Esketamine

A nasal spray for treatment-resistant depression

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Esketamine is a new intranasal antidepressant that is effective in patients with treatment-resistant depression when added to a conventional oral antidepressant. Possible acute side effects include transient hypertension, sedation and dissociation, and it must be administered under direct supervision of a healthcare professional.

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Major depression disorder (MDD) is a psychiatric syndrome comprising pervasive low mood or loss of interest (anhedonia) with associated symptoms such as changes in appetite, sleep or psychomotor activity, as well as suicidality. Globally, more than 264 million people of all ages currently experience depression, making it a leading cause of disability and contributor to the global burden of disease.[1] In Australia, MDD affects one in seven individuals in their lifetime, and one in 16 people every year.[2] Up to a third of patients with MDD fail to respond to multiple trials of standard antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs).[3] These patients with so-called 'treatment-resistant depression' have a high burden of illness and significant functional impairment, and often require augmentation strategies such as lithium or treatments such as electroconvulsive therapy (ECT).

MedicineToday 2022; 23(8): 68-70

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Ketamine is a long-used general anaesthetic and analgesic that has emerged over the past two decades as a novel antidepressant with robust, rapid effects in patients with treatment-resistant depression. Clinical trials have shown antidepressant efficacy for ketamine administered parentally or orally. Its use to treat depression is off-label in Australia. A new ketamine formulation that is administered by intranasal spray and uses the esketamine isomer was recently approved by the TGA for treatment-resistant depression.[4] It is not listed on the PBS.

What is esketamine?

Esketamine is one of the two stereoisomers that comprise ketamine, which is a racemic mixture of S-ketamine (esketamine) and R-ketamine (arketamine). The mechanism of action of ketamine differs from that of conventional antidepressants, most of which act on the monoamine system, including serotonin, noradrenaline and dopamine neurotransmitters. In contrast, ketamine acts on the glutamatergic system as an antagonist of N-methyl-D-aspartate (NMDA) receptors.

Ketamine is extensively metabolised by the liver, with the primary metabolic pathway being N-demethylation to form norketamine. The main cytochrome P450 (CYP) enzymes responsible for ketamine N-demethylation are CYP2B6 and CYP3A4.

How does esketamine work?

Our knowledge of the cellular effects of esketamine is mostly based on studies of racemic ketamine. These suggest ketamine has complex downstream intracellular effects. They include

increased synthesis of brain-derived neurotrophic factor (BDNF), remodelling of dendritic spines with increased synaptogenesis and changes in brain functional connectivity.[5-7]

Is esketamine effective?

Both ketamine and esketamine have been shown to have antidepressant efficacy and antisuicidal effects.[8,9] Initial single-dose studies of racemic ketamine found it has antidepressant effects that emerge within hours but abate after several days.[10] Repeated-dose studies have sought to maintain the antidepressant effect.

Only the branded formulation of esketamine, Spravato, is TGA-approved for use in treatment-resistant depression. Sponsored trials of Spravato include two randomised controlled trials (RCTs) of active drug added to a newly commenced antidepressant and compared with a placebo nasal spray and antidepressant.[11,12] The initial four-week trial of twice weekly fixed-dose esketamine did not find a statistically significant difference in reduction of depression scores.[11] With a subsequent flexible dosing approach, esketamine was found to be more effective than a placebo control when added to newly commenced antidepressant therapy.[12] This and other studies suggest that individualised dosing is important. However, in participants aged 65 years and over, a third RCT did not show a difference in esketamine added to an oral antidepressant compared with a placebo and an oral antidepressant, despite a flexible dosing approach.[13] Esketamine has antisuicidal properties, with intranasal esketamine added to standard-of-care treatment showing rapid improvement in those with depression at imminent risk of suicide (at four hours but not at 24 hours).[14]

In the longer term, continued treatment with esketamine (plus an oral antidepressant) reduced the risk of relapse compared with a placebo spray (plus an oral antidepressant) over a three-month period, with 26.7% versus 45.3% relapsing of those who previously attained remission.[15]

A long-term open label study of esketamine commenced concurrently with an oral antidepressant found a high level of sustained improvement at 48 weeks: 76.5% of participants were classed as 'responders' (over 50% reduction from the initial depression score) and 58.2% as 'remitters' (depression ratings after treatment no different from those seen in a population of nondepressed people).[16]

When should esketamine be used?

All formulations of ketamine, including esketamine, are classed as Schedule 8 (S8) drugs of addiction, and their prescription in Australia is governed by state- and territory-based regulations. Practitioners are required to seek an authority, depending on the duration of treatment and whether a patient is drug dependent.[17] GPs who assess an individual with possible treatment-resistant depression should refer the patient to a psychiatrist to confirm the diagnosis and assess management options (pharmacological, psychological and social and lifestyle interventions), including the suitability of esketamine treatment.[18]

Intranasal esketamine is self-administered by the patient under direct supervision of a healthcare worker via a spray into each nostril

Intranasal esketamine is TGA-listed specifically for adults with treatment-resistant depression. Although this condition is variably defined, the Product Information (PI) defines treatment-resistant depression as MDD in those who have not responded adequately to at least two different antidepressants of adequate dose and durationand have a current moderate to severe depressive episode.[4]

In practice, some patients being considered for esketamine will have greater levels of treatment resistance, having been trialled on multiple classes of antidepressants and with augmentation strategies or neurostimulation treatments such as transcranial magnetic stimulation (TMS). It is possible to use esketamine in patients who have failed to respond to or cannot tolerate ECT because of, for example, cognitive side effects. However, efficacy has not been demonstrated in this group, who were excluded from the clinical trials of intranasal esketamine.

The PI states esketamine should be commenced in conjunction with a newly initiated oral antidepressant and, as such, is not considered a replacement antidepressant or monotherapy.

Important precautions

Because of its propensity to cause acute blood pressure elevation, esketamine is contraindicated in patients in whom an increase in blood pressure or intracranial pressure poses a serious risk, such as those with a history of intracerebral haemorrhage. Caution is also warranted for patients with other cardiovascular or cerebrovascular conditions, such as uncontrolled hypertension.

Further, caution is also warranted in those with a history of psychiatric conditions, such as psychosis or bipolar disorder, because of concern about exacerbating symptoms. The potential for esketamine to be addictive means that careful consideration is needed before its use in people with a history of substance use disorder (including alcohol misuse).

How is esketamine used?

Intranasal esketamine is self-administered by the patient under direct supervision of a healthcare worker, via a spray into each nostril. The starting dose is 28 mg (one device) for those aged 65 years or older, or 56 mg (two 28 mg devices) for those aged under 65 years. Subsequent dose increases up to 84 mg (three 28 mg devices) are based on efficacy and tolerability. The initial dosing frequency is twice weekly for the first month, then weekly for the second month and then either weekly or fortnightly for maintenance dosing, with the aim to maintain response or remission.

PRACTICE POINTS ON INTRANASAL ESKETAMINE FOR DEPRESSION

- A new ketamine formulation (esketamine) that is administered by nasal spray was recently TGA-approved for patients with treatment-resistant depression.
- Esketamine should be commenced in conjunction with a newly initiated oral antidepressant.
- Patients considering esketamine treatment should be referred to a psychiatrist for assessment and management.
- Esketamine treatment must be given in a supervised clinic setting with careful monitoring.
- Esketamine is a Schedule 8 drug with restrictions on its use.

What are important drug interactions?

Coprescribed psychostimulants or monoamine oxidase inhibitors may theoretically interact with esketamine and induce hypertension; concomitant central nervous system depressants (e.g. benzodiazepines, opioids and alcohol) may increase sedation; and use of other nasal sprays may impact the absorption of intranasal esketamine. In addition, medications that are CYP2B6 or CYP3A4 inhibitors or inducers may affect esketamine metabolism.

Common side effects and monitoring

Common acute side effects of esketamine include nausea, sedation, perceptual disturbances, dizziness, vertigo and cognitive impairment. These side effects are generally time limited and resolve spontaneously.[19] Dissociation is also a frequent, transient side effect, which tends to resolve spontaneously. However, if the patient becomes distressed, they can be treated with supportive psychological grounding strategies and, rarely, a benzodiazepine or antipsychotic. The potential for transient rises in systolic and diastolic blood pressure mean that blood pressure should be monitored regularly during the first hour after each esketamine treatment and treated if there is clinical concern. Patients require monitoring in the clinic until blood pressure, sedation and dissociation return to safe levels for discharge.

Consideration should be given to cumulative side effects that may arise with repeated dosing. Interstitial cystitis has been reported in individuals using ketamine recreationally or to treat chronic pain at high doses long term. Although a large open-label maintenance study of esketamine plus an oral antidepressant (median exposure, 23 weeks) found no cases of interstitial cystitis, there were cases of cystitis that resolved despite continuing esketamine treatment, a case of frequent urination requiring dose reduction, and a report of urinary incontinence requiring discontinuation.[16] These cases indicate that monitoring of urinary symptoms using a structured measure is warranted.

In the same study, no cases of drug-seeking or abuse were reported; nevertheless, clinicians should monitor for signs of abuse or dependence. Adverse cognitive side effects have occurred in long-term recreational users of ketamine; however, the open label esketamine study described above found cognitive performance either improved or stabilised.[16]

Overall, the acute safety of intranasal esketamine has been shown during an initial course of up to four weeks of repeated treatments and with maintenance treatment for up to 48 weeks. However, postmarketing surveillance results have led to discussion about whether further clarification of safety is required in the domains of dissociation, sedation and suicidal ideation.[20,21] Furthermore, there are only limited data to date on cumulative and longer-term effects (e.g. bladder toxicity) of repeated treatment, assessed by active enquiry. Given the limited and mixed data in a newly emerging field, it would be prudent for clinicians treating patients with esketamine to implement a comprehensive system for evaluation of acute and longer-term adverse effects, such as the Ketamine Side Effect Tool (KSET).[22]

Conclusion

Esketamine is a new antidepressant with a novel mechanism of action that has rapid, robust effects on depression. Key practice points are summarised in the Box. Intranasal esketamine has demonstrated efficacy when used in conjunction with an oral antidepressant and is TGA-approved for treatment-resistant depression, although not PBS-listed. Esketamine provides a new treatment option for patients who have not achieved remission despite multiple trials of antidepressants, augmentation strategies or neurostimulation treatments such as TMS. The S8 status of esketamine and acute side-effect profile mean administration is required to be under the direct supervision of a healthcare professional. Data are growing on the long-term safety of repeated dosing in domains such as bladder symptoms, dependence and cognition, although active monitoring of these domains using structured measures is recommended until further data accumulate. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Bayes runs the Esketamine Early Access Program at the Black Dog Institute and is Site Principal Investigator for the Esketamine Quality of Life study. Professor Loo has served on advisory boards for Douglass Pharmaceuticals NZ and Janssen; runs the Esketamine Early Access Program at the Ramsay Northside Clinic; is Site Principal Investigator for the Esketamine Quality of Life study; has provided expert input into the Ketamine Clinical Memorandum for RANZCP; and is Director of the Ketamine Course for health professionals provided through the Black Dog Institute.

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