



# Statement on ketamine to treat depression

Position statement CERT02/17

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## KETAMINE TO TREAT DEPRESSION

Despite clinical trials showing rapid improvement in mood after ketamine infusion, there are still significant gaps in our knowledge about dosage levels, treatment protocols and the effectiveness and safety of long term use. Before ketamine can be recommended for use in clinical practice, extensive research is required to understand how to optimally use ketamine for treating depression. The Royal College of Psychiatrists has concerns for patient safety; and hence recommends mental health practitioners to proceed with caution when treating patients with ketamine.

### INTRODUCTION

Ketamine is currently approved as an anaesthetic drug by the Medicines and Healthcare Products Regulatory Agency (MHRA); but is not currently approved for use in treating depression. The antidepressant properties of ketamine were first described just over a decade ago (Berman et al., 2000). Since then, ketamine administration has been assessed in treatment of resistant depression, bipolar depression and in electroconvulsive therapy (ECT) induction. Supportive evidence showing rapid antidepressant effect of ketamine has encouraged some clinicians to use 'off label' ketamine in treating patients with depression.

### BACKGROUND

Ketamine is a well-known general anaesthetic and short acting analgesic, which was first developed in 1962 and was first approved for human use in 1970 (Jansen, 2000). It is also used in veterinary medicine. For humans, it is used as a painkiller to reduce complex regional pain syndrome (CRPS) and neuralgic pain. With anaesthetic benefits, ketamine is known to produce hallucinations; hence its increased popularity as a 'club' or 'party' drug in recent years.

In the past decade, ketamine has emerged as a potential antidepressant. Research investigating the antidepressant effects of ketamine has consistently reported rapid and robust improvement in suicidal depressive symptoms in patients having bipolar disorder (Price et al., 2009). Significant reduction is also seen in depressive symptoms in patients suffering from treatment resistant depression (Larkin and Beautrais 2011; Berman et al., 2000; Prince et al., 2009;

Lai et al., 2014; Murrrough et al., 2012). However, most researchers have measured the effects of ketamine for only 72 hours after infusion, therefore the long term effects of ketamine prescribed in patients with depression are unknown.

#### OPTIMAL DOSE AND MODE OF ADMINISTRATION

There is limited information on ketamine dose-response relationship and the optimal mode of administration (Katalinic et al., 2013). Most studies have tested ketamine's antidepressant effects using 0.5mg/kg infused intravenously over 40 – 60 minutes and reported high response and remission rates, though for most participants the improvement only lasted a few days (Lai et al., 2014; Katalinic et al., 2013). There is no clarity on optimal mode of drug administration, including the dose required for antidepressant effects. In the absence of a strong evidence base, there are risks associated with treating depression with ketamine at this stage.

#### ADVERSE EFFECTS

Use of low dose ketamine (up to 0.5mg/kg) can produce a variety of psychotomimetic, cognitive, or physical adverse effects.

The most common physical adverse effects of ketamine are dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration and restlessness. These effects have mostly been restricted to the time of administration, usually resolving within 60 minutes (Zarate et al., 2006).

In some studies participants reported transient elevation in blood pressure and heart rate during the period of ketamine infusion and the effect lasted up till 80 minutes after dosing (Zarate et al., 2006).

Additionally, ketamine is known for producing psychotomimetic effects, such as hallucinatory behaviour, suspiciousness/paranoia, disorganised thought, unusual thought, blunted affect and emotional withdrawal. In some studies, ketamine administration was shown to produce working memory deficits (Krystal et al., 1999; Larkin et al., 2011). There is no clear evidence showing long term psychotomimetic effect of ketamine when used in repeated doses in depression

treatment. Hepatotoxicity and bladder dysfunction have been reported after repeated use of ketamine (Katalinic et al., 2013).

## SUMMARY

Currently, there is limited evidence to recommend ketamine as a viable treatment option for treatment resistant depression (Rush, 2013, Schalzberg, 2014). Short term efficacy has been demonstrated after a single treatment, but benefits are not lasting for most patients, and mood can rapidly decline after initial improvement, potentially increasing suicide risk. Research is yet to identify strategies which will prolong antidepressant benefits. While repeated dosing has been trialled in a few open label studies, the longer term efficacy and safety of repeated dosing for the treatment of depression are unknown.

## RECOMMENDATION

- The use of ketamine for the treatment of depression is considered a novel treatment.
- Ketamine should be used under research trial conditions that includes oversight by an institutional research or clinical ethics committee and careful monitoring and reporting of outcomes.
- For persons with treatment resistant depression who are not participating in a research trial but are able and willing to consent to treatment with ketamine, the treating psychiatrist should consider such treatment as a novel or innovative treatment, which should include discussion with peers (preferably including a second opinion) and institutional review by the relevant NHS Trust Drugs and Therapeutic Committee or its equivalent.
- People considering ketamine as a treatment and their carers should be provided with clear information and an explanation that this is a novel treatment. This should include a detailed explanation of the current evidence and potential risks, and be documented in the clinical notes.
- Ketamine treatment for depression occurring outside formal research studies should be collated across centres using a regular mood monitoring framework.
- Practice outside of these recommendations should not occur.

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