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Ketamine in treatment-resistant depression

PERSPECTIVES

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Ketamine has a rapid antidepressant effect and appears to be a safe and effective treatment option for treatment-resistant depression.

Depression is a common, serious illness that has a major negative impact on individuals, their families and society. Cardinal symptoms include low mood, loss of interest/pleasure and reduced energy. Depression is the main risk factor for suicide in patients with mental disorders (1).

Approximately 6 % of Norway's population is affected by depression at any given time, and about 18 % will experience a depressive disorder at some point in their life (2). In 2022, the total cost of reduced health and quality of life, lost productivity and treatment for depression in Norway was estimated at nearly NOK 77 billion (2). Up to 55 % of the treatment costs are due to treatment-resistant depression (2), a condition defined by a lack of response to at least two different antidepressants (3). Up to 50 % of patients with depression do not experience adequate relief from treatment, and about 30 % ultimately meet the criteria for treatment-resistant depression (4). This amounted to 11,000–18,000 people in Norway in 2021 (2).

Limitations of current treatment for depression

Depression is treated with psychotherapy and/or antidepressants, with selective serotonin reuptake inhibitors being the first-line choice (5). Known limitations of antidepressants include delayed onset of action, low/moderate efficacy and adverse effects such as emotional blunting (6, 7). Various forms of psychotherapy are effective (8), but there is no definitive evidence that any are more effective than medication. Additionally, there is often a long waiting time for psychotherapy.

Electroconvulsive therapy is an effective and approved treatment option for severe depression and is described as more effective than antidepressants. Despite a good response rate of 58–70 %, use of electroconvulsive therapy is limited by factors such as availability, cognitive side effects and negative attitudes (9–11). Other treatments, such as transcranial magnetic stimulation, are better tolerated but are less effective and harder to access (12).

New treatment methods

New treatment options with better efficacy and fewer adverse effects are needed for treatment-resistant depression. Ketamine is a rapid-acting antidepressant (RAAD), which is a heterogeneous group of psychoactive substances that also includes, for example, psilocybin, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA) and medications such as nitrous oxide or scopolamine (13).

«New treatment options with better efficacy and fewer adverse effects are needed for treatment-resistant depression»

With nearly 50 randomised clinical trials, ketamine is the most studied of these (14), and the s-enantiomer of ketamine is approved as a nasal spray for the treatment of depression in Norway. However, there are still unanswered questions regarding long-term effects, adverse effects and potential for addiction to ketamine (15).

Mechanisms of action of ketamine

Ketamine is approved in Norway as an anaesthetic with analgesic properties. Several studies have shown that ketamine, regardless of the method of administration, can effectively treat depression, often within a matter of hours (16). The effect lasts well beyond the drug's half-life, sometimes for several weeks (17).

The discovery of ketamine's antidepressant effect has led to a new understanding of the neurobiological mechanisms behind depression, particularly the glutamate system and neuroplastic effects. Ketamine is a non-competitive NMDA antagonist and initiates intracellular signalling cascades that promote neuroplasticity through synaptogenesis, which may explain the prolonged effect (18). Ketamine also has anti-inflammatory properties (19), and it is speculated that changes in neuronal networks lead to reduced rumination and decreased hypervigilance (20, 21). However, the mechanism of action is not fully understood.

Ketamine as a treatment for depression in Norway

Since 2020, outpatient and inpatient patients with treatment-resistant depression have received experimental treatment with intravenous racemic ketamine at Østfold Hospital, Innlandet Hospital and Stavanger University Hospital, in accordance with national and international guidelines (22–24).

We developed a protocol based on national clinical guidelines, which is evidence-based and adapted to clinical experiences in Norway (25). This protocol is currently used by health trusts offering ketamine treatment and will provide a strong foundation for ensuring quality and consistency in the establishment of ketamine treatment in Norway.

At Østfold Hospital, ketamine is administered to adult patients with moderate to severe depression who have not responded to or tolerated appropriate pharmacological treatment. Referrals from general practitioners, private psychiatrists and the specialist health service are assessed by an interdisciplinary admissions team, and eligible patients are evaluated by a specialist. One of the requirements is that the patient receives psychotherapy during ketamine treatment. There are few absolute contraindications, but

patients with impaired capacity to consent, psychosis or dissociative disorders, ongoing (hypo)mania, active use of illicit substances or harmful alcohol use, unresolved cardiovascular conditions, and patients who are pregnant or breastfeeding are not given the treatment (25).

Practical execution

Under this national standardised clinical protocol, ketamine treatment consists of an initiation phase followed by a maintenance phase (25). In the initiation phase, two weekly ketamine infusions are administered over a three-week period. After the sixth infusion, the treatment response is systematically evaluated by a specialist, based on a clinical assessment and validated tools for rating depression (Montgomery and Åsberg Depression Rating Scale (MADRS), the Patient Health Questionnaire (PHQ-9)), anxiety symptoms (General Anxiety Disorder 7 (GAD-7)) and side effects (Ketamine Side Effect Tool (KSET)). In the event of a response (≥ 50 % symptom reduction), patients proceed to maintenance treatment consisting of six monthly ketamine infusions.

During the infusions, somatic parameters (blood pressure, heart rate and respiration) are carefully monitored, and a psychiatrist must be available. Suicide risk is assessed before initiation and after the last infusion. Suicidal ideation is also tracked throughout the treatment process using the MADRS.

Ketamine is administered as an intravenous infusion over 40 minutes. In cases of difficult venous access, intramuscular administration may be considered. This does not significantly alter the treatment, but it makes it harder to control.

> ***«The doses induce dissociative experiences in the form of altered consciousness marked by a disconnection from one's thoughts, feelings, memories or sense of identity. It is uncertain whether dissociation contributes to the antidepressant effect»***

The doses induce dissociative experiences in the form of altered consciousness marked by a disconnection from one's thoughts, feelings, memories or sense of identity. It is uncertain whether dissociation contributes to the antidepressant effect (26). However, more specific measures of the patient's subjective psychoactive experience have shown that positive elements, such as spirituality, insight or unity, correlate with better therapeutic outcomes (27). Individualised dose adjustments are made based on the quality, intensity and side effects of the experiences, as well as the antidepressant effect. To minimize stress and anxiety associated with the treatment, it is administered in a safe environment: patients are seated in a recliner chair/bed, wear eye masks, listen to calming music, and are under continuous supervision by a specially trained doctor/nurse.

Safety and potential for abuse

Acute side effects such as anxiety and confusion during dissociative experiences, nausea, increased heart rate/blood pressure, dizziness or visual disturbances are typically mild, transient and self-limiting. In one case, an arrhythmia was detected on an ECG the day after a ketamine infusion.

We are not aware of any patients treated in Norway who have abused ketamine after completing their treatment, and there have been no suicides during ketamine treatment. However, we are aware of two suicides in patients who were either on the waiting list or had been denied treatment.

Positive clinical experience

At Østfold Hospital, over 300 outpatient patients have been treated with intravenous ketamine to date. Our impression is that more than half have shown a significant reduction in depression symptoms.

At Innlandet Hospital and Stavanger University Hospital, approximately 40 geriatric psychiatry inpatients have received ketamine. Older patients seem to have somewhat less response after initiation and less stable effects during maintenance treatment.

The treatment is well-tolerated, including by older patients, and side effects are short-lived and mild. Suicide risk is carefully monitored and has been reduced for most of our patients.

The majority of those who were offered treatment completed the entire course. Our impression is that a large proportion of patients who respond to treatment stabilise during the course of their treatment, and that psychotherapy often consolidates the effect.

Ketamine has demonstrated a good safety and tolerance profile in the treatment of depression. Although psychoactive effects may contribute to ketamine abuse in recreational environments, its controlled use in clinical settings has not been associated with an increased risk of abuse. However, more long-term safety data and further controlled long-term trials are needed to thoroughly assess the risk of abuse (28).

Conclusion

Based on the treatment of approximately 350 patients, our clinical experiences – supported by international research (29) – are that intravenous ketamine is a safe and effective treatment for a patient population with few treatment options.

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In 2023, the growing interest in innovative treatment methods within Norwegian psychiatry led to the establishment of the national Norwegian Rapid Acting Antidepressant Network (NORAAD). This network unites professionals from all regional health authorities for updates on best practice, protocol standardisation and the coordination of collaborative research efforts. This has contributed to, for example, a large national study on ketamine for treatment-resistant depression. This study was awarded NOK 24.9 million in December 2024 by the National Programme for Clinical Treatment Research in the Specialist Health Service. The study is coordinated by Østfold Hospital and includes Oslo University Hospital, Innlandet Hospital, Akershus University Hospital, Vestfold Hospital, Haukeland University Hospital, Fonna Health Trust, Stavanger University Hospital, St Olav's Hospital at Trondheim University, and the University Hospital of North Norway.

To prevent potential negative outcomes from unsystematic trials, we have formed a national collaboration to ensure a universal, evidence-based approach in Norway. As part of this effort, we have devised a national standardised clinical protocol for ketamine treatment, which is followed by NORAAD participants (25).

In 2022, Østfold Hospital applied to the *Nye metoder* system for approval of ketamine for treatment-resistant depression. In June 2025, the results of a clinical and health economic evaluation conducted by the Norwegian Medical Products Agency will be published (30). This will serve as the basis for the way forward. If the Decision Forum for *Nye metoder* approves intravenous ketamine for the treatment of depression, it will mark a turning point for many patients with treatment-resistant depression.

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