

## Review Article

# It is Possible Find an Antidepressant with Faster Onset of Action? Ketamine: Promise or Reality?

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## Introduction

Major Depressive Disorder (MDD) is one of the most prevalent, serious and debilitating forms of mental illness with health, socioeconomic and familiar consequences [1]. In the last six decades, agents that modulate monoaminergic systems are widely used as antidepressants. However, these are limited in terms of overall efficacy and in the delay in the onset of antidepressant response [2-4]. Delay in antidepressant effect increase morbidity, suicidal ideation [5], psychosocial defeat, quality of life loss [6] and non adherence to treatment [7].

For these reasons, there is a growing interest in rapid-onset pharmacological alternatives [2]. To carry out this mini-review, literature was retrieved (July 2014) from PubMed.gov and bibliographic funds of the Alcala University Library, using the keywords ketamine, rapid, fast or early antidepressant effect.

## Current and past strategies to accelerate therapeutic response in depression

In despite that some meta-analysis [8-10], showed an improvement in the first week of classical and modern antidepressant treatment [6-11], response rates were generally small [6], not affect the core symptoms of depression and severe melancholic depression do not showed rapid response. An early antidepressant effect may be an artifact [12]. Thus, with very little controversy [6-11], a delay in antidepressant response for more than two weeks is generally accepted [2,3,7,13].

In order to try a rapid antidepressant response, agents not classified as antidepressants, as pindolol [14,15], mifepristone [16], metyrapone [17], methylphenidate [18,19], Thyrotropin-Releasing Hormone (TRH) [20,21], have been investigated with promising initial results but with limited clinical success. Recently, agomelatine, a melatonergic receptor agonist, with a non-monoaminergic profile [22-25], showed significant improvements in the core symptoms of

## Abstract

Monoaminergic antidepressants have a delay in the onset of response that needs alternatives. Sub anesthetic doses of ketamine, a NMDA receptor antagonist, show a rapid-acting antidepressant effect in Major Depressive Disorder (MDD) and in bipolar depression, and improve suicidal ideation. However, for ketamine routinely use as antidepressant, more clinical research on the relation risks and benefits is needed to decide if ketamine is a promise or a reality.

**Keywords:** Depression; Ketamine; Fast response; Antidepressant effect

depression within the first week of treatment [26]. However, clinical experience with this agent is limited.

On the other hand, some non-pharmacological interventions, as Electroconvulsive Therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), Deep Brain Stimulation (DBS) as well as “sleep deprivation” showed promising results on early response in depression, but these results needs to be confirmed with controlled clinical trials [6].

## Ketamine: A non-monoaminergic pathway for fast antidepressant response

Rapid antidepressant response will require alternative mechanisms of action to “the monoamine hypothesis” [2,4,6]. Glutamatergic system has been shown to be a key pathway in the pathophysiology of a variety of central nervous diseases including MDD [4,27]. In fact, different antidepressants, as Monoamine-Oxidase Inhibitors (MAOIs), Selective Serotonin Reuptake Inhibitors (SSRIs), tricyclic antidepressants, desensitize the locus of glycine in NMDA receptors, down-regulating glutamatergic neurotransmission. This effect was the most sensitive predictor of antidepressant activity [28]. Moreover, NMDA receptor antagonists, as amantadine, or D-cycloserine, has provided conceptual, but limited, clinical support for glutamatergic hypothesis of depression [29,30].

Ketamine, a dissociative anesthetic with hallucinogens properties, is a non-selective non-competitive high affinity of ionotropic glutamatergic NMDA receptors antagonist [31], that show a complex pharmacodynamic profile. Ketamine show preclinical antidepressant response in some predictive tasks [32,33]. Ketamine act primarily as NMDA antagonist and also interact with monoamine, nicotinic and muscarinic cholinergic receptors and opioids receptors [31,34]. Antagonism at NMDA receptor triggers a cascade of events responsible for the antidepressant response to ketamine. Thus, ketamine blocking primarily NMDA receptors increase glutamate synthesis and release that stimulate postsynaptic

AMPA receptor. This stimulation increase expression of Akt/mTOR pathway (mammalian target of rapamycin) [35,36] and Brain-Derived Neurotrophic Factor (BDNF) [37]. These proteins are associated with neuronal growth, differentiation, synaptic plasticity, and general functioning of the neuron. Furthermore, ketamine has been shown to inhibit brain GSK-3 [38,39], a kinase that is also a target of mood stabilizing agents. Moreover, in the rapid mood elevation can be implicated the anti-inflammatory activity [40] or inhibition of nitric oxide synthesis [31] induced by ketamine. Thus, blockade of NMDA receptors by ketamine trigger AMPA receptors stimulation that seems to be essential for its antidepressant effects. In fact, AMPA receptor antagonists block ketamine antidepressant effects in animal models [29,31,41].

### **Ketamine: A prototype for rapid-acting antidepressant in depressed patients**

The seminal study of Berman et al. was the first to show that a single low sub-anesthetic ketamine IV infusion (0.5 mg/kg/40 min.) produces a rapid antidepressant response within 4 hours that persist for at least 3 days [30]. Ketamine improve core symptoms of depression and these effects are disconnected from euphoria or “high” induced by this agent [30]. These findings were replicated in 18 patients with treatment-resistant depression, which reported a more rapid response within 2 hours that persist for 7 days [42]. Several open and controlled trials confirm the rapid antidepressant actions of single infusion of ketamine [5,6,31,43]. Murrrough et al. carry out the largest (n=73) randomized controlled trial of a single infusion of ketamine to date [44]. Ketamine, in comparison with midazolam, show a rapid and broad-spectrum antidepressant effect (response rates: 64% and 28% respectively). Ketamine, independently of antidepressant effect, reversed suicidal ideation. On the other hand, ketamine showed positive results in bipolar depression [45,46] and had significant efficacy in patients resistant to ECT [47].

Moreover, the efficacy of repeated administration of ketamine has been studied. Aan het Rot et al. showed significant improvement of symptoms following six infusions of ketamine over 11 days, although the 9 patients treated in this trial eventually relapsed 19 days after the final infusion [48]. These results were replicated by Murrrough et al. in 24 patients with resistant depression. The overall response rate at study end was 70.8%. Among responders, median time to relapse following the last ketamine infusion was 18 days [49]. Recently, antidepressant effects were obtained in an open trial using repeated ketamine as augmenting in twelve patients that maintain stable doses of antidepressant regimen [50].

On the other hand, ketamine improve mood level and was well tolerated by intramuscular [51], sublingual [52] or intranasal [53,54] administration. Oral administration of ketamine improves depressive symptoms at day 14 of treatment [55]. These data open the option for a more practical use of ketamine, but more controlled studies are needed.

Clinical evidence support that low doses of single or repetitive ketamine infusion have a rapid-acting antidepressant effect in MDD and in bipolar depression and improve suicidal ideation. These effects were independent from euphoria or “high” induced by this agent. Ketamine superiority over standard antidepressants is unequivocal. The response rates with ketamine at 24 and 72 hours is superior to

obtain with traditional monoaminergic antidepressants at 6-8 weeks of treatment [43,56]. However, many of the discussed studies in this review are methodological limited in regard to their sample size. A sample size of 102, 51 in each group, would be required within randomized controlled trials methodology to detect a moderate effect size of 0.5, with a power of 80% and 0.05 significance. But, none included a sample size in this size. The study by Murrrough et al. [44] was the largest to date but still included only 47 patients treated with ketamine. Moreover, despite the fact that some clinical trials were made with the technique of double-blind, caution must therefore be taken in interpreting these results, although several authors identified the difficulties in blinding ketamine administration [43].

### **Safety profile of ketamine and risk-benefits relation**

Routinely use of ketamine as antidepressant can be considered only when tolerability and safety in humans will be established. At this moment, ketamine has a long track record of safety when administered as a surgical anesthetic [57]. However, less is known about single and repetitive infusion at sub anesthetic doses in less intensively monitored depressed patients. On the other hand, generalize the results of clinical trials to practice daily is difficult due to the restrictive criteria of exclusion, as acute suicidal risk, history of psychosis, unstable general medical conditions, substance abuse, abnormal ECGs, applied in studies [58].

Ketamine is one of several “club drugs” that is abused. Misuse of therapeutically relevant agents is a risk but not a new phenomenon in psychiatry (i.e. anticholinergic drugs, stimulants, benzodiazepines, opioids) and should not preclude their study as putative treatments [59].

In antidepressant clinical trials, the dissociative profile of ketamine, as perceptual disturbances, confusion, euphoria, dizziness and increased libido, appears to be similar to that observed in healthy subjects and ceased within 2 hours following the infusion. Interesting, in clinical trials of MDD or bipolar patients, ketamine has not led the transition to mania [29,44,49,60].

Ketamine abuse is related with neural injuries, cognitive impairments, altered thought content as well as alteration of mnemonic functions [31,61,62]. Thus, testing the impact of chronic ketamine on these items in longer-term controlled studies is critical.

Distressing adverse events following ketamine infusion, as anxiety, might raise the risk of suicidal thinking [58] but clinical trials to date [43,44,49] support the premise that ketamine has rapid beneficial effects on suicidal cognition. However, this important issue will need careful prospective study in larger samples.

Although somatic adverse effects have generally been mild, 33% of patients have experienced brief changes in blood pressure and/or heart rate and two subjects required their infusions to be stopped for hemodynamic reasons [49]. Thus cardio respiratory monitoring is an essential component of risk management.

On the other hand, experimental and clinical reports of long-term ketamine induced ulcerative cystitis, increased frequencies of bladder carcinoma and kidney dysfunction need to be controlled with the repeated use of ketamine [31,59].

However, if these findings with ketamine could be directly

compared with monoaminergic antidepressants, ketamine represent some advantages [28]. Thus, considering these methodological limitations, ketamine has shown evidence that it is safe for the treatment of depression [29].

## Conclusion

Current ketamine research has been shown that significant clinical improvement in depression symptoms may occur within hours of drug administration. Moreover, ketamine show that a rapid antidepressant effect can be found beyond the monoaminergic mechanisms of current antidepressant medications that required weeks to months to produce benefits in responding patients. Ketamine is a promising tool to learn more about the pathophysiology of depression and develop more specific rapid-acting antidepressant treatments.

The literature demonstrates evidence supporting that a single intravenous sub anesthetic dose of ketamine exerts rapid antidepressant effects in patients with MDD, bipolar depression and reduces suicidal ideation.

Apparently, safety concerns associated with ketamine dictate a cautious approach to its application outside of research and more clinical research on the risks and benefits of ketamine use is indispensable. At this moment, in despite of tremendous excitement create by ketamine, their administration is not routinely recommended [58,63].

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