

Rapid Onset of Intranasal Esketamine in Patients with Treatment Resistant Depression and Major Depression with Suicide Ideation: A Meta-Analysis

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Objective: We performed a meta-analysis of randomized double-blinded placebo controlled trials (DB-RCTs) to investigate efficacy and safety of intranasal esketamine in treating major depressive disorder (MDD) including treatment resistant depression (TRD) and major depression with suicide ideation (MDSI).

Methods: Mean change in total scores on Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to different time-points were our primary outcome measure. Secondary efficacy measures included rate of remission of depression and resolution of suicidality.

Results: Eight DB-RCTs (seven published and one un-published) covering 1,488 patients with MDD were included. Esketamine more significantly improved MADRS total scores than placebo starting from 2–4 hours after the first administration (standardized mean difference, -0.41 [95% CI, -0.58 to -0.25], $p < 0.00001$), and this superiority maintained until end of double-blinded period (28 days). Sub-group analysis showed that superior antidepressant effects of esketamine over placebo in TRD and MDSI was observed from 2–4 hours, which was maintained until 28 days. Resolution of suicide in MDSI was also greater for esketamine than for placebo at 2–4 hours (OR of 2.04, 95% CIs, 1.37 to 3.05, $p = 0.0005$), but two groups did not statistically differ at 24 hours and day 28. Total adverse events (AEs), and other common AEs including dissociation, blood pressure increment, nausea, vertigo, dysgeusia, dizziness, and somnolence were more frequent in esketamine than in placebo group.

Conclusion: Esketamine showed rapid antidepressant effects in patients with MDD, including TRD and MDSI. The study also suggested that esketamine might be associated with rapid anti-suicidal effects for patients with MDSI.

KEY WORDS: Esketamine; Depression; Treatment resistant depression; Suicide; Meta-analysis.

INTRODUCTION

Major depressive disorder (MDD) is a common debilitating disease with a lifetime prevalence of 15–20%, and it is known to cause severe functional impairment [1,2]. Multiple antidepressants are available, but approximately one-third of patients with MDD fail to achieve adequate response or remission and become treatment-resistant depression (TRD) [3]. Besides low remission and response

rate, delayed onset of efficacy is another important limitation of conventional antidepressants [4,5]. Moreover, around 10–20% of patients with MDD attempt suicide over their lifetime, and 3.4% of patients with MDD actually commit or complete suicide [6,7]. However, due to therapeutic lag between administration of antidepressant and onset of clinical improvement, patients having major depression with suicide ideation (MDSI) remain symptomatic and at risk of suicidal behavior and self-harm for more than two weeks [8]. The monoamine hypothesis of depression received criticisms for more than a decade, and studies suggested that patients with TRD may need novel antidepressants with different mechanisms of action [9,10]. Thus, additional antidepressant having novel mechanism of action, higher potency, faster onset of ac-

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tion, and anti-suicidal effect are urgently needed [11].

Esketamine is a nonselective, noncompetitive antagonist at the *N*-methyl-D-aspartate (NMDA) receptor which modulates glutamatergic transmission [12]. It is an S-enantiomer of ketamine, which is known to have a higher affinity for the NMDA receptor than the R-enantiomer [13]. The US Food and Drug Administration (FDA) approved intranasal esketamine in conjunction (augmentation) with an oral antidepressant first for the treatment of TRD in 2019 [14]. Three double-blinded randomized placebo controlled trials (DB-RCTs) have shown its anti-suicidal effect [15-17], so the US FDA further approved intranasal esketamine augmentation to treatment depressive symptoms in adults with MDD having suicidal ideation or behavior [18].

An earlier study of intranasal esketamine showed its rapid onset of action in TRD [19]. However, findings from subsequent DB-RCTs of intranasal esketamine have been mixed in terms of its rapid antidepressant effect [20,21]. Although studies confirmed its anti-suicidal effects in patients with MDSI, but whether or not the anti-suicidal effects are rapid is still obscure. In terms of understanding efficacy and safety of a new drug, meta-analysis is important because it can overcome limitation of small sample sizes, increase statistical power of group comparisons, enhance generalizability of DB-RCTs, and quantify inconsistencies of DB-RCTs [22,23]. An initial meta-analysis for intranasal esketamine showed that significant superiority of intranasal esketamine over placebo with regard to response and remission in patients with MDD were noted as early as two hours [24]. However, the study included only four DB-RCTs which precluded more detailed elucidation of publication bias for outcome measures. In addition, due to small sample size, the study was unable to confirm its effects in MDSI. A more recent study by Papakostas *et al.* [25] also showed that adjunctive intranasal esketamine was significantly more effective than placebo for Montgomery-Åsberg Depression Rating Scale (MADRS) score change, response, and remission. However, besides having small study numbers (5 DB-RCTs), the timing of primary outcome or end-point measurements differed depending on the studies, but the meta-analysis did not specify their efficacies according to different time after esketamine administration. The study also failed to address whether or not esketamine have rapid antidepressant effect.

We performed a meta-analysis and studied efficacy and safety of intranasal esketamine in treatment of patients

with MDD. We also aimed to investigate its rapid antidepressive actions in patients with TRD and MDSI.

METHODS

Sources of Data

Three investigators (SMW, NKK, and YSW) independently searched from December 1st, 2020 to January 10th, 2021 using following terms: "esketamine," and "depression" (Mesh) at PubMed, Embase, PubMed, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science for published articles. No restrictions were utilized for publication date. In terms of clinical trials, Cochrane Central Register of Controlled Trials Library and ClinicalTrials.gov (www.clinicaltrials.gov) was explored. We also manually searched reference lists from identified articles and reviews to find additional studies. Two other authors (HRN and HKL) re-evaluated potentially eligible papers to determine whether they truly met the selection criteria. The last two authors (CUP and WMB) discussed and reached a consensus for disagreements.

Study Criteria and Data Extraction

Primary inclusion criteria were all DB-RCTs comparing adjunctive treatment of intranasal esketamine with standard antidepressants for MDD. To be included in our meta-analysis, studies were required to: 1) have placebo as a comparator, regardless of having an active comparator, 2) exclusively focused on patients with MDD 3) have clearly described all inclusion and exclusion criteria. No restrictions were utilized for severity of MDD, gender, treatment basis (i.e., inpatient or outpatient), dose range, or study location. Three investigators (SMW, NKK, and YSW) who conducted initial data search also extracted the data. In addition, if a DB-RCT contained multiple double-blinded phases (i.e., Daly *et al.* [19]), only data from the first period were extracted and analyzed. We also assessed quality of DB-RCTs based on recommendations of Cochrane Review [26].

Study Outcomes

The primary outcome measures were change of MADRS total score from baseline to different time points until the end of double blinded phase. The secondary efficacy measures were rate of study-defined remission and reso-

lution of suicidality at different time points during the double blinded phase. In terms of safety and tolerability, total number of adverse events (AEs) and common AEs including dissociation, blood pressure increment, nausea, vertigo, dysgeusia, dizziness, somnolence, and headache were included in the meta-analysis.

Statistical Analysis

Review Manager version 5.4 software (Cochrane Collaboration, Oxford, UK) was used to undertake statistical analysis. Standardized mean difference (SMD) using method developed by Hedges (Hedges g) with 95% confidence intervals (95% CIs) and odds ratio (OR) with 95% CIs using Mantel–Haenszel method were used for continuous and dichotomous outcome measures respec-

tively. Cohen's classification can be used to assess effect size: small = SMD < 0.2, medium = SMD of 0.5, and large = SMD > 0.8 [27]. In terms of heterogeneity, we used I^2 statistic and evaluated what degree of variance between studies can be attributed to actual differences between the studies rather than to chance [28]. Studies suggested that I^2 of 75–100% indicate considerable heterogeneity, and the heterogeneity threshold was defined as 50% or more in I^2 value and $p < 0.10$.

RESULTS

Study Characteristics

Initially 804 abstracts were identified with use of Embase, PubMed, Psychinfo, and Web of Science. After a

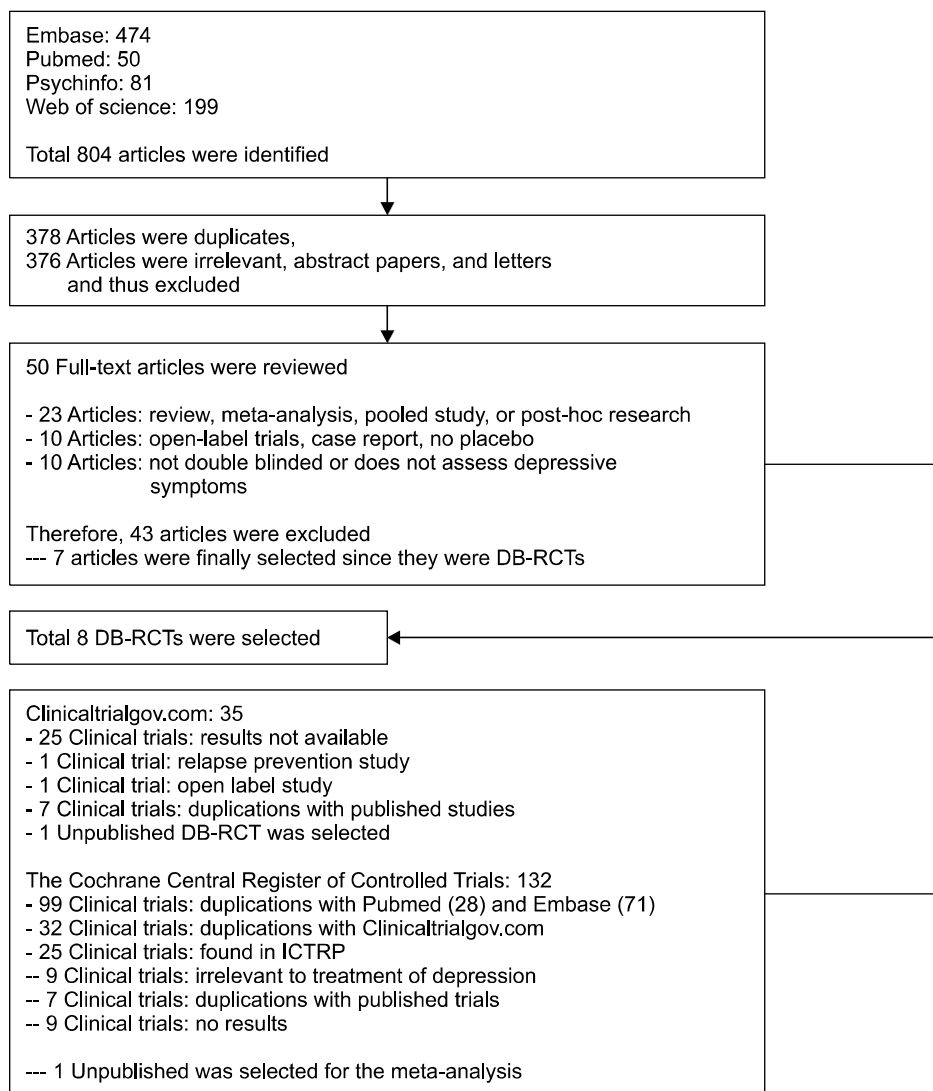


Fig. 1. Schematic presentation of studies selected in the present meta-analysis. DB-RCT, double-blinded, randomized, placebo-controlled clinical trial; ICTRP, international clinical trials registry platform.

Table 1. General characteristics of double-blinded randomized clinical trials included in the meta-analysis

Study name (trial number)	Length of DB	Mean age (SD)	Subjects	Clinical phase	Number of participants	Primary outcome measure	Study location	Intervention Frequency	Remission	Augmentation/Monotherapy
NCT02918318 ^a	4 wk	43.4 (10.35)	MDD with treatment resistant to more than 2 antidepressants	II	PBO: 80 ESK 28 mg: 41 ESK 56: 40 ESK 84: 41	MADRS change at week 4	Japan only	Twice weekly Fixed dose	MADRS < 12	Augmentation
Daly <i>et al.</i> [19] (NCT01998958)	2 wk	44.7 (10.0)	MDD with treatment resistant to more than 2 antidepressants	II	PBO: 33 ESK 28 mg: 11 ESK 56: 10 ESK 84: 12	MADRS change at day 8	13 in US 1 in Belgium	Twice weekly Fixed dose	MADRS < 10	Augmentation
Canuso <i>et al.</i> [17] (NCT02133001)	4 wk	35.8 (13.03)	MDD with imminent suicide risk	II	PBO: 31 ESK 84: 35	MADRS change at 4 hours	11 in US	Twice weekly Fixed dose	MADRS < 12	Augmentation
Fedgchin <i>et al.</i> [29] TRANSFORM-1 (NCT02417064)	4 wk	46.3 (11.16)	MDD with treatment resistant to more than 2 antidepressants	III	PBO: 80 ESK 28 mg: 41 ESK 56: 40 ESK 84: 41	MADRS change at week 4	91 centers in 9 countries	Twice weekly Fixed dose	MADRS < 12	Augmentation
Popova <i>et al.</i> [20] TRANSFORM-2 (NCT02418585)	4 wk	45.7 (11.89)	MDD with treatment resistant to more than 2 antidepressants	III	PBO: 114 ESK 56–84 mg: 109	MADRS change at week 4	39 centers in 5 countries	Twice weekly Flexible dose	MADRS < 12	Augmentation
Ochs-Ross <i>et al.</i> [21] TRANSFORM-3 (NCT02422186)	4 wk	70 (4.52)	MDD (age > 65) with treatment resistant to more than 2 antidepressants	III	PBO: 65 ESK 28–84 mg: 72	MADRS change at week 4	69 centers in 12 countries	Twice weekly Flexible dose	MADRS < 12	Augmentation
Fu <i>et al.</i> [15] ASPIRE-1 (NCT03039192)	25-day	39.3 (12.88)	MDD with suicide intent/idea	III	PBO: 112 ESK 56–84 mg: 112	MADRS change at 24 hrs	51 sites in US, Europe, Asia, and South Africa	Twice weekly Flexible dose	MADRS < 12	Augmentation
Ionescu <i>et al.</i> [16] ASPIRE-2 (NCT03097133)	25-day	40.8 (13.07)	MDD with suicide intent/idea	III	PBO: 113 ESK 56–84 mg: 114	MADRS change at 24 hrs	47 centers in 13 countries	Twice weekly Flexible dose	MADRS < 12	Augmentation

DB, double-blinded phase; SD, standard deviation; MDD, major depressive disorder; PBO, placebo; ESK, esketamine; MADRS, Montgomery-Åsberg depression rating scale; US, United States.
^aUnpublished study.

preliminary review, 754 papers were excluded because they were either duplicates, irrelevant, or non-full articles. The remaining 50 full-text articles were retrieved for a more detailed evaluation. Among them seven published DB-RCTs were included in the meta-analysis. Of the 35 records obtained from ClinicalTrials.gov and 132 studies from Cochrane Central Register of Controlled Trials, we found one DB-RCT having full reports which were not published. Thus, a total of eight DB-RCTs (seven published and one un-published) were finally selected for our meta-analysis (Fig. 1).

Table 1 presents main characteristics of these eight DB-RCTs. All studies were multi-centered, and six studies [15,16,19-21,29] were multi-national while two were conducted either in Japan [30] or US [17] only. Five trials [19-21,29,30] involved TRD while other three [15-17] involved patients with MDSI. A total of 1,488 participants were included, and number of patients included in placebo and intranasal esketamine groups were 661 and 827 respectively. Four [15,16,20,21] studies used flexible doses while other four [17,19,29,30] used fixed doses of intranasal esketamine. Risk of bias assessment showed that all studies included were good in quality in terms of their methodologies (Supplementary Fig. 1; available online). Publication bias could not be tested because only one trial was un-published.

Efficacy

Primary endpoint: mean change of MADRS

Mean change of MADRS total score from baseline to 2–4 hours, 24 hours, week 1, and week 3–4 are presented as forest plots (Fig. 2). Intranasal esketamine more significantly improved MADRS total scores than placebo for treating MDD starting from 2–4 hours after the first injection (SMD, -0.41 [95% CI, -0.58 to -0.25], $p < 0.00001$), and the significant superiority maintained at 24 hours (SMD, -0.36 [95% CI, -0.47 to -0.24], $p < 0.00001$), week 1 (SMD, -0.25 [95% CI, -0.36 to -0.13], $p < 0.0001$), and end of double-blinded period (week 3–4) (SMD, -0.25 [95% CI, -0.35 to -0.14], $p < 0.00001$). Significant heterogeneities were not reported for 2–4 hours ($I^2 = 0\%$, $p = 0.40$), 24 hours ($I^2 = 42\%$, $p = 0.13$), week 1 ($I^2 = 13\%$, $p = 0.33$), and week 3–4 ($I^2 = 0\%$, $p = 0.68$), so we used fixed effect model for all analyses.

We conducted sub-group analysis for patients with TRD and MDSI. In terms of patients with TRD, MADRS improvement was significantly more superior in intranasal esketamine group than in placebo group from 2–4 hours (SMD, -0.67 [95% CI, -1.16 to -0.17], $p = 0.008$) to 24 hours (SMD, -0.48 [95% CI, -0.82 to -0.13], $p = 0.007$), week 1 (SMD, -0.27 [95% CI, -0.42 to -0.12], $p = 0.0003$), and week 3–4 (SMD, -0.23 [95% CI, -0.37 to -0.10], $p = 0.0007$). However, only one study assessed MADRS at 2–4 hours after the first injection (Fig. 3). Significant heterogeneity was noted for 24 hours ($I^2 = 73\%$, $p = 0.02$), so random effect model was used. For 2–4 hours, week 1, and week 3–4 fixed effect model was utilized because no significant heterogeneity was observed. Similar trends of rapid antidepressive effects were noted for subgroup analysis involving patients with MDSI at 2–4 hours (SMD, -0.38 [95% CI, -0.56 to -0.21], $p < 0.0001$), 24 hours (SMD, -0.34 [95% CI, -0.52 to -0.17], $p = 0.0001$), week 1 (SMD, -0.21 [95% CI, -0.39 to -0.02], $p = 0.03$), and week 3–4 (SMD, -0.27 [95% CI, -0.44 to -0.10], $p = 0.002$) (for all heterogeneity = 0), which is illustrated in Figure 4.

Resolution of suicide

Esketamine showed superior efficacy over placebo in resolution of suicide at 2–4 hours after initial nasal infusion with OR of 2.04 (95% CIs, 1.37 to 3.05, $p = 0.0005$; heterogeneity = 0%), but the two groups did not statistically differ at 24 hours (OR = 1.15, 95% CIs, 0.80 to 1.65, $p = 0.46$; heterogeneity = 0%) and week 3–4 (OR = 1.32, 95% CIs, 0.91 to 1.90, $p = 0.44$; heterogeneity = 0%) (Supplementary Fig. 2; available online).

Rate of remission

A total of seven studies were included for comparing rate of remission between intranasal esketamine and placebo groups at week 3–4. Intranasal esketamine group showed superior remission rate than placebo with OR of 1.64 (95% CIs, 1.30 to 2.07, $p < 0.0001$; heterogeneity = 0%) at week 3–4. In addition, superior efficacy was noted at 2–4 hours (OR = 2.43, 95% CIs, 1.27 to 4.67, $p = 0.007$; heterogeneity = 41%, $p = 0.18$) and 24 hours (OR = 2.47, 95% CIs, 1.58 to 3.85, $p < 0.0001$; heterogeneity = 0%) after initial nasal esketamine infusion, but the two groups did not differ at day 8 (OR = 1.46, 95% CIs, 0.96 to 2.23, $p = 0.08$; heterogeneity = 0%) (Supplementary Fig.

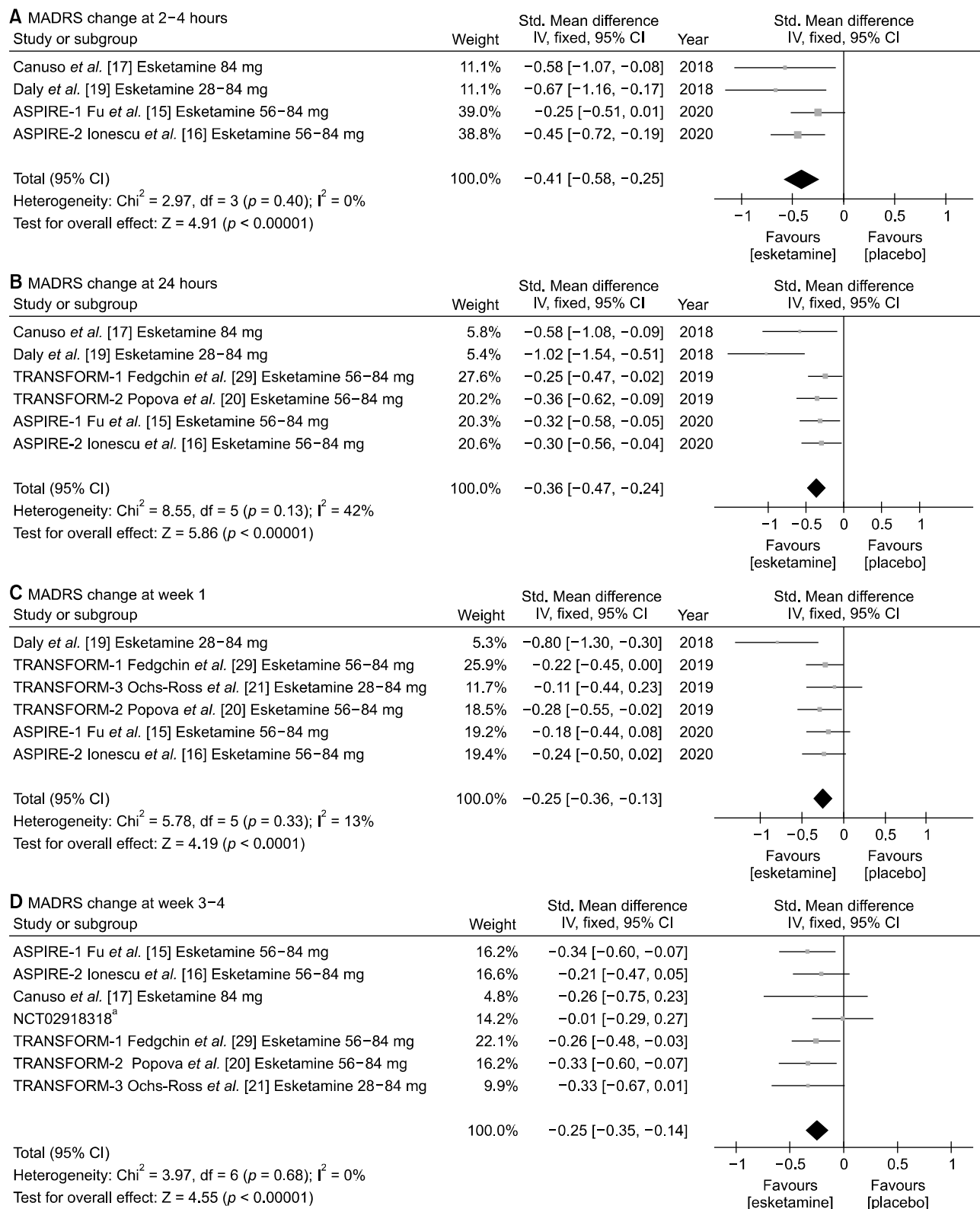


Fig. 2. Mean change of Montgomery-Åsberg depression rating scale (MADRS) at (A) 2–4 hours, (B) 24 hours, (C) week 1, and (D) week 3–4 between intranasal esketamine and placebo.

Std., standard deviation; CI, confidence interval; IV, inverse variance.

^aUnpublished study.

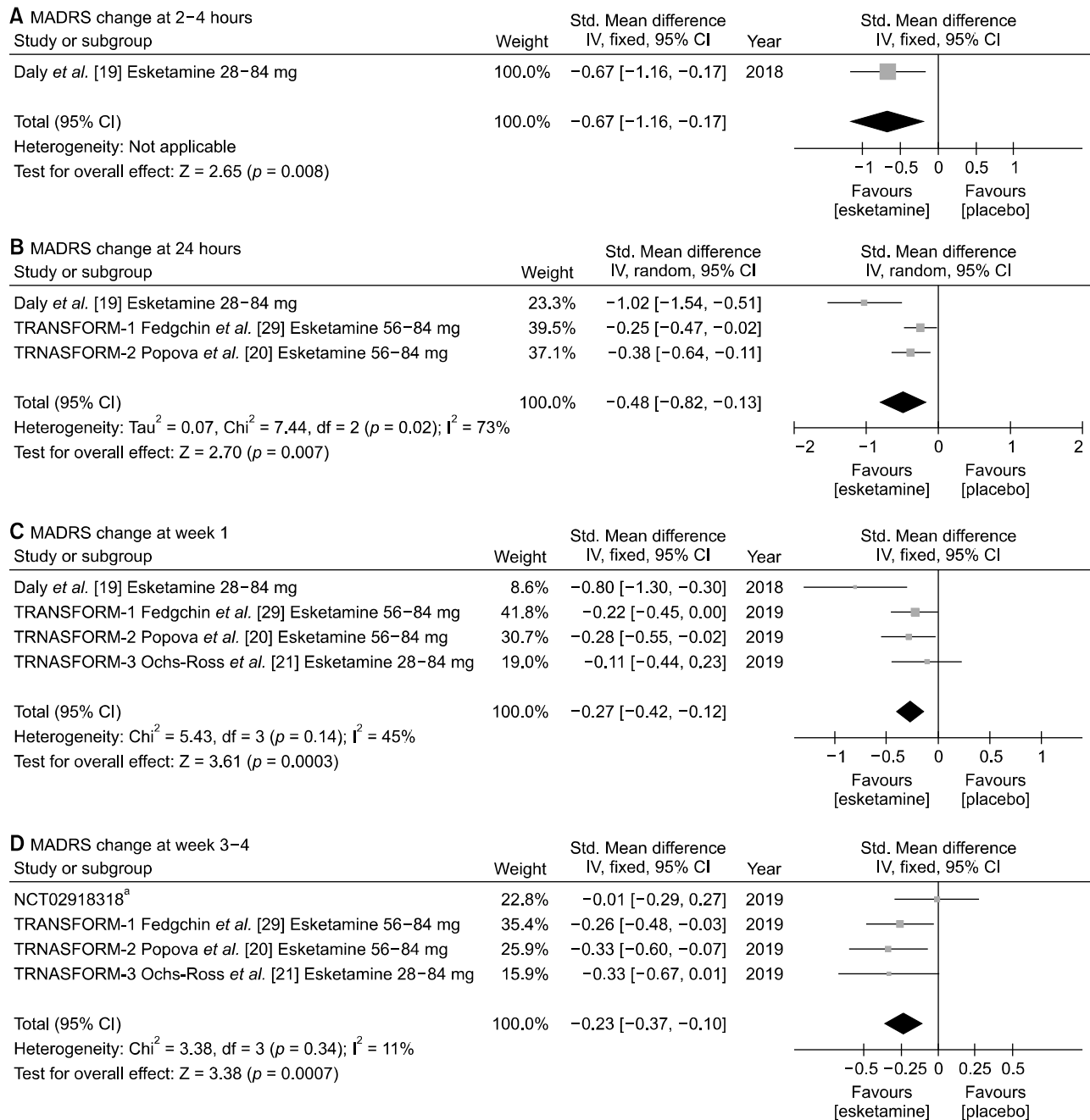


Fig. 3. Mean change of Montgomery-Åsberg depression rating scale (MADRS) at (A) 2–4 hours, (B) 24 hours, (C) week 1, and (D) week 3–4 between intranasal esketamine and placebo in patients with treatment resistant depression (TRD).

Std., standard deviation; CI, confidence interval; IV, inverse variance.

^aUnpublished study.

3; available online).

Safety and Tolerability

In terms of commonly observed side effects, esketamine showed higher incidence of total AEs (OR = 4.23, 95% CIs, 2.85 to 6.27, $p < 0.00001$; heterogeneity =

55%, $p = 0.04$), dissociation (OR = 7.93, 95% CIs, 5.36 to 11.72, $p < 0.00001$; heterogeneity = 0%), blood pressure increment (OR = 7.18, 95% CIs, 4.82 to 10.69, $p < 0.00001$; heterogeneity = 0%), nausea (OR = 3.28, 95% CIs, 2.40 to 4.48, $p < 0.00001$; heterogeneity = 30%, $p = 0.20$), vertigo (OR = 6.22, 95% CIs, 3.97 to 9.73, $p <$

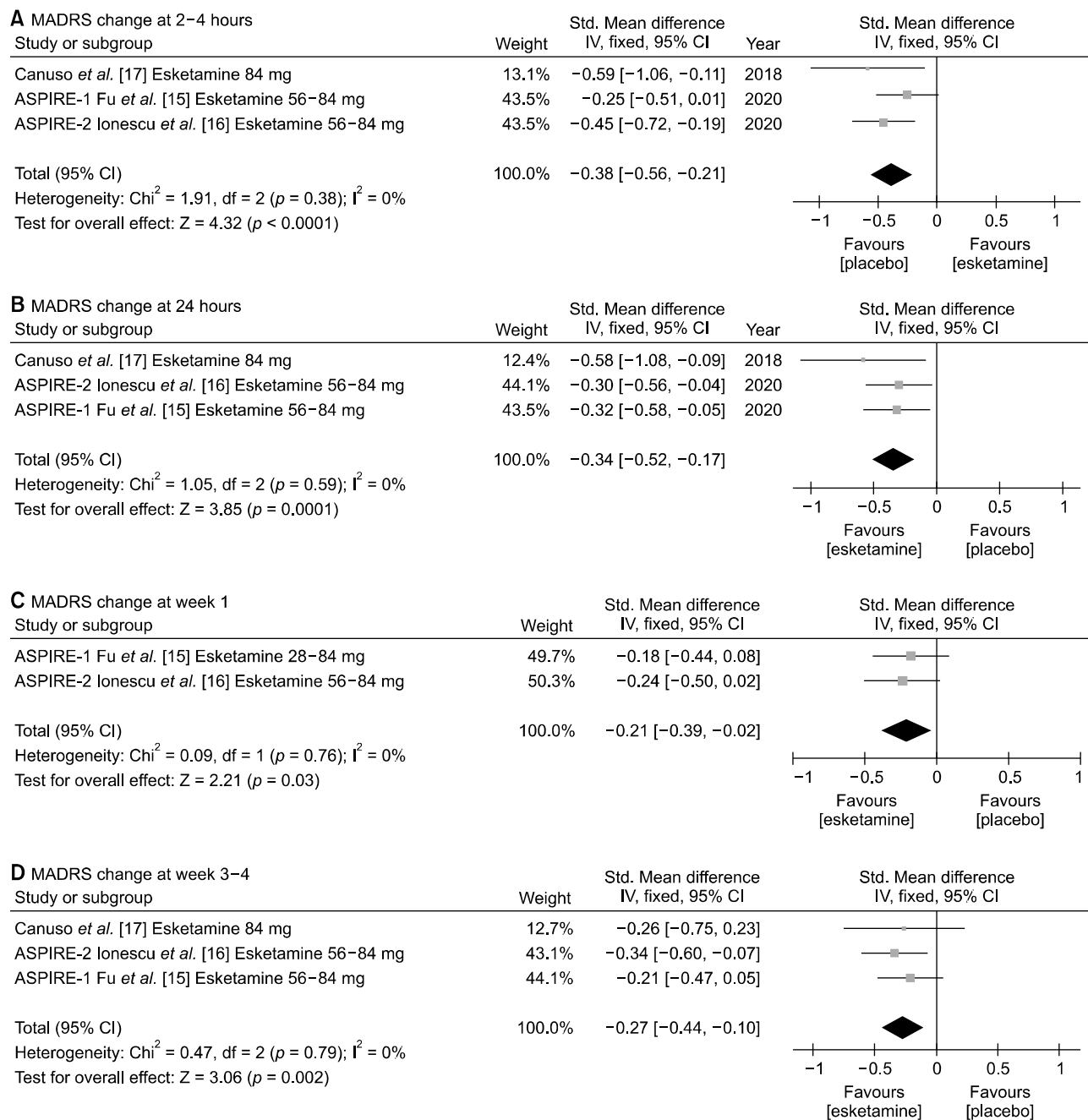


Fig. 4. Mean change of Montgomery-Åsberg depression rating scale (MADRS) at (A) 2–4 hours, (B) 24 hours, (C) week 1, and (D) week 3–4 between intranasal esketamine and placebo in major depression with suicide ideation (MDSI). Std., standard deviation; CI, confidence interval; IV, inverse variance.

0.00001; heterogeneity = 43%, $p = 0.10$), dysgeusia (OR = 1.67, 95% CIs, 1.21 to 2.31, $p = 0.002$; heterogeneity = 0%), dizziness (OR = 4.47, 95% CIs, 3.27 to 6.11, $p < 0.00001$; heterogeneity = 0%), and somnolence (OR = 2.08, 95% CIs, 1.49 to 2.89, $p < 0.0001$; heterogeneity = 0%) compared with placebo (Fig. 5). Although headache

was numerically more common in esketamine group than in placebo group, the two groups did not differ statistically (OR = 1.33, 95% CIs, 1.00 to 1.77, $p = 0.05$; heterogeneity = 5%, $p = 0.39$).

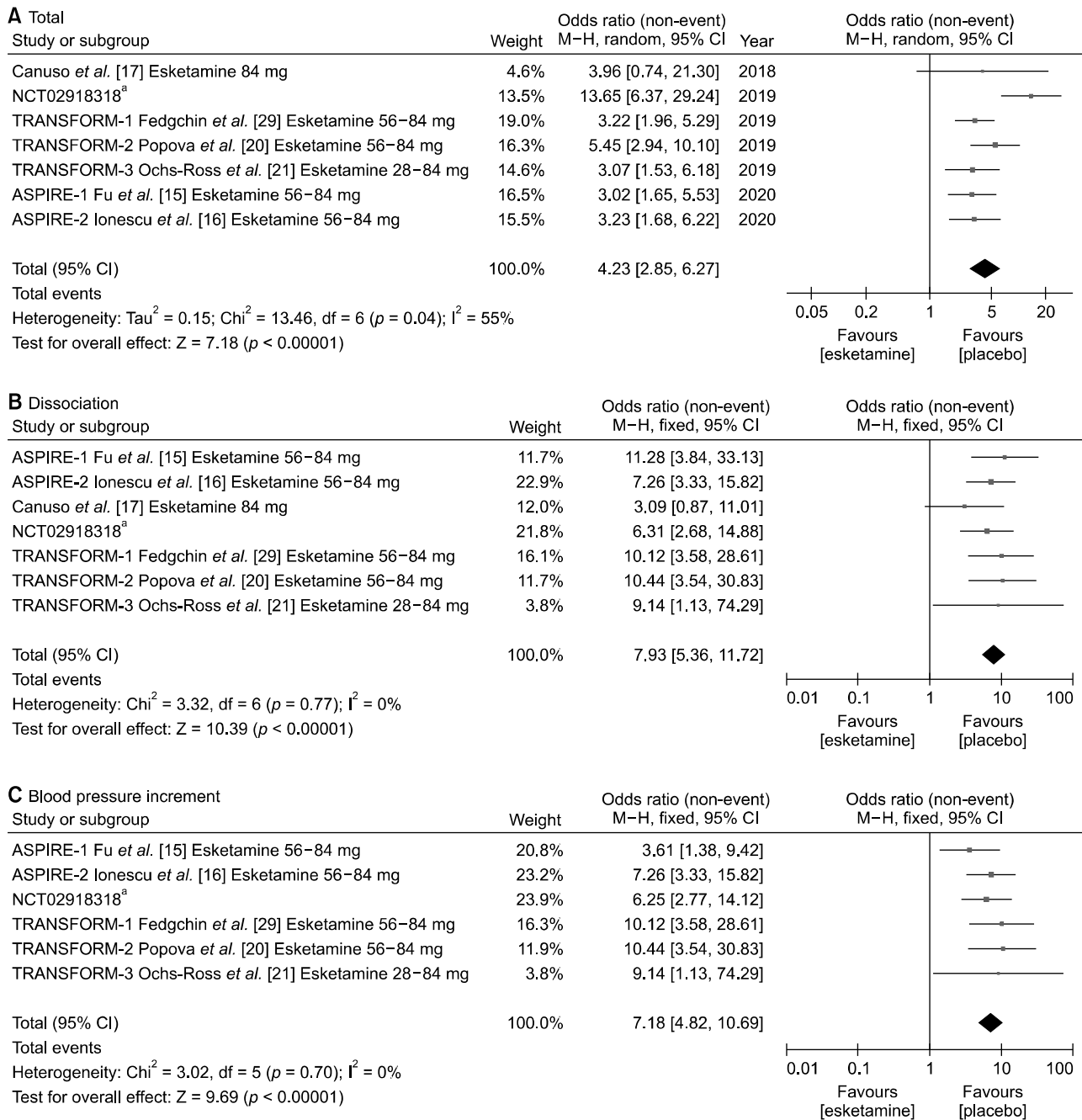


Fig. 5. Safety and tolerability: Rate of (A) total, (B) dissociation, (C) blood pressure increment, (D) nausea, (E) vertigo, (F) dysgeusia, (G) dizziness, (H) somnolence, and (I) headache during the double-blind phase. CI, confidence interval. ^aUnpublished study.

DISCUSSION

To the best of our knowledge, this is the largest meta-analysis (eight DB-RCTs with 1,488 subjects) comparing efficacy and safety of intranasal esketamine and placebo

in patients with MDD. Our study confirmed previous research by showing that augmentation of antidepressants with intranasal esketamine was significantly more effective than with placebo for MADRS score change and depression remission [24,25]. In addition, the superior treat-

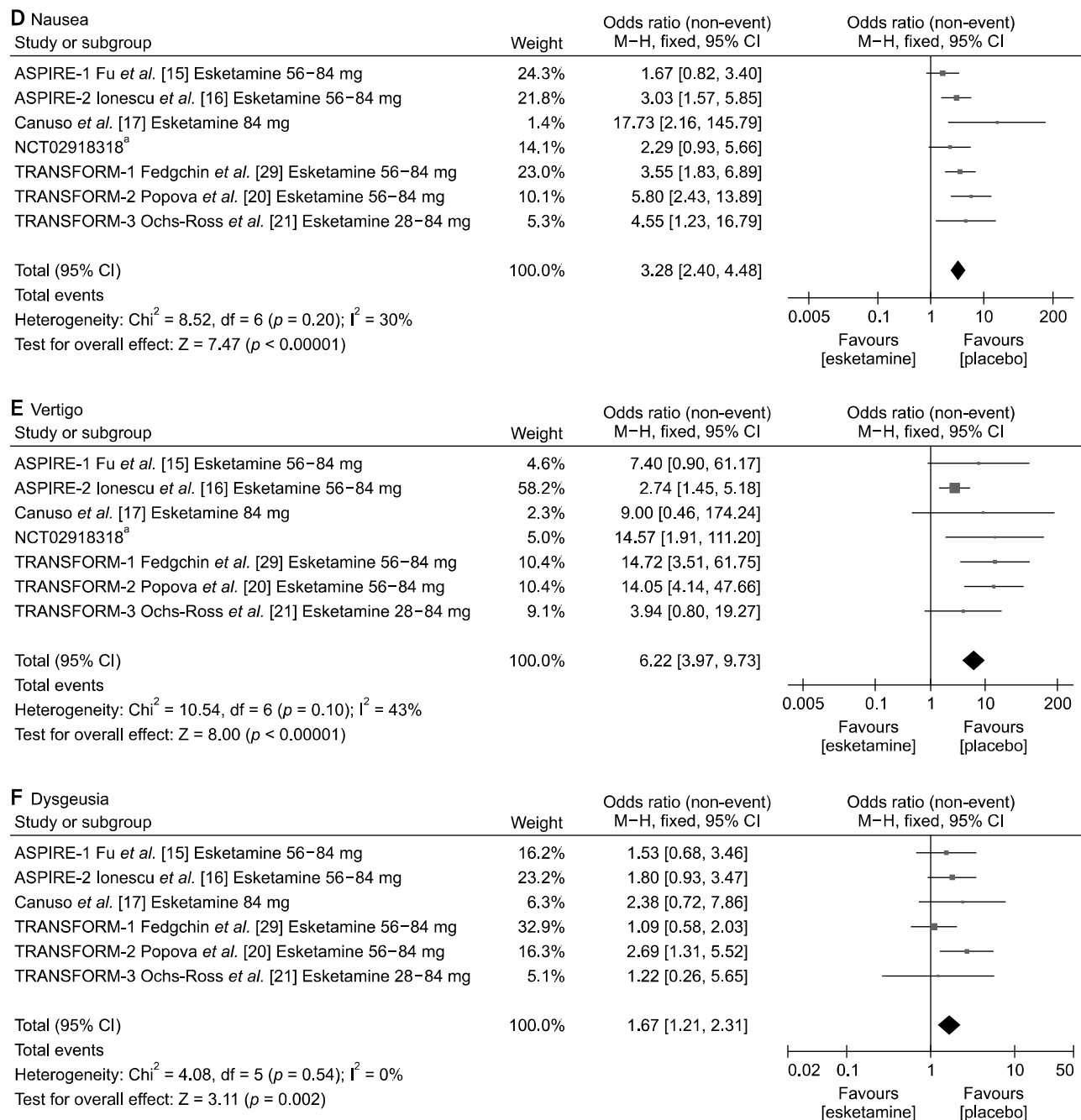


Fig. 5. Continued 1.

ment response and remission of intranasal esketamine were noticeable as early as 2–4 hours after the first intranasal esketamine, and this superior efficacy lasted until end of double blinded phase, which is week 3–4.

By conducting subgroup analysis, we are the first one to show that the rapid improvement of depressive symptoms was evident in patients with TRD and MDSI. Our results also extended previous studies and showed rapid anti-sui-

cidal effect of intranasal esketamine (resolution of suicidality 2–4 hours after the 1st injection) in MDSI. However, although intranasal esketamine showed trend of superior efficacy over placebo, the statistical significance was not maintained at 24 hours and week 3–4. Only three studies were conducted in MDSI, so small number of clinical trials might have been the main cause. More DB-RCTS are needed to define rapid anti-suicidal effects of intra-nasal

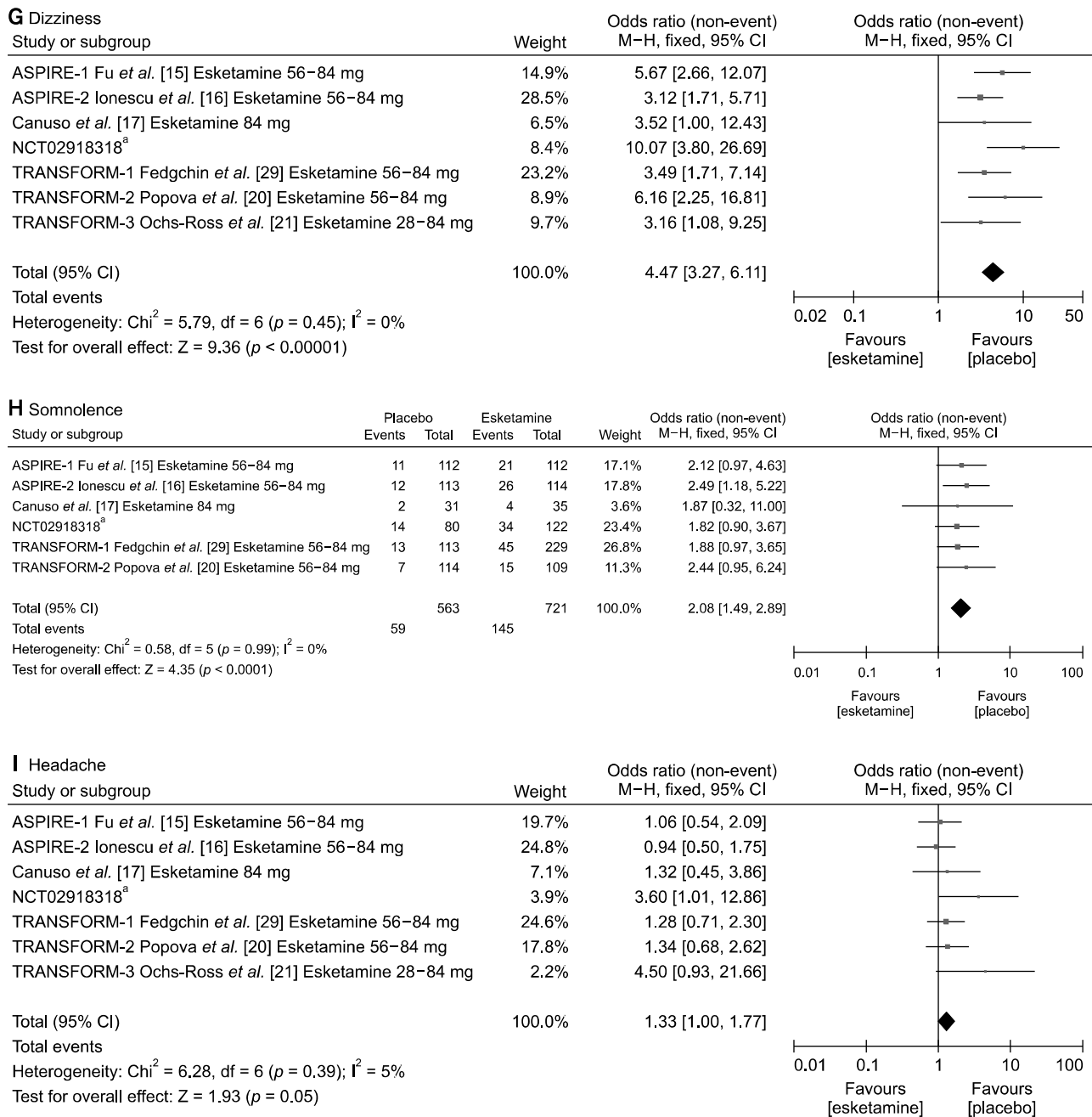


Fig. 5. Continued 2.

esketamine.

The SMD in MADRS across different time ranged from 0.25–0.41, which equal to small~medium effect size according to Cohen’s classification [31]. More importantly, all efficacies including MADRS score change, remission of depression, and resolution of suicidality were greatest either at 2–4 hours or 24 hours after the 1st administration of intranasal esketamine. All patients in the eight

DB-RCTs were taking oral antidepressants in addition to intranasal esketamine or placebo, so the efficacy difference between the two groups might have decreased or attenuated as the onset of actions for oral antidepressants started to show effects. In line with our hypothesis, the mean change of MADRS from baseline to week 3–4 was less than four points difference in all eight DB-RCTs. Thus, as Canuso *et al.* has suggested, intranasal esketamine

could be used to overcome the efficacy gap observed between drug administration and onset of action for the conventional antidepressants [17]. This therapeutic role could be particularly important in patients having MDSI.

In terms of safety and tolerability, intranasal esketamine showed higher total AEs than the placebo group. Since esketamine was initially introduced medically as an anesthetic in Germany in 1997 [32], its higher risk of causing somnolence, dizziness, and vertigo are not surprising. The intranasal esketamine also had significantly higher rate of nausea and dysgeusia.

The risk of intranasal esketamine causing dissociation [33] and blood pressure increment [34] have been well documented. Likewise, the rate of dissociation and blood pressure increment was higher in intranasal esketamine than in placebo with particularly higher odd ratios (7.18–7.93) compared with AEs. Previous studies showed that dissociation and perceptual change symptoms peaked shortly after esketamine administration, which generally resolved by 2 hours after dosing [21,29]. Evidence also showed that rate and intensity of dissociation lowered with repeated administrations of intranasal esketamine. Similarly, studies consistently illustrated that blood pressure increment following intranasal esketamine were transient, asymptomatic, and not associated with serious cardiovascular complications [34]. However, number of studies investing long-term safety and tolerability of intranasal esketamine are scarce [35]. Therefore, whether or not intranasal esketamine result in long-terms adverse events needs further varication.

Our study contained several limitations. First, we combined all doses of intranasal esketamine (28–84 mg/day) so were not able to conduct meta-regression and investigate its dose related efficacy, tolerability, and safety. Second, we found one unpublished DB-RCT which showed negative results. There could have been more unpublished negative trials and possibility of publication bias. Third, we did not investigate rate and severity of diverse side effects across different time. As a result, we were not able to confirm that important side effects such as dissociation and blood pressure increment resolved shortly after and attenuated as the administration of intranasal esketamine repeated.

In conclusion, the present meta-analysis confirmed that intranasal esketamine was effective in patients with MDD including TRD and MDSI. Our meta-analysis further

showed that intranasal esketamine was associated with rapid antidepressant effect for patients with TRD and MDSI. The study also suggested that esketamine might have rapid anti-suicidal effects for patients with MDSI.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Sheng-Min Wang, Won-Myong Bahk. Data acquisition: Nak-Young Kim, Hae-Ran Na. data analysis: Chi-Un Pae, Hyun Kook Lim, Young Sup Woo. Writing article: Sheng-Min Wang. All authors reviewed and approved for publication.

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