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Responsible Committee/Department:	Committee for Therapeutic Interventions and Evidence-based Practice
Document Code:	CM PPP Use of ketamine for treatment-resistant depression

Purpose

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 Australian and New Zealand College of Psychiatrists (RANZCP) has concerns for patient safety and therefore recommends mental health practitioners to proceed with caution when treating patients with ketamine.

Introduction

Ketamine is currently approved as an anaesthetic drug by the Therapeutic Goods Administration (TGA) in Australia 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 effects of ketamine has encouraged some clinicians to promote 'off label' use of ketamine in treating patients with depression.

Background

Ketamine is a well-known general anaesthetic and short acting analgesic, which has been in use for almost 30 years in both human and 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, leading to 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 thoughts 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; Price et al., 2009; Lai et al., 2014; Murrough et al., 2013; Loo et al., 2016; George et al., 2017). Emerging research has also shown improvement in patients with bipolar depression (Zarate et al., 2012). However, most researchers have measured the short term effects of a single dose of ketamine only, therefore the long term effects of ketamine prescribed in patients with depression are currently unknown (Short et al., 2017).

Optimal dose and mode of administration

There is limited information on the ketamine dose-response relationship and the optimal mode of administration (Katalinic et al., 2013). Most studies have tested ketamine's antidepressant effects using 0.5 mg/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). The sublingual route may be promising but there is as yet very little data to support its use (Lara et al., 2013). The intramuscular and subcutaneous routes are simpler to use and may be as effective as intravenous administration (Loo et al., 2016; George et al., 2017). Therefore, there is no clarity on optimal mode of drug administration, including the dose required for antidepressant effects. It is also possible that the optimal dose required (mg/kg) differs between individuals and a dose titration method may be beneficial (Lai et al., 2014; Loo et al., 2016; George et al., 2017). In the absence of a strong evidence base, there are risks associated with treating depression with ketamine at this stage (Singh et al., 2017).

ECT and ketamine

There is limited evidence to support the use of ketamine as part of standard ECT treatment. While studies involving small numbers of people had suggested that ketamine might prevent the memory problems seen after ECT and improve patients' recovery from depression, a larger research trial found that there was no difference between those who used ketamine or placebo during the trial and that ketamine did not make ECT work any faster or better (University of Manchester, 2016). A further study has shown that using ketamine as an anaesthetic does not enhance the efficacy of ECT (Fernie et al., 2017). Additionally, a recent systematic review and meta-analysis found that ECT therapy with ketamine is not associated with greater improvements in depressive symptoms or higher rates of clinical response, nor did it result in pro-cognitive effects (McGirr et al., 2017). Further information will be available in the RANZCP Professional Practice Guideline for the administration of Electroconvulsive Therapy (ECT), expected to be published in 2018.

Adverse effects

Use of low dose ketamine (up to 0.5 mg/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 and Beautrais, 2011). There is no clear evidence showing long term psychotomimetic effects 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; Schatzberg, 2014; Malhi et al., 2016; Sanacora et al., 2017). 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 (Ryan and Loo, 2017). 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 is unknown (Short et al., 2017).

Recommendations

- The use of ketamine for the treatment of depression is considered a novel or 'off-label' treatment. Hence psychiatrists should provide patients and their carers with clear information and an explanation that ketamine is a novel treatment for depression. This should include a detailed explanation of the current evidence and potential risks, and be documented in the clinical notes. See RANZCP ['Professional Practice Guideline: 'Off-label' prescribing in psychiatry'](#) for further information.
- Ketamine should be used under research trial conditions that includes oversight by an institutional research ethics committee and careful monitoring and reporting of effectiveness and safety outcomes.
- Psychiatrists who are considering prescribing ketamine for a patient with treatment-resistant depression, outside a research trial:
 - should ensure the patient is willing and able to consent.

AND

- should discuss this treatment with peer(s), preferably including a second opinion, and/or
- seek institutional review by a Medicines Advisory Committee or equivalent, and/or
- seek consideration by an institutional research ethics committee.

Disclaimer

This information is intended to provide general guidance to practitioners, and should not be relied on as a substitute for proper assessment with respect to the merits of each case and the needs of the patient. The RANZCP endeavours to ensure that information is accurate and current at the time of preparation, but takes no responsibility for matters arising from changed circumstances, information or material that may have become subsequently available.

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