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Review

A review of ketamine in affective disorders: Current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action

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ABSTRACT

Introduction: Recent research has seen low-dose ketamine emerge as a novel, rapid-acting antidepressant. Ketamine, an *N*-methy-D-aspartate (NMDA) receptor antagonist, leads to effects on the glutamatergic system and abnormalities in this neurotransmittor system are present in depression. This article aims to (1) review the clinical literature on low-dose ketamine as a rapid-acting antidepressant in affective disorders, (2) provide a critical overview of the limitations of ketamine and research attempts to overcome these (3) discuss the proposed mechanisms of action of ketamine and (4) point towards future research directions.

Method: The electronic database Pubmed, Web of Science and sciencedirect were searched using the keywords: ketamine, *N*-methyl-D-aspartate receptor antagonist, rapid-acting antidepressant, depression, treatment-resistant depression, bipolar depression, suicidal ideation, electroconvulsive therapy, mechanism of action.

Result: The literature demonstrates evidence supporting a rapid-acting antidepressant effect of low-dose intravenous ketamine in major depressive disorder, in bipolar depression and in depression with suicidal ideation. There are mixed results as to whether ketamine leads to a reduction in time to remission in patients undergoing electroconvulsive therapy (ECT). Efforts to unravel ketamine's therapeutic mechanism of action have implicated the mammalian target of rapamycin (mTOR)-dependent synapse formation in the rat prefrontal cortex, eukaryotic elongation factor 2 phosphorylation (p-eEF2) and glycogen synthase kinase (GSK-3). Ketamine's limiting factors are the transient nature of its antidepressant effect and concerns regarding abuse, and research efforts to overcome these are reviewed.

Conclusion: Current and future research studies are using ketamine as a promising tool to evaluate the glutamatergic neurotransmittor system to learn more about the pathophysiology of depression and develop more specific rapid-acting antidepressant treatments.

Contents

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1. Background

Major depressive disorder (MDD) is a debilitating mental illness that affects millions of people worldwide leading to severe health and socioeconomic consequences (Kessler et al., 2003). Despite antidepressant treatment patients continue to experience low remission rates, residual subsyndromal symptoms, relapses and persistent functional impairment. It is widely accepted that all current antidepressants require a lag period of several weeks before improvements in mood and wellbeing are felt. Another limitation of current monoamine-based antidepressants was highlighted in the large well-known trial; sequenced treatment alternative to relieve depression (STAR*D Trial) (Rush et al., 2006a, 2006b; Trivedi et al., 2006; Nierenberg et al., (2006); Rush, 2006c; Fava et al., 2006). This study showed modest and diminished returns from sequential trials of existing antidepressants in patients who had not benefited from the selective serotonin reuptake inhibitor, citalopram. Thus, there is a critical, unmet need to both identify and test novel drug targets for mood disorders in order to develop more effective treatments.

For years researchers have explored antidepressant options that side-stepped the lag period for improvement in symptoms. Simultaneously, there has been growing appreciation that investigation into the pathophysiology of mood disorders has been focused on monoaminergic systems and recently there has been more extensive research into other neurotransmitter signalling cascades such as the glutamatergic systems (Manji et al., 2003; Skolnick et al., 2001). Leading on from this research, the glutamatergic system may offer a rational, rapid-acting target for drug development in mood disorders (Sanacora et al., 2008). Ketamine is a high affinity non-competitive antagonist at the *N*-methyl-D-aspartate (NMDA) receptor, an ionotropic receptor in the glutamatergic system.

Glutamate is the major mediator of excitatory synaptic transmission in the mammalian brain (Orrego and Villanueva, 1993) and has a prominent role in synaptic plasticity, learning and memory. A growing body of preclinical research implicates the glutamatergic system in the pathophysiology of major depression and the in mechanism of action of antidepressant treatments (Skolnick et al., 1996; Cryan and Dev, 2007; O'Connor and Cryan, 2010; O'Connor et al., 2010). In particular NMDA receptors appear to be specifically involved (Trullas and Stolnick, 1990; Skolnick et al., 1996) although metabotropic (mGlu) receptors are also known to be linked to depression and the effects of antidepressants (O'Connor et al., 2013). Conversely, chronic treatment with traditional antidepressants has been shown to affect NMDA receptor function (Mjellem et al., 1993) and receptor binding profiles (Paul et al., 1994). These findings suggest that NMDA receptor antagonism could form a viable treatment option for depression. However, clinical validation of this hypothesis has only surfaced over the last decade.

Ketamine is an approved anaesthetic agent for diagnostic and surgical procedures in adults, obstetric patients and children (Lanning and Harmel, 1975). Its use had been associated with dissociative reactions on emerging from anaesthesia; however, it remains a desirable anaesthetic because of its short half-life (180 min) and the lack of respiratory depression (Clemens et al. 1982). Over the past 40 years, ketamine has been administered as an anaesthetic to several million people and has a good safety profile (Lahti et al., 2001; Corrsen et al., 1988; Reich and Silvay, 1989; White et al., 1982). Thirteen years ago the first clinical report of ketamine being an effective, rapid-acting antidepressant emerged. The exciting prospect of a rapid-acting antidepressant could lead to significant benefits for patients and would completely change prescribing and how mental health services are delivered.

2. Aims

The overall objective of this article is to review the evidence to date on the use of ketamine as a rapid-acting antidepressant. The specific aims are to:

- Review the clinical literature to date on low-dose intravenous ketamine as a rapid-acting antidepressant in affective disorders,
- Provide a critical overview of the limitations of ketamine use in affective disorders and research attempts to overcome these,
- Discuss the proposed mechanisms of action of ketamine, derived mainly from preclinical studies and
- Point towards future research directions with ketamine as a promising tool to develop novel, more effective, rapid-acting antidepressants.

3. Method

The search was performed using Pubmed, Web of science and sciencedirect for papers published up to June 2013 using the following search terms (MeSH/All fields): ketamine, *N*-methyl-D-aspartate receptor antagonist, rapid-acting antidepressant, depression, treatment-resistant depression, bipolar depression, suicidal ideation, electroconvulsive therapy, mechanism of action. All relevant clinical reports involving the assessment of ketamine's antidepressant potential were considered. In addition, we considered preclinical studies in animal models of depression or those carried out to provide insight into the mechanism of action of ketamine. The bibliographies of relevant studies were also considered. All articles without a focus on ketamine or NMDA receptor antagonists as antidepressants were excluded. Studies were

excluded if the study was only published in abstract form or in a language other than English.

4. Results

Ketamine and treatment-resistant depression as search terms yielded a total of 70 articles of which 60 were relevant. Ketamine and rapid-acting antidepressant yielded 17 papers (15 relevant) and *N*-methyl-D-aspartate receptor antagonist and rapid-acting antidepressant yielded 10 papers (7 relevant). Ketamine and bipolar depression revealed 43 articles of which 29 were relevant. Ketamine and suicidal ideation revealed 10 articles of which 8 were relevant. Ketamine, Electroconvulsive therapy, and depression revealed 21 articles (14 relevant). Ketamine, mechanism of action and rapid-acting antidepressant revealed 12 articles of which 10 were relevant. Overall the search yielded 143 relevant initial papers. Relevance was determined by all authors based on whether a significant proportion of the paper was dedicated to ketamine and added to the body of research on ketamine as an antidepressant.

4.1. Clinical trials of ketamine in depression

Berman et al. (2000) was the first to show that a subanaesthetic (0.5 mg/kg) infusion of intravenous ketamine rapidly reduced depressive symptoms in depressed patients in a randomised, placebo crossover design study. Four of the eight patients demonstrated 50% or greater decrease in Hamilton depression rating scores (HDRS) during the 3-day follow up period and ketamine-induced mood improvement returned to baseline levels (i.e. clinical impression and HDRS within 5 points of baseline) 1–2 weeks after the infusion. Zarate et al. (2006), in a similar randomised, placebo-controlled double-blind crossover study of 18 patients with treatment-resistant depression confirmed ketamine's rapid acting antidepressant effects. In this study, subjects had on average failed six prior antidepressant trials and were medication free at least 2 weeks prior to the infusion. Notably, the response rates obtained with ketamine after 24 h (71%) were similar to those described after 6–8 weeks of treatment with traditional monoaminergic-based antidepressants (65%) (Entsuah et al., 2001; Thase et al., 2005).

Since these 2 landmark studies, there have been numerous other small studies evaluating ketamine's rapid acting antidepressant response and the results have been consistent with rapid reductions in depressive symptomatology maintained for approximately 1–2 weeks following a single infusion. Response rates in the open-label investigations and controlled trials have ranged from 25% to 85% at 24 h post infusion and from 14% to 70% at 72 h post infusion (Aan het Rot et al., 2012). Although adverse effects have generally been mild, some patients have experienced brief changes in blood pressure, heart rate or respiratory rate. However, given the paucity of randomised controlled trials, lack of an active placebo, limited data on long-term outcomes, ketamine administration is not routinely recommended (Aan het Rot et al. 2012).

The largest clinical trial of ketamine to date (Murrough et al., 2013) was a two-site, parallel arm, randomized controlled trial of a single infusion of ketamine compared to an active placebo control condition, the anaesthetic midazolam. Although previous clinical studies provide compelling evidence of the antidepressant effects of ketamine, their major weakness is the lack of a psychoactive placebo-controlled, double-blind design. Ketamine produces psychoactive effects that are easily recognised by patients who report brief, transient feeling of being "high". Hence, limitations in preserving study blinding may bias patient reporting by diminishing placebo effects, thereby potentially confounding results. With this in mind, Murrough et al. (2013) compared intravenous ketamine with midazalom, a benzodiazepine, considered a better comparator than placebo. Patients with treatment-resistant major depression experiencing a major depressive episode were randomly assigned under double-blind conditions to receive a single intravenous infusion of ketamine or midazolam in a 2:1 ratio ($N=73$). They demonstrated that the likelihood of response at 24 h was greater with ketamine than with midazolam (odds ratio 2.18, 95% confidence interval 1.21–4.14) with response rates of 64% and 28%, respectively. Depression scores were not significantly different between treatment groups at 7 days. Similar to previous studies they demonstrated that side-effects associated with ketamine included dissociative symptoms immediately following administration in 17% of patients. However, these side-effects resolved 2 h post-infusion. The authors commented that more information on response durability and safety is required before implementation in clinical practice.

4.2. Clinical trials of ketamine in bipolar affective disorder

Following on from the initial trials of ketamine in MDD others have looked at ketamine in bipolar depression (Diazgranados et al., 2010a; Zarate et al., 2012) and have shown it to be rapidly effective but, similar to MDD studies, not lasting for beyond 1–2 weeks. Patients were maintained on lithium or valproate during the study timeframe. In contrast to traditional antidepressants, a subanaesthetic dose of ketamine does not induce an affective switch in treatment-resistant major depression (Niciu et al., 2013).

4.3. Clinical trials of ketamine on suicidal ideation

Interest has also been generated regarding ketamine's effect on suicidal ideation. Although such patients were excluded from initial RCTs, ketamine rapidly reduced suicidal ideation scores on the depression rating scales used (Berman et al., 2000; Zarate et al., 2006). This has since been replicated in 2 open-label investigations of MDD patients and in one RCT of bipolar patients (Zarate et al. 2012; DiazGranados et al., 2010b; Price et al., 2009). They demonstrated that ketamine was associated with robust and rapid antisuicidal effects. DiazGranados et al. (2010b) gave 33 subjects with treatment-resistant MDD a single open-label infusion of ketamine (0.5 mg/kg). Patients were rated at baseline, 40, 80, 120 and 230 min post-infusion using the scale for suicide ideation (SSI) (Beck et al., 1979). Scores significantly decreased within 40 min of ketamine infusion and remained improved for up to four hours post infusion. In another study, early antisuicidal effects (within one day) were found with ketamine and these effects remained significant for several weeks (Aan het Rot et al., 2010). Repeated ketamine infusions can also reduce suicidality ratings (MADRS-SI) but only as long as the duration of the 12-day repeated infusion trial (Price et al., 2009). A study investigating IV ketamine in the emergency room showed beneficial results but this study was not without its flaws, most notably lack of a control group (Larkin and Beautrais, 2011). However these studies have led the way for further studies to explore this in more detail.

Studies to date have provided us with clinical proof-of-concept that ketamine, an antagonist of the NMDA receptor in the glutamatergic system, has rapid antidepressant effects in affective disorders and appears to reduce suicidal ideation. Questions remain in relation to how these significant findings can be moulded into a coherent treatment strategy. The studies to date have shown that ketamine's effect peaks at 24 h post infusion and, in general, last 1–2 weeks. Clearly, maintaining the transient antidepressant response of ketamine is required. Additionally the psychotomimetic side-effects of ketamine and the concern regarding abuse potential of ketamine make clinical use of ketamine itself unfeasible.

Mechanistic insights are thus urgently required in order to produce a similarly acting agent without the associated safety issues. Thirdly, one wonders could ECT antidepressant effects be expedited if ketamine is used as the induction agent? How the literature has attempted to address these challenges will be discussed below.

4.4. Preclinical studies and clinical trials to sustain the antidepressant effect of ketamine

Strategies to sustain the rapid antidepressant response to ketamine have largely centred on repeated infusions, usually administered on alternate days over an extended period of time. Repeated infusions of ketamine were assessed preclinically by Parise et al. (2013) in adolescent male rats (postnatal day 35) who received two ketamine (0, 5, 10, or 20 mg/kg) injections, 4 h apart, after exposure to day 1 of the forced swim test (FST). The next day, rats were re-exposed to the FST to assess ketamine-induced antidepressant-like responses. Separate groups were exposed to chronic unpredictable stress to confirm findings from the FST. After these initial experiments, adolescent naive rats were exposed to either 1 or 15 consecutive days (PD35-49) of ketamine (20 mg/kg) twice daily. Ketamine's influence on behavioural reactivity to rewarding (i.e., sucrose preference) and aversive (i.e., elevated plus-maze, FST) circumstances was then assessed 2 months after treatment. To control for age-dependent effects, adult rats (PD75-89) were exposed to identical experimental conditions. What was found was that ketamine (20 mg/kg) reversed the chronic unpredictable stress-induced depression-like behaviours in the FST. Repeated ketamine exposure resulted in anxiolytic- and antidepressant-like responses 2 months after drug exposure. None of the ketamine doses used was capable of inducing drug-seeking behaviours as measured by place preference conditioning (Parise et al., 2013). The authors concluded by indicating that repeated ketamine exposure induces enduring resilient-like responses regardless of age of exposure. These findings, although preliminary, point to ketamine, and its repeated exposure, as a potentially useful antidepressant during adolescence. Further similar studies are awaited.

Results with repeated infusions clinically have been less positive. Aan het Rot et al. (2010) looked at response to repeated IV ketamine infusions in 10 patients in an in-patient setting in treatment resistant depression (TRD). The primary efficacy measure was change from baseline in the Montgromery–Asberg depression rating scale (MADRS) score. If patients showed a greater than 50% reduction in MDRAS scores on day 2 (9 of 10 patients) they received five additional infusions on an outpatient basis (days 3, 5,8,10 and 12). Of these nine patients, eight relapsed within an estimated mean 30 days after the first infusion or 19 (SD = 13) after the sixth infusion. However the small sample size and lack of a control group limit the extent to which these findings can be generalised. Murrough et al. (2013b) in a similar study design with 24 participants with treatment-resistant depression had a very similar result with antidepressant effects lasting on average 18 days after the last infusion. Aan het Rot et al. (2010) concluded with the suggestion that the most practical use of repeated ketamine infusions might be on a short-term basis to elicit rapid relief until a more sustainable treatment and relapse prevention strategy could be demonstrated. A more recent study (Segmiller et al., 2013) administered 6 infusions of S-ketamine over a 4 week period to 6 patients with treatment resistant depression and demonstrated an improvement in the 21-item Hamilton depression rating scale scores over the study timeframe but depressive symptoms were only evaluated pre and 120 min post the 6 ketamine infusions and how the improvement was maintained in the longer term was not commented on.

Other clinical studies have attempted to maintain ketamine's antidepressant effects by administering riluzole following a low-dose ketamine infusion. Riluzole is a glutamate-modulating agent with neuroprotective and synaptic plasticity-enhancing properties, used in the treatment of amyotrophic lateral sclerosis (Doble, 1996; Du et al., 2007; Mizuta et al., 2001). Riluzole was administered orally for 28 days to sustained ketamine responders in one study (Mathew et al., 2010) and to all participating MDD patients 4–6 h after receiving an IV ketamine infusion in another study (Ibrahim et al., 2012). Unfortunately, both studies failed to provide any benefit over placebo in maintaining response to a single ketamine dose. One case study found positive results with oral memantine, a low-to-moderate affinity, non-competitive NMDA antagonist (Kollmar et al., 2008), however, a placebo-controlled study of memantine found no antidepressant effects (Zarate et al., 2006b). Thus, to date, efforts to maintain ketamine's antidepressant effect have been disappointing. What is promising is that another low-affinity NMDA receptor antagonist, AZD6765, demonstrated antidepressant effects in humans at doses that do not produce psychosis (Zarate et al., 2013).

4.5. Psychotomimetic side-effects and safety of ketamine

A vital question that should always be asked when a potentially new medication (or an old medication used for a new purpose) is being considered for use is safety. There is significant evidence to demonstrate ketamine's safety profile when given on a single occasion as an anaesthetic agent but a lot less is known about its safety when given repeatedly at subanaesthetic doses. No such safety studies have been done with depressed patients. However Zarate et al. (2006) demonstrated that adverse effects occurred more commonly in participants taking ketamine than those taking placebo and these were perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness and increased libido. The majority of adverse effects ceased within 80 min after the infusion. In no case did euphoria or derealisation/depersonalisation persist beyond 110 min. Murrough et al. (2013), in their two-site randomized controlled clinical trial of ketamine in patients with treatment-resistant depression reported that eight of the 47 patients who received ketamine (17%) had significant dissociative symptoms. Blood pressure in the ketamine group rose from 122/72 mm Hg (pre-treatment) to 141/81 (40 min after infusion), and two subjects required their infusions to be stopped for hemodynamic reasons. Berman et al. (2000) found transient cognitive deficits and euphoria induced by ketamine infusion as evidenced by increases in the brief psychiatric rating scale (Overall and Gorham, 1962). However this increase returned to baseline within 2 h following the infusion. Despite these side-effects one must consider the adverse side effect profile of many currently used antidepressants and if these findings with ketamine could be directly compared with monoaminergic antidepressants, it may represent some advantage for ketamine over existing therapies.

A significant limitation of ketamine as a therapeutic agent is that it is one of several "club drugs" that is abused. ketamine or "Special K" is widely available to induce a dissociative state of relaxed wellbeing. Zarate et al. (2010), however, pointed out that misuse of therapeutically relevant agents is not a new phenomenon in psychiatry (i.e. anticholinergic drugs, stimulants and benzodiazepines) and should not preclude their study as putative treatments. This view point would be reiterated by Nutt et al. (2013) who indicate that important and unfortunate outcomes of controls placed on certain psychoactive drugs makes research into mechanism of actions and potential therapeutic uses difficult. However despite the fact that the studies above demonstrate that the psychotomimetic effects of ketamine appear transient, concerns regarding abuse could lead to the therapeutic benefits being overlooked.

Mathew et al. (2010) in addition to administering riluzole in the study outlined above also looked to see if pre-treatment with

lamotrigine might attenuate ketamine's psychotomimetic effects and enhance antidepressant activity. Unfortunately, lamotrigine failed to reduce the transient psychotomimetic or dissociative side effects associated with ketamine use and did not enhance its antidepressant effects.

Further study is required to determine whether the therapeutic benefits of NMDA receptor inhibition can be realised using alternative agents that target a specific subunit of the NMDA receptors without causing psychotomimetic side-effects. Preskorn et al. (2008) set out to investigate the antidepressant efficacy of the NR2B subunit selective antagonist, CP-101,606, which inhibits NMDA receptors by an allosteric mechanism (Mott et al., 1998) that is distinct from that of ketamine. NMDA receptors are tetrameric proteins composed of 2 NR1 subunits and 2 NR2 subunits (Dingledine et al., 1999). There are 4 different NR2 subunits (NR2A-D) that are differently localised throughout the CNS. NMDA receptors containing the NR2B subunit are localised primarily in the forebrain including the hippocampus, a region implicated in the pathophysiology of major depression (Campbell and MacQueen, 2004). In this study 30 SSRI-resistant patients were randomised to CP-101,606 or a matched placebo infusion (15 in each group). Of the CP-101,606-treated subjects, 60% met criteria for response and 33% met criteria for remission on day 5. This is comparable to previous studies (Berman et al., 2000; Zarate et al., 2006). About 6 of the 15 patients who received CP 101,606 had a dissociative response compared to 2 on placebo and all resolved within 6 hours of discontinuation of the infusion. The authors indicated that 5 of the 9 CP-101,606 treated patients who met HDRS criteria for antidepressant response did not have a dissociative response from the infusion indicating that it is capable of producing an antidepressant response without also producing a dissociative reaction. While this is a small study, it points the way forward for further research to develop a new class of antidepressant with a reduced potential for psychotomimetic side-effects. This might appeal to clinicians and patients alike, particularly those with a history of addictions.

Linked with the concept above is the interesting effect of ketamine on subjects with alcohol dependence and those with family histories of alcohol dependence. Compared to healthy controls, subjects with alcohol dependence had fewer perceptual alterations and decreased dysphoric mood during ketamine infusion (Krystal et al., 2003). This attenuation of ketamine-induced perceptual alterations was also observed in healthy individuals with a positive family history of alcohol dependence (Petrakis et al., 2004). Indeed, Phelps et al. (2009) found that patients with MDD who had a family history of alcohol dependence had a better short-term outcome (greater and faster improvement in depressive symptoms) after ketamine infusion than subjects with no family history of alcohol dependence. Genetic variation in the NMDA receptor 2A gene has been associated with alcohol dependence (Schumann et al., 2008), pointing towards a potential genetic mechanism underlying this variation in the antidepressant response to ketamine in individuals with alcohol dependence.

Despite extensive research in healthy volunteers (Krystal et al., 1994, 1999, 2005; Morgan et al., 2004; Parwani et al., 2005; Perry et al., 2007) there is a paucity of studies examining the neurocognitive effects of ketamine in depressed patients. Murrough et al. (2013c) assessed neuro-cognitive functioning in 25 patients with TRD using a comprehensive battery following a 40-min intravenous infusion of ketamine (0.5 mg/kg). They demonstrated that patients who responded to ketamine 24 h following treatments had poorer baseline neurocognitive performance relative to non-responders and, in particular, slower processing speed. Ketamine was associated with selective impairments in memory recall, and the degree of cognitive change carried negative prognostic significance (e.g., negative cognitive effects immediately after ketamine predicted lower response rate at 24 h). This suggests a potential baseline neurocognitive predictor of ketamine response and an inverse relationship between the cognitive effects of ketamine and antidepressant efficacy.

In humans ketamine abuse has been associated with cystitis (Chen et al., 2009) and bilary dilatation (Wong et al., 2009). However, Krystal et al. (2013) commented that such findings in chronic ketamine abusers may over estimate the clinical risks of long-term treatment. Ketamine abusers often take multiple substances, administer higher ketamine doses than needed to treat depression, and administer these doses more frequently than would be needed for treatment (Morgan and Curran, 2012). Nonetheless, the development of long-term ketamine treatment for depression would need to be accompanied by careful studies of its safety.

4.6. Ketamine combined with electroconvulsive therapy

Electroconvulsive therapy (ECT) is recognised as a highly effective treatment of unipolar and bipolar depression (Weiner, 2001) and it is generally considered to have a more rapid onset of action than standard antidepressant agents. The data on the onset of ECTs antidepressant action suggest that a range of 5–7 treatments (approx 3 weeks) are required to obtain a significant reduction in symptom severity (Nobler et al., 1997) which is still considerably longer than the time of antidepressant effect observed with ketamine. One of the most promising aspects of ketamine is that even patients resistant to electroconvulsive therapy (ECT) may benefit from it (Zarate et al., 2006; Ibrahim et al., 2011). The reverse, whether patients who do not respond to subanaesthetic IV ketamine doses might still benefit from ECT, is still not known. Given the fact that ketamine is a licensed anaesthetic agent, it is reasonable to question whether co administration of ketamine could expedite the antidepressant response of ECT. Interestingly ketamine has been used in ECT anaesthesia for decades (Green, 1973; Brewer et al., 1972) with preliminary evidence suggesting that ketamine anaesthesia in ECT may improve seizure duration relative to other anaesthetic agents that are commonly used (Krystal et al., 2003b; McDaniel et al., 2006). However, there is no evidence that the direct antidepressant effect of the ketamine was considered as a potential benefit to the use of this drug in these early studies.

There have been some case reports in the ECT setting demonstrating a more rapid antidepressant effect with ketamine use (Goforth and Holsinger, 2007). Two uncontrolled studies have since shown that depression scores may decrease faster during ECT in patients given ketamine than in patients given propofol or thiopentone (Okamoto et al., 2010; Kranaster et al., 2011). However, an RCT of thiopental alone or thiopental plus ketamine (0.5 mg/kg) for anaesthesia before each ECT did not appear to enhance or expedite the antidepressant effect of ECT (Abdallah et al., 2012). Thus, further studies investigating ketamine's augmentation to ECT need to be undertaken which should consider the effects of dose, timing and concomitant medications in the study design.

4.7. Postulated mechanisms of action underlying the rapid antidepressant effect of ketamine

The neurobiological mechanisms underlying the antidepressant actions of ketamine are more complex than simple blockade of NMDA receptors given its short half-life relative to the antidepressant effect seen in the afore mentioned clinical studies. The very low dose of ketamine used for these studies first produces mild psychotomimetic and dissociative effects 30–40 min after administration, effects that are transient and completely dissipate by 80 min (Zarate et al., 2006). This is presumably because of the rapid metabolism of

ketamine (half-life is 180 min in humans; Clemens et al., (1982)). After this initial psychotomimetic phase, the antidepressant effects are observed at 110 min and are sustained for approximately 7 days after a single dose of ketamine (Zarate et al., 2006). These findings indicate that ketamine initiates a cascade of events that results in a rapid response that is sustained even after the drug has been metabolised (see Fig. 1). Preclinical studies have been investigating the intriguing question of ketamine's mechanism of action and in this context recent reviews on preclinical ketamine studies are relevant (Duman et al., 2012; Zunszain et al., 2013).

The potential role of dendrites and spines in stress-related illnesses such as depression is supported by basic studies demonstrating that exposure to stress causes atrophy of neurons in limbic brain regions implicated in depression, including the prefrontal cortex (PFC) and hippocampus (McEwen, 2008; Shansky and Morrison, 2009). This includes a decrease in the density of spines, as well as a decrease in the number and length of dendrite branches. These effects could contribute to the reduction in volume of PFC and hippocampus determined by imaging the brains of depressed patients (Drevets and Furey, 2010; Macqueen et al., 2008). In contrast to the effects of stress, Li et al. (2010) reported that administration of a low dose of ketamine results in the rapid induction of spine number in layer V pyramidal neurons of the PFC. Spine analysis was conducted 24 h after ketamine administration, and it is possible that the induction of spine formation occurs sooner, given the rapid induction of synaptic proteins (i.e., as early as 2 h after ketamine administration). At the 24 h time point, there is an increase in the number of mushroom or mature spines, indicating that ketamine increases spine stability and function. This possibility was directly tested by analysis of neurotransmitter-induced excitatory postsynaptic currents (EPSCs) in the same PFC layer V pyramidal neurons that were analyzed for spine density. The results demonstrate that ketamine administration significantly increases the frequency and amplitude of both 5-HT- and hypocretin-induced EPSCs. The increase in EPSP amplitude is consistent with the increase in the density of mushroom spines by ketamine. The increase in 5-HT- and hypocretin-induced EPSCs indicates that there is an increase in corticocortical and thalamocortical connections, respectively.

Consistent with the rapid induction of synaptogenesis, the authors above (Li et al., 2010) also found that ketamine produced rapid antidepressant effects in several different behavioral models. This included a significant decrease in immobility in the forced swim test (FST), decreased escape failure and latency to escape in the learned helplessness (LH) paradigm, and decreased latency to feed in the novelty suppressed feeding test (NSFT) (Li et al., 2010). Although the FST is responsive to acute administration of typical antidepressant agents, LH is only responsive to subchronic (7 days) treatment, and the NSFT, although a model of anxiety, is responsive to chronic (21 days) administration of a typical antidepressant. Together, these findings provide evidence of the fast antidepressant behavioral actions of ketamine in these rodent models. Interestingly, Harkin and colleagues demonstrated that ketamine's antidepressant-like effect in the FST is via a serotonin-dependant mechanism (Gigliucci et al., 2013).

In addition to studies in normal animals, Li et al. (2011) also examined the influence of ketamine in animals exposed to chronic unpredictable stress (CUS). In the CUS model, repeated exposure to stress over the course of several weeks results in the development of anhedonia, a core symptom of depression, and this effect is reversed by chronic administration of a typical antidepressant (Wilner, 2005; Banasr et al., 2007). In addition, chronic stress exposure decreases the density of spines in the PFC (Liu and Aghajanian, 2008; Shansky and Morrison, 2009), providing a morphological endpoint that can be measured and that is relevant to the atrophy of PFC in depression (Drevets and Furey, 2010). They found that exposure to CUS for 3 weeks decreased the density of spines in layer *V* pyramidal neurons, as expected, and decreased 5-HT and hypocretin-induced EPSCs in the same neurons (Li et al., 2011). A single dose of ketamine completely reversed the deficit in spine density, and this was accompanied by a reversal of the deficit in 5-HT and hypocretin induced EPSC. Together these studies demonstrate that ketamine reverses the spine loss caused by chronic stress exposure and normalizes PFC connectivity. To examine the possibility that reversal of the synapse loss caused by CUS influences behavior, Li et al. (2011) also examined sucrose preference, which provides a measure of anhedonia in rodents. CUS exposure for 3 weeks significantly decreased the preference for a sweetened solution, and this effect was completely reversed by a single dose of ketamine. In addition, CUS increased the latency to feed in the NSFT, and this effect was also reversed by a single dose of ketamine. These effects of ketamine were also sustained for approximately 7 days, similar to the time course for the antidepressant actions of ketamine in treatment resistant depressed patients (Zarate et al., 2006).

These synaptogenic and behavioural effects of ketamine outlined above were shown to be dependent on stimulation of the mammalian target of rapamycin (mTOR) (Li et al., 2010). mTOR is a large serine/threonine kinase that regulates the initiation of protein translation. It is ubiquitously expressed and can control new protein synthesis when required for synaptogenesis (Duman et al., 2012). Cryan and O'Leary (2010) commenting on the significance of these findings indicating that m-TOR mediated pathways may be an important and novel strategy for the rational design of fast-acting antidepressants.

Ketamine can enhance AMPA receptor throughput (Zarate and Manji, 2008). Maeng et al. (2008) showed, in rodent models of depression, that the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor is required for its antidepressant effect and postulated that ketamine may result in a rapid antidepressant effect by enhancing AMPA relative to NMDA throughout critical neuronal circuits. They demonstrated at a cellular level that ketamine's antidepressant effects were found to be selectively abolished using an AMPA antagonist (NBQX) prior to ketamine infusion. They also demonstrated that the antidepressant effects of MK-801 (a non-selective NMDA antagonist) and Ro 25-6981 (an NR2B selective antagonist) also require AMPA receptor throughput, again by pre-treating with NBQX. Interestingly, the antidepressant effect of MK-801 or RO25-6981 were not as long-lasting as those of ketamine. An increase in AMPA/NMDA receptor density ratio has been observed in the hippocampus of rats after ketamine treatment (Tizabi et al., 2012). Thus there is an emerging complementary pharmacological approach consisting of targeting AMPA receptors (AMPAR) to modulate glutamatergic transmission. It may appear counterintuitive that AMPA potentiators have antidepressant effects, knowing that antidepressants have been shown to dampen glutamate release (Martinez-Turrillas et al., 2005; Barbon et al., 2006; Tan et al., 2006; Svenningsson et al., 2002). However AMPA potentiators work by increasing the response of AMPAR, which is independent on the actual level of glutamate release. Several classes of AMPA potentiators, including nootropic agents and ampakines, have shown antidepressant efficacy in preclinical studies (O'Neill et al., 2004; Li et al., 2001) and a number of compounds are currently under clinical development. Information on the long-lasting clinical effects of a single dose of AMPA is not yet available however.

Following on from studies above, increasing the ratio of AMPA-to-NMDA receptor medicated neurotransmission is being assessed as a mechanism of antidepressant effect in preclinical behavioral tests of depression with positive results (Tizabi et al., 2012; Andreasen et al., 2013). Akinfiresoye and Tizabi (2013) tested whether AMPA alone has an antidepressant effect and if the combination of AMPA and ketamine provides added benefit in Wistar-Kyoto rats. They demonstrated that chronic AMPA

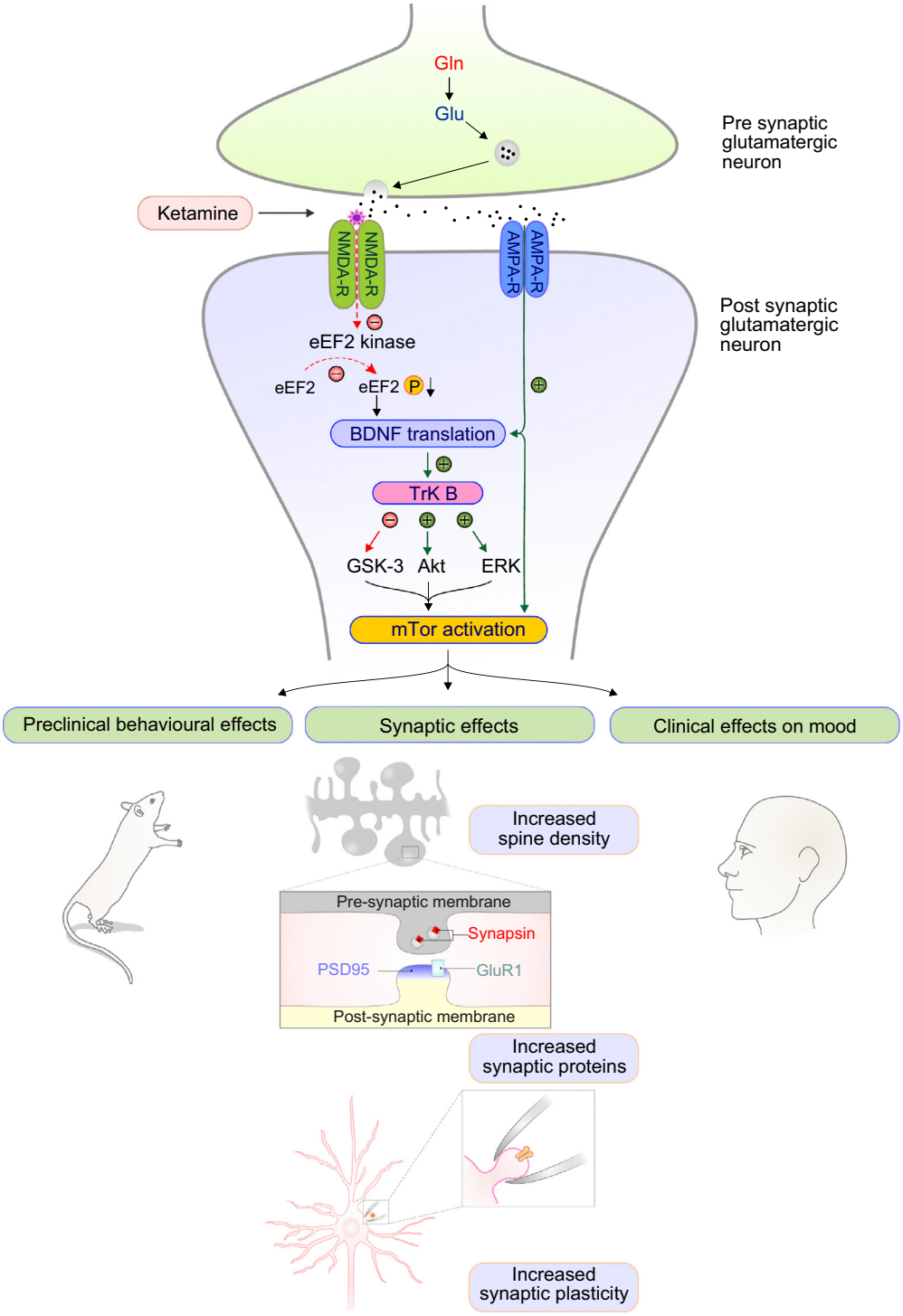

Fig. 1. Diagrammatic representation of the postulated mechanisms of action of ketamine on the glutamatergic neurotransmitter system. Glutamate (Glu) is synthesized in presynaptic neurons from glutamine by glutaminase. It is packaged into synaptic vesicles and released into the synaptic cleft. Glutamate binds to either ionotropic *N*-methyl-D-aspartate (NMDA) or alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic (AMPA) receptors localised in the postsynaptic density (Other receptors such as the metabotrophic receptors are also involved in glutamate's action but not discussed here). Under resting conditions NMDA-receptor activation leads to activation of eukaryotic elongation factor-2 (eEF2) kinase triggering eEF2 phosphorylation and silencing brain-derived neurotrophic factor (BDNF) translation. Ketamine is a high affinity antagonist at the NMDA receptor and blockade of this receptor leads to less activation of eEF2 kinase which gradually results in loss of eEF2 phosphorylation and de-suppression of BDNF translation (Autry et al., 2011). BDNF translation ultimately triggers TrkB (tyrosine-related kinase B) signalling, leading to transphosphorylation and downstream activation of extracellular signalling-related kinases (ERK) and protein kinase B (PKB/Akt) and suppression of glycogen synthase kinase-3 (GSK-3). These signalling events activate mTOR (mammalian target of rapamycin), leading to increased synaptic proteins and spine densities (in preclinical studies of rat prefrontal cortices) resulting in synaptogenesis (Li et al., 2010). The ultimate result of this pathway and synaptogenesis is positive behavioural effects in animal models of depression and thus is considered to be the possible mechanism whereby ketamine induces its antidepressant effect clinically. Increased AMPA receptor throughput has a central role in the antidepressant effect of ketamine possibly by increasing BDNF release, TrkB receptor activation, stimulation of mTOR signalling and local protein synthesis (Akinfiresoye and Tizabi, (2013); Jourdi et al., 2009).

treatment resulted in a dose-dependent antidepressant effect in both the forced swim test and sucrose preference test. Moreover, chronic administration (10–11 days) of combinations of AMPA and ketamine, at doses that were ineffective on their own, resulted in a significant antidepressant effect. The behavioral effects were associated with increases in hippocampal brain-derived

neurotrophic factor, synapsin, and mammalian target of rapamycin. These findings provided evidence for an antidepressant effect of AMPA and suggested the usefulness of AMPA-ketamine combination in treatment of depression. Furthermore, these effects appear to be associated with increases in markers of hippocampal neurogenesis and synaptogenesis, suggesting a mechanism of their action.

Expanding on the clinical study (Preskorn et al., 2008) above, investigating CP-101,606, an NR2B receptor antagonist in the treatment of depression, other selective NR2B antagonists have been assessed preclinically and what is becoming apparent is that they have similar behavioural and molecular effects to ketamine. The rationale for this avenue of research is to determine if ketamine's antidepressant effect can be observed without the psychomimetic side effects. Li et al. (2010) demonstrated that Ro 25-6981 stimulated mTOR signalling and had antidepressant effects in the FST and the novelty suppressed feeding test (NSFT) and that these effects were blocked by infusion with rapamycin. In the CUS paradigm, the NR2B selective antagonist completely blocked the deficits in sucrose consumption and novelty suppressed feeding resulting from CUS exposure (Li et al., 2011). These findings suggest that the actions of ketamine are mediated by blockage of NR2B receptors, and provide further evidence of a functional connection between induction of synaptogenesis and antidepressant behavioural responses (Duman et al., 2012). It has yet to be shown at a preclinical level if NR2B antagonists can have antidepressant-like effects without ketamine's psychomimetic effects.

Recent studies by Monteggia et al. (2013) show that ketamine effects are dependent on brain-derived neurotrophic factor (BDNF) and subsequent activation of the high-affinity BDNF receptor TrkB. Their findings point towards eukaryotic elongation factor 2 kinase (eEF2K), which phosphorylates eEF2 and regulates the elongation step of protein translation, as a major molecular substrate mediating the rapid antidepressant effect of ketamine (Autry et al., 2011) Thus eEF2K is emerging as a potential antidepressant target (see Monteggia et al., 2013 for review).

Administration of ketamine to mice has been shown to inhibit brain glycogen synthase kinase-3 (GSK-3), a kinase that, interestingly, is also a target of mood-stabilising agents (Klein and Melton 1996). Beurel et al. (2011) demonstrated that ketamine increases the phosphorylation of GSK-3, and that mice with a knock out mutation that blocks the phosphorylation of GSK-3 do not respond to ketamine in a behavioral model of depression. A more recent study (Liu et al., 2013) showed that the synaptogenic and antidepressant-like effects of a single otherwise subthreshold dose of ketamine were potentiated when given together with a single dose of lithium chloride (a non-selective GSK-3 inhibitor) or a preferential GSK-3β inhibitor. They also demonstrated that these effects involved rapid activation of the mTOR signaling pathway, increased synaptic spine density/diameter and increased EPSCs in the medial prefrontal cortex (mPFC) layer 5 pyramidal neurons and antidepressant responses that persist for up to 1 week in the FST model of depression. What is exciting is that these results demonstrate that low, subthreshold doses of ketamine combined with lithium or a selective GSK-3 inhibitor are equivalent to higher dose of ketamine indicating the pivotal role of the GSK-3 pathway in modulating the synaptogenic and antidepressant responses to ketamine. The possible mitigation by GSK-3 inhibitors of the eventual fading of ketamine's antidepressant effect remains to be explored. What this research also questions is whether ketamine combined with lithium in a clinical setting in bipolar depression has a more significant effect on depressive symptoms than when combined with valproate or other mood stabilisor.

However the effects of GSK-3 in ketamine's mechanism of action is far from clear and Muller et al. (2013) recently investigated whether ketamine affected the inhibitory serine phosphorylation of the abundant GSK-3b isoform in hippocampal synaptosomes. They did not detect regulation of phosphorylated GSK-3b at 2 h after acute ketamine administration. Several important technical differences exist between (Muller et al. 2013) and the study by Beurel et al. to include the locations and timing of GSK-3 evaluation and the animal model. Ma et al. (2013) examined the effects of ketamine and GSK-3 inhibitor SB216763 in the unpredictable, chronic mild stress (CMS) mouse model of mice and found that a single administration of ketamine, but not GSK-3 inhibitor SB216763, produces a long-lasting antidepressant action. Thus the jury is still out regarding the role of GSK-3 inhibition in the antidepressant effect of ketamine and more work needs to be done in this area.

Using microdialysis, ketamine has been reported to increase the extracellular levels of glutamate in the prefrontal cortex of rodents (Lorrain et al., 2003; Moghaddam et al., 1997), leading to the hypothesis that hyperglutamatergic mechanisms are involved in the antidepressant effect of ketamine. This alongside the idea that structurally non-related antidepressants may have converging mechanisms of actions with relevance for the time of their onset of action prompted Muller et al. (2013) to investigate whether acute administration of ketamine targets the presynaptic molecular machinery. They demonstrated that ketamine rapidly induces changes in the hippocampal presynaptic machinery similar to those that are obtained only with chronic treatments with traditional antidepressants. They demonstrated a large reduction in the accumulation of SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complexes was observed in hippocampal synaptic membranes after 1, 2 and 4 h of ketamine administration. Neurotransmitter release requires the assembly of the core SNARE complex, consisting of the plasma membrane associated proteins syntaxin 1A and SNAP25 (synaptosomal-associated protein 25 kDa) and the synaptic vesicle-associated protein VAMP2 (vesicle-associated membrane protein 2) (Südhof, 2004). Post-mortem studies indicate abnormalities in the expression of individual SNARE proteins and regulatory proteins in the hippocampus and frontal cortex of subjects with depression and bipolar disorder (Fatemi et al., 2001; Scarr et al., 2006). In parallel, Muller et al. found a selective reduction in the expression of the synaptic vesicle protein synaptotagmin I and an increase in the levels of synapsin I in hippocampal synaptosomes suggesting a mechanism by which ketamine reduces SNARE complex formation, in part, by regulating the number of synaptic vesicles in the nerve terminals. Moreover, ketamine reduced Thr (286)-phosphorylated αCaMKII (calcium/calmodulin dependent protein kinase II) and its interaction with syntaxin 1A, which identifies CaMKII as a potential target for second messenger-mediated actions of ketamine. This suggests that reduction of neurotransmitter release in the hippocampus has possible relevance for the rapid antidepressant effect of ketamine and may represent important molecular targets for antidepressant treatment (Muller et al., 2013).

According to Murch (2013) an overlooked connection in the mechanism of action of ketamine in depression is the role of magnesium, which acts as physiological NMDA-receptor antagonist. Murch effectively argues that there is overlap between the actions of ketamine with that of high doses of magnesium in animal models, ultimately leading to synaptic sprouting. Magnesium and ketamine lead to synaptic strengthening, as measured by an increase in slow wave sleep in humans. Elaboration of his theory is outlined in a recent article (Murch, 2013).

Overall, what is emerging from the exciting research discussed above is that ketamine seems to compensate for reduced glutamatergic signaling by disinhibiting the release of glutamate, enhancing the stimulation of AMPA receptors and promoting downstream signaling via the Akt/Mtor pathway. Ketamine also blocks extrasynaptic NMDA glutamate receptors reducing the

phosphorylation of EEF2, reducing the inhibition of BDNF, and alleviating the suppression of dendritic spine growth. The translation of the clinical observations into explanatory neuroscience has had a transformative impact on antidepressant research that will hopefully help in clarifying the future research directions of ketamine and similar compounds.

4.8. Future direction of research on ketamine as an antidepressant

4.8.1. Route of administration of ketamine

There has been limited study of ketamine in depression given orally which would be a preferable route of administration for patients. It is known, however, that oral ketamine is used off-label in palliative care and treatment of therapy-resistant pain. A small case report study with 2 patients given a single, oral ketamine (0.5 mg/kg) in a hospice setting for depression demonstrated rapid and modestly sustained symptom relief of depressive and anxiety (Irwin and Iglewicz 2010). No adverse effects were noted. This was followed up by a larger open-labeled study more recently (Irwin et al., 2013) where 14 subjects with symptoms of depression or depression mixed with anxiety warranting psychopharmacological intervention received daily oral doses of ketamine hydrochloride (0.5 mg/kg) over a 28-day period. The investigators found that over the 28-day trial there was significant improvement in both depressive symptoms and symptoms of anxiety for the eight subjects that completed the trial. Side effects were rare; the most common being diarrhea, trouble sleeping, and trouble sitting still. The response rate for depression in this study is similar to those found with IV ketamine; however, the time to response is more protracted. The findings of the potential efficacy of oral ketamine for depression and the response of anxiety symptoms are novel. Further investigation with randomized, controlled clinical trials is necessary to firmly establish the efficacy and safety of oral ketamine for the treatment of depression and anxiety in patients receiving hospice care or other subject populations.

Another recent study of sublingual ketamine in 26 patients with refractory unipolar and bipolar depression (Lara et al., 2013) demonstrated clear and sustained antidepressant effects on mood, cognition and sleep in 20 (77%) with only mild and transient lightheadedness as a common side-effects (no euphoria, psychotic or dissociative symptoms). Indeed remission remained in some patients after stopping ketamine, demonstrating again the rapid onset of action, high-efficacy and good tolerability of ketamine that may allow extended treatment as needed. There are other studies on-going assessing the oral route of administration. The intranasal route of administration of ketamine is also been evaluated as it has previously been shown to benefit analgesic-refractory chronic pain patients at a dose comparable to that used in most IV ketamine studies (Carr et al., 2004).

4.8.2. Stereoisomers of ketamine

Ketamine is a chiral compound and its R- and S-stereoisomers have different binding affinities. S-ketamine has a greater affinity for the phencyclidine site of the NMDA receptor than R-ketamine (Kohrs and Durieux, 1998). Higher incidence of psychedelic side effects as described above has been reported with R-ketamine when given in similar analgesic doses as S-ketamine (Liu et al. 2006; Raeder and Stenseth, 2000). A case series of 4 patients Paslakis et al., (2010) were administered oral S-ketamine at a dose of 1.25 mg/kg for 14 days alongside traditional antidepressants in an effort to shorten time to onset of action and in 2 of these patients there was a rapid and sustained improvement in mood within the first week of treatment however the limited number of patients do not allow conclusions about efficacy. Oral S-ketamine was well tolerated. Paul et al., (2009) described the effect of ketamine and S-ketamine infusion therapy, respectively, in two patients with treatment-resistant major depression Both patients experienced psychotomimetic side effects during ketamine infusion which were absent during treatment with S-ketamine. They concluded that S-ketamine might exert similar antidepressant effects as ketamine in drug-resistant depression but may be better tolerated by the patients. Further studies of S-ketamine are required.

4.8.3. Caution using ketamine in cancer patients

Concerns have been raised with regard to up-regulation of mammalian target of rapamycin (mTOR) by ketamine (Yang et al., 2011) in patients with cancer. Studies have shown that up-regulated mTOR may cause the acceleration of tumor growth (Shor et al., 2009). Therefore, further, specific studies addressing patient prognosis are needed to investigate whether ketamine is suitable for the treatment of refractory depression in patients with cancer.

4.8.4. Biomarkers of ketamine's antidepressant effects

The general consensus in the literature appears to be that ketamine itself may never reach mainstream use as a treatment for TRD or depression in bipolar affective disorder. However many researchers believe that this body of research will be a means to learn more about the pathophysiology of depression that will hopefully offer novel therapeutic agents that act in a similar fashion to ketamine with longer duration of action and less side-effects or that act on the effectors of ketamine known to be involved in its mechanism of action. Translational research is currently exploring the identification of biomarkers that might be involved in prevention, diagnosis, treatment response, severity and prognosis of depression and Zarate et al., (2013b) reviewed the human biomarkers of antidepressant effects and summarise a range of potential biomarkers identified from genetic, functional neuroimaging, sleep and clinical studies implicated in ketamine's antidepressant action. While, overall, while these biomarker studies have limited practical implications at present they offer huge hope that eventually we will be able to successfully apply these techniques to clinical populations. Moving research in this direction offers opportunities that would ultimately facilitate the development of personalised treatment, increasing the probability of success.

5. Conclusion

Subanaesthetic doses of intravenous ketamine offers a unique opportunity to learn more about the psychopharmacological dysregulation of the glutamatergic system in depression and there have been significant developments in this field in the last decade. Perhaps the greatest opportunity that emerges from this exciting research, however, is to conduct further studies that elucidate the mechanism of action of ketamine's rapid response to determine if NMDA receptor antagonists such as ketamine, S-ketamine or synthetic analogues of ketamine could play a role in the future clinical treatment of depression. Also if by directly targeting AMPA receptors, eEF2K, mTOR activation or GSK-3 suppression, there may be a distinct possibility that one would bring about the possibility of fundamentally changing the treatment of depression by creating an opportunity for rapid relief. If these rapid-acting antidepressants could be safely integrated into treatment, one might shorten or mitigate hospitalisation, prevent lost work or school days, reduce suicide and reduce healthcare costs.

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Conflict of interest

None.

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