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Some clinical trials have shown rapid improvement in mood after ketamine infusion, however, there are still significant gaps in 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 medical practitioners 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 and Medsafe in New Zealand. Ketamine in the form of intranasal esketamine (Spravato) has been approved by the TGA and Medsafe for use in treatment-resistant depression. Ketamine is a controlled medication and is bound by Schedule 8 regulations in Australia and Class C controls in New Zealand. Prescription of ketamine is governed by regulations which are specific to each Australian state and territory as well as New Zealand.

The antidepressant properties of ketamine were first described just over a decade ago.[1] Since then, ketamine administration has been assessed in treatment of resistant depression, bipolar depression and in electroconvulsive therapy induction. Supportive evidence showing rapid antidepressant effects of ketamine has encouraged some clinicians to promote 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. Ketamine is increasingly popular as a recreational drug due to its hallucinogenic effects.

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 with bipolar disorder.[2] Significant reduction is also seen in depressive symptoms in patients with treatment-resistant depression.[1-7] Emerging research has also shown improvement in patients with bipolar depression.[8] 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.[9]

## Optimal dose and mode of administration

There is limited information on the ketamine dose-response relationship and the optimal mode of administration [10]. Most studies have tested ketamine's antidepressant effects using 0.5 mg/kg infused intravenously over 40–60 minutes. These studies reported high response and remission rates, though for most participants the improvement only lasted a few days. [4, 10] The sublingual route may be promising but there is as yet very little data to support its use.[11] The intramuscular

and subcutaneous routes are simpler to use and may be as effective as intravenous administration.[6, 7, 12] Further small scale studies have demonstrated efficacy of the delivery of ketamine or esketamine intranasally [12-14] with a separate study demonstrating poor tolerability of side effects.[13] 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.[4, 6, 7] In the absence of a strong evidence base, there are risks associated with treating depression with ketamine at this stage.[15]

## **Electroconvulsive therapy (ECT) and ketamine**

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There is limited evidence to support the use of ketamine as part of standard ECT treatment. Studies involving small numbers of people have suggested that ketamine might prevent the memory problems that may be seen after ECT and improve patients' recovery from depression. However, 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. [16]. A further study has shown that using ketamine as an anaesthetic does not enhance the efficacy of ECT.[17] Additionally, a recent systematic review and meta-analysis found that ECT used 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.[18] Further information is available in the RANZCP Professional Practice Guideline for the administration of electroconvulsive therapy.[19]

## **Adverse effects**

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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.[20]

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.[20]

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.[3, 21] 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.[10]

## **Summary**

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Currently, there is limited evidence to recommend ketamine as a viable treatment option for treatment-resistant depression.[22-25] 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 [26]. 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.[9]

## **Recommendations**

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- The use of intranasal esketamine for treatment-resistant depression should be in line with the product information approved by the TGA (in Australia) or Medsafe (in New Zealand).
- The use of ketamine for the treatment of depression is considered a novel 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. Psychiatrists who are prescribing ketamine 'off-label' should do so in line with the RANZCP ['Professional Practice Guideline: 'Off-label' prescribing in psychiatry'](#)

- 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 Medicines Assessment Advisory Committee and/or
- seek consideration by an institutional research ethics committee.

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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.

## Revision Record Footer

<b>Contact: Executive Manager, Practice, Policy and Partnerships</b>			
<b>Date</b>	<b>Version</b>	<b>Approver</b>	<b>Description</b>
11/2015	1.1	B2015/7 R16	New document
12/2017	2.0	Board out-of-session	Reviewed and updated
11/2019	3.0	B2019/8 R19	Reviewed and updated
<b>06/2021</b>	3.1	PPPC Chair	Interim update to reflect changes in regulation only
<b>2022</b>			<b>NEXT REVIEW</b>

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