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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