NICE National Institute for Health and Care Excellence

January 2026 exceptional surveillance of depression in adults: treatment and management (NICE guideline NG222)

Surveillance report

Published: 30 January 2026

www.nice.org.uk

Contents

Surveillance proposal

Topic area: treatment-resistant depression

We propose not to update the section on treatment-resistant depression in NICE's guideline on depression in adults: treatment and management.

Context

Depression is characterised by low mood, loss of interest and enjoyment in life, and a range of associated emotional, cognitive, physical and behavioural symptoms.

Standard treatment for depression includes antidepressants or psychological therapies (including cognitive behavioural therapies) or a combination of both. NICE's guideline on depression recommends considering electroconvulsive therapy (ECT) for severe depression when preferred by the patient, when a rapid response is needed, or other treatments have failed.

Depression is treatment-resistant when symptoms have not improved after at least 2 standard treatments.

NICE has not reviewed evidence on ketamine in depression before but it carried out a technology appraisal (TA) of esketamine nasal spray in 2022, which was reviewed again in 2024. NICE did not recommend esketamine for treatment-resistant depression due to limitations in the clinical evidence and economic model. Further research was recommended to address some of these uncertainties.

Triggers for the surveillance review

The review was suggested following an application from the Royal College of Psychiatrists in association with other bodies to the Medicines Repurposing Committee, a programme which was suspended in April 2025. The application concerned the use of intravenous racemic ketamine for the acute treatment of severe or treatment resistance unipolar depression in adults and acknowledged its current off-label use in the private sector.

Methods

The surveillance process consisted of:

- Literature searches to identify relevant evidence.
- Considering the new evidence and intelligence that triggered the review.

- Considering the evidence used to develop the guidance.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for ongoing research.

For further details about the process and the possible update decisions that are available, see processes and methods for NICE-wide guidance surveillance.

Search and selection strategy

Searches were carried out across Medline, CDSR and Epistemonikos to identify systematic reviews of ketamine in depression published since the publication of the esketamine TA in 2022, when treatment-resistant depression was last reviewed.

A search for ongoing trials was conducted in clinicaltrials.gov.

Related NICE guidance

- Esketamine nasal spray for treatment-resistant depression (TA854, last reviewed in June 2024)

Other relevant external guidance

The Royal College of Psychiatrists position statement on psychedelic and related substances for medical use PSO2/25, September 2025, acknowledges increasing interest in these compounds to treat a range of mental illnesses, including in pharmacologically assisted psychotherapy. The publication highlights that high-quality evidence on efficacy remains limited. Specifically on ketamine, they acknowledge methodological limitations in much of the relevant literature, as well as potential side effects and lack of longer-term data.

International guidelines have recommended intravenous ketamine, including the Royal Australian and New Zealand College of Psychiatrists guidelines for the use of ketamine in psychiatric practice (2025), the Canadian Network for Mood and Anxiety Treatments (CANMAT, 2023 update), and the Norwegian Medical Products Agency TA: Intravenous

ketamine for treatment-resistant depression (2025). The guidelines have acknowledged that there is limited guidance translating research findings into clinical practice, particularly evidence for repeated IV ketamine infusions, risk of bias or moderate to very low confidence in reviewed studies. Many guidelines draw on evidence from the Anand (2023) study, discussed below.

Evidence considered when developing the existing guidance recommendations

NICE's guideline on depression includes several different types of treatment for people with treatment-resistant depression. These include oral treatments, augmentation therapy (when an antidepressant is used with a non-antidepressant), combination therapy (an antidepressant with another antidepressant), and ECT. The guideline also includes psychological therapies as options to use in combination with pharmacological agents.

Ketamine is currently approved as an anaesthetic drug by the MHRA. It is not currently approved for treating depression and it has not previously been considered by NICE.

NICE's technology appraisal guidance on esketamine nasal spray for treatment-resistant depression (TA854) was published in December 2022. This did not recommend esketamine in combination with selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). The committee made this recommendation due to:

- treatment positioning and clinical pathway
- choice of comparator treatments
- internal and external validity of the clinical evidence
- long-term effects of treatment
- natural history of the condition
- resource use
- implementation.

Due to these limitations, there was uncertainty around economic modelling, and it was not possible to determine a reliable cost-effectiveness estimate.

NICE published a review decision in June 2024, which states that the evidence received in consultation did not support the need for an update of the existing recommendation.

Previous related surveillance reviews

There are none related to intravenous ketamine in treatment-resistant depression.

New published evidence considered in this surveillance review

Intravenous ketamine has been demonstrated to have a rapid antidepressant effect in small randomised trials, however there is uncertainty about its treatment protocols including dosing levels, effectiveness and safety of long-term use in clinical practice.

Intravenous ketamine has been studied across various disorders in mental health, but most commonly in depression and specifically in treatment-resistant depression. The current NICE guideline has recommendations 1.9 around further line treatment in depression, 1.13 electroconvulsive therapy for depression, and 1.15 treatment resistant depression.

The topic proposer positioned intravenous ketamine as an option for the acute treatment of severe or treatment-resistant depression in patients who are considering ECT, which is an effective treatment with a remission rate of 45% and response rate of 65.4% following an acute course of ECT for depressive episode (ECTAS report 2022). The review considered intravenous ketamine in this context.

The topic suggester submitted 4 randomised controlled trials (RCTs) comparing ketamine with ECT, which were included in the systematic reviews considered in this surveillance review.

To date, there have been only 6 RCTs comparing the 2 treatments, and they are therefore used repeatedly in meta-analyses. In Rhee (2025), findings favour ECT over IV ketamine. There are difficulties in comparing studies due to their heterogeneity, including variability in study design, inpatient versus outpatient settings, age of participants, dosage and outcome measures. They also highlight that only 2 trials are well-powered direct comparisons, and these are discussed in more detail below.

The largest trial, Anand (2023), found ketamine to be non-inferior to ECT but used both suboptimal application of the comparator in unilateral ultra-brief pulse ECT and only 6 to 9 sessions. ECTAS monitoring shows the mean number of ECT applications in a course is 10 and the mode is 12. There was also a higher dropout rate after randomisation to the ECT group.

Ekstrand (2021) had the longest follow-up period and administered up to a maximum of

12 ECT sessions. It found that 63% remitted in the ECT group versus 46% receiving intravenous ketamine. More people dropped out of the ketamine group due to side effects, namely the acute dissociative experience. During the 12-month follow up period, those in remission relapsed at similar rates of 63% in the ECT group and 70% in the ketamine group.

The other RCTs, Ghasemi (2014), Kheirabadi (2019), Kheirabadi (2020) and Sharma (2020) include fewer than 40 patients and have limited follow up periods of 3 months or less, which does not reflect the trajectory of the disease.

It is not currently possible to state that intravenous ketamine is equivalent to or superior than ECT and much is unknown about its long-term effects.

This surveillance review did not examine other comparators in depth, for example other augmentation strategies, as reviewed in Terao (2024) or Jelovac (2025).

Ongoing studies

There are 37 studies on clinicaltrials.gov on treatment-resistant depression using ketamine as an intervention, of which 8 are RCTs. None of these are based in the UK.

There is no phase 4 data available on studies comparing ECT and ketamine.

Health inequalities

Treatment-resistant depression has a negative effect on people, their families and carers. The effectiveness of current treatments for treatment-resistant depression is limited and therefore there is an unmet need for new evidence-based treatment options. However, the proposal not to update the NICE guideline on depression to consider ketamine is not anticipated to worsen health inequalities relating to treatment resistant depression.

How this fits with NHS and NICE priorities

NICE has identified mental health as a priority in its Forward View for 2025 to 2026. Additionally, the 10 Year Health Plan for England: fit for the future (2025) has also prioritised mental healthcare.

Impact of new evidence and intelligence on NICE guidance

The key issue is around the sustainability of ketamine's antidepressant effect and its comparison against known effective treatments, such as ECT. Many trials are small and with short follow up periods. Further research including high-quality RCTs are needed to draw firm conclusions on the long-term effects of intravenous ketamine. Side-effects, particularly if used as a maintenance treatment, are largely unknown. There remain questions about addictive properties and harms including severe urological complications.

Overall proposal

We propose not to update NICE's guideline on depression in adults.

ISBN: 978-1-4731-9409-0