Bachelor Degree Project

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KETAMINE FOR DEPRESSION

The role of dissociative effects

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Abstract

Several trials have reported rapid antidepressant response from the anesthetic drug ketamine although the mechanism behind this effect is not fully understood. Research has focused mainly on ketamine's action in the brain, including its effects on chemical balance, connections between brain cells and networks, and cognition. Trials with psychedelic drugs have had similar antidepressant results as ketamine, and the quality of the subjective psychedelic experience seems to mediate antidepressant action. Ketamine causes similar alterations of consciousness, which have been viewed as side effects. This thesis examines whether ketamine works in a similar way as psychedelics, where the ketamine-induced dissociative-like experience has a relationship to antidepressant response. Leading theories of depression and ketamine's action in the brain are presented, and eight studies examining the relationship between ketamine-induced subjective experience and antidepressant response are reviewed. Three included studies found a relationship between psychedelic- and dissociative-like symptoms and reduction in depression, while five did not. The supposed relationship between psychedelic- and dissociative-like symptoms and antidepressant action has not been adequately explored and needs further examination in clinical trials.

Keywords: antidepressant, depression, dissociation, ketamine, major depressive disorder, NMDA receptor antagonist, placebo, psychedelics

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Introduction

It may be the modern world's greatest paradox: for all our material wealth, long lives, and personal freedoms, many of us are deeply unhappy. Indeed, depression is the leading cause of disability worldwide (Friedrich, 2017) and the most common psychiatric disorder in developed countries (Wittchen et al., 2011). Globally, about 264 million people are diagnosed with depression (World Health Organization, 2020).

There are several depressive disorders, but the most common is Major Depressive Disorder (MDD). MDD is usually treated with psychotherapy and antidepressant medicines, though about one third of patients do not respond to these treatments. The traditional antidepressant drugs have several other limitations, including a delayed effect that can take weeks or months, serious side effects (Kirsch, 2014), and patients receiving several different medications before finding one that works for them (Gaynes et al., 2009). However, an unlikely new treatment presents a promising alternative.

In recent years, ketamine – an anesthetic drug– has emerged as an effective antidepressant when used in small doses. Where traditional antidepressants take weeks to show effects, ketamine works in hours. Small scale studies have continually shown transient clinical improvements for patients that had been considered resistant to treatment (Rot, Zarate, Charney & Mathew, 2012). Yet, researchers still do not fully understand the mechanism behind ketamine's antidepressant action. Leading hypotheses include increased release of glutamate neurotransmitters, new connections between brain cells, and stimulation of reward processing areas (Rot et al., 2012).

Researchers have long known that ketamine gives rise to curious perceptual effects. These vary but often involve detachment from reality. In this way, they resemble the psychological phenomenon of dissociation, and hence ketamine is described as a "dissociative hallucinogen."

While several researchers have asked whether the dissociative subjective experiences are related to antidepressant outcomes (Luckenbaugh et al., 2014; Sos et al., 2013; Walter, Li & Demenescu, 2014), few studies have looked into this possibility. Meanwhile, studies on addiction have found that high-dose ketamine induces altered states of consciousness with transformative significance, which helps patients abstain from substance abuse (Krupitsky et al., 2002; Krupitsky & Grinenko, 1997). Similarly, trials on psychedelic drugs such as lysergic acid diethylamide (LSD) and psilocybin have shown antidepressant results. Several of these studies suggest that the quality of the subjective psychedelic experience predicts antidepressant response (Carhart-Harris et al., 2012; Griffiths, Richards, Johnson, Mccann, & Jesse, 2008; Ross et al., 2016).

Aim, Structure and Method

This thesis asks whether the ketamine-induced dissociative experience is related to antidepressant outcomes. It aims to answer that question by investigating the available literature on the subject. First, depression and ketamine will be characterized. Next, ketamine's efficacy in depression treatment will be presented. This is followed by an account of the current leading theories of ketamine's antidepressant effects, and a review of eight published studies that have measured ketamine's psychoactive effects for patients with MDD. The thesis closes with a discussion of results from the literature review, suggestions for further research, and conclusions.

I have set the following limits for the work: included studies must have evaluated the effects of ketamine on both the antidepressant and subjective psychoactive response in patients with MDD, using standardized scales. Within these limits, I will review the literature, compile results, and interpret the findings.

Depression

It seems humankind has been susceptible to depression for millennia. The ancient Greek physician Hippocrates described “melancholia” around 2 400 years ago, with symptoms including fear and sadness (Telles-Correia & Marques, 2015). Today, clinicians diagnose depression according to criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2017).

The DSM-5 lists several depressive disorders, all classified as mood disorders. They include a highly variable set of symptoms. For example, both insomnia or hypersomnia, and weight loss or weight gain can be signs of a depressive disorder. Therefore, depression should be viewed as a wide-ranging syndrome with many distinct causes and effects, rather than one single disease (Nestler et al., 2002).

Major depressive disorder (MDD) is the most common depressive disorder, as it affects 16.2 % of the population at some point (Kessler et al., 2003). The criteria for diagnosis are that a certain number of symptoms need to be present for longer than two weeks, and their severity needs to impact social and work-related functioning (APA, 2017). Symptoms of MDD include feelings of sadness, hopelessness, low energy, and an inability to experience pleasure (anhedonia) (Morrison, 2017).

Globally, 264 million people have a depressive disorder (World Health Organization, 2020). According to Gotlib (2015), depression plays a role in more than half of all suicide attempts. Hence, clinical depression has potentially devastating consequences. Not only do the afflicted and their loved ones suffer, but the economic costs for health care, work absence, and productivity loss are colossal (Sobocki, Jönsson, Angst, & Rehnberg, 2006).

The most common treatments for MDD are psychotherapy and antidepressant drugs. These antidepressant drugs primarily act on the brain’s monoaminergic system. While helpful in many cases, they have considerable limitations. On average, their therapeutic effects

emerge at 6-8 weeks, and they frequently cause serious side effects (Kirsch, 2014). Only one-third of patients achieve symptom remission from their first medication (Gaynes et al., 2009), and many who improve will later relapse into depression (Rush et al., 2006).

Moreover, about one-third of patients do not respond to any current antidepressant treatments, including psychotherapy (Gaynes et al., 2009). These patients have treatment-resistant depression (TRD). TRD patients generally fall into depression earlier and have a higher suicide risk than other depressive patients (Conway et al., 2015).

Theories of depression

Today, as in ancient times, the origin of depression is poorly understood. Hippocrates thought it came from an excess of black bile in the body (Telles-Correia & Marques, 2015). A standard modern view is that interactions between genes and environment cause depression (Kendler et al., 2010). While twin studies have found a heritable component to depression (33% genetic risk in MDD patients), researchers have found no specific risk-increasing genes. Emotional trauma, disease, and stress-related issues are some environmental factors that increase the risk for MDD (Fava & Kendler, 2000).

Neuroscientists look for the basis of depression in the brain. Many theories attempt to explain depressive disorders, often focusing on different levels of neuroscientific description (Beck, 2008; Delgado, 2000; Hammen, 2005; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Hence, these theories are not necessarily mutually exclusive. Some of the most widespread neuroscientific views of depression will follow below.

Neurochemical deficiencies

A widespread belief is that chemical imbalances in the brain cause depression (Delgado, 2000). These chemicals are neurotransmitters which brain cells use to communicate. Specifically, this theory claims that there is a deficiency of serotonin (5-HT), norepinephrine (NA), and/or dopamine (DA) in the synapses of the brain. All these belong to

the monoamine class of neurotransmitters. Consequently, this is called the monoamine hypothesis (Hirschfeld, 2000).

Indeed, drug treatments that raise monoamine levels in the synaptic clefts have shown antidepressant effects (Delgado, 2000). However, it is unclear why a sizeable minority of depressive people do not respond to monoaminergic drugs, nor why they take several weeks to show effects when they cause a rapid increase in monoamine availability (Hirschfeld, 2000). Also, a meta-analysis found that experimentally lowering monoamine levels does not affect the mood of healthy volunteers without a depressive past (Ruhé, Mason, & Schene, 2007). The authors conclude that the evidence does not support a direct causal relationship between monoamine systems and MDD (Ruhé et al, 2007).

Other neurochemical imbalances may also be related to depression, such as deficits to the gamma-aminobutyric acid (GABA) system (Croarkin, Levinson, & Daskalakis, 2011; Sanacora, 2010) and the glutamate system (Sanacora, Zarate, Krystal, & Manji, 2008). Cowen (2015) and Sanacora et al. (1999) report of decreased GABA levels in the occipital cortex and anterior cingulate cortex of depressed patients. Depressed patients have also had abnormal levels of glutamate in their brain tissue, cerebrospinal fluid, and blood plasma (Sanacora et al., 2008). Additionally, there have been reports of decreased glutamate in the anterior brain regions of depressed people (Cowen, 2015; Yüksel & Öngür, 2010).

Reduced neuroplasticity

Neuroplasticity refers to the brain's ability to change with learning. The neuroplasticity theory posits that depression involves dysfunction with this process. Exposure to stress is a well-known mediator of depression and has been shown to cause atrophy and cell death of synapses and neurons (Hammen, 2005). Notably, acute stress reduces the production of cells in the dentate gyrus of the hippocampus (Gould, Tanapat, Rydel, & Hastings, 2000). The hippocampus is one of the few brain regions in adult animals where new neurons are born

(Ota & Duman, 2012). Brain imaging studies have found volume loss in the hippocampus of depressed patients (Sheline, 2000), and decreased volume, numbers of neurons and glial cells in the subgenual prefrontal cortex (Drevets, 2000).

Depressive symptoms have also been linked with a decreased output of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB). BDNF is a protein that activates genes that protect neurons from cell death and atrophy, and stimulates neurogenesis. Post mortem examinations of depressed people's brains have revealed decreased BDNF levels in cortical and hippocampal regions compared to controls (Ota & Duman, 2012). Low levels of BDNF are thought to affect neuroplasticity, leading to the emergence of depressive symptoms. Both NA and 5-HT affect BDNF, which indicates that BDNF has a functional role in antidepressant drugs (Castrén & Rantamäki, 2010).

Abnormal neural connectivity

Kaiser et al. (2015) suggested that abnormal connections in and between brain networks can explain depression. Indeed, specific brain regions display higher levels of activity during resting states than when performing cognitively challenging tasks. These regions (medial prefrontal cortex, posterior cingulate cortex, anterior cingulate cortex, and inferior parietal lobule) have been dubbed the default mode network (DMN) (Raichle, 2015).

The DMN is thought to be active in mind-wandering and rumination. The active DMN disengages an individual from the external world and here-and-now, turning attention to inward discursive thought (Andrews-Hanna, Reidler, Huang, & Buckner, 2010). Depressive patients show no decrease in DMN activity when faced with external stimuli, and a more active DMN is correlated with depressive rumination as well as maladaptive thought-loops (Scheidegger et al., 2012).

A literature review of neuroimaging for MDD patients found that resting-state functional connectivity was altered in the DMN, along with several other networks. The study

found increased connectivity within the anterior DMN, increased connectivity between the anterior DMN and the salience network (SN), changed connectivity between the anterior and the posterior DMN, as well as decreased connectivity between the posterior DMN and the central executive network (CEN) (Mulders, Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). The SN represents the brain's function during emotional processes and mainly consists of the anterior insula and dorsal anterior cingulate cortex, while the CEN represents cognition and includes the dorsolateral prefrontal cortex and posterior parietal cortex. Both of these processes have shown abnormalities in MDD patients (Mulders et al., 2015).

Maladaptive cognition

The cognitive theory of depression states that negative biases in cognition and dysfunctional attitudes cause depression (Beck, 2008). Studies investigating the matter have indeed found abnormal information processing in both basic cognitive domains (e. g. attention, memory, and perception) and high-level constructs (dysfunctional attitudes towards the self, world, and future) in depressive patients (Beck, 2008; Elliott, Zahn, Deakin, & Anderson, 2010; Roiser & Sahakian, 2016).

There is a distinction between emotion-independent and emotion-dependent cognitive anomalies in depression (Roiser, Elliott, & Sahakian, 2011). Emotion-independent abnormalities are a reliable finding in depressive disorders, and result in deficits of attention, executive function, and memory (Roiser & Sahakian, 2016). Emotion-dependent abnormalities come in two variations: negative biases in emotional processing (Roiser & Sahakian, 2016), and diminished processing of reward and punishment (Eshel & Roiser, 2010). For example, tests asking the subject to distinguish types of emotional faces can reveal negative bias in emotional processing. The same negative bias is evident in both the depressed and those at risk for developing depression. Relatives of depressed patients (Masurier, Cowen, & Harmer, 2006), and people with certain at-risk personality traits (Chan, Goodwin,

& Harmer, 2007) have displayed this type of bias. Eshel and Roiser (2010) reported learning impairments based on reward and punishment in MDD patients. Patients with depression have shown heightened sensitivity to negative feedback and low sensitivity to positive feedback (Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997; Henriques & Davidson, 2000). In 2016, Roiser and Sahakian wrote that impaired processing of reward and punishment might be relevant to understand anhedonia in depression.

Ketamine

Ketamine was developed as an anesthetic and patented in 1963 (Chang, Rajagopalan, & Zarate, 2016)(see Figure 1). It lacks the negative effects on the respiratory and circulatory system of other anesthetics, making it a practical option when life-support machines are unavailable or when the patient has a heart condition. It is usually administered through veins, muscles, or into the nasal cavity. Ketamine in sub-anesthetic doses is effective for pain relief - notably for cancer pain, phantom limb pain, and fibromyalgia (Visser & Schug, 2006). For its wide-ranging clinical utility, ketamine is on the W.H.O. Model List of Essential Medicines (World Health Organization, 2020), a register of the most important and safe drugs in a health system.

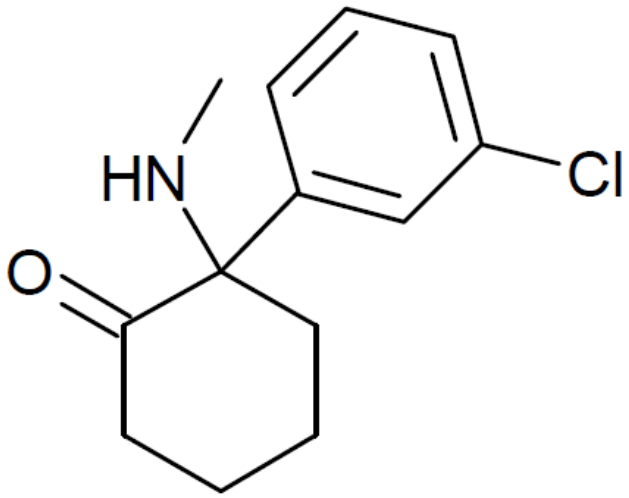

Figure 1. The chemical structure of ketamine. (Wikimedia Commons, 2017.)

As it spread through the medical world in the 1970s, people started to use ketamine recreationally (Chang et al., 2016). In sub-anesthetic doses, it can produce psychoactive effects, causing changes to mood, perception and behaviour (Muetzelfeldt et al., 2008). Symptoms that were considered side-effects in a medical context became sought-after experiences in illicit use (Chang et al., 2016). Ketamine's physically addictive properties are largely unknown. It may lead to psychological dependence, as users rapidly develop tolerance to its effects (Muetzelfeldt et al., 2008). Studies with rodents have shown that ketamine affects dopamine release (Kokkinou, Ashok, & Howes, 2017). This suggests potentially addictive effects, as the dopamine system is involved in amphetamines and other drugs of abuse (Riccardi et al., 2005).

While classified as an N-Methyl-d-aspartic acid (NMDA) receptor antagonist, ketamine has rich and complex pharmacological effects. It has affinity for multiple receptors and systems in the brain, including opioid and AMPA receptors, as well as monoamine transporters (Blier & Blier, 2016). It has also shown downstream effects on brain plasticity, neurotrophic signalling (Wohleb, Gerhard, Thomas, & Duman, 2016), and functional connectivity (Scheidegger et al., 2012).

Ketamine's acute subjective effects

In sub-anesthetic doses, ketamine can produce a range of psychoactive effects, including out-of-body experiences, a felt loss of control, and visual hallucinations. Common effects of positive valence are euphoria, contentedness, and amusement. Common negative aspects of the ketamine experience include paranoia, suicidal ideation, nausea, salivation, and vomiting (Muetzelfeldt et al., 2008).

Most typically, symptoms include derealization (detachment from surroundings), depersonalization (detachment from self), and amnesia (memory loss). These symptoms are similar to states of dissociation, meaning that they involve detachment from reality. At the

doses administered in clinical trials (around 0.5mg/kg), the severity of dissociative effects is mild to moderate, and symptoms disappear within a few hours. Dissociative effects can have either positive or negative affective qualities to the subject (Niciu et al., 2018).

Ketamine as an antidepressant

Ketamine's efficacy for psychological problems was first explored in 1974 as a complement to psychotherapy for depression (Fontana, 1974). Twenty-six years later, Berman et al. (2000) published the first study on ketamine as an antidepressant in its own right. The results showed rapid and robust antidepressant effects on patients with TRD. These results stood in stark contrast to the slow reaction time of classical antidepressants, and the normal non-responsiveness of TRD patients. The publication sparked interest in ketamine's therapeutic effects.

In 2014, a meta-analysis evaluated nine randomized controlled trials totaling 192 patients with MDD and 34 with bipolar depression (Fond et al., 2014). There was a significant improvement in depression scores for ketamine as opposed to controls ($p < 0.001$). In 2015, McGirr et al. published a systematic review and meta-analysis on ketamine's efficacy in major depressive episodes. Merging data from eight randomized controlled trials and 183 patients, they found an association between ketamine administration, clinical response, and clinical remission at one, three, and seven days, compared to placebo. Patients that received ketamine had significantly higher rates of remission at 24 hours ($p < 0.001$), three days ($p < 0.01$), and seven days ($p < 0.01$) after treatment, compared to controls.

Two particular features of ketamine's antidepressant effect are unique: it occurs within hours, and it has mostly been effective for treatment-resistant depression. The response rate for TRD patients has been around 50% in studies with placebo control. The one major downside is that the effect is transient, with relapse into depression typically occurring in seven days. However, repeated ketamine administration has prolonged antidepressant

response in several studies, with no significant adverse effects (Blier & Blier, 2016). As trials consistently show positive results, ketamine has been called "a paradigm shift for depression research and treatment" (Krystal, Abdallah, Sanacora, Charney, & Duman, 2019, p. 774) and "the biggest breakthrough in depression research in a half century" (Abrams, 2012, para. 3).

Theories of ketamine's antidepressant action

A preponderance of evidence speaks to ketamine's ability to alleviate depression. Yet, the mechanism of antidepressant action is poorly understood. If that cause were to be uncovered, it could bring about a fundamental change in the conceptualization and treatment of depression. The most popular theories among researchers are presented below. Note that the theories presented are not necessarily mutually exclusive.

Neurochemical surge

Glutamate is the main excitatory neurotransmitter in the central nervous system (Chang et al., 2016). It plays a functional role in learning and memory and impacts proteins (neurotrophins) that induce the development, survival, and function of neurons. Decreased levels of glutamate have been observed in various cortical regions of MDD patients when compared with controls. These include the dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and the anterior cingulate cortex (Auer et al., 2000).

The "glutamate surge" theory posits that ketamine increases glutamate activity in the prefrontal cortex (Moghaddam, Adams, Verma, & Daly, 1997). This increase is due to inhibition of extra-synaptic NMDA receptors on inhibitory GABA-ergic interneurons. These interneurons cause activity on the pyramidal cells of the prefrontal cortex, which react by releasing glutamate (Blier & Blier, 2016). This restores the levels of this excitatory neurotransmitter to normal, correlating with the reduction of depressive symptoms.

However, neuroimaging studies have come to conflicting conclusions: one study found increased glutamate levels post ketamine infusion (Stone et al., 2012), and one did not

(Taylor, Tiangga, Mhuircheartaigh, & Cowen, 2011). Attempts at finding correlations between glutamate levels (before, during, and after infusion) and reduction in depressive symptoms failed. Moreover, other NMDA antagonists have failed to replicate ketamine's rapid and robust antidepressant effects, leading to speculation that the NMDA receptor may be a dead end (Newport et al., 2015).

Ketamine may affect other neurotransmitters as well. Williams et al. (2018) found that the opioid-blocker naltrexone prevented ketamine's antidepressant effects, and concluded that recovery from depression requires opioid system activation. Further, Nishimura et al. (1998) found that ketamine increases monoaminergic release via at least three mechanisms: inhibition of monoamine reuptake transporter, downstream effects of NMDA receptor inhibition, and binding at the monoamine receptors.

Enhanced neuroplasticity

Depression has been linked to decreased volumes of the hippocampus and prefrontal cortex due to atrophy and cell death of synapses and neurons. Low levels of the protein BDNF may hinder neuroplasticity, leading to depressive symptoms (Castrén & Rantamäki, 2010; Rang, Dale, Flower, & Henderson, 2016). The neuroplasticity hypothesis states that ketamine stimulates BDNF release by a downstream mechanism that starts with antagonism of NMDA receptor activity, glutamate transmission, and activation of AMPA receptors. This process inhibits calcium influx, which halts eukaryotic elongation factor 2 (eEF2) kinase and leads to protein translation. In turn, this activates BDNF gene transcription, initiating neurogenesis. The birth of new neurons helps rewire maladaptive connections in the depressed person's brain (Monteggia, Gideons, & Kavalali, 2013).

Disruption of functional connectivity

Ionescu et al. (2018) reviewed 47 neuroimaging studies (including both healthy and depressed subjects) and found that ketamine's most prominent effects were changes in the

subgenual anterior cingulate cortex, posterior cingulate cortex, prefrontal cortex, and hippocampus. These regions are frequently implicated in neuroimaging studies on depression.

Ketamine may reduce functional connectivity between brain regions involved in rumination, such as the pregenual anterior cingulate cortex and the dorsal posterior cingulate cortex. It also disrupts hyperconnectivity between frontal regions and DMN in MDD patients. A study on healthy subjects corroborates this finding, with decreases of DMN connectivity to other regions: the anterior cingulate cortex, dorsal nexus, medial prefrontal cortex, and posterior cingulate cortex (Scheidegger et al., 2012). Increased DMN connectivity is commonly associated with increased rumination (Bonhomme et al., 2016). Ketamine infusion causes emotional blunting, a process that may lessen depressive symptoms. Reductions in the activity of limbic structures, such as the amygdala, may decrease responses to emotional stimuli and help people shift their focus from internal depressed states toward the acute perceptual changes of ketamine (Ionescu et al., 2018).

Alterations of cognition

Ketamine alters cognition and this may alleviate depressive symptoms. Stone et al. (2010) found ketamine to impair performance in verbal self-monitoring which correlated with reduced activation in the left superior temporal cortex. A functional magnetic resonance imaging (fMRI) study by Abel et al. (2003) found that ketamine decactivated limbic regions when watching a fearful face, whereas the left superior occipital gyrus (a visual processing area) was the only significantly activated region. In contrast, the control group showed activation in the amygdala, cerebellum, and visual processing areas. Hence, ketamine may reduce limbic response to emotional stimuli, resulting in emotional blunting.

Resting-state scans have shown increased activation in neural reward areas induced by ketamine. Blood-oxygen-level-dependent (BOLD) activation increased in the cingulate gyrus, hippocampus, insula, thalamus, and midbrain, according to Stone et al. (2010). Another

BOLD study reported ketamine-induced activation in the anterior cingulate cortex, mid-posterior cingulate and paracingulate cortices, hippocampal and parahippocampal areas, bilateral insula, and thalamus of healthy subjects (Höflich, 2013). Heightened activity in these neural areas suggests that ketamine plays a role in stimulating reward processing, which is reduced in depression (Elliott et al., 1997; Henriques & Davidson, 2000).

Ketamine and the placebo effect

The placebo effect is an experienced benefit after getting an inactive substance. Kirsch (2011) argued that antidepressant drugs and treatments constitute a placebo, where the expectation of improvement creates the antidepressant effect. Given that changes to attitudes and expectancies may relieve depression, and that ketamine has noticeable psychoactive properties, a placebo effect cannot be ruled out.

Double-blind trials purport to test ketamine against an active placebo, meant to imitate ketamine's effects. Trials consistently conclude that patients receiving ketamine feel better than those who receive placebo (Fond et al., 2014; Mcgirr et al., 2015). Still, the psychoactive properties of ketamine complicate things. Patients experiencing dissociative states may realize they have received ketamine, and not the control, possibly enhancing the placebo effect from knowing they are getting "the real drug."

A common active placebo control used in ketamine studies is midazolam, a fast-acting benzodiazepine. Like ketamine, midazolam is anesthetic at high doses. However, unlike ketamine, it primarily affects the GABA neurotransmitters and not glutamate. Subjective effects of midazolam include relieving anxiety, aiding sleep, and calming. It seems doubtful that a drug with such effects could mask as ketamine. Fava et al. (2018) used a double-blind placebo-control design to assess the antidepressant effects of ketamine versus midazolam (n = 99). They found that ketamine was significantly better at relieving depressive symptoms. Additionally, at both 0.5mg/kg and 1.0 mg/kg, ketamine resulted in significantly greater

dissociative symptoms than midazolam ($p < 0.0001$). They also kept track of negative side effects and found higher rates of specific negative side effects in the ketamine-treated patients compared to midazolam: headache (11.3% vs 0%), nausea (10% vs 0%), vomiting (5% vs 0%), and depression (3.8% vs 0%). Also, two ketamine patients reported suicidal ideation, which none of patients treated with midazolam did.

It is impossible to measure the actual subjective impact of ketamine versus midazolam. However, ketamine giving both higher rates of specific side effects and greater dissociative effects indicates an experience that is different in kind from that of midazolam. Therefore, the control condition in this trial, and by extension, other experiments using the same design, might have been compromised.

Dissociative side effects

Ketamine commonly causes transient dissociative-like effects in sub-anesthetic doses (Green, Nakamura, & Johnson, 1990). The dissociative effects start from infusion, peak within an hour, and vanish by 230 minutes (Luckenbaugh et al., 2014). What causes them is unknown; a variety of changes in neural mechanisms have been proposed. They may stem from glutamate release (Rot et al., 2012), alterations of neural network connectivity (Walter et al., 2014), or both (Niciu et al., 2018). Other NMDA receptor antagonists have been tested for depression, but do not show the same antidepressant efficacy as ketamine. Also, they do not induce dissociative side effects. It is therefore uncertain whether acute psychological effects have a causal role in ketamine's antidepressant effect (Rot et al., 2012).

Despite several papers raising the question of a relationship between these effects and antidepressant response (Ionescu et al., 2018; Walter et al., 2014), investigation into this aspect has been limited. An inquiry presents multiple challenges for the experimenter: establishing a methodology, quantifying subjective dissociative experience, performing real-

time interviews with subjects, and difficulty in keeping the blind (Mathai, Meyer, Storch, & Kosten, 2019). These factors may have contributed to the lack of literature.

The intensity of ketamine's alteration of consciousness is dose-dependent, meaning that a higher concentration of ketamine commonly results in a stronger experience (Vollenweider & Kometer, 2010). Most studies on ketamine for depression have used a 0.5mg/kg dose (Ionescu et al., 2018). Studies on ketamine as a tool to combat addiction have used higher dosages. Double-blind, placebo-controlled studies on ketamine for addiction found that both 2.0 mg/kg and 2.5 mg/kg doses induce psychedelic states, mimicking the serotonergic psychedelics (Krupitsky et al., 2002). Features of these states include mystical experiences (transcendent states of unity), out-of-body experiences (sensations of being outside one's own body), and ego-dissolution (loss of subjective self-identity). Also, these studies report that meaningful, transformative experiences helped patients shift to healthier beliefs and behaviors, aiding in abstinence from substance abuse (Krupitsky et al., 2002; Krupitsky & Grinenko, 1997).

More specifically, a study on detoxified alcoholic patients found substantial improvement in standard alcoholism treatment when supplemented with ketamine ($n = 100$). One group received ketamine treatment (2.5 mg/kg), while the control group only had conventional alcoholism treatment. At follow-up one year later, the control group had a 24 % abstinence rate, while 66 % of the ketamine group had remained abstinent from alcohol ($p < 0.01$) (Krupitsky & Grinenko, 1997).

Krupitsky et al. (2002) also performed a ketamine study on detoxified heroin addicts ($n = 70$) where one group received a high ketamine dose and the other, a low dose (2.0 mg/kg, 0.2 mg/kg). The purpose was to elicit a "full psychedelic" experience in one group versus a "sub-psychedelic" experience in the other. At one-month follow-up, the abstinence rates were at 85 % and 55 %, respectively. After two years, the high dose group was still more abstinent

(17 % vs. 2 %, $p < 0.05$). The authors reason that the psychedelic experience was the chief mediator of outcomes: "A psychedelic ketamine experience is to some extent similar to the near-death experience. And, similar to the NDE, it might be transformative and induce changes in spiritual development and worldview" (Krupitsky et al., 2002, p. 280).

The psychedelic treatment model

In a similar development to ketamine research, studies on psychedelics (lysergic acid diethylamide [LSD] and psilocybin) have consistently produced immediate and significant antidepressant effects (Muttoni, Ardissino, & John, 2019). Psychedelics act on the 5HT-2A receptors of the serotonin system, but also affect glutamate transmission in the limbic system – an action they share with ketamine (Vollenweider & Kometer, 2010).

In another similarity, nobody is sure how psychedelics achieve their antidepressant effect. Neuroimaging studies have established that psychedelics affect various cortical and subcortical areas, and decrease blood flow to the DMN (Carhart-Harris et al., 2012; Vollenweider & Kometer, 2010). How long-term antidepressant effects manifest in alterations of brain areas or networks has not been established (Griffiths et al., 2008). Several studies have concluded that the quality of the psychedelic experience (with features such as “ego-dissolution” and “oceanic boundlessness”) predicts long-term improvements in mental health (Carhart-Harris & Goodwin, 2017; Griffiths et al., 2016; Ross et al., 2016).

The “psychedelic treatment model” (Roseman, Nutt, & Carhart-Harris, 2018) is based on the notion that the quality of acute subjective experience facilitates treatment response. Due to their shared action on glutamate in the limbic system and their similar psychological effects, ketamine and psychedelics may elicit clinical response in much the same way. A psychedelic or dissociative experience may lead to clinical improvement by showing the depressed patient that experiences other than the depressed state is possible. An attempt at

applying the psychedelic treatment model to studies on ketamine for depression thus seems warranted.

Literature Review

Exclusion and inclusion criteria

The following is a literature review of eight trials investigating both antidepressant effects and subjective psychological symptoms of ketamine on patients with MDD. All studies were found through the database Google Scholar in February 2020. Subsequent searches using the Scopus database did not produce any further results.

Studies were excluded if: subjects were not human; study investigated the anesthetic effects of ketamine; results measured something other than depression; ketamine was used to treat anything other than major depression; ketamine was administered in concord with some other medicine; ketamine was administered by any method other than intravenously. In total, eight studies matching the inclusion criteria were found.

Depression scales

Hamilton Depression Rating Scale (HDRS)

The HDRS was published in 1960 (Hamilton, 1960) and has been widely used in clinical settings to evaluate depression severity. The original scale consisted of 17 questions but has since been updated into several different versions. The questions are graded from 0-4 or 0-2, depending on the severity of depressive symptoms. The max score varies depending on the version used, but a score above 20 indicates a medium level of depression, and a score of 23 indicates severe depression (Hamilton, 1960).

Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS was designed in 1979 (Montgomery & Åsberg, 1979) and is sensitive to changes brought about by antidepressant treatments. The scale consists of 10 questions graded between 0-6 depending on symptom severity. A total score between 0-6 means there is no

depression present. A mild depression corresponds to a score of 7-19, a medium rate depression to 20-34, and severe depression to a score of 35-60. The scale was designed to rate depression severity, not to make a diagnosis (Williams & Kobak, 2008).

Both the HDRS and MARDS can be used as a self-report tool or interview tool. In the latter, a clinician makes judgments and takes notes. After antidepressant treatment, a new assessment can be made as to how depression symptoms and severity have changed. Remission is usually defined as the patient no longer fulfilling criteria for a diagnosis, and response as the patient showing a reduced symptom score of at least 50 percent of the scale initially used (Snaith, Harrop, Newby, & Teale, 1986).

Subjective experience scales

Brief Psychiatric Rating Scale (BPRS)

The BPRS was developed for assessing psychotic disorders (Overall & Gorham, 1962). It consists of 16 symptom items to be rated on a 7-point Likert scale. A one means symptom is not present, and a seven means the symptom is extremely severe. The BPRS has subscales concerning positive and negative symptoms. The positive symptoms are unusual thought content, conceptual disorganization, hallucinatory behavior, and grandiosity. The negative symptoms are blunted affect, emotional withdrawal, motor retardation, and disorientation (Bell et al., 1992).

Clinician-Administered Dissociative States Scale (CADSS)

The CADSS was developed to reliably measure dissociative symptoms (Bremner et al., 1998). It consists of 19 items ranked by the subject and 8 items scored by an observer. Each self-rated item is concerned with subjective experience and is administered by a clinician reading the item to the subject who then chooses one of five possible answers: 0 = not at all, 1 = slightly, 2 = moderately, 3 = considerably, 4 = extremely. The observer

component consists of 8 items concerned with behavioral factors consistent with a dissociative state (Bremner et al., 1998).

5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)

The 5D-ASC is a self-report measure of individual response to a psychedelic substance (Dittrich, 1998). Response is indicated on a visual analog scale. It consists of 96 items across five dimensions: Oceanic boundlessness (a loss of ego boundaries), Anxious ego-disintegration (loss of self-control), Visual hallucinations, Acoustic alterations, and Altered vigilance. Studerus, Gamma, and Vollenweider (2010) developed a new version with 66 items across 11 subscales: Experience of unity, Spiritual experience, Blissful state, Insightfulness, Disembodiment, Impaired control and cognition, Anxiety, Complex imagery, Elementary imagery, Audio-visual synaesthesia, and Changed meaning of perceptions.

Participants and treatment

All participants were adults ranging between 18-70 years old, diagnosed with MDD. In four of eight studies, participants also had TRD (Aust et al., 2019; Fava et al., 2018; Phillips et al., 2019; Zarate et al., 2006). Patients refrained from using antidepressant drugs for two weeks before the first infusion in three studies (Berman et al., 2000; Valentine et al., 2010; Zarate et al., 2006), while existing medications were unchanged in the other five (Aust et al., 2019; Fava et al., 2018; Phillips et al., 2019; Sos et al., 2013; Vidal et al., 2018). All but two studies administered ketamine by an infusion of 0.5 mg/kg over 40 minutes. The Sos et al. (2013) study used a slightly higher dose (0.54 mg/kg) and Fava et al. (2018) used doses ranging from 0.1, 0.2., 0.5, and 1.0 mg/kg, as that study assigned participants to five different conditions of treatment in a 1:1:1:1:1 fashion (one group received placebo infusions). The number of infusions varied between one (in Fava et al., 2018; Sos et al., 2013; Valentine et al., 2010; Vidal et al., 2018; Zarate et al., 2006) to six – with a subgroup of participants receiving nine infusions in Aust et al. (2019), and seven, with a subgroup receiving 11

infusions in total, in Phillips et al. (2019). Five studies also performed placebo infusions, with three studies using a saline solution (Berman et al., 2000; Sos et al., 2013; Zarate et al., 2006) and two using midazolam for an active placebo control (Fava et al., 2018; Phillips et al., 2019).

Materials and evaluation

Three studies measured depression severity with the HDRS, and four used the MADRS. Fava et al. (2018) used both. Five studies used the BPRS for assessing acute subjective symptoms, three used the CADSS (one study used both BPRS and CADSS: Valentine et al., 2010), and two used the 5D-ASC (Aust et al., 2019; Vidal et al., 2018). Additionally, Berman et al. (2000) used a Visual Analog Scale score for intoxication "high" (VAS-high).

Studies differed in how they evaluated changes in depressive and psychoactive symptoms (all studies measured symptoms at baseline). In Valentine et al. (2010), depressive symptoms were measured with the HDRS at 180 minutes, 24 h, 48 h, 72 h, five days, and seven days after each infusion. Changes in CADSS scores were observed at 20, 60, and 80 minutes, and changes in BPRS scores were first investigated at 10 minutes and assessed again at 20, 60, 80, 110, and 210 minutes after each infusion. Berman et al. (2000) kept a schedule of 10, 40, 80, 110, and 230 minutes for both changes to depression and psychoactive response after each infusion, and Zarate et al. (2006) measured outcomes at 40, 80, 110, and 230 minutes and one, two, three, and seven days after infusion for both HDRS and BPRS scores.

Sos et al. (2013) assessed changes in psychosis-like effects at 30 minutes post infusion, and changes in depression scores at one, four and seven days after each session. Fava et al. (2018) measured dissociative symptoms at baseline, and 40, 80, and 120 minutes after the start of the infusion, and changes in depressive symptoms at one, three, five, seven, 14, and lastly at 30 days after the session. Phillips et al. (2019) evaluated changes at two

hours, four hours, and seven days. In Aust et al. (2019) and Vidal et al. (2018), altered perceptual effects were measured with the 5D-ASC. Due to time and effort for participants, it was applied at a single time point in both studies: at four hours in Aust et al. (2019) and at an undetermined time point in Vidal et al. (2018).

Subjective response from ketamine

BPRS

BPRS scores varied across studies. Berman et al. (2000) found greater total BPRS scores from ketamine infusion at 40 minutes, that did not reach significance ($p = 0.07$). Similarly, Zarate et al. (2006) found increased BRPS scores from ketamine only at 40 minutes ($p = .04$), which barely reached statistical significance. Conversely, Valentine et al. (2010) reported decreased BPRS scores after ketamine administration at several time points (60, 80, 110, and 210 minutes). In Sos et al. (2013) scores did not reach significance ($p = 0.10$) and individual scores were not presented, but a scatter plot shows scores varying widely, from heightened to lowered. In Vidal et al. (2018), this particular data was not presented, but authors commented that increases in BPRS scores were detected in 4 patients shortly after injection and disappeared after 110 minutes.

CADSS

All three studies using the CADSS found significant dissociative symptoms. These emerged after 20 (in Valentine et al., 2010) to 40 minutes (in Fava et al., 2018; Phillips et al., 2019). Dissociative effects returned to baseline levels at two hours post-infusion in Phillips et al. (2019). Comparisons of CADSS scores before and after the 7th infusion found reduced dissociative side effects with repeated infusions ($p = 0.001$). There was no evaluation of dissociative effects in later infusions. The dissociative effects found by Valentine et al. (2010) at 20 minutes after infusion had disappeared at the subsequent 60-minute time-point of evaluation. In Fava et al. (2018), both 0.5 mg/kg and 1 mg/kg doses resulted in significantly

greater dissociative effects ($p < 0.0001$) than placebo, while the lower ketamine doses (0.1, 0.2 mg/kg) did not produce significant differences from placebo treatment.

5D-ASC

Two studies used the 5D-ASC and had differing results. Aust et al. (2019) found increased scores on all its sub-dimensions. Most affected were Sense of time and Emotions, Body control, Depersonalization, and Self-control, though no numbers were reported for these increases. This measurement was only performed once, at four hours after the first ketamine infusion. Meanwhile, Vidal et al. (2018) found large variability in their participant's scores. Six of seven patients had more than 50 % of scale maximum on the sub-dimensions of Vigilance reduction and Dread of ego dissolution, while three patients reported Oceanic boundlessness, and one patient each reported Visionary restructuralization and Auditory alterations. This study also chose to administer the 5D-ASC at one time-point only.

Relationship between clinical response and subjective effects

BPRS

While all studies using the HDRS and BPRS reported marked clinical response, none found a correlation between reduced depression scores and an increase in BPRS symptoms (see Table 1). Zarate et al. (2006) did find a trend between BPRS scores and depression response that did not reach statistical significance ($p = 0.06$). This was the only factor that predicted response to ketamine. The authors did not specify whether they performed these comparisons through all time points or only once.

Berman et al. (2000) reported no correlation between changes in BPRS scores and reduction in depressive symptoms ($p > 0.65$). Their paper does not clarify if comparisons were performed for all time points. VAS-high did not show a relationship with decreased depression scores. Valentine et al. (2010) looked for associations between peak change in BPRS at 20 minutes and depression scores, and found no relationship at any time point,

though this specific data was not presented. Two studies (Sos et al., 2013; Vidal et al., 2018) used the MADRS in concord with the BPRS. Both reported clear antidepressant effects from ketamine treatment but differed on the relationship between clinical response and BPRS score changes as Sos et al. (2013) found a relationship, while Vidal et al (2018) did not.

CADSS

Phillips et al. (2019) found a relationship between CADSS scores and antidepressant effects ($p = 0.03$) at 24 hours, but only investigated the correlation in a subgroup of participants ($n = 22$). It is unclear how the subgroup was selected. With repeated infusions (seven in total), dissociative symptoms decreased ($p = 0.001$), while the antidepressant effect increased, as MADRS scores dropped by two points with each infusion. There was no evaluation of dissociative effects in the last phase of the trial.

Valentine et al. (2010) found no correlation between peak changes in CADSS scores and depression scores at any time point, though these specific data were not presented. Their time points of evaluation were 60 and 180 minutes, 24, 48, and 72 hours, and five and seven days after ketamine infusions. Fava et al. (2018) reported a dose-response curve with respect to dissociative symptoms, but found no correlations between increased CADSS scores at 40 minutes post-infusion and HDRS scores at day one and day three.

5D-ASC

The two studies (Aust et al., 2019; Vidal et al., 2018) that used the 5D-ASC found no correlation between increased 5D-ASC scores and antidepressant response, though this data was not presented in either study. However, Aust et al. (2019) used two-sample t-tests to reveal a significant difference between responders and non-responders to ketamine treatment on the 5D-ASC subscale of “anxious ego-disintegration” ($p < 0.01$). They replicated the result using the 11 lower-order 5D-ASC subscales, where the difference was traced to a single subscale; “anxiety” ($p < 0.004$). These scores were predictive of resistance to treatment, and

Table 1. Design and main outcomes of studies examining ketamine for depression and dissociative symptoms.

Study	**Design**	**Diagnosis**	**Sample size**	**Sample age (avg.), sex**	**No. of Infusions, dose**	**Depression & dissociation Scale**	**Depression & dissociation Correlation**
Berman et al., 2000	Randomized, double blind	MDD (unmedicated 2 weeks)	9	37 M = 4 W = 5	2, 0.5 mg/kg	HDRS (25 items) & BPRS	No correlation found.
Zarate et al., 2006	Randomized, double blind crossover	MDD and TRD (unmedicated 2 weeks)	18	46.7 M = 6 W= 12	1, 0.5 mg/kg	HDRS (21 items) & BPRS	No correlation found.
Valentine et al., 2010	Single blind, non-counter balanced	MDD (unmedicated 2 weeks)	108	41.7 M = 54 W = 54	1, 0.5 mg/kg	HDRS (25 items) + BPRS & CADSS	No correlation found.
Sos et al., 2013	Randomized double blind crossover	MDD (Unchanged medications)	30	43.72 M = 15 W = 15	1, 0.54 mg/kg	MADRS & BPRS	Yes, day 7 (p = 0.04)
Fava et al., 2018	Open-label w/o control condition	MDD and TRD (Unchanged medications)	99	n.a., n.a.	1, 0.1 – 1.0 mg/kg	HDRS + MADRS & CADSS	No correlation found.
Vidal et al., 2018	Open-label w/o control condition	MDD and TRD (Unchanged medications)	10	51 M = 4 W = 6	1, 0.5 mg/kg	MADRS & BPRS + 5D-ASC	No correlation found.
Aust et al., 2019	Open label w/o control condition	MDD (Unchanged medications)	31	49.5 M = 15 W = 16	6 (sub-set = 9), 0.50 mg/kg	MADRS & 5D-ASC	Yes, on subscale ”anxiety”
Phillips et al., 2019	Randomized double blind crossover	MDD and TRD, (Unchanged medications)	41	41.7 M = 17 W = 24	7 (sub-set = 11), 0.5 mg/kg	MADRS & CADSS	Yes, day 1 (p = 0.03, subgroup n = 22)

Note: 5D-ASC = 5-Dimensional Altered States of Consciousness Rating Scale. BPRS = Brief Psychiatric Rating Scale. CADSS = Clinician-Administered Dissociative States Scale. HDRS = Hamilton Depression Rating Scale. M = Men. MADRS = Montgomery-Åsberg Depression Rating Scale. MDD = Major Depressive Disorder. N. A = Not Available. TRD = Treatment-Resistant Depression. W = Women. W/O = without.

there were no significant group differences on state or trait anxiety at baseline (p = 0.784, p = 0.883), nor with depression severity or personality. The only significant difference at baseline was hopelessness ($p < 0.004$). The authors concluded that, since state or trait anxiety at baseline did not differ, experienced anxiety during ketamine infusion is associated with the absence of treatment response.

Discussion

Given the ill-defined mechanism spurring ketamine's antidepressant action and its similarities to psychedelics in altering consciousness, the objective of this essay was to investigate the scientific literature on the relationship between ketamine-induced dissociative symptoms and antidepressant effects. The most significant results from this literature review were: Findings were conflicting in that three studies found some relationship between dissociative effects and decreased depression scores, while five did not; different scales seem to capture different aspects of the subjective ketamine-induced experience; there was a temporal disconnect between peak subjective effects and antidepressant response in all studies; all included studies found significant antidepressant response and transient alterations of consciousness at 0.5 mg/kg infusion of ketamine or higher. These points will be addressed in succession.

Conflicting findings

Contrary to hypothesis, the majority of included studies found no relationship between subjective effects and antidepressant response. This literature review, comprising 308 participants in total, had discrepant results; five studies reported no association between dissociation and reduced depression, while three did. The associations found in these three studies were dissimilar. There was a negative correlation between anxiety at infusion (as measured by the 11-order subscale of the 5D-ASC) and antidepressant response in Aust et al. (2019), while Phillips et al. (2019) found a positive correlation between dissociation and reduction in depressive symptoms at 24 hours. Sos et al. (2013) found a correlation between increased BPRS positive symptoms subscale scores and decreased MADRS scores at day seven ($p = 0.04$). A potential confounding factor is that all three studies allowed existing medication regimens to go unchanged.

Three studies reporting no association (Berman et al., 2000; Valentine et al., 2010; Zarate et al., 2006) had many similar features: a two-week medication washout before the trial, a one-time infusion, and depression severity and subjective effects measured by the HDRS and BPRS, respectively. The Valentine et al. (2010) study also used the CADSS for dissociative effects and had a much bigger sample size (n = 108) than the others (n = 9, n = 18). It was also single-blind and non-counter balanced as opposed to the designs of Berman et al. (2000) and Zarate et al. (2006), which both were randomized and double-blind. The other two studies that failed to find an association (Fava et al., 2018; Vidal et al., 2018) both used an open-label uncontrolled design with TRD patients and the MADRS for assessment of depression severity. However, they differed in other aspects: different scales for dissociative effects, disparate sample sizes, and one study using the same dose for all patients (Vidal et al., 2018) while the other employed a range of doses (0.1 – 1.0 mg/kg) for patients randomized to different conditions (Fava et al., 2018)

As studies varied in methods of measurement, the number of infusions, and time points of evaluation, their conflicting findings should not be surprising. These varying results call for further investigation into the possible mediating role of the dissociative-like ketamine-induced experience in recovery from depressive symptoms. Aside from the scant literature available, the review made clear that there is no agreed-upon methodology in assessing subjective ketamine-induced symptoms.

Different scales

The different scales used seem to measure different aspects of the ketamine-induced subjective experience. All three scales were initially intended for purposes other than ketamine-induced alterations of consciousness, and their items do not always relate entirely to the experience in question. The BPRS was designed to measure changes in the clinical status of psychosis (behavioral), which may limit its use for psychoactive effects. As currently used,

the BPRS frames ketamine-induced perceptual changes as adverse events. These effects may not be experienced as unfavorable by all subjects, as reported in Krupitsky and Grinenko (1997), and Krupitsky et al. (2002).

The five studies using the BPRS came to differing conclusions: higher scores that did not reach statistical significance in Berman et al. (2000), statistically significant heightened scores in Zarate et al. (2006), BPRS scores lowered at several time points in Valentine et al. (2010), and score changes that did not achieve statistical significance in Sos et al. (2013). Finally, Vidal et al. (2018) did not present data but reported increased scores shortly after injection, which resolved after 110 minutes. The variation in scores, as well as its original purpose of detecting behavioral changes, implies that the BPRS may be ill-suited to capture these effects.

The CADSS was designed for patients with dissociative disorders as a product of PTSD (Bremner et al., 1998). Ketamine-induced dissociative states may be different in kind. Indeed, a review that analyzed patient narratives after exposure to ketamine showed the CADSS unable to fully capture ketamine-induced changes to consciousness (Schalkwyk, Wilkinson, Davidson, Silverman, & Sanacora, 2018). Of relevance is that the CADSS lacks a valence dimension – whether the experience feels positive or negative – but valence may be critical for the efficacy of treatment, as observed by Aust et al. (2019).

Vidal et al. (2018) used the 5D-ASC and found no significant correlation between its dimensions and change in MADRS score on day 0 of treatment. It is unclear whether they looked for a correlation at later time points. The Aust et al. (2019) study also used the 5D-ASC and found that the absence of negative emotional experience at infusion predicted antidepressant response, as subjects who scored higher on the subscale of “anxious ego-disintegration” were non-responders. This result was replicated using the 11 lower-order 5D-ASC subscales, where the difference was traced to a single subscale: “anxiety” The fact that

an initial observation could be further clarified in a more fine-grained manner speaks to the 5D-ASC as a valid measurement of ketamine's perceptual effects. Also, the 5D-ASC is designed purposefully to capture transient altered states, making it the closest tool available for measuring the consciousness-altering effects of ketamine.

Temporal disconnect

There was an observed temporal disconnect between ketamine in the body and antidepressant response, which was consistent across all studies. In Berman et al. (2000), peak depression reduction occurred at three days, while ketamine "high" disappeared at 110 minutes. Zarate et al. (2006) had subjective symptoms peak at 40 minutes and disappear at 80 minutes, which is when depression scores started to fall. The reduction was most significant at 24 hours. Valentine et al. (2010) found increased dissociative symptoms at 20 minutes post-infusion, which disappeared before the antidepressant effect occurred at one hour. In Vidal et al. (2018), changes in subjective symptoms appeared at 40 to 80 minutes and resolved thereafter, while antidepressant effects peaked at day 2. Fava et al. (2018) found that dissociative symptoms peaked at 40 minutes, while depression scores were most lowered at day 1. Phillips et al. (2019) found that dissociative effects disappeared at two hours after the first infusion, and diminished with repeated infusions. Yet, the reduction of depressive symptoms peaked at three weeks after the first infusion. In Aust et al. (2019), the 5D-ASC was administered only at four hours post-infusion. It is therefore unknown whether any altered states of consciousness persisted to 24 hours, which was the peak time point of antidepressant response. However, no other ketamine trial reported perceptual changes for that long, and subjects of this trial did not spontaneously report any such symptoms. Similarly, in Sos et al. (2013) changes in subjective symptoms were evaluated at 30 minutes only, while timing of the peak antidepressant response was not reported.

Given that ketamine and its active metabolite norketamine have a short half-life (both < 2 hours) (Zarate et al., 2006), it seems that antidepressant effects start as it leaves the body. Hence, the relationship of perceptual changes and clinical improvement is not immediately evident. As suggested by Walter et al. (2014), secondary neural processes, or a downstream molecular mechanism not requiring active drug levels, could be the causal mechanism. Another possibility is that ketamine causes immediate changes at a molecular level, which takes time to occasion subjective dissociative experiences, and later might lead or relate to alleviation of depressive symptoms. Yet another conceivable explanation is that ketamine's effects are relatively immediate, but the subject needs time to interact with their environment to appreciate that their mind state has changed for the better.

Antidepressant effects and perceptual changes

All eight included studies found a marked improvement in depressive symptoms, regardless of the specific scale chosen, or number of infusions. These results further confirm ketamine's antidepressant efficacy. Also, all studies reported subjective perceptual changes from 0.5 mg/kg ketamine and upwards. These were statistically significant in all except two trials, Berman et al. (2000) and Sos et al. (2013), where BPRS scores did increase, without reaching significance

Limitations

Insofar as possible, a literature review makes a methodical and critical approach possible, by compiling information and data from several sources. One advantage of a literature review is that inclusion criteria can be specified to find only the most relevant sources. Conversely, a downside of a literature review is that limitations can restrain data collection. Another weakness of the literature review method is that potential errors in interpreting statistics and text can lead to incorrect results and conclusions.

This review was limited to ketamine studies that investigated both antidepressant and subjective psychological effects on subjects with MDD. The exclusion criteria and the scarcity of existing literature resulted in few matching studies. Several included studies suffered from small sample sizes, and study designs varied from randomized and placebo-controlled to open-label without placebo. Measures of both depression and subjective experience varied across studies, as did time points of evaluation. The total number of infusions and follow-up periods varied across studies. Since ketamine exhibits a complex time-dependent and dose-dependent response (Vollenweider & Kometer, 2010) studies of comparable design are essential to make conclusions about the drug's effects.

Furthermore, considering ketamine's unique effects, blinding protocol may not be sufficient. No placebo that mimics ketamine's effects has been identified (Aust et al., 2019). Indeed, several studies commented on the potential inefficacy of their blind (Berman et al., 2000; Fava et al., 2018; Phillips et al., 2019; Zarate et al., 2006). Ketamine-induced symptoms may have been evident to researchers and subjects to render the blind useless.

Challenges for depression research

Elucidating the mechanism behind depression is a difficult task, as the myriad of existing theories of depression suggests. As Kirsch (2011) writes, people sometimes recover from depression without any treatment; for instance, when life circumstances change. Walsh, Seidman, Sysko and Gould (2002) found that placebo treatments are highly variable and often give a strong response, which casts some doubt over any theory based on the chemical action of antidepressant drugs. As Ruhé et al. (2007) made clear in their review, the available evidence does not support a direct causal relationship between monoamine levels and MDD.

As many different antidepressant treatments can show effectiveness– whether it be electric shock therapy, talking about problems with a therapist, or receiving a placebo drug – the concept of depression may need rethinking. It could be that some with a diagnosis of

depression have a chemical imbalance and only respond to a monoaminergic drug, while others respond to any treatment, including a placebo (Kirsch, 2011). Notably, depressive symptoms, their duration, and their degree of severity can vary substantially, even within the specific disorder of MDD (Nestler et al., 2002). Perhaps the current diagnosis and terminology are too vague for a one-size-fits-all theoretical approach to depressive disorders. The categorization of mental disorders in DSM according to symptomatology may be wrongheaded altogether; large-scale data analysis has made evident that every single mental disorder predisposes the patient to every other mental disorder (Marshall, 2020). This calls for less splitting of disorders into symptom-based subtypes, and more research into a possible shared biological basis of mental disorders.

What to make then of ketamine's rapid antidepressant effects? As sufferers of MDD often report rigid and uncontrollable self-reflection (Lehmann et al., 2016), a person's whole reality can be limited to a narrow band of negative cognition. A sudden shift in subjective experience may loosen up the reins on cognition caused by depressive rumination, by showing the depressed person that an entirely different experience of reality is possible. Seemingly, this is what occurs in psilocybin-assisted psychotherapy (Carhart-Harris et al., 2012; Griffiths et al., 2008; Ross et al., 2016) and high-dose ketamine treatment for addiction (Krupitsky et al., 2002; Krupitsky & Grinenko, 1997). While effects from those therapies are longer-lasting and reported subjective symptoms more drastic, they may hold clues for ketamine's antidepressant effects. The dissociative symptoms commonly reported from 0.5mg/kg ketamine represent a transient detachment from reality. When that reality is bleak and hopeless, short-term dissociation may represent a glimpse of light in an otherwise unbearably dark tunnel.

Further research

Further research is necessary to uncover ketamine's antidepressant mechanism of action and address the aforementioned challenges. The field may yet be in its infancy, as many potential developments remain unexplored. Ketamine's effects on the brain are rich and varied, as multiple receptors and networks are involved. Currently, these are poorly understood and need more exploration. The measurement of perceptual changes needs improved tools, as there is no instrument designed specifically for ketamine-induced alterations of consciousness. However, since the 5D-ASC was designed explicitly to capture altered states, it seems the most suited for capturing ketamine's effects on consciousness. Applying several scales to participants seems prudent, as outcomes from existing scales can be compared. Also, the underlying mechanism behind the dissociative- and psychedelic-like experience needs investigation, as its origin and significance is currently not understood.

Moreover, researchers may explore the safety and tolerability of repeated ketamine dosing, as it seems to have improved outcomes in Phillips et al. (2019) and Aust et al. (2019). If ketamine-induced alterations of consciousness are related to clinical outcomes, multiple doses will increase opportunities for such experiences to occur. The standard dose of 0.5mg/kg may also be altered to examine clinical outcomes with higher and lower doses, as in Fava et al. (2018). In changing dosage and repeating administration, experimenters should be careful without being alarmist. Ketamine does have abuse potential, but has been used safely in clinical settings for decades as an anesthetic agent (Chang et al. 2016).

Since many subtypes of depression exist, participants in future studies should be carefully selected, to ensure their safety and the accuracy of drug treatment. Larger sample sizes are needed to increase the statistical power of findings. Also, studies should establish the lasting effects of ketamine, both for single and repeated dosing. Alternative routes of administration are showing positive antidepressant effects and should be further explored.

Recently, S-ketamine in nasal spray form was approved for TRD patients in the United States (U.S. Food and Drug Administration, 2019).

The field's most important challenge is doubtlessly how to sustain ketamine's initial dramatic antidepressant effect. While repeated doses improved outcomes in three included studies, continual administration runs the risk of addiction. The potential drawbacks of repeated ketamine dosing might prove to exceed the benefits. A less risky route is to integrate psychotherapy into treatment. There is preliminary evidence that Cognitive Behavioural Therapy (CBT) can prolong antidepressant effects from ketamine (Krystal et al., 2019). Ketamine may alter brain regions related to reward and motivation (Höflich, 2013; Stone et al., 2012), and enhance synaptic plasticity (Wohleb, et al., 2016). Applying CBT or other therapeutic methods that can exploit activated reward pathways and neuroplasticity to reshape dysfunctional thoughts and beliefs may prove the safest and most effective method of prolonging ketamine's effects. The excitement over ketamine's clinical potential is not reduced to depression research. Ongoing trials are investigating ketamine for social impairment in autism spectrum disorder (ClinicalTrials.gov, NCT02611921) and for symptom relief in obsessive compulsive disorder (ClinicalTrials.gov, NCT01349231).

In conclusion, whether ketamine's antidepressant action is mainly physiological or psychological in nature is still anybody's guess. Previous research has left this question largely unanswered, and the available data is still insufficient. A sensible approach is to try and remain undecided; I myself changed opinions multiple times while reading the literature. Some might ask – does it even matter? The point is that it works, and inquiries like this essay are all irrelevant hair-splitting over unknowable interactions between minuscule chemicals. I would argue that yes, it does matter. If the alleviation of depression is physical in origin, it will hold significant implications for future research. Perhaps other NMDA receptor antagonists could do the job without dissociative side-effects. This knowledge could give

researchers the impetus to develop safe, effective, and rapid-acting antidepressant drugs. Conversely, if the effect has a psychological basis, a completely different approach would be necessary. Trials could lend inspiration from psychedelic-assisted therapy with a focus on safe, calm environments and positive mindset for the patient, to maximize opportunities for meaningful, transformative experiences. Regardless of the correct answer, establishing the origin of depression might ultimately assist the advance of strategies to prevent its occurrence. In that light, this line of research holds promise for resolving the leading public health issue of our time – current pandemic notwithstanding.

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