Esketamine for treatment-resistant depression: A review of clinical evidence (Review)

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Abstract. Treatment-resistant depression (TRD) is a challenge for psychiatrists, even after more than seven decades since the first antidepressants were used in clinical practice. Non-monoaminergic-based drugs with antidepressant properties have been developed, but to date, only esketamine and brexanolone have been approved for TRD and postpartum depression, respectively. A narrative review on the efficacy and safety of esketamine in the main categories of depressive disorders has been conducted through four electronic databases (Pubmed, Cochrane, EMBASE and Clarivate/Web of Science) The primary objective of the present review was to find evidence that may support the usefulness of esketamine for patients diagnosed with TRD as well as data about its potential adverse effects in the short and long term. A total of 14 papers were reviewed, and their results support the recommendation of esketamine for treatment of TRD as an add-on to antidepressants, but more data is needed in order to assess its long-term efficacy and safety. It must also be mentioned that there have been a few trials which did not report a significant effect on the severity of depressive symptoms with esketamine in TRD, therefore, caution is indicated for patients initiated on this adjuvant agent. There has been insufficient data to formulate specific guidelines about esketamine administration because evidence about favorable or negative prognostic factors of this treatment has been lacking, and the duration of its administration has not been unanimously accepted. Novel directions for research have been identified, especially in the case of patients with TRD and substance use disorders, geriatric or bipolar depression or in major depression with psychotic features.

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Contents

1. Introduction

Esketamine is the only pharmacological agent with glutamatergic neuromodulatory properties approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2019 to enhance the effects of serotonin selective or serotonin and norepinephrine reuptake inhibitors (1). In the context of high rates of partial responsivity or non-response to currently available antidepressants, multiple mechanisms of action for novel pharmacological agents are being explored besides the stimulation of monoaminergic neurotransmission (2,3). However, although numerous molecules have been studied in phases II and III of clinical research, it is difficult to predict which will reach the market in the following decades. Until now, only esketamine and brexanolone, the latter being a γ-aminobutyric acid (GABA)-A receptor positive allosteric modulator, are antidepressants with non-monoaminergic activity, that have been approved by FDA for use under supervision in patients with treatment-resistant depression (TRD) and post-partum depression, respectively (4). Furthermore, tolerability issues associated with antidepressants already in clinical use indicate the need to find novel pharmacological agents for treating major depression (5).

Esketamine nasal spray is recommended for adults diagnosed with major depressive disorder (MDD) who did not respond to at least two antidepressants, and who currently have a major depressive episode of moderate or severe

intensity (1,6). Intensive monitoring is mentioned in the EMA approval and specified in the summary of the characteristics of the product, with an algorithm of pre- and post-administration assessment (6). Similar recommendations have been formulated by the FDA (1,6).

The pharmacodynamic profile of esketamine is characterized by non-selective, non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors, which are ionotropic glutamatergic receptors (Table I) (6). Activation of NMDA receptors causes a transient increase in glutamate release, leading to stimulation of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (6). Furthermore, signaling via neurotrophic factors is enhanced and synaptogenesis is improved in brain regions involved in regulating mood and emotional behavior (6). Restoring dopaminergic neurotransmission from areas responsible for regulating motivation and reward contributes to a rapid clinical response (for example, reduction of anhedonia), but the release of dopamine in the striatum may explain the psychotomimetic effects of this agent (Fig. 1) (6,7). The fast onset of esketamine may be associated with direct stimulation of the mammalian target of rapamycin complex 1 (mTORC1), a signaling pathway involved in the regulation of protein synthesis, which stimulates synaptogenesis and brain-derived neurotrophic factor production (8).

Glutamatergic mechanisms of depression are currently the focus of attention after preclinical studies supported the importance of this neurotransmission system in the pathogenesis of mood disorders (9,10). Abnormal levels of glutamate are found in cerebrospinal fluid, plasma and brain tissue during autopsy studies in individuals with mood disorders (10). Magnetic resonance spectroscopy detects abnormal levels and ratios of glutamate/GABA in brain areas associated with MDD (10). Glial cell functionality may be decreased after exposure to prolonged stress, leading to synaptic loss and activation of the apoptotic pathway via glutamatergic mediation (10). Ketamine is associated with rapid-acting antidepressant effects and NMDA receptor-mediated signaling, inhibition of extrasynaptic NMDA receptors and blockade of NMDA receptors in the synapse (9,10). Ketamine blocks excitatory glutamate transmission and increases overall activity of the prefrontal cortex by inhibiting NMDA receptors expressed in GABA neurons preferentially (10,11). The disinhibition of cortical GABA interneurons by NMDA receptor inhibition explains the excitatory effect of ketamine on the firing of pyramidal neurons (10,11). Also, ketamine triggers an antidepressant effect through direct inhibition of extrasynaptic NMDA receptors by specific blocking of extrasynaptic GluN2B-NMDA receptors (via mTOR signaling), which leads to the excitation of pyramidal neurons (10). Furthermore, the blockade of NMDA receptors enhances synaptic plasticity based on mTORC1 signaling via Akt and ERK activation; this mechanism explains the increasing number and function of synapses in the prefrontal cortex (10). A less explored mechanism of action of ketamine assumes the existence of NMDA receptor inhibition-independent effects because other pharmacological agents, such as memantine or lanicemine, are not efficient in treating mood disorders (10,12,13).

Intravenous administration of esketamine has been reported to induce rapid-acting and sustained activity in refractory patients with MDD, but it is also associated with favorable results in treatment-resistant patients with imminent risk of suicide in phase II studies (14,15). Additionally, the effects of intranasal esketamine have been explored in patients with depression and suicidal intent because of the rapid onset of antidepressant effects reported after single-dose administration (16,17).

The anti-suicidal effect of esketamine represents a key reason to explore its properties since managing suicidal behavior in patients with MDD is difficult with the use of previous generations of antidepressants. The identification of risk markers for suicidal behaviors by combining genomic assessment and clinical evaluation has led to an increased interest in drugs that may modulate mechanisms such as neural connectivity and activity, immune and inflammatory response (18). Ketamine and esketamine have been explored in this type of pathology because the dysregulation of glutamate neurotransmission has been suggested to serve a central role in the onset of suicidal behavior (18-20). Besides its ability to non-selectively antagonize NMDA receptors, ketamine may modulate the activity of σ and μ opioid, serotonin 5HT3, muscarinic and α7 nicotinic receptors, as well as catecholamine transporters in the prefrontal cortex and hippocampus; these pharmacodynamical properties may be involved to a certain degree in anti-suicidal properties of ketamine (18-20).

However, one study has suggested that 'the excitement over a new treatment for depressed patients with suicidal intentions should be re-evaluated after real-world experience' (16). Therefore, a carefully structured assessment of suicide risk should be combined with an empathic approach focused on the subjective experiences of patients with MDD (16). Suicide is not ingrained in the experience of depression; therefore, suicidal risk should be regarded as a complex dimension that only partially overlaps with the depressive phenomenology (16). This is why suicide may be perceived as a way to escape extreme negative emotions or acute anguish, not simply as another MDD symptom (16,21).

The pharmacokinetic properties of esketamine are summarized in Table II. An active metabolite, (S)-norketamine, has been identified, which results from cytochrome P450 metabolization of its parent compound and possesses a notable affinity for NMDA receptors, higher than that of (R, S)-ketamine and (S)-ketamine [inhibitor constant (Ki)=1.7 μM vs. 0.53 μM and 0.3 μM, respectively] (7,8,22). This metabolite is associated with a rapid and potent antidepressant effect in rodent models of depression (22). While preclinical studies reported the abuse potential of esketamine, its metabolite was reported as being safer (i.e., lower risk of psychotomimetic and addictive potential) (7,8,22).

2. Objectives

The primary objective of the present review was to evaluate the existing evidence in the literature on the efficacy and tolerability of esketamine in the management of TRD. Secondary objectives were: i) To explore other potential benefits and risks of esketamine in short- and long-term administration; ii) to formulate clinical recommendations based on the analysis of these data and iii) to establish future research directions that may enrich knowledge on the effects of esketamine.

Table I. Pharmacodynamic properties of esketamine.

First author/s, year	Receptor/neurotransmitters	Description	(Refs.)
Janssen-Cilag, 2019; Salahudeen *et al*, 2020; De Berardis *et al*, 2018	NMDA receptors	Non-selective, non-competitive, activity-dependent antagonism	(6,8,18)
Janssen-Cilag, 2019; Salahudeen *et al*, 2020	AMPA receptors	Indirect stimulation at the post-synaptic level	(6,8)
Janssen-Cilag, 2019; Salahudeen *et al*, 2020	Neurotrophic factors	Downstream activation	(6,8)
Janssen-Cilag, 2019; Salahudeen *et al*, 2020	Dopamine	Release of endogenous dopamine from the presynaptic terminal in the striatum (in monkey trials)	(6,8)

NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

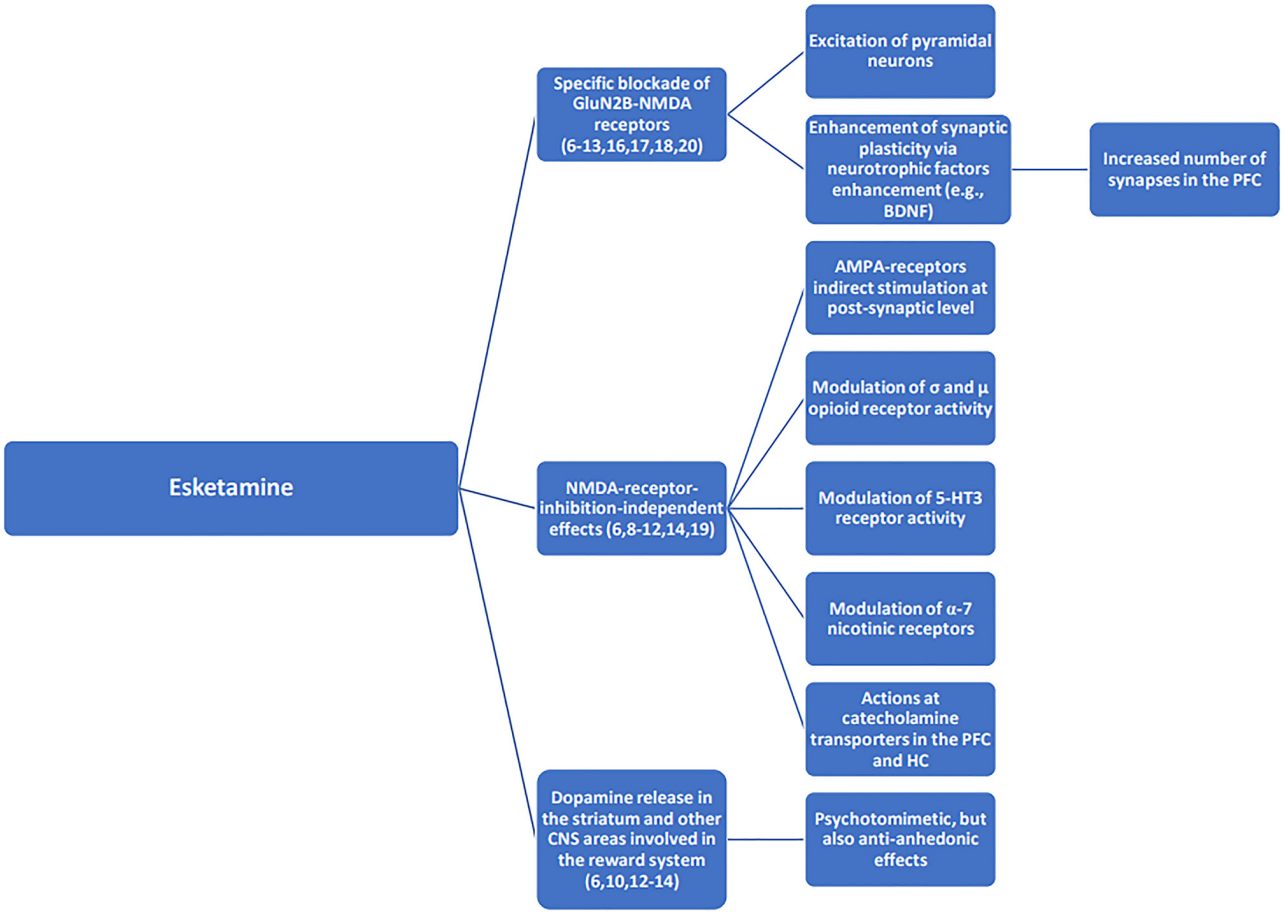

Figure 1. Mechanisms of action of esketamine, based on data from preclinical and clinical studies. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; Glu, glutamate; HC, hippocampus; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex.

3. Subjects and methods

The efficacy and safety profile of esketamine was analyzed by reviewing the results of studies found in electronic databases (PubMed-https://pubmed.ncbi.nlm.nih.gov/, Cochrane-https://www.cochrane.org/, EMBASE-https://www.embase.com and Clarivate Web of Science-https://www.webofscience.com/). All studies published between January 2010 and May 2022 were included in the primary analysis. Prospective clinical trials were included regardless of the methodology used (randomized/non-randomized, open/single-blind/double-blind and controlled/uncontrolled) and retrospective trials were also included. Studies including nasal or intravenous (i.v.) infusion of esketamine were allowed

Table II. Pharmacokinetics of esketamine.

Parameter	Description
Absorption	A total of ~48% of intranasally administered drug is absorbed T_{max}=20-40 min
Distribution	V_d at steady state=709 l Plasma protein binding=43-45% Esketamine is not an inhibitor of the P-glycoprotein transport system
Biotransformation	There is extensive hepatic metabolism, primarily by CYP2B6 and 3A4 isoenzymes; the contribution of CYP2C19 and 2C9 is lower compared with that of CYP2B6
Special populations	Elderly (≥65 years): C_{max} is 18% higher compared with young individuals at a dose of 28 mg and 67% higher at a dose of 84 mg esketamine. $T_{1/2}$ is similar in the elderly and young individuals C_{max} in individuals with kidney failure is 20-26% higher in mild, moderate or severe renal insufficiency compared with individuals without kidney failure. There are no data on the pharmacokinetics of esketamine in patients undergoing dialysis There are no differences in pharmacokinetics between individuals with mild hepatic failure and healthy individuals; C_{max} is 8% higher compared with healthy individuals in the case of moderate insufficiency; in the severe cases, no pharmacokinetic studies have been conducted
Elimination	$T_{1/2}$=7-12 h Elimination occurs via the urine and feces, with only 1% of the administered dose being excreted unchanged in the urine
Pharmacokinetic interactions	Administration of rifampicin, a potent CYP 3A4/2B6 enzyme inhibitor, decreases the concentration of esketamine by 17-28% Rifampicin decreases plasma concentration of midazolam, a CYP3A4 substrate, by ~16%, but does not affect the concentration of bupropion, a CYP2B6 substrate

Adapted from Ref (6). V_d, volume of distribution; C_{max}, maximum concentration; T_{max}, time needed to reach C_{max}; $T_{1/2}$, elimination half-time; CYP, cytochrome P450.

in the reviewing stage. Patients enrolled in the trials within the current review were diagnosed with TRD, MDD, psychotic depression or any other type of depressive disorder. Studies exploring esketamine effects in healthy volunteers were allowed if these effects were evaluated using validated instruments. There were no limitations related to the age or sex of the enrolled patients in the clinical trials. Exclusion criteria were as follows: Case reports, case series, systematic and narrative reviews, and meta-analyses; sources written in languages other than English; studies with unspecified outcomes, duration or outcome measures.

4. Results overview

A total of nine randomized controlled trials exploring the efficacy and tolerability of esketamine nasal spray were included in the review. Additionally, one esketamine vs. ketamine i.v. study, one single dose of esketamine i.v. study, one retrospective analysis, one post-hoc analysis and one esketamine vs. ketamine and R-ketamine i.v. study were also reviewed (Table III).

5. Short-term efficacy results

TRANSFORM-1 was a phase III, double-blind, randomized, multicenter trial, which enrolled 346 patients with moderate/severe MDD that did not respond to ≥2 antidepressants (23). The effects of esketamine nasal spray (56 or 84 mg, twice weekly) were compared with placebo as an add-on to a newly initiated oral antidepressant (such as duloxetine, escitalopram, sertraline or venlafaxine extended release), which was administered in an open-label manner for 4 weeks (23). The primary objective of this trial was to observe the decrease in the Montgomery-Asberg Depression Rating Scale (MADRS) (24) from baseline to the end of the study. After 28 days, there were no significant differences between the active and placebo groups regarding the MADRS score (23).

Another phase III study, TRANSFORM-2, had a double-blind, randomized, multicenter, active comparator design, and 227 patients with moderate/severe MDD who did not respond to ≥2 antidepressants were enrolled (25,26). The intervention consisted of esketamine (56 or 84 mg, twice weekly) vs. placebo nasal spray as an add-on to antidepressants, and the study duration was 4 weeks. The change in MADRS score in patients receiving esketamine + antidepressant was significantly greater than in those treated with an antidepressant + placebo spray (25,26). Patient Health Questionnaire-9 (27) scores also improved significantly in the active group vs. placebo and the improvement in depressive symptoms was observed earlier in patients who received the active intervention (25,26). The most improved items on MADRS in the esketamine vs. placebo group were 'apparent sadness' and 'inability to feel' (26).

Table III. Esketamine efficacy and tolerability.

First author/s, year	Methodology	Key results	Trial registration code	(Refs.)
Fedgchin *et al*, 2019	Phase III, DBL, RCT, 346 participants with moderate/severe MDD non-responsive to ≥2 AD; ESK 56/84 mg vs. placebo + AD, 4 weeks	MADRS scores did not support any significant difference between ESK and placebo at the endpoint	NCT02417064	(23)
Popova *et al*, 2019 Floden *et al*, 2022	Phase III, DBL, RCT, 227 participants with moderate/severe MDD non-responsive to ≥2 AD; ESK 56/84 mg vs. placebo + AD, 4 weeks	ESK differentiated itself from placebo on MADRS and PHQ-9 scales	NCT02418585	(25,26)
Ochs-Ross *et al*, 2020	Phase III, DBL, RCT, 138 participants with TRD; ESK 28/56/84 mg vs. placebo + AD, 4 weeks	No significant difference in decrease of MADRS scores between groups. Patients aged 65-74 years responded better; first MDE <55 years of age was a favorable prognostic factor	NCT02422186	(28)
Correia-Melo *et al*, 2020	DBL, RCT, 63 participants with TRD; ESK vs. KET i.v., single dose	The remission rate was higher under ESK vs. KET treatment at 24 h post-administration based on MADRS scores	UMIN000032355	(29)
Singh *et al*, 2016	DBL, RCT, 30 participants with TRD; ESK vs. placebo i.v., single dose; second phase: Re-randomization of non-responsive patients on ESK vs. placebo, on day 4	ESK was superior to placebo (based on MADRS scores) on day 2 after therapy. The effect of ESK was fast (2 h post-infusion)	NCT01640080	(15)
Souza-Marques *et al*, 2022	Retrospective analysis, 15 patients with PMD; ESK single dose i.v.	ESK improved MADRS scores 24 h post-administration. No difference was observed between patients with MDD and PMD in relation to ESK treatment	N/A	(30)
Fu *et al*, 2020	Phase III, DBL, RCT, 226 participants with MDD + active suicidal ideation and intent; ESK 84 mg vs. placebo + SOC (AD included), 4 weeks	ESK was associated with significantly greater improvement after 24 h post-first dose administration. No difference in severity of suicide risk was reported. The favorable effect was detected earlier in patients who received ESK (4 h post-administration)	NCT03039192	(31)
Ionescu *et al*, 2021	Phase III, DBL, RCT, 230 patients with MDD + suicidal ideation with intent, ESK 84 mg vs. placebo, 4 weeks + SOC (AD included)	ESK led to significantly greater improvement in MADRS scores 24 h from the first dose. The CGI-S scores were improved in both groups, without differences between them. The positive effect was detected earlier in patients with ESK (4 h)	NCT03097133	(32)
Caruso *et al*, 2021	Post hoc analysis, ESK vs. placebo + SOC, 24 h post-treatment administration, two trials	Patients with a history of suicide attempts had a significantly greater decrease in suicidal behavior and/or ideation (CGI-SS-R) post-treatment	N/A	(34)

Table III. Continued.

First author/s, year	Methodology	Key results	Trial registration code	(Refs.)
Takahashi *et al*, 2021	Phase IIb, DBL, RCT, 202 patients with MDD non-responsive to 1-4 Ads; 4 weeks	No differences between active and placebo groups were reported, based on the primary outcome of MADRS scores	NCT02918318	(36)
Araújo-de-Freitas *et al*, 2021	DBL, RCT, 54 patients with TRD; ESK vs. KET i.v. single dose	No difference between groups was observed in cognitive functioning following treatment but both drugs improved cognitive performance in patients with TRD	UMIN000032355	(37)
Pfenninger *et al*, 2002	RCT, DBL, healthy subjects, cross-over design; KET vs. ESK vs. R-KET i.v.	Multiple cognitive parameters improved significantly after 5 min post-isomer administration vs. racemic KET	N/A	(38)
Dijkstra *et al*, 2022	27 participants with mild/moderate MDD; ESK 84 mg vs. placebo, 6±0.5 and 18±2 h post-administration, 3 weeks	ESK did not negatively affect driving performance vs. placebo	NCT02919579	(39)
Daly *et al*, 2019	Phase III, 297 patients, ESK vs. placebo + AD, 16 weeks	The risk of relapse was decreased by 51-70% in patients treated with ESK + AD vs. placebo + AD	NCT02493868	(40)
Wajs *et al*, 2020	Phase III, DBL, RCT, 802 patients with TRD; ESK 28/56/84 mg + AD, 4 weeks (first phase) + OL second phase (48 weeks)	MADRS scores improved compared with baseline up to the end of the second phase	NCT02497287	(41)

AD, antidepressant; CGI-SS-R, Clinical Global Impression-Severity of Suicidality-Revised; CGI-S, Clinical Global Impression-Severity; DBL, double-blind; ESK, esketamine; KET, ketamine; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; OL, open-label; PMD, MDD with psychotic features; RCT, randomized controlled trial; SOC, standard-of-care; TRD, treatment-resistant depression; PHQ, Patient Health Questionnaire; N/A, not applicable.

In TRANSFORM-3, another phase III, double-blind trial, 138 patients ≥65 years of age with TRD were randomized on flexible doses of esketamine (28, 56 or 84 mg, administered twice weekly) or placebo nasal spray in addition to a newly initiated oral antidepressant (28). The duration of the study was 4 weeks, and the primary outcome was change in MADRS total score from baseline to endpoint (28). No significant difference was reported in the improvement of depressive symptoms in patients receiving esketamine + antidepressant vs. placebo + antidepressant, according to the MADRS score (28). However, there were more significant differences between groups that favored patients aged 65 to 74 years vs. those >75 years of age and patients with an earlier onset of depression (<55 years of age) (28).

A randomized, double-blind, non-inferiority clinical trial compared the effects of esketamine and ketamine, both administered as i.v. infusion, in a single dose of 0.25 and 0.5 mg/kg, respectively, in 63 patients with TRD (29). The results collected 24 h post-infusion showed that 24.1% of patients who received ketamine and 29.4% of those treated with esketamine obtained remission, according to MADRS scores (29). Therefore, the non-inferiority hypothesis was confirmed in this trial at 24 h post-treatment (29).

Another randomized, multicenter, double-blind, placebo-controlled study included 30 patients with TRD who received 0.2 or 0.4 mg/kg i.v. infusion of esketamine or placebo for 40 min (15). In the second phase, non-responsive patients who received a placebo in the first stage were randomized again to i.v. esketamine or placebo on day 4 (15). Patients treated with esketamine (both dosing regimens) achieved clinical improvements (according to MADRS scores) vs. placebo on the second day after therapy (15). The effect of esketamine was fast, its onset being detected 2 h post-treatment administration (15).

A retrospective analysis of medical records included 15 patients with MDD with psychotic features and evaluated the effects of a single dose of 0.5 mg/kg esketamine (30). A significant difference was observed in MADRS scores 24 h after administration, but no differences were reported between patients with MDD who exhibited psychotic features vs. those who do not (30).

6. Efficacy of esketamine in lowering suicide risk

In a double-blind, multicenter, phase III study, ASPIRE I, 226 patients with MDD and active suicidal ideation who also presented suicidal intent were randomized to 84 mg esketamine or placebo nasal spray twice/week for 4 weeks as an add-on to standard-of-care therapy (hospitalization and newly initiated or enhanced oral antidepressant) (31). MADRS scores indicated a significantly greater improvement in patients treated with esketamine 24 h after the first dose (31). The favorable effect was observed earlier in the esketamine group vs. placebo (4 h after administration of the drug) (31). However, no differences were reported between groups in the severity of suicide risk during monitoring (31).

In ASPIRE II, a phase III, double-blind, randomized trial, 230 patients with MDD and active suicidal ideation with intent received treatment with 84 mg esketamine or placebo nasal spray twice/week with a monitoring period of 4 weeks, together with comprehensive standard care (antidepressant being included) (32). MADRS scores indicated a significantly greater improvement in patients treated with esketamine after 24 h from the first dose of treatment (32). The favorable effect was observed earlier in the active group vs. placebo, at 4 h after esketamine administration (32). The Clinical Global Impression-Severity (33) scores also improved in both groups, but without significant differences between groups (32).

A post hoc analysis of data collected from the ASPIRE I and II studies on 24 h post-treatment outcomes of patients at risk of suicide showed that the active group improved significantly (indicated by MADRS scores) vs. placebo + standard care (34). Patients who had ≥1 suicide attempt in their history showed a more significant reduction in suicidal behavior and/or ideation, based on the between-group difference in the Clinical Global Impression-Severity of Suicidality-Revised (35) scores 24 h post-treatment (34).

A placebo-controlled phase IIb study involved the enrollment of 202 patients with MDD who were non-responsive to ≥1 but <5 different antidepressants, randomized to esketamine (28, 56 or 84 mg) or placebo nasal spray as an add-on to a new antidepressant, with an active monitoring period of 4 weeks (36). In the double-blind phase, a similar improvement in depressive symptoms was observed in all groups, with no difference between the active substance and placebo, according to the primary outcome (MADRS score) (36).

7. Efficacy of esketamine on cognitive functioning

A randomized, double-blind study that evaluated the comparative efficacy of esketamine and ketamine i.v. infusion on cognition in 54 patients with treatment-resistant MDD at 24 h and 7 days post-treatment found no significant differences between the two substances on cognitive function (37). Both drugs improved short-term visuospatial memory, executive functioning, processing speed and episodic verbal memory, evaluated via neuropsychological tests (37). These results were different from those of a previous study, which compared i.v. racemic ketamine (0.5 mg/kg) with esketamine (0.25 mg/kg) and R-ketamine (1 mg/kg), in a prospective, randomized, double-blind, crossover design on healthy subjects (38). Objective concentration capacity and retention in primary memory were less affected by esketamine compared with R-ketamine and racemic ketamine at 1 min post-administration (38). After 5 min, immediate recall, anterograde amnesia, retention in primary memory, short-term storage memory and intelligence quotient were less decreased after administration of isomers vs. racemic ketamine (38).

A single-blind, randomized, cross-titration study compared the effects of 84 mg intranasal esketamine vs. placebo on driving performance at 18±2 h post-administration (38). Another phase of the same study evaluated the impact of the same drug on driving ability at 6.0±0.5 h post-administration, in a regimen of esketamine delivered twice/week for three weeks (39). All patients had a diagnosis of mild-to-moderate MDD without psychotic features (n=27) (39). In both the first and second phase, esketamine did not significantly alter driving performance compared with placebo (39).

8. Efficacy of esketamine in the prevention of depressive recurrence

SUSTAIN-1 was a phase III study that monitored the effects of controlled withdrawal of active medication in patients (n=297) who achieved a stable level of remission/response under esketamine + antidepressant and who were randomized to continue this drug or discontinue it and switch to placebo nasal spray (40). The duration of monitoring was 16 weeks. The risk of relapse was lower by 51-70% under continued treatment with esketamine + antidepressant vs. placebo + antidepressant (40).

9. Long-term results of esketamine administration

In another phase III trial, SUSTAIN-2, which had an open, multicenter design, 802 patients with treatment-resistant MDD were randomized to 28, 56 or 84 mg esketamine nasal spray added to a new oral antidepressant (41). Esketamine was administered twice/week during a 4-week induction phase, then weekly or every 2 weeks in patients who obtained a response in the first phase of the study. The duration of monitoring was 48 weeks; MADRS scores decreased during the induction phase (41). This improvement was maintained in the continuation, open-label phase, with decreased MADRS scores from baseline at the endpoint (41).

10. Safety profile of esketamine in clinical trials

The overall tolerability of intranasally administered esketamine in clinical trials is good, with no mood switches or emergent psychotic manifestations being observed (23). Adverse effects, such as transient dissociative phenomena as well as a potential addictive risk (unconfirmed in short-term clinical trials and ≤2 weeks after completion of adjuvant therapy), require caution in the administration of esketamine (23,25,26,28). In the TRANSFORM-1 study, the most commonly reported side effects were nausea, dissociation, dizziness, and headache (23). In the TRANSFORM-2 study, patients primarily reported nausea, dizziness, dissociation, dysgeusia and dizziness (25,26). In the TRANSFORM-3

Table IV. Advantages and disadvantages of esketamine use in clinical practice.

Advantages	Disadvantages
Short and medium-term effectiveness	Cost
Add-on to SSRI/SNRI treatment	Need to monitor the tolerability of the drug
Superior tolerability to racemic ketamine	Accessibility (special prescription regimen)
Intranasal administration once weekly	Limited experience of psychiatrists with this medication
Emergency treatment, which allows rapid reduction of the symptoms of acute depression	The risk of abuse cannot be ruled out on the basis of existing evidence

SSRI, serotonin selective reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

study, the incidence of the reported adverse effects in the esketamine + antidepressant therapy group was 70.8% vs. 60% in the esketamine + placebo group and were primarily dizziness, nausea, transient increase in blood pressure, fatigue, headache and dissociation (28).

Adverse events in the SUSTAIN-1 and -2 trials in patients receiving esketamine were dysgeusia, vertigo, dissociation, drowsiness, nausea, headache and dizziness (40,41). These side effects were of moderate or mild intensity, being detected especially following administration of the medication and typically remitted on the same day (40,41). Discontinuation due to side effects was reported in 7% of patients in the SUSTAIN-2 trial (41).

In the ASPIRE I and II trials, the most commonly reported side effects (>20%) were dizziness, dissociation, nausea, drowsiness and headache (31,32,34).

11. Synthetic parameters

Based on results from four phase III studies, the number needed to treat (NNT) value (the number of patients that would need to be treated to obtain a favorable outcome) was 8 for patients treated with esketamine + antidepressant in the acute phase trials (38). Regarding the relapse prevention study, the NNT value was <10 (42). These values suggest a potential benefit of combining esketamine with an antidepressant for both acute and maintenance phases.

Another NNT for esketamine was 6 in the short-term, based on the results of 297 adults treated with esketamine as an add-on to antidepressants in a double-blind study (40). In the long term, the NNT was 4 for preventing relapse during esketamine treatment (40).

Based on analysis of the results from the same four phase III studies, the number needed to harm (NNH) value (the number of patients that would need to receive treatment to report an adverse effect) was <10 for patients treated with esketamine and antidepressants (34). NNH reached 17 for discontinuation due to adverse effects in the acute phase studies and 178 (insignificant) in the maintenance study (38).

12. Limitations of the review

The present study is not a systematic review, and therefore, relevant studies on this topic may be missing. Also, several trials included in the present review are short-term, which limits the possibility of analyzing the efficacy and tolerability of esketamine in the long term.

13. Conclusions

Esketamine has been shown to be effective in decreasing the severity of short-term depressive symptoms, but questions about its medium- and long-term action, as well as its tolerability profile, remain to be elucidated as novel clinical studies explore its pharmaco-clinical properties. The advantages and disadvantages of esketamine treatment are presented in Table IV.

Regarding the secondary objectives, based on the reviewed data, esketamine nasal spray may be recommended in patients with TRD (defined by ≥2 periods of treatment with different antidepressants that did not result in remission of symptoms) as an adjunct to antidepressant treatment. No significant results have been shown in patients >75 years of age, but this conclusion is based on limited data (28). There are also studies exploring esketamine which reported a lack of significant efficacy on depressive severity symptoms in patients with TRD, but there is insufficient data about potential factors that may adversely influence the progression of these patients (23,28,36,37). Active suicidal ideation with intent was not significantly decreased by esketamine, but prior suicidal behavior may indicate a favorable response to this drug (31,34). Regarding suicidal risk in MDD and the potential benefits of esketamine, several models show the complexity of the suicide dimension and its partial overlap with MDD (16,17,21). This makes the interpretation of pharmacological trials difficult as these are based on limited descriptions of suicidal scenarios (43).

The presence of psychotic features in MDD was not apparently associated with a different progression compared with non-psychotic depression during esketamine treatment (30). The impact of esketamine on cognitive functioning may be positive or neutral (37-39).

As reported by previous reviews and expert opinions (44,45), the data about the effects of esketamine in TRD might position it above racemic ketamine in terms of safety (although it must be noted that no direct comparison between S-ketamine, R-ketamine and racemic ketamine exists). Several aspects in this domain require further investigation, including methodological variables, such as duration, frequency of administration and continuing with safety data (such as abuse potential), as well as logistical parameters, such as cost and

availability (44,45). Unlike the aforementioned reviews, in the present paper, studies regarding the cognitive effects of esketamine were included in healthy individuals and patients with MDD (37-39). Also, studies comparing ketamine and esketamine were included, as well as trials exploring both nasal spray and i.v. infusion forms of administration. The present review supports conclusions similar to the meta-analysis of Papakostas *et al* (46), which found that esketamine is significantly more effective than placebo as an adjuvant to ongoing antidepressant treatment, based on MADRS scores. These results remained significant regardless of whether esketamine was added to newly initiated antidepressants or to already ongoing treatment (46). The safety of intranasal esketamine was also supported by a meta-analysis conducted by Jawad *et al* (47), which explored the tolerability of this agent in long-term studies (>4 weeks and ≤1 year).

Research directions for future studies are the efficacy of esketamine for bipolar and geriatric depression, depression with addictive comorbidities and MDD in adolescents, as well as the detection of favorable/unfavorable response factors of this treatment. The pharmacogenetics of adjuvant therapy with esketamine is another potential domain that should be explored from the perspective of individualized medicine.

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Availability of data and materials

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Authors' contributions

OV was responsible for collecting, analyzing and presenting data within the current review. Data authentication is not applicable. OV has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that they have no competing interests.

References

1. Gastaldon C, Papola D, Ostuzzi G and Barbui C: Esketamine for treatment resistant depression: A trick of smoke and mirrors? Epidemiol Psychiatr Sci 29: e79, 2020.
2. Vasiliu O: Investigational drugs for the treatment of depression (Part 1): Monoaminergic, orexinergic, GABA-ergic, and anti-inflammatory agents. Front Pharmacol 13: 884143, 2022.
3. Vasiliu O: Investigational drugs for the treatment of depression (Part 2): Glutamatergic, cholinergic, sestrin modulators, and other agents. Front Pharmacol 13: 884155, 2022.
4. Cristea IA and Naudat F: US Food and Drug Administration approval of esketamine and brexanolone. Lancet Psychiatry 6: 975-977, 2019.
5. Vasiliu O: Effects of the selective serotonin reuptake inhibitors over coagulation in patients with depressive disorders-a systematic review and retrospective analysis. Rom J Mil Med CXXII 2: 7-11, 2019.
6. Janssen-Cilag Intl. Spravato, Summary of Product Characteristics. 2019. Retrieved online at https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf. Accessed 19 July 2022.
7. Hashimoto K, Kakiuchi T, Ohba H, Nishiyama S and Tsukada H: Reduction of dopamine $D_{2/3}$ receptor binding in the striatum after a single administration of esketamine, but not R-ketamine: A PET study in conscious monkeys. Eur Arch Psychiatry Clin Neurosci 267: 173-176, 2017.
8. Salahudeen MS, Wright CM and Peterson GM: Esketamine: New hope for the treatment of treatment-resistant depression? A narrative review. Ther Adv Drug Saf 11: 2042098620937899, 2020.
9. Tomasetti C, Montemitro C, Fiengo ALC, Santone C, Orsolini L, Valchera A, Carano A, Pompili M, Serafini G, Perna G, *et al*: Novel pathways in the treatment of major depression: Focus on the glutamatergic system. Curr Pharm Des 25: 381-387. 2019.
10. Shin C and Kim YK: Ketamine in major depressive disorder: Mechanisms and future perspectives. Psychiatry Investig 17: 182-192. 2020.
11. Homayoun H and Moghaddam B: NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci 27: 11496-11500, 2007.
12. Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, Manji HK and Charney DS: A double-blind, placebo-controlled study of memantine in the treatment of major depression. Am J Psychiatry 163: 153-155, 2006.
13. Zarate CA Jr, Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, Jolkovsky L, Brutsche NE, Smith MA and Luckenbaugh DA: A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. Biol Psychiatry 74: 257-264, 2013.
14. De Berardis D, Tomasetti C, Pompili M, Serafini G, Vellante F, Fornaro M, Valchera A, Perna G, Volpe U, Martinotti G, *et al*: An update on glutamatergic system in suicidal depression and on the role of esketamine. Curr Top Med Chem 20: 554-584, 2020.
15. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, Tadic A, Sienaert P, Wiegand F, Manji H, *et al*: Intravenous esketamine in adult treatment-resistant depression: A double-blind, double-randomization, placebo-controlled study. Biol Psychiatry 80: 424-431, 2016.
16. Pompili M: Intranasal esketamine and current suicidal ideation with intent in major depression disorder: Beat the clock, save a life, start a strategy. Front Psychiatry 11: 325, 2020.
17. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, Thase ME, Winokur A, Van Nueten L, Manji H and Drevets WC: Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. JAMA Psychiatry 75: 139-148, 2018.
18. De Berardis D, Fornaro M, Valchera A, Cavuto M, Perna G, Di Nicola M, Serafini G, Carano A, Pompili M, Vellante F, *et al*: Eradicating suicide at its roots: Preclinical bases and clinical evidence of the efficacy of ketamine in the treatment of suicidal behaviors. Int J Mol Sci 19: 2888, 2018.
19. Bernstein HG, Tausch A, Wagner R, Steiner J, Seeleke P, Walter M, Dobrowolny H and Bogerts B: Disruption of glutamate-glutamine-GABA cycle significantly impacts on suicidal behaviour: Survey of the literature and own findings on glutamine synthetase. CNS Neurol Disord Drug Targets 12: 900-913. 2013.
20. Tomasetti C, Iasevoli F, Buonaguro EF, De Berardis D, Fornaro M, Fiengo AL, Martinotti G, Orsolini L, Valchera A, Di Giannantonio M and de Bartolomeis A: Treating the synapse in major psychiatric disorders: The role of postsynaptic density network in dopamine-glutamate interplay and psychopharmacologic drugs molecular actions. Int J Mol Sci 18: 135, 2017.
21. Schneidman ES: Suicide as psychache. J Nerv Ment Dis 181: 145-147, 1993.

22. Hashimoto K and Yang C: Is (S)-norketamine an alternative antidepressant for esketamine? Eur Arch Psychiatry Clin Neurosci 269: 867-868, 2019.
23. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, Vitagliano D, Blier P, Fava M, Liebowitz M, *et al*: Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: Results of a randomized, double-blind, active-controlled study (TRANSFORM-1). Int J Neuropsychopharmacol 22: 616-630, 2019.
24. Montgomery SA and Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 134: 382-389, 1979.
25. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, Mazzucco C, Hough D, Thase ME, Shelton RC, *et al*: Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. Am J Psychiatry 176: 428-438, 2019.
26. Floden L, Hudgens S, Jamieson C, Popova V, Drevets WC, Cooper K and Singh J: Evaluation of individual items of the Patient Health Questionnaire (PHQ-9) and Montgomery-Asberg Depression Rating Scale (MADRS) in adults with treatment-resistant depression treated with esketamine nasal spray combined with a new oral antidepressant. CNS Drugs 36: 649-658, 2022.
27. Spitzer RL, Kroenke K and Williams JB: Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. JAMA 282: 1737-1744, 1999.
28. Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, Hough D, Manji H, Drevets WC, Sanacora G, *et al*: Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM 3. Am J Geriatr Psychiatry 28: 121-141, 2020.
29. Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, Caliman-Fontes AT, Echegaray MVF, Bandeira ID, Silva SS, *et al*: Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: A randomized, double-blind, non-inferiority study. J Affect Disord 264: 527-534, 2020.
30. Souza-Marques B, Telles M, Leal GC, Faria-Guimarães D, Correira-Melo FS, Jesus-Nunes AP, Vieira F, Souza L, Lins-Silva D, Mello RP, *et al*: Esketamine for unipolar major depression with psychotic features: A retrospective chart review and comparison with nonpsychotic depression. J Clin Psychopharmacol 42: 408-412, 2022.
31. Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, Hough D, Manji H, Drevets WC and Canuso CM: Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: Double-blind, randomized study (ASPIRE I). J Clin Psychiatry 81: 19m13191, 2020.
32. Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, Hough D, Drevets WC, Manji H and Canuso CM: Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: Results of a phase 3, double-blind, randomized study (ASPIRE II). Int J Neuropsychopharmacol 24: 22-31, 2021.
33. Busner J and Targum SD: The clinical global impressions scale: Applying a research tool in clinical practice. Psychiatry (Edgmont) 4: 28-37, 2007.
34. Caruso CM, Ionescu DF, Li X, Qiu X, Lane R, Turkoz I, Nash AI, Lopena TJ and Fu DJ: Esketamine nasal spray for the rapid reduction of depressive symptoms in major depressive disorder with acute suicidal ideation or behavior. J Clin Psychopharmacol 41: 516-524, 2021.
35. Lindenmayer JP, Czobor P, Alphs L, Nathan AM, Anand R, Islam Z and Chou JC; InterSePT Study Group: The InterSePT scale for suicidal thinking reliability and validity. Schizophr Res 63: 161-170, 2003.
36. Takahashi N, Yamada A, Shiraishi A, Shimizu H, Goto R and Tominaga Y: Esketamine as add-on therapy to oral antidepressant in Japanese patients with treatment-resistant depression: A phase 2b randomized clinical study. BMC Psychiatry 21: 526, 2021.
37. Araújo-de-Freitas L, Santos-Lima C, Mendoça-Filho E, Vieira F, França RJAF, Magnavita G, Cardoso TL, Correia-Melo FS, Leal GC, Jesus-Nunes AP, *et al*: Neurocognitive aspects of ketamine and esketamine on subjects with treatment-resistant depression: A comparative, randomized and double-blind study. Psychiatry Res 303: 114058, 2021.
38. Pfenninger EG, Durieux ME and Himmelseher S: Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. Anesthesiology 96: 357-366, 2002.
39. Dijkstra FM, van de Loo AJ, Abdulahad S, Bosma ER, Hartog M, Huls H, Kuijper DC, de Vries E, Solanki B, Singh J, *et al*: The effects of intranasal esketamine on on-road driving performance in patients with major depressive disorder or persistent depressive disorder. J Psychopharmacol 36: 614-625, 2022.
40. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D, *et al*: Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: A randomized clinical trial. JAMA Psychiatry 76: 893-903, 2019.
41. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim R, George JE, Morrison RL, Sanacora G, Young AH, *et al*: Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: Assessment of long-term safety in phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry 81: 19m12891, 2020.
42. Citrome L, DiBernardo A and Singh J: Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: Number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Affect Disord 271: 228-238, 2020.
43. Pompili M: Critical appraisal of major depression with suicidal ideation. Ann Gen Psychiatry 18: 7, 2019.
44. Swainson J, Thomas RK, Archer S, Chrenek C, MacKay MA, Baker G, Dursun S, Klassen LJ, Chokka P and Demas ML: Esketamine for treatment resistant depression. Expert Rev Neurother 19: 899-911, 2019.
45. Sapkota A, Khurshid H, Qureshi IA, Jahan N, Went TR, Sultan W and Alfonso M: Efficacy and safety of intranasal esketamine in treatment-resistant depression in adults: A systematic review. Cureus 13: e17352, 2021.
46. Papakostas GI, Salloum NC, Hock RS, Jha MK, Murrough JW, Mathew SJ, Iosifescu DV and Fava M: Efficacy of esketamine augmentation in major depressive disorder: A meta-analysis. J Clin Psychiatry 81: 19r12889, 2020.
47. Jawad MY, Di Vincenzo JD, Ceban F, Jaberi S, Lui LMW, Gillissie ES, Alnafeesi Y, Rosenblat JD and McIntyre RS: The efficacy and safety of adjunctive intranasal esketamine treatment in major depressive disorder: A systematic review and meta-analysis. Expert Opin Drug Saf 21: 841-852, 2022.