Ketamine Antidepressant Properties: a Systematic Review of Clinical Trials

Diogo Ferreira[1], **Agostinho Cruz**[2], **Marlene Santos**[3]

[1] Wells, SONAE MC
diogo19951918@hotmail.com

[2] CISA – Centro de Investigação em Saúde e Ambiente, Escola Superior de Saúde – Instituto Politécnico do Porto
agostinhocruz@ess.ipp.pt

[3] CISA – Centro de Investigação em Saúde e Ambiente, Escola Superior de Saúde – Instituto Politécnico do Porto; Centro de Investigação - Instituto Português de Oncologia do Porto
mes@ess.ipp.pt

Abstract. *Ketamine has been used to provide a rapid and persistent antidepressant effect in patients with treatment-resistant depression. This drug reverses depressive symptoms by blocking N-methyl-D-Aspartate receptors, which causes a downstream effect on glutamatergic system. The main goal of this work consisted in a systematic review of the antidepressant and adverse events of Ketamine in patients with treatment-resistant depression. Keywords were defined with PICO´s strategy and systematic review was performed by using the PUBMED database. After inclusion and exclusion criteria, a total of 21 articles were included. Results showed a rapid antidepressant action from the resynchronization of neural circuits upon Ketamine use. However, this drug was also associated with several induced side-effects, including changes in blood pressure, dissociative symptoms, headache, nausea and vomits. Different routes of administration and ketamine metabolites may be used to help to overcome some of the induced side-effects.*

Keywords. Major depressive disorder, treatment-resistant depression, electroconvulsive therapy, ketamine, antidepressant

University of Maribor Press

DOI https://doi.org/10.18690/um.3.2022.11
ISBN 978-961-286-658-7

1 Introduction

1.1 Depressive disorders

Depressive disorders, such as major depressive disorder (MDD), are among the most disabling illnesses in the world, with a considerable significant burden and morbidity, including the Disability-Adjusted Life Years (DALY) [1]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of a Major Depression Episode (MDE) requires five or more symptoms to be present within a 2-week period [2]. One of should include either depressed mood or anhedonia. The secondary symptoms of MDE are appetite or weight changes, sleep disturbances, psychomotor retardation or agitation, fatigue or loss of energy, reduced ability to think or concentrate, feelings of worthlessness or guilt, and thought or attempt to suicide [2]. Depressive disorders' prevalence and incidence have risen in recent years, with a lifetime prevalence of MDD estimated to be around 10% [3].

1.2 Molecular mechanisms of depression

The precise etiology of depression continues to be fully understood, despite the plethora of research describing the neuroanatomical, neuroendocrinological, and neurophysiological changes in depression [2], [4]. Multiple theories have been proposed to explain the molecular mechanisms behind depression, which is recognized to be a complex disease and most likely to develop as a result of hereditary and environmental variables [5]. The main mechanisms include the monoamine hypothesis, the HPA axis hyperactivity hypothesis, the neurotrophic hypothesis, the inflammatory hypothesis, and the glutamatergic hypothesis of depression [6].

The classic theory is the monoamine hypothesis of depression [7], and according, depression is the result of monoamine neurotransmitters (e.g. serotonin and/or norepinephrine and/or dopamine) depletion [7], [8]. Other theory is the hyperactivity of the HPA axis, in which depression is an endocrinological and stress illness, and is linked to the dysregulated levels of free T4, TSH, CRH, arginine vasopressin, corticotropin, corticosteroid release, and ACTH [9]. Regarding the neurotrophic hypothesis depression is associated with the loss of neurotrophic support and that effective antidepressant therapies increase neurogenesis and synaptic connectivity in cortical areas such as the hippocampus [10]. Brain-derived neurotrophic factor (BDNF) is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B (TrkB) in both neurons and glia [11]. On the inflammatory hypothesis, chronic exposure to elevated levels of inflammatory cytokines can lead to neuropsychiatric disorders, including depression [12]. Mechanisms of cytokine behavioral effects involve activation of inflammatory signaling pathways in the brain, as well as dysregulated inflammatory markers, that results in changes in monoamine, glutamate, and neuropeptide systems, and decreases in growth factors [13]. One of the most recent hypotheses of the depression relays on the glutamatergic system. The glutamatergic system is one of the more recent theories for depression [14]. Accordingly, changes in GABA, AMPA, EAAT, NMDA, and metabotropic glutamate receptors (mGluR1 through mGluR8) are associated

with depression, and fast-acting antidepressants like ketamine and esketamine have been shown to have an immediate neuroprotective and antidepressant effect [4],[15].

1.3 Treatment-resistant depression and ketamine

Despite the number of antidepressants available, only approximately two thirds of patients benefit from the currently prescribed antidepressant drugs. Patients who have already failed to improve following two or more trials of antidepressant treatments at sufficient doses and duration have significantly lower response rates, and display what is known as Treatment-resistant depression (TRD) [16]. As a result, patients undergo useless treatments for long periods of time, without displaying any favorable outcome. Furthermore, antidepressants that target the monoaminergic system usually take 6–12 weeks to act and reverse depressive symptoms. More effective and fast-acting antidepressants are clearly needed [3].

New therapeutic approaches have been targeting these concerns. Glutamatergic pathways have been associated with a robust novel antidepressant target, particularly for those with TRD, who are less probable to benefit from other monoaminergic treatments [17].

Several clinical trials had demonstrated that ketamine would be a suitable strategy to suppress the acute symptoms of depression due to its quick and long-lasting effect. Authors approved the clinical benefit of this drug when given an off-label use (subanesthetic dosage) [18]. Ketamine has shown antidepressant effects in patients with major depressive disorder (MDD) resistant to first-line treatments and approved for use in this patient population.

1.4 Ketamine mechanism of action

Ketamine induces several forms of synaptic plasticity, which are proposed to underlie its antidepressant effects [16]. The putative mechanism of action of ketamine consists in inhibiting, in a competitive way, the glutamate receptors, however the molecular mechanism of action directly responsible for ketamine's antidepressant effects remains under active investigation [19]. It may include pre-synaptic excitation/inhibition of glutamatergic neurons, reduction of the glutamate release, activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), NMDA receptor antagonism, post-synaptic activation of Brain-Derived Neurotrophic Factor (BDNF), targeting mTOR pathway, and the recovery of synaptic connectivity in PFC (Pre-Frontal Cortex) [18]–[20]. It was recently demonstrated that the effectors of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway, namely, eukaryotic initiation factor 4E (eIF4E) binding proteins 1 and 2 (4E-BP1 and 4E-BP2), are central in mediating ketamine-induced synaptic plasticity and behavioral antidepressant-like effect [21], [22].

1.5 Ketamine use and adverse reactions

Ketamine is known to have several therapeutic applications such as anesthesia, neuropathic pain, or associated with other drugs in various conditions [16]. Ketamine adverse reactions include changes in blood pressure, dissociative symptoms, headache, nausea and vomits.

However, drug-drug interactions are possible [23]. Opioid, benzodiazepines or even alcohol are some of the examples in which the association of ketamine was reported to have an impact on patients' health, namely changes in intraocular pressure, convulsions, and renal or hepatic problems [23]. Simultaneously, in individuals with an high risk of stroke or with previous allergy to ketamine, its use should be carefully evaluated [23].

The aim of this paper is to provide a systematic analysis about the antidepressant and adverse reactions of Ketamine in TRD patients.

2 Methodology

2.1 Data sources and search strategy

PICO strategy was defined to structure the algorithm: defining the Population (adult people with treatment-resistant depression), Intervention (use of Ketamine to eliminate Depression), Comparison with the intervention (Electroconvulsive therapy) and Outcome (rapid and robust antidepressant effects).

The PUBMED database was selected to obtain the articles for this review. Once inserted the keywords, synonyms (*Mesh* platform) and Boolean operators the search algorithm result was *((“ketamine” OR "cetamine") AND ("adverse events" OR "side-effects" OR "pain" OR "chronic pain" OR "symptoms" OR "symptomatology" OR "adverse drug reactions" OR "medication adverse reactions") AND ("effects" OR "efficacy" OR "response" OR "success therapy" OR "success treatment" OR "treatment" OR "therapy" OR "medical" OR "clinical" OR "clinical practice") AND ("apathy" OR "depression" OR “major depressive disorder” OR "refractory depression" OR "resistant depressant" OR "major disorder")))*.

2.2 Study eligibility criteria and selection

Articles were included if they were clinical study or trial, including clinical trial phase I, II, III or IV, controlled clinical trial, comparative study, observational study, were published up to five years of the mentioned period of searching (from 2013 to 2018), approached patients with treatment-resistant depression, and described the therapeutic outcome and side-effects of Ketamine. Articles were excluded if they discussed other depressive disturbances besides treatment-resistance depression, used animal models or were review papers.

For eligibility assessment, one author (D.F.) reviewed titles and abstracts of database records and retrieved full texts. The full-text records were reviewed for eligibility by two authors independently (D.F. and M.S.). Disagreements were settled using a consensus process. The manuscripts that were found to be eligible were then independently reviewed and information was retrieved by two authors (D.F. and M.F.). A standard electronic form was used to extract data.

3 Results

3.1 Study selection

The search query on Pubmed revealed a total of 580 articles, which were screened for inclusion in the study, and a final number of 21 articles were included (Fig.1). Of the 580 references screened, 56 were selected for full-text reading based on the inclusion and exclusion criteria. For various reasons, 35 of them were excluded. As a result, the systematic review comprised 21 studies. In Figure 1, a PRISMA Flowchart presents the procedures adopted in study selection.

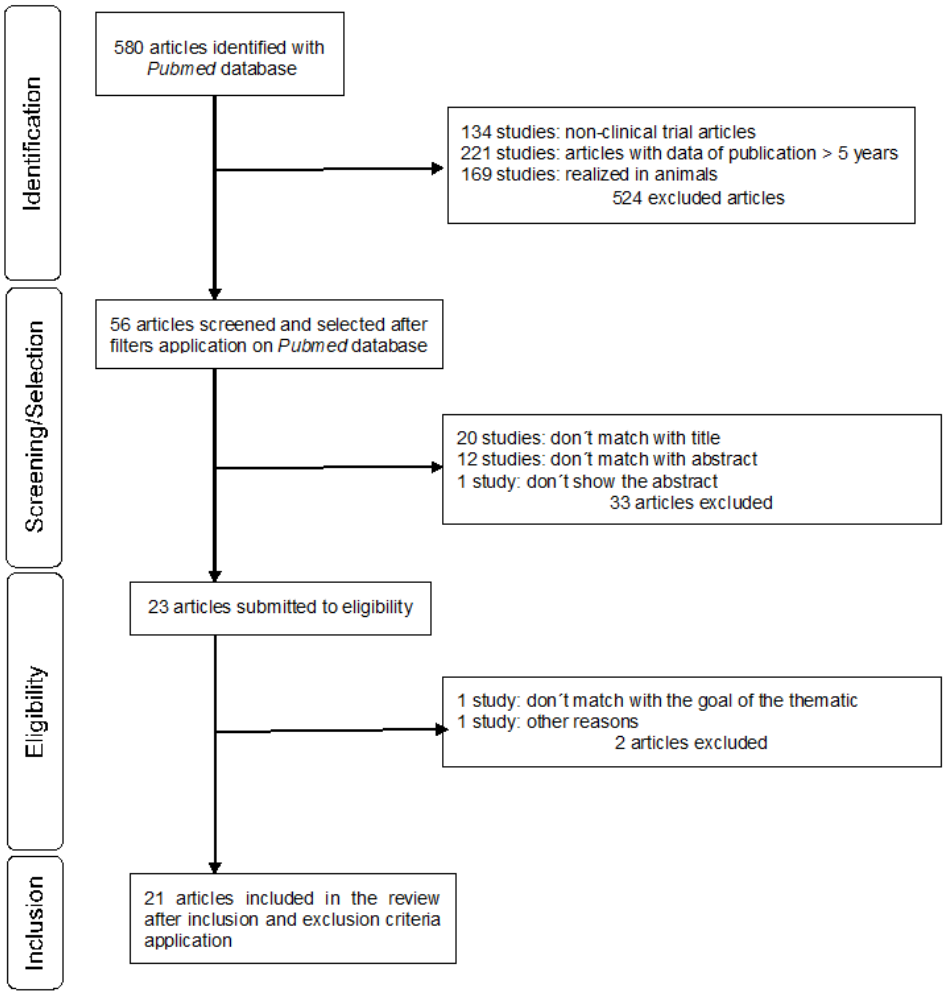

Figure 1. PRISMA diagram of study selection

3.2 Rating scores for Depression

The studies included in this systematic review presented different scores to evaluate the Depression severity. Beck Depression Inventory, Brief Psychiatric Rating Scale, Montgomery-Asberg Depression Rating Scale, Clinician Administered Dissociative States Scale, Hamilton Depression Rating Scale and Inventory of Depressive Symptomatology, and Bond-Laden Visual Analogue instruments were among the most used ones [24]–[27][28]. Furthermore, the Systematic Assessment of Treatment Emergent Events (SAFTEE) was reported in the studies to determine the influence of using different administration routes of Ketamine on the incidence of adverse reactions [29].

3.3 Primary outcomes: antidepressant properties of ketamine

Modulation of the neuro-circuits may suppress symptomatology caused by depression and provide an improvement in health. Table 1 represents the overall overview characteristics of the antidepressant properties of ketamine. Many of the studies examined the effect of ketamine, observed a decrease of anhedonia, suicidal thoughts, anxiety, and other symptoms with an infusion dose of 0,5 mg/kg in 40 minutes [30], [31]. In addition, the efficacy of ketamine is long-lasting, and some clinical trials have demonstrated a consistent action of ketamine, regardless of whether there has been previous treatments with other psychiatric drugs [32], [33].

Three studies, two of them randomized controlled trials, showed changes in different brain areas, such as in the pregenual anterior dorsal cortex, orbitofrontal cortex, superior temporalis gyrus, prefrontal cortex and habenula with the administration of ketamine [25], [34], [35]. Within these previously mentioned aspects, some remarkable studies reported that ketamine has the ability to increase BDNF levels, causing modulation of neuroplasticity, and conversely a reduction of depression symptoms [36], [37].

To assess the precise beneficial effect of ketamine use, the route of administration was investigated. And it has been found in several studies that the intravenous route promotes, within a few minutes, the attenuation of depressive symptoms, although side effects are more common [29].

In one study, in which the intranasal route was tested, five inhalations of 10 mg ketamine were performed within 20 minutes and the results showed an improvement in depressive symptoms. Thus, the intranasal route is being considered as a possible alternative to the intravenous route, in order to avoid the most likely adverse side effects and with the same therapeutic properties [26].

In order to understand the outcome in the association of ketamine with other drugs, a study used Lanicemine in a double-blind, placebo-controlled, randomized trial and the outcome was an effective antidepressant response [28]. In another study, the administration of ketamine to electroconvulsive therapy and to other drugs such as Clonazepam, Aripripazole, Diazepam, among others, was considered [26]. Some studies have tested the use of electroconvulsive therapy to enhance ketamine activity in patients with treatment-resistant

Depression, and one open-label study reported that one-third of patients gained significant, positive benefit from this procedure [38].

3.4 Secondary outcomes: ketamine adverse reactions

In the set of articles included in this systematic review, it was observed that dissociative/psychomimetic symptomatology (13 articles), changes in blood pressure values (10 articles) and headache, nausea, and vomiting (10 articles) were the most frequent adverse reactions. Others may include xerostomia (4 articles), among other less frequent adverse reactions (Table 2).

4 Discussion

4.1 Antidepressant properties of Ketamine

This paper reviewed the scientific evidence for the use of ketamine in treatment-resistant depression patients.

Ketamine proved to decrease depressive symptoms more efficiently and more rapidly than traditional antidepressants. All studies have really demonstrated the fast and powerful function of intravenous ketamine, which provides an opportunity to use this drug in cases of emergency in clinical practice, for example, suicidal thoughts [39]. Second, several of the studies were randomized controlled trials, which represents an advantage to reduce possible bias [40]. Thirdly, the observed literature applied different measurement scales to assess different parameters of the patient's Depression, which brings more precision to the evaluation and final diagnosis and, consequently, to put into practice the best possible treatment. Finally, while these studies began to offer a new chance to treat severe cases of depression, they also highlighted the fact that more research is needed to assess the effectiveness of ketamine in individuals with treatment-resistant depression. The majority *(n=13)* of the studies mentioned the fast-acting and long-lasting anti-depressant properties of ketamine to minimize symptoms of Depression. Ballard et al., 2017 observed that Ketamine decreased the probability of suicidal ideation in approximately 41% after 230 minutes, due to its anti-anhedonia effect, regardless of whether other symptoms were associated [30]. In another study (Ballard et al., 2014), ketamine minimized the suicide risk however whether depressive and anxiety symptoms were present [8]. Still focusing on the powerful effect of Ketamine, Price, et al., 2014 report that individuals who have an increased baseline risk of suicide and diagnosed treatment-resistant depression are more likely to benefit from ketamine.

The modulation of the glutamatergic system has been taken as an essential target in the treatment of depressive symptoms. To reinforce this, Haile et al., 2014 also found that BDNF levels reached peak plasma levels four hours after intravenous (IV) administration of ketamine at 0.5 mg/kg for 40 minutes, and subsequently Price et al., 2014 made a connection between quinolinic acid receptor inflammation and suicidal thoughts in depression [21].

Table 1. Papers on antidepressant properties of Ketamine

Author, Year	Scales	Trial type	Sample Characteristics	Drug (s)	Dosage	Preview therapeutic	Outocomes
Ballard et al. (2017)	SHAPS BDI SSI HAM-D	Retrospective (obtained from a controlled open-label and two placebo-controlled trials)	N= 100; Age: 18-65 State of health: patients with antidepressant resistant depression and *Major* Depression or only Bipolar Depression Ethnicity: not shown Study time: 25 hours	Ketamine (IV)	0.5 mg/kg in 40 min.	Riluzole	Decrease of anhedonia and improvement of suicidal thoughts
Li et al. (2016)	_____	Double-blind, placebo-controlled, randomized	N= 26; Age: 19-50 State of health: healthy patients Ethnicity: not shown Study time : 25 hours	Ketamine (IV)	Racemic mix of Ketamine 0.5 mg/kg in 40 min.	_____	Changes in cerebral metabolism that induced a better response to symptoms
Burger et al. (2016)	BHS BSS BDI	Double-blind, placebo-controlled, randomized	N= 10; Age: 18-65 State of health: not shown Ethnicity: Hispanic, Afro-American, Asian, among others Study time: ≥ 11 months	Ketamine (IV)	0.2 mg/kg in 2 min.	_____	Improvement of suicidal thoughts and the majority of symptoms
Singh et al. (2016)	BPRS CADSS CGI MADRS	Double-blind, placebo-controlled, randomized	N= 67; Age: 18-64 State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: not shown Study time : 40 days	Ketamine (IV)	0.5 mg/kg in 40 min. 2/3 times a week	Fluoxetine Citalopram Bupropion	Improvement of symptoms till 15 days

Author, Year	Scales	Trial type	Sample Characteristics	Drug (s)	Dosage	Preview therapeutic	Outocomes
Loo et al. (2016)	BRIEF CADSS MADRS SAFTEE YMRS	Pilot and placebo-controlled	N= 15; IV(n=4), IM(n=5) and SC(n=6) ; Age: ≥ 18 State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: not shown Study time: 7 days	Ketamine (IV/IM/SC) Midazolam (IV)	Ketamine 0.1 to 0.5 mg/kg OR Midazolam a 0.1 to 0,3 mg/kg in 5 min.	Shock therapy	Variable results from different administration routes with different dosages. In general, all of these induced relief of symptomatology
Lenze et al. (2016)	BPRS CGI MADRS	Pilot, placebo-controlled, randomized clinical trial	N= 20; Age: 18-65 State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: Caucasian and Asian Study time: until 8 weeks	Ketamine (IV) Clonazepam (*per os*)	1st phase: Ketamine 0.6 mg/kg/h in 96h OR 95h20min. 2nd phase: At last 40 min., ketamine 0.5 mg/kg OR Clonidine 0,6 mg	Shock therapy	High levels of ketamine had sustained in the best way the more effective therapeutic response
Li et al. (2016)	BPRS HDRS-17	Placebo-controlled, randomized	N= 48; Age: 21-65 State of health: patients with antidepressant resistant depression Ethnicity: not shown Study time : 2 years	Ketamine (IV)	0.2 and 0.5 mg/kg in 40 min.	Aripripazole Quetiapine Valproic Acid Lithium SSRI SSNRI Bupropion	Group A and B had an effective response caused by Ketamine in PFC, MSA, AMS, ADCC and PCT. Values of SCV were low in cerebellar amygdala and higher in PFC.

Author, Year	Scales	Trial type	Sample Characteristics	Drug (s)	Dosage	Preview therapeutic	Outocomes
Singh et al. (2015)	BPRS IDS-C_{30} MADRS CADSS C-SSRS	Double-blind, placebo-controlled, randomized	N= 30; Age: 18-64 State of health: patients with antidepressant resistant depression Ethnicity: white patients and others Study time: 4 weeks	Esketamine (IV)	0.20 OR 0,40 mg/kg in 40 min.	Mirtazapine Paroxetine Escitalopram Bupropion Sertraline Venlafaxine Duloxetine	After 2 hours, the drug had induced a quick and a huge improvement in symptoms
Hu et al. (2016)	BPRS CADSS MADRS YMRS	Placebo-controlled, randomized	N= 30: Age: 18-60 State of health: patients with antidepressant resistant depression and with suicidal clinical report Ethnicity: not shown Study time: 2 years and 3 months	Ketamine (IV) Escitalopram (*per os*)	Escitalopram 10 mg/day + 0.5 mg/kg Ketamine OR Escitalopram 10 mg/day + Placebo (saline solution) in 40 min.	_____	*Escitalopram + Placebo* group had revealed An improvement of depression symptoms until 2 weeks
Salehi et al. (2015)	HDRS-17	Double-blind randomized clinical trial	N= 160; Age: 20-60 State of health: patients with antidepressant resistant depression and had experimented shock therapy after use of ketamine or thiopental sodium Ethnicity: not shown Study time: not shown	Ketamine (IV) Sodium Thiopental (IV)	Ketamine 0.8 mg/kg OR Sodium Thiopental 1-1.5 mg/kg	_____	Ketamine is more effective than Sodium Thiopental on the recover-phase and in the reduction of the symptoms

Author, Year	Scales	Trial type	Sample Characteristics	Drug (s)	Dosage	Preview therapeutic	Outocomes
Preskorn et al. (2015)	BECH-6 BPRS+ C-SSRS HDRS-17	Double-blind, placebo-controlled, randomized	N= 116; Age: 18-65 State of health: patients with antidepressant resistant depression Ethnicity: Native American, Asian, White, Black and others Study time: 1 year and 3 months	GLYX-13 (IV)	1, 5, 10 or 30 mg/kg until 28 days	Paroxetine	5 or 10 mg/kg (IV) had reduced the symptoms over 7 days
Lally et al. (2015)	CADSS MADRS SHAPS SPM5	Double-blind, placebo-controlled, randomized	N= 52; Age: not shown State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: Caucasian Study time: 4 weeks	Ketamine (IV) Riluzole (*per os*)	Ketamine hydrochloride 0.5 mg/kg in 40 min. OR Riluzole 50-200 mg/day in 4 weeks	Fluoxetine	Reduction in dissociative symptoms and patients with a alcohol disturbance in the past had a better experience with the effect of Ketamine than the others who never ever had any problem with this drink
Ballard et al. (2014)	BDI HAM-A HAM-D SSI	Retrospective (obtained from a double blind, placebo-controlled, crossover trial)	N= 133; Age: 18-65 State of health: patients with antidepressant resistant depression and *Major* Depression or Bipolar Depression type I/II Ethnicity: not shown Study time: ~ 4 days	Ketamine (IV)	0.5 mg/kg in 40 min.	_____	An increase to desire to live and a less expectation to desire to die and suicidal thoughts when the symptoms and the anxiety are controlled

Author, Year	Scales	Trial type	Sample Characteristics	Drug (s)	Dosage	Preview therapeutic	Outocomes
Lai et al. (2014)	BPRS CADSS CGI MADRS SAFTEE YMRS	Double-blind, pilot and placebo-controlled	N= 4; Age: ≥ 18 years State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: not shown Study time: 7 days	Ketamine (IV)	0.1 -0.4 mg/kg in 2-5 min.	Alprazolam Olanzapine Quetiapine Tranilcipromine ; Shock therapy	Reduction of the symptoms including the use of the lower dosage of the drug
Lapidus et al. (2014)	BPRS CADSS HAM-A MADRS YMRS	Double-blind, placebo-controlled, randomized	N= 20; Age: 21-65 years State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: Caucasian, Asian, Black, Hispanic and others Study time: 1 week	Ketamine (IN)	5 inhalations of 10 mg in 20 min.	Shock therapy	Improvement of depressive symptoms (p<0.05 and p<0.001). Via intranasal was well tolerated and not caused significant changes in hemodynamic parameters.
Diamond et al. (2014)	BDI HSRD VAS	Open-label	N= 28; Age: not shown State of health: patients with antidepressant resistant depression and with Unipolar or Bipolar Depression Ethnicity: not shown Study time: 26 weeks	Ketamine (IV)	3 or 6 administrations 0.5 mg/kg in 40 min., inside of recover-time after shock therapy	Aripripazole Clonazepam Diazepam Duloxetine Fluoxetine Gabapentin Olanzapine (...) Shock therapy	Only 1/3 of patients had effective results with this therapy. The shock therapy allowed the monitoring of Ketamine´s therapeutic

Author, Year	**Scales**	**Trial type**	**Sample Characteristics**	**Drug (s)**	**Dosage**	**Preview therapeutic**	**Outocomes**
Price et al. (2014)	BHS CADSS IAT MADRS STAI-S VAS	Placebo-controlled, randomized	N= 57; Age: not shown State of health: patients with antidepressant resistant depression Ethnicity: Caucasian not Hispanics Study time: 2 days at hospital	Ketamine (IV) Midazolam (IV)	Ketamine hydrochloride 0.5 mg/kg OR Midazolam 0.045 mg/kg in 40 min.	_____	Improvement of symptoms and Ketamine was more effective in those who have high level of suicidal thoughts
Sanacora et al. (2013)	BL-VAS BPRS CADSS CGI-I CGI-S HAM-A HAM-D MADRS	Double-blind, placebo-controlled, randomized	N= not shown; Age: 30-45 years State of health: patients with normal state of antidepressant resistant depression and *Major* Depression or moderate/high level of antidepressant resistant depression and *Major* Depression (1st phase) Ethnicity: not shown Study time: 8 weeks	Lanicemine (IV) Ketamine (IV)	1st phase: 75 and 150 mg Lanicemine and 0.5 mg/kg Ketamine 2nd phase type A: 100 mg Lanicemine in 30 min. 2nd phase type B: treatment in 3 weeks	_____	Both dosages of Lanicemine had demonstrated an effective antidepressant response. Adverse events had reported with the use of both drugs but in less scale with Ketamine
Haile et al. (2013)	MADRS	Double-blind randomized clinical trial	N= 22; Age: 21-80 years State of health: patients with antidepressant resistant depression Ethnicity: not shown Study time : 7 days	Ketamine (IV) Midazolam (IV)	0.5 mg/kg Ketamine OR 0.045 mg/kg Midazolam in 40 min.	_____	Ketamine had increased the plasma levels of NFDB and the cortical somatosensory response

Author, Year	Scales	Trial type	Sample Characteristics	Drug (s)	Dosage	Preview therapeutic	Outocomes
Carlson et al. (2013)	MADRS	Open-label	N= 20; Age: 18-65 years State of health: patients with no therapy for antidepressant resistant depression and *Major* Depression Ethnicity: not shown Study time: until 3 days	Ketamine (IV)	Racemic Ketamine Hydrochloride 0.5 mg/kg in 40 min.	Shock therapy	Metabolic changes in specific regions on the brain such as habenulla and gyrus temporalis superior were reported
Jr et al. (2012)	MADRS YMRS	Double-blind randomized clinical trial	N= 30; Age: 18-65 State of health: patients with antidepressant resistant depression and *Major* Depression Ethnicity: not shown Study time: 2 days	Ketamine (IV)	Ketamine hydrochloride 0.5 mg/kg in 40 min.	_____	Levels of NFDB and LAW had increased although this final occurred over the first non-REM episode

ADCC – Anterior Dorsal Cingulate Cortex ; AMS – Motor Supplemental Area ; ARD- Antidepressant Resistant Depression ; BD – Bipolar Depression ; BDI - Beck Depression Inventory ; BHS- Back Hopelessness Suicidality ; BL-VAS- Bond-Lader Visual Analogue Scale ; BPRS - Brief Psychiatric Rating Scale ; BSS - Back Suicidality Scale ; CADSS - Clinician -Administered Dissociative States Scale ; CGI- Clinical Global Impressions ; CGI-I- Clinical Global Impressions of Improvement ; CGI-S- Clinical Global Impressions of Severity ; C-SSRS - Colombia- Suicide Severity Rating Scale; h – hours ; HAM-A - Hamilton Anxiety Rating Scale ; HAM-D- Hamilton Depression Rating Scale ; HDRS-17- Hamilton Depression Rating Scale (17 items) ; IAT- Implicit Association Test; IDS-C_{30} – Inventory of Depressive Symptomatology- Clinician Rated ; IM - route of administration Intramuscular ; IN- route of administration Intranasal ; IV - route of administration Intravenous ; LAW – Low Amplitude Wave ; MADRS - Montgomery-Asberg Depression Rating Scale ; MD - Major Depression ; min. – minutes ; OFC- Orbifrontal Cortex ; PACC - Pregenual Anterior Dorsal Cortex ; per os – route of administration Oral ; PCT- Post-Central Turn ; PFC- Pre-frontal Cortex ; REM - Rapid Eye Movement ; SAFTEE - Systematic Assessment for Treatment Emergent Events ; SC – route of administration Subcutaneous ; SHAPS - Snaith-Hamilton Pleasure Scale ; SSI - Scale for Suicide Ideation ; SSNRI- Selective Serotonin and Noradrenaline Reuptake Inhibitor; SSRI- Selective Serotonin Reuptake Inhibitor ; STAI-S - State-Trait Anxiety Inventory Scale ; VCP - Valores de Captação Padronizados YMRS -Young Mania Rating Scale

Table 2. Papers on adverse reactions of Ketamine

Author, Year	Dissociative Symptoms (psicomimmetic disturbances)	Anxiety	Changes in Blood Pressure or Heartbeats	Tiredness	Changes in Vision	Changes in Sleep	Suicidal thought or Suicide	Confusion	Dizziness	Headache, Nausea or/and Vomiting	Specific symptoms
Ballard et al. (2017)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Li et al. (2016)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Burger et al. (2016)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Singh et al. (2016)	(+)	(+)	(–)	(–)	(–)	(–)	(+)	(+)	(+)	(+)	Cold sensation, Hypoaesthesia (…)
Loo et al. (2016)	(+)	(–)	(+)	(+)	(+)	(–)	(–)	(+)	(+)	(–)	Xerostomia, Emotional lability
Lenze et al. (2016)	(+)	(+)	(+)	(–)	(+)	(+)	(–)	(+)	(–)	(+)	Sialorrhea, Changes in production of hepatic enzymes (…)
Li et al. (2016)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(+)	(–)	(+)	Cry
Singh et al. (2015)	(+)	(–)	(+)	(–)	(–)	(–)	(–)	(+)	(–)	(+)	Xerostomia, Oropharyngeal pain, Paresthesia (…)
Hu et al. (2016)	(+)	(–)	(+)	(+)	(+)	(+)	(–)	(–)	(+)	(+)	Xerostomia, Diarrhea, Sialorrhea, Restleness

Author, Year	Dissociative Symptoms (psicomimmetic disturbances)	Anxiety	Changes in Blood Pressure or Heartbeats	Tiredness	Changes in Vision	Changes in Sleep	Suicidal thought or Suicide	Confusion	Dizziness	Headache, Nausea or/and Vomiting	Specific symptoms
Salehi, et al. (2015)	(+)	(–)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(+)	Pain at the local of the injection
Preskorn et al. (2015)	(–)	(–)	(+)	(+)	(–)	(+)	(–)	(+)	(–)	(–)	Dystonia, Low back pain, Dysgeusia
Lally et al. (2015)	(–)	(–)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Ballard et al. (2014)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	Changes in hemodynamic parameters
Lai et al. (2014)	(+)	(–)	(+)	(–)	(+)	(–)	(–)	(–)	(+)	(+)	Restlessness, Perioral numbness
Lapidus et al. (2014)	(+)	(–)	(–)	(+)	(–)	(–)	(–)	(+)	(–)	(+)	Flu, Irritability, Loss of libido, Awkward taste in mouth (…)
Diamond et al. (2014)	(+)	(+)	(+)	(+)	(–)	(–)	(+)	(+)	(–)	(+)	Tachypnea, Panic Attack (…)
Price et al. (2014)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	Transient euphoria
Sanacora et al. (2013)	(+)	(–)	(+)	(+)	(–)	(+)	(–)	(+)	(–)	(+)	Desinhibition Xerostomia, Hypoaesthesia, Syncope, UTI (…)
Haile et al. (2013)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)

Author, Year	Dissociative Symptoms (psicomimmetic disturbances)	Anxiety	Changes in Blood Pressure or Heartbeats	Tiredness	Changes in Vision	Changes in Sleep	Suicidal thought or Suicide	Confusion	Dizziness	Headache, Nausea or/and Vomiting	Specific symptoms
Carlson et al. (2013)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Jr et al. (2012)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)

UTI – Urinary Tract Infection
(+) symptom present; (–) symptom not present

The deregulated sleep activity has been related to the resistance of conventional treatments of Depression in detriment of the cerebral metabolism changes observed. For example, Duncan et al., 2013 discovered a correlation expressed between the values obtained from low amplitude waves in non-REM episode and BDNF through electroencephalogram analysis which, in turn, promoted an improvement in the depressive mood [20]. Even according to this and as considered upon, Ketamine (an inhibitor of N-methyl-D-aspartate receptor) is more effective with higher severity symptomatology. Gorgulu & Caliyurt, 2009 indicates that sleep deprivation contributes to the production of a great amount of neurotrophic factors and recruitment of AMPA receptors which doesn´t happen with the most of antidepressants due to the fact that adjustment of synaptic neuroplasticity occurs only a few weeks later. Metabolic activity is increased in individuals with this type of Depression, for example, in the right habenula region, middle temporal gyrus and, controversially, reduced at the right cerebellar amygdala. However, the habenular stimulation area is a particular region of interest to understand the rapid and vigorous ketamine effect on the neuronal metabolism cells [9].

Many of the studies included in this review used a 0.5 mg/kg dosage. However, some of them demonstrated that dosages below 0.5 mg/kg may be enough to reach the similar effectiveness of the usual dosage. Katalinic et al., 2013 referred to a subanesthetic dosage of 0.2 mg/kg might be sufficient to revert quickly and efficiently all depressive symptoms [25]. In a double-blind, randomized and placebo-controlled study, Singh et al., 2016 found that Ketamine when administered 0.5 mg/kg twice a week the response rate was around 69% [17].

The administration route is one of the most important features must be checked to ensure the efficacy and safety of the treatment. Furthermore, some alternatives such as Oral (*per os*), Sublingual, Intramuscular (IM), Intravenous (with more evidence in literature), Subcutaneous (SC) and Intranasal (IN) have been reported in the literature. Recently, IN route may be appointed as an option to treat resistant-depression because of the prominent reduction of adverse-effects. The only disadvantage is related to the fact of IN route has a lower half-time than the IV route [26]. Currently, Esketamine (an isomer obtained from Ketamine) nasal spray - Spravato® - displayed impressive improvements in depressive symptomatology when compared to a common oral administration [42]. In addition, Loo et al., 2016 showed some comparisons between administration routes: IM has similar efficacy when compared with the SC and IV route [13]. However, both IM and IV routes are more rapid to generate a physiological response. SC route also brings several advantages due to its efficacy/side-effects racio.

Combining other medications with ketamine can aid recovery. Lenze et al., 2016 found that clonidine, when co-administered with Ketamine, decreases the severity of symptoms without minimizing the antidepressant effect. In another study. Hu et al., 2015 verified that when Escitalopram and Ketamine were both administered, an increased ketamine plasma concentration was observed. Accordingly, they considered that Escitalopram acts as a catalyst/enhancer of ketamine activity.

Electroconvulsive therapy is recognized as a complementary treatment for resistant-treatment depression. In the study of Salehi, et al, 2015 they concluded that Ketamine, when

given before Electroconvulsive procedures, was beneficial [16]. Although seizures and blood pressure changes are present, the proven benefits outweigh its risks, and this drug may complement the treatment with electroconvulsive therapy. Similarly, D-cycloserine - a partial agonist of the Glycine with the binding site in the NR2B receptors of NMDA - is mentioned because of their antidepressant properties and practically no psychomimetic/dissociative adverse effects [11]. Other drugs have been described, such as Memantine and Lanicemine (weak NMDA receptor blockers) [27].

4.2 Adverse reactions induced by Ketamine

Preskorn et al., 2015 mentioned the challenge in depression is to find new effective therapies with a low risk of adverse reactions [11]. For example, GLYX-13 (a partial NMDA receptor antagonist) may be equally effective with a much lower quantity of side-effects than Ketamine. Between the more frequent side-effects found in Table 2 (dissociative symptoms and hearth parameters changes), most of them are attenuated with successive administrations over 2 hours and after Ketamine administration [17]. So, Loo et al., 2016 demonstrated the risk of some administration routes to side-effects appears discussing IV route as the main responsible for the beginning of those symptoms [13].

The association of other drugs might be beneficial as previously mentioned. As an example, Lenze et al., 2016 had proved the use of ketamine with Clonidine for a consecutive period of 96 hours and this resulted in a minimization of side-effects even Ketamine plasma concentrations were elevated [27].

In relation to Electroconvulsive therapy, Salehi et al., 2015 recommended administrating Ketamine before the electroconvulsive procedure because seizure duration is prolonged when both are used at the same time [16].

The side-effects are also explained by the possible mechanisms of Ketamine: extra-synaptic inhibition of NMDA receptors, blockade of the activation of NMDA receptor, production of metabolites (hydroxynorketamine) and inhibition of NMDA receptors in lateral habenulla area [43]. To better understand how Ketamine performs, Sanacora et al., 2013 encourage to the research of biomarkers to identify changes during treatment with Ketamine in individuals with resistance to the traditional antidepressants, specifically in brains areas more affected by the symptomatology of the disease [12].

4.3 Study limitations and future perspectives

For this systematic review, we identified several limitations. Most studies were conducted in small samples, the majority using intravenous administration and with a fixed dosage for Ketamine, additionally, heterogenous rating scores were used to classify depressive symptoms. Taken in account these limitations, further studies should address different routes of ketamine administration, different dosages, and frequencies of administration to analyze the most suitable treatment. Regarding sample size, studies including large samples should be developed. Finally, it would be beneficial to search for new targets on the glutamatergic

pathway, to explore the allosteric modifications of the BDNF TRKB receptor, and, finally, the sphingolipid system which may give hope for the development of new, rapid-acting antidepressants.

5 Conclusions

In this systematic review, ketamine has been shown to be effective when given to individuals with treatment resistant depression, particularly those who present a more aggressive phenotype (suicidal ideation). This drug represents a powerful tool to suppress depression due to the resynchronization of neural circuits upon its use. However, ketamine was also associated with several induced side-effects, including changes in blood pressure, dissociative symptoms, headache, nausea and vomits, which may limit its use. Different routes of administration and ketamine metabolites may be explored to overcome some of these induced side-effects. Furthermore, new research should focus on innovative therapeutic approaches, targeting mTORC1 signaling pathway, and the BDNF TRKB receptor allosteric manipulation.

Disclosure statement

The authors identified no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] World Health Organization, "Depression and other common mental disorders: global health estimates," *World Health Organ.*, pp. 1–24, 2017, doi: CC BY-NC-SA 3.0 IGO.

[2] American Psychiatric Association and American Psychiatric Association, Eds., *Diagnostic and statistical manual of mental disorders: DSM-5*, 5th ed. Washington, D.C: American Psychiatric Association, 2013.

[3] Direção Geral de Saúde, "Depressão e outras Perturbações Mentais Comuns," pp. 1–104, 2017.

[4] U. E. Lang and S. Borgwardt, "Molecular Mechanisms of Depression: Perspectives on New Treatment Strategies," *Cell. Physiol. Biochem.*, vol. 31, no. 6, pp. 761–777, 2013, doi: 10.1159/000350094.

[5] A. S. F. Kwong *et al.*, "Genetic and Environmental Risk Factors Associated With Trajectories of Depression Symptoms From Adolescence to Young Adulthood," *JAMA Netw. Open*, vol. 2, no. 6, p. e196587, Jun. 2019, doi: 10.1001/jamanetworkopen.2019.6587.

[6] S. M. Stahl, *Stahl's essential psychopharmacology: neuroscientific basis and practical application*, 4th ed. Cambridge ; New York: Cambridge University Press, 2013.

[7] R. M. Hirschfeld, "History and evolution of the monoamine hypothesis of depression," *J. Clin. Psychiatry*, vol. 61 Suppl 6, pp. 4–6, 2000.

[8] G. Hasler, "Pathophysiology of depression: do we have any solid evidence of interest to clinicians?," *World Psychiatry*, vol. 9, no. 3, pp. 155–161, Oct. 2010, doi: 10.1002/j.2051-5545.2010.tb00298.x.

[9] J. Mikulska, G. Juszczyk, M. Gawrońska-Grzywacz, and M. Herbet, "HPA Axis in the Pathomechanism of Depression and Schizophrenia: New Therapeutic Strategies Based on Its Participation," *Brain Sci.*, vol. 11, no. 10, p. 1298, Sep. 2021, doi: 10.3390/brainsci11101298.

[10] E. Castrén and T. Rantamäki, "The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity," *Dev. Neurobiol.*, vol. 70, no. 5, pp. 289–297, Apr. 2010, doi: 10.1002/dneu.20758.

[11] R. S. Duman and N. Li, "A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists," *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, vol. 367, no. 1601, pp. 2475–2484, Sep. 2012, doi: 10.1098/rstb.2011.0357.

[12] J. C. Felger and F. E. Lotrich, "Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications," *Neuroscience*, vol. 246, pp. 199–229, Aug. 2013, doi: 10.1016/j.neuroscience.2013.04.060.

[13] G. E. Hodes, V. Kana, C. Menard, M. Merad, and S. J. Russo, "Neuroimmune mechanisms of depression," *Nat. Neurosci.*, vol. 18, no. 10, pp. 1386–1393, Oct. 2015, doi: 10.1038/nn.4113.

[14] G. Sanacora, G. Treccani, and M. Popoli, "Towards a glutamate hypothesis of depression," *Neuropharmacology*, vol. 62, no. 1, pp. 63–77, Jan. 2012, doi: 10.1016/j.neuropharm.2011.07.036.

[15] B. Kadriu, L. Musazzi, I. D. Henter, M. Graves, M. Popoli, and C. A. Zarate, "Glutamatergic Neurotransmission: Pathway to Developing Novel Rapid-Acting Antidepressant Treatments," *Int. J. Neuropsychopharmacol.*, vol. 22, no. 2, pp. 119–135, Feb. 2019, doi: 10.1093/ijnp/pyy094.

[16] S. J. Mathew *et al.*, "Ketamine for Treatment-Resistant Unipolar Depression: Current Evidence," *CNS Drugs*, vol. 26, no. 3, pp. 189–204, Mar. 2012, doi: 10.2165/11599770-000000000-00000.

[17] K. E. DeWilde, C. F. Levitch, J. W. Murrough, S. J. Mathew, and D. V. Iosifescu, "The promise of ketamine for treatment-resistant depression: current evidence and future directions: Ketamine for treatment-resistant depression," *Ann. N. Y. Acad. Sci.*, vol. 1345, no. 1, pp. 47–58, May 2015, doi: 10.1111/nyas.12646.

[18] C. G. Abdallah, G. Sanacora, R. S. Duman, and J. H. Krystal, "Ketamine and Rapid-Acting Antidepressants: A Window into a New Neurobiology for Mood Disorder Therapeutics," *Annu. Rev. Med.*, vol. 66, no. 1, pp. 509–523, 2015, doi: 10.1146/annurev-med-053013-062946.

[19] G. Mion and T. Villevieille, "Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings)," *CNS Neurosci. Ther.*, vol. 19, no. 6, pp. 370–380, Jun. 2013, doi: 10.1111/cns.12099.

[20] K. Hashimoto, "Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine," *Biochem. Pharmacol.*, vol. 177, p. 113935, Jul. 2020, doi: 10.1016/j.bcp.2020.113935.

[21] V. Lewis *et al.*, "Translational control by ketamine and its implications for comorbid cognitive deficits in depressive disorders," *J. Neurochem.*, p. jnc.15652, Jun. 2022, doi: 10.1111/jnc.15652.

[22] A. Aguilar-Valles *et al.*, "Antidepressant actions of ketamine engage cell-specific translation via eIF4E," *Nature*, vol. 590, no. 7845, pp. 315–319, Feb. 2021, doi: 10.1038/s41586-020-03047-0.

[23] Stephen M. Stahl, *Prescriber´s Guide*, 5ª. EUA: Cambridge University Press, 2014.

[24] E. D. Ballard *et al.*, "Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety," *J. Psychiatr. Res.*, vol. 58, pp. 161–166, Nov. 2014, doi: 10.1016/j.jpsychires.2014.07.027.

[25] P. J. Carlson *et al.*, "Neural Correlates of Rapid Antidepressant Response to Ketamine in Treatment-Resistant Unipolar Depression: A Preliminary Positron Emission Tomography Study," *Biol. Psychiatry*, vol. 73, no. 12, pp. 1213–1221, Jun. 2013, doi: 10.1016/j.biopsych.2013.02.008.

[26] K. A. B. Lapidus *et al.*, "A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder," *Biol. Psychiatry*, vol. 76, no. 12, pp. 970–976, Dec. 2014, doi: 10.1016/j.biopsych.2014.03.026.

[27] S. Preskorn, M. Macaluso, D. V. Mehra, G. Zammit, J. R. Moskal, and R. M. Burch, "Randomized Proof of Concept Trial of GLYX-13, an N-Methyl-D-Aspartate Receptor Glycine Site Partial Agonist, in Major Depressive Disorder Nonresponsive to a Previous Antidepressant Agent:," *J. Psychiatr. Pract.*, vol. 21, no. 2, pp. 140–149, Mar. 2015, doi: 10.1097/01.pra.0000462606.17725.93.

[28] G. Sanacora *et al.*, "Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects," *Mol. Psychiatry*, vol. 19, no. 9, pp. 978–985, Sep. 2014, doi: 10.1038/mp.2013.130.

[29] C. K. Loo *et al.*, "Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression," *Acta Psychiatr. Scand.*, vol. 134, no. 1, pp. 48–56, Jul. 2016, doi: 10.1111/acps.12572.

[30] E. D. Ballard *et al.*, "Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials," *J. Affect. Disord.*, vol. 218, pp. 195–200, Aug. 2017, doi: 10.1016/j.jad.2017.04.057.

[31] N. Lally, A. C. Nugent, D. A. Luckenbaugh, M. J. Niciu, J. P. Roiser, and C. A. Zarate, "Neural correlates of change in major depressive disorder anhedonia following open-label ketamine," *J. Psychopharmacol. (Oxf.)*, vol. 29, no. 5, pp. 596–607, May 2015, doi: 10.1177/0269881114568041.

[32] B. Salehi, A. Mohammadbeigi, A. Kamali, M. Taheri-Nejad, and I. Moshiri, "Impact comparison of ketamine and sodium thiopental on anesthesia during electroconvulsive therapy in major depression patients with drug-resistant; a double-blind randomized clinical trial," *Ann. Card. Anaesth.*, vol. 18, no. 4, p. 486, 2015, doi: 10.4103/0971-9784.166444.

[33] J. B. Singh *et al.*, "A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression," *Am. J. Psychiatry*, vol. 173, no. 8, pp. 816–826, Aug. 2016, doi: 10.1176/appi.ajp.2016.16010037.

[34] C.-T. Li *et al.*, "The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: A randomized controlled study: Ketamine Modulates the PFC," *Hum. Brain Mapp.*, vol. 37, no. 3, pp. 1080–1090, Mar. 2016, doi: 10.1002/hbm.23085.

[35] M. Li *et al.*, "Temporal Dynamics of Antidepressant Ketamine Effects on Glutamine Cycling Follow Regional Fingerprints of AMPA and NMDA Receptor Densities," *Neuropsychopharmacology*, vol. 42, no. 6, pp. 1201–1209, Jan. 2016, doi: 10.1038/npp.2016.184.

[36] W. C. Duncan *et al.*, "Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder," *Int. J. Neuropsychopharmacol.*, vol. 16, no. 02, pp. 301–311, Mar. 2013, doi: 10.1017/S1461145712000545.

[37] C. N. Haile *et al.*, "Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression," *Int. J. Neuropsychopharmacol.*, vol. 17, no. 02, pp. 331–336, Feb. 2014, doi: 10.1017/S1461145713001119.

[38] P. R. Diamond *et al.*, "Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic," *J. Psychopharmacol. (Oxf.)*, vol. 28, no. 6, pp. 536–544, Jun. 2014, doi: 10.1177/0269881114527361.

[39] J. Burger *et al.*, "A Double-Blinded, Randomized, Placebo-Controlled Sub-Dissociative Dose Ketamine Pilot Study in the Treatment of Acute Depression and Suicidality in a Military Emergency Department Setting," *Mil. Med.*, vol. 181, no. 10, pp. 1195–1199, Oct. 2016, doi: 10.7205/MILMED-D-15-00431.

[40] D. C. Jupiter, "Propensity Score Matching: Retrospective Randomization?," *J. Foot Ankle Surg.*, vol. 56, no. 2, pp. 417–420, Mar. 2017, doi: 10.1053/j.jfas.2017.01.013.

[41] N. Katalinic, R. Lai, A. Somogyi, P. B. Mitchell, P. Glue, and C. K. Loo, "Ketamine as a new treatment for depression: A review of its efficacy and adverse effects," *Aust. N. Z. J. Psychiatry*, vol. 47, no. 8, pp. 710–727, Aug. 2013, doi: 10.1177/0004867413486842.

[42] N. J. Titusville, "New Phase 3 Data Show Esketamine Nasal Spray Demonstrated Rapid Improvements in Depressive Symptoms in Patients with Treatment-Resistant Depression," *U. S.*, 2018, [Online]. Available: https://www.janssen.com/new-phase-3-data-show-esketamine-nasal-spray-demonstrated-rapid-improvements-depressive-symptoms

[43] P. Zanos and T. D. Gould, "Mechanisms of ketamine action as an antidepressant," *Mol. Psychiatry*, vol. 23, no. 4, pp. 801–811, Apr. 2018, doi: 10.1038/mp.2017.255.