The rise (and possible fall) of ketamine treatment in New Zealand

Ben Beaglehole, James Foulds, Roger Mulder

Existing treatments for depression have limitations, including side effects and inadequate response rates. Thus, the recent interest in new treatments such as ketamine and psychedelic medications is not surprising. The use of psychedelics such as psilocybin for depression has been much hyped, but the evidence base for ketamine is more robust. In this editorial we outline the current status of ketamine in the treatment of mental illness in New Zealand and how we see it is evolving.

Ketamine treatment of mental illness has been the subject of formal research since the 1990s. By 2021, the rapidly expanding literature included more than 29 randomised trials and other non-randomised studies.[1] Most studies evaluated treatment-resistant depression and reported that ketamine treatment is associated with large short-term improvements in depression symptoms.[1] Key features of this research include the predominant use of parenteral dosing, marked dissociative symptoms at the time of dosing, and high rates of relapse when treatment ends. Additionally, there are concerns about the abuse potential of ketamine and other adverse factors including ketamine-associated cystitis, and possible memory side effects.

New Zealand research is making a significant contribution in this area. Researchers in the University of Otago have evaluated the pharmacokinetics and dosing of ketamine,[2] predictors of ketamine response and cross-diagnostic indications for ketamine treatment,[3] and the role of adjunctive psychotherapy.[4] The University of Auckland's research includes a focus on the challenges associated with expectancy and blinding with ketamine and psychedelic research,[5] qualitative aspects of ketamine associated antidepressant response[6] and neuroimaging.[7]

A key challenge for clinicians is translating the evidence for ketamine treatment of depression into usual care. The Royal Australian and New Zealand College of Psychiatrists (RANZCP) position statement[8] suggests restricting use to treatment-resistant depression (outside of research settings) and ensuring its use only occurs in services where clinicians are familiar with the drug and support structures are in place.

In New Zealand, ketamine use for psychiatric indications is off-label, although Esketamine (the S-enantiomer of ketamine) nasal spray is approved for use in treatment-resistant depression in combination with a conventional antidepressant. Esketamine is not funded by Pharmac and can only be administered in an appropriate clinic, making it expensive. The RANZCP mood disorder guidelines also report that Esketamine has not been compared directly with ketamine, most Esketamine data stems from industry-sponsored trials and longer-term outcomes are unknown.[9] To date, ketamine use in New Zealand has mainly occurred in research settings, although we are aware of limited use by publicly funded speciality services and, recently, treatment being offered by private providers.

A recent trial published in the New England Journal of Medicine showed ketamine to be non-inferior to electro-convulsive therapy (ECT) for outpatients with non-psychotic treatment-resistant depression.[10] In that study, the response rate was 55.4% in the ketamine group compared to 41.2% in the ECT group, while ketamine was better tolerated. However, a prior meta-analysis of inpatient studies drew differing conclusions.[11] Consequently, ECT should still be considered the treatment of choice for severe inpatient depression, but ketamine may be more desirable for outpatients and should be considered prior to ECT for community treatment-resistant depression.

Psychiatric disorders are chronic conditions. Longer courses of psychoactive medications are often utilised to reduce risk of relapse. Over time, neuroadaptation with some medications contributes to a number of phenomena, including fading benefits over time, discontinuation symptoms, physiological dependence and risk of broader substance disorder. While short term efficacy of ketamine is established, several questions about its longer-term role are unanswered. What is the role of maintenance ketamine treatment for enduring mood and anxiety disorders? Will factors such as reduced effectiveness over time,

dose escalation and tolerance/withdrawal emerge as issues? Despite striking short-term efficacy in most studies, how will ketamine perform given the longer-term issues often faced by patients with mental illness such as childhood adversity, discrimination and socio-demographic disadvantage?

This history of psychiatry includes treatments such as diazepam that are heralded with strong initial enthusiasm followed by overuse, re-evaluation, and recalibration of use after better awareness of the risk–benefit profile. This profile resembles the recent opiate epidemic in the United States and elsewhere. A key concern is the influence of pharmaceutical companies on consumer and doctor-led demand.

The desire for greater use of ketamine for depression is not just led by clinicians. In Australia, the Therapeutic Goods Administration has down-scheduled psilocybin and MDMA in response to intensive lobbying, despite advice from experts. This has promulgated therapeutic use of these agents despite a lack of evidence and expertise.[12] A further context in the demand for new treatments for depression is increasing rates of psychological distress in the community. We predict that the mislabelling of distress as depression will fuel demand for perceived "quick fixes" such as ketamine. We are also concerned that greater ketamine use may not be impactful, since the underlying drivers of psychological distress include early childhood adversity, poverty, and disadvantage, rather than a lack of antidepressant treatment.

Ketamine is known as "K", "special k", "ket" and "jet" by recreational users. Most ketamine consumed by recreational users in New Zealand is produced offshore. At this stage, prescribed ketamine is unlikely to contribute much to the pool of recreational ketamine. However, lessons learned from methylphenidate, benzodiazepines and opiates suggest there will be some misuse and diversion of prescribed ketamine. Careful patient selection and monitoring for these adverse outcomes will be needed.

Despite these reservations, we believe that greater availability of ketamine for treatment-resistant depression is desirable, but do not support a large-scale rapid increase in ketamine use. At present, ketamine treatment is best initiated by specialty services for the primary indication of treatment-resistant depression, although careful attention to equity of access is required. The management of relapse following courses of ketamine treatment will challenge clinicians. Adjunctive psychotherapy should be considered and there may be a role for general practitioners in selected individuals in which longer-term courses are indicated. Greater use of oral ketamine will assist management. This is currently limited to liquid ketamine for injection sipped over 30–60 minutes to reduce dissociation, but long-acting tablet formulations are in development. Clinical audit and service oversight are needed to support monitoring of outcomes and side effects. In conclusion, the potential offered by ketamine is exciting, but history suggests tempering our enthusiasm given lessons learned from other exciting treatments in our past.

COMPETING INTERESTS

Dr Beaglehole researches the impact of ketamine on mood and anxiety disorders using public funding. Prof Mulder has served on the data safety monitoring committee of a ketamine trial sponsored by Douglas Pharmaceuticals. The other author does not have any relevant conflicts of interest to declare.

AUTHOR INFORMATION

Ben Beaglehole: Department of Psychological Medicine, University of Otago, Christchurch.

James Foulds: Department of Psychological Medicine, University of Otago, Christchurch.

Roger Mulder: Department of Psychological Medicine, University of Otago, Christchurch.

CORRESPONDING AUTHOR

Dr Ben Beaglehole: Department of Psychological Medicine, University of Otago, Christchurch.
E: ben.beaglehole@otago.ac.nz

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