Clinical Memorandum

Use of ketamine for treatment-resistant depression

November 2019

The Royal Australian & New Zealand College of Psychiatrists

Authorising Body:	Board
Responsible Committee(s):	Committee for Evidence-Based Practice
Responsible Department:	Practice, Policy and Partnerships
Document Code:	**CLM PPP Use of ketamine for treatment-resistant depression**

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 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 it 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. 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 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. These studies 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; Lapidus et al., 2014). Further small scale studies have demonstrated efficacy of the delivery of ketamine or esketamine intranasally (Lapidus et al., 2014; Galvez et al., 2018; Carla M. Canuso et al., 2018), with a separate study demonstrating poor tolerability of side effects (Galvez et al., 2018). 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. 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 (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 is available in the RANZCP Professional Practice Guideline for the administration of Electroconvulsive Therapy (Weiss, A. et al.,2019).

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).

It is noted that the U.S Food and Drug Administration has approved the use of esketamine intranasally (Spravato) for treatment resistant depression and there are current trials underway in Australia for the use of esketamine in treatment resistant depression (Galvez et al., 2018).

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

Disclaimer

References

Berman RM, Cappiello A, Anand A, et al. (2000) Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry* 47: 351-354.

Carla M. Canuso, M.D. ,, Jaskaran B. Singh, M.D. ,, Maggie Fedgchin, Pharm.D. ,, et al. (2018) Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. *American Journal of Psychiatry* 175: 620-630.

Fernie G, Currie J, Perrin JS, et al. (2017) Ketamine as the anaesthetic for electroconvulsive therapy: the KANECT randomised controlled trial. *The British Journal of Psychiatry* 210: 422-428.

Galvez V, Li A, Huggins C, et al. (2018) Repeated intranasal ketamine for treatment-resistant depression - the way to go? Results from a pilot randomised controlled trial. *J Psychopharmacol* 32: 397-407.

George D, Galvez V, Martin D, et al. (2017) Pilot Randomized Controlled Trial of Titrated Subcutaneous Ketamine in Older Patients with Treatment-Resistant Depression. *The American Journal of Geriatric Psychiatry* 25: 1199-1209.

Katalinic N, Lai R, Somogyi A, et al. (2013) Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. *Australian and New Zealand Journal of Psychiatry* 47: 710-727.

Krystal JH, D'Souza DC, Karper LP, et al. (1999) Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology* 145: 193-204.

Lai R, Katalinic N, Glue P, et al. (2014) Pilot dose-response trial of i.v. ketamine in treatment-resistant depression. *The World Journal of Biological Psychiatry* 15: 579-584.

Lapidus KAB, Levitch CF, Perez AM, et al. (2014) A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biological Psychiatry* 76: 970-976.

Lara DR, Bisol LW and Munari LR. (2013) Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. *International Journal of Neuropsychopharmacology* 16: 2111-2117.
Larkin GL and Beautrais AL. (2011) A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *International Journal of Neuropsychopharmacology* 14: 1127-1131.
Loo CK, Galvez V, O'Keefe E, et al. (2016) Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatrica Scandinavica* 134: 48-56.
Malhi GS, Byrow Y, Cassidy F, et al. (2016) Ketamine: stimulating antidepressant treatment? *BJPsych open* 2: e5-e9.
McGirr A, Berlim MT, Bond DJ, et al. (2017) Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis. *The British Journal of Psychiatry* 210: 403-407.
Murrough JW, Iosifescu DV, Chang LC, et al. (2013) Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *The American Journal of Psychiatry* 170: 1134-1142.
Price RB, Nock MK, Charney DS, et al. (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biological Psychiatry* 66: 522-526.
Rush AJ. (2013) Ketamine for treatment-resistant depression: ready or not for clinical use? *The American Journal of Psychiatry* 170: 1079-1081.
Ryan CJ and Loo C. (2017) The practicalities and ethics of ketamine for depression. *Lancet Psychiatry* 4: 354-355.
Sanacora G, Frye MA, McDonald W, et al. (2017) A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry* 74: 399-405.
Schatzberg AF. (2014) A word to the wise about ketamine. *The American Journal of Psychiatry* 171: 262-264.
Short B, Fong J, Galvez V, et al. (2017) Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*.
Singh I, Morgan C, Curran V, et al. (2017) Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. *Lancet Psychiatry* 4: 419-426.
University of Manchester. (2016) *Results of the Ketamine-ECT study*. Available at: http://research.bmh.manchester.ac.uk/ketECT/studydocuments/Ketamine-ECT-Study-newsletter-Feb2016.pdf.
Zarate CA, Jr., Brutsche NE, Ibrahim L, et al. (2012) Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biological Psychiatry* 71: 939-946.
Zarate CA, Jr., Singh JB, Carlson PJ, et al. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry* 63: 856-864.

Revision Record Footer

Contact:	**Executive Manager, Practice, Policy and Partnerships**		
Date	**Version**	**Approver**	**Description**
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
2020			**NEXT REVIEW**