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Ketamine and its enantiomers in the treatment of depressive and anxiety disorders: a systematic review

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Version 1

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Abstract

Background

Ketamine is a racemic mixture, consisting of equal amounts of its two enantiomers. It has been recognized for its rapid-acting antidepressant effects and some data also suggest safety and efficacy in treating anxiety disorders. However, it is unclear which ketamine formulation has the highest efficacy and most tolerable safety profile, in treating these conditions.

Aim

This systematic review aimed to assess whether there is any clinical evidence favoring the use of either of the two ketamine enantiomers over the racemat, in the treatment of depressive or anxiety disorders.

Methods

PubMed, Cochrane, PsycINFO and Scopus databases were searched for relevant studies published from their respective inception to April 19, 2021. Reference lists of topical reviews were also hand-searched for potentially relevant articles.

Result

Five trials with a total of 140 subjects were included. Of these, three studies investigated the effects of differing ketamine formulations on treatment-resistant major depressive disorder and two studies investigated the subjective effects on healthy volunteers. All three ketamine formulations show promise in treating depressive disorders, but it is unclear which formulation has the highest efficacy.

Conclusions

There is too little data comparing the efficacy of the different ketamine formulations to suggest superiority of any of the two ketamine enantiomers over the racemate. Large scale, head-to-head studies are warranted.

Abbreviations

5D-ASC – Five-Dimensional questionnaire for the assessment of Altered States of Consciousness

AIA – Dread of ego dissolution

AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

APZ – Abnormal Mental States

AWV – Auditory alterations

BDNF – Brain-Derived Neurotrophic Factor

EMA - European Medicines Agency

ERK – Extracellular signal-Regulated Kinase

EWL – Eigenschaftswörterliste

FDA – Food and Drug Administration

GABA – *gamma*-Aminobutyric acid

LS mean – Least Squares mean

MADRS – Montgomery Åsberg Depression Rating Scale

MDD – Major Depressive Disorder

MeSH – Medical Subject Headings (MeSH)

mTOR – mammalian Target Of Rapamycin

NMDA – *N*-methyl-D-aspartate

OAD – Oral Antidepressant

OSE – Oceanic boundlessness

PFC – Prefrontal cortex

PICOS – Population, Intervention, Comparison, Outcome, Study design

PTSD - Post-Traumatic Stress Disorder

RCT – Randomized Controlled Trial

TGF-β – Transforming Growth Factor Beta

TRD – Treatment-Resistant Depression

TRD MDD – Treatment-Resistant Major Depressive Disorder

TrkB – Tropomyosin receptor kinase B

USA – United States of America

VIR – Reduction of vigilance

VUS – Visual restructuralization

YLD – Years Lived with Disability

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1. Introduction

1.1 Depression and anxiety

Depressive and anxiety disorders are common illnesses, with a worldwide prevalence of about 280 million (3.8%) and 301 million (4.1%), respectively. These conditions are major contributors of years lived with disability (YLDs) globally, with depressive disorders being the second leading cause (5.5% of all YLDs) and anxiety disorders the eighth leading cause (3.3% of all YLDs) [1]. There is also a substantial overlap between these conditions, with many people suffering from both depression and anxiety at the same time. Furthermore, depression is the leading cause for the approximately 800 000 deaths from suicide that occurs annually [2]. About two thirds of patients with major depressive disorder (MDD) do not achieve remission from treatment with traditional antidepressant pharmacotherapies [3], which can be divided into a number of different classes of drugs that all target the monoaminergic systems [4]. Even after several trials with different drugs or augmentation strategies, one third of patients do not achieve remission [3]. Although there is no consensus, the most commonly used definition of treatment-resistant depression (TRD) is failure to achieve at least 50% reduction of symptoms from at least two antidepressant treatments with adequate dose and duration [5]. In patients that do respond to antidepressants, there is often a lag period of several weeks to months before these compounds exert their full effect [3].

1.2 Ketamine

Originally developed as a general anesthetic, the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine has caught attention in the recent decades as a potential agent in treating depression [6]. This novel therapy has been described as 'the most important breakthrough in depression research in the last 50 years' [7]. In 2000 Berman et al. showed that ketamine, given as a single intravenous dose of 0.5 mg/kg, can significantly reduce symptoms in patients with MDD [8] within a few hours. These results were reproduced by Zarate et al. in 2006, even in patients with treatment-resistant depression [9]. In a review by Bobo et al. it was reported that nine meta-analyses with a total of 1657 subjects showed statistically significant benefits from using ketamine compared to placebo or active control, in the treatment of depressive disorders [10]. The effects are rapid (within hours) and can last for up to 7 days following a single infusion [9] or for at least fifteen days, when given twice or thrice a week [11]. There is also evidence suggesting ketamine can improve suicidal ideation in patients with MDD. These effects are believed to be at least partially independent of ketamine's antidepressant properties [12].

Furthermore, a small number of studies have demonstrated positive effects of ketamine in the treatment of anxiety disorders [13–15].

1.3 Comparative effects of (S)-ketamine vs (R)-ketamine

It has been known since the 1980ies that ketamine is a racemic mixture ((R,S)-ketamine) [16], composed of its two enantiomers ((S)-ketamine and (R)-ketamine) in equal amounts. Vollenweider et al. [17] demonstrated that (S)-ketamine given at subanesthetic doses has the potential of inducing acute psychotic symptoms including hallucinations and derealization in healthy volunteers, whereas (R)-ketamine given at equimolar doses does not. In contrast, (R)-ketamine was reported to induce 'a state of relaxation' in the same subjects. Furthermore, (S)-ketamine significantly raised the subjects' feelings of anxiety and emotional irritability. These same feelings tended to decrease in the subjects by (R)-ketamine [17]. Psychotomimetic side effects of (S)-ketamine, but not (R)-ketamine, have also been reported in rodents [18]. Furthermore, several animal studies have implicated that (R)-ketamine might have a more robust and longer lasting antidepressant effect, with fewer side effects compared to (S)-ketamine [18–20].

1.4 Mechanisms of action

Both (R,S)-ketamine and the enantiomers act as non-competitive NMDA receptor antagonists, with (S)-ketamine having an almost 5 times higher affinity for the NMDA receptor [21]. It has been proposed that the inhibition of the NMDA receptor occurs at inhibitory *gamma*-aminobutyric acid (GABA)-ergic interneurons, resulting in decreased inhibition of excitatory glutamatergic neurons and an increase in glutamate transmission [22]. However, the antidepressant effects of ketamine cannot be explained by simple inhibition of the NMDA receptor, as evidenced by the failure of other NMDA receptor antagonist to exert ketamine-like antidepressant effects in patients with depression [23,24] It has been shown that subsequent activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor is required for the antidepressant effects of ketamine [18,25]. Furthermore, activation of the brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) signaling pathway [18,25] and subsequent activation of the mammalian target of rapamycin (mTOR) signaling pathway [25] leading to synaptogenesis and improvements in synaptic function [26] has been implicated in several studies as necessary for ketamine's rapid-onset and long-lasting antidepressant actions. It has been recognized that mood disorders, such as depression and anxiety, are associated with decreased synaptic density and brain volume, particularly in the prefrontal cortex (PFC), hippocampus (depression) and amygdala (anxiety) [27].

1.5 Possibly unique mechanisms of the ketamine enantiomers

As for the difference between the two enantiomers, there is evidence suggesting that mTOR (mammalian target of rapamycin) signaling contributes to the antidepressant effect of (S)-ketamine, but not to that of (R)-ketamine. Extracellular signal-regulated kinase (ERK) signaling on the other hand, is implicated in the antidepressant effect of (R)-ketamine [28]. Furthermore, (R)-ketamine seems to be more potent than (S)-ketamine in producing the BDNF-induced synaptogenesis associated with its antidepressant effects [18]. Additionally, a role for microglial transforming growth factor beta (TGF-β) in the antidepressant effects of (R)-ketamine, but not (S)-ketamine, has been reported [29]. In recent years, a link between the gut microbiota and mood disorders has been established [30]. Interestingly, both (R,S)-ketamine [31] and (R)-ketamine [32] have been shown to improve the gut microbiota composition in rodent models of depression.

1.6 Ketamine clinics

In the Unites States of America (USA) there has been a steady rise in clinics offering the off-label use of ketamine as a treatment for MDD and other psychiatric disorders since the middle of the 2000s [33]. The off-label use of ketamine in Europe has been much more limited [34].

1.7 Spravato

On March 5, 2019, the use of an (S)-ketamine nasal spray, developed by Janssen Pharmaceutical (brand name Spravato) in conjunction with an oral antidepressant was approved in the USA by the Food and Drug Administration (FDA) for treatment of adults suffering from treatment-resistant depression that has failed to improve from at least two other therapies [35]. On December 18, 2019 the nasal spray was approved in Europe by the European Medicines Agency (EMA) for the same indication [36]. Roughly a year later, the indication was broadened to also encompass acute short-term use for ‘psychiatric emergencies’, as judged by a clinician, in patients with MDD [37].

Since the discovery of its antidepressant properties, most studies proving safety and efficacy of ketamine have been done using the racemate [10]. However, Janssen Pharmaceutical chose S-ketamine in the development of Spravato. Seemingly, the basis for this decision was a proof-of-concept study in which intravenous (S)-ketamine was proven efficacious in treating individuals with TRD. In this article the authors emphasize the greater affinity of (S)-ketamine over (R)-ketamine for the NMDA receptor, which seems to be the rationale for choosing the S-enantiomer of ketamine [38]. However, as reported above, the NMDA receptor binding does not seem to be pivotal for the antidepressant effect of ketamine [23,24]. Also reported above, there are

indications of (R)-ketamine being able to produce a more potent and longer lasting antidepressant effect, with a more tolerable safety profile, compared to (S)-ketamine [18–20].

2. Aim

The aim of this systematic review is to investigate whether there is any clinical evidence favoring the use of either of the two ketamine enantiomers over the racemate, in the treatment of depressive or anxiety disorders.

3. Material and Methods

3.1 Inclusion criteria

When formulating the inclusion criteria, the Population, Intervention, Comparison, Outcome, Study design (PICOS) format was used. Initially, only randomized controlled trials (RCTs) comparing intravenous (S)-ketamine or (R)-ketamine to any of the other ketamine forms in the treatment of depressive or anxiety disorders, either as a standalone treatment or as an adjunctive to other antidepressant therapies, were included. Since this approach provided only one result, eligibility was broadened to include studies comparing intravenous (S)-ketamine or (R)-ketamine to any of the other ketamine forms regarding the effects on mood, psychopathology, and states of consciousness. Any non-comparative, interventional study (including open label studies) examining the effects on depressive disorders, anxiety disorders, mood, psychopathology, or states of consciousness, of either enantiomer administered intravenously, was included as well.

3.2 Exclusion criteria

Articles not written in English, preclinical animal studies, observational studies, review articles, studies on ketamine's effect on bipolar depression and studies using other forms of administration than intravenous infusions were excluded.

3.3 Identification and selection of studies

A systematic literature search was conducted in PubMed (Table 1), Cochrane (Table 2), PsycINFO (Table 3) and Scopus (Table 4) from the inception of each database to April 19, 2021. Relevant Medical Subject Headings (MeSH) terms were combined with free text search in title and abstract by using Boolean operators OR and AND. Reference lists of topical reviews were also hand-searched for potentially relevant articles. Among the identified studies, all duplicates were removed. Titles and abstracts of remaining studies were screened for possible eligibility. Studies displaying relevant titles and abstracts were read in full-text for the final assessment of eligibility and the ones that met the criteria were included in the review.

Table 1 Search terms used for database search in PubMed and corresponding number of results.

Search terms		Results
Depression and anxiety block		
1	(("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) OR ("Anxiety Disorders"[Mesh] OR "Anxiety"[Mesh])) OR (depression[Title/Abstract] OR depressive[Title/Abstract] OR anxiety[Title/Abstract])	611245
Ketamine block		
2	("Ketamine"[Mesh] OR "Esketamine" [Supplementary Concept]) OR (ketamine[Title/Abstract] OR esketamine[Title/Abstract] OR arketamine[Title/Abstract] OR "CI-581"[Title/Abstract] OR "CL-369"[Title/Abstract] OR "CM-52372-2"[Title/Abstract] OR ketalar[Title/Abstract])	21600
Intravenous block		
3	("Administration, Intravenous"[Mesh]) OR (intravenous[Title/Abstract])	370485
RCT block		
4	("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh]) OR ((randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR (randomized[Title/Abstract] AND clinical[Title/Abstract] AND trial[Title/Abstract]))	729006
All blocks combined		
5	1 AND 2 AND 3 AND 4	153
Filters: English		
6		148

Table 2 Search terms used for database search in Cochrane and corresponding number of results.

Search terms		Results
Depression and anxiety block		
#1	MeSH descriptor: [Depression] explode all trees	12649
#2	MeSH descriptor: [Depressive Disorder] explode all trees	12452
#3	MeSH descriptor: [Anxiety] explode all trees	8129
#4	MeSH descriptor: [Anxiety Disorders] explode all trees	7079
#5	(depression OR depressive OR anxiety):ti,ab,kw	110231
#6	#1 OR #2 OR #3 OR #4 OR #5	111886
Ketamine block		
#7	MeSH descriptor: [Ketamine] explode all trees	2213
#8	(ketamine OR esketamine OR arketamine OR "CI-581" OR "CL-369" OR "CM-52372-2" OR ketalar):ti,ab,kw	5491
#9	#7 OR #8	5491
Intravenous block		
#10	MeSH descriptor: [Administration, Intravenous] explode all trees	18743
#11	(intravenous):ti,ab,kw	88761
#12	#10 OR #11	88761
RCT block		
#13	MeSH descriptor: [Randomized Controlled Trial] explode all trees	119

#14	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	14774
#15	((randomized AND controlled AND trial) OR (randomized AND clinical AND trial)):ti,ab,kw	654328
#16	#13 OR #14 OR #15	659995
All blocks combined		
#17	#6 AND #9 AND #12 AND #16	253
Limits: trials		
#18		249

Table 3 Search terms used for database search in PsycINFO and corresponding number of results.

Search terms		Results
Depression and anxiety block		
S1	(DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression") OR (DE "Depression (Emotion)")	163169
S2	DE "Anxiety" OR DE "Anxiety Sensitivity" OR DE "Computer Anxiety" OR DE "Death Anxiety" OR DE "Health Anxiety" OR DE "Mathematics Anxiety" OR DE "Performance Anxiety" OR DE "Social Anxiety" OR DE "Speech Anxiety" OR DE "Test Anxiety" OR DE "Anxiety Disorders" OR DE "Castration Anxiety" OR DE "Generalized Anxiety Disorder" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Attack" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Separation Anxiety Disorder" OR DE "Trichotillomania"	141810
S3	TI (depression OR depressive OR anxiety) OR AB (depression OR depressive OR anxiety)	417955
S4	S1 OR S2 OR S3	459368
Ketamine block		
S5	DE "Ketamine"	2769
S6	(TI (ketamine OR esketamine OR arketamine OR "CI-581" OR "CL-369" OR "CM-52372-2" OR ketalar) OR AB (ketamine OR esketamine OR arketamine OR "CI-581" OR "CL-369" OR "CM-52372-2" OR ketalar)	3829
S7	(S5) OR (S6)	3949
Intravenous block		
S8	DE "Intravenous Injections"	1355
S9	TI intravenous OR AB intravenous	10188
S10	S8 OR S9	10734
RCT block		
S11	DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials" OR DE "Randomized Clinical Trials"	931
S12	TI (randomized AND (controlled OR clinical) AND trial) OR AB (randomized AND (controlled OR clinical) AND trial)	45465
S13	S11 OR S12	45637
All blocks combined		
S14	S4 AND S7 AND S10 AND S13	51

Table 4 Search terms used for database search in Scopus and corresponding number of results.

Search terms	Results
(TITLE-ABS-KEY(ketamine OR esketamine OR arketamine OR "CI-581" OR "CL-369" OR "CM-52372-2" OR ketalar)) AND (TITLE-ABS-KEY(depression OR depressive OR anxiety)) AND (TITLE-ABS-KEY(intravenous)) AND ((TITLE-ABS-KEY(randomized controlled trial)) OR (TITLE-ABS-KEY(randomized clinical trial)))	302

3.4 Outcomes

The following outcomes were used:

1. Changes in any validated quantitative scale used for measuring degree of depression, anxiety, mood, psychopathology, or states of consciousness.
2. Response rates in treatment of depression, defined as a drop of at least 50% from baseline depression scores.
3. Remission rates in treatment of depression, differently defined in individual studies.

3.5 Ethical considerations

Considering the nature of a systemic review, several ethical considerations are irrelevant. No original data from study subjects have been collected. All data applied here have been extracted from already published articles. All included studies have been approved by ethical committees. In at least four out of five included studies, written consent was obtained from all participants. In one study, informed consent was given by participants, but it is unclear whether this consent was written.

4. Results

4.1 Study selection

The applied systematic literature search strategy managed to identify 750 records (Figure 1), of which 325 were duplicates. The remaining 425 unique records were screened by title and abstract, resulting in 2 records eligible for full-text review. After full-text review, two randomized controlled trials met the inclusion criteria for this systematic review. Three articles identified through the reference lists of topical review articles were included as well, for a total of five articles.

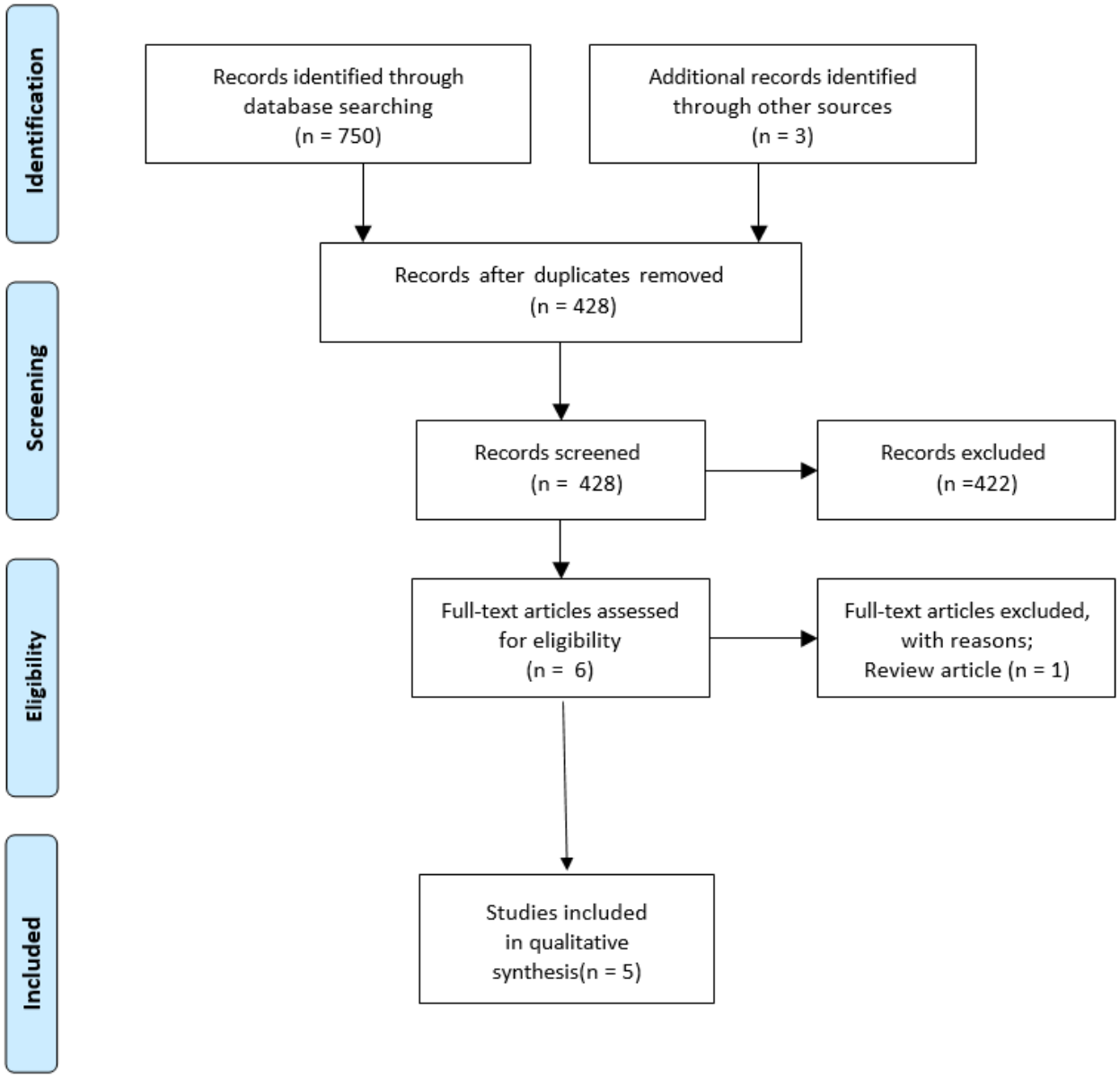

Figure 1. PRISMA flow chart describing the systematic review process.

4.2 Study characteristics

Table 5 provides and overview of study characteristics. Three studies examined the effects of different ketamine formulations on treatment-resistant major depressive disorder (TRD MDD), using the Montgomery Åsberg Depression Rating Scale (MADRS) [39] to measure outcomes. One of these was a comparative trial between different ketamine forms, one was a placebo-controlled trial, and one was an open-label trial. Two studies examined ketamine's effect on healthy volunteers regarding its effect on mood, psychopathology and altered states of consciousness. Sample sizes between studies varied from seven to 63 participants. While one study included only females and another study included only males, the average distribution

among all studies was 49.3 % females and 50.7 % males. The mean age varied from 25.8 to 48.9 years.

Table 5 Characteristics of included studies.

Authors, year	Population	Study design	Study size	Female (%)	Mean age	Substance	Dose	Comparator(s)	Quantitative scale(s)
Correia-Melo et al. 2020	TRD MDD	RCT	63	63.2 %	46.95 ± 14.77	(R,S)-ketamine	0.5 mg/kg IV	(S)-ketamine (0.25 mg/kg IV)	MADRS
Singh et al. 2016	TRD MDD	RCT	30	60.0%	43.0 ± 11.59	(S)-ketamine	0.20 mg/kg or 0.40 mg/kg IV	Placebo	MADRS
Leal et al. 2020	TRD MDD	Open label	7	100.0%	48.86	(R)-ketamine	0.5 mg IV	None	MADRS
Passie et al. 2021	Healthy volunteers	RCT	30	0.0%	25.83 ± 3.41	(R,S)-ketamine	0.92 mg/kg IV	(S)-ketamine 0.46 mg/kg IV or placebo	5D-ASC
Vollenweider et al. 1997	Healthy volunteers	Placebo controlled crossover trial	10	40.0%	30.4	(S)-ketamine	15 mg + 0.742-1,06 mg/kg IV	(R)-ketamine (equimolar amount) or placebo	EWL, APZ

4.3 Study results

4.3.1 The effects of ketamine on treatment-resistant major depressive disorder

Correia-Melo et al. [40] conducted a study of 63 patients with treatment-resistant major depressive disorder, of which 29 were given (R,S)-ketamine and 34 given (S)-ketamine. The primary endpoint was the difference in remission rates between the two groups 24 hours after infusion, with remission being defined as a MADRS score of ≤ 7. Seven (24.1%) patients treated with (R,S)-ketamine and ten (29.4%) of patients treated with (S)-ketamine achieved the primary endpoint. With a difference of 5.3% (95% CILB -13.6%) between the groups, no statistically significant difference was found (Figure 2). During follow up at 72 h and 7 days, no statistically significance was found between the groups regarding remission or response, defined as a ≥ 50% reduction from baseline MADRS (Figure 2). Difference in MADRS scores between groups were

1.3 (95% CI = -4.6, 6.1; p = 0.67) at 24 h, 2.6 (95% CI = -4.0; 9.1p = 0.44) at 72 h, 6.3 (95% CI -0.9, 13.5; p = 0.08) at 7 days (Figure 3).

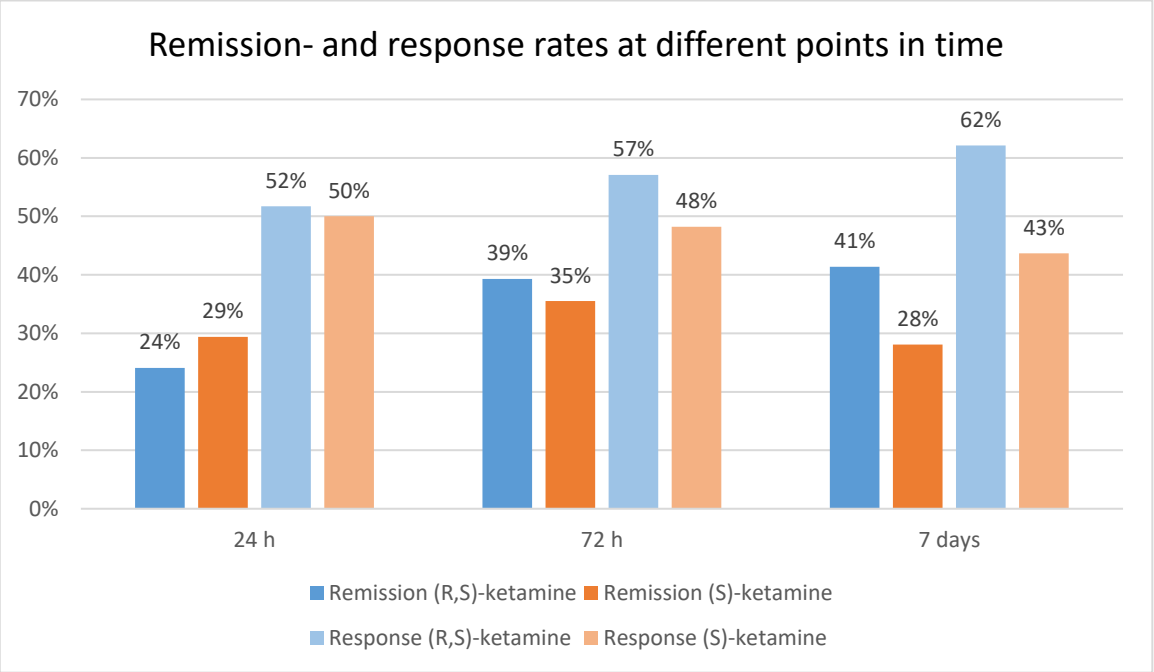

Figure 2. Remission (Montgomery Åsberg Depression Rating Scale (MADRS) score ≤ 7) and response (≥ 50 % reduction from baseline MADRS score) rates at different points in time, following intravenous infusion of either (R,S)-ketamine (0.5 mg/kg) or (S)-ketamine (0.25 mg/kg).

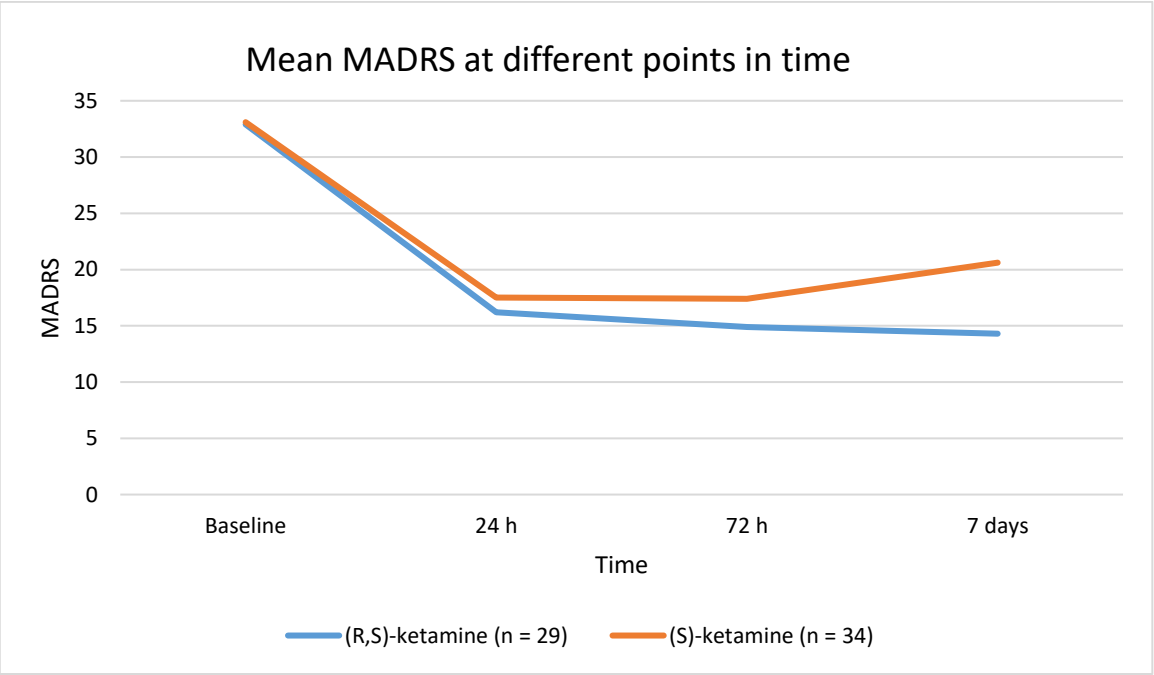

Figure 3. Mean Montgomery Åsberg Depression Rating Scale (MADRS) score at different points in time, following intravenous infusion of either (R,S)-ketamine (0.5 mg/kg) or (S)-ketamine (0.25 mg/kg).

Singh et al. [38] compared two different doses (0.20 mg/kg or 0.40 mg/kg) of (S)-ketamine to placebo in a study of 30 participants, randomly assigned into three equally sized arms. The

primary endpoint was the difference from baseline to 24 h after the infusion, in MADRS score. The primary endpoint was met, proving a significant difference from baseline to 24 h for both (S)-ketamine groups compared to placebo. The least squares (LS) mean change (SE) in MADRS score at 24 h were -16.8 (3.00) and -16.9 (2.61) for 0.20 mg/kg and 0.40 mg/kg (S)-ketamine, respectively, and -3.8 (2.97) for placebo (Table 6).

Table 6. LS mean change in Montgomery Åsberg Depression Rating Scale (MADRS) score at different points in time, following intravenous infusion of either (S)-ketamine (0.2 mg/kg), (S)-ketamine (0.4 mg/kg) or placebo.

Group	Baseline MADRS	LS mean change (SE) in MADRS score at 24 h	LS mean change (SE) in MADRS score at 72 h
(S)-ketamine (0.2 mg/kg)	33.1	-16.8 (3.00)	-14.2 (3.59)
(S)-ketamine (0.4 mg/kg)	33.7	-16.9 (2.61)	-13.2 (3.16)
Placebo	33.9	-3.8 (2.97)	-3.1 (3.51)

Leal et al. [41] analyzed the efficacy and safety of (R)-ketamine in an open label study of seven patients. Change from baseline to 24 h following infusion in MADRS score was the primary outcome. Mean MADRS score at baseline was 30.7 and the mean change at 24 h was -20.3 points [CI 95% 13.6–27.0, $p < 0.001$]. Decrease in mean MADRS score was greater at each measurement compared to those of the (S)-ketamine arm in the study by Correia-Melo et al. [40] (Table 7).

Table 7. Mean Montgomery Åsberg Depression Rating Scale (MADRS) score at different points in time, following intravenous infusion of (R,S)-ketamine (0.5 mg/kg), (S)-ketamine (0.25 mg/kg), or (R)-ketamine (0.5 mg/kg).

Study, year	Ketamine formulation	Baseline MADRS	24 h MADRS	72 h MADRS	7 days MADRS
Correia-Melo et al. 2020	(R,S)-ketamine (0.5 mg/kg)	32.9	16.2 (-50.8%)	14.9 (-54.7%)	14.3 (-56.5%)
	(S)-ketamine (0.25 mg/kg)	33.1	17.5 (-47.1%)	17.4 (-47.4 %)	20.6 (-37.8%)
Leal et al. 2020	(R)-ketamine (0.5 mg/kg)	30.7	10.4 (-66.1%)	10.4 (-66.1%)	14.0 (-54.4%)

4.3.2 The effects of ketamine on healthy volunteers

Vollenweider et al. [17] conducted a within-subject, placebo controlled, counterbalanced study in which ten healthy volunteers participated. All subjects were given either placebo, (S)-ketamine, or (R)-ketamine on three different occasions. To assess changes in mood and states of consciousness, the Eigenschaftswörterliste (EWL) mood rating scale [42] and the Abnormal Mental States (APZ) questionnaire [43] were applied. In this study, it was reported that subanesthetic doses of (S)-ketamine, but not (R)-ketamine, induced acute psychotic symptoms as well as a heightened sense of emotional irritability and anxiety. Contrastingly, most subjects reported experiencing a state of relaxation when given equimolar doses of (R)-ketamine.

Passie et al. [44] performed a placebo controlled trial in which they compared the effects on psychopathology and states of consciousness of (R,S)-ketamine and (S)-ketamine in 30 healthy volunteers. Divided in to three equally sized arms, the subjects were either given (R,S)-ketamine, (S)-ketamine or placebo. Compared to placebo, both (R,S)-ketamine and (S)-ketamine induced consequential changes in states of consciousness. This was (in part) measured by using the five-dimensional questionnaire for the assessment of altered states of consciousness (5D-ASC) scale [45]. Although no statistically significant differences between the two ketamine groups were found, (R,S)-ketamine scored highest in subscales associated with beneficial effects, whereas (S)-ketamine scored highest in subscales associated with adverse effects (Table 8).

Table 8. Comparative psychopathology and states of consciousness between subjects receiving (R,S)-ketamine or (S)-ketamine, measured by 5D-ASC [45] with Bonferroni adjusted p-values.

Ketamine formulation	Oceanic boundlessness (OSE)	Visual restruc-turalization (VUS)	Dread of ego dissolution (AIA)	Reduction of vigilance (VIR)	Auditory alterations (AWV)	5D-ASC total score
(R,S)-ketamine (0.92 mg/kg)	25.01	19.97	20.4	48.81	6.68	25.13
(S)-ketamine (0.46 mg/kg)	22.80	17.08	27.37	58.61	11.30	27.25
Difference	2.21 (p>0.999)	2.89 (p>0.999)	-6.97 (p=0.579)	-9.77 (p=0.826)	-4.62 (p=0.792)	-2.12 (p>0.999)

5. Discussion

The safety and efficacy of intravenous (R,S)-ketamine for treatment of depressive disorders has been thoroughly documented [9–11]. To a lesser extent, there is also evidence suggesting it could be beneficial in the treatment of anxiety disorders [13–15]. Since (R,S)-ketamine is a racemic mixture consisting of two enantiomers with differences in their psychopharmacological profiles [17,21,28], it could be hypothesized that their effects on depressive and anxiety disorders might differ as well. The number of providers offering intravenous (R,S)-ketamine as an off-label treatment for depressive disorders in the US has seen a steady incline in the last decade. However, the only FDA [35] and EMA [36,37] approved uses of ketamine for psychiatric indications, are in the form of a nasal spray containing only the S-enantiomer of ketamine. This systematic review aimed to investigate whether there is any clinical evidence proving superiority for any of the enantiomers, when given intravenously, in the treatment of

depressive and anxiety disorders. Our results highlight an obvious lack of evidence regarding this matter and points out an urgent need for further studies investigating this topic.

The studies included in this review were of a heterogeneous nature, making any direct comparisons difficult. Of the three studies using ketamine for treatment of TRD MDD, two measured remission rates at different points in time. However, the definition of remission varied between these studies. Although response rates were defined in the same way across all three studies, only two of the studies measured response at the same points in time. Furthermore, two of the studies were single-dose interventions, while two doses were given in one study. In one study, the MADRS score was adjusted using least square means, while the scores were unadjusted in the other two. In addition, the lack of a uniform definition of TRD further complicates any direct comparisons between studies since the severity of disease among subjects may vary quite a bit. Concerning the two studies examining the effects of ketamine on mood, psychopathology and states of consciousness, different scales were used, making only inferences possible.

Seeing that an extensive literature search found only one study comparing different forms of ketamine in the treatment of depressive or anxiety disorders, the present study calls attention to an understudied area of research. Herein, we found that too little clinical data exist to derive any conclusions advocating the use of either enantiomer over the racemic form of ketamine in this setting. However, a case favoring (R)-ketamine over (S)-ketamine could be made. With a greater proportion of responders and remitters at 72 h and 7 days, the results from Correia-Melo et al. [40] indicate that (R,S)-ketamine has a longer lasting antidepressant effect, compared to (S)-ketamine. The notion that the R-enantiomer is responsible for this is further supported by the results from Leal et al. [41], which used only (R)-ketamine. When comparing total mean MADRS score and reduction in mean MADRS score between the two studies, both (R,S)-ketamine and (R)-ketamine showed greater results compared to (S)-ketamine at all time points measured. These results are in line with evidence from preclinical trials [18–20]. However, a comparison between a randomized controlled trial and an open-label trial warrants extreme caution in any interpretation, especially considering the very small sample size (seven) and uneven gender distribution (100% females) in the open-label trial. Furthermore, the differences between the ketamine groups in the Correia-Melo et al. study [40] did not reach statistical significance. Additional value could have been added to this comparison, if the study by Singh et al. [38] was included. Unfortunately, this was not possible since the data presented there was adjusted, as opposed to the data in the formerly mentioned studies. Although a trend favoring

(R)-ketamine can be discerned from the present data, the lack of statistically significant differences between groups, differing study designs and definitions of TRD and remission, as well as a limited sample size, makes it impossible to draw any definite conclusions.

Nevertheless, a recent meta-analysis [46] of 24 trials with a total of 1877 subjects, compared intravenous (R,S)-ketamine to intranasal (S)-ketamine for the treatment of unipolar or bipolar major depression. In line with the results presented here, the authors found that (R,S)-ketamine, overall, produced greater levels of response and remission, and had fewer dropouts compared to (S)-ketamine [46]. However, the results could be interpreted as either (R,S)-ketamine having a more potent antidepressant effect than (S)-ketamine or as intravenous administration being superior to intranasal. It is also possible that both interpretations are valid at the same time.

Interestingly, this was tested in another recent meta-analysis [47] where the effect size of different formulations of ketamine and routes of administration was examined. Unfortunately, although differences were found, the authors were not able to draw any conclusions due to pronounced heterogeneity between included studies. Most trials with (R,S)-ketamine have been done as intravenous single-dose interventions, whereas most (S)-ketamine trials are conducted with repeated nasal spray doses, and often in conjunction with oral antidepressants (OAD).

Taken together, this calls for further investigations into which formulation of ketamine and which route of administration has the greatest impact, regarding antidepressant and anxiolytic effect. Ideally, large scale head-to-head studies comparing the effects of all three ketamine formulations, should be done. Also, in order to parse out which route of administration is the most effective, it would be possible to design a double dummy study comparing intravenous to intranasal administration of the same ketamine formulation in a more homogenous patient group.

Differing degree of alterations in mood, states of consciousness and psychopathology in healthy subjects given different ketamine formulations cannot be directly translated into differences in the antidepressant or anxiolytic effect of these formulations. However, it is possible to make some inferences from such results. It is plausible to assume that heightened feelings of anxiety and emotional irritability, as recorded in subjects receiving (S)-ketamine [17], could be a disadvantage, while a state of relaxation, as recorded in subjects receiving (R)-ketamine [17], might be beneficial, when treating depressive or anxiety disorders. This reasoning is in line with the conclusion of Passie et al: “If the antidepressant effect of ketamine is associated with an anxiety-free and pleasant experience of altered consciousness and perceptions, the ideal ketamine preparation used to treat TRD should include (R)-ketamine”. Although no statistical

differences were found between ketamine groups in their study, there was a trend pointing to formulations including (R)-ketamine being perceived as more pleasant than just (S)-ketamine [44].

Interestingly, the relationship between subjectively experienced side effects of ketamine and its antidepressant effects has caught attention recently [48–50]. In one study, it was found that ketamine-induced anxiety was negatively correlated with antidepressant response [48]. On the other hand, a correlation between the dissociative and psychotomimetic side effects of ketamine, and changes in depression was found in only three (37.5%) out of eight included studies in a systematic review [49]. Ballard and Zarate wrote a perspective piece in which they concluded that the present literature does not support the necessity of dissociation for the antidepressant effects of ketamine [50]. Taken together, this data is inconclusive. To which degree the ketamine-induced side effects are related to treatment outcomes and how this play into designing the ideal ketamine formulation, needs further investigation.

Given the fact that most studies have been done on (R,S)-ketamine [10], and an evident lack of head-to-head studies comparing the two enantiomers, the basis for Janssen Pharmaceuticals' decision to only use the S-enantiomer in the development of Spravato can be viewed as premature. However, there was already a patent filed for intranasal (R,S)-ketamine for treatment of depression [51] when Janssen Pharmaceuticals filed their patent, for the use of (S)-ketamine in treatment of TRD, in 2013 [52]. Furthermore, the preclinical studies implying superiority of (R)-ketamine over (S)-ketamine have all been conducted after the patent was filed [18–20]. Nevertheless, the studies used for FDA and EMA approval did not unequivocally prove benefits of intranasal (S)-ketamine compared to placebo [53]. Considering this, it could be speculated that the approval of the (S)-ketamine nasal spray was, in part, influenced by the extensively documented benefits of intravenous (R,S)-ketamine.

One strength of this systematic review is that four databases were used, making for an exhaustive literature search. Despite this, eligible studies were few. This highlights another strength of this review: the identification of a knowledge gap. Racemic ketamine as an antidepressant has been studied extensively, but conclusive data on the comparative effects of its enantiomers is lacking, implying the need for additional studies in this area.

Narrow eligibility criteria, likely contributing to the small number of included studies, constitutes a limitation of this systematic review. The exclusion of studies using other forms of administration than intravenous, severely limited the number of included studies. To our

knowledge, however, there are no studies comparing different forms of intranasal ketamine. In addition, there are studies on the effects of ketamine in the treatment of other psychiatric indications, such as bipolar disorder, post-traumatic stress disorder (PTSD) and suicidal ideation. The inclusion of these conditions could have increased the number of studies eligible for review. However, a narrower approach was chosen, aiming to zoom in on the most common psychiatric disorders. Furthermore, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines [54] were not used. These guidelines were designed to promote the creation of transparent systematic reviews, in which accurate and complete information is reported. Considering the nature of this paper and the time frame given for its completion, the use of these guidelines was not deemed crucial. Finally, the exclusion of articles not written in English can be seen as a limitation; although not likely, possibly excluding informative studies.

6. Conclusion

The result of this systematic review emphasizes a shortage of studies comparing the efficacy of different ketamine formulations for the treatment of depressive and anxiety disorders. Presently, there is too little evidence to suggest superiority of any of the two ketamine enantiomers. An urgent need for safe, effective, and rapid-acting antidepressant and anxiolytic agents calls for further investigations into the most suitable formulation. Large scale, head-to-head studies are clearly warranted.

7. References

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