Viewpoint

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Royal Australian and New Zealand College of Psychiatrists professional practice guidelines for the use of ketamine in psychiatric practice

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Abstract

Professional practice guidelines for the use of ketamine in psychiatric practice have been developed by the Royal Australian and New Zealand College of Psychiatrists to provide guidance on the use of ketamine in clinical practice in Australia and Aotearoa New Zealand, based on scientific evidence and supplemented by expert clinical consensus. Articles and information were sourced from existing guidelines and published literature. The findings were then formulated into consensus-based recommendations and guidance by the authors. The guidelines were subjected to rigorous successive consultation within the Royal Australian and New Zealand College of Psychiatrists, involving the Section of Electroconvulsive Therapy and Neurostimulation Committee, its broader membership and expert committees. The guidelines are intended for psychiatrists and clinicians engaged in the use of ketamine therapy to facilitate best practice to optimise outcomes for patients. They strive to find the appropriate balance between promoting best evidence-based practice and acknowledging that evidence for ketamine use is continually evolving.

Keywords

Guidelines, ketamine, psychiatric disorders, professional practice, depression

Introduction

Ketamine[1] has been used for almost 50 years predominantly as a general anaesthetic, as a short-acting analgesic, and for treatment of conditions such as complex regional pain syndrome. Over two decades ago, antidepressant effects of ketamine were demonstrated in placebo-controlled trials, leading to rapidly increasing interest in this treatment (Berman et al., 2000). Its dissociative and psychotomimetic effects have also meant it is used illicitly as a recreational drug.

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

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and/or dopamine neurotransmitter systems. However, ketamine has multi-receptor functions, at various doses, that includes monoamine, cholinergic, opioid and cytokine systems. Its precise mechanism of antidepressant action is not fully understood (Zanos and Gould, 2018).

Recent attention on the potential benefits of ketamine, as well as approvals of ketamine in the form of intranasal ketamine (Spravato©) by the Therapeutic Goods Administration (TGA) in Australia and Medsafe in New Zealand for use in treatment-resistant depression (TRD), has increased interest from the medical community seeking to prescribe ketamine and individuals with mental health disorders seeking to use it as a treatment. The Royal Australian and New Zealand College of Psychiatrists (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 into 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[2] selection, risk for precipitating substance use disorder, as well as appropriate personnel and settings for competent and safe administration (Bayes et al., 2019, 2021; McIntyre et al., 2021). 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. Psychiatrists wishing to expand their scope of practice to include ketamine therapy should make themselves familiar with the available evidence base and best practices.

Methodology

To develop the guidelines, information was sourced from existing international guidelines and published literature focusing on peer-reviewed empirical studies, particularly meta-analyses and systematic reviews, peer-reviewed case studies/reports and standards of care documents. Primary sources include recent systematic reviews, meta-analyses and recently published models of care (Bahji et al., 2021a; Bayes et al., 2021; Beaglehole et al., 2023; Dean et al., 2021; McIntyre et al., 2020, 2021; Nikolin et al., 2023; Swainson et al., 2021). While care has been taken to ensure that most relevant literature is included, these guidelines are not a full academic review of ketamine therapy in psychiatric practice as formal literature search methodology was not used. Literature was sourced regarding specific issues as discussed by the RANZCP Bi-national Section of Electroconvulsive Therapy (ECT) and Neurostimulation (SEN) and Committee for Evidence-Based Practice and findings formulated into consensus-based recommendations and guidance. Given the procedural nature of the ketamine therapy and that members with experience in its use sit on the SEN Committee, these members (who form most of the authors of this article) were appointed to lead the review. The guidelines were subjected to rigorous successive consultation and review within the RANZCP involving all College committees, including community members with lived experience. Clinicians from Australia and New Zealand with expertise in using ketamine therapy were identified and invited to comment. The draft guidelines were available on the RANZCP Consultation Hub, open to all members, to comment on from 26 March to 15 April 2024.

Throughout this process, the draft guidelines were regularly reviewed by the SEN Executive Committee at its bi-monthly meeting, and the Committee for Evidence-Based Practice. The guidelines were approved in line with RANZCP processes by the Practice, Policy and Partnerships Committee, the Corporate Governance and Risk Committee, and finally by the RANZCP Board in October 2024. To allow for greater dissemination and to allow for a process of peer review, the Board agreed that the guidelines be submitted to a journal.

Definitions and scope

There are two main ketamine isomers, (R)-ketamine (arketamine) and (S)-ketamine (esketamine), each displaying differing pharmacological properties. Racemic ketamine (typically used in anaesthesia in Australia) is a preparation containing a mixture of each isomer.

The pharmacological and clinical research literature describe several routes of administration, including via the intravenous (IV) route (typically an infusion), intramuscular injection or subcutaneously (infusion or injection), per oral, intranasal, sublingual or per rectal. A summary of the two key formulations of ketamine in use are provided in Table 1.

This guidance when referring to 'ketamine' covers all formulations of ketamine all modes of administration, and all settings. Safety concerns and associated risks are attributable to both regulatory approved Spravato and other formulations of ketamine. Psychiatrists should be aware of varying risks of different formulations. Where there are different considerations for racemic ketamine and Spravato, these are identified within this guidance.

Controlled medicines regulation in Australia and New Zealand

Ketamine in all formulations 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 is a Class C(4) controlled drug 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

Table 1. Key formulations of ketamine.

Esketamine
A patented formulation of intranasal esketamine (Spravato) is the only formulation of ketamine that has been specifically approved by the TGA in Australia for use in treatment-resistant depression (TRD), and by Medsafe in New Zealand for treatment resistant depression and depressive symptoms in patients with Major Depressive Disorder who have acute suicidal ideation or behaviour. Its prescription parameters are clearly set out in the licence and product information, which requires administration in conjunction with a new antidepressant medication.
Intranasal esketamine spray (Spravato) co-initiated with an antidepressant has demonstrated rapid clinically meaningful efficacy in patients with TRD. There are also data demonstrating long-term (i.e., greater than 3-year) safety and tolerability for this formulation (Zaki et al., 2023).
Racemic Ketamine
Racemic ketamine formulated for parenteral injection is currently approved as an anaesthetic drug by the TGA in Australia and Medsafe in New Zealand but is not currently licenced in any formulation for treating mental disorders, and therefore other use of this formulation of ketamine is considered 'off-label'. Off label prescription should be guided by the RANZCP guidelines for off-label prescribing in psychiatry (Royal Australian and New Zealand College of Psychiatrists, 2023).
Intravenous (IV) (typically an infusion) racemic ketamine has been found to rapidly improve depressive symptoms and suicidal ideation in adults with TRD, and its efficacy has been confirmed in multiple studies (Nikolin et al., 2023). In the largest phase 3 study of generic racemic ketamine for TRD, the drug was administered by subcutaneous injection, results demonstrating safety and high efficacy (Loo et al., 2023).
Note: esketamine is also available in other formulations (including IV and intranasal formulations) but only Spravato is approved by the TGA and Medsafe and use of these is off-label.

each Australian state and territory as well as New Zealand (Bayes et al., 2019).

There are also rules relating to prescribing to substance-dependent patients. Considerations in prescribing to those with prior drug dependence and abuse were recently reviewed (Carroll et al., 2024). Practitioners also need to comply with appropriate ketamine storage, disposal and record-keeping policies (Bayes et al., 2019).

What is the evidence for use of ketamine in the treatment of mental illness?

Depression

Currently, TRD is the only indication for which there is sufficient evidence of efficacy and safety, from phase 3 clinical trials, to support clinical use of ketamine. Effect sizes are large in placebo-controlled trials in TRD with outcomes in the order of 50-70% response and 30% remission rates (Bahji et al., 2021a; Nikolin et al., 2023). A full review of evidence for use of ketamine in depression has been published in several systematic reviews and meta-analyses and summarised in models of care that propose the appropriate setting, infrastructure, and personnel required for their competent and safe implementation (Bahji et al., 2021a; Bayes et al., 2021; Beaglehole et al., 2023; Dean et al., 2021; McIntyre et al., 2020, 2021; Nikolin et al., 2023; Swainson et al., 2021).

The short-term efficacy of intranasal esketamine (Spravato) and racemic ketamine given by IV infusion or subcutaneous injection, has been demonstrated for adults with TRD (Bahji et al., 2021a; Loo et al., 2023; McIntyre et al., 2020; Nikolin et al., 2023; Popova et al., 2019). Maintenance of benefits and safe use with repeated treatments over a 3-year period has been demonstrated for intranasal esketamine (Spravato) (Zaki et al., 2023). For racemic ketamine, ongoing benefit during a 4 week (Loo et al., 2023) and 12 week (Glue et al., 2024) treatment course was demonstrated. While meta-analyses show some ongoing benefit after cessation of treatment (Nikolin et al., 2023) most remitters relapsed over the next 4 weeks after treatment cessation (Loo et al., 2023). Meta-analyses of randomized controlled trials (RCTs) of single and repeated dosing with racemic ketamine and esketamine have found that both showed significant antidepressant efficacy, though with the superiority over placebo/comparator greater for racemic ketamine than esketamine (Bahji et al., 2021a; Nikolin et al., 2023). However, no conclusions can be drawn about relative efficacy in the absence of a direct comparison of the two formulations.

As ketamine is a new treatment, there is as yet no consensus on the optimal approach to use of racemic ketamine and intranasal esketamine (Spravato) in treatment algorithms for depression and their comparative effectiveness.

Ketamine has advantages to standard antidepressants in terms of speed of onset, with potential reduction of symptoms within 6–12 hours after a single dose, though this effect generally lasts less than a week (Bayes et al., 2021; Malhi et al., 2021; Nikolin et al., 2023; Xu et al., 2016). The additional anti-suicidal effects of ketamine also make it a promising novel treatment (Wilkinson et al., 2018; Witt et al., 2020).

Study populations. Use of ketamine to treat depression has mainly been examined in adults, with more limited data in older people (George et al., 2017; Ochs-Ross et al., 2020).

Current trials are examining use to treat depression in those under 18 years of age. A study of single dose racemic ketamine or midazolam given to adolescents (aged 13–17) with TRD, found ketamine treatment was effective and safe (Dwyer et al., 2021) although there is need to better determine the efficacy and safety of ketamine in treatment of depression in children (Meshkat et al., 2022). Studies have focused on the safety and tolerability of ketamine use in general in children (Dolansky et al., 2008) including emergency departments (Guthrie et al., 2021).

Comparison with ECT. Evidence on the relative efficacy of ketamine and ECT in the treatment of TRD suggests that ketamine may have efficacy comparable to that of ECT. Meta-analyses based on mostly small studies, including non-randomised comparisons, suggested ECT may be more efficacious (Menon et al., 2023; Rhee et al., 2022). Of the two large multisite RCTs completed, one found the treatments did not differ except in subgroup analyses, with ECT superior in older patients (Ekstrand et al., 2022); the other found ketamine non-inferior to ECT (primary outcome), with secondary outcomes showing higher response rates for ketamine (Anand et al., 2023). Noting that there is variation in the study populations analysed, overall, the data suggest that ketamine has high efficacy in suitable clinical settings, comparable to that of ECT.

Bipolar depression

There are only limited studies for use in refractory bipolar depression (Bahji et al., 2021b; Cavenaghi et al., 2021; Jawad et al., 2023; Zarate et al., 2012). There is preliminary evidence that IV racemic ketamine has some benefit in patients with treatment resistant bipolar depression as an adjunctive therapy given with concurrent mood stabilisers. This evidence is much more limited than that for unipolar depression but provides some support for the use of ketamine in TRD occurring within bipolar disorder. Some of these studies also highlighted safety and risk issues in this population (Alberich et al., 2017; Bahji et al., 2021b; Fancy et al., 2023; Jawad et al., 2023; McCloud et al., 2015).

Anxiety disorders

Ketamine studies have examined changes in anxiety symptoms in patients with depression (Salloum et al., 2019) although few have examined effects in anxiety disorders specifically. Some small studies have demonstrated a reduction of anxiety symptoms in those with social anxiety or generalised anxiety disorder and obsessive-compulsive disorder (OCD) (Feder et al., 2014; Glue et al., 2021; Rodriguez et al., 2013; Taylor et al., 2018). Larger scale multi-site trials are required in these populations before efficacy can be determined.

Post-Traumatic Stress Disorder

Some but not all studies report benefits from ketamine treatment for post-traumatic stress disorder (PTSD; Abdallah et al., 2022; Du et al., 2022; Feder et al., 2014; Fremont et al., 2023; Johnston et al., 2024). As yet, there is insufficient evidence from adequately powered, phase 3 studies to support the routine clinical use of ketamine in PTSD.

Substance use 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 (Dakwar et al., 2019; Das et al., 2019; Grabski et al., 2022). Older studies assessing ketamine used in conjunction with psychotherapy have shown potential efficacy in treating alcohol and heroin dependence (Krupitsky et al., 2002; Krupitsky and Grinenko, 1997). Further research is needed in this area.

Eating disorders

Case reports suggest ketamine may be beneficial in the management of eating disorders, but adequate trials in this field have not been undertaken (Johnston et al., 2024).

Key considerations for use of ketamine therapy in clinical practice

Further ketamine research is encouraged, under conditions that include 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 must:

1. Ensure they are fully familiar with the complexities of ketamine dosing, management and safety monitoring, and have established appropriate clinical infrastructure for such treatment.
2. Ensure they are familiar with and practise within, all relevant state, territory or jurisdictional legislation.
3. Ensure the patient is willing and able to consent, or follow appropriate informed substitute decision making via the relevant jurisdictional mental health act legislation.
4. 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.
5. Be informed by RANZCP guidelines for off-label prescribing in psychiatry if using racemic ketamine.

Only patients with TRD should be treated with ketamine therapy within clinical practice. All other indications should be treated as part of a clinical trial under research trial conditions or as part of an approved, regulated 'access with evidence programme' where treatment is provided as part of a programme funded for evaluation of the treatment (McCabe et al., 2010; Mohr and Tunis, 2010), or as part of a formal quality improvement program.

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. Psychiatrists and medical practitioners 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 (Bayes et al., 2021; McIntyre et al., 2021; Swainson et al., 2021). The practitioner should be responsible for the ketamine treatment process including post-delivery care, and for review in the case of any medical complication.

A specific plan for follow-up after the cessation of the ketamine acute treatment course is necessary. As risk of relapse after treatment cessation is high, patients should not embark on ketamine treatment unless this is in place. The follow-up does not need to be by the ketamine clinic and could be the patient's own ongoing clinicians providing care although, as ketamine is not a first line community treatment for TRD, those presenting for ketamine therapy should already have received secondary level care, ideally by psychiatrist.

The use of intranasal esketamine (Spravato) for TRD should be in line with the product information approved by the TGA (in Australia) or Medsafe (in New Zealand).

Ketamine and psychotherapy

There is increasing interest in the combination of therapy and ketamine. Multiple approaches have been described, with no consensus to date on the optimal approach (Kew et al., 2023). 'Ketamine Assisted Psychotherapy' or KAP refers to dosing with ketamine to induce a trance-like state to facilitate therapy, using a model akin to psychedelic assisted therapy. Observational reports suggest this approach may be useful (Dore et al., 2019) though this approach has not been studied in controlled study designs. Other studies have delivered therapy after ketamine treatment(s), with reports of enhanced or prolonged mood benefits (Price et al., 2022; Wilkinson et al., 2021). Psychiatrists are encouraged to consider the role of therapy in improving outcomes of ketamine treatment for TRD, and to familiarise themselves with the evolving evidence base. If using ketamine therapy with psychotherapy, extrapharmacological safety topics should also be considered such as using appropriate types of therapy and managing boundaries relating to touch (Calder and Hasler, 2023).

ECT and ketamine anaesthesia

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 (beyond the first week of treatment), nor did it result in procognitive effects (Anderson et al., 2017; Fernie et al., 2017; McGirr et al., 2017). Further information is available in the RANZCP Professional Practice Guideline for the administration of ECT (Weiss et al., 2019).

Patient selection, consent, and professional practice considerations

Informed consent must be obtained before commencing ketamine and should be in line with Principle 5 of the RANZCP Code of Ethics. 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.

Details relating to the current evidence-base, alternative treatments, description of the treatment process, acute and longer-term efficacy (including response and remission data), acute and longer term safety considerations, side effects, and cost should be provided. Patients should be informed of what to expect before, during and after treatment, including the likely duration of the treatment course, and effects after cessation of treatment including that risk of relapse is high and will require a specific follow-up plan to be in place.

Ketamine therapy should be conducted in a respectful manner and privacy should be maintained throughout the procedure.

Ketamine administration

Clinical settings

Services providing ketamine therapy should have clear practice policies and guidelines, preferably overseen by an appropriate clinical governance committee.

Each clinical setting that provides ketamine therapy should have appropriate infrastructure to administer ketamine therapy and have in place formal policies and procedures which outline:

- The clinical assessment of patients considered for ketamine therapy and its prescription, incorporating evidence-based parameters and consideration of appropriate clinical indications.
- The qualifications and training of clinicians involved in ketamine therapy provision in line with section '*Skills required for clinicians delivering ketamine therapy*' of this guidance.
- Appropriate use of a multidisciplinary team and documented processes for ascertaining that each clinician involved has the requisite skills and training for their role, i.e. a credentialling process and register for clinicians involved in the treatment.
- How the treatment facility:
  1. meets all required regulatory requirements for storage and handling of ketamine as a S8 drug in Australia or Class C drug in New Zealand
  2. provides a low-stimulus environment which is appropriate particularly for parenteral ketamine treatment
  3. ensures availability of attendance of a doctor and pharmacological intervention as required.
- the process for monitoring and managing outcomes, including both efficacy outcomes and adverse events. This includes:
  1. monitoring a patient post drug administration for 2 hours
  2. outlining processes for monitoring and management of acute and severe elevation in blood pressure
  3. provision for managing any adverse outcomes, including acute and severe psychological effects of ketamine (e.g. psychotomimetic effects, dissociative effects, distress, heightened emotions/abreaction) including immediate availability of a medical doctor to attend, and provision of pharmacological intervention and psychological support as necessary
  4. a regular clinical audit process, conducted at least annually, in place to ensure high quality, patient-focused treatment is always delivered.

There are risks associated with at-home use of compounded ketamine formulations (United States Food and Drugs Administration, 2023), and its use is not currently supported.

Equity and access

Ketamine therapy includes costs not just of the drug but also due to the required in-clinic monitoring for 2 hours after each treatment, when ketamine is given by parenteral or intranasal routes and follow-up assessments. This treatment cost is currently not subsidised by the Australian and New Zealand governments and initiatives to ensure equitable and affordable access to ketamine treatment are supported.

It is recognised that the outlined high training and intensity model of care required for ketamine therapy may limit access and lead to inequity of treatment availability particularly in less well-resourced areas including those serving rural and remote populations. A balanced approach to ensuring high standards of care should be the priority while attending to the accessibility issue in particular in rural and regional areas. Treatment models can be adapted to suit local circumstances as has been proposed in New Zealand (Beaglehole et al., 2023).

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 (Bayes et al., 2021; McIntyre et al., 2021; Swainson et al., 2021).

There is no consensus on the optimal mode of drug administration. Placebo-controlled RCTs have demonstrated antidepressant efficacy of racemic ketamine administered intravenously (Bahji et al., 2021b; Nikolin et al., 2023), subcutaneously (Loo et al., 2016, 2023), intramuscularly (George et al., 2017; Loo et al., 2016) and orally (Arabzadeh et al., 2018; Domany et al., 2019; Glue et al., 2024; Smith-Apeldoorn et al., 2024) and esketamine given intranasally (Daly et al., 2019; Popova et al., 2019). Further research is needed to determine the relative benefits and risks of the different modes of administering ketamine (e.g. IV, intramuscular, subcutaneous, oral, intranasal routes), and different formulations (racemic ketamine vs (S)- and (R)- isomers) (Bahji et al., 2021b; Glue et al., 2021; Nikolin et al., 2023). The route of administration has implications for the pharmacokinetics of the bioavailability of ketamine and its compounds, which in turn is likely to have implications for efficacy and safety (pharmacodynamics). The relationship between drug pharmacokinetics and antidepressant response is complex and is yet to be fully explored (Abuhelwa et al., 2022; Glue et al., 2021; Loo et al., 2016; Zanos et al., 2016).

Treatment should be given in line with the current evidence base. Further information can be found in a range of relevant studies (Abuhelwa et al., 2022; Glue et al., 2021; Lenze et al., 2016).

Dosing

Several studies have examined the dose required for antidepressant effects. Trials of racemic ketamine and intranasal esketamine Spravato found that response-guided dosing was effective, but not a fixed dose approach, suggesting that response-guided dosing is optimal (Fedgchin et al., 2019; Loo et al., 2023; Ochs-Ross et al., 2020; Popova et al., 2019; Smith-Apeldoorn et al., 2024). This is supported by evidence in dosing

Table 2. Dosing protocols.

Formulation	Dosing	Comments	Key studies
Protocols supported by evidence of efficacy and safety from randomised controlled trials with sample size *N* > 100 or meta-analyses of multiple smaller RCTs			
Spravato intranasal esketamine	Start 56 mg (28 mg if >65 years age). Increase dose as required to 84 mg. Commence twice per week, then taper to weekly fortnightly	Approved by Medsafe (NZ) and TGA (Aus) for TRD	Popova et al. (2019) Daly et al. (2019) Wajs et al. (2020) Zaki et al. (2023)
Racemic ketamine (generic)	IV infusion (over ⩾30 minutes) 0.5 mg/kg. Variable treatment frequency protocols.	Off label	Bahji et al. (2021a) Nikolin et al. (2023)
	Subcutaneous injection. Start 0.5 mg/kg, increase dose as required, to 0.9 mg/kg. Commence twice per week, then customise.	Off label	Loo et al. (2023)
Racemic ketamine, oral slow release tablet	120 mg daily for 5 days (initiation), then 180 mg twice per week	Patented, undergoing clinical trials, not clinically available	Glue et al. (2024)
Other protocols with limited RCT evidence			
Oral generic ketamine	Racemic ketamine IV solution taken orally, 1 mg/kg, 3 times per week	Off label. RCT *N* = 41	Domany et al. (2019)
	Racemic ketamine capsules, 50 mg daily	Major depression (not treatment resistant depression). RCT *N* = 81	Arabzadeh et al. (2018)
	Esketamine capsules, 90 mg daily	Not effective vs placebo. Response guided dosing in open label phase suggests benefit RCT *N* = 111	Smith-Apeldoorn et al. (2024)

studies that the mg/kg dose required for response differed between individuals (George et al., 2017; Loo et al., 2016). Dosing will vary between individuals, formula and routes. Table 2 gives a guide for treatment options. It is noted that this is a rapidly evolving field so readers should continue to keep updated with current literature to inform best practice regarding clinical indications and treatment advances. There is not sufficient systematic randomised data comparing all forms of ketamine used in clinical practice to confidently recommend commencing with one over another.

Protocols in Table 2 are not prescriptive. The consensus is that dosing should be adjusted based on response and tolerability for all routes. Prescribers may wish to commence with lower dosage and exercise caution in some clinical groups, e.g., older adults, those with liver or kidney impairment, and to refer to product information in gauging relative or absolute contraindications to the use of ketamine, and potential drug interactions. Table 2 should be used with these considerations in mind.

Longer-term maintenance treatment

Guidelines and meta-analysis outline the effectiveness of longer-term treatment (Kryst et al., 2020; Swainson et al., 2021). A range of studies demonstrate the effectiveness of repeated dosing for intranasal esketamine (Daly et al., 2019; Ochs-Ross et al., 2020; Zaki et al., 2023) and racemic ketamine (Loo et al., 2023).

There is evidence of a risk of relapse with discontinuation of ketamine after a successful acute course of treatment. Practitioners should familiarise themselves with the evidence for repeated dosing verses 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.

Duration of treatment, and the need for maintenance therapy, is affected by

factors such as efficacy, safety, tolerability and cost to the patient (Bayes et al., 2021).

Further data are needed on safety, especially examining cumulative and longer-term effects with repeated treatments (Short et al., 2018; Swainson et al., 2021), with some data available to date mostly for Spravato (Zaki et al., 2023) and limited data for combined Spravato and racemic ketamine (Bayes et al., 2025).

Managing risks and side effects: contraindications and precautions

Prescribers should be aware of relative contraindications for ketamine therapy related to severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction, history of stroke, cerebral trauma, intracerebral mass or haemorrhage, and hypersensitivity. Precautions should be undertaken in patients with hepatic or renal impairment, seizure disorder, glaucoma, schizophrenia or other psychosis, with careful weighing of risks and benefits. It is recommended a structured screening and assessment process is in place, e.g. using the Ketamine Side Effect Tool (KSET) Screening module (Short et al., 2020) as well as assessments for drug and alcohol issues.

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. Many initial studies of ketamine examined side effects only acutely and after a single dose (Short et al., 2018). More recently, studies have examined safety over a course of treatment (Daly et al., 2019; Loo et al., 2023; Popova et al., 2019) with safety data published for intranasal esketamine given for 3–4 years of ongoing treatment (Zaki et al., 2023).

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 within 2 hours after treatment is given. Effects are less marked with the oral route of administration.

Occasionally, ketamine can result in intense psychotomimetic effects, including fear of death experiences. These can occur unexpectedly in patients who have had multiple prior treatments at the same dose without problem. These experiences can be very psychologically distressing and often require close support and monitoring. Medical intervention with rescue medications (e.g. benzodiazepines) may be required. Adequate staff should be available to safely manage and support the patient.

The potential of ketamine to induce acute hypertension, lower urinary tract dysfunction, cystitis and interstitial cystitis, and alter hepatic function (ketamine is metabolised by the liver) warrants screening for relevant pre-existing conditions.

Ketamine therapy requires a structured framework for safety monitoring of acute, cumulative and longer term effects of ketamine treatment. Safety monitoring only immediately after each treatment, with reliance on patient self-reporting of side effects at other times, including cumulative side effects over multiple treatments, is not sufficient. The evidence base for this is the systematic review finding lack of data on cumulative effects (Short et al., 2018), the study on the KSET framework to address this (Short et al., 2020), the KSET-Revised (KSET-R) (Bayes et al., 2025) and frequencies of side effects from naturalistic settings as well as the Janssen 2 and 3 year data (Wajs et al., 2020; Zaki et al., 2023) showing important adverse effects including cystitis with ongoing use. Specifically:

1. Ongoing monitoring for urinary and hepatic effects over cumulative and longer-term treatment is necessary, and a structured framework for assessment, such as the Ketamine Side Effect Tool Revised (KSET-R) (Bayes et al., 2025) or equivalent, should be used. Monitoring should be done by active, structured enquiry about side effects, not relying only on spontaneous, patient-initiated reports, to detect side effects.
2. A system should be in place to screen for early and emerging signs of bladder inflammation, i.e. symptoms of dysuria, ideally before each treatment, so that the incidence of cystitis is minimised. If dysuria occurs, the patient should have a medical review before further ketamine treatment is provided, to guide treatment decisions such as whether dosing should be suspended, reduced in frequency, dosage reduced, or treatment should continue with close monitoring. If dysuria occurs, relevant investigations include urinalysis (including culture to assess urinary tract infection). Further investigation and treatment of urinary tract disorder may be required, including referral to a urologist.

Prescribers should be aware that frequent and long-term ketamine use in non-medical circumstances has been associated with cognitive dysfunction (Bayes et al., 2021; Short et al., 2018) and screening and monitoring for cognitive function should be considered, as well as referral for formal neuropsychological evaluation if there are subjective reports of impaired cognition in the context of treatment with ketamine.

Those with depression and comorbid personality disorder (in particular borderline personality disorder) warrant careful evaluation, as ketamine can have rapid-onset and rapid-offset effects on mood and suicidality. This can result in heightened fluctuations in mood, and unpredictable shifts in suicidality. In

such patients, safety management plans should be carefully reviewed and updated in partnership with the patient and carers to ensure that they adequately address these risks (Danayan et al., 2023; Ryan and Loo, 2017).

Prescribers should carefully assess for current and past drug abuse and dependence when considering ketamine treatment for a patient. State and other regulations restricting the provision of an S8 drug (Class C in NZ) for those with drug dependence must be observed. In some circumstances, written approval is required from regulatory authorities prior to initiating treatment with ketamine as a S8 drug. Additional considerations in prescribing ketamine to those with prior dependence is discussed in the review by Carroll et al. (2024). The KSET addresses routine pre-treatment screening, including urinalysis; a urine drug screen could also be undertaken if indicated.

Psychiatrists should also be aware of the risks for addiction, misuse and diversion, including level of risk based on past history (Carroll et al., 2024). Though the risk of developing addiction has been low and negligible in formal clinical trials of ketamine for depression, the risk in clinical use is less certain (Chubbs et al., 2022). A structured framework for monitoring the development of craving and addiction is recommended (Wang et al., 2022).

As the cost is prohibitive for many individuals, broader societal strategies are required to discourage illicit use and self-medication.

Skills required for delivering ketamine therapy

Psychiatrists

All psychiatrists who are administering ketamine therapy should be credentialed. Every service offering ketamine therapy should have a process for the assessment and subsequent credentialing and re-credentialing of psychiatrists who administer ketamine therapy to ensure that they meet required professional standards. This should be undertaken and monitored in accordance with local governance systems. Institutions that deliver ketamine should detail their credentialing requirements in a local policy document.

Psychiatrists prescribing ketamine should have attended a comprehensive course (the RANZCP website lists accredited courses) or equivalent, covering the following content:

- theory and evidence base underpinning use of ketamine (all preparations), including the pharmacology, pharmacodynamics, pharmacokinetics, indications for treatment, side effect profile.
- indications, situations of potential risk, and contraindications for ketamine therapy (both medical and psychiatric).
- safety including potential acute, cumulative and long-term side effects of ketamine, and how these may be further investigated and/or managed.

Ketamine therapy by psychiatry trainees or other health care professionals

When ketamine therapy is administered as a treatment for psychiatric disorders by a psychiatry trainee or other clinician (e.g. psychiatric nurse, GP), this should be done under the supervision of a psychiatrist who has professional training in ketamine and is credentialed as detailed above.

Ongoing education

It is acknowledged that ketamine therapy is a specialised and evolving practice. All clinicians involved in the provision of ketamine therapy must be up to date on clinical indications and treatment advances.

Psychiatrists working in this field will need to ensure they undergo ongoing Continuing Professional Development (CPD) requirements for ketamine therapy including CPD activities completed annually relating to ketamine therapy spread across any of the following CPD sections:

- Section 2: Formal Peer Activities (e.g. participation in a ketamine therapy peer-review group)
- Section 3: Practice Improvement Activities (e.g. audit of a practice or service offering ketamine therapy).
- Section 4: Self-Guided Learning Activities (e.g. attending ketamine therapy workshops, conferences, reading journal articles).

Where required, psychiatrists may need to engage in peer-review or primary/secondary consultation processes to determine the appropriateness of ketamine therapy for a given patient. Collaboration, peer review and sharing of knowledge and experience across psychiatrists practising ketamine therapy are recommended.

Research- and outcome-based measures

Psychiatrists should contribute to continued service development, quality improvement and research by monitoring treatment outcomes. This is important for both more established and evolving ketamine therapy treatment protocols to contribute to a more complete understanding and improvement in clinical practice.

Further optimisation of treatment protocols, and efficacy in different patient groups, and other psychiatric conditions are important foci of ongoing research.

Psychiatrists are encouraged to contribute to frameworks to improve practice and collect data for benchmarking and research (Martin et al., 2018).

Conclusion

There is evidence to support a role for ketamine therapy in TRD, specific

to certain formulations and routes of administration. Treatment will usually need to be ongoing to maintain antidepressant benefits. Evidence on the effectiveness and safety of longer term use are still emerging, though reports to date suggest safe and effective use, with detailed structured monitoring of mood and safety outcomes. For all routes of administration, safety monitoring should include structured active assessment for cumulative and longer term effects. For parenteral routes of administration, close monitoring for 2 hours after each treatment dose is also required. 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. More data are needed on cumulative and longer-term effects with repeated treatments. 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.

Ongoing research into optimising ketamine treatment for TRD, and to examine other indications in mental disorders, is encouraged.

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

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Disclaimer

Compiled for the Royal Australian and New Zealand College of Psychiatrists (RANZCP), this information and advice is intended to provide general guidance to practitioners as at the date of publication, 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 relying upon the information contained in this publication, or from changed circumstances or information or material that may have become subsequently available.

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Notes

1. The term ketamine is used to include all formulations of ketamine, including esketamine and racemic ketamine.
2. The term patient is used through this document for clarity and consistency although it is recognised that there is a range of terms preferred by different individuals, for example person with lived experience, consumer, client or service user.

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