Purpose

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has developed this memorandum to provide information for psychiatrists about the potential utility of ketamine in psychiatric practice.

Key messages

- Ketamine is a complex drug that has strong effects on the mental and physical states of patients. Psychiatrists should ensure they are fully aware of these effects and required precautions when treating patients with ketamine.

- Ketamine is emerging as a new treatment in psychiatry, but further active research is required to understand how to optimally use ketamine for treating mental illness.

- At present there is sufficient evidence only for use in treatment-resistant depression, and not any other psychiatric conditions. Ketamine is not recommended as a first line treatment, and should only be initiated after due consideration of published evidence for its use.

- Ketamine treatment should only be initiated after assessment by a psychiatrist familiar with the evidence and effects of ketamine. Only a psychiatrist or a medical practitioner (under the supervision of a psychiatrist) with appropriate expertise in ketamine treatment should prescribe ketamine and take responsibility for its use in treating depression.

- Ongoing research into ketamine under research trial conditions is encouraged, including 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 outside of a research trial should ensure they are fully familiar with the complexities of ketamine dosing and management and have established appropriate clinical infrastructure for such treatment. This includes an appropriate structured framework for safety monitoring and outcome measures for the recording of side effects and benefits when used in clinical practice.

- Services providing ketamine therapy should have clear practice policies and guidelines for its use.
Definitions and scope

Ketamine has been used for almost 50 years predominantly as a general anaesthetic, as a short-acting analgesic, as well as for treatment of conditions such as complex regional pain syndrome. Over two decades ago, antidepressant effects of ketamine were demonstrated reigniting interest in this treatment. [1] Its dissociative and hallucinogenic effects have also meant it is used illicitly as a recreational drug.

There are two main ketamine isomers, (R)-ketamine (arketamine) and (S)-ketamine (esketamine), each displaying differing pharmacological properties. Ketamine is considered a ‘novel’ antidepressant due to its operation on the glutamatergic system, compared to standard antidepressants, which mainly act on the serotonin, noradrenaline and/or dopamine neurotransmitter systems. However, ketamine has multi-receptor functions, at various doses, that includes monoamine, cholinergic, opiate and cytokine systems. Its precise mechanism of antidepressant action is not fully understood.

Ketamine can be administered via the intravenous (IV) route (typically an infusion), intramuscular injection or subcutaneously (infusion or injection), per oral, intranasal, sublingual or per rectal.

This document covers all types of ketamine, all modes of administration, and all settings. It is intended to provide an overview of considerations relevant to the use of ketamine as a potential treatment for mental illnesses. It is not a directive about clinical practice, or instructions as to what must be done for a given patient.

This document does not relate to the recreational use of ketamine, or for medical use in conditions other than mental illness.

Background

Recent attention on the potential benefits of ketamine, as well as approvals of ketamine in the form of intranasal esketamine (Spravato) by the Therapeutic Goods Administration (TGA) in Australia and Medsafe in New Zealand for use in treatment-resistant depression, has increased interest from the medical community seeking to prescribe ketamine and people with mental disorders seeking to use it as a treatment. The RANZCP recognises that there is a growing body of evidence for the efficacy of ketamine, particularly in the treatment of depression. Accordingly the use of ketamine, particularly for the treatment of depression, is transitioning to clinical practice in Australia, New Zealand and overseas.

Increasing access to novel treatments is welcome, however legitimate concerns have been raised with respect to long-term efficacy, safety, tolerability, patient selection, risk for precipitating substance use disorder, as well as appropriate personnel and settings for competent and safe administration. [2] There is currently limited guidance translating research findings into clinical practice, with respect to treatment approaches, dosing protocols, the effectiveness and safety of long-term use, and safety monitoring. This requires due consideration by psychiatrists prior to expanding their scope of practice to include ketamine therapy.

Regulation

Ketamine is currently approved as an anaesthetic drug by the TGA in Australia and Medsafe in New Zealand. Only ketamine in the form of intranasal esketamine (Spravato) has been approved by the TGA and Medsafe for use in treatment-resistant depression, and its prescription parameters are clearly set out in the licence. No other forms of ketamine are licensed for treating mental disorders, and therefore its use is considered ‘off-label’ and these require parameters informed by models of care and by RANZCP guidelines for off-label prescribing in psychiatry.

Ketamine in all forms is a controlled medication and is bound by Schedule 8 regulations in Australia (as it is considered to have a high potential for abuse and addiction) and Class C controls in New Zealand (as it is considered to have a moderate risk of harm) under the Misuse of Drugs Act (NZ), 1975. Prescription of ketamine is governed by regulations which are specific to each
Australian state and territory as well as New Zealand. [3] The regulations relate to the maximum time period of prescribing ketamine without seeking an authority. There are also rules relating to prescribing to substance-dependent patients. Practitioners also need to comply with appropriate ketamine storage, disposal and record-keeping policies. [3]

**Evidence and current research**

- There is currently only evidence of clinical efficacy and effectiveness for the use of ketamine in treatment-resistant depression. Effect sizes compared to placebo in treatment-resistant depression are in the order of 50-70% response and 30% remission rates. A full review of evidence for use of ketamine in depression has been published in several recent systematic reviews and meta-analyses and summarised in recent models of care. [2, 4-7]

- The short-term efficacy of intravenous and intranasal ketamine for adults with treatment resistant depression is established. [6, 8] Ketamine has advantages to standard antidepressants in terms of speed of onset, showing observable reduction in symptoms of those with whom it is effective within 6–12 hours, though this effect generally lasts less than a week following a single dose. [9, 10] The anti-suicidal effects of ketamine make it a promising novel treatment. [4]

- A meta-analysis of RCTs of single and repeated dosing with ketamine and esketamine found both showed significant antidepressant efficacy, with the superiority over placebo/comparator greater for ketamine than esketamine. [6] Evidence is still limited for efficacy of repeated infusions and for relapse prevention although studies showing longer term benefit with repeated dosing are emerging. A range of studies demonstrating effectiveness of repeated esketamine and ketamine have been published. [4, 11-13] Practitioners should familiarise themselves with the evidence for repeated dosing versus single dose, selection of dosage levels, route of administration, and the safety of single and multiple doses, including acute and longer-term effects, prior to using repeated doses in clinical practice.

- Serious adverse effects have been reported after repeated ketamine use in the recreational context, including cystitis/severe bladder dysfunction. Serious adverse effects have not been reported where there has been careful monitoring of treatments within clinical trials, with frequency and level of dosing adjusted where necessary, though few trials have examined for cumulative and longer-term effects. [14-16] Thus, repeated dosing with ketamine or esketamine should only be undertaken with an appropriate structured framework for safety monitoring. [5, 17] Further data are also needed on safety, especially examining cumulative and longer-term effects with repeated treatments. [4, 7, 15]

- Consensus has not been reached on the appropriate use of ketamine and esketamine in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for their competent and safe implementation though models of care have been proposed.[2, 5]

- Placebo-controlled RCTs have demonstrated antidepressant efficacy of ketamine administered intravenously [6] by subcutaneous, intramuscular [18, 19] and oral [20, 21] routes; and esketamine given intranasally. [14, 22] Further research is needed to determine the relative benefits and risks of the different modes of administering ketamine (e.g. intravenous, intramuscular, subcutaneous, oral, intranasal routes), different formulations (racemic ketamine vs (S)- and (R)- isomers) and how dosing should be optimised.

- Use of ketamine to treat depression has mainly been examined in adults, with more limited data in older people. [19] Current trials are examining use to treat depression in those under 18 years of age. There are also only limited studies for use in refractory bipolar depression. [23]

- Ketamine studies have examined changes in anxiety symptoms in patients with depression though few have examined anxiety disorders specifically. [24] Some small studies have demonstrated a reduction of anxiety symptoms in those with social anxiety disorder and in
patients with posttraumatic stress disorder and obsessive-compulsive disorder. [25-28] Larger scale multi-site trials are required in anxiety disorder populations before efficacy can be determined, including whether there is a differential response of ketamine in specific anxiety disorders.

- Small studies on the use of ketamine in people with substance use disorders have identified potential use in cocaine dependence and hazardous levels of alcohol consumption. [29, 30] Older studies assessing ketamine used in conjunction with psychotherapy have shown potential efficacy in treating alcohol and heroin dependence. [31, 32] Further research is needed.

Risks and side effects

- Ketamine has potential to cause acute physical, psychiatric, psychotomimetic and cognitive side effects following a single dose and cumulative side effects resulting from repeated dosing. The majority of studies of ketamine in depression have examined side effects only acutely and after a single dose, with limited studies examining safety in repeated doses. [15]

- Acute physical adverse effects of ketamine include hypertension, sedation, nausea or vomiting, headache, poor coordination, poor concentration, dizziness, blurred vision, and restlessness. These effects have mostly been restricted to the hour after treatment dosing, usually resolving with a few hours after treatment is given.

- The potential of ketamine to induce acute hypertension, lower urinary tract dysfunction and interstitial cystitis, and alter hepatic function, and noting that ketamine is metabolised by the liver, warrant screening for relevant pre-existing conditions. Screening for cognitive impairment is recommended, as frequent and long-term ketamine use has been associated with cognitive dysfunction. [5]

- Initiation with a newly initiated oral antidepressant may cause serotonin syndrome/withdrawal syndromes, that may lead to worsening agitation, mental state, suicidality. A systematic approach should be implemented to monitor symptoms.

- Ketamine therapy is expensive due to the required in-clinic monitoring after each treatment and it is currently not subsidised by the Australian and New Zealand governments. The cost is prohibitive for many individuals so broader societal strategies are required to discourage illicit use and self-medication. Psychiatrists should also be aware of the risks for addiction, misuse and diversion.

Considerations for use of ketamine therapy in practice

- Further ketamine research is encouraged, 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 outside of a research trial should
  
  i. Ensure they are fully familiar with the complexities of ketamine dosing, management and safety monitoring, and have established appropriate clinical infrastructure for such treatment.

  ii. Ensure they are familiar with and practise within, all relevant state legislation.

  iii. Ensure the patient is willing and able to consent.
iv. Seek institutional review e.g. by a Medicines Advisory Committee or Clinical Governance Committee and/or discuss the treatment with peers, preferably seeking an opinion from a psychiatrist with expertise in the use of ketamine.

v. Be informed by RANZCP guidelines for off-label prescribing in psychiatry.

- Ketamine treatment should only be initiated after assessment by a psychiatrist with relevant expertise in the use of ketamine.

- Only a psychiatrist or a medical practitioner (under the supervision of a psychiatrist) familiar with the evidence on the antidepressant effects of ketamine, including specifics of dosage and route of administration, should prescribe ketamine. The practitioner should be responsible for the ketamine treatment process including post-delivery care, and for review in the case of any medical complication.

- Informed consent must be obtained before commencing ketamine and should be in line with Principle 5 of the RANZCP Code of Ethics. Details relating to the current evidence-base, alternative treatments, description of the treatment process, acute and longer-term efficacy (including response and remission data), safety considerations, side effects, and cost should be provided. Patients should be informed of what to expect before, during and after treatment. During the consent process, psychiatrists should ensure patients understand that therapeutic outcomes of ketamine cannot be guaranteed. It would usually be appropriate for whānau, families and carers to be involved in this process depending on the patient’s preference.

- Services providing ketamine therapy should have clear practice policies and guidelines, preferably overseen by an appropriate clinical governance committee. This includes outlining appropriate use of a multidisciplinary team, processes for monitoring and management of acute and severe hypertension blood pressure, and escalation mechanisms in the treatment of adverse events.

- Psychiatrists should be confident that they have appropriate infrastructure to administer ketamine therapy and to monitor a patient post drug administration, which is particularly relevant if outside of a hospital setting.

- Psychiatrists should familiarise themselves with the evidence for the use of ketamine prior to use, including the associated risks and potential side-effects. Seeking advice from up-to-date published models of care is advisable. [2, 4, 5] The importance of keeping records for side effects and safety monitoring, as well as outcome measures, should be recognised.

- 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).

**Dose and mode of administration**

- Patient presentations may differ and treatment with ketamine needs to be tailored to the individual in line with published evidence and models of care. [2, 4, 5]

- There is no clarity on optimal mode of drug administration. Various routes of administration lead to differences in bioavailability and pharmacokinetic profile, though the relationship between drug pharmacokinetics and antidepressant response is not well understood. [5]

- Several studies have examined the dose required for antidepressant effects. It is possible that the optimal dose required (mg/kg) differs between individuals and a dose titration method may be beneficial. [5]

- Duration of treatment, and the need for maintenance therapy, is affected by factors such as efficacy, safety, tolerability and cost to the patient. [5]
**Electroconvulsive therapy (ECT) and ketamine**

There is limited evidence to support the use of ketamine as part of standard ECT treatment. Early studies involving small numbers of people suggested that ketamine might prevent the memory problems that may be seen after ECT and improve patients’ recovery from depression. However, more substantive studies did not find that using ketamine as an anaesthetic enhanced the efficacy of ECT and such use was not associated with greater improvements in depressive symptoms or higher rates of clinical response, nor did it result in pro-cognitive effects. [33-35] Further information is available in the RANZCP Professional Practice Guideline for the administration of electroconvulsive therapy. [36]

**Summary**

There is evidence to support a role for ketamine therapy in treatment resistant depression, although there remains some uncertainty about the most appropriate position of these agents in treatment algorithms, their comparative effectiveness, safety and tolerability. Further research is needed to determine the relative benefits and risks of the different modes of administering ketamine, different formulations and how dosing should be optimised. Cumulative and longer-term effects with repeated treatments needs further examination [2, 4, 7]. There is a need for continued education, shared decision-making with patients, responsible practice, and gathering of systematic, long-term data to inform the use of ketamine in clinical practice.

Ketamine use under research trial conditions is encouraged. Psychiatrists should proceed with caution when treating patients with ketamine, and due consideration is required prior to prescribing in clinical practice.

As the evidence for the use of ketamine in the treatment of mental illness continues to evolve, this memorandum will be reviewed and revised.

**References**


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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