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Ketamine as Antidepressant? Current State and Future Perspectives

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Abstract: Major depressive disorder (MDD) is a serious mental disorder that ranks among the major causes of disease burden. Standard medical treatment targeting cerebral monoamines often provides only insufficient symptom relief and fails in approximately every fifth patient. The complexity of MDD therefore, reflects more than monoaminergic dysregulation. Initial research argues the case for excessive glutamate levels, suggesting that antiglutamatergic drugs might be useful in treating MDD. Ketamine is a non-selective, high-affinity N-methyl-D-aspartate receptor (NMDAR) antagonist most commonly used in pediatric and animal surgery. In the past, ketamine has gained popularity because of its ability to rapidly elevate mood, even in treatment-resistant and bipolar depression. However, there are still many obstacles before widespread clinical approval of ketamine treatment could become reality. In this review, ketamine's powerful antidepressant effects are discussed and further research necessary for therapeutic application is outlined. NMDAR antagonists provide an entirely new way of treating the manifold appearances of depression that should not be left unused.

Keywords: Antidepressants, glutamate, ketamine, major depression, monoamines, NMDAR.

INTRODUCTION

The Affective Tsunami

MDD is a debilitating condition with a lifetime prevalence of 16.2% [1]. By 2020, it is expected to be a leading cause of disease burden in the industrialized world, impairing nearly every aspect of everyday life [2]. Consequences of depression are grave: Averaged over all possible causes of death, sufferers are twice as likely as healthy peers to die [3], with suicide rates increasing more than twentyfold [4]. In terms of financial costs, depression is a national and familial disaster [5,6]. As not even two out of three patients achieve remission under standard drug regimen, the lack of a "silver bullet" treatment is painfully obvious [7]. Even worse, depression has proven to be refractory in approximately 15% cases [8]. Taken together, current psychiatric practice is insufficiently equipped to deal with this "affective tsunami" and more efficacious treatments are direly needed.

ALL ABOUT MONOAMINES?

The state of the human mind has always been an object of keen scientific attention and philosophers as well as doctors have been puzzled about what they referred to as "melancholia" since antiquity. The monoamine hypothesis can be considered the first scientific etiological approach to what is nowadays summarized as depression. In the original theoretical form, low synaptic levels of monoamines (especially noradrenaline and serotonin) were assumed to directly trigger MDD [9]. These reductions could be caused by pathological synthesis, metabolization, reuptake or storage processes or monoamine levels could, in fact, be normal but ineffective due to receptor abnormalities (currently more accepted) [10]. The monoamine view was developed, like so many seminal discoveries in psychiatry, after accidental findings that monoaminergic drugs also alleviate depressive symptoms [11]. For instance, the monoamine oxidase inhibitor isoniazid, originally employed in tuberculosis treatment, was found to improve mood [12]. Imipramine, a derivate of the antipsychotic chlorpromazine, was likewise discovered as an antidepressant by chance [13]. In keeping with the monoamine hypothesis, the anti-hypertensive drug reserpine can induce depression because it antagonizes monoamines (but see [14]).

However, the "traditional" monoamine hypothesis struggles with certain characteristics of antidepressant treatment, amongst others the week-long delay of therapeutic (but not side) effects. This is paradoxical, given that monoamine levels increase within hours after drug ingestion [15]. These (and other) drawbacks have led to a revision of the original hypothesis, in that the focus was shifted from synaptic neurotransmitter concentrations to pre- and postsynaptic receptor adaptation. Monoamine receptor sensitivity has gained prominent interest as a possible molecular pathway through which lowered synaptic transmitter levels could induce MDD. Even though deficient synaptic levels cause postsynaptic receptor upregulation, monoaminergic neurotransmission could be blunted because of receptor abnormalities [15]. Indeed, antidepressant treatment has been shown to lead to postsynaptic receptor downregulation, temporally consistent with therapeutic delay (for a review, see [16]). Still, many theoretical findings are at odds with this approach. For instance, monoaminergic treatment is effective only in 60% of cases [7] and precursor

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depletion is mood-neutral in healthy subjects [17]. Furthermore, the effectiveness of atypical drugs, such as buproprion (minimal affinity for monoamine transporter proteins) and mecamylamine (non-selective, non-competitive nicotinic acetylcholine receptor antagonist with negligible affinity for monoamine transporter proteins), is irreconcilable with either monoamine hypotheses [18].

Taken together, it is likely that the relationship between depression and monoamines exceeds the linearity that was initially hypothesized. Solely manipulating synaptic transmitters is insufficient to treat affective disorders and ignores the brain's adaptive makeup. Downstream mechanisms, such as gene expression, synaptic plasticity or neurotrophins, increasingly receive consideration as underlying mechanisms of antidepressant actions [19].

KETAMINE: A RAY OF LIGHT?

Even though the etiological value of the monoamine hypothesis lies beyond doubt, it is equally clear that many aspects remain unresolved. In any case, monoamine deregulation alone is not a satisfactory therapeutic target and research on additional pathways is needed more than ever. Evidence is accumulating that excessive glutamate levels play a major role in depressive pathophysiology and, consequentially, glutamate antagonists could prove fruitful [20]. The aim of this review is to provide a summary first of current antidepressants and then to discuss involvement of the glutamatergic system in affective disorders. The thrilling possibility of using ketamine constitutes the scaffold of this article, aggregating and reviewing studies on its clinical profile.

TREATMENT OF MDD: AN OVERVIEW

Successful treatment of depressive disorders remains as challenging today as it was nearly 100 years ago. Specific somatic treatment of depression started in the 1920s/1930s with medically induced seizures, first using herbs (e.g. camphor) and later electricity [21]. The advent of amphetamines as powerful antidepressants in the 1930s marks the birth of pharmacotherapy [11]. From the 1950s onwards, the world saw a surge in both marketing and development of antidepressants, making them one of most commonly prescribed drugs. The following section will provide a brief, chronological summary of all major pharmaceutical antidepressant treatments that have been employed since the 1950s. Even though clinical evidence argues a case for some herbs (especially St. John's wort, see [22]), discussing their suitability would exceed the scope of this review. Other possible treatment venues, such as atypical antipsychotics for augmentation or treatment of psychotic depression, are reviewed elsewhere (e.g. [23]).

Tricyclic Antidepressants (TCAs)

TCAs, a class of drugs named after their chemical structure, were developed in the 1950s after serendipitous findings. The first of its kind, imipramine was discovered to have positive effects on patients' mood in 1956 and provided the fundament for later drugs [13]. The neurochemical mechanisms of TCAs are very complex, but therapeutic pathways most likely include: serotonin and noradrenaline reuptake inhibition, anticholinergic/antimuscarinic activity, blockade of α_1-adrenoceptors and antagonism at histamine H_1 receptors [24]. A complete understanding has, however, remained elusive. TCAs are associated with low overall tolerability [25] and acceptability [26], which is why they are rarely prescribed nowadays (except in some patients resistant to other drugs, see below). Chemical non-specificity of TCAs arguably accounts for common side effects, such as sexual dysfunction, dizziness and drowsiness [27].

Monoamine Oxidase A Inhibitors (MAOIs)

Interest in monoamine oxidase arose in the 1950s, after its role in neurotransmitter catabolism had been discovered [28]. Monoamine oxidase is an enzyme that occurs in two isoforms (A and B), with the A subtype being more relevant to affective disorders because of higher affinity for serotonin and noradrenaline [28]. MAOIs inhibit enzyme activity and thereby non-specifically increase synaptic monoamine availability, which can cause severe side effects if used incautiously. Especially cumbersome, at least with older compounds, was strictly required dietary adherence and avoidance of serotonergic medication. Consumption of foodstuff high in tyramine or tryptophan (e.g. red wine or beer) has the potential to trigger hypertensive crises or serotonin syndrome, reflecting the sudden surge in transmitter availability and impaired synaptic clearance [29]. Even though long considered treatment of choice for mood disorders, opinions began to swing in favor of safer drugs in the 1960s (although toxicity has presumably been overrated, see [30]). Today, MAOIs are still prescribed, especially in the treatment of atypical depression, treatment-resistant depression and particular forms of bipolar depression [31] For some, MAOIs have remaine done of the most effective pharmacotherapies of MDD [32,33].

Selective Serotonin Reuptake Inhibitors (SSRIs)

The development of SSRIs 20 years ago revolutionized the psychiatric landscape, making them the most commonly prescribed antidepressants of today [34]. Their suspected working mechanism revolves around dampening of serotonin reuptake from the synaptic cleft by inhibiting membrane serotonin transporter proteins. Affinity for other amine transporters is generally considered minimal (which differentiates them from TCAs) [35]. The surge in synaptic serotonin availability leads to somatodendritic 5-HT_{1A} autoreceptor desensitization in Raphé cells, disinhibiting further cellular serotonin release. Increased extracellular serotonin levels then induce adaptive changes such as postsynaptic downregulation of some receptor types (especially 5-HT_{1A} and 5-HT_{2A}), which are hypothesized to eventually mediate mood improvements [36]. These neuronal adaptions could be the biological explanation of delayed clinical effects, although the final neurobiological mechanisms still warrant clarification [37]. Indeed, it has not even been resolved whether blunting of serotonin reuptake is the common pathway of SSRI action. For instance, the serotonin reuptake enhancer tianeptine possesses comparable antidepressant effects, although superficially doing the exact opposite of SSRIs [38].

Even though SSRIs have largely supplanted TCAs, attributing their prescription superiority to increased effectiveness would be mistaken. Quite to the contrary, effectiveness in treating depression does not seem to differ between both classes [39,40]. According to a recent meta-analysis [41], SSRIs are slightly superior to placebo in severe, but not mild or moderate depression. Response rates do not differ between SSRIs and TCAs (approximately 60% each), which is superior to placebo (approximately 30%) [42]. But the main reasons for preferring SSRIs is unequivocally better safety and tolerability [11]. Still, they also suffer from long therapeutic delay and common side effects, such as sleep disturbances, sexual dysfunction or anxiety [24]. Very worrying are reports about increases in juvenile and adolescent suicidal behavior after SSRI treatment (for a review, see [43]).

Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)

The first SNRI to be approved for treatment was venlafaxine in 1994, but many more compounds have been approved since. SNRIs are dual reuptake inhibitors like TCAs and MAOIs (i.e. they block serotonin and noradrenaline transporter proteins), but exhibit higher safety and tolerability because of chemical specificity [33]. Dual action is supposed to increase antidepressant effectiveness, yet evidence of clinical superiority to older compounds is lacking [44,45]. Therefore, SNRIs fail to qualify as universal treatment of major depression and, if at all, possess negligible additional benefits when compared to SSRIs.

Need for Alternative Treatments

Reviews of the most common pharmaceutical treatments suggest current antidepressants lack clinical effectiveness, safety or tolerability (see above). Indeed, drug classes do not seem to differ in terms of effectiveness, but rather side effect profile (e.g. [33]). To sum up, current approaches to major depression are highly unsatisfactory. As a consequence, initial reports of rapid mood elevation by ketamine shine like a "ray of light'' on the rather dark pharmaceutical horizon of today. Research on the involvement of glutamate would, furthermore, help scientists detach themselves from the biased focus on monoamines. Critically, it could lead to more appropriate disease models, paving the way for a better understanding of affective disorders.

THE GLUTAMATE SYSTEM: A NEW TARGET

While the monoamine hypothesis of depression has undoubtedly propelled clinical and pharmacological research, critical review unravels that it is an insufficient explanation: Major depression exceeds monoaminergic deficiency. Thus, a first-line treatment is still as far out of reach as when antidepressant pharmaceuticals entered the world and as such, the need to develop appropriate medication and disease models is ever more pressing. Recent studies have shown that the antiglutamatergic drug ketamine seemingly possesses rapid antidepressant effects, making all other treatments pale in comparison. The following section will, therefore, give a brief overview of glutamate and attempt to outline the role it plays in depression.

What is Glutamate?

Until very recently, it had been unknown that glutamate acted as a neurotransmitter, although scientists acknowledged its opulent distribution throughout the brain early on [46]. Today, it is clear that glutamate is the most common excitatory neurotransmitter, both in cortical and subcortical areas. Chemically, glutamate classifies as an amino acid that is synthesized from glutamine *via* glutaminase and released from presynaptic vesicles mainly *via* voltage-gated Ca^{2+} channels [47]. Glutamic acid decarboxylase transforms glutamate into gamma-Aminobutyric acid (GABA), while glutamine synthetase degrades glutamate to glutamine. The effects of synaptic glutamate are terminated by glutamate transporter proteins, triggering glial reuptake and subsequent metabolization. Thus, extracellular glutamate homeostasis is tightly regulated as too little glutamate impairs synaptic plasticity while too much causes oxidative damage and excitotoxicity [48]. Postsynaptically, signals are transmitted by both ionotropic and metabotropic receptors. Beside eight different metabotropic receptors ($mGluR_1$ – $mGluR_8$), there are three families of ionotropic receptors: NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs) and kainate receptors [47].

Glutamate and Depression

Owing to its opulent trafficking, glutamate is involved in many aspects of cognition and emotion [49]. During depressive episodes, glutamate serum, blood plasma and cerebrospinal fluid concentrations were found to be increased [49-51]. Likewise, imaging studies showed heightened levels in the occipital, frontal, cingulate and midcingulate cortex, but not dorsolateral prefrontal cortex (DLPFC) in unipolar [52-55] and bipolar [56] depressed individuals. This is reflected by Wang *et al*. [57], who discovered that increased frontal glutamate levels differentiated between depressed and non-depressed stroke patients.While the exact pathogenesis of excessive glutamate has not been conclusively understood, low glial levels (especially PFC astrocytes) have been found throughout the brain of patients with MDD, which implicates blunted glutamate reuptake mechanisms [58,59]. Intriguingly, glutamate transporter 1 (GT1) inhibition in prefrontal areas induces anhedonia in a rat model of depression [60], paralleling reduced GT1 activity in mediotemporal/frontal areas (but also locus coeruleus, see [61]) during MDD in humans [62-64].

Psychopharmacological research has shown extensively that some functional antidepressants downregulate glutamatergic neurotransmission, including fluoxetine, buproprion, urcumin, lamotrigine, riluzole, imipramine and phenelzine [51, 65-68]. After chronic antidepressant treatment, withdrawal induces hippocampal NMDAR density upregulation [69], while short-term antidepressant effects of sleep deprivation could be mediated by NMDA receptor internalization [70]. PFC NMDAR protein irregularities (especially NR2A and NR2B subunits) have been reported in patients with depression post-mortem [71]. However, considerable controversy still surrounds associations between glutamate and mood disorders, as some studies found reduced or inconspicuous glutamate levels during depressive episodes.

For instance, Järnum *et al*. [72] failed to detect heightened glutamate levels in the cerebrospinal fluid of unipolar patients and others even found decreased glutamate/Glx (a compound index consisting of glutamate, glutamine and GABA) ratios in the anterior cingulate cortex [73-75] and left DLPFC [76].

Exactly why the literature is laced with inconsistencies has remained unresolved to the present moment. Possible reasons include choice of imaging method, sample selection or methodological differences. For example, Wang *et al*. [57] restricted enrollment to stroke patients with good prognosis and, moreover, failed to correct for multiple testing. Many magnetic resonance spectroscopy studies suffer from problems with spatial resolution and signal-to-noise ratio, forcing them to resort to the less precise aggregate measure Glx (see [77]). More crucially even, glutamate and glutamine levels are dissociable, which counteracts straightforward interpretation of Glx [78].

Scientific findings, even when keeping the stated inconsistencies in mind, hint at an involvement of excessive glutamate levels in depressive pathogenesis. Even though disease pathways of hyperglutamatergia have not been uncovered yet, excitotoxicity-mediated neuronal atrophy is a likely candidate [79,80]. Extrapolating this to clinical medicine, there is a lot of evidence to suggest antiglutamatergic drugs might be useful in alleviating depression. Critically, reducing glutamate excitotoxicity could be the underlying mechanism of standard antidepressant drugs, rather than a favorable side effect [66,69]. Especially NMDAR antagonism has proven of interest and recent evidence argues a case for the efficacy of ketamine.

KETAMINE: ANTIDEPRESSANT OF THE FUTURE?

Ketamine, or RS-2-2-Chlorophenyl-2-methylaminocyclo-hexanone, is a derivate of phencyclidine, a substance originally used as anesthetic. Ketamine is mainly employed in veterinary medicine, but also pediatrics (as children seem relatively immune to psychotomimetic side effects, see [81]) and human pain management, where it is valued for its potential to induces edation and analgesia without cardiorespiratory paralysis [82]. It can be ingested as powder *via* snorting or inhaling, as a pill or by intramuscular/-venous injection. In recreational users, oral application is rare because of faster hepatic metabolization, leading to stronger sedative than psychotomimetic effects [82]. Pharma-cologically, ketamine can be classified as a non-selective, non-competitive, high-affinity NMDAR antagonist [83-85].

Beside NMDAR receptor antagonism, it seems ketamine blocks muscarinic acetylcholine receptors, interacts with CN1 channels and possesses some affinity for both σ receptors [82], which could explain why it modulates nerve growth factor (NGF) production and synaptic remodeling [86]. Neuroplastic effects of ketamine (probably mediated *via* increased mTORC1 signaling) have been advanced as one possible reason for persistent effects after complete drug washout [87,88]. Indeed, a study by Duman and Li [89] showed a single injection of ketamine increased prefrontal synaptogenesis and reversed stress-induced atrophy. This is consistent with findings that mice carrying a mutant form of glycogen synthase kinase 3 – an enzyme involved in synaptic plasticity- are unresponsive to ketamine [90]. Furthermore, ketamine possesses a weak affinity for mμ and *K* opioid receptors [91], but a high affinity for D_2 and 5-HT_{2A} receptors, where it commonly acts as an agonist [92]. Because NMDA receptors are widely distributed throughout cortical and subcortical areas, ketamine modulates many other neurotransmitter systems, including striatal and nucleus accumbens dopamine release, dopamine, serotonin as well as noradrenaline transporter proteins and GABAergic activity [82, 93-98].

Ketamine's precise short-term and long-term neuro-biological effects are still poorly understood. For instance, even though ketamine antagonizes postsynaptic NMDARs, it simultaneously increases presynaptic glutamate synthesis and release [99,l00]. In keeping with this, Li *et al*. [101] opine its antidepressant efficacy hails from ketamine's ability to increase glutamate release, which is supported by a study finding lamotrigine and risperidone to attenuate ketamine-induced hemodynamic responses [102]. Others assert rapid mood elevation is mediated by fast-acting anti-inflammatory activity [103] or inhibition of nitric oxide synthesis [104]. Thus, it is clear that attributing ketamine's multiple effects purely to NMDAR antagonism does not tell the full story. Indeed, some authors believe that the antidepressant effects of ketamine are, in fact, caused by increased AMPAR signaling [86,105].

OVERVIEW OF LITERATURE

Literature was retrieved (June 2013) from PubMed.gov searches using the keywords "ketamine" and "major depression" or "bipolar depression" and scanned for: duration of clinical assessment (> 30 min. post-treatment), verified diagnosis of mood disorder and restriction to human participants. Table **1** gives an alphabetical summary of all publications matching inclusion criteria, with details on study design, response rate and effect size where data were provided. Fortunately, most studies chose the same application method (40 minutes IV infusion) and formula to calculate ketamine hydrochloride dosage (0.5 mg/kg) - amounting to 0.75 mg/kg ketamine per hour, see Table **1** for exceptions - which facilitates direct comparison. Beside four studies where comorbid diagnoses are unfortunately not assessed [106-109], the most frequently reported comorbidity is anxiety disorder. It should be noted that case studies are not aggregated here because of limited explanatory value. In any case, the results from single case studies (e.g. [110,111]) can, *with a pinch of salt*, be taken to support conclusions drawn from experiments with larger sample sizes.

The first controlled study to unravel ketamine's effectiveness intreating depression was conducted by Berman *et al*. [87]. They infused eight participants with MDD and one participant with bipolar depression saline and ketamine in a double-blind manner, each one week apart. Over the course of three days, Hamilton Depression Rating Scale (HDRS) scores decreased by 50% or more in half of the participants after ketamine injection. Three participants remained above baseline and one participant showed ketamine-like antidepressant relief after placebo injection.

Zarate *et al*. [88] built on these results and conducted a placebo-controlled, double-blind study, in which they found a single injection produced rapid and strong symptom relief within 110 minutes in treatment-resistant unipolar patients. Impressively, more that 70% clinically responded to ketamine and nearly every third patient was in clinical remission within 24 hours. This is especially astounding because the recruited sample had previously not reacted to electroconvulsive therapy (ECT), arguably the most effective handling of refractory affective disorders [112]. Furthermore, half of the participants receiving ketamine showed significant mood elevation for at least one week.

In 2009, four open-label studies showed one-time intravenous ketamine led to rapid improvement of treatment-resistant depression [106,107,113,114]. Quickest significant antidepressant response was noted within 40 minutes [106] and slowest within four hours [113]. Another study with treatment-resistant patients found ketamine to decrease suicidal ideation within 24 hours, which can be taken as proxy measure of mood elevation [115]. Kudoh *et al*. [116] randomized patients with MDD awaiting surgery to two groups receiving anesthesia either *via* injection of ketamine (1 mg/kg), propofol and fentanyl or *via* propofol and fentanyl alone. Ketamine addition significantly reduced post-operative depression and pain ratings, without causing major side effects.

Further studies underlined the powerful effects of a single injection of ketamine in treatment of MDD [117-122] and treatment-resistant unipolar depression [109,123,124]. Aan het Rot *et al*. [125] injected unipolar treatment-resistant patients with three doses of ketamine weekly for the duration of twelve days. Ketamine provided symptom relief within four hours and, impressively, depression ratings had, on average, decreased by 85% after the sixth infusion. Even though mean relapse time was 19 days following the last injection, these findings powerfully underline ketamine short-term effectiveness in the treatment of acute depression, especially considering the suicide prevention aspect raised by Price *et al*. [115]. Beside studies examining unipolar depression, ketamine has also been proved effective in treatment of bipolar depressive episodes. Rybakowski *et al*. [126] found a single ketamine injection administered open-label improved bipolar depression resistant to current mood-stabilizing drugs. Zarate *et al*. [127] conducted a randomized, cross-over, placebo-controlled design in which they found the low-trapping NMDA channel blocker ASZD6765 to significantly improve mood after 80 minutes (see conclusion).

An open-label investigation by Rasmussen *et al*. [128] used a lowered administration formula and infused patients with depression 0.5 mg/kg of ketamine over the course of 100 minutes (i.e. 0.3 mg/kg per hour). Five out of ten patients achieved remission, with symptom reduction first surfacing 120 minutes post-injection. Thus, lowering ketamine dosage does not seem to affect clinical efficacy in a major way, which might help increase tolerability.

A ground-breaking study by Laje *et al*. [129] investigated the role of Val66Met, a single nucleotide polymorphism implicated in brain-derived neurotrophic factor (BDNF) regulation and affective disorders [130], in treatment response to ketamine. They found greater antidepressant response in homozygous Val than Met carriers, consistent with hypothesized modulatory functions of BDNF in ketamine action. These results offer a possible genetic explanation for non-response, as the reported prevalence of Met alleles approximately resembles ketamine immunity (*ca*. 30%, see [131]). This could, theoretically, be overcome by increasing BDNF levels prior to ketamine therapy, for instance with standard antidepressant treatment [129]. Likewise, it is conceivable that antidepressant effects of ketamine could be potentiated by adding current somatic treatment. Furthermore, it would be of great interest to determine Val66Met polymorphism of patients sampled in previous studies and to check whether Met allele carriers were overrepresented in the non-responder category. If so, the effectiveness of ketamine would even have been underestimated.

All studies did, unfortunately, not investigate for separate sex effects in evaluating ketamine. This is problematic, because initial evidence suggests menorrhea mediates ketamine susceptibility, i.e. females can evince antidepressant response at doses ineffective in males [132]. In keeping with this, studies show estrogen potentiates hippocampal NMDA signaling and, in general, affective disorders are more common in pre- or peri-menopausal women [133,134]. Another shortcoming of current ketamine research concerns insufficient blinding. Of the four studies examining ketamine in a placebo-controlled and double-blind design, none employed an active comparator with commensurable psychotomimetic side effects [87,88,117,127]. Because ketamine produces strong and distinct dissociative impressions, it is conceivable that subjects were not effectively blinded to their condition. As such, it remains a possibility that rapid symptom improvement seen after one-time ketamine injection amounts to an enhanced placebo effect. Of course, as Zarate *et al*. [88] note, antidepressant effects unambiguously exceed short-term hallucinogenic effects. However, this argument is also consistent with the notion that ketamine possesses moderate antidepressant action, but that initial and powerful symptom reduction is due to placebo. Thus, these studies suffer from low internal validity and it remains possible that ketamine is, in fact, not a real antidepressant drug.

SAFETY PROFILE OF KETAMINE

Before clinical use of ketamine can be considered, its safety for human use first has to be established. Very few methodologically sound studies have been conducted and it is clear that "the jury is still out" on this topic. The following section shortly discusses recent findings with respect to short-term and long-term effect of ketamine as well as possible links with psychotic disorders.

Short-Term Side Effects and Toxicity

Ketamine is a dissociative anesthetic with hallucinogenic side effects, such as visual or auditory hallucinations, out-of-body experiences or abnormal sensations [135]. Therefore, ketamine is increasingly used to create NMDAR hypo-function animal models of schizophrenia [136]. Peripherally, ketamine inhibits catecholaminergic reuptake and stimulates

the cardiovascular system, causing hypertension and tachycardia. In anesthetic practice, ketamine possesses a broad therapeutic ratio with little danger of overdose [137]. Because of NMDAR antagonism, ketamine acutely suppresses hippocampal long-term potentiation (LTP) and mnemonic functions. Indeed, a review by Morgan and Curran [138] revealed dose-dependent deficits in episodic, semantic, procedural and working memory as well as attention, but not executive functions. A randomized, double-blind and placebo-controlled study found subanesthetic ketamine injection caused linear decrements in verbal and nonverbal declarative memory performance in healthy males [139]. There is evidence to suggest ketamine impairs delayed recall and recognition memory (e.g. [140]). Of note, memory decreases occurred at or even below plasma concentration sufficient for other effects. To sum up, acute ketamine use curtails both declarative and non-declarative mnemonic processes.

Ketamine induces feelings of pleasure and elation *via* stimulated nucleus accumbens dopamine release, accounting for abuse potential and addictive properties [95]. Withdrawal symptoms and tolerance have been reported [141]. Ketamine seems to mainly act on frontal areas, with most distinctive effects in medial/inferior parts [142]. Because metabolism in prefrontal cortices is acutely increased after consumption, neuropsychological disruptions surface most prominently on prefrontal-dependent task measures [143-146]. On the other hand, an fMRI study demonstrated a negative correlation between acute psychedelic effects of ketamine and baseline ventromedial PFC activity [147]. Scheidegger *et al*. [148] found ketamine reduced resting state functional connectivity in healthy volunteers, the implication of which is currently unclear. Neurotoxic potential has been repeatedly shown [149,150].

Long-Term Effects

There are reports of ketamine-induced ulcerative cystitis, increased frequencies of bladder carcinoma and kidney dysfunction [82]. In rats, chronic ketamine use is cardiotoxic [151]. One study found 33% of chronic ketamine users suffered from "K-cramps", i.e. spontaneous abdominal pain [152]. Continuous ketamine consumption is associated with impairments in episodic memory, semantic memory, attention and selective deficits in working memory [93]. It is currently unknown whether these effects can be reversed by abstinence [138,153,154].

A correlational study detected elevated serum BDNF but not NGF levels in chronic ketamine users [155]. Indeed, it seems intact BDNF expression is a prerequisite of ketamine responsivity [156]. Narendran *et al*. [157] found DLPFC D_1 receptor upregulation in chronic ketamine users, while cognitive measures and regional brain volumes did not differ from control. There is evidence of abnormal bilateral frontal and left temporoparietal white matter [158] as well as reduced gray matter in the left superior frontal gyrus and the right middle frontal gyrus [159] after long-term consumption. Reduction in dorsal PFC gray matter reported by Liao *et al.* [159] was correlated with length of prior ketamine abuse, although this could also reflect an index of addiction in general [160]. Furthermore, chronic ingestion of NMDAR antagonists elevates cellular markers of oxidative stress [161]. A study by Yeung *et al.* [162] found evidence of elevated hyperphosphorylated tau levels in prefrontal and entorhinal cortices in animals that had received ketamine for six months, suggesting accelerated brain ageing processes. The most conclusive study on long-term effects to date found that monkeys chronically treated with ketamine showed hypofunctions in the ventral tegmentum, substantia nigra, posterior cingulate cortex and visual cortex, while increased neuronal activity was reported for striatal and entorhinal areas [163].

Ketamine and Schizophrenia

Ketamine causes transient positive as well as negative psychotic symptoms and some suggest regular users evince characteristics of prodromal schizophrenia [93]. Krystal *et al.* [140] injected healthy volunteers with subanesthetic doses of ketamine (0.1 and 0.5mg/kg, respectively) and noted a broad variety of temporary symptoms common in psychotic disorders (e.g. altered perception, hallucinations or impaired vigilance). Another study found ketamine was able to trigger short-term relapse of positive symptom in remitted patients with schizophrenia [164]. Schizophrenia-specific abnormalities under ketamine influence have also been reported, including eye-tracking [165] and EEG abnormalities [166]. Kegeles *et al*. [167] found that ketamine altered striatal dopamine release patterns in healthy volunteers to resemble individuals with schizophrenia after amphetamine challenge tests. In general, negative and cognitive hallmarks of psychosis seem most sensitive to ketamine [168]. A review by Morgan and Curran [82], however, concludes there is insufficient evidence to claim a connection between long-term ketamine use and psychotic disorders. More research, especially experimental, is needed to come to a definite answer.

To sum up, there is irrefutable evidence of adverse short-term and long-term effects associated with customary ketamine use. In human studies, effects of chronic ketamine consumption are usually studied in addicts in a cross-sectional design without controlling for poly-drug use and other confounders. Thus, it is difficult to extrapolate findings from non-representative human populations to supervised application in the context of clinical depression. Especially concerning are accounts that implicate increased mTOR signaling – the suspected mechanism through which ketamine enhances synaptic plasticity- in neoplasm growth [169].

CONCLUSION

The need to develop a viable treatment for depression has become an ever more pressing concern for the entire scientific community. Not least because standard antidepressant treatments often do not live up to their name, reports of ketamine's astounding effects fall on fertile soil. The previous section gave an overview over all studies on the effectiveness of ketamine in treating depression in human subjects. In the majority of cases, significant symptom relief was achieved within 24 hours and sometimes even less than 40 minutes. Observed effect sizes mostly range between moderate (0.5) and extremely large (> 5), all testifying to robust antidepressant effectiveness of ketamine. Response

rates, on the other hand, show more diversity and vary between 25% [87] and 100% [174]. While these findings can be taken to, overall, point in the same direction, extensive methodological heterogeneity across sampled studies warrants caution when interpreting the sometimes staggeringly strong effects (especially contrasting [119] with [120]). Compared to standard antidepressant treatment, however, these data yield unequivocal superiority of ketamine in terms of effectiveness, onset of action and response rates.

Research on ketamine is still in its infancy and many facets have remained obscure. For instance, little to nothing can be stated about the effects of controlled long-term use. Most studies are conducted with drug abusers in a correlational manner and thus generalization to "physically healthy" human population is difficult. This represents another issue with ketamine, as it can presently not be determined whether ketamine increases the risks of developing full-blown psychosis. Even though a review by Morgan and Curran [82] casts doubt on this association, there are studies in which a positive connection is established in both humans [93,170] and animals [171,172]. This bars patients with psychotic forms of depression from ketamine treatment. As most studies enrolled disproportionately many young patients, it is questionable whether results can be translated to more vulnerable depressed populations (e.g. elderly, patients with cardio-vascular impairments).

Indications of neurotoxicity [149,l50] should be carefully investigated to prevent serious adverse reactions and, this goes without saying, widely prescribed ketamine can only be considered in case its benefits outweigh the consequences of MDD. Also, feelings of euphoria and pleasure associated with subanesthetic ketamine injection pose possible abuse problems. If ketamine should become an officially available antidepressant one day, this hedonic aspect has to be neutralized. Tolerance and withdrawal, as seen in chronic drug abusers [82], should also be investigated, as the need for dose escalation would be a major clinical hindrance.

The form of delivery poses a further obstacle, since costly intravenous injection seems to rule out easily and widely available ketamine treatment in the near future. This could be overcome by developing user-friendly and safe application forms, such as tablet or nasal delivery [135]. Oral consumption leads to higher concentrations of norketamine, a metabolite predominantly associated with sedative effects, which represents a clear drawback of this route of administration [82]. On the other hand, there are indications that oral application of S-ketamine could serve as add-on medication [173]. Because bioavailability of ketamine after oral ingestion approximates 20% of levels seen after intravenous injection, it should be possible to export injection dosages to other formats. Irwin *et al*. [174] substantiated this speculation with a recent proof-of-concept trial (see Table **1**), indicating that higher dosages are required in case of delivery other than intravenous injection.

Furthermore, it is presently impossible to state that ketamine really is an antidepressant. Because of its strong hallucinogenic side effects and the fact that all studies so far have employed an inactive comparator as placebo, it is conceivable that people who achieve rapid symptom relief are, in fact, experiencing an active placebo effect. Studies that compare ketamine to a non-inert comparator are needed to specifically pinpoint the origin of ketamine's astoundingly rapid effects. A recent study by Zarate *et al*. [127] compared ketamine to AZD6765, a low-affinity NMDAR antagonist with less severe hallucinogenic side effects. While subjects are generally able to recognize whether they have been injected with ketamine, they did not manage to differentiate between placebo and AZD6765 in this study. Interestingly, AZD6765 produced only mild improvements compared to placebo. These results allow for two conclusions: First, it is possible that NMDAR antagonism does, indeed, produce a mild-to-moderate antidepressant effect, but that the swift relief after ketamine injection is due something else – possibly hallucinogenesis. Second, it could be taken to support the initial hypothesis that ketamine truly is an antidepressant and that the discrepancy between ketamine and AZD6765 is grounded in different NMDAR affinities. Interestingly, Zarate *et al*. [88] reported significant mood maintenance for the course of one week post-injection, which argues against prolonged placebo effects (especially when keeping in mind that the half-life of subanesthetic ketamine is approximately 2.5 hours, see [135]). A clinical trial with an active comparator would finally settle this debate and provide more inside into ketamine's antidepressant mechanisms. Memantine could be such a substance, because high doses cause psychedelic experiences similar to ketamine, while at the same time being devoid of antidepressant impact [175,176].

What is left on the plus side? It remains beyond doubt that ketamine has the potential to revolutionize the treatment of affective disorders. Especially in people who have failed different antidepressants, it should at least be considered as last resort. What is more, evidence suggests using ketamine for anesthesia prior to ECT could potentiate seizure-induced mood elevation [177, 178]. Interestingly, ketamine is helpful in both unipolar and bipolar depression, two forms of affective disorders that are regarded as fundamentally (and pharmaceutically) different (e.g. [179]). The anti-glutamatergic component of ketamine could help bridge the gap between, and offer a composite treatment for both phenotypes. At the same time, the global effectiveness of ketamine implicates glutamatergic dysregulation as shared pathophysiology of unipolar and bipolar affective disorders, providing fruitful opportunities for further etiological research.

To conclude, the possibility of treating major depression with ketamine is thrilling. However, more research needs to be conducted, especially on safety and tolerability, before clinical application can be considered. A phase IIa trial (i.e. a pilot trial investigating short-term effectiveness and safety with larger patient population) of the NMDAR partial agonist GLYX-13 revealed ketamine-like antidepressant impact in treatment-resistant unipolar patients without psychotomimetic side effects [180]. This dissociation between NMDAR antagonism (and its assumed antidepressant working) and tolerability could trigger a revolution in the first-line treatment of affective disorders. But before ketamine can cross the barrier between theory and practice,

future research needs to shed more light on key areas, including: long-term effects, suitability for vulnerable populations (e.g. elderly patients), maintenance of mood elevation and drug delivery method.

CONFLICT OF INTEREST

The author reports no biomedical financial or potential conflict of interest.

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APPENDIX

Table 1. Studies Examining the Antidepressant Effects of Ketamine

Authors	Diagnosis	Manipulation	Ø Effect Lag	Response Rate[a]	Effect Size[b]
aan het Rot *et al*. [125]	MDD/TRD	Six ketamine injections over the course of 2 weeks, three weekly	< 4 hours	90%[c]	d = 5.61[c]
Berman *et al*. [87]	MDD/BD	R, PPC, C, DB	< 3 days	25%[c]	d = 1.35[c]
Carlson *et al.* [184]	MDD/TRD	Single ketamine injection, OL	<230 min.	30%[d]	d = 1.19[d]
Cornwell *et al*. [122]	MDD	Single ketamine injection, OL	< 230 min.	45%[d]	???
DiazGranados *et al*. [108]	MDD	Single ketamine injection, OL	< 40 min.	90% (40 min.)[e]	d = 0.45[d]
DiazGranados *et al.* [117]	BD	R, PPC, C, DB	< 40 min.	41%[c]	d = 0.67[d]
Duncan *et al.* [123]	MDD/TRD	Single ketamine injection, OL	< 230 min.	43%[d]	d = 4.48[c]
Duncan *et al*. [181]	MDD/TRD	Single ketamine injection, OL	< 1 day	40%[c]	???
Ibrahim *et al*. [109]	MDD/TRD	Single ketamine injection, OL	< 230 min.	50%[d]	d = 0.5 vs. d = 1[d]
Ibrahim *et al*. [182]	MDD/TRD	R, PPC, OL	< 1 day	62% (total study duration)	d = 1.02 (2 days)
Irwin *et al*. [174]	MDD	Singe oral dose (0.5 mg/kg), OL	< 14 days	100%[f]	d= 1.14
Kudoh *et al*. [116]	MDD	R, either ketamine, propofol and fentanyl, or just propofol and fentanyl*	< 1 day	???	d = 2[c]
Laje *et al*. [129]	MDD	Either Single ketamine injection, OL or OL/DB, PC	< 230 min.	???	d = 0.62 vs. d = 1.68[d]
Larkin &Beautrais [120]	MDD	Single ketamine injection**	< 40 min.	92%[d]	d = 14.45[d]
Mathew *et al*. [113]	MDD/TRD	Single ketamine injection, OL	< 240 min.	65%[c]	d = 2.1[c]
Machado-Vieira *et al*. [106]	MDD/TRD	Single ketamine injection, OL	< 40 min.	48%[d]	???
Murrough *et al*. [183]	MDD/TRD	Up to six ketamine injections over 12-day period	< 120 min.	70.8% (total study duration)	d = 2.03 (2 hours)
Okamoto *et al*. [178]	MDD/TRD	8 OL ketamine (0.8 mg/kg) injections[g]	< 7 days	???	Greater symptom reduction in ketamine anesthesia groups
Phelps *et al*. [107]	MDD/TRD	Single ketamine injection, OL	< 120 min.	43%[d]	d = 1.06[d]
Price *et al*. [115]	MDD/TRD	Single ketamine injection	Reduction of SI < 24 hours	81%[e]	d = 1.37[c]
Rasmussen *et al*. [128]	MDD	OL, up to 4 ketamine injections***	< 120 min.	80% (total study duration)	d = 1.69[c]

Table 1. contd….

Authors	Diagnosis	Manipulation	Ø Effect Lag	Response Rate[a]	Effect Size[b]
Rybakowski *et al*. [126]	BD	Single ketamine injection, OL	< 24 hours	52% (total study duration)	d = 0.71[c]
Salvadore *et al*. [114]	MDD/TRD	Single ketamine injection, OL	< 230 min.	???	d = 1.5[d]
Salvadore *et al*. [118]	MDD	Single ketamine injection, OL	< 230 min.	45%[d]	d = 1.52[d]
Salvadore *et al*. [121]	MDD	Single ketamine injection, OL	< 230 min.	40%[d]	d = 0.98[d]
Thakurta *et al*. [124]	MDD/TRD	Single ketamine injection, OL	< 40 min.	???	d = 4.61[d]
Valentine *et al*. [119]	MDD	Saline injection, ketamine injection 1 week later, SB	< 60 min.	40%[c]	d = 0.21 (3 hours)
Wang *et al*. [177]	MDD	Single ketamine injection[h], R, DB	< 1day	???	Greater symptom reduction in ketamine anesthesia groups
Zarate *et al*. [88]	TRD/MDD	R, PPC, C, DB	< 110 min.	71%[c]	d = 1.46[c]

BD = bipolar depression, C = cross-over, DB = double-blind, MDD/TRD = major depressive disorder/treatment-resistant depression, OL= open-label, PPC= passive placebo-controlled, R = randomized, SB = single-blind, SI = suicidal ideation

[a]Response is defined as ≥ 50% reduction on primary measure unless stated otherwise

[b]Effect sizes reflect Cohen's d

[c]Measured 24 hours post-injection

[d]Measured 230 minutes post-injection

[e]Defined as Montgomery-Asberg Depression Rating Scale Suicidality Item score ≤ 1

[f]Defined as ≥ 30% reduction on Hospital and Anxiety Depression Scale questionnaire

[g]Patients received either a single injection of ketamine (0.8 mg/kg) or a combination of ketamine (0.8 mg/kg) and propofol (1.5 mg/kg) prior to undergoing ECT

[h]prior to ECT

* injection of 1 mg/kg ** injection of 0.2 mg/kg over 1-2 minutes *** injection of 0.5 mg/kg over 100 minutes

REFERENCES

[1] Kessler, R.C.; Berglund, P.; Demler, O.; Jin, R.; Koretz, D.; Merikangas, K.R.; Rush, A.J.; Walters, E.E.; Wang, P.S. The epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R). *JAMA,* **2003**, *289(23)*, 3095-3105. doi: 10.1001/jama.289.23.3095

[2] Simon, G.E. Social and economic burden of mood disorders. *Biol. Psychiatry,* **2003**, *54(3)*, 208-215. doi: 10.1016/S0006-3223(03)00420-7.

[3] Obsy, U.; Brandt, L.; Correia, N.; Ekbom, A.; Sparen, P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch. Gen. Psychiatry*, **2001**, *58(9)*, 844-850. doi:10.1001/archpsyc.58.9.844

[4] Lepiné, J.-P.; Briley, M. The increasing burden of depression. *Neuropsychiatric Disease and Treatment*, **2001**, *7(1)*, 3-7. doi: 10.2147/NDT.S19617

[5] Broadhead, W.E.; Blazer, D.G.; George, L.K.; Tse, C.K. Depression, disability days, and days lost from work in a prospective epidemiologic study. *JAMA*, **1990**, *264(19)*, 2524-2528.

[6] Pape, K.; Bjorngaard, J.H.; Holmen, T.L.; Krokstad, S. The welfare burden of adolescent anxiety and depression: a prospective study of 7500 young Norwegians and their families: the HUNT study. *BMJ Open*, **in press**, *2*, doi: 10.1136/bmjopen-2012-001942

[7] Steffens, D.C.; Krishnan, K.R.; Helms, M.J. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. *Depress. Anxiety*, **1997**, *6(1)*, 10-18. doi: 10.1002/(SICI)1520-6394(1997)6:1<10::AID-DA2>3.0.CO;2-9

[8] Messer, M.M.; Haller, I.V. Maintenance ketamine treatment produces long-term recovery from depression. *Primary Psychiatry*, **2010**, *17(4)*, 48-50.

[9] Schildkraut, J.J.; Kety, S.S. Biogenic amines and emotion. *Science*, **1967**, *156(771)*, 21-37.

[10] Hindmarch, I. Expanding the horizons of depression: beyond the monoamine hypothesis. *HumanPsychopharmacology: Clinical and Experimental,* **2001**, *16(3),* 203-218. doi: 10.1002/hup.288

[11] Hirschfeld, R.M.A. The epidemiology of depression and the evolution of treatment. *J. Clin. Psychiatry*, **2012**, *73(1)*, 5-9. doi: 10.4088/JCP.11096su1c.01

[12] Crane, G.E. The psychiatric side-effects of iproniazid. *Am. J. Psychiatry*, **1956**, 112(7), 494-501.

[13] Ban, T.A. The role of serendipity in drug discovery. *Dial. Clin. Neuroscience*, **2006**, 8(3), 335-344.

[14] Amsterdam, J.D.; Berwish, N. Treatment of refractory depression with combination reserpine and tricyclic antidepressant therapy. *J. Clin. Psychopharmacol.*, **1987**, 7(4), 238-242.

[15] Lee, S.; Jeong, J.; Kwak, Y.; Park, S.K. Depression research: where are we now? *Mol. Brain*, **2010**, *3(8)*, 3-8. doi: 10.1186/1756-6606-3-8

[16] Smith, D.F.; Jakobsen, S. Molecular neurobiology of depression: PET findings on the elusive correlation with symptom severity. *Front. Psychiatry,* in press. doi: 10.3389/fpsyt.2013.00008

[17] Linda, G. The biology of antidepressants. *Ann. Fam. Med.*, **2005**, *3*, 449-456.

[18] Shytle, R.D.; Silver, A.A.; Sanberg, P.R. Comorbid bipolar depression in tourette syndrome responds to nicotinic receptor antagonist, mecamylamine (Inversine). *Biol. Psychiatry*, **2000**, *48(10)*, 1028-1031.doi: 10.1016/S0006-3223(00)00945-8

[19] Mill, J.; Petronis, A. Molecular studies of major depressive disorder: the epigenetic perspective. *Mol. Psychiatry*, **2007**, *12(9)*, 799-814. doi:10.1038/sj.mp.4001992

[20] Shytle, R.D.; Silver, A.A.; Lukas, R.J.; Newman, M.B.; Sheehan, D.V.; Sanberg, P.R. Nicotinic acetylcholine receptors as targets for antidepressants. *Mol. Psychiatry*, **2002**, *7(6)*, 525-535. doi: 10.1038/sj.mp.4001035

[21] Fink, M. Meduna and the origins of convulsive therapy. *Am. J. Psychiatry*, **1984**, *141(9)*, 1034-1041.

[22] Ernst, E. Herbal remedies for depression anxiety. *Adv. Psych. Treatment*, **2007**, *13*, 312-316. doi: 10.1192/apt.bp.105.001735

[23] Dupuy, J.M.; Ostacher, M.J.; Huffman, J.; Perlis, R.H.; Nierenberg, A.A. A critical review of pharmacotherapy for major depressive

disorder. *Int. J.Neuropsychopharmacol.*, **2011**, *14(10),* 1417-1431. doi: 10.1017/S1461145711000083

[24] Yildiz, A.; Gönül, A.S.; Tamam, L. Mechanism of actions of antidepressants: beyond the receptors. *Bull. Clin. Psychopharmacol.*, **2002**, *12(4),* 194-200.

[25] Barbui, C.; Hotopf, M.; Freemantle, N.; Boynton, J.;Churchill, R.; Eccles, M.P.; Geddes, J.R.; Hardy, R.; Lewis, G.; Mason, J.M. Treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) vs. tricyclic antidepressants (TCAs). *Cochrane Database of Systematic Reviews*, **2003**, *3*, Art.No. CD002791.

[26] Guaiana, G.; Barbui, C.; Hotopf, M. Amitriptyline for depression. *Cochrane Database of Systematic Reviews*, **2007**, *3*, Art.No. CD004186.

[27] Ferguson, J.M. SSRI antidepressant medications: adverse effects and tolerability. *Prim. Care Companion to J. Clin. Psychiatry*, **2001**, *3(1)*, 22-27. doi: 10.4088/PCC.v03n0105

[28] Duncan, J.; Johnson, S.; &Ou, X.-M. Monoamine oxidases in major depressive disorder and alcoholism. *Drug Discov. Therap.*, **2012**, *6(3)*, 112-122. doi: 10.5582/ddt.2012.v6.3.112

[29] Flockhart, D.A. Dietary restrictions and drug interactions with monoamine oxidase inhibitors: an update. *J. Clin. Psychiatry*, **2012**, *73(1)*, 17-24. doi: 10.4088/JCP.11096su1c.03

[30] Grady, M.M.; Stahl, S.M. Practical guide for prescribing MAOIs: debunking myths and removing barriers. *CNS Spectrums*, **2012**, *17(1)*, 2-10. doi: 10.1017/S109285291200003X

[31] Thase, M.E. The role of monoamine oxidase inhibitors in depression treatment guidelines. *J. C. Psychiatry*, **2012**, *73(1)*, 10-16. doi: 10.4088/JCP.11096su1c.02.

[32] Fiedorowicz, J.G.; Swartz, K.L. The role of monoamine oxidase inhibitors in current psychiatric practice. *J. Psych. Pract.*, **2004**, *10(4)*, 239-248. doi:10.1097/00131746-200407000-00005

[33] Barbui, C.; Butler, R.; Cipriani, A.; Geddes, J.; Hatcher, S. Depression in adults: drug and physical treatments. *Clin. Evidence*, **2007**, *6*, 1003.

[34] Helms, R.A.; Eric, T. (2006). *Textbook of therapeutics: drug and disease management*. Lippincott Williams & Wilkins: Philadelphia, PA, **2006**.

[35] Zhou, Z.; Zhen, J.; Karpowich, N.K.; Law, C.J.; Reith, M.E.A.; Wang, D.-N. Antidepressant specificity of serotonin transporter suggested by three LeuT-SSRI structures. *Nat.Struct. Mol. Biol.*, **2009**, *16(6),* 652-657. doi: 10.1038/nsmb.1602

[36] Stahl, S.M. Mechanism of action of serotonin selective reuptake inhibitors – Serotonin receptors and pathways mediate therapeutic effects and side effects. *J. Affect.Disord.,* **1998***, 51(3),* 215-135. doi: 10.1016/S0165-0327(98)00221-3

[37] Charney, D.S.; Delgade, P.L.; Price, L.H.; Henninger, G.R. The receptor sensitivity hypothesis of antidepressant action: a review of antidepressant effects on serotonin function. In:*The role of serotonin in psychiatric disorders;* S.L. Brown & H.M. van Praag (Eds.); Brunner/Mazel: New York, **1991**.

[38] Uzbekov, M.G. Antidepressant action of tianeptine is connected with acceleration of serotonin turnover in the synapse: a hypothesis. *NeuropsychopharmacologicaHungarica*, **2009**, *11(2)*, 83-87.

[39] Geddes, J.R.; Freemantle, N.; Mason, J.; Eccles, M.P.;Boyton, J. Selective serotonin reuptake inhibitors (SSRIs) for depression. *Cochrane Database of Systematic Reviews*. **2002**, *2*, Art.No. CD00185.

[40] Wilson, K.; Mottram, P.; Sivanranthan, A.; Nightingale, A. Antidepressants vs. placebo for the depressed elderly. *Cochrane Database of Systematic Reviews,* **2003***, 2*, Art.No. CD000561.

[41] Kirsch, I.; Deacon, B.J.; Huedo-Medina, T.B.; Scoboria, A.; Moore, T.J.; Johnson, B.T. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Medicine*, **2008**, *5(2)*, 260-268. doi:10.1371/journal.pmed.0050045

[42] Walsh, B.T.; Seidman, S.N.; Sysko, R.; Gould, M.Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*, **2002**, *287(14)*, 1840-1847. doi: 10.1001/jama.287.14.1840

[43] Barbui, C.; Esposito, E.;Cipriani, A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *CMAJ*, **2009**, *180(3)*, 291-297. doi: 10.1503/cmaj.081514

[44] Jain, R. Single-action versus dual-action antidepressants.*Prim. Care Companion to J. Clin. Psychiatry,* **2004***, 6(1)*, 7-11.

[45] Papakostas, G.I.; Thase, M.E.; Fava, M.; Nelson, J.C.; Shelton, R.C. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. *Biol. Psychiatry*, **2007**, *62(11)*, 1217-1227. doi: 10.1016/j.biopsych.2007.03.027

[46] Meldrum, B.S. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J.Nutr.*, **2000**, *130(4)*, 1007-1015.

[47] Fonnum, F. Glutamate: a neurotransmitter in mammalian brain. *J. Neurochem.,* **1984**, *42(1)*, 1-11.

[48] Mark, L.P.; Prost, R.W.; Ulmer, J.L.; Smith, M.M.; Daniels, D.L.; Strottmann, J.M.;Brown, W.D.; Hacein-Bey, L. Pictorial review of glutamate excitotoxicity: fundamental concepts for neuroimaging. *Am. J. Neuroradiol.,* **2001***, 22(10)*, 1813-1824.

[49] Sanacora, G.; Treccani, G.; Popoli, M. Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*, **2012**, *62(1)*, 63-77. doi: 10.1016/j.neuropharm.2011.07.036

[50] Mitani, H.;Shirayama, Y.; Yamada, T.; Maeda, K.; Ashby, C.R.; Kawahara, R. Correlation between plasma levels of glutamate, alanine and serine with severity of depression. *Prog. Neuro-Psychopharmacol.& Biol. Psychiatry*, **2006**, *30(6)*, 1155–1158. doi: 10.1016/j.pnpbp.2006.03.036

[51] Kendell, S.F.; Krystal, J.H.;Sanacora, G. GABA and glutamate systems as therapeutic targets in depression and mood disorders. *Expert Opinion on Therapeutic Targets*, **2005**, *9(1)*, 153-168. doi: 10.1517/14728222.9.1.153

[52] Sanacora, G.; Gueorguieva, R.; Epperson, C.N.; Wu, Y.-T.; Appel, M.; Rothman D. L.; Krystal, J.H.; Mason, G.F. Subtype-specific alterations of {gamma}-aminobutyric acid and glutamate in patients with major depression. *Arch. Gen. Psych.,* **2004***, 61(7),* 705-713**.** doi:10.1001/archpsyc.61.7.705

[53] Bhagwagar, Z.; Wylezinska, M.; Jezzard, P.; Evans, J.; Ashworth, F.; Sule, A.;Matthews, P.M.; Cowen, P.J. Reduction in occipital cortex gamma-aminobutyric acid concentrations in medication-free recovered unipolar depressed and bipolar subjects. *Biol. Psychiatry*, **2007**, *61(6)*, 806-812. doi: 10.1016/j.biopsych.2006.08.048

[54] Hasler, G.; van der Veen, J.W.; Tumonis, T.; Meyers, N.; Shen, J.; Drevets, W.C. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined by magnetic resonance spectroscopy. *Arch. Gen. Psych.*, **2007**, *64(2)*, 193-200. doi: 10.1001/archpsyc.64.2.193

[55] Grimm, S.; Luborzewski, A.; Schubert, F.; Merki, A.; Kronenberg, G.; Colla, M.;Heuser, I.; Bajbouj, M. Region-specific glutamate changes in patients with unipolar depression. *J. Psych. Res.*, **2012**, *46(8)*, 1059-1065. doi: 10.1016/j.jpsychires.2012.04.018

[56] Frye, M.A.; Watzl, J.; Banakar, S.; O'Neill, J.; Mintz, J.; Davanzo, P.;Fischer, J.; Chirichigno, J.W.; Ventura, J.; Elman, S.; Tsuang, J.; Walot, I.; Thomas, M.A. Increased anterior cingulate/ medial prefrontal cortical glutamate and creatine in bipolar depression. *Neuropsychopharmacology*, **2007**, *32(12)*, 2490-2499. doi:10.1038/sj.npp.1301387

[57] Wang, X.; Li, Y.H.; Li, M.H.; Lu, J.; Zhao, J.G.; Sun, X.J.; Zhang, B.; Ye, J.L. Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression. *Eur. Arch. Psych. Clin. Neurosci.,* **2012**, *262(1)*, 33-38. doi: 10.1007/s00406-011-0209-3

[58] Rajkowska, G.; Miguel-Hidalgo, J.J.Gliogenesis and glial pathology in depression. *CNS & Neurological Disorders – Drug Targets*, **2007**, *6(3)*, 219-233. doi: 10.2174/187152707780619326

[59] Miguel-Hidalgo, J.J.; Waltzer, R.; Whittom, A.A.; Austin, M.C.; Rajkowska, G.;Stockmeier, C.A. Glial and glutamatergic markers in depression, alcoholism, and their comorbidity. *J. Affect. Disord.* , **2010**, *127(1-3)*, 240-240. doi: 10.1016/j.jad.2010.06.003

[60] John, C.S.; Smith, K.L.; Van'T Veer, A.; Gompf, H.S.; Carlezon, W.A.; Cohen, B.M.;Öngür, D; Bechtholt-Gompf, A.J. Blockade of astrocytic glutamate uptake in the prefrontal cortex induces anhedonia. *Neuropsychopharmacology*, **2012**, *37(11)*, 2467-2475. doi: 10.1038/npp.2012.105

[61] Bernard, R.; Kerman, I.A.; Thompson, R.C.; Jones, E.G.; Bunney, W.E.; Barchas, J.D.;Schatzberg, A.F.; Myers, R.M.; Akil, H.; Watson, S.J.. Altered expression of glutamate signaling, growth factor and glia genes in the locus coeruleus of patients with major depression. *Mol. Psych.*, **2011**, *16(6)*, 634-646. doi: 10.1038/mp.2010.44

[62] Tordera, R.M.; Totterdell, S.; Wojcik, S.M.; Brose, N.; Elizalde, N.; Lasheras, B. Enhanced anxiety, depressive-like behavior and

impaired recognition memory in mice with reduced expression of the vesicular glutamate transporter 1 (VGLUT1). *Eur. J. Neurosci.*, **2007**, *25(1)*, 281-290. doi: 10.1111/j.1460-9568.2006.05259.x

[63] Garcia-Garcia, A.L.; Elizalde, N.; Matrov, D.; Harro, J.; Wojcik, S.M.; Venzala, E.;Ramirez, M.J.; Del Rio, J.; Tordera, R.M.. Increased vulnerability to depressive-like behaviour of mice with decreased expression of VGLUT1. *Biol. Psychiatry*, **2009**, *66(3),* 275-282. doi: 10.1016/j.biopsych.2009.02.027

[64] Uezato, A.; Meador-Woodruff, J.H.; McCullumsmith, R.E. Vesicular glutamate transporter mRNA expression in the medial temporal lobe in major depressive disorder, bipolar disorder, and schizophrenia. *Bipolar Disord.*, **2009**, *11(7)*, 711-725.doi: 10.1111/j.1399-5618.2009.00752.x.

[65] Wang, S.J.; Su, C.F.; Kuo, Y.H. Fluoxetine depresses glutamate exocytosis in the rat cerebrospinal nerve terminals (synaptosomes) *via* inhibition of P/Q-type Ca2+ channels. *Synapse*, **2003**, *48(4)*, 170-177. doi: 10.1002/syn.10200

[66] Lin, T.Y.; Yang, T.T.; Lu, C.W.; Wang, S.J. Inhibition of glutamate release by bupropion in rat cerebral cortex nerve terminals. *Prog.Neuro-Psychopharmacol.& Biol. Psych.,* **2011**, *35(2),* 598-606. doi: 10.1016/j.pnpbp.2010.12.029

[67] Lin, T.Y.; Lu, C.W.; Wang, C.-C.; Wang, Y.-C.; Wang, S.-J. Curcumin inhibits glutamate release in nerve terminals from rat prefrontal cortex: possible relevance to its antidepressant mechanism. *Prog. Neuro-Psychopharmacol. & Biol. Psych.,* **2011**, *35(7),* 1785-1793. doi: 10.1016/j.pnpbp.2011.06.012

[68] Michael-Titus, A.T.; Bains, S.;Jeetle, J.; Whelpton, R. Imipramine and phenelzine decrease glutamate overflow in the prefrontal cortex: a possible mechanism of neuroprotection in major depression. *Neuroscience*, **2000**, *100(4)*, 681-684. doi: 10.1016/ S0306-4522(00)00390-0

[69] Harvey, B.H.; McEwen, B.S.; Stein, D.J. Neurobiology of antidepressant withdrawal: implications for the longitudinal outcome of depression. *Biol. Psychiatry*, **2003**, *54(10)*, 1105-1117. doi:10.1016/S0006-3223(03)00528-6

[70] Krystal, J.H.; Sanacora, G.; Blumberg, H.;Anand, A.; Charney, D.S.; Marek, G.; Epperson, C.N.; Goddard, A.; Mason, G.F.. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol. Psych.*, **2002**, *7(1)*, 71-80. doi: 10.1038/sj/mp/4001021

[71] Feyissa, A.M.; Chandran, A.; Stockmeier, C.A.;Karolewicz, B. Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. *Prog. Neuro-Psychopharmacol. & Biol. Psych.*, **2009**, *33(1)*, 70-75. doi: 10.1016/j.pnpbp.2008.10.005

[72] Järnum, H.;Eskildsen, S.F.; Steffensen, E.G.; Lundbye-Christensen, S.; Simonsen, C.W.; Thomsen, I.S.;Fründ, E.T.; Theberge, J.. Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. *ActaPsychiatr. Scand.*, **2011**, *124(6)*, 435-446. doi: 10.1111/j.1600-0447.2011. 01766.x

[73] Auer, D.P.; Pütz, B.; Kraft, E.; Lipinski, B.; Schill, J.; Holsboer, F. Reduced glutamate in the anterior cingulate cortex in depression: an *in vivo* proton magnetic resonance spectroscopy study. *Biol. Psychiatry*, **2000**, *47(4)*, 305-313.

[74] Rosenberg, D.R.; Macmaster, F.P.; Mirza, Y.; Smith, J.M.; Easter, P.C.; Banerjee, S.P.; Bhandari, R.; Boyd, C.; Lynch, M.; Rose, M.; Ivey, J.; Villafuerte, R.A.; Moore, G.J.; Renshaw, P. Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study. *Biol. Psych.*, **2005**, *58(9)*, 700-704. doi: 10.1016/j.biopsych.2005.05.007

[75] Price, R.B.; Shungu, D.C.; Mao, X.; Nestadt, P.; Kelly, C.; Collins, K.A.;Morrough, J.W.; Charney, D.S.; Mathew, S.J. Amino acid neurotransmitters assessed by proton magnetic resonance spectroscopy: relationship to treatment resistance in major depressive disorder. *Biol. Psych.*, **2009**, *65(9)*, 792-800. doi: 10.1016/j.biopsych.2008.10.025

[76] Michael, N.; Erfurth, A.; Ohrmann, P.; Arolt, V.; Heindel, W.; Pfleiderer, B. Metabolic changes within left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychol. Med.,* **2003**, *33(7)*, 1277-1284.

[77] Brennan, B.P.; Hudson, J.I.; Jensen, J.E.; McCarthy, J.; Roberts, J.L.; Prescot, A.P.; Cohen, B.M.; Pope, H.G.; Renshaw, P.F.; Ongür, D. Rapid enhancement of glutamatergic neurotransmission in bipolar depression following treatment with riluzole, *Neuro-psychopharmacology*, **2010**, *35(3)*, 843-846. doi: 10.1038/npp. 2009.191

[78] Walter, M.; Henning, A.; Grimm, S.; Schulte, R.F.; Beck, J.; Dydak, U.;Schnepf, B.; Boeker, H.; Boesinger, P.; Northoff, G. The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. *Arch. Gen. Psych.*, **2009**, 65(5), 476-486. doi: 10.1001/archgenpsychiatry.2009.39

[79] Zarate, C.A.; Quiroz, J.; Payne, J.; Manji, H.K. Modulators of the glutamatergic system: implications for the development of improved therapeutics in mood disorders. *Psychopharmacol. Bull.*, **2002**, *36(4)*, 35-83.

[80] McNally, J.; Bhagwagar, Z.;Hannestad, J. Inflammation, glutamate, and glia in depression: a literature review. *CNS Spectrums*, **2008**, *13(6)*, 501-510.

[81] Reich, D.L.; Silvay, G. Ketamine: an update on the first twenty-five years of clinical experience. *Can. J.Anesth.,* **1989**, *36(2)*, 186-197.

[82] Morgan, C.J.; Curran, H.V. Ketamine use: a review. *Addiction*, **2011**, *107*, 27-38. doi: 10.1111/j.1360-0443.2011.03576.x

[83] Lorrain, D.S.; Baccei, C.S.; Bristow, L.J.; Anderson, J.J.; Varney, M.A. Effects of ketamine and N-methyl-D-aspartate on glutamate and dopamine release in the rat prefrontal cortex : modulation by a group II selective metabotropic glutamate receptor agonist LY379268. *Neuroscience*, **2003**, *117(3)*, 697-706. doi: 10.1016/S0306-4522(02)00652-8

[84] Rowland, L.M.;Bustillo, J.R.; Mullins, P.G.; Jung, R.E.; Rhoshel, L.; Landgraf, E.; Barrow, R.; Yeo, R.; Lauriello, J.; Brooks, W.M. Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: A 4-T proton MRS study. *Am. J. Psych.*, **2005**, *162(2)*, 394-396. doi: 10.1176/appi.ajp.162.2.394

[85] Stone, J.M.; Dietrich, C.; Edden, R.; Mehta, M.A.; De Simoni, S.; Reed, L.J.; Krystal, J.H.; Nutt, D.; Barker, G.J. Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Mol. Psych.*, **2012**, *17*, 664-665.doi:10.1038/mp.2011.171

[86] Robson, M.J.; Elliott, M.; Seminerio, M.J.; Matsumoto, R.R. Evaluation of sigma (σ) receptors in the antidepressant-like effects of ketamine *in vitro* and *in vivo*. *Eur. Neuropsychopharmacol.*, **2012**, *22(4)*, 306-317. doi: 10.1016/j.euroneuro.2011.08.002

[87] Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S.; Krystal, J.H. Antidepressant effects of ketamine in depressed patients. *Biol. Psych.,* **2000**, *47(4)*, 351-354.

[88] Zarate, C.A.; Singh, J.B.; Carlson, P.J.; Brutsche, N.E.; Ameli, R.; Luckenbaugh, D.A.; Charney, D.S.; Manji, H.K. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psych.*, **2006**, *63(8),* 856-64. doi:10.1001/archpsyc.63.8.856

[89] Duman, R.S.; Li, N. A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **2012**, *367(1601)*, 2475-2484. doi:10.1098/rstb.2011.0357

[90] Beurel, E.; Song, L.; Jope, R.S. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Mol. Psych.,* **2011**, *16(11)*, 1068-1070. doi: 10.1038/ mp.2011.47

[91] Oye, I.; Paulsen, O.; Maurset, A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. *J.Pharmacol. Exp.Ther.*, **1992**, 260, 1209-1213.

[92] Kapur, S.;Seeman, P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D2 and serotonin 5-HT2receptors-implications for models of schizophrenia. *Mol. Psych.*, **2002**, *7(8)*, 837-844. doi: 10.1038/sj.mp.4001093

[93] Morgan, C.J.;Muetzelfeldt, L.; Curran, H.V.. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological well-being: a 1-year longitudinal study. *Addiction*, **2009**, *105(1)*, 121-133. doi: 10.1111/j.1360-0443.2009. 02761.x

[94] Rabiner, E.A. Imaging of striatal dopamine release elicited with NMDA antagonists: Is anything there to be seen? *J.Pharmacol.*, **2007**, *21(3)*, 251-258. doi: 10.1177/0269881107077767

[95] Smith, G.S.; Schloesser, R.; Brodie, J.D.; Dewey, S.L.; Logan, J.; Vitkun, S.A.;Simkowitz, P.; Hurley, A.; Cooper, T.; Volkow, N.D.; Cancro, R. Glutamate modulation of dopamine measured *in vivo*

with positron emission tomography (PET) and 11-raclopride in normal human subjects. *Neuropsychopharmacology*, **1998**, *18(1)*, 18-25. doi:10.1016/S0893-133X(97)00092-4

[96] Nishimura, M.; Sato, K. Ketamine stereoselectively inhibits rat dopamine transporter. *NeurosciLett*, **1999**, *274(2)*, 131-134. doi: 10.1016/S0304-3940(99)00688-6

[97] Martin, D.C.; Imtrona, R.P.; Aronstam, R.S. Inhibition of neuronal 5-HT uptake by ketamine, but not halothane, involves disruption of substrate recognition by the transporter. *NeurosciLett*, **1990**, *112(1)*, 99-103. doi: 10.1016/0304-3940(90)90329-8

[98] Quibell, R.; Prommer, E.E.; Mihalyo, M.; Twycross, R.; Wilcock, A. Ketamine. *J.Pain Symptom Manage.,* **2011**, *41(3)*, 640-649. doi:10.1016/j.jpainsymman.2011.01.001

[99] Moghaddam, B.; Adams, B.; Verma, A.; Daly, D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NDAM receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J. Neurosci.*, **1997**, *17*, 2921-2927.

[100] Anand, A.; Charney, D.S.; Oren, D.A.; Berman, R.M.; Hu, X.S.; Cappiello, A.;Krystal, J.H. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for the hyper-glutamatergic effects of N-methyl-D-aspartate receptor antagonists. *Arch. Gen. Psych.*, **2000**, *57(3)*, 270-276. doi: 10.1001/archpsyc.57.3.270

[101] Li, N.; Lee, B.; Liu, R.J.; Banasr, M.; Dwyer, M.; Iwata, M.; Li, X.-Y.; Aghajanian, G.; Duman, R.S. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, *2010*, *329 (5994)*, 959-964.doi: 10.1126/science.1190287

[102] Dolye, O.M.; De Simoni, S.; Schwarz, A.J.; Brittain, C.; O'Daly, O.G.; Williams, S.C.R.; Mehta, M.A. Quantifying the attenuation of the ketamine phMRI response in humans: a validation using antipsychotic and glutamatergic agents. *J. Pharmacol. Exp. Ther.*, **in press**.doi: 10.1124/jpet.112.201665

[103] Yang, J.J.; Zhou, Z.Q.; Yang, C. Letter to the editor: does ketamine exert a fast-acting antidepressant effect *via* inhibition of pro-inflammatory cytokines? *Psycholog. Med.*, **2011**, *41(8)*, 1787-1789. doi: 10.1017/S0033291711000699

[104] Doucet, M.V.; Levine, H.; Dev, K.K.; Harkin, A. Small molecule inhibitors at the PSD-95/nNOS interface have antidepressant-like properties in mice. *Neuropsychopharmacology,* **in press**. doi: 10.1038/npp.2013.57

[105] Maeng, S.; Zarate, C.A.; Du, J.; Schloesser, R.J.; McCammon, J.; Chen, G.; Manji, H.K. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylsioxazole-4-propionic acid receptors. *Biol. Psychiatry*, **2008**, *63(4)*, 349352. doi:10.1016/j.biopsych.2007.05.028

[106] Machado-Vieira, R.; Yuan, R.; Brutsche, N.; DiazGranados, N.; Luckenbaugh, D.;Manji, H.K.; Zarate, C.A. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. *J. Clin. Psych.*, **2009**, *70(12)*, 1662-1670.doi:10.4088/JCP.08m04659

[107] Phelps, L.E.; Brutsche, N.; Moral, J.R.; Luckenbaugh, D.A.; Manji, H.K.; Zarate, C.A. Family history of alcohol dependence and initial antidepressant response to an NMDA antagonist. *Biol. Psychiatry*, **2009**, *65(2)*, 181-184. doi: 10.1016/j.biopsych.2008.09.029

[108] DiazGranados, N.; Ibrahim, L.A.; Brutsche, N.E.; Ameli, R.; Henter, I.D.; Luckenbaugh, D.A.;Machado-Vieira, R.; Zarate, C.A. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J. Clin. Psych.*, **2010**, *71(12),* 1605-1611. doi: 10.4088/JCP.09m05327blu

[109] Ibrahim, L.; Diazgranados, N.; Luckenbaugh, D.A.; Machado-Vieira, R.; Baumann, J.;Mallinger, A.G.; Zarate, C.A. Rapid decrease in depressive symptoms with an N-methyl-D-aspartate antagonist in ECT-resistant major depression. *Prog.Neuro-Psychopharmacol. & Biol. Psych.,* **2011***, 35(4)*, 1155-1159. doi: 10.1016/j.pnpbp.2011.03.019

[110] Correll, G.E.; Futter, G.E. Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med. J.*, **2006**, *7(1)*, 92-95. doi: 10.1111/j.1526-4637.2006.00101.x

[111] Paul, R.; Schaaff, N.; Padberg, F.; Moller, H.J.; Frodl, T. Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: report of two cases. *World J. Biol. Psych.*, **2009**, *10(3)*, 241-244.doi: 10.1080/15622970701714370

[112] Pagnin, D.; deQueiroz, V.; Pini, S.; Cassano, G.B. Efficacy of ECT in depression: a meta-analytic review. *J. ECT,* **2004**, *20(1)*, 13-20.doi: 10.1097/00124509-200403000-00004

[113] Mathew, S.J.; Murrough, J.W.; aan het Rot, M.; Collins, K.A.; Reich, D.L.; Charney, D.S. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int. J. Neuropsychopharmacol.*, 2**010**, *13(1)*, 71-82. doi: 10.1017/S1461145709000169

[114] Salvadore, G.; Cornwell, B.R.; Colon-Rosario, V.; Coppola, R.; Grillon, C.; Zarate, C.A.; Manji, H.K. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biol. Psychiatry*, **2009**, *65(4)*, 289-295. doi:10.1016/j.biopsych.2008.08.014

[115] Price, R.B.; Nock, M.K.; Charney, D.S.; Mathew, S.J. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol. Psychiatry,* **2009**, *66(5)*, 522-526. doi:10.1016/j.biopsych.2009.04.029

[116] Kudoh, A.; Takahira, Y.; Katagai, H.; Takazawa, T. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth. Analg., 95(1),* **2002**, 114-118. doi: 10.1213/01.ANE.0000020693.65934.B7

[117] DiazGranados, N.; Ibrahim, L.; Brutsche, N.E.; Newberg, A.; Kronstein, P.;Khalife, S.; Kammerer, W.A.; Quezado, Z.; Luckenbaugh, D.A.; Salvadore, G.; Machado-Vieiera, R.; Manji, H.K.; Zarate, C.A. A randomized add-on trial of an N-methyl-d-aspartate antagonist in treatment-resistant bipolar depression. *Arch. Gen. Psych.*, **2010**, *67(8)*, 793-802. doi:10.1001/archgenpsychiatry.2010.90

[118] Salvadore, G.; Cornwell, B.R.; Sambataro, F.; Latov, D.; Colon-Rosario, V.; Carver, F.; Holroyd, T.; Diaz-Granados, N.; Machado-Vieira, R.; Grillon, C.; Drevets, W.C.; Zarate, C.A. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology*, **2010**, *35(7)*, 1415-1422. doi: 10.1038/npp.2010.24

[119] Valentine, G.W.; Mason, G.F.; Gomez, R.; Fasula, M.; Watzl, J.; Pittman, B.; Krystal, J.H.; Sanacora, G. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. *J. Psych. Res.*, **2011**, *191(2)*, 122-127. doi: 10.1016/j.pscychresns.2010.10.009

[120] Larkin, G.K.; Beautrais, A.L. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int. J. Neuropsychopharmacol.*, 2**011**, *14(8)*, 1128-1131. doi: 10.1017/S1461145711000629

[121] Salvadore, G.; van der Ween, J.W.; Zhang, Y.;Marenco, S.; Machado-Vieira, R.; Baumann, J.;Ibrahim, L.A.; Luckenbaugh, D.A.; Shen, J.; Drevets, W.C.; Zarate, C.A. An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression. *Int. J. Neuro-psychopharmacol.*, **2011**, *15(8)*, 1063-1072. doi:10.1017/S1461145711001593

[122] Cornwell, B.R.; Salvadore, G.; Furey, M.; Marquardt, C.A.; Brutsche, N.E.; Grillon, C.; Zarate, C.A. Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. *Biol. Psychiatry*, **2012**, *72(7)*, 555-561. doi: 10.1016/j.biopsych.2012.03.029

[123] Duncan, W.C.; Sarasso, S.; Ferrarelli, F.; Selter, J.; Riedner, B.A.; &Hejazi, N.S. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. *Int. J. Neuropsychopharmacol.*, **2013**, *16(2),* 301-311. doi: 10.1017/S1461145712000545

[124] Thakurta, R.G.; Das, R.; Bhattarcharya, A.K.; Saha, D.; Sen, S.; Singh, O.P. Rapid response with ketamine on suicidal cognition in resistant depression. *Ind. J. Psychol. Med.*, **2012**, *34(2)*, 170-175. doi: 10.4103/0253-7176.101793

[125] aan het Rot, M.; Collins, K.A.;Murrough, J.W.; Perez, A.M.; Reich, D.L.; Charney, D.S.;Mathew, S.J. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol. Psychiatry*, **2010**, *67(2)*, 139-145. doi: 10.1016/j.biopsych.2009.08.038

[126] Rybakowski, J.K.;Permoda-Osip, A.; Skibinska, M.; Adamski, R.; Bartkowska-Sniatkowska, A. Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved? *Hum. Psychopharmacol.: Clin. Exp.*, **2013**, *28(1)*, 87-90 doi: 10.1002/hup

[127] Zarate, C. A.; Mathews, D.; Ibrahim, L.; Chaves, J.F.; Marquardt, C.; Ukoh, I.;Jolkovsky, L.; Brutsche, N.E.; Smith, M.A.; Luckenbaugh, D.A. A randomized trial of a low-trapping nonselective N-Methyl-D-Aspartate channel blocker in major depression.*Biol. Psychiatry*, in press. doi: 10.1016/j.biopsych. 2012.10.019

[128] Rasmussen, K.G.; Lineberry, T.W.; Galardy, C.W.; Kung, S.; Lapid, M.I.; Palmer, B.A.; Ritter, M.J.; Schak, K.M.; Sola, C.L.; Hanson, A.J.; Frye, M.A. Serial infusions of low-dose ketamine for major depression. *J. Psychopharmacol.,* **2013**, 27(5), 444-450.doi: 10.1177/0269881113478283

[129] Laje, G.;Lally, N.; Mathews, D.; Brutsche, N.; Chemerinski, A.;Akula, N.; Kelmendi, B.; Simen, A.; McMahon, F.J.; Sanacora, G.; Zarate, C.A. Brain-derived neurotrophic factor val66Met polymorphism and antidepressant efficacy of ketamine in depressed. *Biol. Psychiatry,* **2012***, 72(11)*, 27-28. doi: 10.1016/j. biopsych.2012.05.031

[130] Pattwell, S.S.; Bath, K.G.; Perez-Castro, R.; Lee, F.S.; Chao, M.V.; Ninan, I. The BDNF Val66Met polymorphism impairs synaptic transmission and plasticity in the infralimbic medial prefrontal cortex. *J. Neurosci.,* **2012***, 32(7)*, 2410-2421. doi: 10.1523/ JNEUROSCI.5205-11.2012

[131] Liu, R.-J.; Lee, F.S.; Li, X.-Y.; Bambico, F.; Duman, R.S.; Aghajanian, G.K. Brain-derived neurotrophic factor Val66Met allele basal and ketamine-stimulated synaptogenesis in prefrontal cortex. *Biol. Psychiatry,* **2012***, 71(11)*, 996-1005. doi: 10.1016/j. biopsych.2011.09.030

[132] Carrier, N.; Kabbaj, M. Sex differences in the antidepressant-like effects of ketamine.*Neuropsychopharmacology*, in press. doi: 10.1016/j.neuropharm.2012.12.009

[133] Woolley, C.S.; McEwen, B.S. Estradiol regulates hippocampal dendritic spine density *via* an N-methyl-D-aspartate receptor-dependent mechanism. *J. Neurosci.*, **1994**, *14(12)*, 7680-7687.

[134] Smith, C.C.; Vedder, L.C.; McMahon, L.L. Estradiol and the relationship between dendritic spines, NR2B containing NMDA receptors, and the magnitude of long-term potentiation at hippocampal CA3-CA1 synapses. *Psychoneuroendocrinology*, **2009**, *34(1)*, 130-142. doi: 10.1016/j.psyneuen.2009.06.003

[135] Mathews, D.C.; Henter, I.D.; Zarate, C. A. Targeting the glutamatergic system to treat major depressive disorder: rationale and progress to date. *Drugs,* **2012***, 72(10)*, 1313-1333. doi: 10.2165/11633130-000000000-00000

[136] Fletcher, P.C.; Honey, G.D. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn. Sci.*, **2006**, *10(4),* 167-183. doi: 10.1016/j.tics.2006.02.008

[137] Long, H.N.L.S.; Hofmann, R.S. Ketamine medication error resulting in death. *J.Toxicol.-Clin.Toxicol.* , **1988**, *40 (1)*, 614.

[138] Morgan, C.J.; Riccelli, M.; Maitland, C.H.; Curran, H.V. Long-term effects of ketamine: evidence of a persisting impairment of source memory in recreational users. *Drug Alcohol Depend*, **2004**, *75(3)*, 301-308. doi: 10.1016/j.drugalcdep.2004.03.006

[139] Newcomer, J.W.; Farber, N.B.; Jevtovic-Todorovic, V.; Selke, G.; Melson, A.K.; Hershey, T.; Craft, S.; Olney, J.W. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology,* **1999***, 20(2),* 106-118. doi:10.1016/S0893-133X(98)00067-0

[140] Krystal, J.H.; Karper, L.P.; Seibyl, J.P.; Freeman, G.K.; Delaney, R.; Bremner, J. D.; Heninger, G.R.; Bowers, M.B.; Charney, D.S.Subanesthetic effects of the noncompetitive NMDA antagonist ketamine in humans – psychotomimetic, perceptual, cognitive and neuroendocrine responses. *Arch. Gen. Psych.,* **1994**, *51(3)*, 199-214. doi:10.1001/archpsyc.1994.03950030035004

[141] Morgan, C.J.; Rees, H.; Curran, H.V. Attentional bias to incentive stimuli in frequent ketamine users. *Psychol. Med.*, **2008**, *38(9)*, 1331-1340. doi: 10.1017/S0033291707002450

[142] Holcomb, H.H.; Lahti, A.C.; Medoff, D.R.; Weiler, M.; Tamminga, C.A. Sequential regional cerebral blood flow brain scans during PET with H2(15)O demonstrate ketamine actions in CNS dynamically. *Neuropsychopharmacology*, **2001**, *25(2)*, 165-172. doi: 10.1016/S0893-133X(01)00229-9

[143] Breier, A.; Malhotra, A.K.; Pinals, D.A.; Weisenfeld, N.I.; Pickar, D. Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *Am. J. Psych.,* **1997**, *154(6)*, 805-811.

[144] Honey, R.A.; Honey, G.D.; O'Loughlin, C.; Sharar, S.R.; Kumaran, D.; Bullmore, E.T.; Menon, D.K.; Donovan, T.; Lupson, V.C.; Bisbrown-Chippendale, R.; Fletcher, P.C. Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: an fMRI study. *Neuropsychopharmacology*, **2004**, *29(6)*, 1203-1214. doi: 10.1038/sj.npp. 1300438

[145] Honey, G.D.; Honey, R.A.; O'Loughlin, C.; Sharar, S.R.; Kumaran, D.; Suckling, J.; Menon, D.K.; Sleator, C.; Bullmore, E.T.; Fletcher, P.C. Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: an fMRI study. *Cereb. Cortex*, **2005**, *15(6)*, 749-759. doi: 10.1093/cercor/bhh176

[146] Corlett, P.R.; Honey, G.D.; Aitken, M.R.; Dickinson, A.; Shanks, D.R.; Absalom, A.R.; Lee, M.; Pomarol-Clotet, E.; Murray, G.K.; McKenna, P.J.; Robbins, T.W.; Bullmore, E.T.; Fletcher, P.C. Frontal responses during learning predict vulnerability to the psychotogenic effects of ketamine: linking cognition, brain activity, and psychosis. *Arch. Gen. Psych.*, **2006**, *63(6)*, 611-621. doi:10.1001/archpsyc.63.6.611

[147] Deakin, J.F.; Lees, J.; McKie, S.; Hallak, J.E.; Williams, S.R.; Dursun, S.M. Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. *Arch. Gen. Psych.*, **2008**, *65(2)*, 154-164. doi: 10.1001/ archgenpsychiatry.2007.37

[148] Scheidegger, M.; Walter, M.; Lehmann, M.; Metzger, C.; Grimm, S.; Boeker, H.; Boesinger, P.; Henning, A.; Seifritz, E. Ketamine decreases resting state functional network connectivity in healthy subjects: implications for antidepressant drug action. *PLOS ONE*, **2012**, *7(9),* e44799doi:10.1371/journal.pone.0044799

[149] Olney, J.W. Neurotoxicity of NMDA receptor antagonists: an overview. *Psychopharmacol. Bull.*, **1994**, *30*, 533-540.

[150] Mak, Y.T.; Lam, W.P.; Lu, L.; Wong, Y.W.; Yew, D.T. The toxic effect of ketamine on SH-SY5Y neuroblastoma cell line and human neuron. *Microsc. Res. Tech.*, **2010**, *73(3)*, 195-201. doi: 10.1002/ jemt.20774

[151] Chan, W.M.; Liang, Y.; Wai, M.S.M.; Hung, A.S.M.; Yew, D.T.Cardiotoxicity induced in mice by long term ketamine and ketamine plus alcohol treatment. *Toxicol. Lett.,* **2011***, 207(2)*, 191-196. doi: 10.1016/j.toxlet.2011.09.008

[152] Muetzelfeldt, L.; Kamboj, S.K.; Rees, H.; Taylor, J.; Morgan, C.J.; Curran, H.V. Journey through the K-hole: phenomenological aspects of ketamine use. *Drug Alcohol Depend.,* **2008***, 95(3)*, 219-229. doi: 10.1016/j.drugalcdep.2008.01.024

[153] Curran, H.V.; Monaghan, L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction*, **2001**, *96(5)*, 749-760. doi: 10.1046/j.1360-0443.2001.96574910.x

[154] Sun, L.; Lam, W.P.; Wong, Y.W.; Lam, L.H.; Tang, H.C.; Wai, M.S.Permanent deficits in brain functions caused by long-term ketamine treatment in mice. *Hum. Exp.Toxicol.*, **2011**, *30(9)*, 1287-1296.doi: 10.1177/0960327110388958

[155] Ricci, V.; Martinotti, G.; Gelfo, F.; Tonioni, F.; Caltagirone, C.; Bria, P.; Angelucci, F. Chronic ketamine use increases serum levels of brain-derived neurotrophic factor. *Psychopharmacology*, **2011**, *215(1)*, 143-148. doi: 10.1007/s00213-010-2121-3

[156] Dwyer, J.M.;Duman, R.S. Activation of mammalian target of rapamycin and synaptogenesis: role in the actions of rapid-acting antidepressants. *Biol. Psychiatry*, **in press**. doi:10.1016/j. biopsych.2012.11.011

[157] Narendran, R.; Frankle, W.G.; Keefe, R.; Gil, R.; Martinez, D.; Slifstein, M.; Kegeles, L.S.; Talbot, P.S.; Huang, Y.; Hwang, D.R.; Khenissi, L.; Cooper, T.B.; Laruelle, M.; Abi-Dargham, A. Altered prefrontal dopaminergic function in chronic recreational ketamine users. *Am. J. Psych.,* **2005***, 162(12)*, 2352-2359. doi: 10.1176/appi. ajp.162.12.2352

[158] Liao, Y.; Tang, J.; Ma, M.; Wu, Z.; Yang, M.; Wang, X.; Liu, T.; Chen, X.; Fletcher, P.C.; Hao, W. Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. *Brain*, **2010**, *133*, 2115-2122. doi: 10.1093/brain/ awq131

[159] Liao, Y.; Tang, J.;Corlett, P.R.; Wang, Y.; Yang, M.; Chen, H.; Liu, T.; Chen, X.; Hao, W.; Fletcher, P.C. Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biol. Psychiatry*, **2011**, *69*, 42-48. doi:10.1016/j.biopsych.2010.08.030

[160] Yuan, Y.; Zhu, Z.; Shi, J.; Zou, Z.; Yuan, F.; Liu, Y.; Lee, T.M.; Weng, X. Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. *Brain Cogn.*, **2009**, *71(3)*, 223-228. doi: 10.1016/j.bandc.2009.08.014

[161] Zuo, D.Y.; Wu, Y.L.; Yao, W.X.; Cao, Y.; Wu, C.F.; Tanaka, M. Effect of MK-801 and ketamine on hydroxyl radical generation in the posterior cingulate and retrosplenial cortex of free-moving mice, as determined by *in vivo* microdialysis. *Pharmacol. Biochem.Behav.*, **2007**, *86(1)*, 1-7. doi: 10.1016/j.pbb.2006.05.010

[162] Yeung, L.Y.; Wai, M.S.M.; Fan, M.; Mak, Y.T.; Lam, W.P.; Li, Z.; Lu, G.; Yew, D.T. Hyperphosphorylated tau in the brains of mice and monkeys with long-term administration of ketamine. *Toxicol. Lett.*, **2010**, *193*, 189-193. doi: 10.1016/j.toxlet.2010.01.008

[163] Yu, H.; Li, Q.; Wang, D.; Shi, L.; Lu, G.; Sun, L.; Wang, L.; Zhu, W.; Mak, Y.T.; Wong, N.; Wang, Y.; Pan, F.; Yew, D.T. Mapping the central effects of chronic ketamine administration in an adolescent primate model by functional magnetic resonance imaging (fMRI). *NeuroToxicology,* **2012**, *33(1),* 70-77. doi: 10.1016/j.neuro.2011.11.001

[164] Lahti, A.C.; Weiler, M.A.; Michaelidis, T.; Parwani, A.; Tamminga, C.A. Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology,* **2001**, *25(4)*, 455-467.

[165] Radant, A.D.; Bowdle, T.A.; Cowley, D.S.; Kharasch, E.D.; Roy-Byrne, P.P. Does ketamine-mediated n-methyl-d-aspartate receptor antagonism cause schizophrenia-like oculomotor abnormalities? *Neuropsychopharmacology,* **1998**, *19(5)*, 434-444. doi:10.1016/S0893-133X(98)00030-X

[166] Thoma, R.J.; Hanlon, F.M.; Moses, S.N.; Ricker, D.; Huang, M.; Edgar, C.; Irwin, J.; Torres, F.; Weisend, M.P.; Adler, L.E.; Miller, G.A.; Canive, J.M.. M50 sensory gating predicts negative symptoms in schizophrenia. *Schizophr. Res.,* **2005**, *73(2-3)*, 311-318. doi: 10.1016/j.schres.2004.07.001

[167] Kegeles, L.S.; Abi-Dargham, A.; Zea-Ponce, Y.; Rodenhiser-Hill, J.;Mann, J.J.; Van Heertum, R.L.; Cooper, T.B.; Carlsson, A.; Laruelle, M. Modulation of amphetamine-induced striatal dopamine release by ketamine in humans. *Biol. Psychiatry,* **2000**, *48(7)*, 627-640. doi: 10.1016/S0006-3223(00)00976-8

[168] Coyle, J. T. Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cell. Mol. Neurobiol.,* **2006**, *26(4-6)*, 365-384. doi: 10.1007/s10571-006-9062-8

[169] Zoncu, R.; Efeyan, A.; Sabatini, D.M. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev.: Mol. Cell Biol.,* **2011**, *12(1)*, 21-35. doi: 10.1038/nrm3025

[170] Curran, H.V.; Morgan, L. Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction*, **2000**, *95(4)*, 575-590. doi: 10.1046/j.1360-0443.2000.9545759.x

[171] Becker, A.; Peters, B.; Schroeder, H.; Mann, T.; Huether, G.;Grecksch, G. Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. *Prog. Neuro-Psychopharmacol. & Biol. Psych.,* **2003**, *27(4),* 687-700.doi: 10.1016/S0278-5846(03)00080-0

[172] Kellhoff, G.; Bernstein, H.G.; Becker, A.; Grecksch, G.; Wolf, G. Increased neurogenesis in a rat ketamine model of schizophrenia. *Biol. Psychiatry*, **2004**, *56(5)*, 317-322. doi: 10.1016/j.biopsych.2004.06.010

[173] Paslakis, G.; Gilles, M.; Meyer-Lindenberg, A.; Deuschle, M. Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy on depression: A case series. *Pharmacopsychiatry*, **2010**, *43(1)*, 33-35. doi: 10.1055/s-0029-1237375

[174] Irwin, S.A..; Iglewicz, A.; Nelesen, R.A.; Lo, J.Y.; Carr, C.H.; Romero, S.D.; Lloyd, L. S. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. *J. Palliat. Med.*, **2013**, *13(7)*, 903-908.doi: 10.1089/jpm.2012.0617

[175] Bisaga, A.; Evans, S.M. Acute effects of memantine in combination with alcohol in moderate drinkers. *Psychopharmacology*, **2004**, *172(1)*, 16-24. doi: 10.1007/s00213-003-1617-5

[176] Zarate, C.A.; Singh, J.B.; Quiroz, J.A.; De Jesus, G.; Denicoff, K.K.; Luckenbaugh, D.A.; Manji, H.K.; Charney, D.S. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am. J. Psych.*, **2006**, *163(1)*, 153-155. doi: 10.1176/appi.ajp.163.1.153

[177] Wang, X.; Chen, Y.; Zhou, X.; Liu, F.; Zhang, T.; Zhang, C. Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder. *J ECT*, **2012**, *28(2)*, 128-132. doi: 10.1097/YCT.0b013e31824d1d02

[178] Okamoto, N.; Nakai, T.; Sakamoto, K.; Nagafusa, Y.; Higuchi, T.; Nishikawa, T. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression. *J. ECT.*, **2010**, *26(3)*, 223-227. doi: 10.1097/YCT.0b013e3181c3b0aa

[179] Fountoulakis, K.N.; Kelsoe, J.R.; Akiskal, H. Receptor targets for antidepressant therapy in bipolar disorders: an overview. *J. Affect.Disord.*, **2012**, *138(3)*, 22-238.doi: 10.1016/j.jad.2011.04.043

[180] Burgdorf, J., ; Zhang, X.-L.; Nicholson, K.L.; Balster, R.L.; Leander, J.D.; Stanton, P.K.; Gross, A.L.; Kroes, R.A.; Moskal, J.R. GLYX-13 an NMDA receptor glycine-site functional partial agonist induces antidepressant-like effects without ketamine-like side effects. *Neuropsychopharmacology,* **2013**, *38(5),* 729-742. doi: 10.1038/npp.2012.246

[181] Duncan, W.C.; Selter, J.; Brutsche, N.; Sarasso, S.; Zarate, C.A. Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder. *J. Affect. Disord.*, **2013**, *145(1)*, 115-119. doi: 10.1016/j.jad.2012.05.042

[182] Ibrahim, L.; DiazGranados, N.;Chaves, J.F.;Brutsche, N.;Henter, I. D.;Kronstein, P.; Moaddel, R.; Wainer, I.; Luckenbaugh, D.A.; Manji, H. K.; Zarate, C.A. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs. add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology*, **2012**, *37(6)*, 1526-1533. doi:10.1038/npp.2011.338

[183] Murrough, J.W.;Perez, A.M.; Pillemer, S.; Stern, J.; Parides, M.K.; aan het Rot, M.; Collins, K.A.; Mathew, S.J.; Charney, D.S.; Iosifescu, D.V. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression.*Biol. Psychiatry*, **in press**. doi: 10.1016/j.biopsych.2012.06.022

[184] Carlson, P.J.; Diazgranados, N.; Nugent, A.C.; Ibrahim, L.; Luckenbaugh, D.A.; Brutsche, N.; Herscovitch, P.; Manji, H.K.; Zarate, C.A.; Drevets, W.C. Neural correlates of rapid antidepressant response to ketamine in treatment-resistant unipolar depression: a preliminary positron emission tomography study. *Biol. Psychiatry*, **2013**, *73(12)*, 1213-1221. doi: j.biopsych.2013.02.008

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