Degree project

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Ketamine for Treatment-Resistant Depression: Moving Away From Conventional Antidepressants

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Abstract

An increasing amount of research suggests Ketamine in subanaesthetic doses to be an effective antidepressant for Major Depressive Disorder (MDD) and Treatment-Resistant Disorder (TRD). After the finding that NMDA-receptor antagonists may hold antidepressant effect, several studies have suggested Ketamine to have great effect in relief of depressive symptoms. A time lag between biological and behavioural effects have been shown in currently available antidepressants and are not guaranteed to be efficient; only 30% of patients reach adequate response. The aim for this thesis is to systematically review available studies on the efficiency of Ketamine's antidepressant effects in patients with TRD. Scopus, Web of Science, and PubMed were the databases searched for relevant research regarding the subject. Six articles were included in the analysis. A compilation of the results presented a moderate to large effect size for Ketamine compared to placebo at 24 hours through day seven. It is of immense weight that prolonged adverse effects and possible abuse are taken into consideration for future research, as well as how to sustain the dramatic acute antidepressant effect of Ketamine.

Keywords: ketamine, antidepressant, treatment-resistant depression, NMDA-receptor antagonist, glutamate

Ketamine for Treatment-Resistant Depression: Moving Away from Conventional Antidepressants

Major Depressive Disorder (MDD) is the world's leading cause of disability, with 322 million people globally suffering (World Health Organization, 2017). In the Diagnostic and statistical manual of mental disorders 5th edition (American Psychiatric Association, 2013), MDD is defined by symptoms such as fatigue, mood changes, feelings of hopelessness, and suicidal thoughts. There is currently a wide range of psychopharmacological agents available, but only 30 % of the patients reach adequate response to these. An additional 30 % meet the criteria for Treatment Resistance Depression (TRD; Trivedi et al., 2006), a condition characterised by inadequate response to antidepressants. Not achieving remission is associated with an increased risk of relapse and increases the likelihood of being diagnosed with concurrent substance abuse and anxiety disorders (Crown et al., 2002).

Treatment-Resistant Depression

The pathological process behind TRD is currently unknown, and there is no clear definition of the disease. However, the general assumption is failed response to at least two different types of antidepressants consumed for at least four weeks (Serafini et al., 2014). Besides the suffering of people diagnosed with TRD leading to both work- and socially related issues, their costs related to depression can be up to 19 times more expensive than for healthy individuals (Crown & Russell, 2002).

Depression Scales

Different scales of depression are often assessed to measure the severity of the depression. Three common scales used are Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI).

The HDRS is commonly used in clinical settings and was first formulated in the 1960s (Hamilton, 1960). The first version published consisted of 17 questions and has since been altered to include various lengths of the scale. The scoring depends on the version. However, a score between 0-7 is accepted as no depression (clinical remission), and a score above 20 is considered moderately severe. Originally, variables are graded from 0-5 depending on severity. See Appendix A for example questions.

Published in 1979, MADRS was developed especially sensitive to changes in depression (Montgomery & Asberg, 1979). The scale consists of 10 items graded from 0-6. A core of 0-6 corresponds to no depression, 7-19 to mild depression, 20-34 to a medium rate, 35-60 to severe depression. See Appendix B for example questions.

BDI was published in 1961 and contains 21 items (Beck et al., 1996). It has since been developed in different forms, e.g., computerised forms and a short 13-item version.

Monoamine Theory of Depression

The monoamine theory of depression is one of the most acknowledged theories and was first formulated over 50 years ago (Hillhouse & Porter, 2015). Examples of monoamines are serotonin, norepinephrine, and dopamine. In the '50s, the alkaloid Reserpine was used to treat high blood pressure. Patients receiving Reserpine consequently experienced depressive symptoms, which provided evidence for the involvement of serotonin, norepinephrine and dopamine in depression, following the discovery that Reserpine attenuated these monoamines. The underlying mechanisms of
monoamine oxidase (MAO) inhibitors, tricyclic antidepressants (TCA), and subsequently selective serotonin reuptake inhibitors (SSRI) further demonstrated the involvement of monoamines in depression.

Monoaminergic Modulators

There are five major classes of antidepressants; MAO, TCA, SSRI, serotonin-norepinephrine reuptake inhibitor (SNRI) and atypical antidepressants. The first type of antidepressant to be used in the treatment of MDD was MAO inhibitors (Hillhouse & Porter, 2015). MAO breaks down monoamines, and by inhibiting MAO, an increase in concentration is present at the presynaptic terminal, ready to fire when triggered by an action potential.

TCA is characterised by its diverse pharmacological profile. It inhibits presynaptic norepinephrine and serotonin reuptake transporters and blocks three receptor proteins (postsynaptic adrenergic α1 and α2, muscarinic, and histamine H1 receptors; Hillhouse & Porter, 2015). It is believed that the inhibition of the reuptake of serotonin and norepinephrine at the transport proteins increases the levels of the monoamines in their respective synaptic cleft.

SSRIs inhibit the reuptake of serotonin, enabling increased concentration of serotonin in the synaptic cleft and stimulate postsynaptic receptors. SNRI's work in a similar fashion as SSRI's but also inhibits the reuptake of norepinephrine in addition to serotonin (Sansone & Sansone, 2014).

Newer antidepressants that do not fit any of these classes are called atypical antidepressants. Although these differ in action from traditional antidepressants, they do modulate the monoaminergic system.

Critique of the Monoamine Hypothesis

The monoamine hypothesis is the most prominent and established theory of MDD; however, a significant amount of research has indicated that the monoamine theory of depression might not be the single underlying mechanism for MDD (Sanacora et al., 2012). In turn, the efficiency of monoaminergic modulators has been questioned, for instance, because of the prolonged behavioural effects despite an instant increase in monoamines. In a meta-analysis by Turner et al. (2008) partly containing unpublished data, 51% of the data provided positive results regarding antidepressant effect, while published data provided 94%

positive results. In another meta-analysis by Undurraga and Baldessarini (2012), a response rate to U.S Food and Drug Administration (FDA) approved antidepressants were at 54% compared to 37% for placebo, favouring the medications by 17%. Further, it was found that the depletion of monoamines did not decrease mood in healthy individuals, and causality between monoaminergic systems and MDD could therefore not be concluded (Ruhé et al., 2007).

Glutamate

Glutamate is the major excitatory amino acid in the central nervous system (CNS). It is involved in the vast majority of excitatory connections, as well as more than half of the synapses in the brain (Sanacora et al., 2012; Serafini et al., 2014). It cannot pass the blood-brain barrier and must therefore be synthesised in the brain (Purves et al., 2008). The glutamate interacts with several different types of receptors. One of the two main glutamate classes of receptors is ionotropic receptors (a protein complex coupling neurotransmitter receptor to the ion channel), and they are segregated into three groups; *N*-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and kainate receptors.

The sequence of events occurring for there to be an adequate supply of glutamate maintained in the CNS is called the glutamate-glutamine cycle (Figure 1). Glutamate is removed from the synaptic cleft by a class of transporter proteins called excitatory amino acid transporters (EAAT). These transporters are located primarily on the surface of glial cells and carry the glutamate into neurons and glial cells. Here, the glutamate is converted into glutamine, another amino acid, by the enzyme glutamine synthetase. Glutamine no longer has excitatory properties and is transported back to the postsynaptic neuron and subsequently convert back to glutamate.

It is crucial for glutamate to be tightly regulated to avoid toxic effect on neurons. An overflow of glutamate is implicated in a range of diseases in the CNS, including Amyotrophic Lateral Sclerosis (commonly referred to as ALS), Ataxia, Alzheimer's, and neurological disorders such as mood- and anxiety disorders (Willard & Koochekpour, 2013).

Dysfunctional glutamate signalling can result from increased release of presynaptic glutamate, direct release of glutamate in glial cells, or impaired ability to clear glutamate from extracellular space (O'shea, 2002).

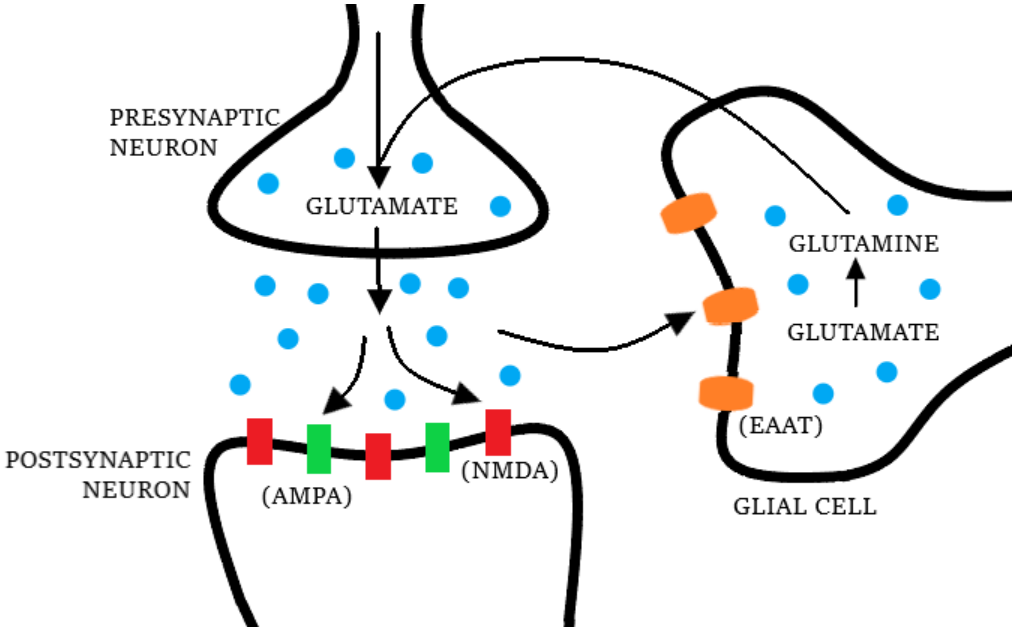
Glutamate Hypothesis of Depression

The glutamate hypothesis of depression was first articulated in the early 1990s when early findings suggested that NMDA receptor antagonists had antidepressant-like actions (Sanacora et al., 2012). Since then, additional compelling evidence has been published. Indirect studies have measured increased concentration levels of glutamate in plasma and

increased levels in glutamine in cerebrospinal fluid (Hillhouse & Porter, 2015). These levels were consequently reduced when treated with monoamine antidepressants, indicating that monoamines modulate the glutamatergic system. Using the more direct method Proton Magnetic Resonance Spectroscopy demonstrated reduced metabolic, typically unresolved, glutamate/glutamine exchange in both cortical and subcortical brain areas that have been purported to play an essential role in MDD, e.g., hippocampus (Block et al., 2009) and anterior cingulate cortex (Mirza et al., 2004). Concentration went back to normal after receiving Electrocompulsive Therapy, a type of antidepressant therapy using small electrical currents passing through the brain (Hillhouse & Porter, 2015).

Figure 1

Glutamate-glutamine cycle



Note. Glutamate binds with AMPA- and NMDA-receptors. Extracellular glutamate is transported into the glial cell by EAAT and converted into glutamine, then transported back to the presynaptic neuron, converted back into glutamate. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, NMDA=N-methyl-D-aspartate, EAAT=excitatory amino acid transporters.

NMDA-receptors

A significant amount of clinically relevant studies has focused on glutamate modulators via NMDA receptors (Serafini et al., 2014). The first use of a glutamate modulator as an antidepressant was in the late 50's early 60's. Amino acid Cycloserine is an antibiotic drug that at the time was used to treat tuberculosis. It was noticed that when depressed patients with tuberculosis were treated with high doses of Cycloserine, it also had antidepressant-like effects, however, with significant adverse neuropsychiatric side effects,

such as impaired memory, disorientation, and paraesthesia (abnormal sensation in the skin, such as tingling, burning, and numbness; Crane, 1959).

NMDA receptors and AMPA receptors are co-localised, and the release of glutamate into the synaptic cleft activates the AMPA receptors. This allows for sodium to pass into the postsynaptic membrane, and in turn, depolarise the membrane. This process facilitates the activation of the NMDA receptor (Matveychuk et al., 2020).

Ketamine

A commonly studied NMDA receptor antagonist for MDD is Ketamine. Ketamine was first developed in the 1960s by Dr Calvin Lee Stevens (Hillhouse & Porter, 2015). It was tested in clinical trials for its anaesthetic properties, with no adverse side effects reported. Subjects reported dissociative symptoms as if they were floating and numbness in limbs. It was approved by the FDA in 1970 as a short-acting anaesthetic agent in both humans and animals and was used by American soldiers in the Vietnam War.

In the mid-'90s, Ketamine became a popular drug in recreational contexts known as e.g., Special K and was often used at night clubs in subanaesthetic doses (Hillhouse & Porter, 2015). It induced feelings of disconnectedness and hallucinations. The effect lasts for about 30-60 minutes and is in recreational contexts referred to as a "K-hole". Ketamine was first clinically tested for its antidepressant effects in the year 2000 (Berman et al.) and has since been administered intravenously at clinics. In 2019 Ketamine in the form of a nasal spray was approved by the FDA (2019).

Antidepressant Action of Ketamine

Although Ketamine is referred to as an NMDA receptor antagonist, its underlying antidepressant action is yet to be fully disclosed and may be more complex than NMDA receptor antagonism (Matveychuk et al., 2020). The uncertainty is based on the finding that other NMDA receptor antagonists do not assess the same therapeutic effect as Ketamine, suggesting a cascade of events to be responsible. Ketamine has a greater affinity for NMDA receptors on gamma-aminobutyric acid (GABA) interneurons (neurons connecting two brain regions). GABA neurons are inhibitory neurons that act to suppress the excitation of downstream glutamatergic neurons, meaning that an NMDA receptor antagonist prevents the inhibition of downstream glutamatergic neurons, causing a surge. This increase in extracellular glutamate initiates activation of postsynaptic AMPA receptors, consequently leading to potentiation of brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin complex 1 (mTORC1) signalling pathway.

BDNF. A significant amount of research supports the role of BDNF in the antidepressant effect of Ketamine. BDNF is a growth factor protein supporting cell growth and survival of neurons (Matveychuk et al., 2020). It also promotes neurogenesis and synaptogenesis (the production of new neurons and synapses) in the CNS. mTOR is a

component in two distinct protein complexes; mTOR Complex 1 (mTORC1) and mTOR Complex 2. Ketamine is believed to affect the mTORC1 pathway. mTOR regulates metabolic cell growth by promoting lipid, nucleotide, and protein synthesis while inhibiting cellular autophagy (a process regulating removal and rebuilding of cells) and is suggested to play a part in neural development and neuronal circuit formation.

AMPA. A significant amount of research regarding Ketamine's antidepressant properties comes from animal studies and provides evidence of the AMPA receptor's critical role in Ketamine's antidepressant effect. In one animal study, an AMPA receptor inhibitor was co-administered, and the antidepressant effects were abolished (Matveychuk et al., 2020). In a study by Iskandrani and collegues (2015), Ketamine seemed to enhance AMPA evoked electrophysiological response in rat hippocampus and medial prefrontal cortex, suggesting that Ketamine increase AMPA receptor transmission.

In Ketamine studies where animals were pre-treated with an AMPA receptor antagonist, reduced levels of BDNF and mTOR were present (Matveychuk et al., 2020). When instead pre-treating with an AMPA receptor agonist, the levels were increased. When pre-treating with rapamycin, a mTORC1 inhibitor, antidepressant effects in animals were abolished. Several studies have come to conclusions akin to the aforementioned research (Li et al., 2010; Li et al., 2011); however, contradicting results were found in mice, indicating that the role of mTORC1 might not be as clear-cut as thought (Matveychuk et al., 2020).

For decades MDD and other mood disorders have been referred to as a default monoaminergic system. An increasing amount of research has indicated that a chemical imbalance might not be the complete mechanism behind the troubling disease. Instead, a significant body of research has presented compelling results of glutamatergic systems involvement in MDD, and thus new types of antidepressants can further the knowledge behind MDD's biology. Patients who have lost hope after several trials of current antidepressants can get the treatment they need by exploring the antidepressant properties of Ketamine. By further exploring the possibilities of Ketamine as an antidepressant agent, a more precise theory can be formed.

For this paper, the aim is to systematically review current studies on the efficiency of Ketamine's antidepressant effects in patients with TRD. Based on previous research regarding Ketamine it is hypothesized in this thesis that a single dose of intravenous (IV) Ketamine will be superior to placebo interventions.

Methods

Search Process

The author conducted the search process. Scopus, Web of Science, and PubMed were searched on March 6th 2021, and again on March 17th 2021 to check for recently published articles. References in included studies were reviewed for additional publications, as well as a

systematic review from 2020 (Marcantoni et al., 2020). Only original papers in English were reviewed. Because the first clinical study on the antidepressant effect of Ketamine was published in 2000 (Berman et al.), a year limit was set from 2000 and onward. Search strain assessed: (Ketamine) AND (treatment) AND (major depressive disorder OR unipolar depression OR bipolar depression OR Depression) AND (NMDA antagonist OR N-methyl-D-aspartate antagonist) AND (placebo).

After formulating the search string databases were searched ending with a total of 202 articles (Scopus n=56, Web of Science n=76, PubMed n=70), as well as the systematic review (n=35; Marcantoni et al., 2020; Figure 2). All results were exported into an Excel spreadsheet (n=237), and duplicates were discarded manually by listing them in alphabetical order (n=75). Based on the title and abstract, articles were removed if deemed irrelevant for the present paper (n=47). If uncertain, articles were kept for further evaluation. The remaining articles were reviewed in their full length (n=15) and included if meeting inclusion criteria presented below (n=6). Two papers were excluded for being open-label studies, two for testing several different dosages without specific data regarding the dose of 0.5 mg/kg, and one was discarded for using multiple infusions. One article assessed the same sample as another study already included, and an additional three articles were excluded for acquiring an outcome unrelated to this paper. All steps were conducted in separate spreadsheets to keep track. The steps involved in the search process are illustrated in the PRISMA flow chart in Figure 2.

Inclusion & Exclusion Criteria

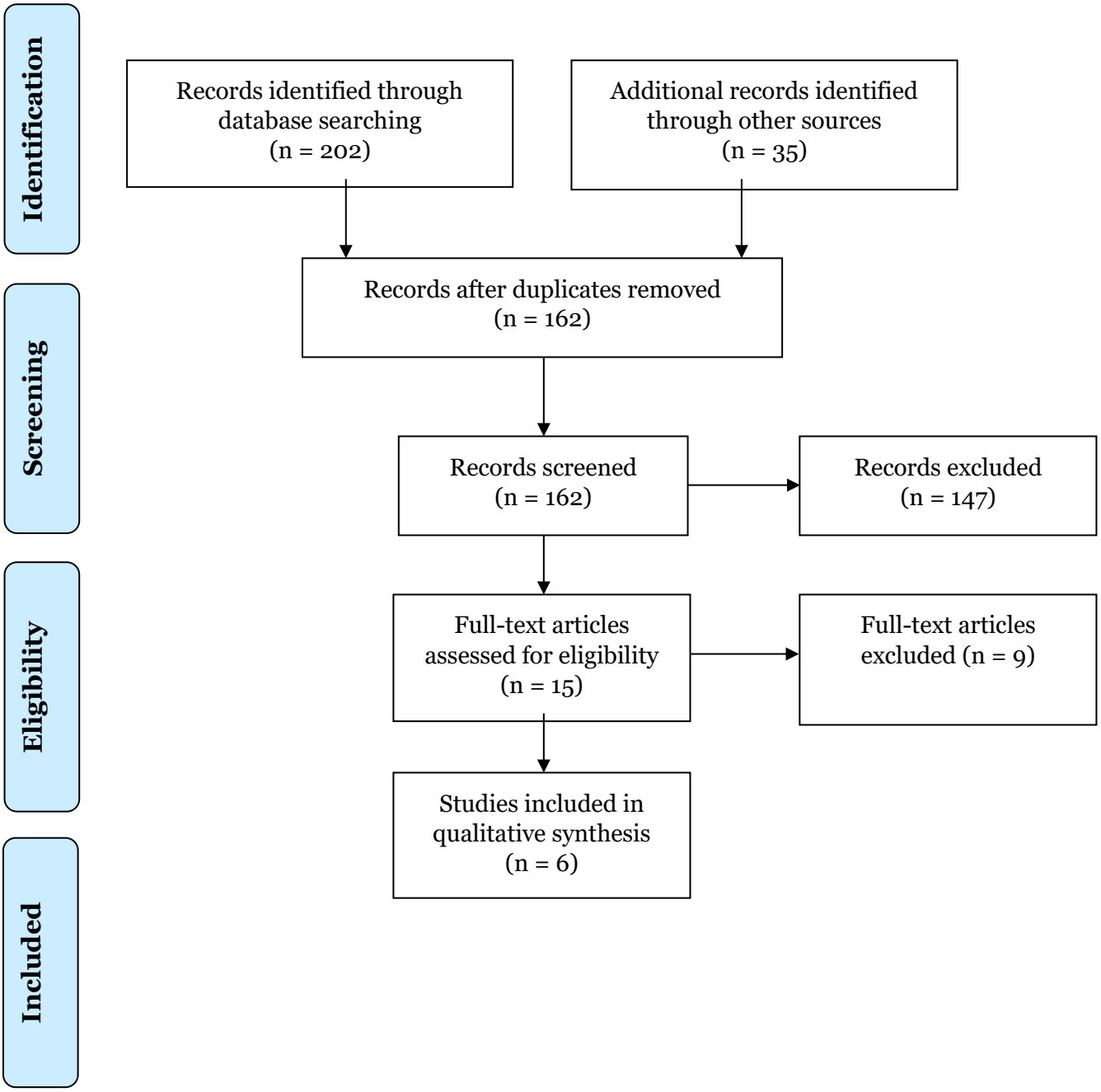
Studies with human subjects were included if participants 1) is of age 18 and upwards, 2) diagnosed with major depressive disorder or bipolar disorder (depressive state) defined by DSM-V, 3) had failed adequate response to at least two antidepressants, i.e., meet criteria for treatment-resistant depression (even if not referred to as TRD). Studies must also assess the effect of single IV Ketamine sub-anaesthetic dose (≈ 0,5 mg/kg of total body weight). Articles were included regardless of the primary and secondary outcome, as long as depression rates were measured at baseline and post-infusion, assessed by MADRS (Montgomery & Åsberg, 1979), BDI (Beck, Steer, & Brown1996), or HDRS (Hamilton, 1960). Studies using Ketamine in adjunction with other drugs or therapy were excluded. However, studies that did not conduct a washout (i.e., participants remained on a stable dosage of antidepressant) were included. Further, studies that were not placebo-controlled or double-blinded were excluded.

Data extraction

Data will be extracted regarding 1) study design, 2) sample size, 3) whether the study used an active control, 4) if a wash-out was assessed, 5) what scale was assessed, 6) response rate for both Ketamine group and control group, 7) the effect size if available, and 8) pre- and post-infusion depression scores.

Figure 2

PRISMA Flowchart of study selection (Moher et al., 2009)



Results

Studies Characteristics & Participants

Six studies were included in the systematic review (Berman et al., 2000; Chen et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Sos et al., 2013; Zarate et al., 2006; Table 1), all randomised in a double-blind manner, and placebo controlled. Two of the studies were parallel armed (Chen et al., 2018; Murrough et al., 2013), while the rest was conducted cross-over. In three of the studies, a washout of antidepressant medication was conducted (Berman

et al., 2000; Murrough et al., 2013; Zarate et al., 2006) where participants had to be drug-free for at least two weeks up until the initial trial. In two studies, participants remained on a stable dosage of antidepressants (Phillips et al., 2019; Sos et al., 2013), while one did not provide an answer regarding washout (Chen et al., 2018). The number of participants ranged from 9 to 73. While Chen et al., (2018) consists of 71 participants, 23 participants are in 0.2 mg/kg group.

All of the participants enrolled in the included studies were diagnosed with MDD and between ages 18 and 80 and the majority were female (Berman et al., 2000; Chen et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Sos et al., 2013; Zarate et al., 2006). Two of the studies recruited in-patients (Sos et al., 2013; Zarate et al., 2006).

Materials and Evaluation

All studies but one used a single IV Ketamine dose of 0.5 mg/kg over 40 minutes (Berman et al., 2000; Chen et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Zarate et al., 2006). Sos et al., (2013) administered 0.54 mg/kg over 30 minutes. Two of the studies used an active control (Midazolam; Murrough et al., 2013; Phillips et al., 2019), which mimics the psychomimetic effects of Ketamine. The rest used normal saline, containing no mind-altering effects. Four of the studies used MADRS as the scale for measuring depressive symptoms (Chen et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Sos et al., 2013), the remaining three used HDRS.

All studies measured depressive scores at baseline and post-infusion (Table 2). Murrough et al. (2013) and Phillips et al. (2019) assessed depressive symptoms at 24 hours, Zarate et al. (2006) at 24 hours and seven days, Berman et al. (2000) at three days, and Sos et al. (2013) at one, four and seven days. Chen et al. (2018) provided no clear answer at what time the measure was assessed.

Clinical Response

Regardless of the depression scale assessed, all studies but one defined clinical response as a decrease of 50% or more (Chen et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Sos et al., 2013; Zarate et al., 2006). Berman et al. (2000) used HDRS and did not assess clinical response but presented participants displaying a decrease of 50% or more on the scale.

Berman et al. (2000) and Zarate et al. (2006) used HDRS (Table 1). Berman et al. (2000) presented that 50% of participants displayed a 50% decrease in depression score for Ketamine group, and 12.5% for placebo group, at 72 hours. An effect size for the study was obtained from Marcantoni et al. (2020) of 0.93. Zarate et al. (2006) presented a response rate for the Ketamine group of 71%, and for placebo group 0%, at 24 hours. The study also provided an effect size of 1.46 at 24 hours and 0.68 at seven days.

Murrough et al. (2013), Phillips et al. (2019), Chen et al. (2018) and Sos et al. (2013) used MADRS (Table 1). Murrough et al. (2013) and Phillips et al. (2019) assessed MADRS scores at 24 hours, with 64% and 27% respectively of participants in the Ketamine groups clinically responding, and 28% and 0% respectively responding in the placebo groups. Murrough et al. (2013) provided an effect size of 0.81 at 24 hours. Chen et al. (2018) provided no clear endpoint for the MADRS measure but presented a response rate of 45.8% for the Ketamine group and 12.5% for the placebo group. Sos et al. (2013) assessed MADRS scores at day one, day four, and at day seven. In the Ketamine group, 37% responded at day one, 40.7% at day four, and 37% at day seven, compared to the placebo group, where 3.7% at day one, 3.7% at day four, and 11.1% met the criteria for clinical response. There was an effect size of 0.62 on day one, 0.57 on day four, and 0.44 on day seven.

Depression Scores

Changes in depression scores (assessed by either HDRS or MADRS) were available for all articles (Berman et al., 2000; Chen et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Sos et al., 2013; Zarate et al., 2006). The baseline scores and changes in depression scores are presented in Table 2.

Berman et al. (2000) presents a baseline HDRS score for Ketamine group of 33.0 and for placebo group 26.9., and a mean decrease of 14 points at endpoint (day three) for Ketamine group, and a mean decrease of zero points for placebo group.

Chen et al. (2018) presents a baseline MADRS score of 33.96 for Ketamine group and 34.96 for placebo group. At 40 minutes a decrease of 10.04 points is attained, at 80 minutes 11.21, at 120 minutes 12.25, at 240 minutes 13.5, at day two 13.67, at day three 11.54, at day four 11.63, at day five 11.96, at day six 10.58, and at day seven 9.54 for Ketamine group. For placebo group at 40 minutes 3.37, at 80 minutes 4.58, at 120 minutes 5.83, at 240 minutes 5.63, at day two 6.67, at day three 6.04, at day four 6.54, at day five 5.21, at day six 5.75, and at day seven 4.38.

Murrough et al. (2013) obtains a baseline MADRS score of 32.6 for Ketamine group and 31.1 for placebo group. A new mean score post infusion 14.76 is shown for Ketamine group, and 22.2 for placebo group.

In Phillips et al. (2019), the group receiving Ketamine first had a baseline MADRS score of 34.6, and the group receiving placebo first had a baseline score of 35.4. After receiving Ketamine, a mean decrease of 10.9 is presented, and after receiving placebo there was a mean decrease of 2.8 points.

Sos et al. (2013) presents a baseline MADRS score of 20.4 for the group receiving Ketamine first, and 24.6 for those receiving placebo first. The mean decrease of points was 5.7 for day one, 4.7 for day four, and 4.0 for day seven.

In Zarate et al. (2006) a baseline HDRS score of 24.9 was obtained for the group receiving Ketamine first, and 24.4 for the group receiving placebo first. Post infusion there was a mean decrease of 56.2 % after receiving Ketamine, and 9.8 % after receiving placebo.

Table 1

Summary of results obtained from included studies.

Article	Study design	N of participants (N of females)	Mean age (SD)	Active control	Wash-out	Outcome measure	Response rate % Ketamine	Response rate % placebo	Effect size
Berman et al., 2000	Randomized, double-blind, controlled, cross-over	N=9 (5)	37 (10)	No	Yes	HDRS	Day 3=50	Day 3=12.5	Day 3=0.93
Chen et al., 2018	Randomized, double-blind, controlled	N=71 (Ket group 21 of 24, Pla group 15 of 24)	Ket group 48.46 (11.01), Pla group 48.63 (8.12)	No	NA	MADRS	NA=45.8	NA=12.5	NA
Murrough et al., 2013	Randomized, double-blind, controlled	N=72 (Ket group 26/47, Pla group 11/25)	Ket group 46.9 (12.8), Pla group 42.7 (11.6)	Yes	Yes	MADRS	24 h=64	24h=28	24 h=0.81
Phillips et al., 2019	Randomized, double-blind, controlled, cross-over	N=41 (24)	41.7 (12.3)	Yes	No	MADRS	24 h=27	24 h=0	NA
Sos et al., 2013	Randomized, double-blind, controlled, cross-over	N=30 (K-P 6 of 11, P-K 9 of 19)	K-P 42.2 (15.1), P-K 44.6 (10.9)	No	No	MADRS	Day 1=37 Day 4=40.7 Day 7=37	Day 1=3.7 Day 4=3.7 Day 7=11.1	Day 1=0.62 Day 4=0.57 Day 7=0.44
Zarate et al., 2006	Randomized, double-blind, controlled, cross-over	N=18 (12)	46.7 (11.2)	No	Yes	HDRS	24 h=71	24 h=0	24 h=1.46 Day 7=0.68

Note. Ket=Ketamine, Pla=Placebo, K-P=Ketamine received first in cross-over study, P-K received first in cross-over study. Scales used as outcome measures assesses the participants severity of depression. HDRS=Hamilton Depression Rating Scale, MADRS=Montgomery-Åsberg Depression Rating Scale, NA=not applicable

Table 2.

Changes in depression scores.

Article	Scale	Baseline score (SD)	Score response Ketamine (SD)	Score response placebo (SD)
Berman et al., 2000	HDRS	Ketamine=33.0 (6.7) Placebo=26.9 (55.8)	Mean decrease day 3=14 points (10)	Mean decrease day 3=0 points (12)
Chen et al., 2018	MADRS	Ketamine=33.96 (7.35) Placebo=34.96 (4.86)	Mean decrease points 40 min=10.04 (9.47) 80 min=11.21 (10.67) 120 min=12.25 (10.69) 240 min=13.54 (10.14) Day 2=13.67 (9.49) Day 3=11.54 (9.78) Day 4=11.63 (10.20) Day 5=11.96 (9.90) Day 6=10.58 (10.18) Day 7=9.54 (9.29)	Mean decrease points 40 min=3.37 (4.75) 80 min=4.58 (4.97) 120 min=5.83 (5.07) 240 min=5.63 (5.42) Day 2=6.67 (7.36) Day 3=6.04 (6.02) Day 4=6.54 (6.26) Day 5=5.21 (5.31) Day 6=5.75 (6.71) Day 7=4.38 (5.93)
Murrough et al., 2013	MADRS	Ketamine=32.6 (6.1) Placebo=31.1 (5.6)	Mean score 14.77 points	Mean score 22.72 points
Phillips et al., 2019	MADRS	K-P=34.6 (4.1) P-K=35.4 (5.6)	Mean decrease 10.9 points (8.9)	Mean decrease 2.8 points (3.6)
Sos et al., 2013	MADRS	K-P=20.4 (4.7) P-K=24.6 (4.8)	Mean decrease points Day 1=5.7 Day 4=4.7 Day 7=4.0	NA
Zarate et al., 2006	HDRS	K-P=24.9 (6.9) P-K=24.4 (6.9)	Mean decrease 56.2% (20.4%)	Mean decrease 9.8% (20.1%)

Note. Changes in depression scores for every study at set time points for the Ketamine group and placebo group. With HDRS, a score of 0-7 indicates no depression present (clinical remission), and a score above 20 indicates moderately severe depression. With MADRS, a score between 0-6 indicates no depression, 7-19 mild, 20-34 medium, and 35-60 severe depression. Score changes are presented in mean decrease (points or percentage) or the new mean score for the different studies.

Discussion

This systematic review assessed whether a single infusion of IV NMDA receptor antagonist Ketamine is effective for reducing MDD symptoms in patients with TRD. The presented studies suggest that Ketamine as an antidepressant is superior to placebo interventions, with one study (Chen et al., 2018) observing an effect as early as 40 minutes post-infusion. These results are in line with previously published systematic reviews (e.g., Coyle & Laws, 2015; McGirr et al., 2015).

Four of the studies provided effect sizes for their set endpoints. Although the effect sizes at different time points provided vary across studies, they are all significant and indicate a medium to large effect after one week. The endpoints set for the studies included in this systematic review range from 24 hours to seven days. The two studies providing effects sizes at both of those time points indicate a larger effect at 24 hours, compared to day seven.

Notably, the effect sizes Zarate et al. (2006) and Berman et al. (2000) stands out compared to the other studies, with significantly greater effects. This may in part be due to their use of HDRS, while the rest of the included studies used MADRS. A comparison (Carmody et al., 2006) has suggested that MADRS is twice as accurate for measuring depressive symptoms compared to HDRS. However, another meta-analysis (Heo et al., 2007) came to the conclusion that the two scales are comparable in depressed elderly. Further, Zarate et al. (2006) and Berman et al. (2000) also had smaller samples, nine and 18 respectively, compared to the other included studies with samples sizes between 27 and 73. It has been suggested that effect sizes of small sample sizes may not reflect the actual effect (Button et al., 2013).

Further, the use of different scales makes it difficult to compare changes in depression scores where an effect size is not available. In addition, the different studies present their scores in various manners, with a mean decrease in scores, a mean decrease in percentage, and a mean score post-infusion. A standardised protocol for studies testing IV Ketamine's efficacy with scales, endpoints and presentation would make it possible to conclude the efficacy more accurately.

Four of the studies assessed Ketamine's effect in a cross-over design (Berman et al., 2000; Phillips et al., 2019; Sos et al., 2013; Zarate et al., 2006). Two of these studies did not report any carry-over effects (Berman et al., 2000; Sos et al., 2013). However, in two of the studies, carry-over effects were reported (Phillips et al., 2019; Zarate et al., 2006). In both of these, it was observed that those receiving Ketamine first and placebo second had slightly lower pre-infusion scores at their second infusion. There could be a possibility that the participants were "breaking blind" since the Ketamine infusion induce a subjective experience that normal saline (placebo) does not, meaning that there would be a significant difference in experience.

One way to limit the risk of unblinding is using an active placebo (Moncrieff et al., 1998), mimicking the symptoms of the drug being tested. Two of the studies in this review used Midazolam as a control, tightening the gap in subjective experience difference.

This systematic review solely contains studies testing a single infusion of 0.5 mg/kg. Studies administering different dosages have been published and indicate 0.5 mg to be most effective (e.g., Chen et al., 2018). However, studies administering multiple infusions, e.g., twice or thrice weekly, provide greater effect sizes and higher response and remission rates than those with a single dose (Marcantoni et al., 2020). Although it is not unusual for medications to give a greater effect when repeated or with a heightened dosage, the studies administering multiple infusions seldom assess a blinded, controlled design, which could result in a placebo effect causing the significant results.

While the studies investigating multiple infusions show a prolonged relapse compared to a single infusion (Marcantoni et al., 2020), more studies investigating longitudinal antidepressant effects of Ketamine are needed. In Murrough et al. (2013), out of the patients who showed response to a single infusion at day seven, almost half of the patients had not experienced relapsed at day 25. Further, there is a need for research regarding how to sustain the effect most effectively. Phillips et al. (2019) let participants who met response criteria following repeated infusions reduce infusion rate to once weekly for four weeks, and results suggest that 91% of participants maintained antidepressant response criteria throughout the maintenance infusions.

Because of the short-lived effectiveness of a single dose of Ketamine, there is concern regarding the risk of multiple infusions. With numerous infusions over time, there is an increased risk of abuse. Not only because of Ketamine's addictive properties (Liu et al., 2016) but also because of the vulnerability of its target population. Therapies preventing addiction has to be researched, along with safe maintenance infusion schemes. However, Ketamine has been safely administered as an analgesic agent for decades, and treatments of published research contain only subanaesthetic doses.

Although IV Ketamine has been shown to be the most effective compared to e.g., intranasally administered Ketamine, the procedure of going to a specialised clinic having the infusion administered by a nurse or doctor brings about concerns. It is time-consuming, and there is a need for taking days off work, expenses of transportation, and as is the case in the U. S, the treatment itself costs a lot, not being covered by insurance (Ketamine, 2020). Other alternatives like a nasal spray or taking Ketamine orally has been proposed. Nevertheless, the bioavailability of these is limited, intranasally 25-50% (Lapidus et al., 2014) and orally 20% (Yanagihara et al., 2003) compared to IV, and therefore do not contain an as immense effect. The FDA (2019) approved Spravato is administered intranasally but still require supervision

by certified personnel. The adverse impact of Ketamine, such as psychotomimetic actions, constitute difficulty in being able to take the medication from home.

Research has tried to eliminate the psychotomimetic effects, which could be an alternative to possibly take Ketamine out of clinic (Masuzawa et al., 2003). However, one theory as to why Ketamine holds its antidepressant mechanism is because of its dissociative effects. There is a limited research on this topic published, and most available does not show a significant effect (e.g., Valentine et al., 2011; Berman et al., 2000). Nevertheless, studies on alternative NMDA receptor antagonists, such as memantine, known not to contain the dissociative effects, does not induce the same antidepressant effect as Ketamine (Gideons et al., 2014). Further, in studies on LSD and in psilocybin-assisted therapy, the participant is subjected to a different kind of subjective experience, which may be needed for the participant to experience a reduction in depressive symptoms (Carhart-Harris & Goodwin, 2017).

Ketamine has been proposed to be a candidate for antidepressant in hospice care by means of its rapid onset. In one study, it was taken orally, and improved patients' mood and a significant reduction in depressive symptoms were observed (Irwin et al., 2013). Not only does this shed some hope on the possibility of orally administering Ketamine, but it gives hope for patients in need of a fast-acting antidepressant.

Limitations

A few limitations of this review need to be mentioned. Firstly, the search process was not assessed by a second opinion. The selection of search string and selection of studies depended on the authors' knowledge. Boolean operators might have caused the literature search too limited, e.g., using a more open term for MDD would have opened up to studies using alternative terms. Secondly, the number of selected studies for the systematic review was limited. Further, the included studies all assessed different endpoints, making it difficult to compare and get enough results for the different times with the limited numbers of studies. Third, the review could have benefitted from revising the inclusion criteria after an initial search. Not being restricted to single infusions could have further the number of studies and present a more accurate answer to Ketamine's true effect on MDD.

Depression typically co-occur with other mental disorders, such as anxiety or social phobia. These additional disorders may alter the effect of Ketamine on depression, either by inhibiting the antidepressant effect, or enhancing it. Although the studies included in this review excluded participants with certain disorder it may be unknown to the participant that another disorder is present. This may indeed affect the results of this review.

Societal and Ethical Aspects

In many countries the look on drugs is political and socially driven. There is an assumption that the use of drugs (both recreationally and medically) is solely dangerous and

opens up a path for abuse. Although there is a need for some kind of judicial regulation, as with alcohol, this societal consensus may hinder the progression of research; resistance leads to less funding and even laws making it illegal to study. For instance, psychedelic drugs, known for their recreational purpose, have been put forward as potential therapeutics for different psychiatric disorders, and research indicates their efficiency (Carhart-Harris & Goodwin, 2017). Focusing on the potential of these substances would create possible potential of medication and treatments, subsequently furthering the research knowledge regarding many conditions and diseases.

As mentioned above, the look on Ketamine as a drug could be considered problematic. In addition, depression and other psychiatric disorders is still stigmatised, and some may experience difficulties in receiving support e.g., from their workplace. These two occurrences combined could make it difficult to receive e.g., time of to go get the treatment.

Future Research

Ketamine surely is on the verge as a prominent antidepressant; however, some aspects and challenges aforementioned needs to be considered for future research to evaluate the effect further. Ketamine's antidepressant mechanism of action is yet to be fully discovered, with many processes involved that are poorly understood and needs more research. There is a need for more randomised, controlled studies. Studies including an active placebo such as Midazolam and keeping the study blind are of particular importance in order to receive a correct effects size. Because of Ketamine's psychoactive properties, an inactive placebo serves little purpose. For participants who is familiar with the acute psychoactive effects, a placebo resembling Ketamine to a greater extent than Midazolam is needed, especially for longitudinal studies to remain blind. There should also be of focus to compare studies conducting a wash-out of antidepressants and those which have participants remain on a stable dosage, to explore the possibility of the antidepressants ability to perhaps enhance, or decrease, the antidepressant effect of Ketamine.

Animal studies have shown that sensitisation follow prolonged use of Ketamine (Trujillo et al., 2008). Therefore, the risk of abuse needs to be addressed for Ketamine's addictive properties and vulnerable target population, as well as long-term adverse effect beyond the infusion period. Longitudinal studies must also be of interest regarding the sustainability of Ketamine's prominent acute antidepressant effect. This review shows promising results for Ketamine, but finding a protocol for sustaining would increase and prolong the response and decrease the relapse rate (Marcantoni et al., 2020). The frequency of infusions, adjunctive medication, and risk of abuse should all be considered in future research.

Most, if not all studies regarding Ketamine's antidepressant effect focus on participants with severe depression or TRD. One could argue that it would be beneficial both

for the society in terms of costs and a need for increased work force, and personally for patients to be able to receive antidepressant treatment early in the diagnosis, countering chronification of depression. Nevertheless, it is of importance to accurately choose the sample with caution to find the correct treatment for a certain population. There should also be a focus on sub-diagnosis within MDD, since the antidepressant effect might affect different diagnosis.

Conclusion

Because of the unstable effects of modern antidepressants, novel therapies are needed to treat MDD, especially TRD. Ketamine has been shown to have an antidepressant effect in subanaesthetic doses. Studies included in this systematic review are in line with previously published reviews; a large effect was observed at 24 hours, and a moderate to large effect was observed at seven days. Clinical response was met in around 50% of participants in all studies but one. More research is needed regarding how to sustain the dramatic acute effect, and longitudinal studies must investigate potential abuse and take adverse effects into consideration when further developing Ketamine as a therapy.

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Appendix A

Example of questions included in HDRS.

DEPRESSED MOOD (sadness, hopeless, helpless, worthless)

0 Absent.

1 These feeling states indicated only on questioning.

2 These feeling states spontaneously reported verbally.

3 Communicates feeling states non-verbally, i.e., through facial expression, posture, voice and tendency to weep.

4 Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

WORK AND ACTIVITIES

0 No difficulty.

1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.

2 Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).

3 Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.

4 Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

Appendix B

Example of questions included in MADRS.

Apparent sadness Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.

2 Looks dispirited but does brighten up without difficulty.

4 Appears sad and unhappy most of the time.

6 Looks miserable all the time. Extremely despondent.

Inability to feel Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.

2 Reduced ability to enjoy usual interests.

4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.

6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.