Clinical Neuropsychiatry (2014) ***11****, 2, 55-60*

EDITORIAL

KETAMINE FOR DEPRESSION: AN OLD DRUG WITH A NEW INDICATION

Chiara Schepisi, Diletta Sabatini, Paolo Nencini

Declaration of interest: none

Chiara Schepisi, Diletta Sabatini, Paolo Nencini
Department of Physiology and Pharmacology, Sapienza University, Rome, Italy

Corresponding author
Prof. Paolo Nencini
paolo.nencini@uniroma1.it

Introduction

Major depressive disorder (MDD) is a severe and chronic condition affecting 350 million subjects worldwide with 1 million subjects committing suicide every year (World Health Organization 2008). MDD is prevailing in wealthy countries including Italy, where lifetime prevalence was estimated at 9.9% (Bromet et al. 2011). Diagnosis is defined by fulfilling at least five of the nine criteria described in the Diagnostic and statistical manual of mental disorders (DMS-5; American Psychiatric Association 2013). Symptoms should be present for at least 2 consecutive weeks and should "represent a change from previous functioning". Moreover, the presence of "depressed mood" or "loss of interest or pleasure" (criteria 1 and 2, respectively) is mandatory for the diagnosis of MDD (DSM-5; American Psychiatric Association 2013). A wide array of treatment options are currently available for MDD, spanning from pharmacotherapy and psychotherapy to their combination, as well as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).

Despite all these therapeutic options, only a fraction of patients achieves remission (a period of at least 2 months without significant signs or symptoms of the disease) and chronicity of symptoms predisposes to treatment resistance. Treatment-resistant depression (TRD), defined as the failure of at least two antidepressant treatments from two different classes, is a major concern for public health (Souery et al 2006). A great deal of research has been addressed to develop new therapeutic strategies based on innovative psychopharmacological approaches. In this frame, glutamatergic system represents a promising target for an effective intervention as long as NMDA receptor antagonism has been found to produce fast acting antidepressant effects. Ketamine has been instrumental in developing this new concept. This drug is a non-selective NMDA antagonist with anaesthetic (Marland et al. 2013), analgesic (Persson 2013) and anticonvulsivant properties (Dorandeu 2013). Despite its promising clinical application, ketamine use in limited by potentially harmful psychotomimetic effects (Krystal et al. 1994, Lahti et al. 1995, Moore et al. 2011) which are responsible for its recreational use and abuse (Morgan et al. 2004, Muetzelfeldt et al. 2008). More recently, the potential clinical use of ketamine for the treatment of MDD and bipolar depression (BD) has been evaluated (Aan Het Rot et al. 2010, Messer et al. 2010, Blier et al. 2012, Cusin et al. 2012, Krystal et al. 2013, Murrough et al. 2013 a,c, Niciu et al. 2013). Hereafter we summarize the most recent findings on the antidepressant activity of ketamine, together with a brief update on the potential mechanism of action.

Neurobiological substrate of ketamine-induced antidepressant effects

That at sub-anaesthetic doses ketamine reverses depressive symptoms in behavioral tests of depression, such as the test of learned helplessness (LH), the forced swim test (FST) and the novelty suppressed feeding test (NSFT) has been a breakthrough finding (Li et al. 2010, Autry et al. 2011, Duman and Aghajanian 2012, Duman et al. 2012). Moreover, while conventional antidepressants require chronic administration to improve animal's performance on these experimental models, ketamine effects are rapid and long lasting. That being so, a great deal of research has been dedicated to understand how ketamine contrasts the neurobiological alterations underpinning depression. It is well known that depression is associated with altered connectivity in brain areas subserving cognitive functions, such as prefrontal cortex (PFC) and hippocampus (HC). In the PFC, a decrease in the size of pyramidal neurons (which represent the main excitatory output from PFC), as well a decrease in GABA interneurons and glia were observed. Similar morphological abnormalities were found in the HC. Neuronal atrophy is associated with qualitative and quantitative abnormalities of synapses (i.e., decrease in spine density, reduced dendritic branching and length, loss of synaptic proteins; Duman and Aghajanian 2012, Duman et al. 2012).

Since the Brain Derived Neurotrophic Factor (BDNF) plays a key role in synaptic growth and consolidation (Carvalho et al. 2008, Gottmann et al. 2009, Greenberg et al. 2009, Cowansage et al. 2010, Kuczewski et al. 2010, Santos et al. 2010) it is not surprising that BDNF signalling is impaired in depression, in both humans (Masi and Brovedani 2011) and rodents (Chourbaji et al. 2011). The dysregulation of BDNF signalling is probably the consequence of the stress-induced hyperactivation of the hypotalamus-pituitary axis (HPA) and of the loss of glucocorticoid feedback tipically observed in depressed patients (Naert et al. 2011). Importantly, ketamine increases both the synthesis and the release of BDNF through different

Submitted January 2014, Accepted April 2014

pathways. A first mechanism involves ketamine-induced deactivation of the Ca2+/calmodulin-dependent protein kinase II (CAMKII), which in turn blocks phosphorilation of the eucariotic elongation factor II (eEFII) that inhibits BDNF translation (Autry et al. 2011). Therefore, administration of ketamine produces a net increase of BDNF protein expression.

It has been widely reported that antidepressants positively target neurotrophins signalling and, as such, they modulate neuroplasticity (Masi and Brovedani 2011). In particular, serotonergic antidepressants have been found to promote neurogenesis, but repeated administrations are required to reach this effect. Conversely, a significant increase in BDNF expression occurs after a single ketamine administration and, most importantly, ketamine also boosts BDNF release (Zunszain et al. 2013). The mechanism of ketamine-induced BDNF release has been recently defined. Briefly, ketamine-mediated antagonism at NMDA receptors provokes an increased release of glutamate that targets α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which in turn activate voltage-dependent Ca2+ channels. The massive increase of Ca influx facilitates BDNF release. BDNF binding to the tropomyosin receptor kinase B (TrkB), the high affinity receptor for neurotrophins, induces phosphorilation of both protein kinase B (PKB) and extracellular signal regulated kinase (ERK), which are responsible for the activation of the mammalian target of rapamycin (mTOR). mTOR plays a pivotal role in synaptic plasticity, as it controls the expression of synaptic proteins involved in neurotransmitter release and in synaptic consolidation (Kelleher et al. 2004). Accordingly, the administration of the mTOR inhibitor rapamycin blocks the antidepressant effects of ketamine in several behavioral models of depression (Li et al. 2010).

A further putative mechanism of the antidepressant action of ketamine involves the neuroinflammatory process underpinning neuronal degeneration observed during depression (Hurley and Tizabi 2013). Indeed, by blocking NMDA receptors ketamine produces an inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which controls cytokine release (Zunszain et al. 2013). Cytokines (such as IL-6 and IL-8) interfere with tryptophan metabolism, while leading to the formation of quinolinic acid, a molecule with NMDA agonist properties. Interestingly, high levels of IL-6 and quinolinic acid have been observed in cerebrospinal fluid of suicide attempters (Erhardt et al. 2013).

To summarize, ketamine exhibits antidepressant properties in different validated models of depression. These effects are mediated by activation of different pathways that results in neurogenesis and synaptic consolidation.

Clinical evidences on the potential antidepressant activity of ketamine

In the last decade several trials have been conducted to assess efficacy and safety of ketamine treatment with a particular focus on TRD. Moreover, many case reports have been published showing beneficial effects of ketamine in severely depressed patients.

In most trials ketamine is administered intravenously (i.v) at the dose of 0.5 mg/kg along 40 minutes, vital signs and side effects being continuously monitored (Diazgranados et al. 2010, Blier et al. 2012, Laje et al. 2012, Zarate et al. 2012, Murrough 2013a). Some authors suggest that repeated administrations, better than a single one, may be needed to obtain stable remission (Aan Het Rot et al. 2010, Messer et al. 2010, , Murrough et al. 2011, 2013c). In trials wherein protocols with multiple administrations are adopted, ketamine is usually administered at 0.5 mg kg every other day until a maximum of 6 infusions along two weeks of treatment. In 2011 Glue et al. simulated a concentration-time curve for intramuscular (i.m.) vs i.v 0.5 mg/kg of ketamine. They showed that i.m ketamine is associated with a better pharmacokinetic profile with respect to i.v. infusion (peak is higher and faster). This result may be explained by the fact that when ketamine is administered i.v, a slow infusion procedure is used to minimize cardiovascular side effects (Glue et al. 2011). However, higher doses of i.m. ketamine (0.7-1.0 mg/kg) are required to ameliorate depressive symptoms and to obtain remission. One year later Cusin et al. confirmed the efficacy of i.m. ketamine in two patients with bipolar depression. Interestingly, one of the patients had been treated with i.v. ketamine with no significant improvement (Cusin et al. 2012). In spite of differences of opinion about the route and the number of administrations, most of the authors agree that ketamine has a rapid and robust antidepressant effect (Zarate et al. 2010, Krystal et al. 2013). Clinical response is monitored through scales, such as the Montgomery-Asberg depression rating scale (MADRS; Montgomery and Asberg 1979), the Hamilton depression rating scale (HAM-D; Hamilton 1960) or the Beck depression inventory (BDI; Beck et al. 1961) that are administered at baseline as well as at different time points after ketamine infusion (usually at 40, 120 and 230 minutes). In some cases, patients are followed along weeks or months after the end of ketamine treatment or until relapse. A clinical response develops shortly after the 40 minutes infusion. In chronic treatments, depressive symptoms are decreased by the first ketamine dose and further improvement of the clinical condition usually occurs across subsequent infusions. Full remission was observed in some patients, even in those with TRD that did not even respond to ECT.

The finding that the antidepressant effect appears shortly after ketamine administration suggests a potential role for ketamine in the management of patients with suicidal intent, especially in cases where a rapid intervention is required. Considering the delay in response onset observed with the other antidepressants, patients prone to suicide are particularly at risk in the days or weeks just after antidepressant initiation. This makes treatment with ketamine a promising solution to overcome this critical interval. In a recent study, Murrough et al. (2013c) analysed the differences between responders and non-responders to ketamine treatment reaching two remarkable conclusions. First, distinction between responders and non-responders emerges at the 230 minutes time point after ketamine treatment: if an improvement is not observed after that interval, the patient is unlikely to benefit from ketamine treatment and should be switched to other medications. A second major finding is that suicidal thoughts are reduced also in non-responder subjects (evaluated through the MADRS). Therefore, it comes out that ketamine could be useful also in those patients in which it does not work against other depressive symptoms (Murrough et al. 2013c).

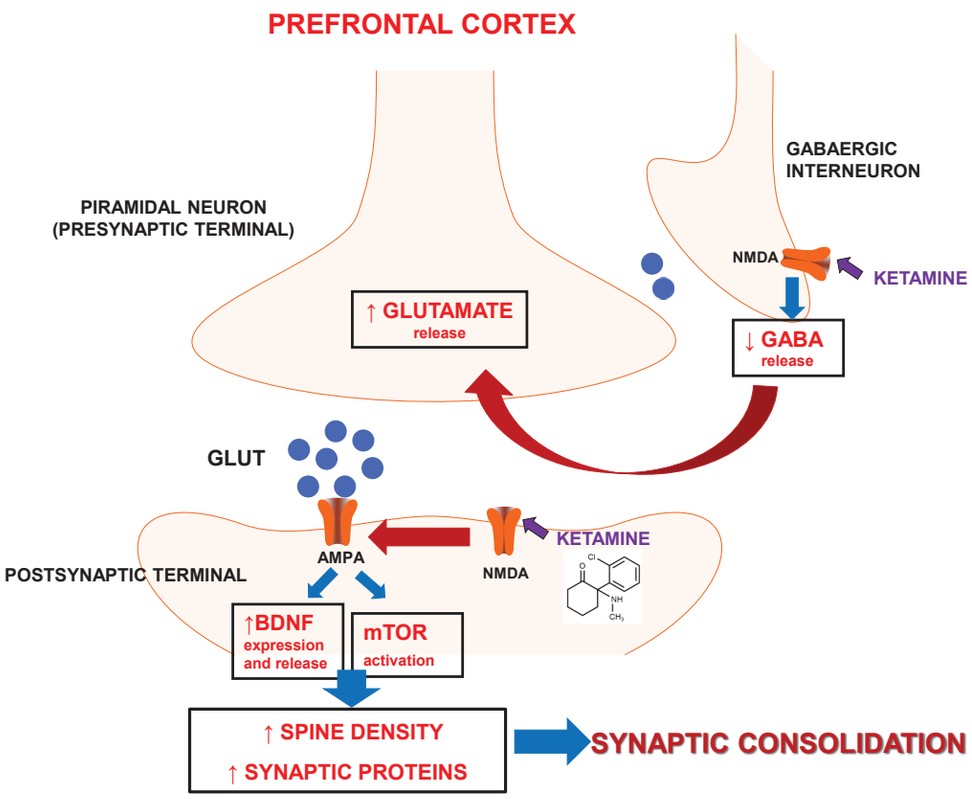
Genetic factors may influence the efficacy of ketamine treatment. In 2012 Laye and co-authors demonstrated that subjects carrying the val66met single

Table 1. *Summarizes case reports and clinical studies on the antidepressant effects of ketamine administration. Type of study, number of subjects and their diagnosis are reported. Procedure of ketamine administration and major outcomes are briefly described. BD: Bipolar Depression; MDD: Major Depressive Disorder; TRD: Treatment-Resistant Depression. i.v.: intravenous; i.m.: intramuscular. SSI: Scale for Suicidal Ideation; HAM-D: Hamilton Depression Rating Scale; MADRS: Montgmomery-Asberg Depression rating Scale; BDI: Beck Depression Inventory*

AUTHOR	TYPE OF STUDY	SUBJECTS (DIAGNOSIS)	PROCEDURE	RESULTS
Blier 2012	Case report	N=1 (MDD)	Repeated i.v. infusions (0.5 mg/kg)	↓ depressive symptoms (anxiety, dysphoria)
Cusin 2012	Case report	N=2 (BD)	Repeated i.m. infusions (50 mg)	Remission (pz A); ↓ suicidal ideation (pz B)
DiazGranados 2010	Open label trial	N=33 (MDD)	Single i.v infusion (0.5 mg/kg)	↓ SSI score; ↓HAM-D, MADRS and BDI suicide item at 40' and 230' post infusion ($p<0.01$)
Glue 2011	Case report	N=2 (MDD)	Single i.m. infusion (0.5 and 0.7 mg/kg)	↓ MADRS score
Laye 2012	Genetic study:Single blind / double blind	N=62 (MDD/BD)	Single i.v. infusion (0.5 mg/kg)	↓HAM-D score (20% in Met carriers vs 40 % in Val/Val; $p<.007$)
Messer 2010	Case report	N=2 (MDD)	Repeated i.v. infusions (pz A: day 1-3-5-7-9-11; pz B: day 1-7)	↓BDI score
Murrough 2011	Case report	N=1 (MDD)	Repeated i.v infusions (0.5 mg/kg; day 1-3-5-7-9-11)	Remission (89%↓ MADRS score) 24 h after the first infusion
Murrough 2013	Double blind randomized controlled trial (ketamine *vs* midazolam)	N=73 (MDD)	Single i.v. infusion (0.5 mg/kg)	↓ MADRS score ($p<.001$ vs midazolam)
Murrough 2013-II	Open label	N=24 (TRD)	Repeated i.v infusions (0.5 mg/kg; day 1-3-5-7-9-11)	↓ MADRS score at 120' post infusion ($p<.001$)
Rot (2010)	Open label	N=10 (TRD)	Repeated i.v infusions (0.5 mg/kg; day 1-3-5-8-10-12)	85% ↓ MADRS score

nucleotide polymorphism were less sensitive to the antidepressant effect of ketamine (with the val/met genotype being more responsive than the met/met one; Laje et al. 2012). Antidepressant activity of ketamine has been investigated also in patients with BD where depressive episodes alternate with manic ones over the course of the disease (Cusin et al. 2012, Zarate et al. 2012). As for MDD, bipolar patients seem to benefit from ketamine treatment during the depressive episode and, most importantly, ketamine does not increase the risk of affective switch in these patients. In fact, although during infusion a transient elevation of the Young Mania Rating Scale (YMRS; Young et al. 1978) score has been observed, this parameter returned to baseline shortly after the end of the infusion (Niciu et al. 2013). Since ketamine half-life is very short, metabolites are likely to play a critical role in the development and maintenance of the antidepressant response. This issue was recently addresses by Zarate and collaborators (2012) on two different populations: patients with MDD and BD. The authors showed that levels of ketamine demethylation are higher in bipolar than in depressed patients, so that demethylated metabolites (i.e. norketamine) and their hydroxylated derivatives could be involved in the clinical response to ketamine in bipolar depression, but not in MDD. Unfortunately, only a negative correlation between blood levels of HNK4c (one of the hydroxylated metabolites of norketamine) and clinical response was found (Zarate et al. 2012).

Figure 1. *Ketamine effects at glutammatergic synapses in prefrontal cortex: ketamine antagonizes NMDA receptor on gabaergic interneurons, thus blocking gaba-mediated inhibition of glutamate release from pyramidal neurons. When glutamate is released, it preferentially binds to AMPA receptor, being NMDA blocked by ketamine. This unbalance between AMPA and NMDA signallings results in the activation of AMPA mediated pathways that in turn elicits BDNF release as well as mTOR activation, eventually promoting synaptic consolidation*



Safety and tolerability of ketamine-based pharmacotherapy of depression.

While adopting the algorithm of drug harm evaluation proposed by David Nutt, ketamine scored low to moderate on physical and social harm, as well as on risk to develop dependence. However, many authors are still skeptical about a wide clinical use of ketamine, mainly because of its cognitive and psychotomimetic side effects (Nutt et al. 2007).

Psychotic-like symptoms, including perceptual disturbances, dissociation and derealization may occur in healthy volunteers with sub-anesthetic doses of ketamine (Krystal et al. 1994, Malhotra et al. 1996, Krystal et al. 2005, Perry et al. 2007). Therefore, several studies dealt with the risk to develop these symptoms under ketamine treatment, as measured by scales such as the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) and the Positive and Negative Symptoms Scale (PANSS; Kay et al. 1987) for psychosis, and the Clinician Administered Dissociative Symptoms Scale (CADSS; Bremner et al. 1998) for dissociation. In the study of Aan Het Rot and collaborators (2010), 3 over 10 patients had very high CADSS score during infusion, whereas BPRS score was only slightly increased; both parameters normalized after two hours from treatment. Similarly, Mourrough and collaborators (2013) reported that 17% of patients experienced dissociative symptoms immediately after infusion. However, symptoms resolved within two hours postinfusion. Psychotic manifestations were not observed in any patient.

Cognitive deficits are unlikely to develop when ketamine is administered to healthy subjects. However, working and episodic memory impairments have been described, together with disruption of information encoding (Malhotra et al. 1996, Morgan et al. 2004, Honey et al. 2005, Morgan and Curran 2006). Long-term cognitive effects may occur in ketamine abusers, in which impairments in episodic memory persist even after ketamine cessation (Morgan et al. 2010.). Neurotoxicity induced by chronic NMDA antagonism could be responsible for the cognitive deficits observed in these patients. More recently, selective impairments in memory recall have been described also in depressed patients after ketamine treatment (Mourrough et al. 2013b).

Even less information is available concerning the risk to develop ketamine abuse. Indeed, a few studies addressed this issue by measuring craving and tolerance (Messer at al. 2010, Blier et al. 2012). Until now, no cases of ketamine abuse have been described in under treatment patients. Ketamine at subanesthetic doses does not seem to induce severe physical harm. Transient cardiovascular side effects (hypertension, heart rate variation) have been observed in patients during infusion, but they were usually mild and did not require quitting the treatment (Messer et al. 2010, Aan Het Rot et al. 2010). Interestingly, none of patients treated with ketamine developed bladder dysfunction, a severe side effect of ketamine abuse (Wood et al. 2011).

Conclusion

Ketamine is a promising option for the treatment of depression, especially for those patients that do not respond to both conventional antidepressants and non-pharmacological treatment. Ketamine acts much faster than any other antidepressant drug and this makes it useful in patients at risk for suicide, in which a quick response is critical. Importantly, response to the first ketamine infusion is predictive for the overall efficacy of the treatment, so that non-responders may be promptly identified and switched to other medications. Although mild physical side effects as well as dissociative symptoms may appear during infusion, symptoms resolve shortly after the end of treatment. In the complex mechanism of action of the drug, particular attention has been addressed to the increase of BDNF synthesis and release caused by a single administration of ketamine, as long as BDNF promotes synaptic connectivity, which is altered in depression. Interestingly, ketamine may also prevent neuroinflammation, which is one of the leading cause of neuronal loss. Although some critical issues deserve more detailed investigation, ketamine represents an innovative and promising approach to the pharmacotherapy of MDD.

References

Aan Het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 15, 67, 2, 139-145.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., revised. American Psychiatric Association, Washington.

Autry A, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM (2011). NMDA receptor blockade at rest triggers rapid behavioral antidepressant responses. *Nature* 475, 7354, 91-95.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. *Arch Gen Psychiatry* 4, 561-71.

Blier P, Zigman D, Blier J (2012). On the safety and benefits of repeated intravenous injections of ketamine for depression. Biol. *Psychiatry* 72, e11-e12.

Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM (1998). Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress* 11, 1, 125-36.

Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur AJ, Kostyuchenko S, Lepine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine* 26, 9-90.

Carvalho AL, Caldeira MV, Santos SD, Duarte CB (2008). Role of the brain-derived neurotrophic factor at glutamatergic synapses. *Br J Pharmacol* 153, suppl. 1, s310-24.

Chourbaji S, Brandwein C, Gass P (2011). Altering BDNF expression by genetics and/or environment: impact for emotional and depression-like behaviour in laboratory mice. *Neurosci Biobehav Rev* 35, 3, 599-611.

Cowansage KK, LeDoux JE, Monfils MH (2010). Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. *Curr Mol Pharmacol* 3, 1, 12-29.

Cusin C, Hilton GQ, Nierenberg AA, Fava M (2012). Long-term maintenance with intramuscular ketamine for treatment-resistant bipolar II depression. *Am J Psychiatry* 169, 8, 868-9.

DiazGranados N, Lobna I, Brutsche N, Ameli R, Henter ID, Luckenbaugh D, Machado-Vieira R and Zarate CA Jr (2010). Rapid resolution of suicidal ideation after a single infusion of an NMDA antagonist in patients with treatment-resistant major depressive disorder. *Clin Psychiatry* 71, 12, 1605-1611.

Dorandeu F, Dhote F, Barbier L, Baccus B, Testylier G (2013). Treatment of status epilepticus with ketamine, are we there yet?. *CNS Neurosci Ther* 19, 6, 411-427.

Duman RS and Aghajanian G (2012). Synaptic dysfunction in depression: potential therapeutic targets. *Science* 338, 6103, 68-72.

Duman RS, Li N, Liu R, Duric V, Aghajanian G (2012). Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology* 62, 1, 35-4.

Erhardt S, Lim CK, Linderholm KR, Janelidze S, Lindquist D, Samuelsson M, Lundberg K, Postolache TT, Traskman-Bendz L, Guillemin GJ, Brundin L (2013). Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology* 38, 5, 743-2.

Glue P, Gulati A, Le Nedelec M Duffull S (2011). Dose- and Exposure-Response to Ketamine in Depression. *Biol Psychiatry* 70, e9-e10.

Gottmann K, Mittmann T, Lessmann V (2009). BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses. *Exp Brain Res* 199, 3-4, 203-34.

Greenberg ME, Xu B, Lu B, Hampstead BL (2009). New insights in the biology of BDNF synthesis and release: implications in CNS function. *J Neurosci* 29, 41, 12764-7.

Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23, 56-62.

Honey GD, Honey RA, O'Loughlin C, Sharar SR, Kumaran D, Suckling J, Menon DK, Sleator C, Bullmore ET, Fletcher PC. (2005). Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: an fMRI study. *Cereb Cortex* 15, 6, 749-59.

Hurley LL and Tizabi Y (2013). Neuroinflammation, neurodegeneration, and depression. *Neurotox Res* 23, 2, 131-44.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13, 2, 261-76

Kelleher RJ 3rd, Govindarajan A, Tonegawa S (2004). Translational regulatory mechanisms in persistent forms of synaptic plasticity. *Neuron* 44, 1, 59-73.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51, 3, 199-214.

Krystal JH, Perry EB Jr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D'Souza DC (2005). Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model of psychoses and cognitive function. *Arch Gen Psychiatry* 62, 9, 985-94.

Krystal JH, Sanacora G, Duman RS (2013). Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biol Psychiatry* 15, 73, 12, 1133-41.

Kuczewski N, Porcher C, Gaiarsa JL (2010). Activity-dependent dendritic secretion of brain-derived neurotrophic

factor modulates synaptic plasticity. *Eur J Neurosci* 32, 8, 1239-44.

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA (1995). Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuropsychopharmacology* 13, 9-19.

Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akulaa N, Kelmendi B, Simen A, McMahon FJ, Sanacora G, Zarate CA Jr (2012). Brain-derived neurotrophic factor Val-66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. *Biol Psychiatry* 72, e27-e28.

Li N, Lee B, Liu R, Banasr M, Dwyer JM, Iwata M, Li X, Aghajanian,G and Duman RS (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 20, 329, 5994, 959-964.

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier (1996) A. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 14, 5, 301-7

Marland S, Ellerton J, Andolfatto G, Strapazzon G, Thomassen O, Brandner B, Weatherall A, Paal P (2013). Ketamine: use in anesthesia. *CNS Neurosci Ther* 19, 6, 381-9.

Masi G and Brovedani P (2011). The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. *CNS Drugs* 25, 11, 913-31.

Messer M, Haller IV, Larson P, Pattison-Crisostomo J, Gessert CE (2010). The use of a series of ketamine infusions in two patients with treatment-resistant depression. *J Neuropsychiatry Clin Neurosci* 22, 4, 442-444.

Montgomery SA and Asberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134, 382-9.

Moore JW, Turner CD, Corlett PR, Arana FS, Morgan HL, Absalom AR, Adapa R, de Wit S, Everitt JC, Gardner JM, Pigott JS, Haggard P, Fletcher PC (2011). Ketamine administration in healthy volunteers reproduces aberrant agency experiences associated with schizophrenia. *Cogn Neuropsychiatry* 16, 4, 1-18.

Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004). Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* 29, 1, 208-18.

Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004). Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose response study. *Psychopharmacology* 172, 3, 298-308.

Morgan CJ and Curran HV (2006). Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology* (Berl) 188, 4, 408.

Morgan CJ, Muetzelfeldt L, Curran HV (2010). Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction* 105, 1, 121-33.

Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJ, Curran HV (2008). Journey through the K-hole: phenomenological aspects of ketamine use. *Drug Alcohol Depend* 95, 3, 219-29.

Murrough JW, Perez AM, Mathew SJ, Charney DS (2011). A case of sustained remission following an acute course of ketamine in treatment resistant depression. *J Clin Psychiatry* 72, 3, 414-5.

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CM, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A,Charney DS, Mathew SJ (2013a). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *Am J Psychiatry* 170, 10, 1134-42.

Murrough JW, Wan LB, Iacoviello B, Collins KA, Solon C, Glicksberg B, Perez AM, Mathew SJ, Charney DS, Iosifescu DV, Burdick KE (2013b). Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. *Psychopharmacology* DOI: 10.1007/s00213-013-3255-x.

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV (2013c). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 15, 74, 4, 250-6.

Naert G, Ixart G, Maurice T, Tapia-Arancibia L, Givalois L (2011). Brain-derived neurotrophic factor and hypothalamic-pituitry-adrenal axis adaptation processes in a depressive-like state induced by chronic restraint stress. *Mol Cell Neurosci* 46, 1, 55-66.

Niciu MJ, Luckenbaugh DA, Ionescu DF, Mathews DC, Richards EM, Zarate CA Jr (2013). Subanesthetic dose ketamine does not induce an affective switch in three independent samples of treatment-resistant major depression. *Biol Psychiatry* 74, 10, e23-4.

Nutt D, King LA, Saulsbury W, Blakemore C (2007). Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 369, 1047-1053.

Overall JE, Gorham DR (1962). The brief psychiatric rating scale. *Psychological Reports* 10,799812.

Persson J (2013). Ketamine in pain management. *CNS Neurosci Ther* 19, 6, 396-402.

Perry EB Jr, Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, O'Donnell E, Krystal JH, D'Souza DC (2007). Yale Ketamine Study Group. Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology* (Berl) 192, 2, 253-60.

Santos AR, Comprido D, Duarte CB (2010). Regulation of local translational at the synapse by BDNF. *Prog Neurobiol* 92, 4, 505-16.

Souery D, Papakostas GI, Trivedi MH (2006). Treatment-resistant depression. *J Clin Psychiatry* 67, Suppl 6, 16-22.

Zarate C Jr, Machado-Vieira R, Henter I, Ibrahim L, Diazgranados N, Salvadore G (2010). Glutamatergic modulators: the future of treating mood disorders? *Harv Rev Psychiatry* 18, 5, 293-303.

Zarate CA Jr, Brutsche N, Laje G, Luckenbaugh DA, Vattem Venkata SL, Ramamoorthy A, Ruin M, Wainer IW (2012). Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry* 15, 72, 4, 331-338.

Zunszain PA, Horowitz MA, Cattaneo A, Lupi MM, Pariante CM (2013). Ketamine: synaptogenesis, immunomodulation and glycogen synthase kinase-3 as underlying mechanisms of its antidepressant properties. *Molecular Psychiatry* 18, 12, 1236-41.

World Health Organization (2008) The Global Burden of Disease 2004 update. http://www.who.int/healthinfo/global_burden_disease/2004_report_update.

Wood D, Cottrell A, Baker SC, Southgate J, Harris M, Fulford S, Woodhouse C, Gillatt D (2011). Recreational ketamine: from pleasure to pain. *BJU Int* 107, 2, 1881-4.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 133, 429-35.