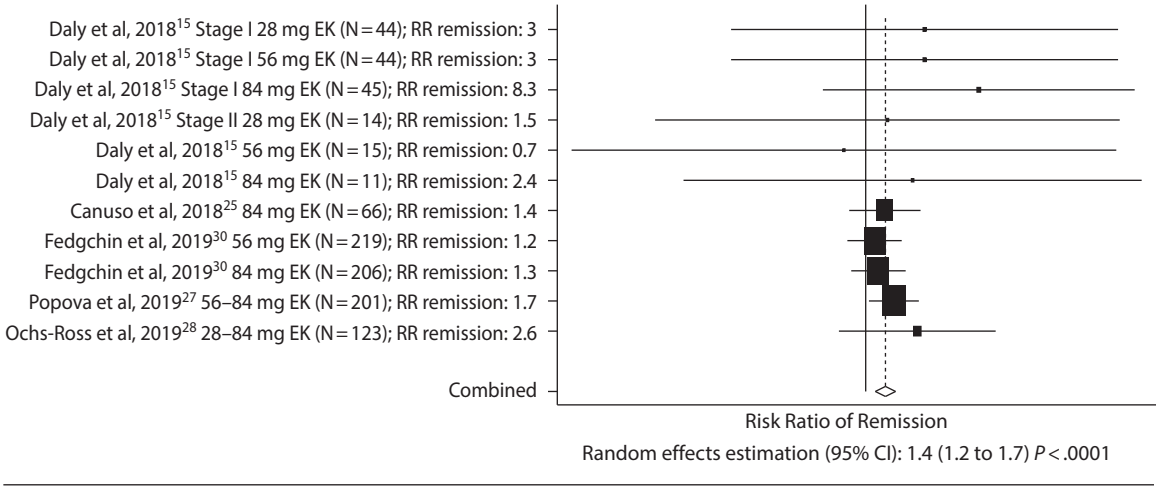


Figure 3. Forest Plot of Risk Ratio (RR) of Remission Rate Between Adjunctive Esketamine (EK) and Placebo



Most importantly, these figures remained statistically significant and at least of comparable magnitude regardless of whether we focused on TRD subjects only, whether the underlying antidepressant was kept constant or optimized during the double-blind period (although the magnitude of the difference was much larger among studies where the augmented antidepressant was kept at a fixed dose [SMD = 0.6, risk ratio for response 2.94]).

In order to place these findings into clinical perspective, it is worth noting that our previously estimated NNT for response to antidepressant monotherapy in standard MDD clinical trial populations (not selected for treatment resistance or acute suicidality) among published trials was, approximately, 6.[31,32] In fact, one could argue that the real NNT of antidepressant monotherapy for TRD patients and including unpublished studies (which are often negative) is much lower (the pooled response rates for antidepressant nonresponders in switch studies from a meta-analysis[33] was 39%, while the range of response rates in the Sequenced Treatment Alternatives to Relieve Depression study for antidepressant monotherapy after patients who failed 2 treatments was only 13.4%–16.5%).[34] Yet, in the present analysis, the NNT at 4 weeks for response and remission for intranasal esketamine versus placebo among trials focusing on resistant or suicidal patients, where either a new antidepressant was introduced or the existing antidepressant was optimized was, approximately, 6 and 7, respectively. This indicates that adjunctive treatment with these agents produces an effect that is at least equal to the overall effect of standard antidepressants, thereby doubling the efficacy of the overall intervention (antidepressant optimization plus augmentation). In yet another clinically relevant contrast, the NNT for response to augmentation with atypical antipsychotics versus placebo in patients with resistant depression has been noted as, approximately, 9 (olanzapine, risperidone, quetiapine, and aripiprazole),[35,36] despite the underlying antidepressant being established well prior to randomization and continued at a fixed dose during the double-blind period in most of those trials. Taken together, these contrasts point to a treatment effect for intranasal esketamine that is larger than those of standard antidepressants or atypical antipsychotics in TRD.

At first glance, it appears that treatment effects seen with repeated infusions of intravenous ketamine in TRD are greater than with the intranasal preparation. Specifically, the results of a randomized, double-blind trial of repeated doses (either 2 or 3 times per week) of intravenous ketamine (0.5 mg/kg) in TRD[9] showed a NNT for response at week 2 for twice (similar to all trials in this meta-analysis) or thrice a week dosing of nearly 2. However, it should be pointed out that (1) repeated dose-administration studies involving intravenous esketamine, a more potent NMDA antagonist than ketamine, have not been studied and may have yielded different results, while (2) the aforementioned repeat-dose intravenous ketamine study did not involve concurrent antidepressant optimization, a study design element that serves to enhance effect sizes because of a smaller treatment effect in the control group, and (3) intravenous studies were dosed by weight whereas intranasal studies were not.[37,38] Thus, it would be worthwhile for future studies to shed light on the actual difference in efficacy between intravenous and intranasal esketamine. If, in turn, there is a substantial difference in favor of the intravenous route, it would be interesting to test the efficacy, safety, and tolerability of achieving remission with IV esketamine and maintaining remission with IV esketamine versus intranasal esketamine, the latter having established maintenance efficacy[26,29] and being easier to administer.

There are several limitations to this analysis. First and foremost, there may be other studies with different results that were not published or presented and thus not included in this analysis. Definitions of treatment resistance are still evolving, and there is no single standard across all pooled studies.[39] Yet, the methods used to define treatment resistance in the atypical trials were relatively more rigorous than previous augmentation trials, often including state of the art measures of resistance such as the MGH Antidepressant Treatment History Questionnaire[40] as well as remote assessment of subject eligibility such as SAFER.[41] In addition, while the number of patients included in these trials is fairly large, the number of trials on which this trial level data analysis is based is relatively limited. Furthermore, the vast majority of the dataset involves adjunctive use along with approved antidepressant drugs. Thus, the role of this agent when used alone or in conjunction with other nonpharmacologic antidepressants (ie, psychotherapy, transcranial magnetic stimulation, or natural remedies) for patients who wish to avoid side effects associated with traditional antidepressant treatment remains unclear. Additionally, the studies reviewed had different durations, and the primary outcome was defined after a variable number of days and/or esketamine treatment doses. Finally, the present dataset exclusively addresses twice-weekly treatment. Whether more frequent treatment is efficacious for subjects who do not respond to twice-a-week therapy should be studied.

In conclusion, augmentation with intranasal esketamine for patients with MDD who are either treatment-resistant or acutely suicidal appeared to be more effective than adjunctive placebo in terms of symptom reduction and response and remission rates in this meta-analysis. Given that the majority of studies involved either introducing a new antidepressant or actively optimizing one during the double-blind phase of the study (as opposed to the more traditional augmentation study design involving pre-established antidepressant therapy that remains constant during the study),[42] these results indicate a larger effect size with intranasal esketamine than traditional approved antidepressants or antipsychotics in MDD.

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Potential conflicts of interest: **Dr Papakostas** has served as a consultant for Abbott, Acadia*, Alkermes, AstraZeneca, Avanir, Axsome*, Boston Pharmaceuticals, Brainsway, Bristol-Myers Squibb, Cephalon, Dey, Eli Lilly, Genentech*, Genomind*, GlaxoSmithKline, Evotec AG, H. Lundbeck A/S, Inflabloc, Janssen Global Services*, Jazz, Johnson & Johnson*, Methylation Sciences, Mylan*, Novartis Pharma AG, One Carbon Therapeutics*, Osmotica*, Otsuka, PAMLAB, Pfizer, Pierre Fabre, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, Sunovion, Taisho, Takeda, Theracos, and Wyeth; has received honoraria (for lectures or consultancy) from Abbott Laboratories, Acadia, Alkermes, Asopharma America Cntral Y Caribe, AstraZeneca, Avanir, Bristol-Myers Squibb, Brainsway, Cephalon, Dey, Eli Lilly, Evotec AG, Forest, GlaxoSmithKline, Inflabloc, Grunbiotics, Jazz, H. Lundbeck A/S, Medichem, Meiji Seika, Novartis Pharma AG, Otsuka, PAMLAB, Pfizer, Pharma Trade SAS, Pierre Fabre, Ridge Diagnostics, Shire, Sunovion, Takeda, Theracos, Titan, and Wyeth; has received research support (paid to hospital) from AstraZeneca, Bristol-Myers Squibb, Forest, the National Institute of Mental Health, Neuralstem*, PAMLAB, Pfizer, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sunovion, Tal Medical, and Theracos; and has served (not currently) on the speakers bureau for Bristol-Myers Squibb and Pfizer. **Dr Salloum** has worked in the digital medicine group at Pfizer and, as of October 2019, is a full-time employee at Biogen. His work at Pfizer and Biogen is in no conflict of interest with the content of this report. **Dr Jha** has received contract research grants from Janssen and Acadia. **Dr Murrough** has provided consultation services to Otsuka, Clexio Biosciences, FSV7, Boehreinger Ingelheim, Sage Therapeutics, Novartis, Allergan, Fortress Biotech, Janssen, Genentech, MedAvante-Prophase, and Global Medical Education; has received research support from Avanir; and is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders. The Icahn School of Medicine (employer of Drs Jha and Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine or esketamine for the treatment of depression. The Icahn School of Medicine is also named on a patent related to the use of ketamine for the treatment of posttraumatic stress disorder. Drs Jha and Murrough are not named on this patent and will not receive any payments. **Dr Mathew** has received consulting fees from Clexio Biosciences, Alkermes, Janssen, Perception Neurosciences, and SAGE Therapeutics; has received research support from Biohaven, NeuroRx, Janssen, and VistaGen Therapeutics; and is supported by the use of facilities and resources at the Michael E. DeBakey VA Medical Center, Houston, Texas. **Dr Iosifescu** has received consulting fees from Alkermes, Axsome, Centers for Psychiatric Excellence, Jazz, Lundbeck, MyndAnalytics (CNS Response), Otsuka, Perception Neuroscience, and Sunovion and research grants from LiteCure and Neosync. **Dr Fava** has received research support from Abbott, Acadia, Alkermes, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir, AXSOME Therapeutics, Biohaven, BioResearch, BrainCells Inc, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Cerecor, Clintara, LLC, Covance, Covidien, Eli Lilly, EnVivo, Euthymics Bioscience, Forest, FORUM Pharmaceuticals, Ganeden Biotech, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffman-LaRoche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen, Jed Foundation, Johnson & Johnson, Lichtwer Pharma GmbH, Lorex, Lundbeck, Marinus, MedAvante, Methylation Sciences Inc, National Alliance for Research on Schizophrenia & Depression, National Center for Complementary and Alternative Medicine, National Coordinating Center for Integrated Medicine, National Institute of Drug Abuse, National Institute of Mental Health, Neuralstem, NeuroRx, Novartis AG, Organon, Otsuka, PamLab, Pfizer, Pharmacia-Upjohn, Pharmaceutical Research Associates, Pharmavite, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche, RCT Logic (formerly Clinical Trials Solutions, LLC), Sanofi-Aventis, Shire, Solvay, Stanley Medical Research Institute, Synthelabo, Taisho, Takeda, Tal Medical, VistaGen, and Wyeth-Ayerst; has received advisory board/consultant fees from Abbott, Acadia, Affectis Pharmaceuticals AG, Alkermes, Amarin, Aspect Medical Systems, AstraZeneca, Auspex, Avanir, AXSOME Therapeutics, Bayer AG, Best Practice Project Management, Biogen, BioMarin, Biovail

Corporation, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Cerecor, CNS Response, Compellis, Cypress, DiagnoSearch Life Sciences, Dainippon Sumitomo, Dov, Edgemont, Eisai, Eli Lilly, EnVivo, ePharmaSolutions, EPIX, Euthymics Bioscience, Fabre-Kramer, Forest, Forum, GenOmind, GlaxoSmithKline, Grunenthal GmbH, Indivior, i3 Innovus/Ingenis, Intracellular, Janssen, Jazz, Johnson & Johnson, Knoll, Labopharm, Lorex, Lundbeck, Marinus, MedAvante, Merck, MSI Methylation Sciences, Naurex, Navitor Nestle Health Sciences, Neuralstem, Neuronetics, NextWave, Novartis AG, Nutrition 21, Orexigen, Organon, Osmotica, Otsuka, Pamlab, Pfizer, PharmaStar, Pharmavite, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa, PPD, Purdue Pharma, Puretech Ventures, PsychoGenics, Psylin Neurosciences, RCT Logic (formerly Clinical Trials Solutions, LLC), Relmada Therapeutics, Rexahn, Ridge Diagnostics, Roche, Sanofi-Aventis, Sepracor, Servier, Schering-Plough, Shenox, Solvay, Somaxon, Somerset, Sunovion, Supernus, Synthelabo, Taisho, Takeda, Tal Medical, Tetragenex, Teva, TransForm, Transcept, Usona Institute, Vanda, Versant Venture Management, and VistaGen; has speaking/publishing-related disclosures for Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon, CME Institute/Physicians Postgraduate Press, Eli Lilly, Forest, GlaxoSmithKline, Imedex, Massachusetts General Hospital (MGH) Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon, Pfizer, PharmaStar, United BioSource, and Wyeth-Ayerst; has equity holdings in Compellis and PsyBrain; has received royalty/patent/other income from patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven; and patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691); holds the copyrights for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; and has received publishing-related income from Lippincott, Williams & Wilkins, Wolters Kluwer, and World Scientific Publishing Co Pte Ltd. **Dr Hock** reports no financial relationships with commercial interests.

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Supplementary Material

Article Title: Efficacy of Esketamine Augmentation in Major Depressive Disorder: A Meta-Analysis

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List of Supplementary Material for the article

1. Figure 1 Funnel Plots and Egger Tests for Response and Remission Rates
2. Figure 2 PRISMA Diagram of Study Inclusion

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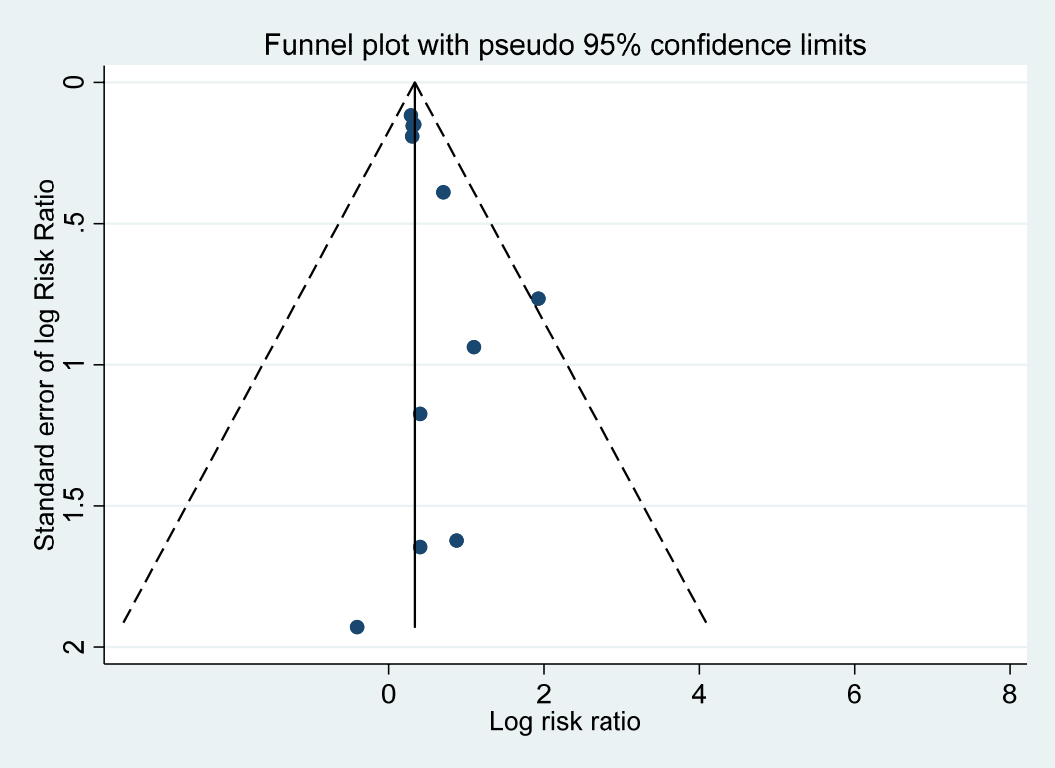
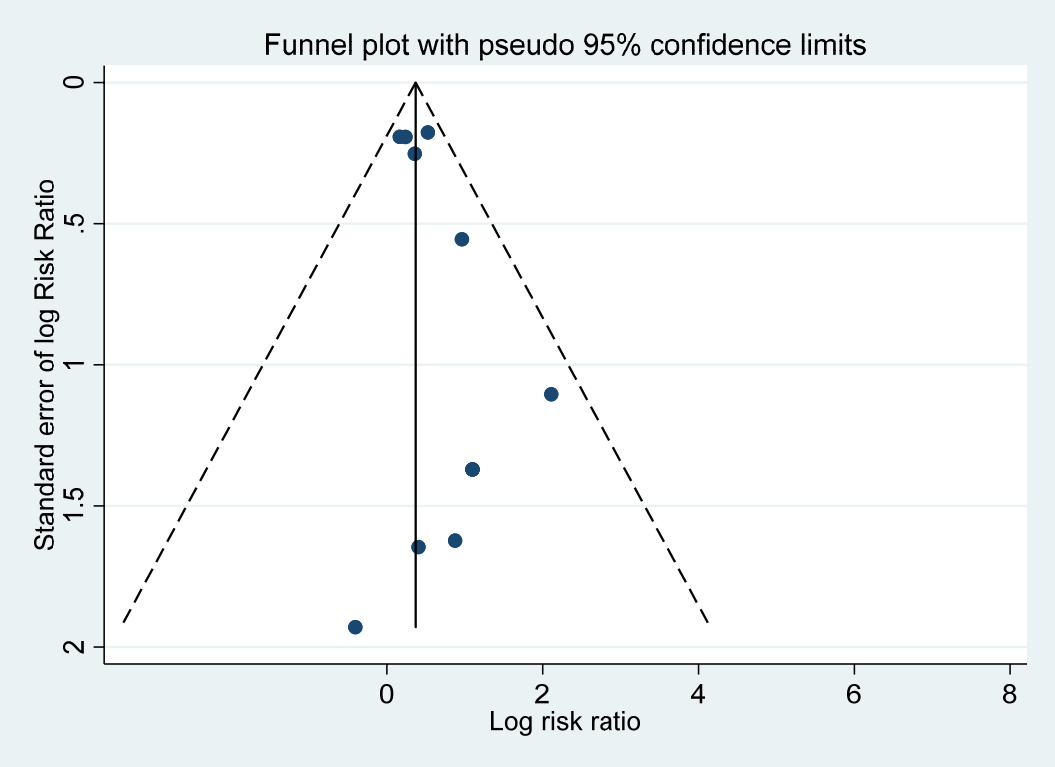
Supplementary Figure 1

Funnel Plot and Egger Test for Response Rate

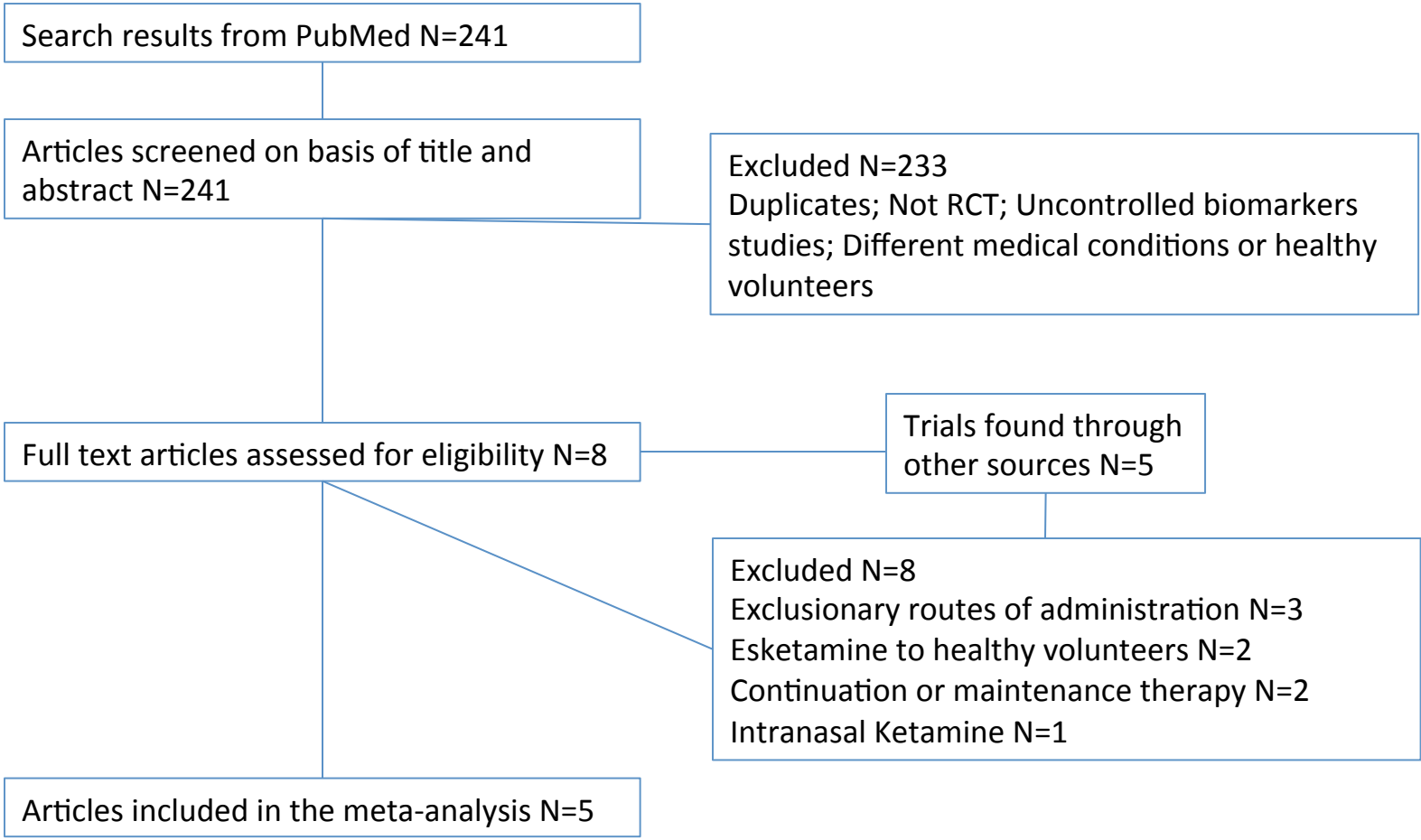


Egger test: bias = 0.6083153 (95% CI = -0.1082251 to 1.324856), P = 0.087

Funnel Plot and Egger Test for Remission Rate



Egger test: bias = 0.5785872 (95% CI = -0.2115034 to 1.368678), P = 0.132



Supplementary Figure 2. PRISMA Diagram of Study Inclusion

RCT: Randomized controlled trial