Treatment-resistant depression

An emerging role for esketamine

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There is a growing burden of depression in Australia, with treatment-resistant depression posing a major clinical challenge. Esketamine, a novel antidepressant recently added to the PBS, is showing promise as an effective option for patients who do not respond to traditional therapies.

KEY POINTS

- Mental illness accounts for 15% of Australia's total burden of disease, with rates of depression increasing faster than rates of many physical illnesses.
- One-third of patients with major depressive disorder have treatment-resistant depression, defined as depression that does not respond to two or more adequate courses of antidepressant medication.
- Esketamine, a nasal spray formulation of ketamine, has demonstrated efficacy in treatment-resistant depression and is now PBS listed for this indication.
- Careful monitoring is required, but long-term data indicate sustained benefits with no significant safety concerns.

The 2023 Australian Burden of Disease Study identified that mental and substance use disorders were responsible for 15% of Australia's total burden of disease (as measured in disability-adjusted life years), with only cancer representing a higher burden of disease, at 17%.[1] Rates of disability-adjusted life years resulting from depression are increasing significantly compared with rates of disability-adjusted life years resulting from physical illnesses. This trend suggests that mental illnesses including depression may soon overtake cancer as the leading contributor to the total burden of disease in Australia.[1]

Although disability-adjusted life years provide a numerical measure of the burden of depression, they cannot fully capture the personal suffering experienced by individuals with depression. An estimated one-third of people with a major depressive disorder have treatment-resistant depression, defined as depression that fails to improve despite trials of two or more antidepressants of adequate dose and duration. This poses further challenges to treatment decision-making at a primary care level. As the prevalence and global burden of depression grows, so too does our understanding of emerging treatment modalities. This article explores the role of esketamine as a novel approach for the management of treatment-resistant depression.

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Depression: treatment planning

As with any mental illness, ensuring an accurate diagnosis and grading the severity of illness are crucial in guiding a treatment plan. Screening for comorbid conditions (such as substance use disorders) is integral to formulating the most appropriate management plan. Following diagnosis and consideration of comorbidities, every person with depression should be offered lifestyle advice and psychological support. This includes discussion of sleep hygiene, diet and exercise, as well as evidence-based psychological interventions such as cognitive behavioural therapy and interpersonal therapy.[2]

Pharmacological approaches are an additional treatment option that the Royal Australian and New Zealand College of Psychiatrists recommends in moderate and severe depression. Regardless of the antidepressant chosen, supportive clinical care should always involve psychoeducation and psychological interventions in

tandem with antidepressant medication. This forms a biopsychosocial approach, with biological treatments such as pharmacotherapy or neurostimulation considered based on severity and duration of depressive symptoms.[3] A treatment plan including psychological, pharmacological and social treatment modalities is more likely to result in symptom remission.

When commencing pharmacotherapy, exploring patient preferences and attitudes towards medication is important in improving adherence and follow up. Counselling on realistic expectations regarding efficacy, side effects and the importance of psychological and social interventions can greatly increase adherence and subsequent symptom remission. As much as possible, antidepressant choice should be personalised to the individual's preferences regarding efficacy and tolerability.

The efficacy of traditional antidepressants in depression remains modest. Realistic expectations regarding the efficacy of traditional antidepressants should be explored when providing education about antidepressants, as only 40% of individuals with depression will experience remission with use of a first antidepressant.[4] Following the failure of an initial trial of one antidepressant, a second antidepressant, from an alternative class, should be tried. Further details regarding antidepressant selection are available in the Royal Australian and New Zealand College of Psychiatrists guidelines for the treatment of mood disorders.[3]

With subsequent trials of alternative antidepressants, remission rates decrease further. The Sequenced Treatment Alternatives to Relieve Depression trial highlighted that only two-thirds of individuals experienced remission after adequate trials of two antidepressants.[5]

In addition to traditional antidepressants, other treatment modalities should be explored when managing treatment-resistant depression. These include augmentation with mood stabilisers, such as lithium, and atypical antipsychotics. Neurostimulation approaches such as transcranial magnetic stimulation and electroconvulsive therapy are also evidence-based treatment options. More recently, esketamine has emerged as a novel treatment for treatment-resistant depression.

Esketamine

Ketamine has been used for almost 50 years as an anaesthetic and analgesic agent in the short-term treatment of severe and postoperative pain. Its dissociative effects have also seen it used illicitly as a recreational drug. In the 21st century, ketamine has emerged as a new approach in the management of treatment-resistant depression. Both ketamine and esketamine have shown clinically significant antidepressant effects, and research into their use in the clinical management of treatment-resistant depression is ongoing.

Ketamine is composed of two enantiomers, (S)-ketamine (esketamine) and (R)-ketamine (arketamine), which share the same chemical structure but are mirror images of each other. Esketamine is the more pharmacologically active form. Unlike ketamine, esketamine can be administered through a nasal spray, offering a less invasive and more accessible route of administration. Esketamine is believed to act primarily by increasing glutamate levels in the central nervous system. As most antidepressants act on serotonin, noradrenaline and dopamine systems, ketamine is considered a novel antidepressant. In addition to its modulation of the glutamatergic system, it has multiple other receptor functions, including activity at monoamine, cholinergic and cytokine systems.

Evidence for use in depression

Randomised clinical studies have demonstrated the efficacy and tolerability of intranasal esketamine, leading to its approval by the TGA as a treatment for individuals with treatment-resistant depression.[6] Real-world data have consolidated trial findings, showing clinically significant improvements in quality of life, productivity and depression severity.[7]

Esketamine remains the focus of substantial ongoing research and clinical trials, particularly regarding efficacy and tolerability in long-term use. Research is also exploring its role in the treatment of other mental illnesses – including bipolar depression, anxiety and post-traumatic stress disorder – although treatment-resistant depression remains the only indication with sufficient phase 3 clinical trial evidence for efficacy and safety.

The Royal Australian and New Zealand College of Psychiatrists has recognised the growing evidence base for intranasal esketamine in the treatment of depression and, in April 2025, released a guideline for the use of ketamine and esketamine in clinical practice.[8]

At present, esketamine can only be prescribed by a psychiatrist. Prescribers must be aware of the relative contraindications for esketamine, such as severe cardiovascular disease and severe hypertension. They should exercise caution when treating patients with comorbidities including hepatic or renal impairment and seizure disorders, weighing the potential risks against the benefits. Concurrent substance use disorders should ideally be treated first, or prescribing should proceed with caution in patients with a history of substance misuse, particularly ketamine misuse.

Acute adverse side effects most often occur within the first hour after dosing and include restlessness, sedation, hypertension and nausea. Because of this, individuals are monitored in a treatment centre for two hours following each administration. Following its recent PBS listing (April 2025), esketamine costs $31.60 per dose, or $7.70 for concession card holders and pensioners. The estimated total cost of each treatment is about $300, representing nursing and pharmacy costs, including post-dose monitoring under the supervision of a nurse, exclusive of the drug cost.

As with most pharmacological treatments for depression, concerns have been raised about the safety, tolerability and efficacy of esketamine with long-term use.

However, four-year safety data have shown sustained improvement in depression ratings with no significant safety concerns or adverse outcomes.[9]

With its inclusion on the PBS, esketamine is significantly more accessible and affordable in Australia, and its use in clinical practice is likely to increase. It represents a novel and effective treatment option for individuals with treatment-resistant depression.

Conclusion

Major depressive disorder and treatment-resistant depression impose a substantial and growing disease burden in Australia. Treatment-resistant depression becomes progressively more challenging to treat with each failed antidepressant trial, and conventional antidepressant medications generally provide only modest benefit even when combined with psychological support and lifestyle changes in these patients. Esketamine represents a new management option for treatment-resistant depression, and with its recent PBS listing it is expected to become more widely accessible, offering renewed hope for patients who have not responded to existing therapies. MT

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