Esketamine Treatment for Depression in Adults: A PRISMA Systematic Review and Meta-Analysis

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Objective: Intranasal esketamine has been approved as an adjunctive therapy for treatment-resistant major depressive disorder with acute suicidal ideation and behavior. The authors conducted a systematic review and meta-analysis of the available data on its efficacy against depression and suicidality as well as its side effects.

Methods: MEDLINE was searched with the keyword "esketamine" on March 24, 2024, using the PRISMA method. Data processing and statistical analysis were performed with R, version 4.3.3, and the meta-analysis was performed with the METAFOR package.

Results: Of 1,115 articles initially identified, 87 were included for analysis and discussion. At weeks 2–4, randomized controlled trials were mostly negative or failed; however, the meta-analysis returned a weak but significant positive effect for depression (effect size range, 0.15–0.23 at weeks 2–4), similar to augmentation strategies with atypical antipsychotics for treatment-resistant depression. The effect size concerning suicidality was not significant at any time point. The sensitivity analysis produced the same results.

Conclusions: The study findings suggest that esketamine's efficacy as an add-on to antidepressants is modest in treatment-resistant depression (similar to augmentation strategies with atypical antipsychotics) and is absent against suicidality itself. These findings need to be considered in light of esketamine's abuse potential and the fact that long-term effects are still not fully known. Some alarming signs concerning deaths and emerging suicidality during the testing phase are discussed, along with other regulatory issues.

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Although the efficacy of antidepressants is solidly proven (1), a significant proportion of patients with depression do not respond to treatment, and in large pragmatic effectiveness trials, such as the Sequenced Treatment Alternatives to Relieve Depression study, only 40% of patients achieved sustained remission after a few months of treatment (2). The most frequently used criterion to define refractoriness is the failure to respond to two trials of pharmacological therapy of adequate dosage and duration in the current episode (3). For bipolar disorder, the definition is more complex (4).

While several augmentation options have been proposed, including atypical antipsychotics and lithium (5–7), more recently research has focused on the use of stimulants and psychedelics for treatment-resistant depression (TRD) (8–10). The true biological substrate of depression is largely unknown (11). Ketamine's antidepressant properties may stem from its effect on glutamate neurotransmission (12), and its enantiomer esketamine has an affinity three to four times higher for these receptors than the (R)-enantiomer (13). Similar differential activity has been observed for mu-opioid binding (14, 15). Thus, it was reasonable to suggest that esketamine should theoretically yield a better therapeutic effect than *R*-ketamine. In March 2019, the U.S. Food and Drug Administration (FDA) approved intranasal esketamine as an adjunctive therapy for TRD. This approval was followed in 2020 by a second indication for major depression with acute suicidal ideation and related behavior (16). This was considered to be a landmark approval for a first-of-its-class agent with rapid antidepressant effects in suicidally depressed patients. The European Medicines Agency (EMA) soon followed with an approval, but only for the first indication (that is, for the treatment of major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode) (17).

In spite of the significant bulk of publications on esketamine concerning both its clinical efficacy and its possible neurobiological pathways for exerting a therapeutic effect, many questions remain unanswered. While it seems certain that esketamine exerts a very early therapeutic effect, its efficacy over a period of weeks remains unknown, partly due to the way both trials and reviews and meta-analyses have been conducted. This question concerns esketamine's therapeutic effect both on depression and on suicidality. Its relative efficacy in comparison to other augmentation strategies is also unknown.

To understand the relative efficacy and risks of using esketamine and the need for new and effective treatments in patients with TRD (18–20), our aim in this study was to conduct a systematic review of the randomized controlled trials (RCTs) and other data on esketamine in adult patients with depression by using the patients–intervention–comparison–outcome (PICO) method to define the aim, and focusing especially on those with TRD (patients) concerning esketamine (intervention) specifically in comparison to placebo (comparison), in terms of improvement of depressive symptoms and suicidality (outcome) (21, 22).

METHODS

A MEDLINE search for reports on esketamine was conducted using the keyword "esketamine," on March 24, 2024; the method was over-inclusive and intended to identify all studies published concerning esketamine for any reason. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was followed in the selection of relevant studies. The present study was registered in PROSPERO (ID CRD42024516053).

To be included, studies had to be RCTs, case reports, case series, retrospective chart reviews, open trials, post hoc analyses of RCTs and open trials, systematic reviews, or meta-analyses concerning depression and suicidality in depression. Only articles in English were considered. The search results and data extraction were carried out by two of the authors (K.N.F. and A.S.). Where necessary, the data were extracted from plots, histograms, and other graphic representations. Data processing and statistical analysis were performed with R, version 4.3.3 (23), and the meta-analysis was performed with the METAFOR package (24).

A trial was considered to be "positive" at a specific time point when there was a statistically significant finding concerning the outcome (depression or suicidality). If such a significant result was not present, then the trial was considered "negative." "Failed" trials included those in which an extremely high placebo response led to a nonsignificant result.

Both a common-effect model and a random-effects model were applied. Heterogeneity (I) and the Q test were calculated. The meta-analytic method included the inverse variance method with a restricted maximum-likelihood estimator for tau-squared, the Q profile method for a confidence interval of tau-squared, and calculation of Hedges' g (bias-corrected standardized mean difference; using exact formulae).

The meta-analysis included the outcomes (standardized mean differences [SMDs]) concerning depression (Montgomery-Åsberg Depression Rating Scale [MADRS] scores) at up to 72 hours and at 1, 2, and 4 weeks separately (four time points) and suicidality (any available measure) at days 2–5 and at week 4 separately (two time points). The time points were defined after inspection of the dataset and the available data across time. Sensitivity analysis included the analysis separately of RCTs with patients with treatment-resistant and non-treatment-resistant depression, and separately all the analyses without the inclusion of the 28-mg arms (since this is considered to be a subtherapeutic dose by official labeling). All the outcome data were based on a mixed-effects model using repeated measures (MMRM), not intent-to-treat, since only this kind of data were available.

RESULTS

The MEDLINE search returned 1,115 articles, of which 574 remained after the first selection. One meta-analysis that included an unpublished trial in bipolar depression was also added. Eventually, 87 articles were included for this review. The FDA and EMA review reports provided additional information.

The PRISMA flowchart concerning the process of selecting the relevant papers is shown in Figure S1 in the online supplement.

Treatment of Depression

Randomized placebo-controlled trials (N=11).

Acute phase (N=10). Concerning the acute treatment of depressive episodes, there were 10 double-blind placebo-controlled trials, the details of which are summarized in Table 1. In total, they included 1,774 patients, of whom 979 were randomized to esketamine treatment (55.19%) and 795 (44.81%) to placebo. All included patients with unipolar TRD without psychotic features or other major mental disorders, except two that included non-treatment-resistant major depression (25, 26) and one that possibly included some patients with bipolar disorder but did not clarify this (27). That particular study utilized intravenous administration, whereas the other studies utilized a nasal spray. Two trials included patients with active suicidal ideation (25, 28). All studies utilized esketamine on top of ongoing or newly initiated standard treatment with antidepressants (termed treatment as usual [TAU]).

The results based on the change from baseline in MADRS score are shown in Table 2, with the studies' primary outcomes indicated. Taken together, the primary and secondary outcomes of these trials (before meta-analysis) indicate that results were positive at 2–4 hours (25–29), at 24 hours (25–32), and at 48–72 hours (27, 28); possibly positive at 4 days (25–27); inconsistent from day 8 onward (25, 26, 28, 31–33); and negative at week 4 (26, 30–34). Especially at week 2, all four trials, and at week 4, five of six trials, were negative (25, 26, 30, 32, 34) despite continued twice-weekly nasal administration, and for four of them, this negative finding constituted their primary outcome. The lack of continued superiority for esketamine may reflect the placebo plus TAU arm catching up to the esketamine plus TAU arm rather than a decreasing effect in the esketamine arm over time. An interesting observation is that in one study, on day 25 with the application of the nasal spray, the response rate in the placebo arm jumped from a previous 48% to 61% while the

esketamine arm remained stable (from 59% to 60%). A similar picture was observed with the remission rates (from 27% to 37% and from 43% to 47%, respectively) (25).

In the only study in elderly patients, 138 participants with TRD were randomized to esketamine or placebo, and esketamine was not superior to placebo at day 28 (33).

In summary, the acute-phase trials suggest that esketamine is effective during the first week of administration, but the difference from placebo wanes with time. One should keep in mind that the standard endpoint for the primary outcome in antidepressant trials is at 4–6 weeks. However, after 24 hours, only one of five trials had a primary positive outcome at 2 days that lasted up to 4 weeks (Table 2), suggesting that esketamine does not fulfill the standard FDA and EMA requirements of two positive phase 3 trials for an agent to receive approval. Moreover, the findings do not meet recent FDA guidelines on psychedelics in depression, where durability must be demonstrated in the pivotal trials, nor recent recommendations from our group on the so-called rapidly acting antidepressants (35).

Maintenance/randomized discontinuation phase trial (N=1). There was only one maintenance trial (SUSTAIN-1; NCT02493868), which tested the effect of discontinuation after long-term treatment. It included 297 patients (mean age, 46.3 years; 66.3% female) who had achieved at least a 50% reduction from baseline in MADRS score after esketamine nasal spray administration in two previous clinical trials (31, 34). The maintenance trial included a randomized withdrawal event-driven maintenance phase design of variable duration, after 16 weeks of optimized treatment with a flexible dosage of esketamine and antidepressants. The primary outcome (time to relapse) was significant both for patients with response at baseline ($p=0.003$) and for those who were in remission at baseline ($p<0.001$). Among the patients with stable remission, relapse was experienced by 26.7% in the esketamine plus TAU group and 45.3% in the placebo plus TAU group ($p=0.003$; number needed to treat [NNT]=6), while among those with response, relapse was experienced by 25.8% in the TAU plus esketamine group and 57.6% in the TAU plus placebo group ($p<0.001$; NNT=4). This suggests that continued esketamine in addition to an antidepressant decreased the risk of relapse by 51% (hazard ratio=0.49, 95% CI=0.29, 0.84) in patients with remission and by 70% (hazard ratio=0.30, 95% CI=0.16, 0.55) in patients with a response (36). These data have been utilized as supportive data on the efficacy of esketamine in major depression.

It is important to note that the FDA raised the concern that the positive results of this study could be driven by a single site in Poland (N=16, with a 100% relapse rate in the placebo arm vs. N=81 and a 33% relapse rate in this arm at all other sites) (37, 38). The exclusion of this particular site from the calculations extinguished any significant difference between arms (the p value changes from 0.012 to 0.48) (39), leading to the conclusion that esketamine does no better than placebo in the long term.

The interpretation of this study is complex because it depends heavily on the assumptions concerning efficacy during the acute phase. It is clear that all patients were receiving esketamine for several weeks before entering the study, and randomization in the placebo arm meant discontinuation from esketamine but not from TAU. Depending on the interpretation of the acute phase results, if one accepts that there is some acute positive effect for esketamine, then the maintenance data should also be considered positive, with the reservation concerning the Polish center. On the other hand, if one accepts that the acute-phase blinded studies did not support the acute and continued efficacy of esketamine (see the subsection "Acute phase," above), then the interpretation of this maintenance study is unclear. Could it be that the dramatic relapse rates after discontinuation of esketamine (but not of TAU) signify a withdrawal syndrome triggering a depressive relapse?

Head-to-head comparisons (N=4). Esketamine was not inferior to ketamine at 24 hours after administration in a randomized, double-blind, active-controlled, non-inferiority clinical trial (UMIN000032355), which randomized 63 patients with TRD without psychotic features (it is unknown whether any patients with bipolar disorder were included) to a single 40-minute intravenous infusion of ketamine (0.5 mg/kg) or esketamine (0.25 mg/kg) (40).

The comparison of a single 40-minute intravenous infusion of esketamine (N=30; 0.25 mg/kg) versus ketamine (N=29; 0.5 mg/kg) at 24 hours, at 72 hours, and at 7 days postinfusion revealed no difference between the two arms in terms of changes in suicidality (41).

After approval by the regulatory authorities, a 6-week double-blind pilot trial (ChiCTR2100050335) in 30 patients with unipolar non-treatment-resistant depression without psychosis and with fluctuating antidepressant response was reported. Patients were randomized to receive a single dose of intravenous esketamine (0.2 mg/kg) or midazolam (0.045 mg/kg) on top of their ongoing antidepressant treatment. The response rate at 2 weeks (primary outcome) was significantly higher in the esketamine-treated group (66.7% vs. 6.7%; $p<0.001$), and there was also a significant difference in the reduction in MADRS score (reduction of 15.7 vs. 3.1; $p<0.001$) (42).

In the ESCAPE-TRD trial (NCT04338321), which was a multicenter open-label, single-blind, phase 3b, randomized, active-controlled trial of esketamine versus extended-release quetiapine, both in combination with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) (N=676), esketamine was found to be superior in terms of remission at week 8 (27.1% vs. 17.6%; $p=0.003$) and no relapse through week 32 after remission (21.7% vs. 14.1%) (43).

The head-to-head comparison trials suggest that esketamine is equal to ketamine and superior to add-on quetiapine for TRD. However, both head-to-head studies of esketamine versus ketamine were small and were not powered to detect superiority of one treatment over the other.

TABLE 1. Characteristics of the randomized controlled trials of esketamine for the acute treatment of depressive episodes[a]

Study	Diagnosis	Diagnostic Tool	Duration	Primary Outcome	Route	Mean Age (years)
Canuso et al. (28) (NCT02133001)	Unipolar depression with suicidal ideation, without psychotic features or personality disorders	MINI	8 weeks	MADRS change at 4 hours	Nasal spray	35.8
Singh et al. (27) (NCT01640080)	TRD without psychotic features, suicidality, anxiety disorder, or OCD	MINI	4 days	MADRS change at 24 hours	Intravenous	43.0
Fu et al. (26) (NCT03039192; ASPIRE I)	Unipolar depression and active suicidal ideation with intent, without psychotic features, OCD, or personality disorders	MINI	4 weeks	MADRS change at 24 hours	Nasal spray	39.3
Ionescu et al. (25) (NCT03097133; ASPIRE II)	Unipolar depression and active suicidal ideation with intent, without psychotic features, OCD, or personality disorders	MINI	4 weeks	MADRS change at 24 hours	Nasal spray	40.8
Daly et al. (29) (NCT01998958)	Unipolar TRD of moderate or severe symptom severity, without psychotic features, suicidal tendencies, or personality disorders	Unknown	2 weeks	MADRS change at week 1 and week 2	Nasal spray	44.7
Fedgchin et al. (34) (NCT02417064; TRANSFORM-1)	Unipolar TRD of moderate or severe symptom severity, without psychotic features, suicidal tendencies, or personality disorders	MINI	4 weeks	MADRS change at day 28 for the 84-mg arm	Nasal spray	46.3
Ochs-Ross et al. (33) (NCT02422186)	Unipolar TRD of moderate or severe symptom severity, without psychotic features, suicidal tendencies, or personality disorders	Unknown	4 weeks	MADRS change at day 28	Nasal spray	70.5
Popova et al. (31) (NCT02418585; TRANSFORM-2)	Unipolar TRD of moderate or severe symptom severity, without psychotic features, suicidal tendencies, or personality disorders	MINI	4 weeks	MADRS change at day 28	Nasal spray	45.63
Takahashi et al. (32) (NCT02918318)	Unipolar TRD without psychotic features or suicidal ideation	MINI	4 weeks	MADRS change at day 28 for the 84-mg arm	Nasal spray	43.4
Chen et al. (30) (NCT03434041)	Unipolar TRD without suicidal ideation, psychotic features, OCD, or personality disorders	MINI	4 weeks	MADRS change at day 28 for the 84-mg arm	Nasal spray	37.3

[a] BIW=twice per week; MADRS=Montgomery-Åsberg Depression Rating Scale; MINI=Mini International Neuropsychiatric Interview; OCD=obsessive-compulsive disorder; TRD=treatment-resistant depression.
[b] At 24 hours.
[c] The first number refers to week 1, and the second to week 2.
[d] The study had a complex design that included subsequent phases with re-randomization.
[e] Only response rates were reported, and only for the Chinese subsample.

Post hoc analyses (N=36). There have been several post hoc analyses of existing datasets, and they have varied in their conclusions. One analysis of the pooled data from the TRANSFORM-1 and -2 studies (31, 34) suggested that sleep was significantly improved at all time points with esketamine. Response of depression was unrelated to baseline sleep problems, but it correlated with its improvement with a strong predictive value (44). A second post hoc analysis suggested that the symptoms predictive of a better response to esketamine were anhedonia, hopelessness, and fatigue (45). A third analysis reported that by day 28, 78.2% of patients in the esketamine group reached or exceeded the threshold for clinically meaningful change, compared with 65% in the placebo group (46). A fourth analysis rejected the idea that there is an association between esketamine's antidepressant effect and the dissociation patients feel after it is administered (47). A fifth analysis found that patients treated with esketamine who had not responded on days 2 and 8 still had a higher odds ratio for response on day 28 in comparison to those who received placebo (odds ratio=1.61, 95% CI=1.09, 2.40) (48). A sixth analysis reported no effect of baseline irritability on the treatment outcome (49). The post hoc analysis of the TRANSFORM-2 data alone (31) suggested that the esketamine effect at day 28 was significant irrespective of the presence of comorbid anxiety (50) and beneficial in terms of functional impairment and quality of life (51), and that at the end of 4-week treatment, the MADRS and the Clinical Global Impressions severity scale (CGI-S) were equally efficacious in the detection of response to esketamine (52). Attainment of response and remission was more likely in patients who were employed, did not have significant anxiety at baseline, and experienced a reduction

Female (%)	Study Arms	N	Primary Outcome (mean)	Response (%)	Remission (%)	Dropout Rate (%)	Comments
65.2	84 mg (total dose)	35	−13.4		34.3[b]	14.3	Positive trial; positive at day 4 (effect size=0.61), negative at day 25
	Placebo	31	−9.1		16.1[b]	3.2	
60.0	0.20 mg/kg once	9	−16.8	67.0		0.0	Positive trial; some patients with bipolar disorder may be included
	0.40 mg/kg once	11	−16.9	64.0		9.0	
	Placebo	10	−3.8	0.0		0.0	
61.6	56–84 mg BIW	112	−16.4		19.0	16.1	Positive trial; probably negative results at day 28
	Placebo	112	−12.8		9.0	21.4	
59.9	56–84 mg BIW	115	−15.7	35.0	22.0	21.7	Positive trial; negative results after day 2
	Placebo	115	−12.4	24.0	11.0	18.3	
56.7	28 mg BIW	11	−9.8; −7.6[c]	13.0	13.0	27.3	Positive trial
	56 mg BIW	11	−12.4; −8.9[c]	0.0	0.0	0.0	
	84 mg BIW	12	−15.3; −11.4[c]	20.0	20.0	8.3	
	Placebo	33	−4.9; −4.5[c]	0.0	0.0	0.0[d]	
70.5	56 mg BIW	115	−19.0	54.1	36.0	5.1	Negative trial concerning the primary outcome; positive (p=0.02) for the secondary outcome involving the 56-mg dose
	84 mg BIW	114	−18.8	53.1	38.8	16.4	
	Placebo	113	−14.8	38.9	30.6	5.3	
62.0	28/56/84 mg BIW	72	−10.1	27.0	17.5	13.89	Negative trial concerning the primary outcome; older patients (>65 years old)
	Placebo	66	−6.1	13.3	6.7	9.09	
38.1	56–84 mg BIW	114	−21.4	69.3	52.5	15.8	Positive trial
	Placebo	109	−17.0	52.0	31.0	11.0	
47.5	28 mg BIW	41	−15.2	33.3	23.1	3.8	Negative trial concerning the primary outcome
	56 mg BIW	40	−14.5	35.3	11.8	0.0	
	84 mg BIW	41	−15.1	43.6	23.1	4.3	
	Placebo	80	−15.3	37.5	20.8	5.7	
45.2	56–84 mg BIW	126	−10.1	34.0[e]		14.3	Negative trial concerning the primary outcome
	Placebo	126	−8.1	35.5		15.9	

in CGI-S score on day 8 (53). The pooled analysis of all three TRANSFORM trials (31, 33, 34) found no effect of sex in the therapeutic efficacy of esketamine (54). The post hoc analysis of the TRANSFORM trials and the SUSTAIN-1 trial (31, 33, 34, 36) found significantly more remitters in the esketamine arm among patients over age 65, but not more responders, and found neither more responders nor more remitters among the rest of the patients at day 28 (55). The post hoc analysis of the TRANSFORM-2 and SUSTAIN-1 data suggested that within the dose range tested, the dissociative and antidepressant effects of esketamine were not significantly correlated (56). MADRS response resulted in NNTs of 8 for response and 6 for remission for esketamine versus placebo. Maintenance demonstrated NNT values <10 for relapse and/or maintenance of remission (57).

The pooling of the data from the ASPIRE I and II studies (25, 26) suggested that esketamine was superior to placebo at 4 hours, at 24 hours, and at day 25 (58). Another pooled analysis of the same studies suggested that the esketamine effect was independent of the concomitant use of benzodiazepines, but the incidence of sedation was higher with benzodiazepine use, whereas dissociation was similar in the groups (59). A third pooled analysis found that most patient-reported outcomes about the inner experience and quality of life were significantly in favor of the esketamine group (60). A fourth pooled analysis reported that the median times to remission and consistent remission were significantly shorter in the esketamine arm and that a greater proportion of patients in the esketamine arm achieved remission and consistent remission by day 25 (65.2% vs. 55.5% and 54.2% vs. 39.8%, respectively) (61). A fifth analysis reported that 24-hour nonresponders were more likely to achieve response or remission after 4 weeks of treatment (response: odds ratio=1.89, 95% CI=1.17, 3.05; remission: odds ratio=1.48, 95% CI=0.93, 2.35) (62). The Asian subgroup showed an efficacy and safety profile similar to that of the total ASPIRE I cohort (63).

A post hoc analysis of the Daly et al. study (29) suggested that blinded remote ratings (without the likelihood of

TABLE 2. Change in MADRS score from baseline at different time points in randomized controlled trials of esketamine for depression[a]

Study	TRD	2–4 Hours	24 Hours	48 Hours	72 Hours	4 Days	8 Days	11 Days	Week 2	Week 3	25 Days	Week 4	81 Days
Canuso et al. (28) (NCT02133001)		P[b]	P	P	P			P	N	N	N		N
Singh et al. (27) (NCT01640080)	Yes	P	P[b]	P	P	P							
Fu et al. (26) (NCT03039192 or ASPIRE I)		P	P[b]			P			N		P	N	
Ionescu et al. (25) (NCT03097133 or ASPIRE II)		P	P[b]			N	N		N	N	N[c]		
Daly et al. (29) (NCT01998958)	Yes	P	P				P						
Fedgchin et al. (34) (NCT02417064 or TRANSFORM-1)	Yes		N[d]						P[e]			N[b,d]	
Ochs-Ross et al. (33) (NCT02422186)	Yes						N		N	N		N	
Popova et al. (31) (NCT02418585 or TRANSFORM-2)	Yes		P				P		P	P		P	
Takahashi et al. (32) (NCT02918318)	Yes		N						N			N	
Chen et al. (30) (NCT03434041)	Yes		P									N	

[a] MADRS=Montgomery-Åsberg Depression Rating Scale; N=negative; P=positive; TRD=treatment-resistant depression.
[b] Primary outcome in the study.
[c] Positive before administration, but no difference afterwards.
[d] Positive for 56 mg, but negative for 84 mg; overall, it is considered a negative result.
[e] Data derived from a figure in the report's appendix.

functional unblinding) were comparable to site-based ratings of the efficacy of esketamine nasal spray (64). This approach could deal with the functional unblinding of raters but not of participants. A post hoc analysis of the Correia-Melo et al. study (40) suggested a positive relationship between dissociation intensity and the antidepressant effect 24 hours after ketamine and esketamine infusion (65). Another post hoc analysis of the same study reported that the number of past treatment failures and severity of illness were predictors of fewer remissions and responses (66). A third post hoc analysis of the same trial found that trait dissociation is a predictor of degree of induced dissociation with esketamine in patients with TRD (67). Two post hoc analyses of various studies found that there were clinically meaningful changes in patients with TRD treated with augmentation strategies, but these studies did not separately study esketamine per se (68, 69).

An important post hoc analysis of the Takahashi et al. study (32) suggested that there are different patterns of symptom improvement between esketamine and placebo, but only during the early phase of the intervention (70). This adds to the conclusion that esketamine acts in the early phase but that later its relative efficacy wanes.

Systematic reviews and meta-analyses (N=34).

Systematic reviews (N=18). Unfortunately, most systematic reviews did not "dig deep" into the data (71–74). One downgraded the negative efficacy data and pointed to safety issues (75). Another reported positive conclusions that appeared contradictory to the actual findings presented (76). A third argued that the TRANSFORM-1 and -2 studies found significant reduction in the MADRS score at day 28 for the fixed and the flexible 56-mg dosing, but that the fixed-dose 84-mg arm of TRANSFORM-1 and TRANSFORM-3 had negative results (77).

A systematic review supported the efficacy of esketamine during the acute phase and during maintenance (78), but another one suggested that the data concerning its long-term use are insufficient (79).

Short reviews that included only the trials submitted to the FDA expressed doubts concerning the clinical usefulness of esketamine (38, 80).

One review that included only four of the RCTs, one open-label clinical study, and one case series reported on the efficacy of ketamine or esketamine on subjective measures of general functioning. Overall, mixed results were reported concerning the effect across disparate functional measures. Functional outcomes in adults with TRD receiving ketamine or esketamine were insufficiently characterized and not well documented (81).

One umbrella review (82) identified only two systematic reviews or meta-analyses on esketamine, and although they reported positive conclusions, they either missed most recent studies or pooled outcomes at different time points (83, 84), while another one concluded that there was more or less sufficient diversity inclusion in the esketamine trials (85).

One systematic review confirmed the efficacy of non-intranasal esketamine (86).

Overall, systematic reviews and meta-analyses have concluded that esketamine is effective and well tolerated, although the quality of the included reviews and the original studies is poor, resulting in low certainty of evidence (87).

Meta-analyses (N=16). Earlier meta-analyses included only early studies or were very selective, and they often mixed outcomes across different time points. Two were positive for both the acute effect and the effect at 3–4 weeks (88, 89). Another confirmed esketamine efficacy at 24 hours (90). The meta-analyses of the TRANSFORM-1 and -2 studies reported a greater improvement in MADRS score for esketamine compared with placebo (mean difference=−3.84, 95% CI=−6.29, −1.39). Patients in the esketamine arm were more likely to achieve clinical response (relative risk=1.30, 95% CI=1.08, 1.56) but not clinical remission (relative risk=1.37, 95% CI=0.99, 1.91) (91). Another meta-analysis suggested that adding esketamine to antidepressants was superior to adding an antipsychotic (92), and another found esketamine to be inferior to lithium but superior to other augmentation strategies (93). Racemic ketamine relative to esketamine demonstrated greater overall response (relative risk, 3.01 vs. 1.38) and remission rates (relative risk, 3.70 vs. 1.47) as well as lower dropout rates (relative risk, 0.76 vs. 1.37) (94), a finding not confirmed by a later meta-analysis by the same authors (95). One meta-analysis pooled data from seven RCTs, but it is unclear whether it pooled outcomes at different time points. It reported that esketamine was more effective than placebo at decreasing depressive symptoms (d=−0.239, 95% CI=−0.335, −0.142; p<0.0001), with higher rates of response (relative risk=1.221, 95% CI=1.055, 1.428; p=0.017) and remission (relative risk=1.366, 95% CI=1.182, 1.578; p<0.0001) (96). A more updated meta-analysis reported a positive conclusion concerning the efficacy and usefulness of esketamine (97).

More recent meta-analyses have reported favorable efficacy results, despite identifying the negative results of individual studies. One included some apparent errors (for example, considering the results of the NCT01998958 study positive at week 4) (98). Another reported that all main outcomes (MADRS score reduction and response and remission rates) were significantly in favor of the esketamine arm (99, 100). That meta-analysis included only three of the studies with data on day 28 (31, 33, 34). It is not clear why two trials were not included (26, 32); the seventh RCT (30) was not published at that time.

Another meta-analysis found esketamine to be efficacious in the treatment of early-stage TRD, but it was not superior to other augmentation strategies (101). The two most recent meta-analyses found no effect of esketamine on suicidality (102) and a slight superiority of psilocybin in comparison to esketamine (103).

The Effect of Esketamine on Suicidality

RCTs on the effect of esketamine on suicidality (N=11). In total, studies included 1,774 patients, of whom 979 were randomized to esketamine (55.19%) and 795 (44.81%) to placebo. The data suggest that there is a significant effect of esketamine on suicidality 2–4 hours after administration (28, 89). Data on assessment at 24 hours after administration are equivocal, with one study reporting positive results (25) and three being negative (26, 28, 89). With the data pooled from all placebo-controlled RCTs reporting data until week 1, one was positive (28) and four were negative (25, 26, 30, 31). All seven trials reporting on the effect of esketamine on suicidality around week 4 were negative (25, 26, 28, 30, 31, 34, 89).

The second FDA labeling on TRD with suicidal ideation was based on the trial by Fu et al. (26). While the labeling does not directly refer to suicidality, it implies an efficacy against it. In that specific trial, four of five suicidality indices were negative, including the key secondary outcome. Only the MADRS suicidal item was positive at two of four time points.

In four of the trials, there was no significant increase in suicidality, but the report was based on adverse events (27, 32, 34, 36). In another study, however, eight of 70 (11.4%) patients in the esketamine versus nine of 65 (13.8%) in the placebo group had postbaseline suicidal ideation, although none had suicidal ideation at baseline (33).

Post hoc analyses of the effect of esketamine on suicidality (N=6). Across the ASPIRE I and II studies, the resolution of suicidality was significant at 4 hours (33.2% vs. 20.0%) but not at 24 hours (34.5% vs. 32.9%) or at day 25 (61.9% vs. 54.7%) (58). The post hoc analysis of pooled data from both ASPIRE studies suggested that the time to achieving a score ≤1 on the Clinical Global Impression–Severity of Suicidality–Revised Version (CGI-SS-r) (indicating not suicidal/questionably suicidal) was significantly shorter in the esketamine group, with a median time of 17 days versus 25 days (adjusted hazard ratio=1.51, 95% CI=1.15, 1.98; p=0.003) (61). No difference between arms concerning the Patient Health Questionnaire–9 and MADRS items on suicidality was reported (45). A post hoc analysis of the NCT02133001 and ASPIRE I and II trials suggested that esketamine reduces suicidal thoughts at 4 hours but not at any other time point (104). Post hoc analysis of the NCT02918318 trial found no significant effect of esketamine on suicidal thoughts (70). The subanalysis of the Asian subsample from the ASPIRE I study revealed no significant effect of esketamine on the CGI-SS-r score on day 2 (63).

Reviews and important papers concerning the effect of esketamine on suicidality (N=18). There were several alarming reviews and opinion papers that noted that six deaths, of which three were suicides, occurred in the trials, all of them in the esketamine arm (25, 26, 43, 105, 106). The three suicides occurred 4, 12, and 20 days, respectively, after the last dose of esketamine. Two of the patients who died by suicide showed no previous signs of suicidal activity during the study, either at baseline or at the last visit (107). This report was based on an FDA document. Another review (106)

identified an increase in depression and suicidality during esketamine treatment compared with placebo, since in the short-term trials, six participants (1.4% of the total) in the esketamine group became more depressed, compared with only one in the placebo group (0.2%); five participants in the esketamine group (0.9%) expressed increased suicidal ideation, compared with two in the placebo group (0.5%). Furthermore, in the safety study, one in seven patients developed "treatment-emergent" suicidal ideation, and six patients attempted suicide, in a group selected for not being actively suicidal. Overall, some authors suggest that a disproportionate number of suicides have been attributed to esketamine in the first year of its use in the United States (37, 80, 108).

Two reviews concluded that the long-term data on suicidality are inconsistent (79, 109). One review supported esketamine efficacy up to 24 hours (110), while an umbrella review reported that the effects of esketamine on suicidal ideation were apparent up to 72 hours postintervention, but not at later time points compared with controls (82). One systematic review concluded that esketamine is efficacious at week 4, although its own findings from the review of the literature did not support it (73), while another three were negative (83, 111, 112).

The comparison of a single 40-minute intravenous infusion of esketamine (N=30; 0.25 mg/kg) versus ketamine (N=29; 0.5 mg/kg) at 24 hours, at 72 hours, and at 7 days revealed no difference between the two arms in terms of changes in suicidality (41).

Meta-analytic studies concerning the effect of esketamine on suicidality (N=6). One meta-analysis found no effect of esketamine on suicidality (55), and another found it equal to ketamine (94). A third meta-analysis found no significant increase in suicidal thoughts with esketamine treatment (77). A more recent meta-analysis identified a significant antisuicidal effect at 4–6 hours (Cohen's d=0.26, 95% CI=0.09, 0.44) and at 24 hours (Cohen's d=0.30, 95% CI=0.17, 0.47), but this effect was inferior to that of ketamine (113). In terms of number needed to treat, the meta-analysis of the data from the TRANSFORM-1, -2, and -3 studies and the SUSTAIN studies suggested that remission defined on the basis of the CGI-S score yielded an NNT of 12. Only a different criterion was significant at all the time points assessed (days 8, 15, 22, and 28), and that outcome was the decline of CGI-S score ≥2 points from baseline to endpoint (NNT=8) (57). The most recent meta-analysis found no effect of esketamine on suicidality (102).

Meta-Analysis of Findings for Depression and Suicidality

Main findings. Figures 1 and 2 show forest plots of the results of the meta-analysis for depression (MADRS scores) concerning the placebo-controlled randomized trials for all four time points. For all studies, the results were significant at all time points, with the effect size being 0.33 for the first 24 hours; it dropped to 0.25 at week 1 and 0.15 at week 2, and it was 0.23 at week 4 (random-effects model).

In Figure 3, the results for suicidality are shown at two time points—days 2–5 and week 4. For all studies, the results were not significant at any time point; the effect size was 0.10 for the first 2–5 days, and it dropped to 0.04 at week 4 (random-effects model).

Overall, the heterogeneity was variable. The Q testing for heterogeneity is summarized in Table 3.

Sensitivity analyses. For the MADRS, the results were similar for patients with TRD (0.33, 0.26, 0.15, and 0.21 for the four time points respectively) and those with non-treatment-resistant depression (0.26, 0.20, 0.15, and 0.29 respectively), with overlapping confidence intervals. Without the inclusion of the 28-mg arms for all studies, the effect sizes were 0.32, 0.25, 0.15, and 0.24, respectively (random-effects model).

For suicidality, all the results were negative and were similar for patients with TRD (0.01 and 0.02 for the two time points, respectively) and those with non-treatment-resistant depression (0.24 and 0.17 respectively). Without the inclusion of the 28-mg arms for all studies, the effect sizes were exactly the same (random-effects model).

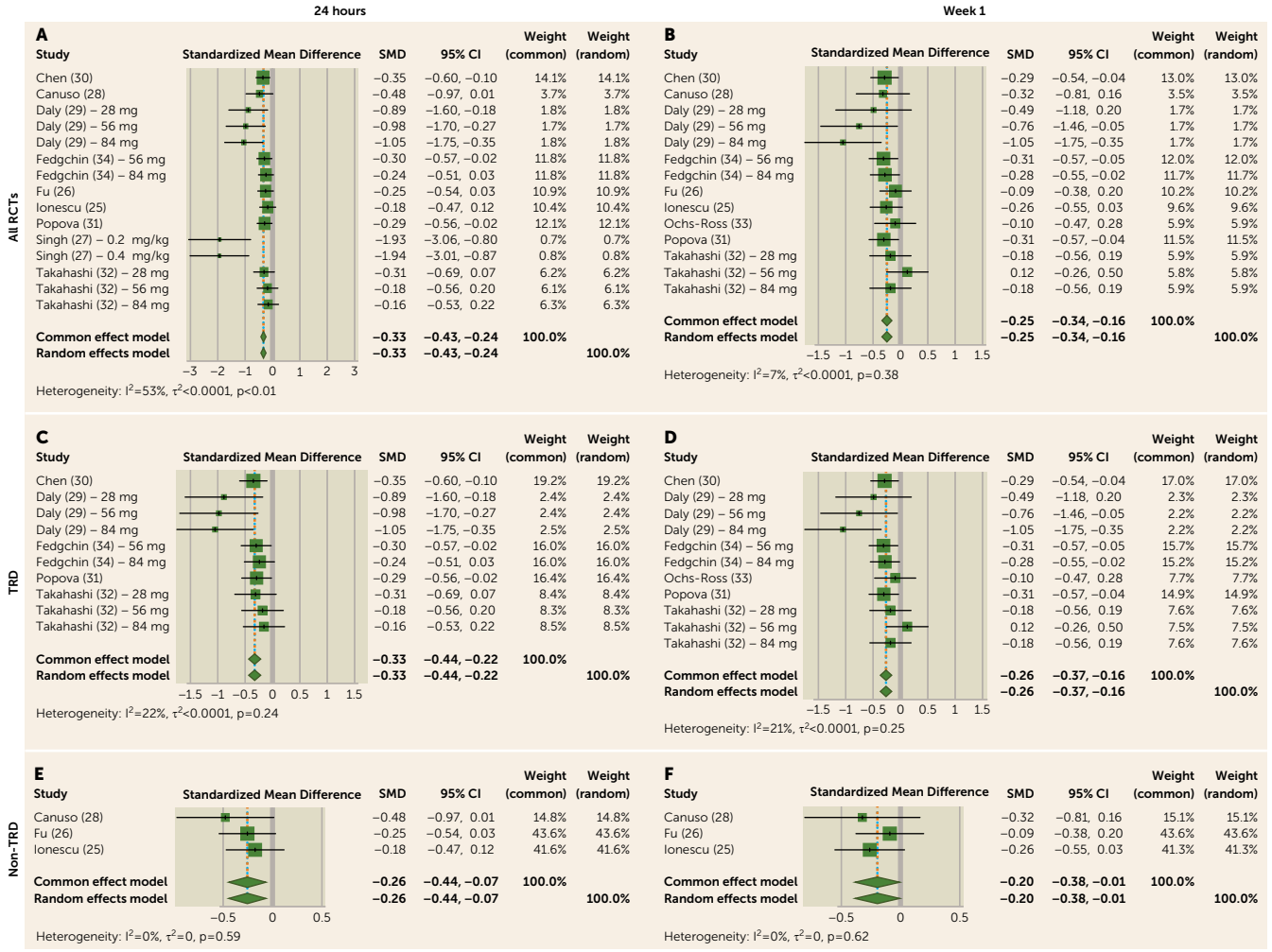
Overall, sensitivity analyses did not produce different results.

DISCUSSION

In this systematic review and meta-analysis, we found that the trial data concerning the efficacy of intranasal esketamine as an add-on treatment in depression are mostly negative after the first few days, despite a significantly greater early improvement in comparison to placebo. Only one of five studies returned positive results on depressive symptoms at week 4 concerning the primary outcome (the sixth was also negative; see Table 2). The meta-analysis suggested the presence of a weak effect, similar to augmentation strategies with atypical antipsychotics (93, 101, 114), with the strongest effect seen on depressive symptoms acutely and smaller effects at 4 weeks. Moreover, both the individual studies and meta-analysis were negative concerning an effect on suicidality at all time points, even acutely, other than one early study (28). This finding questions the reason behind the second indication of the product. Interestingly, the effect size seems to be the same in TRD and non-TRD, and the difference from placebo attenuates over time. The relatively strong effect during the first 24 hours is very interesting, taking into consideration the delayed onset of the treatment effect with antidepressants (115). In exploring effect sizes on depression, the data were understandably similar to the efficacy data.

The present paper is not the first to report negative conclusions about esketamine. Previous reviews and meta-analyses have pointed out that the data are inconclusive at

FIGURE 1. Forest plots of results of randomized controlled trials concerning depression at 24 hours and 1 week, and separately for treatment-resistant and non-treatment-resistant depression[a]

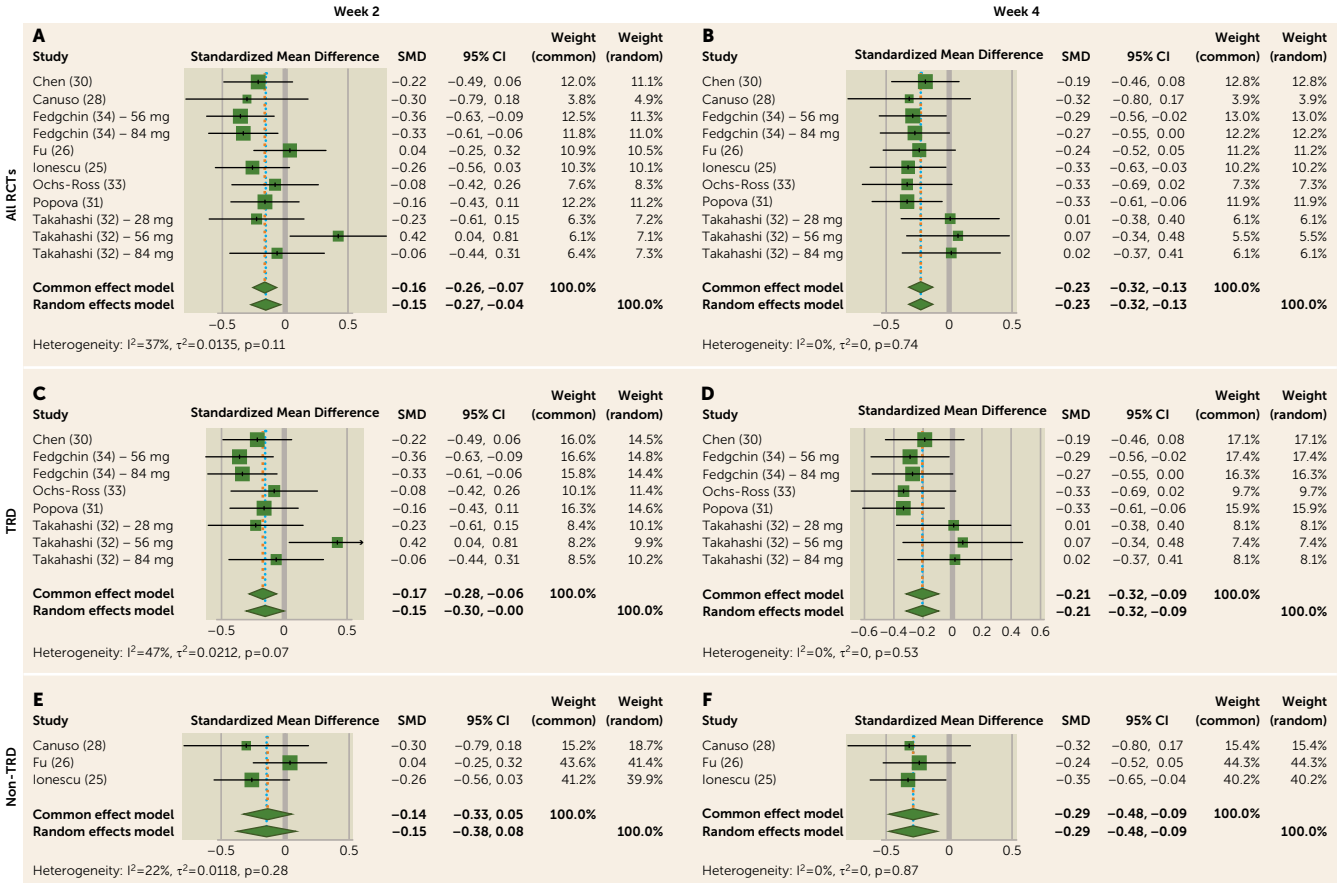


[a] Depression was assessed with the Montgomery-Åsberg Depression Rating Scale. SMD=standardized mean difference.

best, especially concerning the sustainability of the effect (84, 102) and its being antisuicidal (102). Sustainability of the effect may be more important than rapid action, since the main unmet need in TRD is to have treatments that produce sustained effects rather than rapidity of onset of effect (35). Given the extreme majority of negative (N=5) versus positive RCTs (N=1) at weeks 2–4, skepticism seems warranted, especially since the disappearance of the early positive effect and the possibility of the presence of a withdrawal effect have been discussed since the first appearance of ketamine as an antidepressant agent.

Several authors argue that many factors may contribute to the failure to observe statistically significant therapeutic differences; however, this would be the same for virtually all clinical trials of add-on agents (116–119). This line of thinking implies that these esketamine studies are not "negative" but are "failed," suggesting that they failed to find a positive effect while it is certainly there. Two trials may have a high enough placebo response to be considered as failed (25, 26), but on the other hand, the "failed" argument is inconsistent with the strong positive early response during the first week or so, since the placebo effect size was not high enough to mask the difference. Additionally, the trial results suggest that the studies were powered sufficiently and adequately designed to identify a significant difference if one appeared. However, the early superiority of esketamine over placebo tends to disappear over time. One particular problem that should kept in mind when interpreting the results is that in the development program for esketamine, the FDA took the unprecedented step of requiring that a novel antidepressant be started at the same time as randomization to drug (in this case, esketamine) or placebo. However, this would be expected to increase placebo response by enhanced expectancy effects; in fact, the placebo response in those trials with TRD was rather low, and the literature suggests that switching to a new antidepressant is not superior to continuing on the same one (120). The hospitalization of all subjects in several of the studies may have accounted for higher placebo responses in combination with the initiation of standard therapy. In addition, taking into consideration the inherent problems with

FIGURE 2. Forest plots of results of randomized controlled trials concerning depression at 2 weeks and 4 weeks, and separately for treatment-resistant and non-treatment-resistant depression[a]

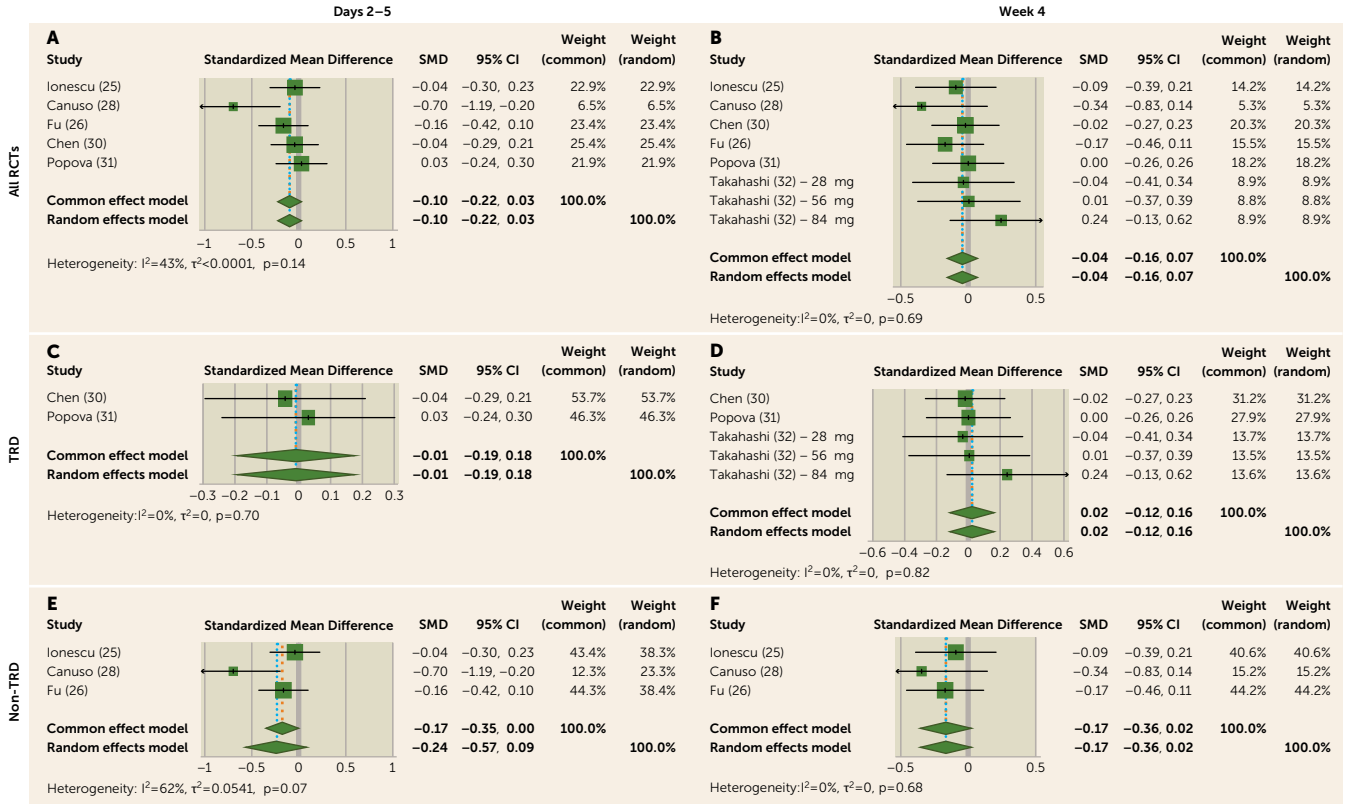


[a] Depression was assessed with the Montgomery-Åsberg Depression Rating Scale. SMD=standardized mean difference.

psychometric scales (e.g., the MADRS) (118), especially with the inclusion of items corresponding to nonspecific symptoms, effect sizes as low as those identified here should be interpreted with caution since they may reflect nonspecific changes in the clinical picture and not an antidepressant effect as such. For example, any agent that increases appetite, or any sedative, might change the rating of the respective items and subsequently the total MADRS score but without any true effect on depression per se. The lack of effect on the MADRS item that is specific for suicidality points to this possible alternative interpretation. Also, one should take into consideration that the dramatic manifestation of mental adverse effects in patients receiving esketamine makes study blinding problematic, which could further complicate the interpretation of positive effects. The use of a comparator that mimics some of the responsible adverse events might be important. Another line of argument suggests that the continuous use of an oral antidepressant—and, more importantly, of a new one—masks esketamine efficacy, or at least part of it. Few data are available on monotherapy with esketamine, although a completed double-blind placebo-controlled phase 4 trial (NCT04599855), in which patients with TRD were randomly assigned to receive esketamine monotherapy (nasal spray 56 mg or 84 mg twice weekly) or placebo, has been reported in a poster presentation (https://www.janssenscience.com/media/attestation/congresses/neuroscience/2024/ascp/efficacy-and-safety-of-esketamine-nasal-spray-as-monotherapy-in-adults-with-treatmentresistant-depre.pdf). At week 4, there was a significant change in MADRS score (least-square mean difference −5.1 for 56 mg and −6.8 for 84 mg; $p<0.001$), and the improvement was already observed 24 hours after the first dose of esketamine. While these results, if verified, point to an efficacy of esketamine as monotherapy in TRD, they are not superior to the results expected by continuing the same antidepressant or switching to a new one (see Table 1). It is also important to have in mind the superiority shown by esketamine in comparison to quetiapine in the head-to-head comparison, in combination with an SSRI or SNRI (although in an open label/single-blind design), in 676 patients (43).

One thought could be that since esketamine manifests an early effect that diminishes over time, its sole use could be as an accelerator of response, and after response is achieved, administration of esketamine should be stopped since there are no data to indicate continued benefit over TAU. Yet, we now have many patients who are taking esketamine on a long-term basis. This quandary has been created by the design of the phase 3 program that tried to ensure that

FIGURE 3. Forest plots of results of randomized controlled trials concerning suicidality at days 2–5 and 4 weeks, and separately for treatment-resistant and non-treatment-resistant depression[a]



[a] Suicidality was assessed with the Beck Scale for Suicidal ideation, the Clinical Global Impressions–Severity of Suicidality–Revised scale, or the Columbia-Suicide Severity Rating Scale. SMD=standardized mean difference.

patients were being treated with a purportedly active therapy for depression to lessen the risk of treating suicidal patients with esketamine or placebo alone. The phase 3 program thus not only did not prove efficacy in a standard two-positive-trial approach but also does not indicate that patients should be continued on esketamine beyond a few days. What would be useful here is to have a study that initially treated patients for 1 week with TAU plus esketamine and then randomized them to TAU plus either esketamine or placebo. That could answer the question of whether continuing the drug beyond a few days is needed.

Phase 3 efficacy overall was inferred partly from results in the maintenance discontinuation trial. This strategy has been used at times to determine whether a specific agent is clinically active, but a review of all the acute studies points to a dilemma here, where the discontinuation may not indicate continued efficacy but could reflect another phenomenon, such as psychological or physical dependence. This would explain the much higher rates of relapse when stopping the agent even while remaining on a known antidepressant. Thus, veering away from requiring two positive trials, coupled with the reliance on a discontinuation trial with an agent that has now been shown to have mu-opioid properties, may result in having many patients being on a longer-term regimen that has little positive data to support it. The FDA has addressed the need for durability beyond initial effects in a letter on issues in the development of psychedelics (121), but "the cow is now out of the barn" on esketamine.

A major concern is the six deaths in the RCTs, all in the esketamine arms. Three were suicides (4, 12, and 20 days after the last dose of esketamine; none had shown previous signs of suicidality), one was a motor vehicle accident (26 hours after esketamine administration), one was due to acute respiratory and cardiac failure (5 days after esketamine in a patient with risk factors), and one was due to myocardial infarction (6 days after esketamine in a patient with risk factors) (122). The argument that the rate of deaths by suicide is the expected rate among patients with TRD (123, 124) does not tackle the fact that all of them occurred in the esketamine arm and none in the placebo arm and in individuals who had not been suicidal before. Since all study subjects who died of suicide manifested an initial improvement, it is quite possible that worsening after an initial improvement is a likely cause. The interim analysis of the open-label SUSTAIN-3 study suggested that the therapeutic effect is sustainable over a period of 200 weeks. This result seems reliable at least until week 144, after which dropout increases dramatically, making the interpretation of results difficult. However, again, one death due to suicide was reported (105). There was no mention of what happens when patients try to go off the

TABLE 3. Q testing for heterogeneity in randomized controlled trials (RCTs) of esketamine for depression[a]

Measure	Q	df	p
MADRS			
24 hours			
All RCTs	29.63	14	0.0086
TRD	11.60	9	0.2367
Non-TRD	1.07	2	0.5861
7 days			
All RCTs	13.96	13	0.3768
TRD	12.60	10	0.2469
Non-TRD	0.96	2	0.6179
15 days			
All RCTs	15.77	10	0.1065
TRD	13.13	7	0.0690
Non-TRD	2.55	2	0.2797
28 days			
All RCTs	6.80	10	0.7440
TRD	6.10	7	0.5284
Non-TRD	0.20	2	0.9070
Suicidality			
2–5 days			
All RCTs	6.98	4	0.1368
TRD	0.15	1	0.7001
Non-TRD	5.20	2	0.0743
28 days			
All RCTs	4.76	7	0.6889
TRD	1.55	4	0.8175
Non-TRD	0.76	2	0.6841

[a] MADRS=Montgomery-Åsberg Depression Rating Scale; TRD=treatment-resistant depression.

medication entirely, which would mirror the timing of the early suicides in the open-label continuation studies. Other severe adverse events in RCTs included one nonfatal cerebral hemorrhage (125) and five nonfatal motor vehicle accidents (126), all in the esketamine arm. Some authors have argued that these deaths and severe adverse events resemble a pattern of a severe withdrawal reaction similar to that of opioids (127), and this also fits with reports of suicide linked to recreational ketamine use (128, 129). Another major issue is the observation that in some patients, there is a worsening of their clinical symptoms. In the short-term trials, six participants (1.4%) in the esketamine arm versus one on placebo (0.2%) became more depressed, and five (0.9%) in the esketamine arm versus two on placebo (0.5%) expressed increased suicidal ideas (125). The numbers and percentages are not high, but still, they point to the presence of a vulnerable subgroup for which the use of esketamine might be contraindicated.

There is considerable research suggesting that prolonged or repeated frequent exposure to high dosages of ketamine-like drugs could exert catastrophic effects on neurocognition and behavior (130, 131), and reservations about these drugs' clinical usefulness and long-term outcomes emerged (37, 38, 107, 132). On the other hand, there are some reports suggesting that long-term low-dose esketamine treatment shows no adverse effects on cognition and, on the contrary, it induces improvement in some cases (133).

Taken together, all the above indicates that the long-term usefulness of intranasal esketamine is an open question and difficult to answer. The case for a withdrawal effect that worsens the long-term outcome seems possible as the most appropriate interpretation of the results of the single existing maintenance trial (36). In that trial, half (48.7%) of relapses occurred in the first 4 weeks after esketamine cessation, and this is a strong indicator that there is a withdrawal effect, a note also made by the FDA (134). The argument that this is not a surprising observation in patients with TRD (123) is not sufficiently supported by the timing of the relapses. However, for comparison, one should bear in mind that long-term antidepressant monotherapy is associated with a 24% relapse rate during the first year, which is significantly better than the rate for placebo (44%). Most of the relapse difference (86.5%) occurs in the first 6 months (135), and abrupt discontinuation increases the chances of relapse in a way similar to what is observed with the abrupt discontinuation of esketamine (136). Overall, the nature and the usefulness of long-term prophylactic treatment with antidepressants is a topic of hot debate. The presence of a withdrawal effect in clinical trials is probably present, but this in itself does not indicate a lack of long-term efficacy (135–143). This is not the case, however, with esketamine, because it is given as an add-on to antidepressants as monotherapy, and relapse is probably too early and at too high a rate.

The combination of weak (if not absent) efficacy at week 4 and a high "relapse" rate after cessation of the drug is a pattern seen also with benzodiazepines when given for the treatment of anxiety. Another key issue raised by the FDA was that in this maintenance study of esketamine, the "positive effect" was driven by a single site in Poland, where, as noted earlier, the relapse rate in the placebo arm was 100%, compared with 33% for all other sites combined, and when this outlier site is excluded from the analysis, significance disappears (39).

Whether the intranasal formulation is specifically responsible for the weak efficacy of esketamine remains unanswered. Still, esketamine produces adverse events similar to those of intravenous ketamine, and at similar rates, so in general there is no solid ground to question the use of intranasal formulations. Last but not least, the issue of esketamine-related addictive behaviors remains open, and research has not studied it adequately. Still, limiting the exposure to twice weekly as a maximum is likely to connote considerable safety in terms of acquisition of dependence. The effect of long-term treatment with esketamine on neurocognition is unknown since although its acute effect on depression and suicidal ideation may occur at least partially via procognitive mechanisms targeting neural circuits involved in executive function and cognitive-emotional processing, in the long term the use of high doses at high frequencies may lead to cognitive impairment (144).

One disturbing detail we observed in reviewing all the reports was the lack of consistency in reporting the data from

the RCTs and the significant discrepancies even within the same paper. For example, the data submitted to the FDA were those included in the publication for the NCT02417064 or TRANSFORM-1 study, and it concerned study completers (N=98, MMRM analysis; p. 30 of the FDA document, Table 6), while in the EMA, the data concerned results from the TRANSFORM-1 and -2 studies using the intent-to-treat set (N=115, last-observation-carried forward [LOCF] analysis; p. 73 of the EMA document, Table 5). In the FDA document, the one-sided test resulted in a significant difference (p=0.04), whereas in the EMA document, the two-sided test resulted in nonsignificant results with MMRM analysis (p=0.08); additionally, in the same document, the use of LOCF data resulted in even stronger negative findings (p=0.250). In general, the two-sided test is more appropriate with new agents, since there is no guarantee that they will not be associated with worsening symptoms in the patient. Another example of problematic reporting can be found in the NCT03039192 or ASPIRE I study, where there are significant differences in the graphs contained in the publication body and the supplement for the same time point (25 days pre-dose, Figure 2 for the main body and supplement Figure 3 on p. 10). The interpretation of these graphs is completely contrasting since the overlapping of confidence intervals determines significance. Finally, LOCF results were available only through the EMA document and for only a few studies; all the publications followed the MMRM methodology and reported results on completers, not on the whole study sample.

The major limitation in the esketamine literature is the lack of controlled long-term studies. Although short-term trials provide information concerning the acute efficacy, conclusions on the long-term effects are hypothetical to a significant extent, and the projection of trends to the future is also hypothetical, since the time course is often not monotonic.

CONCLUSIONS

In this systematic review and meta-analysis, we did not find robust evidence for the efficacy of add-on intranasal esketamine in depression and related suicidality. There seems to be a weak early effect on depressive symptoms but virtually no beneficial effect over placebo on suicidality. The effect on depressive symptoms at week 4 and beyond seems to be of the same magnitude as with augmentation strategies utilizing newer-generation antipsychotics.

The main questions to be answered by further analysis of patient-level data of existing studies and by future research are the following:

- Does esketamine treatment provide a true antidepressant effect, both acutely and in the long term, as demonstrated by an effect on the individual MADRS items rating depressed mood and anhedonia?
- Is there a withdrawal effect with esketamine that mimics relapse?
- What is the true value of esketamine given that it is similar in efficacy to other augmentation strategies, when taking into consideration safety issues, the financial cost, and the long-term outcome?
- Is esketamine superior to other augmentation strategies? There is one open-label, single-blind trial that suggests that it is superior to quetiapine when either agent is used in combination with an SSRI or SNRI (43), but further research in this area is needed.

The major strength of this analysis is that we searched the entire esketamine literature and included all available trials. The meta-analysis included all published RCTs to date, and we analyzed the data at different and clinically important time points instead of pooling all results together as several previous meta-analyses did.

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