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PSYCHEDELIC-ASSISTED THERAPY: A PHARMACOLOGICAL PERSPECTIVE ON PSILOCYBIN AND KETAMINE IN DEPRESSION

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ABSTRACT

Depression is one of the main causes of disability among the global populations and even the existing anti-depressant treatment sometimes has a slow onset or poor effects. A new treatment method has appeared, namely psychedelic-assisted therapy, especially involving psilocybin, a serotonergic psychedelic, and ketamine, an NMDA receptor antagonist. Psilocybin also has a mechanism of action by agonizing 5-HT 2A receptors regulating neural circuits including the default mode network to decrease rumination and increase emotional processing. The effects of ketamine are rapid: the drug enhances the glutamate transmission, stimulates the activation of AMPA receptor, and induces synaptogenesis mediated by brain-derived neurotrophic factor (BDNF), which induces effects of antidepressants. Both agents are characterized by a high level of effectiveness in terms of treatment-resistant depression when used in controlled settings along with psychotherapy. Even though pre-clinical trials demonstrate a long-term improvement of mood, additional large-scale, research is required to assess their safety over time, dose optimization, and to understand how they work. Psilocybin and ketamine, used as a psychedelic-assisted therapy, is a paradigm shift in the treatment of depression, which provides a fast and long-term resolution of patients who fail to respond to traditional therapies.

KEYWORDS: Psychedelic-assisted therapy, Psilocybin, Ketamine, Treatment-resistant depression, 5-HT_2A receptor, Brain-derived neurotrophic factor (BDNF), Synaptogenesis.

INTRODUCTION

Humphrey Osmond came up with the word psychedelic meaning to produce a mind manifestation and that it served to disclose some useful or beneficial features of the mind in 1957 [1]. Psychedelics have long been used therapeutically and spiritually (hundreds of years old) and in the past psychedelics have been used in treating and during rituals, which include psilocybin mushrooms, peyote, and ayahuasca [2]. The psychedelic-assisted therapy where psychedelic drugs are used under therapeutic settings has had its own history and encountered its significant revival in the recent years [3]. Nevertheless, psychedelics became popular in the Western treatment of the middle 20th century [4].

Psychedelic drugs alter the perception, cognition and mood without delirium [5]. Their interaction is very high based on the influences of set and setting references to the mind of the individual and environment which the individual was administered [6].

Figure:1 Classification of Classic and Non-Classic Psychedelic Compounds.

Classic and non-classic psychedelics.

Researchers still debate on the category of drug to be considered as psychedelics [7]. Considering the phenomenological perspective, substances that have a diverse array of pharmacologic actions will cause psychedelic subjective effects [8]. Indicatively, LSD actions

are generated through serotonin 2A receptor agonism; ketamine, N-methyl-D-aspartate receptor antagonism and MDMA, serotonin release into the synaptic cleft [9]. Nevertheless, others maintain that purely the compounds that have the effects by acting through serotonin 2A receptor agonism (e.g. LSD, psilocybin, dimethyltryptamine) qualify as psychedelics [10]. Serotonergic psychedelics called classic psychedelics are used as a promising alternative, such as psilocybin, and compounds with similar effects by other pharmacologic mechanisms known as non-classic psychedelics [11].Psychedelic-assisted therapy has become a promising alternative, including psilocybin, a serotonergic psychedelic, as well as the compounds that exhibit similar effects through other pharmacologic mechanisms called non-classic psychedelics [12]. Psilocybin mainly acts as an agonist of 5-HT 2A receptors that regulate neural mechanisms, including the default mode network, as a result of rumination and emotional processing are promoted [13]. Ketamine heightens glutamate transmission speedily, facilitates the activation of AMPA receptors, and leads to brain-derived neurotrophic factor(BDNF)-mediated synaptogenesis, which promptly decreases the symptoms of depression, even in TRD [14].

Classic psychedelics are agonists or partial-agonists of serotonin (5- hydroxy tryptamine, 5-HT) 2A receptors, the main pharmacological target of the substance in the brain and serotonin 5-HT1A and 5-HT2C receptors [15]. Their affinity to the 5-HT receptors can be attributed to their tryptamine moiety, which is identical scaffold in the chemical structure of serotonin [16].

Historical Perspective

Psychedelic pre-clinical uses medical use pre-clinical use of psychedelics dates back thousands of years in humans and the ritual usage by indigenous people informs the provision of psychedelic-assisted therapy [17]. The practice of using psychedelics in Western medicine is not new [18]. Following the discovery of LSD by a Swiss chemist known as Albert Hoffman who found out about its psychoactive properties in 1943, his employer Sandoz sent LSD to physicians to determine the possible clinical use of LSD [19] . The 1950s and 1960s clinical data were promising in LSD use as a treatment of alcohol use disorder, psychological distress caused by cancer, and more [20]. In 1958, Hoffman recognized the psilocybin as the main psychoactive substance of Psilocybe Mexicana mushrooms samples and synthesized psilocybin in 1959 [21]. It was later also widely spread by Sandoz to psychiatric research [22].

In the middle of 1960s, the FDA started to demand that the drugs undergo monitored clinical trials in order to determine safety and efficacy in particular indications [23]. With the public interest in the nonmedical application of psychedelics, and the impending expiration of the patent of LSD in 1965, Sandoz never followed up on such trials, and thus clinical application of psychedelics ended [24]. In 1970, the majority of psychedelics were included under the Controlled Substances Act as Schedule I drugs (i.e., no accepted medical use and a high potential of abuse) in the United States, which placed significant bureaucratic and financial obstacles in the path of doing preliminary research on the therapeutic effects of psychedelics [25].

Pharmacology of Psilocybin

The primary psychedelic of Psilocybe Mexicana (and most other mushrooms called magic mushrooms, sacred mushrooms and teonacatl (Altecian name meaning god flesh)) is psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine), a psychedelic compound with entheogenic properties [26]. Magic mushrooms were used ritualistically, religiously and socially by primitive American people (primarily by the Mayans and Aztecs) [27]. Besides the spiritual and ritualistic purposes, Psilocybe mushrooms have been utilized in healing by the primitive people and Indigenous people, as well as recently, by the general people in recreational and medical purposes [28]. Psilocybin is an indole alkaloid, which upon absorption is dephosphorylated to its active metabolite psilocin, an indolamine, which bears a very similar structure to serotonin and this is what makes it act as a potent serotonergic agonist [29]. Psilocybin and psilocin are serotonin agonists of the various subtypes of the 5-HT receptors, predominantly the 5-HT2A receptor, with moderate affinity at the 5-HT1A and 5-HT2C receptors [30]. Majority of the research on psilocybin can be traced back to the 1950-1970 decades, although significant interest in this drug has developed over the last decade [31].

The drug is still found in the Schedule 1 of the Controlled Substances Act, which is a dangerous one with no medical utility according to the United Nations Convention on Psychotropic Substances [32]. Conversely, more recent research has proposed the possibility of psilocybin in the treatment of a number of mental disorders, such as depressed mood, anxiety disorders (along with anxiety and depression secondary to terminal and life-threatening illnesses), obsessive-compulsive disorder [33].

Figure:2 Morphology of Psilocybin Containing (Magic) Mushroooms.

Chemistry

Psilocybin is a typical hallucinogenic drug that is classified under tryptamine, and it is usually found in more than 200 species of fungi [34]. The strongest ones belong to the Psilocybe genus, especially, P. azurescens, P. semilanceata, and P. cyanescens [35]. In 1958, Albert Hofmann extracted this compound by the P. Mexicana mushroom that the Aztecs called teonanacatl [36]. Psilocybin, being a typical hallucinogen, has had its psychedelic effects mainly ascribed to its working as a 5HT2A agonist [37]. Its chemical composition is much similar to that of serotonin [38]. The psychoactivity of psilocybin is highly attributed to the fact that it is quickly metabolized to psilocin [39]. Psilocybin is not necessarily pharmacologically active itself, but dephosphorylation of this substance when it is ingested is rapid, and it is difficult to assess the effects of psilocybin independently of the effect of other substances.

Psilocybin is a substituted tryptamine naturally occurring, which has an indole ring with an aminoethyl substituent [40]. It has a structural connection with serotonin, a monoamine neurotransmitter, which is a derivative of the amino acid tryptophan [41]. Psilocybin belongs to the general group of tryptophan-based substances that initially served as antioxidants in the earlier life, but then took up more complex roles in multicellular organisms, such as human beings. Other related indole-based psychedelic drugs are dimethyltryptamine, which is

present in a range of plant species, and in minimal quantities in several mammals, and bufotenine, which is present in the skin of several amphibians, especially the Colorado River toad [42].

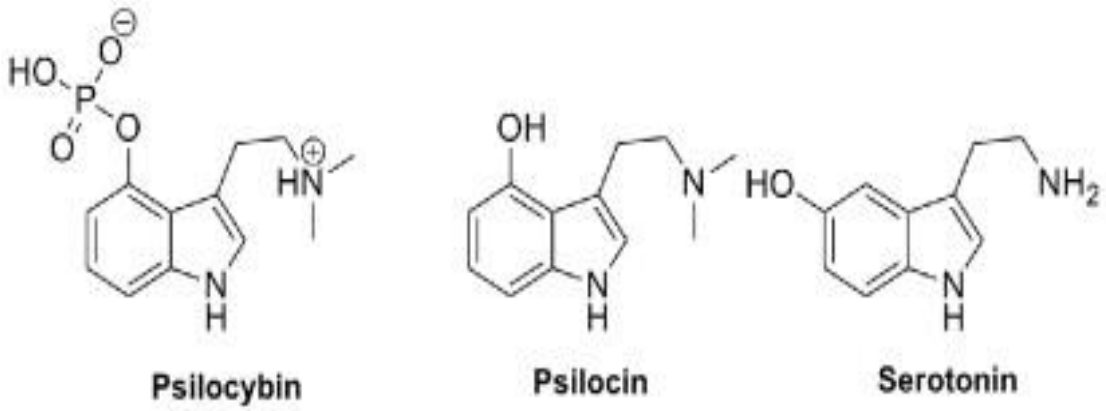

Figure:3 Metabolic Conversion of Psilocybin to Psilocin.

Metabolism

In vivo studies have indicated that psilocybin quickly decays through its phosphate group and is altered to its active metabolite psilocin, produced in the acidic condition of the stomach or by the activity of the alkaline phosphatase in the intestine and kidney [34]. It can therefore be said that Psilocybin is a pro-drug of psilocin [34]. The pharmacokinetic studies that are observed after the administration of psilocybin are the reflection of the properties of the metabolite rather than the parent drug [34]. Plasma and urine detection of psilocybin were not found following an increase in oral doses of the drug, and psilocin was detected in plasma 2030 min [34]. Peak levels of psilocin occurred in 3 h after oral administration of psilocybin [34]. Psilocin had linear pharmacokinetics in the dosage 0.3-0.6mg/kg psilocybin in terms of maximum drug concentration (Cmax) and area under the plasma concentration time curve [34]. A larger investigation in healthy individuals has found comparable findings at the dose of 15 to 30 mg psilocybin (i.e. comparable dose range to the prior study due to the average body weight) [34]. The apparent volume of distribution of psilocin was greater than that of total body water and this value implies that psilocin is widely distributed throughout the body [34]. Oral administration of psilocin in 3 human subjects yielded an absolute bioavailability of 52 percent [34]. Although the distribution of psilocin to the tissues is very large distribution, the half-life of psilocin is rather small, in one study the mean of psilocin is 3 ± 1.1 h [34]. Conversely, more than twice this mean value of half-lives of plasma eliminations

have been reported. This variation is most likely to be due to personal enzyme polymorphisms that cause metabolic routes.

The first pass metabolism of psilocin is very intensive in the liver and mainly excreted through the kidneys [34]. A number of metabolites have been detected in plasma and urine, however, none of them is deemed to be pharmacologically active [34]. Psilocin is excreted as 2 to 4 percent of urine. Psilocin is metabolized to psilocin-O-glucuronidate by extensive glucuronidation by UDP glucuronosyltransferases, and excreted in the urine and faeces[30]. Psilocin is converted to unconjugated psilocin which gets metabolised into the inactive 4-hydroxyindole-3-acetic acid (4-HIAA) by means of monoamine oxidase and aldehyde dehydrogenase [34]. The psilocin metabolites are found in high concentration in plasma than psilocin itself.

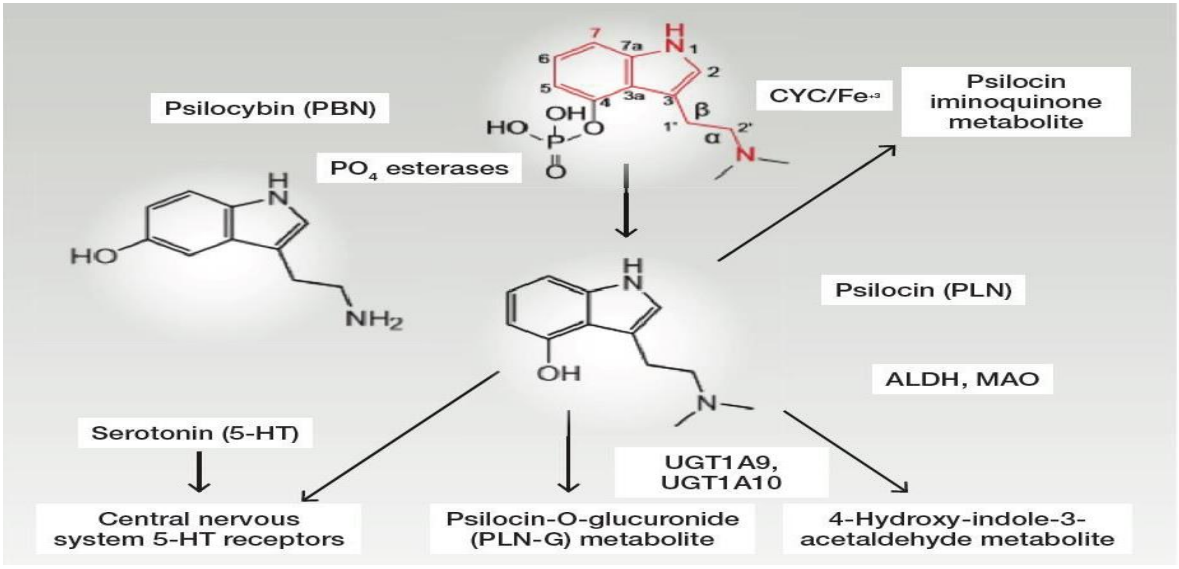

Figure:4 Pharmacokinetic Pathway of Psilocybin Metabolism.

Mechanism

Similar to other conventional psychedelic drugs, at least part of the effects of psilocybin is explicable by an agonist activity of the drug at 5HT2A receptors [28]. The effective dose of psilocybin and other indoleamine hallucinogens, such as binding to this receptor subtype, is highly correlated with the effective dose of a drug to induce the desired pharmacological effect in half the population [28]. The occupied 5HT2A receptors were dose dependent after taking psilocybin (3-30mg) as single oral doses [28]. The receptor occupancy of EC50 was determined to be around 2 0g/L. Also, it is proven that the 5HT2A antagonist, ketanserin, has the ability to inhibit the hallucinogenic activity of psilocybin [33]. The effect of an agonist behavior at the 5HT2A receptor triggers a cascade of interactions via the second messengers

systems [33]. Disparities in these second messenger pathways in hallucinogenic and non-hallucinogenic 5HT2A agonists have been shown [33]. The change in G-protein stimulation and selective signalling pathway or biased agonism has been suggested as the cause of the psychoactive variance between hallucinogen and highly related non-hallucinogen 5HT2A receptor agonists. Psychedelic drugs act on 5HT2A-Gq/11 and 5HT2A-Gq/11 transducers, although recent reports indicate that 5HT2A-Gq recruitment predicts psychedelic activity. Moreover, the 5HT2A-Gq needs to be activated to a certain level to cause psychedelic effects and this is the reason why and how 5HT2A partial agonists are inactive psychedelics. Other 5HT2 receptor binding and non-5HT2 receptor binding might also help mediate the effects of psilocybin. Therefore, hallucinogenic agonists (but not non-hallucinogenic agonists) have been suggested to mediate their effects by a complex between 5HT2A and a metabotropic glutamate-2 (mGlu2) receptor. There are also various early growth response genes that are activated by hallucinogens, which are associated with synaptic enhancement, which are in turn associated with the antidepressant effects of psilocybin [33].

Other receptor subtypes of serotonergic system action, including 5HT1A partial agonist activity, serotonin transporter inhibition, also have a potential contribution to the behavioural actions of the compound. In the same manner, there are dopamine D2 receptor and glutamatergic system activity that is believed to have an effect on drugs. Similar to traditional antidepressants [including selective serotonin reuptake inhibitors (SSRI)], via its effects at these receptors, psilocybin has been shown to induce rapid rise in brain derived neurotrophic factor (BDNF) levels in the brain [35]. It has been demonstrated that serotonergic psychedelics induce fast dendritic and axonal remodelling. Dendritic Arbor-complex in response to cortical neurons treated with serotonergic psychedelics has been shown to increase. This seemed to be as a result of an increment in the quantity of dendritic branches and total length of dendritic branches. The same effects have been demonstrated to take place with traditional antidepressant drugs. Combined, it is hypothesized that the psychedelic and conventional antidepressant effects have a similar neurobiological mechanism. Neuroimaging research has been conducted on how the so-called default mode network (DMN) of the brain, which consists of a number of interconnected areas, is also influenced by psilocybin, including the medial prefrontal cortex, the anterior cingulate cortex, the precuneus, and the angular gyrus [29]. The DMN occurs at a time when the brain does not concentrate on a particular, external activity. It is defined by higher activity, during rest, wandering of the mind and self-thinking, like remembering past or thinking of the future. On the other hand, DMN activity is generally reduced when a person is occupied with a specific attention on external

stimuli or challenging assignments. There have been altered functional connectivity of the DMN that is implicated in various psychiatric disorders such as major depression. It has been suggested that the therapeutic effects of the psychedelic agents decrease the functional connectivity of the DMN and enhance the connectivity between the DMN and the other networks that are associated with the altered states of consciousness of the users and the therapeutic effects of the interaction [29].

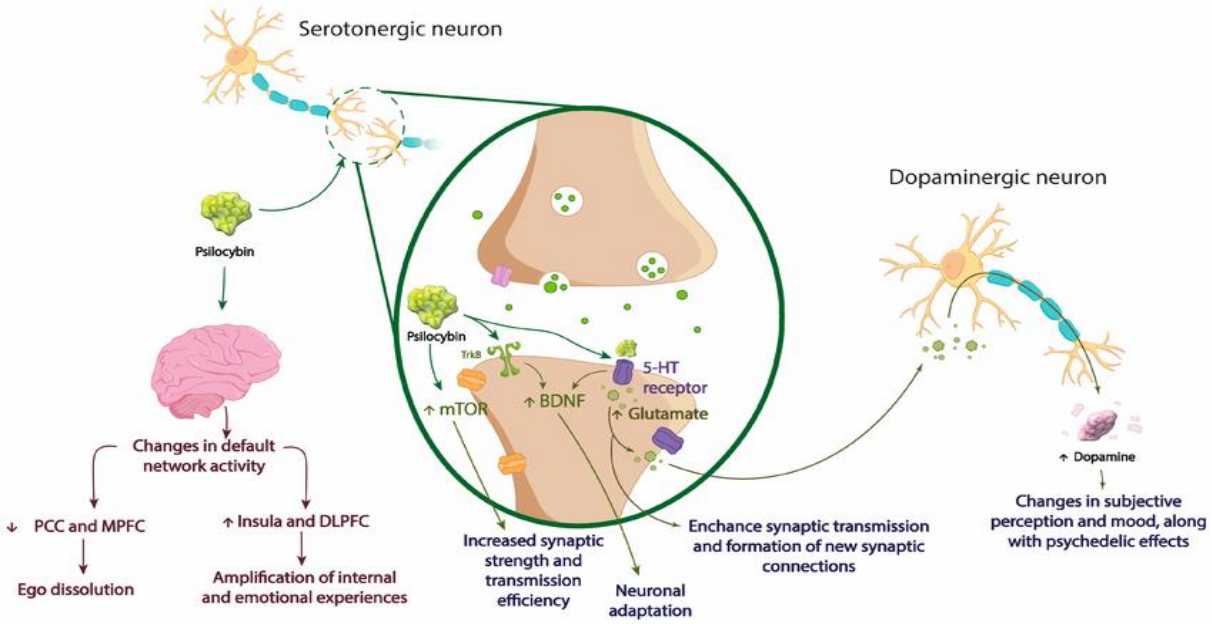

Figure:5 Mechanism of Action of Psychedelic Compounds in Brain.

History of Psilocybin in Depression Therapy.

The evidence of the efficacy of psilocybin in depression was presented in research of the drug on patients with terminal illnesses [31]. As an example, psilocybin (22 or 30 mg/70 kg) was better able to alleviate the symptoms of depression and anxiety in patients with life-threatening cancer with developed clinically significant symptoms of these issues than a low dose of the drug (1 or 3 mg/70 kg) [31]. The low dose was considered as a placebo dose of the agent. Similar results were obtained with relatively small samples of the drug and other studies using different dosages of psilocybin in patients with life-threatening conditions[31] but a Cochrane review found the drug was likely to be useful in such patients[31]. Likewise, with the case of a major depressive disorder (MDD) that is severe, a few studies will testify to the efficacy of psilocybin assisted psychotherapy[29]. Since the role of resistant cases in the field of major depression treatment is significant, it is no wonder that the effectiveness of the use of psilocybin in specifically defined cases has started to be considered.

Clinical implications

Psilocybin-assisted treatment has demonstrated the possibility to provide a quick and long-lasting decrease in the symptom of depression and anxiety in cancer patients, which is particularly important in palliative care practice [31]. The described long-term effects imply that a few sessions of psilocybin can result in long-term effects on distress [29]. The findings are, however, not conclusive, but need to be taken in moderation until they are supported by larger and more rigorous studies.

Effects

The effects of psilocybin are the same as those of Lysergic acid diethylamide mostly. These are a distorted perception of time and space and severe mood and feeling shifts [28].

Contraindication

It is also deemed that Psilocybin should be contraindicated in pregnant women or breastfeeding women since there is a lack of research studies in this demographic [30]. Psilocybin increases and decreases heart rate and blood pressure temporarily and therefore uncontrolled cardiovascular conditions are a relative contraindication to psilocybin [30]. An antipsychotics and some antidepressants are serotonin 5-HT2A receptor antagonists that might prevent the hallucinogenic effects of psilocybin and may be contraindicated in this regard [28]. There is a chance that monoamine oxidase inhibitors (MAOIs) enhance the effects of psilocybin and increase its risks [30].

Pharmacology of Ketamine

Ketamine was synthesised in 1962; it is an analogue of phencyclidine in an attempt to create a safer anaesthetic with less hallucinogenic properties [43]. It was permitted to be used in the United States in 1970 [43]. It has been under veterinary use since the time in which it was widely used in surgical anaesthesia during the Vietnam War [44]. It subsequently became notable due to the discovery of its fast antidepressant action in 2000 that made a significant breakthrough in the treatment of depression [45]. Esketamine in comparison to racemic ketamine may possess stronger and lasting antidepressive effects [45]. The World Health Organization has it on the List of Essential Medicines [46]. It comes in the form of a generic drug. Medically Ketamine is legally used as anesthetic, in pain treatment as well as the treatment of depression that does not respond to drugs [46]. It is however being strictly followed since it is a psychoactive drug that has side effects. Ketamine may cause

dissociation, dizziness, and nausea and must not be administered in patients with severe heart or liver illness, and uncontrolled psychosis [46].

Ketamine is an anaesthetic agent is employed in the dissociative mode of anaesthesia producing a trance state that is painkilling, sedative and amnesic when used in an anaesthetic level [47]. The typical features of anaesthetic are breathing and airway reflexes, excited cardiopulmonary activity with increase in blood pressure and moderate bronchodilation [47]. It is a special anaesthetic that is especially used in trauma, emergency and cases involving children [47]. It is also taken as treatment of depression that is resistant to treatment in lower, sub-anaesthetic dosage [48].At anaesthetic dosage, ketamine will cause a trance-like state known as dissociative anaesthesia, which is an exercise that produces pain relief, sedation, and amnesia [47]. The characteristics that make it a unique anaesthetic include preserved breathing and airway reflexes, stimulated cardiac activity with elevated blood pressure, and moderate bronchodilation [47]. It is an anaesthetic that is particularly applied in emergency, paediatric, and trauma cases [47]. It is also administered at lower levels, below the anaesthetic dose as a pain treatment and treatment resistant depression treatment [48].

Chemistry

Ketamine is a general anaesthetic and NMDA receptor antagonist derived by cyclohexanone that is analgesic, hallucinogenic and commonly used in medicine as an anaesthetic, to treat depression and also in pain management [43]. Ketamine is a derivative of aryl cyclohexylamine as a chiral molecule, which exists in two enantiomers S-(+)-ketamine (esketamine) and R-(−)-ketamine (arketamine) [45]. Of these, the more pharmacologically active enantiomer is esketamine (S -ketamine), which is a marketed drug under the brand name Ketanest S, though arketamine (R -ketamine) has not been commercialized as an enantiopure drug [45]. S-ketamine has a stronger analgesic and anaesthetic action due to its antagonistic effect on the NMDA receptor whereas R-ketamine has a longer-lasting antidepressant effect indicating that other mechanisms other than the NMDA receptor inhibitory effect may play a role in antidepressant effect of ketamine [45]. Interestingly, optical rotation of ketamine depends on the form of the compound hence; the free base of (S)-ketamine will have dextrorotational rotation and is termed (S)-(+)-ketamine hydrochloride whereas the hydrochloride salt form of ketamine will have a Levo-rotational rotation and is hence termed (S)-(−)-ketamine hydrochloride [46].

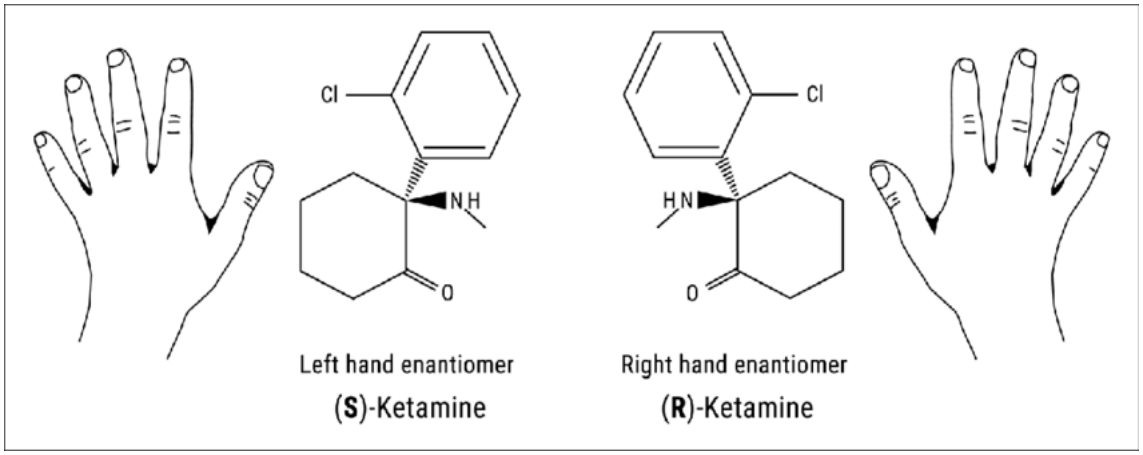

Figure:6 Configuration of Ketamine.

Pharmacokinetics

Absorption: IV administration of ketamine has a rapid absorption rate with the high plasma levels being attained readily [47]. IM route of administration has a high bioavailability of 93 and peak plasma levels in 5 to 30 minutes [47]. Nevertheless, oral ketamine is much less bioavailable (approximately 16 29 per cent) to eliminate first-pass liver metabolism [47]. Conversely, intranasal and intrarectal injection of ketamine has proved to have better bioavailability of 45 percent to 50 percent and 25 percent to 30 percent respectively [47].

Metabolism: Ketamine is metabolised principally by CYP3A4 enzyme, and secondarily, CYP2B6 and CYP2C9 enzymes. It is subject to N-dealkylation, hydroxylation, conjugation and dehydration [48].

Elimination: After IV, ketamine is redistributed to the periphery, after CNS, ketamine is redistributed to the periphery [49]. It has a half-life of between 2 and 4 hours [49]. Most ketamine and its metabolites are excreted via urine following administration with 91% of the radioactivity of administered drug excreted within 5 days. Parent drug or major metabolites only are found in about 20% [49]. Also, metabolites of ketamine and nor-ketamine, which are hydroxylated, are excreted in urine and bile [49].

Mechanism

Ketamine is a racemix of two enantiomers; esketamine and arketamine [45]. Esketamine is one much stronger NMDA receptor pore blocker when compared to arketamine [45]. The anaesthetic, analgesic and psychotomimetic actions of ketamine are caused by pore blocking of the NMDA receptor [45]. When the NMDA receptor is blocked, this will cause analgesia through prevention of central sensitization of the dorsal horn neurons i.e. the effect of ketamine will be disrupting the transmission of pain in the spinal cord [45]. Ketamine

hydrochloride is a dissociative anaesthetic that is not barbiturate and a derivative of cyclohexanone, which has fast effects creating a deep anaesthetic state and analgesia [43]. It is a hydrochloride of 2-(o-chlorophenyl)-2-(methylamino)-cyclohexanone (C 13H 6ClNO) [43]. Being a non-competitive antagonist at the N methyl D aspartate receptor (NMDA R) and glutamate receptors, and also blocking the channels of HCN1 receptors, the distinctive dissociative effect of ketamine and its semi-agonistic μ-opioid receptor activity allow performing painful procedures without inhibiting sedation and comfort [50]. It usually maintains pharyngeal and laryngeal reflexes, and has intact or exaggerated skeletal muscle tone; thus, it is specifically eminently employed in the emergency department to carry out short-term procedures in unprepared patients [50]. With that being said, airway protection is not guaranteed and immediate or high-dose delivery can lead to short-term respiratory depression clinicians should be prepared to address airway management [50].

Ketamine works better than the plasma levels in the chronically painful situation when it is used as an antidepressant off-label [45]. One of the existing postulations is that NMDA-R antagonism triggers a hyper-glutamatergic condition, which promotes synaptogenesis and increases the production of Brain derived neurotrophic factor (BDNF) [45]. This, in its turn, facilitates the structural synaptic connectivity [45]. Nonetheless, despite the major role that the NMDA receptor plays in the etiology of depression, the exact mechanism of the antidepressant effect of ketamine is yet to be clearly comprehended [45]. An example of this is that, several other NMDA antagonists which include Memantine, Lanicemine,Rapastinel and 4 Chlorokynurenine have hitherto failed to exhibit strong antidepressant properties [45]. This indicates that NMDA antagonism is not necessarily the entire cause of antidepressant effects of ketamine [45].

It has been suggested that one effect is the release of glutamate is increased by the inhibition of NMDA receptors on GABA-ergic inhibitory neurons (and hence the disinhibition of pyramidal neurons) on the production of an acute glutamate surge that stimulates alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) by ketamine [45]. Activation of AMPAR and stimulation of BDNF release and TrkB (tropomyosin-receptor-kinase B) receptor follow this effect [45]. It activates downstream signalling cascades such as the mammalian target of rapamycin (mTOR) pathway, and deactivation of glycogen synthase kinase-3 (GSK-3) and also inhibits eukaryotic elongation factor 2 (eEF2) kinase [45]. The overall result is the stimulation of the synthesis of synaptic proteins, the formation of spines and the increase of synaptic connections, particularly in the prefrontal cortex and the hippocampus [45]. The active metabolite (2R,6R) Hydroxynorketamine

(HNK) can take its part as well by enhancing transmission via AMPAR despite the insignificant NMDA-R affinity [45]. Such a combination of mechanisms is believed to be underlying the onset of antidepressant effect and maintenance of its effect in spite of comparatively low pharmacokinetic half-life of ketamine [45].

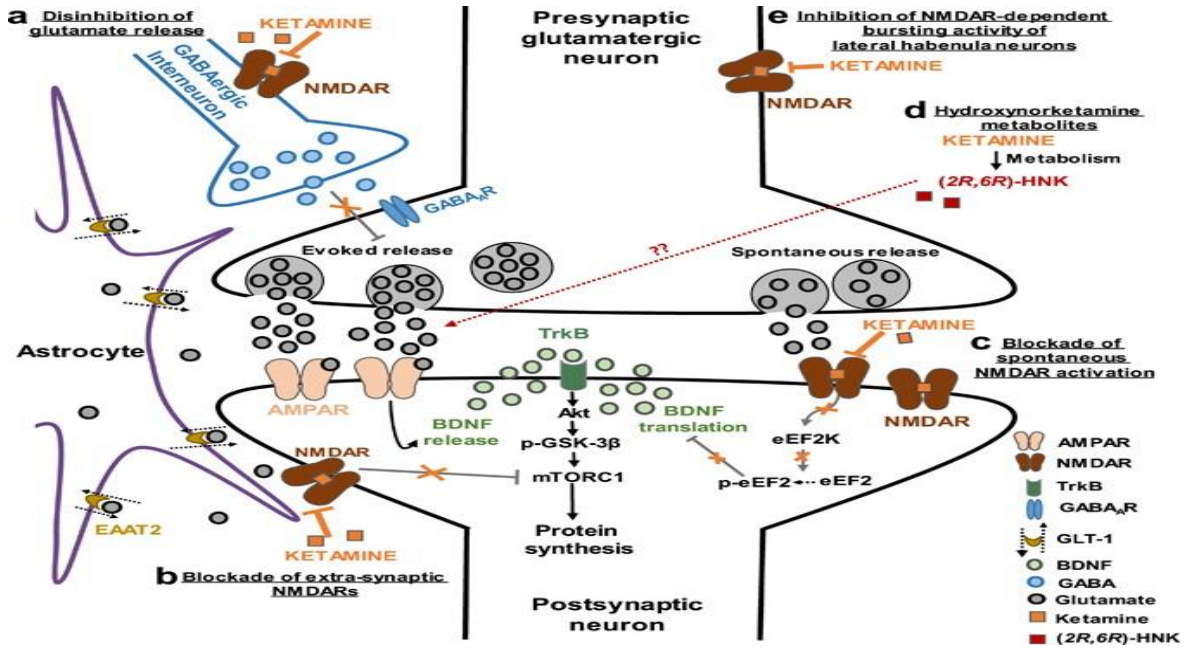

Figure:7 Molecular Mechanism of Ketamine in Depression.

Ketamine Background to the use of ketamine in treating depression

Ketamine is a quick acting antidepressant whose effect is temporary [51]. The use of intravenous ketamine infusion in the treatment-resistant depression can lead to the enhancement of the mood in 4 hours where the peak is achieved at 24 hours [52]. Only one dose of intravenous ketamine has reported a response rate of more than 60 per cent at 4.5 hours of administration (with a lasting effect at 24 hours) and over 40 per cent at 7 days [53]. Even though very few pilot studies have tried to establish the optimum dose, there is a rising trend that 0.5 mg/kg dose injected in 40minutes provide an optimum result [54]. The antidepressant of ketamine effect wears off after 7 days and the majority of individuals relapse after a period of 10 days [55]. Nevertheless, to a considerable proportion of people, the enhancement can be in the form of 30 days or more [56].

The duration of time in which the antidepressant effects of ketamine treatment last after a course of treatment can be one of the greatest challenges with ketamine treatment [56]. Maintenance therapy with ketamine is also a possible alternative, as it is normally

administered twice or once a week [56]. Ketamine can also reduce suicidal ideation to a period of up to three days following injection [57].

Contraindication

Ketamine should not be used in patients that have comorbidities where raised blood pressure can result in the risk of complications including aortic dissection, uncontrolled hypertension, heart attack, or an aneurysm [58]. It should be avoided in patients who have demonstrated previous hypersensitivity; anaphylaxis and angioedema have been reported [58].

Warning and Precautions

Pregnancy and lactation: The FDA does not recommend the use of ketamine in obstetrics or pregnancy as well as during breastfeeding [59].

Paediatric neurotoxicity: Paediatric neurotoxicity may occur because of the prolonged use (above 3 hours) of ketamine in children under 3 years, which causes cognitive impairment [60]. Neuronal apoptosis in which the NMDA receptors are blocked is one of the potential mechanisms [60].

Effects

- Nausea and Vomiting [51]
- Dizziness [51]
- Hallucinations [51]
- Increased blood pressure [58]

METHODOLOGY

Research Design

The current research is an analytical, descriptive, and qualitative review of the pharmacological processes and therapeutic opportunities of psilocybin and ketamine on depression treatment [51]. The method was chosen to collect, assess, and analyse existing scientific data concerning psychedelic-assisted therapy [51]. No experimental procedures are applied in the study on any human or animal. Rather, it focuses on the synthesis of the accessible information in published scientific and clinical research to present a holistic view of pharmacology[52].

Goals of the Methodology

The primary aim of this methodology is to gather, analyse, and compare scientific literature on the topic of psilocybin and ketamine existing in a systematic manner [53]. The specific aims are:

- To investigate the mechanism of action and pharmacodynamics of the two compounds [54].
- To determine their efficacy and clinical outcomes in treatment-resistant depression as antidepressants [54].
- To compare safety, duration effect, and therapeutic potential of psilocybin and ketamine [55].

Sources and Search Strategy Data.

Systematic search of the literature was carried out in the respectable databases including PubMed, ScienceDirect, Scopus, Google Scholar and ClinicalTrials.gov [55]. The date of search was between 2010 and 2025 [56].

The relevant articles were located with the help of the following keywords and combinations: Psilocybin, Ketamine, Psychedelic-assisted therapy, Depression, Treatment-resistant depression, NMDA receptor antagonist, 5-HT 2A receptor, Neuroplasticity, Rapid-acting antidepressant [56].

Moreover, the reference lists of large review papers and clinical trials were also filtered manually to reveal any other relevant works [57].

Inclusion and Exclusion Criteria

Inclusion Criteria

- Research done on humans or animals on antidepressants of psilocybin or ketamine [57].
- Published English clinical trials, meta-analyses and pharmacological studies [58].
- Studies whose results are quantifiable, like clinical rating scales, e.g. Hamilton Depression Rating Scale (HDRS) or Beck Depression Inventory (BDI) [58].

Exclusion Criteria

- Research that investigated other psychedelic drugs (like LSD, MDMA or DMT) not pertaining to psilocybin or ketamine [60].
- Publications not peer-reviewed, conference abstracts, or unfinished data [60].
- Articles which were not relevant pharmacologically or therapeutically to depression [60].

Data Analysis

Having determined the qualified research, the data were collected manually and examined concerning the pharmacological and therapeutic parameters [60]. The information that was extracted consisted of:

- Action mechanism and receptor targets [60].

Pharmacodynamics and pharmacokinetics.

- Dosing rules and routes of administration [60].
- Antidepressant effects and duration of clinical outcomes [60].
- Safety profiles and negative effects [60].

Thereafter, it was compared to demonstrate major similarities and differences between psilocybin and ketamine [51]. Particular attention was paid to their interaction at the receptor level, effects on neurotransmitters, and outcomes of neuroplasticity [52]. The data were organized and presented in tables and summaries to make them easily understandable [52].

In this study, the pharmacological analysis was founded on the mechanism of action of both compounds on the molecular and receptor levels [53]. In the case of psilocybin, we have analysed its conversion to psilocin, which is a partial agonist of 5-HT 2A receptors, resulting in the release of glutamate, activation of AMPA receptors, and synaptic plasticity that occurs via BDNF [53].In the case of ketamine, its action as non-competitive NMDA receptor antagonist was analysed in connection with glutamate release, AMPA receptor activation, and BDNF-mediated synaptic plastic.

Data Interpretation and Outcome Measures.

Data that were collected were then interpreted qualitatively in order to comprehend pharmacological as well as therapeutic aspects [55].

The main result of the research was to assess the effectiveness of psilocybin and ketamine in the management of depression, especially cases of the treatment-resistant type [55].

RESULT AND DISCUSSION

1. Overview of Findings

The compounds work in treatment compared to the conventional antidepressants that take weeks to manifest their action [56]. The main effect of Psilocybin is the activation of serotonin (5-HT2A) receptor; and the main effect of ketamine is the antagonist action on

NMDA receptor and the regulation of glutamate transmission which leads to heightened synaptic plasticity [57]

2. Pharmacological Findings

2.1 Psilocybin

- Psilocin: 5-HT 2A receptors of the prefrontal cortex bind with psilocin to cause improved serotonin signalling, alterations of neural network connectivity, and alterations in consciousness and emotional perception [57].
- Clinical trials have reported that one or both courses of guided psilocybin sessions have a considerable effect of decreasing the symptoms of depression and as well there is an improvement in a depression rating scale such as the Hamilton Depression Rating Scale [58].

2.2 Ketamine

Ketamine, is a dissociative anaesthetic that has been implicated in its rapid antidepressant action that is seen even in sub-anaesthetic dosages [59]. Ketamine has immediate antidepressant effects that last in a few hours especially in treatment-resistant depression [59]. Mechanism It exerts a non-competitive inhibitory effect on the NMDA receptors on the inhibitory interneurons [60]. This blockade triggers the release of glutamate causing stimulation of AMPA receptors and a subsequent stimulation of the mTOR signalling pathway and subsequent expression of BDNF [60]. All these biochemical processes contribute to the growth and connection of the synapses and neurons and overturn the neuronal damage caused by stress [60]. According to clinical studies, esketamine has its ability to cause a rapid reduction in depressive symptoms and the effects of the medication will last a number of days after administration [51].

3. Comparative Evaluation

Psilocybin and ketamine are rapid antidepressant acting substances that are mediated through a number of pharmacological mechanisms [52]. Psilocybin is capable of causing the prolonged psychological change and ketamine the rapid and relatively short-lived weakening effects regarding the symptoms [53].

4. Clinical and Therapeutic Implications

Psychedelic assisted therapies such as psilocybin and ketamine could be applied in the treatment-resistant depression treatment [54]. These agents would exponentially increase the mood and stability of emotions in a strictly controlled clinical setting. Further research is required so as to get standardized treatment and safety during the long-term [55].

Research Limitations

Although evidence on their application is strong, the two compounds have serious research constraints [56].

Regarding ketamine, it has been linked to dependency, a short-term effect, and a lack of neurobiological information on the issue of long-term effects of repeated ketamine dosing [57]. More scientific studies are needed to assess long-term safety, common dose of psychedelic-assisted therapies [58].

Future Perspective

This would necessitate further research to carry out larger randomized controlled studies which identify the adverse long-term effects, optimal dosage schedules and standardized therapy regimens of psychedelic-assisted therapies [59]. Additional neuroimaging and molecular pharmacological studies can assist in gaining a better insight into the mechanisms of rapid antidepressant effects of psilocybin and ketamine [60].

CONCLUSION

These findings suggest the greater relevance of psychedelic-assisted treatment in the modern psychiatric research. Psilocybin and ketamine are new emerging therapeutic agents that would be effective in treating depression, particularly in cases of treatment-resistant depression. Their pharmacological action is the regulation of the serotonergic and glutamatergic system, which comprises of the facilitated neuroplasticity and emotion control. Although nowadays the therapeutic potential has become promising in the clinical context, further large-scale, longitudinal research is needed, which can offer safety, customize the dosing scheme, and give a universal approach to treatment.

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REFERENCES

1. Osmond H. A review of psychotomimetic agents. Ann NY Acad Sci. 1957;66:418–434.
2. Nichols DE. Psychedelics. Pharmacol Rev. 2016;68:264–355.
3. Carhart-Harris RL, Goodwin GM. The therapeutic potential of psychedelic drugs. Neuropsychopharmacology. 2017;42:2105–2113.
4. Rucker JJH, Iliff J, Nutt DJ. Psychedelics in psychiatry. J Psychopharmacol. 2018;32:119–134.
5. Vollenweider FX, Kometer M. The neurobiology of psychedelic drugs. Nat Rev Neurosci. 2010;11:642–651.
6. Hartogsohn I. Set and setting in psychedelic research. J Psychopharmacol. 2017;31:1259–1277.
7. Johnson MW, Richards WA, Griffiths RR. Classic hallucinogens in therapy. Neurotherapeutics. 2017;14:734–740.
8. Nichols DE. Hallucinogens. Pharmacol Rev. 2004;56:243–347.
9. Krystal JH, Sanacora G, Duman RS. Ketamine pharmacology and therapeutics. Biol Psychiatry. 2019;85:659–667.
10. Halberstadt AL. Serotonergic hallucinogens. Pharmacol Ther. 2015;148:115–147.
11. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. Addiction Biol. 2002;7:357–364.
12. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin therapy for depression: sustained remission outcomes. Lancet Psychiatry. 2016;3: 104–113.
13. Carhart-Harris RL, Erritzoe D, Williams T, et al. Neural correlates of psilocybin. Proc Natl Acad Sci USA. 2012;109:2138–2143.
14. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and ketamine. Science. 2019;364: eaat8078.
15. Nichols DE. Psychedelic pharmacology. Pharmacol Rev. 2016;68:264–355.
16. Halberstadt AL. Mechanisms of serotonergic hallucinogens. Pharmacol Ther. 2015; 150: 19–39.

17. Guzmán G. Hallucinogenic mushrooms in Mexico. Econ Bot. 2008;62: 155–174.
18. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin research review. J Psychopharmacol. 2016;30:1181–1199.
19. Hofmann A. Discovery of LSD. Experientia. 1943;1:7–9.
20. Bogenschutz MP, Johnson MW. Psychedelic therapy history. Curr Top BehavNeurosci. 2018;36:17–39.
21. Hofmann A, Heim R, Brack A, Kobel H. Isolation of psilocybin. Experientia. 1958;14:397–399.
22. Nichols DE. Chemistry of psychedelics. Pharmacol Rev. 2016;68:264–355.
23. Johnson MW, Griffiths RR. Clinical trials with psychedelics. Psychopharmacology. 2018;235: 2363–2375.
24. Nutt DJ, King LA, Nichols DE. Effects of drug policy on research. Nat Rev Neurosci. 2013;14:577–585.
25. United States Controlled Substances Act. 1970.
26. Nichols DE. Psychedelics. Pharmacol Rev. 2016;68:264–355.
27. Guzmán G. Hallucinogenic mushrooms in Mexico. Econ Bot. 2008;62:155–174.
28. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin research. J Psychopharmacol. 2016;30:1181–1199.
29. Passie T, Seifert J, Schneider U, Emrich HM. Pharmacology of psilocybin. Addiction Biol. 2002;7:357–364.
30. Halberstadt AL. Serotonergic hallucinogens. Pharmacol Ther. 2015;148:115–147.
31. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin therapy. Lancet Psychiatry. 2016;3:104–113.
32. United Nations Convention on Psychotropic Substances. 1971.
33. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin for anxiety and depression. J Psychopharmacol. 2016;30:1165–1180.
34. Stamets P. Psilocybin Mushrooms of the World. 2nd ed. Berkeley: Ten Speed Press; 1996.
35. Guzmán G. Distribution of Psilocybe species. Mycol Res. 2005;109: 987–995.
36. Hofmann A, Kobel H, Frey A, Heim R. Isolation of psilocybin. Experientia. 1958;14:397–399.
37. Nichols DE. Hallucinogens pharmacology. Pharmacol Rev. 2016;68:264–355.
38. Vollenweider FX, Kometer M. Psychedelic neurobiology. Nat Rev Neurosci. 2010;11:642–651.

39. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. Pharmacokinetics of psilocybin. Addiction Biol. 2002;7: 357–364.
40. Nichols DE. Tryptamine chemistry. Pharmacol Rev. 2016;68:264–355.
41. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Pharmacology. 8th ed. Elsevier; 2016.
42. Barker SA. N,N-Dimethyltryptamine (DMT) review. Psychopharmacol. 2018;235:131–160.
43. Krystal JH, Sanacora G, Duman RS. Ketamine: pharmacology and therapeutics. Biol Psychiatry. 2019;85:659–667.
44. Domino EF. Pharmacologic effects of ketamine. Drug Dev Res. 2010;71:21–29.
45. Zhang K, Hashimoto K. R- and S-ketamine: differential pharmacology and antidepressant effects. Front Pharmacol. 2019;10:120.
46. Corssen G, Domino EF. Structure-activity relationships of phencyclidine analogs: ketamine. Anesth Analg. 1966;45:29–38.
47. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES. Ketamine pharmacokinetics and routes of administration. Anesth Analg. 2018;127:1406–1419.
48. Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 to ketamine metabolism in human liver microsomes. Br J Anaesth. 2002;89:681–689.
49. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: pharmacokinetics and pharmacodynamics. Anesth Analg. 2016;122:143–164.
50. White PF, Schüttler J, Shafer A, Stanski DR. Ketamine: clinical considerations. Anesth Analg. 1982;61:201–216.
51. Sanacora G, et al. Ketamine and rapid-acting antidepressants. Biol Psychiatry. 2017;81:259–268.
52. Zarate CA Jr, et al. A randomized trial of an NMDA antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63:856–864.
53. Murrough JW, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013;74:250–256.
54. McGirr A, et al. Efficacy and safety of ketamine in bipolar depression: systematic review. J Affect Disord. 2015;188:270–275.
55. Newport DJ, et al. Ketamine and other NMDA antagonists: early clinical trials. Curr Psychiatry Rep. 2015;17:115.
56. Wilkinson ST, et al. Maintenance ketamine for treatment-resistant depression. Am J Psychiatry. 2017;174:1109–1117.

57. Ionescu DF, et al. Ketamine's effect on suicidal ideation: a systematic review. CNS Drugs. 2016;30:1095–1108.
58. Caddy C, et al. Ketamine safety profile in depression: a systematic review. J Psychopharmacol. 2015;29:956–963.
59. Short B, et al. Side-effects associated with ketamine use in depression. CNS Drugs. 2018;32:485–502.
60. Olney JW, et al. NMDA antagonist neurotoxicity and paediatric concerns. NeurosciBiobehav Rev. 2000;24:291–303.