THERAPEUTIC MECHANISMS OF KETAMINE

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received: 14.6.2020;

revised: 24.9.2020;

accepted: 7.10.2020

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 its 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 its 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 research 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 revolutionary 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 antituberculous 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 research 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, researchers 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 dysregulation 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 down-regulate the adenosine triphosphate/adenosine diphosphate metabolite ratio and increased levels of enzymes that are part of the oxidative phosphorylation pathway, which all led 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 threshold 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 & Himmler 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 enantiomers. 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 administered 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). Bioavailability 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 its 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 (Koehtop 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 personnel 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 its 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 alpha 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.

Acknowledgements: None.

Conflict of interest: None to declare.

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 Čačić: literature searches and analyses, manuscript writing.

References

1. Aanheth Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al: Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 2010; 67:139–145
2. Abdallah CG, Krystal JH: Ketamine and rapid acting antidepressants: Are we ready to cure, rather than treat depression?: *Behav Brain Res* 2020 May 11. doi:10.1016/j.bbr.2020.112628. [Epub ahead of print]
3. Abdallah CG, Sanacora G, Duman RS, Krystal JH: The neurobiology of depression, ketamine and rapid-acting antidepressants: Is it glutamate inhibition or activation? *Pharmacol Ther* 2018 May 25. doi:10.1016/j.pharmthera.2018.05.010. [Epub ahead of print]
4. Abdallah CG, Jackowski A, Sato JR, Mao X, Kang G, Cheema R, et al: Prefrontal cortical GABA abnormalities are associated with reduced hippocampal volume in major depressive disorder. *Eur Neuropsychopharmacol* 2015 May 5. doi:10.1016/j.euroneuro.2015.04.025. [Epub ahead of print]
5. Abdallah CG, Jackowski A, Salas R, Gupta S, Sato JR, Mao X, et al: The Nucleus Accumbens and Ketamine Treatment in Major Depressive Disorder. *Neuropsychopharmacology* 2017 Mar 8. doi:10.1038/npp.2017.49. [Epub ahead of print]

6. Allen AP, Naughton M, Dowling J, Walsh A, Ismail F, Shorten G, et al: Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: A comparison of ketamine and ECT. *J Affect Disord* 2015 Jul 29. doi:10.1016/j.jad.2015.06.033. [Epub ahead of print]
7. Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM: Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. *Biol Psychiatry* 2007; 63:642-649
8. Andrade C: Ketamine for Depression, 5: Potential Pharmacokinetic and Pharmacodynamic Drug Interactions. *J Clin Psychiatry* 2017; 78:858-861
9. Ban TA: The role of serendipity in drug discovery. *Dialogues Clin Neurosci* 2006; 8:335-344
10. Bow A: Is Electroconvulsive Therapy any More Effective than Simulated Electroconvulsive Therapy in Treatment-Resistant Depression?. *Psychiatr Danub* 2018; 30:502-507
11. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al: Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000; 47:351-354
12. Baduni N, Sanwal MK, Jain A, Kachru N: Recurrent episodes of intractable laryngospasm followed by laryngeal and pulmonary oedema during dissociative anaesthesia with intravenous ketamine. *Indian J Anaesth* 2010; 54:364-365
13. Bylund W, Delahanty L, Cooper M: The Case of Ketamine Allergy. *Clin Pract Cases Emerg Med* 2017 Oct 3. doi:10.5811/cpcem.2017.7.34405. [Epub ahead of print]
14. Chaki S: Beyond Ketamine: New Approaches to the Development of Safer Antidepressants. *Curr Neuropharmacol* 2017; 15:963-976
15. Canuso CM, Singh JB, Fedgchin M, Alphas L, Lane R, Lim P, et al: Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 2018 Apr 16. doi:10.1176/appi.ajp.2018.17060720. [Epub ahead of print]
16. Crane GE: Cycloserine as an antidepressant agent. *American Journal of Psychiatry* 1959; 115: 1025-6
17. Choi M, Lee SH, Wang SE, Ko SY, Song M, Choi JS, et al: Ketamine produces antidepressant-like effects through phosphorylation-dependent nuclear export of histone deacetylase 5 (HDAC5) in rats. *Proc Natl Acad Sci USA* 2015 Dec 22. doi:10.1073/pnas.1513913112. [Epub ahead of print]
18. Celesia GG, Chen RC, Bamforth BJ: Effects of ketamine in epilepsy. *Neurology* 1975; 25:169-72
19. Dundee JW: Twenty-five years of ketamine. A report of an international meeting. *Anaesthesia* 1990; 45:159
20. Dravid SM, Burger PB, Prakash A, Geballe MT, Yadav R, Le P, et al: Structural determinants of D-cycloserine efficacy at the NR1/NR2C NMDA receptors. *J Neurosci* 2010; 30:2741-54
21. Duman RS, Aghajanian GK, Sanacora G, Krystal JH: Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* 2016; 22:238-249
22. Duclot F, Kabbaj M: Epigenetic mechanisms underlying the role of brain-derived neurotrophic factor in depression and response to antidepressants. *J Exp Biol* 2015; 218:21-31
23. Domino EF: Taming the ketamine tiger. *Anesthesiology* 2010; 113:678-684
24. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al: Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 2018; 75:139-148
25. Driver BE, Reardon RF: Apnea After Low-Dose Ketamine Sedation During Attempted Delayed Sequence Intubation. *Ann Emerg Med* 2016 Sep 28. doi:10.1016/j.annemergmed. [Epub ahead of print]
26. Ebert B, Mikkelsen S, Thorkildsen C, Borghjerg FM: Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* 1997; 333:99-104
27. Finsterwald C, Carrard A, Martin JL: Role of salt-inducible kinase 1 in the activation of MEF2-dependent transcription by BDNF. *PloS One* 2013 Jan 22. doi:10.1371/journal.pone.0054545. [Epub ahead of print]
28. Ferrer-Allado T, Brechner VL, Dymond A, Cozen H, Crandall P: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. *Anesthesiology* 1973; 38:333-44
29. Fang Y, Wang X: Ketamine for the treatment of refractory status epilepticus. *Seizure* 2015 May 19. doi:10.1016/j.seizure.2015.05.010. [Epub ahead of print]
30. Ford N, Ludbrook G, Galletly C: Benzodiazepines may reduce the effectiveness of ketamine in the treatment of depression. *Aust N Z J Psychiatry* 2015 Jun 9. doi:10.1177/0004867415590631. [Epub ahead of print]
31. Goyal S, Agrawal A: Ketamine in status asthmaticus: A review. *Indian J Crit Care Med* 2013; 17:154-161
32. Howland RH: Serendipity and psychopharmacology. *J Psychosoc Nurs Ment Health Serv* 2010 Sep 22. doi:10.3928/02793695-20100903-01. [Epub ahead of print]
33. Hirshman CA, Krieger W, Littlejohn G, Lee R, Julien R: Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology* 1982; 56:464-7
34. Ionescu DF, Swee MB, Pavone KJ, Taylor N, Akeju O, Baer L: Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. *J Clin Psychiatry* 2016; 77:719-725
35. Ito H, Uchida T, Makita K: Ketamine Causes Mitochondrial Dysfunction in Human Induced Pluripotent Stem Cell-Derived Neurons. *PloS One* 2015 May 18. doi:10.1371/journal.pone.0128445. [Epub ahead of print]
36. Jakovljevic M & Borovecki F: Epigenetics, Resilience, Comorbidity and Treatment Outcome. *Psychiatr Danub* 2018; 30:242-253
37. Jaso BA, Niciu MJ, Iadarola ND, Lally N, Richards EM, Park M, et al: Therapeutic Modulation of Glutamate Receptors in Major Depressive Disorder. *Curr Neuropharmacol* 2017; 15:57-70
38. Jonkman K, Duma A, Velzen M, Dahan A: Ketamine inhalation. *Br J Anaesth* 2017; 118:268-269
39. Jonnavithula N, Kulkarni DK, Ramachandran G: Prolonged apnea with intramuscular ketamine: a case report. *Paediatr Anaesth* 2008; 18:330-1
40. Kurdi MS, Theerth KA, Deva RS: Ketamine: Current applications in anesthesia, pain, and critical care. *Anesth Essays Res* 2014; 8:283-90
41. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003; 289:3095-105

42. Krystal JH, Sanacora G, Duman RS: Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biol Psychiatry* 2013; 73:1133-141
43. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, et al: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994; 51:199-214
44. Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R: NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. *Psychopharmacology (Berl)* 2003a Sep 2. doi:10.1007/s00213-003-1582-z. [Epub ahead of print]
45. Krystal JH, Petrakis IL, Krupitsky E, Schutz C, Trevisan L, D'Souza DC: NMDA receptor antagonism and the ethanol intoxication signal: from alcoholism risk to pharmacotherapy. *Ann N Y Acad Sci* 2003b; 1003:176-84
46. Kienbaum P, Heuter T, Paviakovic G, Michel MC, Peters J: S(+)-ketamine increases muscle sympathetic activity and maintains the neural response to hypotensive challenges in humans. *Anesthesiology* 2001; 94:252-258
47. Kohrs R, Durieux ME: Ketamine: teaching an old drug new tricks. *Anesth Analg* 1998; 87:1186-193
48. Koehntop DE, Liao JC, Van Bergen FH: Effects of pharmacologic alterations of adrenergic mechanisms by cocaine, tropolone, aminophylline, and ketamine on epinephrine-induced arrhythmias during halothane-nitrous oxide anesthesia. *Anesthesiology* 1977; 46:83-93
49. Li SX, Han Y, Xu LZ, Yuan K, Zhang RX, Sun CY, et al: Uncoupling DAPK1 from NMDA receptor GluN2B subunit exerts rapid antidepressant-like effects. *Mol Psychiatry* 2017 Apr 25. doi:10.1038/mp.2017.85. [Epub ahead of print]
50. Mion G: History of anaesthesia: The ketamine story - past, present and future. *Eur J Anaesthesiol* 2017; 34:571-575
51. McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, et al: Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord* 2013 Nov 15. doi:10.1016/j.jad.2013.10.043. [Epub ahead of print]
52. Machmutow K, Meister R, Jansen A, Kriston L, Watzke B, Harter MC, et al: Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults. *Cochrane Database Syst Rev* 2019 May 20. doi:10.1002/14651858.CD012855.pub2. [Epub ahead of print]
53. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, Aan het Rot, et al: Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 2012 Jul 27. doi:10.1016/j.biopsych.2012.06.022. [Epub ahead of print]
54. Monteggia LM, Gideons E, Kavalali ET: The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. *Biol Psychiatry* 2012 Oct 11. doi:10.1016/j.biopsych.2012.09.006. [Epub ahead of print]
55. Melo A, Kokras N, Dalla C, Ferreira C, Ventura-Silva AP, Sousa N, Pego JM: The positive effect on ketamine as a priming adjuvant in antidepressant treatment. *Transl Psychiatry* 2015; 5:e573
56. Mahgoub M, Monteggia LM: Epigenetics and psychiatry. *Neurotherapeutics* 2013 Oct 4. doi:10.1007/s13311-013-0213-6. [Epub ahead of print]
57. Modica PA, Tempelhoff R, White PF: Pro- and anti-convulsant effects of anesthetics (Part II). *Anesth Analg* 1990; 70:433-44
58. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW: A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med* 2014 Jul 10. doi:10.1017/S0033291714001603. [Epub ahead of print]
59. Morgan CJ, Muetzelfeldt L, Curran HV: Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction* 2010; 105:121-33
60. Morgan CJ, Curran HV: Independent Scientific Committee on D. Ketamine use: a review. *Addiction* 2012; 107:27-38
61. Mathais Q, Paleiron N, Vatin L, Bordes J, Gaillard PE: Ketamine-induced anaphylactic shock during elective parotidectomy: A case report. *Eur J Anaesthesiol* 2019; 36:70-71
62. Niiya S: The effect of ketamine on epinephrine-induced arrhythmias in dogs anesthetized with halothane-nitrous oxide. *Masui* 1990; 39:1652-9
63. Pereira VS, Hiroaki-Sato VA: A brief history of antidepressant drug development: From tricyclics to beyond ketamine. *Acta Neuropsychiatrica* 2018 Feb 1. doi:10.1017/neu.2017.39. [Epub ahead of print]
64. Price RB, Mathew SJ: Does ketamine have anti-suicidal properties? Current status and future directions. *CNS Drugs* 2015; 29:181-188
65. Park H, Poo MM: Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci* 2013; 14:7-23
66. Pfenninger E, Himmelseher S: Neuroprotection by ketamine at the cellular level. *Anaesthesist* 1997; 46:47-54
67. Perry EB Jr, Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, et al: Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berl)* 2007 Feb 16. doi:10.1007/s00213-007-0706-2. [Epub ahead of print]
68. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; 163:1905-1917
69. Rasmussen KG, Lineberry TW, Galaray CW, Kung S, Lapid MI, Palmer BA, et al: Serial infusions of low-dose ketamine for major depression. *J. Psychopharmacol (Oxford)* 2013; 27:444-450
70. Reich DL, Silvey G: Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989; 36:186-97
71. Rolan P, Lim S, Sunderland V, Liu Y, Molnar V: The absolute bioavailability of racemic ketamine from a novel sublingual formulation. *Br J Clin Pharmacol* 2013 Oct 28. doi:10.1111/bcp.12264. [Epub ahead of print]
72. Renthal W, Maze I, Krishnan V, Covington HE 3rd, Xiao G, Kumar A, et al: Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. *Neuron* 2007; 56:517-529
73. Razin A, Riggs AD: DNA methylation and gene function. *Science* 1980; 210:604-610
74. Rathmell JP, Rosow CE: Intravenous Sedatives and Hypnotics. In: Flood P, Rathmell JP, Shafer S (eds): *Stoelting's pharmacology and physiology in anesthetic practice*. 160-203. Wolters Kluwer Health, 2015
75. Strasburger SE, Bhimani PM, Kaabe JH, et al: What is the mechanism of Ketamine's rapid-onset antidepressant

- effect? A concise overview of the surprisingly large number of possibilities. *J Clin Pharm Ther* 2017 Jan 22. doi:10.1111/jcpt.12497. [Epub ahead of print]
76. Schoepp DD, Conn PJ: Metabotropic glutamate receptors in brain function and pathology. *Trends Pharmacol. Sci* 1993; 14:13–20
 77. Sanacora G, Zarate CA, Krystal JH, Manji HK: Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 2008; 7:426–437
 78. Skolnick P, Popik P, Trullas R: Glutamate-based antidepressants: 20 years on. *Trends Pharmacol Sci* 2009; 30:563–569
 79. Sheinin A, Shavit S, Benveniste M: Subunit specificity and mechanism of action of NMDA partial agonist D-cycloserine. *Neuropharmacology* 2001; 41:151–8
 80. Strahl BD, Allis CD: The language of covalent histone modifications. *Nature* 2000; 403:41–45
 81. Salat K, Siwek A, Starowicz G, Librowski T, Nowak G, Drabik U, et al: Antidepressant-like effects of ketamine, norketamine and dehydronorketamine in forced swim test: Role of activity at NMDA receptor. *Neuropharmacology* 2015 Aug 1. doi:10.1016/j.neuropharm.2015.07.037. [Epub ahead of print]
 82. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al: Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biol Psychiatry* 2015 Nov 3. doi:10.1016/j.biopsych.2015.10.018. [Epub ahead of print]
 83. Szarmach J, Cubala WJ, Włodarczyk A, Wiglusz MS: Short-term ketamine administration in treatment-resistant depression: focus on cardiovascular safety. *Psychiatr Danub* 2019; 31:585–590
 84. Short B, Fong J, Galvez V, Shelker V, Loo CK: Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry* 2017 Jul 27. doi:10.1016/S2215-0366(17)30272-9. [Epub ahead of print]
 85. Soliman MG, Brindle GF, Kuster G: Response to hypercapnia under ketamine anaesthesia. *Can Anaesth Soc J* 1975; 22:486–94
 86. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006; 163:28–40
 87. Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ: Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci* 2006 Feb 26. doi:10.1038/nn1659. [Epub ahead of print]
 88. Tweed WA, Minuck M, Mymin D: Circulatory responses to ketamine anesthesia. *Anesthesiology* 1972; 37:613–9
 89. Tejinder S, Singh S, Elahi F, Cheney B: Ketamine-induced QTc interval prolongation. *J Anaesthesiol Clin Pharmacol* 2017; 33:136–138
 90. Vlerick L, Devreese M, Peremans K, Dockx R, Croubels S, Duchateau L, et al: Pharmacokinetics, absolute bioavailability and tolerability of ketamine after intranasal administration to dexmedetomidine sedated dogs. *PLoS One* 2020 Jan 13. doi:10.1371/journal.pone.0227762. [Epub ahead of print]
 91. Wajs E, Aluisio L, Holder R, et al: Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). *J Clin Psychiatry* 2020; 28; 81:19m12891
 92. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al: The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; 21:655–679
 93. Weckmann K, Deery MJ, Howard JA, Feret R, Asara JM, Dethlof F, et al: Ketamine's antidepressant effect is mediated by energy metabolism and antioxidant defense system. *Scientific Reports* 2017 Nov 17. doi:10.1038/s41598-017-16183-x [Epub ahead of print]
 94. Wang Y, Liu H, Sun Z: Lamarck rises from his grave: Parental environment-induced epigenetic inheritance in model organisms and humans. *Biol Rev Camb Philos Soc* 2017 Feb 20. doi:10.1111/brv.12322. [Epub ahead of print]
 95. Wang Y, Liu L, Xia Z: Brain-derived neurotrophic factor stimulates the transcriptional and neuroprotective activity of myocyte-enhancer factor 2C through an ERK1/2-RSK2 signaling cascade. *J Neurochem* 2007; 102:957–66
 96. White PF, Way WL, Trevor AJ: Ketamine: its pharmacology and therapeutic uses. *Anesthesiology* 1982; 56:119–136
 97. White PF, Ham J, Way WL, Trevor AJ: Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* 1980; 52:231–239
 98. White PF, Eng MR: Intravenous Anesthetics. In: Barash PG, Cullen BF, Stoelting RK, Calahan MK, Stock MC, Ortega R (eds): *Clinical Anesthesia*. 478–500. Lippincott Williams and Wilkins, 2013
 99. Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, Yan Z: Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc Natl Acad Sci USA* 2009 Jul 29. doi:10.1073/pnas.0906791106. [Epub ahead of print]
 100. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen Psychiatry* 2006; 63:856–864

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