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THERAPEUTIC MECHANISMS OF KETAMINE

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SUMMARY

Major depressive disorder is the greatest burden of developed countries in the context of morbidity caused by mental disorders. Until recent, ketamine has been mostly used for anesthesia, analgesia, sedation and treatment of chronic pain syndromes. However, unique pharmacodynamic properties of ketamine have increased interests in it's use for treatment of depression. It is assumed that ketamine reverses synaptic chronic stress pathology within one day of administration by postsynaptic glutamate activation, providing synaptic connectivity restoration that last for days or weeks. Potential glutamatergic agents, in context of treatment of major depressive disorder are not entirely novel phenomenon. Considering the aforementioned, current neurobiological view of depression as a solely monoaminergic phenomenon should be reassessed in order to prompt discovery of putative antidepressant drugs of novel generation. Acute side effects, such as increased salivation, increase in heart rate, systemic arterial pressure and intracranial pressure necessitate careful monitoring during intravenous administration of ketamine, even in subanesthetic doses. However, major burden of ketamine administration lies in it's ability to produce psychotomimetic side effects and emergence delirium. Esketamine nasal spray has now been widely approved and is considered safe in terms of acute side effects, tolerability and consistent therapeutic benefit.

Key words: *ketamine – depression – neurobiology*

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INTRODUCTION

It has been half a century since ketamine is widely known to medical professionals around the world as a safe anesthetic and sedation drug (Dundee 1990, Mion 2017, Kurdi et al. 2014). The dynamics of the epidemiological data required the intensification of the efforts of the entire scientific community to adapt to the rapid changes in society. As depression has become one of the leading scourges of modern society, and current advances in treatment are far from satisfactory, scientists seek to think outside the box to better understand the pathophysiology and psychopathology of depression (Pereira & Hiroaki-Sato 2018, Jakovljevic & Borovecki 2018, Rush et al. 2006, McIntyre et al. 2014). More than half a century ago, psychiatrists investigated the effects of psychotomimetics on certain mental disorders and the past decade has suggested that the same trend will continue in this century. In modern times, ketamine is known to the general population as a club drug and to the medically educated people as a dissociative anesthetic. Why would anyone take a dissociative anesthetic for recreational purposes? Through a decade of everyday global use in clinical practice, ketamine has shown a number of interesting but also confusing side effects. There has been improvement in mood in patients who received a certain dose of ketamine and that effect would last for days. Years of research into the effects of ketamine on the central nervous system have led to a revision of the current theory of depression as purely a disorder of the monoamine systems of the brain, neglecting the importance of the leading cortical neurotransmitter, glutamate. Recent research suggests that the effect of ketamine, in addition to the receptor, is achieved within the cell. Ketamine acts on a cascade of intracellular signaling pathways responsible for generating the inflammatory response, now proven to be involved in the pathophysiology of depression (Pereira & Hiroaki-Sato 2018, Strasburger et al. 2017, Chaki 2017). Ketamine has recently been approved for the treatment of therapeutically resistant depression, with well-defined indications, contraindications, and treatment regimens (Ban 2016, Canuso et al. 2018, Wajs et al. 2020). As ketamine is a psychotomimetic, during the administration of the drug patients will be in a state of consciousness to which they were not previously accustomed. Psychiatrists face the challenge of developing new psychotherapeutic approaches to patients with partially dissociated states of consciousness, altered perceptions, with potentially anxious, if not transient psychotic-like reactions. What follows is a time of questioning and re-examining current concepts in the treatment of depression. This is a narrative review article on pharmacological properties and clinical potential of ketamine in treatment of depression.

TREATMENT OF DEPRESSION AND WHERE WE ARE TODAY

Major depressive disorder (MDD) is the greatest burden of developed countries in context of morbidity caused by mental disorders with estimated prevalence in nearly 17% (Wittchen et al. 2011, Kessler 2003). In classification of depressive disorders, persistent depressive disorder (PDD) is defined by minimal two-year illness duration while treatment-resistant depression (TRD) is defined as depression with an unsatisfactory response to two different classes of prescribed antidepressant drugs (Bow 2018, Machmutow et al. 2019). Majority of approved antidepressant drugs for treatment of MDD primarily modulates monoaminergic brain circuits (serotonin, norepinephrine, or dopamine) (Jaso et al. 2017). Among those groups of psychiatric medications most widely prescribed drugs belong to class of selective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI). It is estimated that approximately 70% of patients with depression respond positively at some degree to prescribed antidepressants, while approximately 30% of patients stay nonrespondant (Rush et al. 2006, Trivedi et al. 2006). According to National Institute of Mental Health only 27% of patients suffering from depression achieve remission within 12 weeks while adjunctive medication made very little impact (Howland 2010). In addition, average time needed for achieving stable remission was 7 weeks in patients that responded well to prescribed antidepressants. That being said, urgency for a new antidepressant treatment mechanisms is evident (Krystal et al. 2013). Furthermore, current neurobiological view of depression as a solely monoaminergic phenomenon should arguably be reassessed in order to expand the field of reasearch into other potential systems and prompt the discovery of putative antidepressant drugs of novel generation.

HISTORY OF GLUTAMATERGIC AGENTS AND FUTURE OF KETAMINE

Metabotropic glutamate (mGlu) receptors identified as an important regulators of glutamatergic transmission with possible significant role in the expression of moods and emotions (Schoepp & Conn 1993). Vast amounts of clinical data confirmed that ketamine, a non-competitive N-methyl-D-aspartate glutamate receptor antagonist produces remarkable rapid-onset antidepressant effect in both rodents and humans (Krystal et al. 1994). In contrast to the delayed onset in significant therapeutic effect (typically 3-6 weeks) of available antidepressants, it have been proved that ketamine produces significant antidepressant effect in just few days, or even hours after administration (Strasburger et al. 2017, Chaki 2017). This surprising and potentially revolutional discovery could guide researchers to the development of a possible life-saving agent for depressed patients, primarily by reducing the risk of suicide associated with delayed onset of action of currently available antidepressants (Strasburger et al. 2017). Also, this discovery opened the door for investigation of the whole new class of non-monoamine-based agents for treatment of depression (Chaki 2017). The focus has shifted from monoaminergic system research to glutamatergic system research, which has now been identified as a potential target of action in a new generation of antidepressants (Sanacora et al. 2008, Skolnick et al. 2009). Glutamate is the major excitatory neurotransmitter in the central nervous system, and with its cognate receptors takes part in the pathophysiology of MDD (Jaso et al. 2017). Potential glutamatergic agents, in context of MDD treatment are not entirely novel phenomenon. In 1959, Dr. George Crane discovered that antituberculotic drug D-cycloserine induced mood improvement in 30 out of 37 patients suffering from tuberculosis and comorbid depression, predominately within 2 weeks (Crane 1959). More than half century later, first placebo-controlled trial replicating this reasearch reported progressive mood improvement over 6 weeks of treatment with D-cycloserine (Kurdi et al. 2014). D-cycloserine is a partial agonist at the glycineB coagonist site of N-methyl-D-aspartate (NMDA) glutamate receptors bearing the GluN2A and GluN2B subunits (previously NR2A and NR2B subunits) and a full agonist of NMDA receptors containing the GluN2C and GluN2D subunits (Sheinin et al. 2001, Dravid et al. 2010). In the late 1980's researches on the effects of ketamine in healthy subjects were started with an aim of determination the correlation between dysfunction of glutamate synaptic transmission in schizophrenia and in alcoholism (Krystal et al. 1994, Krystal et al. 2003a, Krystal et al. 2003b). Later on the same paradigm of dosing and administration was used to investigate the effects of ketamine in depressed patients with an aim of characterizing alterations in NMDA receptor function related to depression. In 2000 researchers proved that a single subanesthetic intravenous injection of ketamine in dose of 0.5 mg per kg over 40 minutes exerted rapid (few hours) and sustained (approximately one week) antidepressant effect in patients suffering from MDD and in subsequent studies also in patients suffering from TRD (Berman et al. 2000, Zarate et al. 2006). Following these discoveries, reasearchers studied the effects of repeated administration of ketamine in patient suffering from TRD and those studies have determined that no tolerance occurred for a short period of repeated administration while some patients relapsed after cessation of administration (Aan het Rot et al. 2010, Murrough et al. 2013, Rasmussen et al. 2013). Several studies reported that ketamine administration has shown beneficial results in suicidal ideation reduction (Ionescu et al. 2016, Price & Mathew 2015). Discovery of the antidepressant effects and anti-suicide potential of ketamine is the most promising finding in depression research in over 60 years (Chaki 2017).

NEUROBIOLOGY AND ANTIDEPRESSANT PROPERTIES OF KETAMINE

Ketamine blocks the NMDA receptor, presumably on GABA interneurons, leading to disinhibition of pyramidal neural activity in cortex, subsequently increasing the glutamate release triggering a cascade of signaling pathways, including α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor activation, secretion of brain-derived neurotrophic factor (BDNF) secretion and activation of mammalian target of rapamycin (mTOR) signaling (Krystal et al. 2013). Some authors suggest that NMDA receptor antagonism results inhibiting eukaryotic elongation factor 2 kinase and increased BDNF production (Monteggia et al. 2013). Both of these hypothesis underlie the theory of increased cortical synaptic connectivity. Model of the synaptic chronic stress pathology (CSP) in the prefrontal cortex (PFC), hippocampus and dopaminergic nucleus accumbens (NAc) suggests that synaptic disconnectivity could be a common pathology in numerous psychiatric disorders correlated with chronic distress (Abdallah & Krystal 2020). The model of synaptic CSP proposes that chronic stress results in glial cell reduction, decreased capacity of overall glutamate reuptake, increased extrasynaptic glutamate levels and subsequent excitotoxicity, resulting in neuronal atrophy, loss of dendritic spine density and decreased glutamate neurotransmission (Abdallah et al. 2018). According to CSP model during chronic stress, neurotransmission strength in sustained synapses of PFC also gets affected by reduced number of postsynaptic NMDA and AMPA receptors (Li et al. 2017). It is assumed that ketamine reverses CSP in prefrontal cortex, hippocampus and NAc within one day of administration by postsynaptic glutamate activation with subsequent upregulation of neurotrophic signaling and increased protein synthesis, providing synaptic connectivity restoration that last for days or even weeks (Yuen et al. 2010, Abdallah et al. 2018). Also, according to the model of synaptic CSP chronic stress induces synaptic monoaminergic disregulation and hyperconnectivity in dopaminergic NAc (Melo et al. 2015, Abdallah et al. 2018). These synaptic alterations in the PFC and NAc were both associated with depressive symptoms in earlier preclinical studies (Duman et al. 2016). These findings propose that synaptic hypoconnectivity in PFC and hippocampus as well as hyperconnectivity of dopaminergic NAc, reflect two independent pathways underlying clinical depression (Abdallah et al. 2015, 2017). This Dual Pathology model suggests that patients with underlying glutamatergic impairment would be treatment-resistant with widely used monoaminergic antidepressants in contrast to those with monoaminergic pathology that would effectively respond to same monoaminergic antidepressants (Abdallah et al. 2017).

Antidepressant properties of ketamine might also be due to effect on mitochondrial energy metabolism. In a study on mice models, ketamine tended to downregulate the adenosine triphosphate/adenosine diphosphate metabolite ratio and increased levels of enzymes that are part of the oxidative phosphorylation pathway, which all leaded to less protein damage by decreasing reactive oxygen species (ROS) production (Weckman et al. 2017). However, it is to mention that in higher concentrations, ketamine can increase ROS generation and apoptosis in human neurons (Ito et al. 2015).

EPIGENETIC ASPECTS OF KETAMINE

Gene and environment interplay underlie the pathophysiology of depression and these interactions are possibly mediated by the epigenetic mechanisms, defined as alterations of gene expression without structural changes in the DNA (Duclot & Kabbaj 2015). Through these mechanisms, the environment interacts with the genome to generate plastic phenotypic exposures which are a consequence of controlled gene regulation and transcription in a long term manner (Renthal et al. 2007). Epigenetic modulation consists of DNA methylation (Razin & Riggs 1980), histone modification (Strahl & Allis 2000), and regulation of non-coding RNAs (Wang et al. 2017). Recent studies have discovered that epigenetic regulation is closely involved in the pathophysiology of depression and the therapeutic mechanisms of typical antidepressants (Mahgoub & Monteggia 2013, Tsankova et al. 2006). BDNF is now known as a crucial developmental factor in the adult central nervous system, acting as a modulator of activity-induced neuronal plasticity (Park & Poo 2013). It is clear that BDNF plays a critical role in the pathophysiology of depression but the lack of clear genetic etiology has made the regulation of BDNF expression a focal point of extensive research (Duclot & Kabbaj 2015). It is proven that antidepressant treatment with ketamine increases plasma BDNF levels in patients suffering from depression, but serum levels of BDNF were significantly elevated only at one week following the first ketamine infusion (Allen et al. 2015). Preclinical studies showed that an insufficient BDNF expression and signaling per se do not lead to depression, rather affecting the efficacy of antidepressant treatments (Adachi et al. 2007). Previous studies demonstrate that the class II histone deacetylase (HDAC and HDAC5) epigenetically controls behavioral adaptations to chronic emotional stimuli in nucleus accumbens (Renthal et al. 2007). Ketamine rapidly stimulates phosphorylation of histone deacetylase 5 (HDAC5) and nuclear export in rat hippocampal neurons resulting in enhancement of the transcriptional activity of the myocyte enhancer factor 2 (MEF2) and subsequent activation of MEF2 target genes (Choi et al. 2015). Substantial evidence supports a role for MEF2-mediated transcription in neuronal survival, differentiation, and synaptic function (Finsterwald et al. 2013). BDNF was shown to activate MEF2-mediated transcription in cerebellar granule and cortical neurons (Wang et al 2007).

CENTRAL NERVOUS SYSTEM EFFECTS OF KETAMINE

Effects of ketamine on electroencephalogram are characterized by abolition of alpha rhythm and dominance of theta activity. Appearance of delta activity coincides with loss of consciousness and onset of "dissociative anesthesia", which is characterized by dissociation between the thalamocortical and limbic systems. Dissociative anesthesia resembles a cataleptic state in which eyes remain open with a slow nystagmic gaze. Ketamine-induced excitatory activity, clinically evident as myoclonic and seizure-like movements, occurs in both the thalamus and limbic systems without evidence of spread of seizure activity to cortical areas (Rathmell & Rosow 2015, Ferrer-Allado et al. 1973). Indeed, ketamine does not alter the seizure treshold and does not precipitate convulsions in patients with seizure disorders (Rathmell & Rosow 2015, Celesia et al. 1975). On contrary, ketamine is considered to possess anticonvulsant activity and has been effectively used in treatment of refractory status epilepticus (Fang & Wang 2015, Modica et al. 1990). Ketamine is considered to increase cerebral blood flow, intracranial pressure and cerebral rate of oxygen consumption (Rathmell & Rosow 2015, Reich & Silvay 1989). For that reason, patients with intracranial pathology are considered vulnerable to increase in intracranial pressure after ketamine administration (Rathmell & Rosow 2015). NMDA antagonism suggests a possible neuroprotective role of ketamine during cerebral ischemia, although this remains an unproved hypothesis (Pfenninger & Himmelseher 1997).

Emergence from ketamine may be associated with visual, auditory, proprioceptive, and confusional illusions, which may progress to delirium. Cortical blindness may be transiently present. Dreams and hallucinations can occur up to 24 hours after administration but usually disappear within few hours of onset. Loss of skin and musculoskeletal sensations results in decreased ability to perceive gravity, thereby producing a sensation of bodily detachment or floating in space (Rathmell & Rosow 2015, White et al. 1982).

RACEMIC, S (+), R (-) KETAMINE AND NORKETAMINE

Ketamine structurally resembles phencyclidine and consists of two optical isomers (Rathmell & Rosow 2015, Kohrs & Durieux 1998). Racemic ketamine is a mixture containing equal parts of S (+) ketamine and R(-) ketamine enantiomeres. Compared to racemic form, S(+) ketamine produces more intense analgesia, has more rapid metabolism and consequent recovery, produces less salivation, and causes less emergence delirium (Rathmell & Rosow 2015, Kienbaum et al. 2001, White et al. 1980). S (+) ketamine has higher affinity for the NMDA receptors and higher anesthetic potency comparing to the R (-) enantiomere (Domino 2010). Some authors suggest that R (-) ketamine is an enantiomere with greater antidepressant potential than S (+) enantiomere, arguably with less ketamine-related side-effects (Kohrs & Durieux 1998). Norketamine is an active metabolite of ketamine with approximately 7-fold lower affinity for the NMDA receptor than racemic ketamine. Some studies have shown promising results of rapid antidepressant effects of norketamine, with lower potency correlating its lower NMDA affinity (Sałat et al. 2015). In a multicenter, randomized, placebo-controlled trial of intravenously administrated S (+) ketamine in doses of 0.2/0.4 mg/kg over 40 minutes conducted in 30 patients suffering from TRD, results proved significant antidepressant effect with early onset (2h) after the administration following a 3-day response in 67% of patients treated with 0.2 mg/kg and 65% treated with 0.4 mg/kg, while reported adverse effects of intravenously administered S(+) ketamine were transient dissociative and psychotic-like symptoms, which subsided within 4 h of cessation (Singh et al. 2016). Nevertheless, ketamine administration at sub-anesthetic doses hasn't shown any unacceptable level of risk in healthy individuals while self-reported transient negative adverse events were described as "very unpleasant sensations", "no control, not a good feeling", "weird", "panicky", and "too high, walls closing in", nightmares, insomnia, a lower ability to concentrate, tearfulness, and no response to verbal and painful stimuli (Perry et al. 2007). One meta-analysis showed that transient psychotomimetic effects, following a single administration of ketamine, did not cause a persistent psychosis or rapid affective switches in patients suffering from unipolar and bipolar depression (McGirr et al. 2015).

ESKETAMINE NASAL SPRAY SAFETY, EFFICACY AND TOLERABILITY

The Food and Drug Administration (FDA) has recently approved nasal spray formulation of S (+) ketamine for treatment of patient suffering from TRD (Szarmach et al. 2019). Several studies conducted in past two years investigated long-term effects, possible toxicity and side-effects during and after repeated administration of nasal formulation of S (+) ketamine, adjunctive to an oral antidepressant in subjects suffering from TRD and results have shown superior efficacy of S (+) ketamine compared with placebo nasal spray, not only in TRD patients but also in depressed patients at imminent risk for suicide (Daly et al. 2018, Canuso et al. 2018). Potential safety concerns of long-term ketamine/esketamine use have naturally emerged after numerous observations of cognitive deficits, bladder toxicity with interstitial/ulcerative cystitis, hepatotoxicity, and dependence associated with prolonged, „recreational" long-term (3 times a week or daily) use of ketamine (Morgan et al. 2010, Morgan & Curran 2012, Short et al. 2018). An open label, multicenter trial,

investigated safety, tolerability, and efficacy of nasal formulation of S(+) ketamine adjunctive to newly prescribed oral antidepressant. Authors concluded that treatment with esketamine nasal spray over a period of up to 1 year, results in consistent benefits and acceptable tolerability. There were no reported cases of esketamine abuse and the most common "withdrawal" symptoms included fatigue after discontinuation of maintenance phase and insomnia at the endpoint (Wajs et al. 2020).

PHARMACOKINETIC CHARACTERISTICS OF KETAMINE

Ketamine can be administered via intravenous, subcutaneous, intramuscular, intranasal, oral and sublingual route (Mion 2017). Peak plasma concentrations of ketamine occur within one minute after intravenous administration, within five minutes after intramuscular injection and within fifteen minutes after intranasal administration (Rathmell & Rosow 2015, Vlerick et al. 2020). Bioavailabilty of ketamine is only 29% and peak plasma concentrations occur within 45 minutes after peroral or sublingual administration (Rolan et al. 2014). One study conducted on healthy volunteers, investigated pharmacokinetic properties of ketamine in subanesthetic doses, after inhalational administration. Results of the mentioned study are shown in table 1 (Jonkman et al. 2017). Extreme lipid solubility of ketamine ensures its rapid transfer across the blood–brain barrier and hence the rapid onset of action, which usually occurs within 45 to 60 seconds after intravenous administration (Rathmell & Rosow 2015, White & Eng 2013). Subsequently, ketamine is redistributed from the brain and other highly perfused tissues to less perfused tissues, such as fat and muscles. Release of ketamine from less perfused tissues results in late psychodynamic effects after emergence. High rate of hepatic clearance results in relatively short elimination half-time of two to three hours. Demethylation by cytochrome P450 enzymes leads to formation of norketamine, which is one-fifth to one-third as potent as ketamine and may contribute to prolonged effects of ketamine, especially with repeated intravenous boluses or a continuous intravenous infusion (Rathmell & Rosow 2015, White & Eng 2013, White et al. 1982).

SYSTEMIC EFFECTS OF KETAMINE

Apart from causing dissociative anesthesia, ketamine is unique among intravenous anesthetics due to it's analgesic properties, ability to produce emergence delirium, having mild properties of local anesthetic and stimulating the cardiovascular system (Reich & Silvay 1989, Kurdi et al. 2014).

Direct negative inotropic effect of ketamine is usually overshadowed by central sympathetic stimulation, which leads to increase in systemic blood pressure, heart rate, cardiac output and myocardial oxygen consumption (Rathmell & Rosow 2015, Tweed et al. 1972). Consequently, ketamine is not recommended in patients with severe coronary artery disease (White & Eng 2013). Blood pressure typically increases during the first few minutes after intravenous administration of ketamine and then decreases over the next 10 to 20 minutes. Effect of ketamine on cardiac rhythm is a matter of debate. There is evidence that ketamine may abolish epinephrine-induced cardiac arrhythmias (Niiya 1990). However, ketamine might enhance the arrhythmogenic effect of epinephrine and ketamine-induced prolongation of QT interval, as well as transient elevation of ST segment, have been reported (Koehntop et al. 1977, Tejinder et al. 2017).

Ketamine does not produce significant ventilatory depression and medullary response to carbon dioxide is maintained (Rathmell & Rosow 2015, Soliman et al. 1975). Breathing frequency typically decreases for few minutes after administration of ketamine. However, rare cases of apnea following ketamine administration have been reported (Driver & Reardon 2016, Jonnavithula et al. 2008). For that reason, administration of ketamine necessitates airway equipment and medical personell capable of advanced airway management.

Table 1. Pharmacokinetic properties of S-ketamine and S-norketamine after inhalation

Parameter	First inhalation	Second inhalation	Third inhalation
Dose (mg/kg)	0.35	0.5	0.7
Duration of inhalation (min)	22 (7)	33 (8)	41 (7)
S-ketamine			
Cmax (ng/ml)	128 (3)	180 (39)	227 (36)
Range (ng/ml)	80-165	107-224	158-277
Tmax (min)	22 (7)	15 (0)	25 (0)
CV(%)	26	22	16
S-norketamine			
Cmax (ng/ml)	52 (15)	97 (21)	153 (27)
Range (ng/ml)	40-81	68-126	75-219
Tmax (min)	63 (7)	48 (7)	41 (7)
CV(%)	27	22	20

Legend: Values are shown as mean (SD), except where otherwise indicated. C max: maximal concentration during or following inhalation; CV: coefficient of variation; Tmax: time of Cmax from the initiation of inhalation

Ketamine increases production of mucous secretions by salivary and tracheobronchial glands, leading to frequent recommendation of administering anticholinergic drug before administration of ketamine (Rathmell & Rosow 2015). Due to effect of increasing upper respiratory secretions, administration of ketamine can rarely lead to laryngospasm, which is more of an issue in pediatric population (Baduni et al. 2010). Due to bronchodilatory activity, ketamine has been used successfully for treating refractory bronchospasm, as well as status asthmaticus (Goyal & Agrawal 2013). Ketamine does not significantly alter laboratory tests that reflect hepatic or renal function (Rathmell & Rosow 2015). Even though ketamine does not cause release of histamine and rarely leads to allergic reactions, cases of anaphylaxis after administration of ketamine have been reported (Mathais et al. 2019, Bylund et al. 2017).

DRUG INTERACTIONS

Small number of studies suggests that concurrent benzodiazepine medication may diminish the antidepressant effects of ketamine (Anrade 2017, Ford et al. 2015). Some drugs that inhibit glutaminergic signaling, such as lamotrigine, may reduce the adverse effects of ketamine, but it is unclear whether these drugs also diminish the antidepressant effect. However, data from clinical trials indicate that most antidepressants can be combined with ketamine without compromising it's antidepressant efficacy (Anrade 2017). Administering diaepam or midazolam prior to administration of ketamine, is effective in preventing cardiovascular effects of ketamine, as well as ketamine-induced increase in intracranial pressure (Rathmell & Rosow 2015). Chronic therapy with drugs that block adrenergic receptors, such as beta blockers, reduces ketamine-induced increase in heart rate and blood pressure. However, in the presence of heart failure, chronic alfa or beta blockade might unmask direct myocardial depressant effect of ketamine (White & Eng 2013, Rathmell & Rosow 2015). Combination of ketamine and theophylline, used in chronic asthma therapy, might be epileptogenic (Hirshman et al. 1982).

CONCLUSIONS

Current potentials in the treatment of depression, the greatest psychopathological burden of today's society, are still modest, and for some patients fatal. Currently available psychopharmaceuticals used in the treatment of depression are effective after almost a month of continuous use. If we take into account that patients are most vulnerable during this period, and many of them ruminate about suicide during this period, there is a significant need for urgent hospitalizations in the wards of intensive psychiatric treatment. Considering the aforementioned, surprising discovery of a drug that is effective after a few hours or days, after a single dose, and significantly decreases the risk of suicide faster than any other currently available psychopharmaceutical, the optimism of the psychopharmacologists seems entirely justified. Since it acts quickly and efficiently, it could significantly reduce the need for urgent hospitalizations in psychiatric wards. Despite numerous controversies still associated with ketamine, recent clinical trials have proven its efficacy and acceptable tolerance if taken according to a clearly prescribed regimen while monitored by the medical staff. However, as this is a new drug, but also a new concept in the treatment of depression, further research is needed regarding its application, efficacy and safety, not only in the treatment of depression, but also regarding its potential in treatment of other psychiatric disorders.

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Contribution of individual authors:

Slobodan Mihaljević: design of the study, literature searches and analyses, interpretation of data, manuscript writing.

Matko Pavlović: literature searches and analyses, interpretation of data, manuscript writing.

Krešimir Reiner: literature searches and analyses, interpretation of data, manuscript writing.

Marko Ćaćić: literature searches and analyses, manuscript writing.

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