


Efficacy and Safety of Esketamine Combined with Antidepressants for Treatment-Resistant Depression: A Meta-Analysis

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Objective: To evaluate the efficacy and safety of esketamine + antidepressant in treatment-resistant depression.

Methods: We searched PubMed, Web of Science, Embase, CNKI, and Wanfang databases to obtain published information on esketamine + antidepressant from inception to July 2022. We searched for randomized controlled studies on the treatment of depression with a double-blind induction phase. Outcome indicators included changes in Montgomery-Asberg Depression Rating Scale (MADRS) scores before and after treatment, effective response rate, remission rate, and changes in self-rating depression scale (SDS). We analyzed data using Review Manager 5.4 and assessed the quality of evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) analysis.

Results: A total of seven articles were included, including 701 patients in the esketamine + antidepressant group and 551 in the placebo group. Meta-analysis results showed that esketamine + antidepressant could improve the MADRS score in patients with treatment-resistant depression (MD = -2.68, 95% CI -3.98 to -1.37, $P < 0.0001$), SDS (MD = -2.9, 95% CI -4.01 to -1.79, $P < 0.00001$), response rate at the end of the double-blind induction period (RR = 1.28, 95% CI 1.12 to 1.46, $P = 0.0002$), remission rate at the end of the double-blind induction period (RR = 1.39, 95% CI 1.18 to 1.63, $P < 0.0001$), Five-Dimensional Health Scale (EQ-5D-5L) (MD = 0.05, 95% CI 0.02 to 0.08, $P = 0.00009$), Visual Analogue Scale of Health Status (EQ-VAS) (MD = 5.54, 95% CI 2.37 to 8.71, $P = 0.0006$).

Conclusion: Esketamine + antidepressant has an obvious curative effect in treatment-resistant depression and can rapidly improve depression in patients, quality of life and satisfaction, but minor adverse reactions can occur.

Keywords: esketamine, treatment-resistant depression, refractory depression, antidepressant, meta-analysis

Introduction

Major depressive disorder is a common mental illness. The prevalence of major depressive disorder varies widely in countries worldwide, but about 6% of cases seriously affect social and psychological functions and reduce the quality of life. The mechanism of action is unclear,¹ but about 10% to 30% of cases are refractory.² Treatment-resistant depression is defined as the failure to achieve clinical remission even after receiving a sufficient amount and course of two completely different drugs with good patient compliance.^{3,4} Authoritative experts worldwide believe that the direction of depression treatment should be to improve health status, reduce recurrence, and improve quality of life.⁵ However, the ineffectiveness of existing clinical therapy prompted the US Food and Drug Administration to approve a new nasal spray antidepressant in 2019, esketamine, for treating adult patients with refractory depression. Due to its special development history (K powder) and mild side effects, it requires strict and standardized use.

Esketamine, the S enantiomer of racemic ketamine, belongs to the NMDA receptor blocker. Compared with racemic ketamine, esketamine has less psychomimetic effect, more anesthetic, and analgesic activity, and 3 to 4 times more affinity for NMDA receptors than R-ketamine.⁶ The literature has reported that the radioligand-binding properties of

NMDA receptors produce region-specific adaptive changes in patients with long-term antidepressant use,⁷ suggesting that it may be one of the antidepressant mechanisms. A review reported that esketamine could also activate the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA),⁸ which can regulate multiple signaling pathways of synaptic plasticity; induce brain-derived neurotrophic factor expression; increase the release of monoamine transmitters in the central nervous system; promote angiogenesis and synapse regeneration, and enhance neuronal activity.⁹

Despite the growing interest in the treatment of refractory depression, current treatment options still do not improve the patient's symptoms well, nor do they improve patient and physician satisfaction, and the application of esketamine nasal spray is a major innovation in this area in anticipation of satisfactory results. Therefore, the present study included more studies, increased the sample size and indicators, and set stricter inclusion and exclusion criteria, to provide more evidence to support the application of esketamine + antidepressant in treatment-resistant depression.

Methods

Study Design

Since this is a meta-analysis of published studies, ethical approval and informed consent were not necessary, and we calculated all pooled results based on published data. This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.¹⁰ The data relevant to our study are available from the corresponding author upon request.

Eligibility Criteria

Original research studies published in English and meeting the following criteria were included: 1) the patient met the diagnostic criteria of the US Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); 2) the patient met the criteria for treatment-resistant depression; 3) gender and age are not limited; (4) the types of studies included in this analysis were published randomized controlled studies. Exclusion criteria: 1) non-randomized controlled trial, animal experiments, reviews, inconsistent outcome indicators, and others; 2) non-double-blind induction period in the experimental phase, such as maintenance phase, open-label phase; 3) experimental design is not rigorous; 4) the subjects of the study were patients with non-refractory depression.

Search Strategy

We searched PubMed, Web of Science, Embase, CNKI, and Wanfang databases to obtain information on esketamine + antidepressant published from the establishment of the databases to July 2022. Boolean logic was used for the database search, and Boolean search operators “AND” and “OR” were used to link search terms. Search terms were as follows: “treatment-resistant depression” AND (“esketamine” AND “antidepressant”) AND “randomized controlled trial”. Moreover, the reference section of the included literature and previously published articles for other studies that met the criteria were searched.

Study Selection

Two researchers (PL and SS-Z) screened the first-time searched literature according to the guidelines, extracted data, and checked the data. In case of discrepancies, a third person was consulted (BH-D or WG).

Data Extraction

The two reviewers (YL and ZJ-G) collated the final included studies and used the standardized data extraction format to extract the data. After data extraction, the reviewers matched the data before rereading the papers wherever discrepancies arose. Any discrepancies were resolved through discussion with a third reviewer (BH-D or WG). The extracted data included the following: first author, year, basic demographic characteristics, intervention protocol, outcome indicators, and pre-and post-change values for cognitive assessments. If the required data were missing, not reported in the paper, or reported in an unusual form, we contacted the corresponding author of the related paper for clarification.

Assessment of Risk of Bias

The other authors independently evaluated the risk of bias of the included studies by using the RCT risk of bias assessment tool recommended in Cochrane Handbook 5.1, and finally cross-checked the results. Evaluation entries include random sequence generation, allocation concealment, performer and participant blinding, outcome assessment blinding, outcome data completeness, selective reporting, and other biases. Each project was described as “low risk”, “high risk” or “unclear risk”, depending on the judgment of the two authors.⁹⁷

Statistical Analysis

We used risk ratio (RR) and 95% confidence interval (CI) to express dichotomous variables and used mean difference (MD) and 95% CI to express continuous variables; I^2 values were used to determine the magnitude of heterogeneity, and smaller heterogeneity ($I^2 < 50\%$, $P > 0.1$) was used for meta-analysis with the fixed-effects model, and vice versa with a random-effects model. We used Stata 16.0 software to detect publication bias, and $P > 0.05$ indicated no bias. For statistical analysis, we used Review Manager 5.4 software. Stata 16.0 was used to test publication bias by Egger’s method. Empirically, the funnel plot asymmetry test should be used only if at least 10 studies are included in the analysis.

Assessment of the Quality of Evidence

The quality of evidence for each outcome indicator was judged according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) grading system¹¹ and evaluated using the GRADE profiler 3.6 software.

Results

Literature Search

A total of 122 relevant papers were searched through the databases, including 11 in Chinese and 160 in English. We used the endnote software to exclude 56 duplicate papers and 97 irrelevant studies. Eighteen papers were excluded after reading through the full text according to the literature screening the PRISMA flowchart. Seven studies were included in the final meta-analysis. The literature screening process is shown in [Figure 1](#).

Characteristics of Eligible Studies

Of the 171 identified articles, 18 were comprehensively evaluated for content and quality, leaving 7 articles. All seven studies were randomized controlled trials, most of which were in Europe and the United States. All of them were conducted in the last 3 years, the treatment phase of the patients was a double-blind induction treatment period, and the patients were all treated with conventional antidepressants combined with esketamine or placebo. The main characteristics of the included literature are shown in [Table 1](#).

Risk of Bias

Seven studies^{12–18} adopted the random number table method and the random timetable generated by the computer system for randomization. Only one study¹² did not specify allocation concealment; all seven studies^{12–18} were double-blind, except for some missing data in the study by Popova et al 2019;¹⁸ the rest of the results were found to be complete, but it was unclear whether other sources of bias existed ([Figure 2](#)).

Changes in Montgomery-Asberg Depression Rating Scale (MADRS) Score Before and After Treatment

A total of 10 active arms in the seven articles^{12–18} reported the change value of MADRS at the end of the double-blind induction period from baseline ($I^2 = 0\%$, $P = 0.56$). The fixed effect model was selected, and the results showed that the combined effect value was located on the left side of the null line. Compared with the control group, the esketamine + antidepressant group showed significantly improved MADRS score of patients with treatment-resistant depression (MD = -2.68 , 95% CI -3.98 to -1.37 , $P < 0.0001$) ([Figure 3](#)).

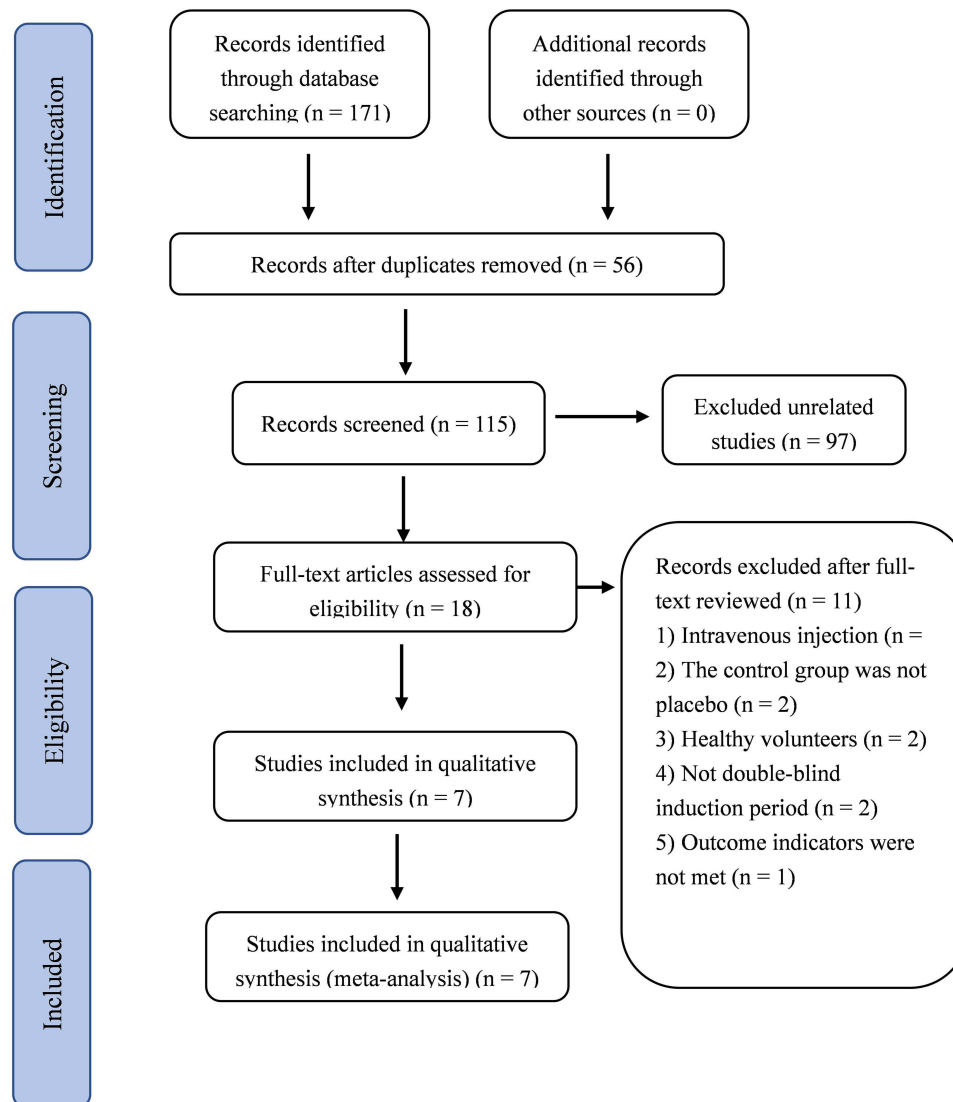


Figure 1 PRISMA flowchart for the article screening and selection.¹⁰

Notes: PRISMA figure adapted from Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. Creative Commons.

Effective Response Rate at the Endpoint of the Double-Blind Induction Period

The effective response rate was defined as a $\geq 50\%$ reduction in MADRS score at the endpoint of the double-blind induction period. Five articles^{12,15–18} in eight active arms documented the above data, involving 911 study subjects. No significant heterogeneity was observed among study subjects ($P = 0.64$, $I^2 = 0\%$), analyzed using a fixed-effects model. Compared with the control group, esketamine + antidepressant significantly improved the response to antidepressants in patients with treatment-resistant depression (RR = 1.28, 95% CI 1.12 to 1.46, $P = 0.0002$) (Figure 4).

Remission Rate at the Endpoint of the Double-Blind Induction Period

Remission was defined as a MADRS score ≤ 12 at the endpoint of the double-blind induction period, and data were recorded in six active arms of five articles^{13–15,17,18} with 1112 study subjects. No significant heterogeneity was observed among study subjects ($P = 0.56$, $I^2 = 0\%$). The results of the fixed-effects model analysis showed significant differences. Compared with placebo + antidepressants, esketamine + antidepressants significantly improved remission in patients with treatment-resistant depression (RR = 1.39, 95% CI 1.18 to 1.63, $P < 0.0001$) (Figure 5).

Table 1 Basic Information of the Included Literature

References	NO. (T/C)	Age (Years)		Interventions		Treatment Duration	Antidepressants
		T	C	T	C		
Canuso 2019 ¹²	35/31	36±12.82	35.70±13.40	Esketamine:84mg	Placebo	4 weeks	NR
Ionescu 2021 ¹³	114/113	40.2±12.73	41.40±13.43	Esketamine:84mg	Placebo	4 weeks	NR
Fu DJ 2020 ¹⁴	111/112	40.80±13.11	37.90±12.54	Esketamine:84mg	Placebo	4 weeks	NR
Ochs-Ross 2019 ¹⁵	72/65	70.60±4.79	69.40±4.15	Esketamine:28, 56, 84mg	Placebo	4 weeks	ADs
Takahashi 2021 ¹⁶	122/80	41.90±10.26	43.30±11.40	Esketamine:28, 56, 84mg	Placebo	4 weeks	ADs
Fedgchin 2019 ¹⁷	229/113	46.10±11.12	46.80±11.36	Esketamine:56, 84mg	Placebo	4 weeks	ADs
Popova 2019 ¹⁸	114/109	44.90±12.58	46.40±11.14	Esketamine:56, 84mg	Placebo	4 weeks	ADs

Abbreviations: NR, Not reported; Antidepressants (ADs); Duloxetine, Escitalopram, Sertraline, Venlafaxine.

Depression Self-Rating Scale (SDS) Changes

Four articles^{15–18} with seven activity arms documented SDS changes from baseline in 758 study subjects, with little heterogeneity between study subjects ($P = 0.74$, $I^2 = 0\%$); compared with the control group, esketamine + antidepressant significantly improved the SDS score in patients (MD = -2.9 , 95% CI -4.01 to -1.79 , $P < 0.00001$) (Figure 6).

Other Outcome Indicators

Other outcome indicators were summarized, and the European Five-Dimensional Health Scale (EQ-5D-5L), health status visual scale (EQ-VAS), depression screening scale (PHQ-9), and 24-hour (next day) remission rate at the end of the double-blind induction period were statistically analyzed. No significant heterogeneity was observed among the studies, and the differences in the meta-analysis results were significant ($P < 0.05$). However, no large heterogeneity was observed among the included studies in terms of sustained effective response rate; the results of the meta-analysis were not significant ($P > 0.05$) (Table 2).

Adverse Events

A total of seven studies^{12–19} documented the occurrence of adverse reactions during treatment. With the current focus on common adverse events during treatment, the data showed that the experimental group was significantly more prone to symptoms such as nausea, dizziness, schizophrenia, vomiting, vertigo, dysgeusia, lethargy, dysesthesia, increased blood pressure, and sedation ($P < 0.05$). However, the difference in adverse reactions such as headache and anxiety was not significant ($P > 0.05$) (Table 3).

Sensitivity Analysis

When comparing the sustained effective response rate of esketamine + antidepressant for patients, a certain degree of heterogeneity was observed among the studies. After excluding the study by Takahashi et al 2021,¹⁶ the heterogeneity between the experimental group and the control group changed ($P = 0.44$, $I^2 = 0\%$), and the difference was significant (RR = 2.79, 95% CI 1.42 to 5.50, $P = 0.003$).

Publication Bias

Stata 16.0 was used to test publication bias by Egger's method. Due to the lack of included literature, only the changes in MADRS scores recorded in seven studies were tested. The results showed no obvious publication bias among the studies ($P = 0.1416$).

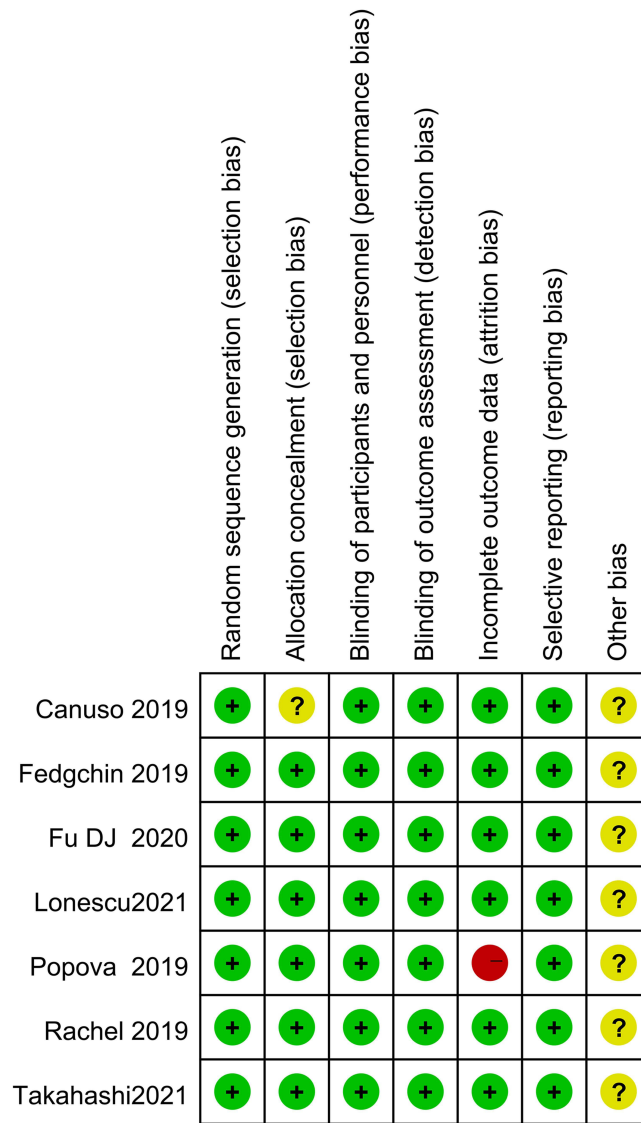


Figure 2 Risk of bias summary of each eligible study.

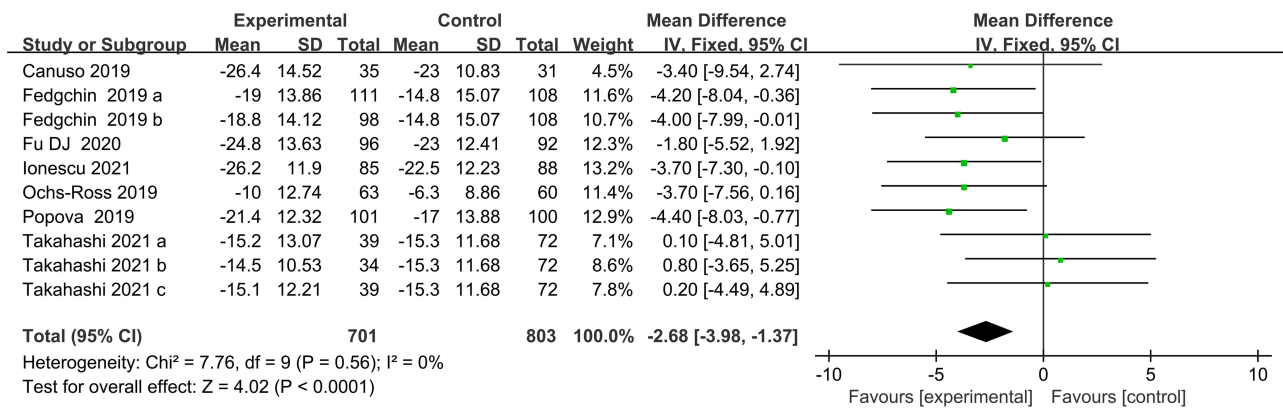


Figure 3 Forest plot of esketamine + antidepressant to improve MARDs scores.

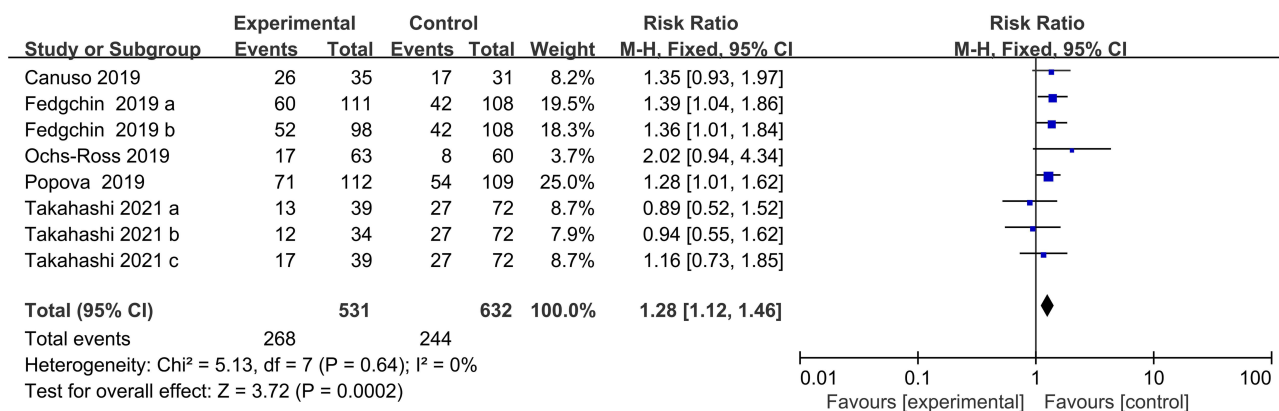


Figure 4 Forest plot for effective response rate comparison.

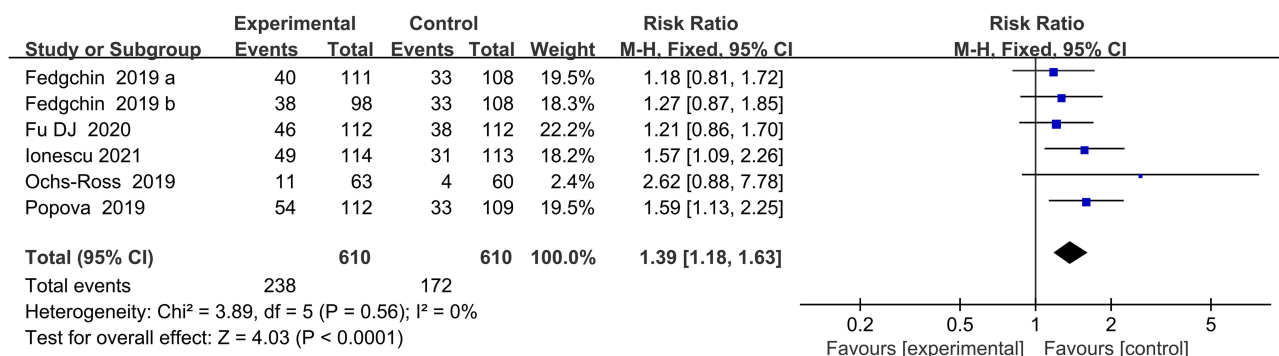


Figure 5 Forest plot of remission rate comparison.

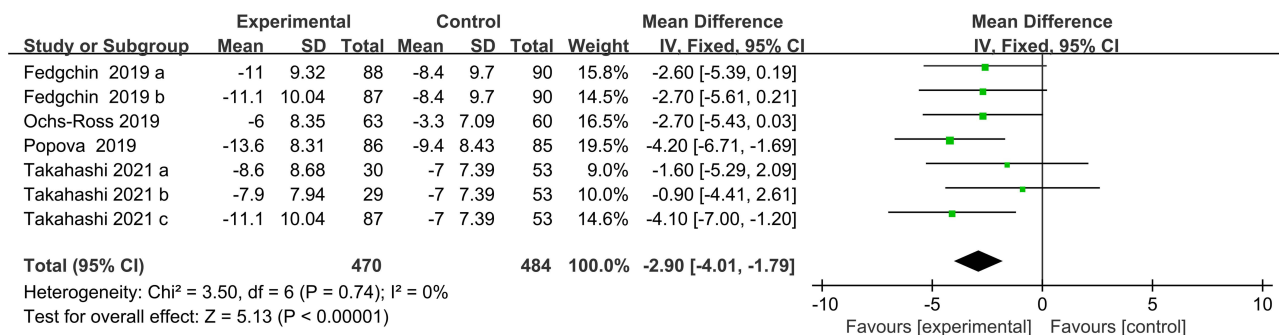


Figure 6 Forest plot comparing changes in SDS.

GRADE Level of Evidence

The GRADE systematic review results showed that the evidence for remission at the end of the double-blind induction period was of high quality. The evidence for the effective response rate, changes in MADRS score before and after, and changes in SDS at the end of the double-blind induction period were moderate (Table 4).

Discussion

This study found that in the treatment of refractory depression, the clinical efficacy of esketamine nasal spray combined with conventional antidepressants in the double-blind treatment period was significantly better than that of the control group, and it could treat clinical symptoms quickly and effectively. Esketamine can act as an antidepressant as early as 2

Table 2 Summary of Remaining Outcome Indicators

Variables	No. of Studies	Sample Size (T/C)	Heterogeneity		Follow Up Endpoint		
			P	I ²	MD/RR	95% CI	P
EQ-5D-5L	4	532/410	0.98	0%	0.05	0.02 to 0.08	0.00009
24h remission rate	3	345/303	0.77	0%	1.96	1.29 to 2.99	0.002
EQ-VAS	4	532/410	0.62	0%	5.54	2.37 to 8.71	0.0006
PHQ-9	3	376/268	0.94	0%	-2.5	-3.6 to -1.41	<0.00001
Sustained effective response rate	4	499/332	0.2	31%	1.76	0.88 to 3.53	0.11

hours.¹⁹ Esketamine nasal spray, in combination with antidepressants, may help relieve depressive symptoms based on its role as an N-methyl-D-aspartate (NMDA) receptor antagonist.^{20,21} This study conducted a comprehensive analysis of depression remission from multiple-scale scores. The meta-analysis results showed that the clinical efficacy and statistics of the experimental group were significantly different. However, in terms of adverse reactions, the incidence of side effects in the experimental group was higher. One long-term safety data showed that most adverse events were mild or moderate and were transient, self-limited, and resolved within the same day,^{22,23} consistent with the results of the included study.

In recent years, studies conducted in European countries have found that treatment-resistant depression can increase patients' anxiety and comorbidities.^{24,25} Although many treatment options are currently available for treatment-resistant depression,^{20,21} studies suggest that these therapies may lack consistent long-term efficacy,²⁶ and approximately one-third of

Table 3 Summary of Adverse Events

Adverse Events	No. of Studies	Heterogeneity		Meta-Analysis Results		
		P	I ²	RR	95% CI	P
Nausea	7	0.27	21%	2.63	2.01 to 3.44	<0.00001
Dizziness	7	0.45	0%	3.20	2.46 to 4.16	<0.00001
Dissociation	7	0.63	0%	5.57	3.92 to 7.91	<0.00001
Headache	7	0.37	7%	1.23	0.98 to 1.56	0.08
Vomiting	7	0.31	16%	3.35	2.02 to 5.54	<0.00001
Vertigo	7	0.93	0%	9.21	4.82 to 17.57	<0.00001
Dysgeusia	6	0.68	0%	1.50	1.14 to 1.97	0.003
Anxiety	6	0.08	49%	1.44	0.96 to 2.16	0.08
Somnolence	6	0.99	0%	1.82	1.37 to 2.41	<0.0001
Hypoesthesia	6	0.84	0%	5.32	2.86 to 9.91	<0.00001
Blood pressure increased	6	0.56	0%	3.36	2.23 to 5.06	<0.00001
Sedation	5	0.83	0%	5.07	2.45 to 10.49	<0.0001
Euphoric mood	4	0.35	8%	4.56	1.9 to 10.91	0.0007
Paresthesia	5	0.62	0%	4.25	2.42 to 7.46	<0.00001

Table 4 Quality of Evidence

Variables	No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Level of Evidence
MADRS change	7	Serious ^a	No	No	No	No	Moderate
Effective response rate	5	Very serious ^{ab}	No	No	No	No	Low
Remission rate	5	No	No	No	No	No	High
SDS change	4	Serious ^b	No	No	No	No	Moderate

Notes: ^aSome studies have unclear hidden allocation; ^bSome studies did not report the results of no observed efficacy.

patients with major depressive disorder do not respond significantly to first-line treatment.²⁷ Even when two antidepressants with different pharmacological mechanisms are combined, treatment in 10% to 30% of patients is ineffective.²⁸ As early as 2003, Daly et al²⁹ evaluated the efficacy of intranasal esketamine and placebo in treating treatment-resistant depression and then re-evaluated clinical trials at the international level to verify the safety and efficacy of the experiment. Another study reported that using esketamine nasal spray for treating patients with suicidal tendencies and refractory depression could also achieve rapid and effective relief.¹³ Currently, esketamine is not recommended as a first-line drug in China's treatment guidelines for treatment-resistant depression, but it has been approved as a first-line drug for treatment-resistant depression in Europe and the United States.³⁰ The use of esketamine to treat treatment-resistant depression is an advance in the understanding and treatment of the disorder.³¹ Another psychedelic drug was reported to produce a significant antidepressant effect one day after dosing,^{32,33} which may be another approach for treating refractory depression.

Our study focused on the efficacy of esketamine in refractory depression and differs significantly from published studies. For example, there are studies^{34,35} that evaluate the effect of ketamine and esketamine on depression or evaluate the efficacy of ketamine on major depression.³⁶ However, combined with the current research reports, the exact mechanism of esketamine in the treatment of antidepressants is still not very clear.³⁷ Individual patients and their conditions lead to different responses to drugs, so optimizing the treatment strategy, ie, individualized treatment is the best choice to effectively improve patients' quality of life.³⁸

Limitations

The main limitation of the study is the small number of included references. A large number of clinical studies are needed for further verification; secondly, the allocation concealment of some included studies is not very clear, so a potential bias may be possible; thirdly, the dose and frequency of esketamine are inconsistent, so the optimal dose has not yet been obtained in this analysis; finally, this analysis only focused on the double-blind treatment period, and did not analyze the subsequent open treatment period.

Conclusions

This analysis showed that the application of esketamine nasal spray for refractory depression could relieve and improve depressive symptoms quickly and effectively. Since the current relevant data are still relatively small, further experimental evaluation is needed. At the same time, esketamine, as an anesthetic drug, has the characteristics of analgesia and sedation, which provides new ideas and development prospects for the treatment of patients with depression. It is possible to treat patient's symptoms of depression while operating on them, but this requires extensive research validation and high quality data.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

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Disclosure

The authors declare that they have no competing interests.

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