Protocol for intravenous ketamine treatment for patients with therapy-resistant depression

Prepared by The Ketamine Unit at DPS Nordre, Østfold Hospital

1 Indication and patient group

The offer is aimed at people over the age of 18 with therapy-resistant depression. It is a requirement that the patient is motivated, cooperative and competent to consent to receive ketamine treatment.

1.1 Diagnosis and severity

The treatment applies to patients with moderate to severe depressive episode (Montgomery-Åsberg-Depression-Rating-Scale; MADRS ÿ 20) without psychotic symptoms.

The patient may have comorbid psychiatric disorders as long as they are not mentioned under the exclusion criteria (see below) and the patient's depressive episode is considered the main cause of their depressive symptomatology.

1.2 Therapy resistance criteria

The patient must have tried at least two different antidepressants (preferably from two different classes) that either produced intolerable side effects or insufficient efficacy despite treatment with an effective dose and over a sufficient period of time. In the case of bipolar depression, mood stabilizers should be included in the assessment.

1.3 Psychotherapy

There is a requirement that the patient receive psychotherapeutic follow-up during ketamine treatment. If the treating institution does not offer psychotherapy during ketamine treatment, there is a requirement that the patient receive psychotherapy from a local DPS, a private practicing psychiatrist/psychologist or a contracted specialist.

There are currently no requirements for the type of psychotherapy used, but it is recommended that the patient be offered conversations after the ketamine infusions and throughout the entire course of treatment.

This is called an integration conversation. Integration conversations are conversations where one processes experiences, feelings, or insights from an experience or treatment. The goal is to help a person understand and integrate what they have experienced in a meaningful way into their daily life.

Practical implementation

- Preparatory conversations before treatment starts. One conversation to establish a safe treatment relationship and one conversation to prepare the patient for the ketamine experience.
- At least weekly calls during the start-up phase
- At least one integration interview within one week after each maintenance infusion

1.4 Exclusion criteria

The exclusion criteria go beyond those considered absolute contraindications, of which there are few.
This reflects the extra attention being paid to patient safety when using medicines outside of their approved indication.
See Appendix 6.1 for a structured overview of all inclusion and

exclusion criteria for ketamine treatment.

o Psychiatric exclusion criteria

Patients with primary psychotic disorders or ongoing manic or hypomanic symptoms, current harmful use of alcohol or illicit drugs, or patients subject to compulsory mental health care are not treated.
Affect-congruent delusions or psychotic symptoms in severe depression are not considered an absolute contraindication and must be assessed individually.
For some comorbid psychiatric disorders, extra consideration is given to assessing patient safety, feasibility, and benefit of treatment. This applies in particular to severe personality pathology, dissociative disorders, eating disorders, mental retardation, and developmental disorders.

o Somatic exclusion criteria

Patients who are pregnant or breastfeeding, have severe lung, liver, kidney or bladder disease, uncontrolled diabetes or certain cardiovascular risk factors are excluded from the treatment offer or require clearance from a physician of the relevant specialty. If the patient has unresolved conditions that are considered relevant for ketamine treatment, any investigation and treatment of these is awaited first.

2 Referral practices and patient logistics

The referral applies to ketamine treatment, and does not include assessment of the right to health care. Ketamine treatment is a treatment option that is primarily offered to patients who have been assessed for eligibility by their own Health Authority/HF.

o Patients are referred internally or from:

- General practitioners
- Contract specialists in psychiatry
- Privately practicing psychiatrist/psychologist
- Psychiatric treatment facilities outside the treating health institution

o The referral should contain:
- Current main psychiatric diagnosis with secondary diagnoses
- The patient's current situation with present mental status
- Briefly describe the patient's psychiatric history including previous psychotherapy, mapping therapy resistance (effect/side effects of antidepressants/mood stabilizing medications), and any other treatment attempts (e.g. ECT)
- MADRS, to assess depression depth
- Mapping of drug use
- Somatic diseases
- Drugs in use

2.1 Assessment procedure

The referral is assessed by a multidisciplinary intake team with a specialist in psychiatry present.

If the patient meets the inclusion criteria, the patient is offered a conversation with a specialist for information and a conclusive assessment of whether ketamine treatment can be offered.

o The assessment interview reviews:
- Current issues
- Relevant history
- Inclusion criteria
- Exclusion criteria
- Requirements for local psychotherapeutic anchoring
- Drug history
- Clarify the patient's motivation
- Other relevant information
- Practical treatment implementation
- Necessary examinations before start-up

2.2 Application for use of a medicinal product outside of an approved indication

Intravenous ketamine is not currently approved as a medication for treatment-resistant depression in Norway. Therefore, it must be applied for as an individual decision for use of a drug outside the approved indication,

for each patient unless there is group approval from the local/regional health authority responsible for the treatment provision and implementation.

Application for use of a drug outside of an approved indication

Appendix 6.2 shows the application template.

Ketamine for treatment-resistant depression is under review at Nye metods

2.3 Psychotherapeutic anchoring

In parallel with the ketamine treatment, patients should receive psychotherapeutic treatment from a psychological specialist, psychiatrist or under the auspices of the specialist health service.

2.4 Collaboration with referrers

An information letter is sent to the referring physician before the start of treatment to request updated information and necessary examinations.

See Appendix 6.3 for the examinations that should not be older than 4 weeks before the start of treatment.

3 Ketamine treatment

The patient receives 6 infusions of intravenous ketamine in the initiation phase, which extends over 3 weeks, i.e. 2 infusions per week.

After the 6th infusion, a response evaluation is conducted, which is discussed and quality assured with the responsible psychiatric consultant. On this basis, the patient is either offered 6 maintenance infusions or the course is terminated.

Maintenance infusions start one month after the last initiation infusion. The intervals between maintenance infusions should generally be four weeks.

Normally, the course ends after 6 starting and 6 maintenance infusions, i.e. after a total of 12 infusions.

Based on individual assessments, the number and interval of initiation and maintenance infusions may differ from the standard setup. In such cases, it may be appropriate to have multiple response assessments along the way.

3.1 Practical implementation

o Preparatory interview

During the first treatment, extra time is set aside for a preparatory conversation.
Personnel not involved in treatment inform the patient about research participation and sign. Informed consent for experimental treatment, Broad consent and biobank (NORSMI)
and/or project-specific consents.

The patient then meets with the treating physician and the therapist. The following will be discussed during this conversation:

- Relationship building
- Patient expectations • Review of procedure, risks and side effects
- Preparatory measures (fasting 4 hours before treatment, adjustment of medications, m.m.)
- Ensure adequate follow-up and support after treatment

o Ketamine treatment

Ketamine treatment is carried out by a doctor or nurse with a senior consultant on call. Necessary documentation must be available before treatment begins. Before the first treatment, the patient must have met with a specialist in psychiatry.

In the morning meeting, the day's treatments, response evaluations, and other relevant information are reviewed in an interdisciplinary team.

Each treatment is planned to last 120 minutes. It is important that the infusion is given in a calm and pleasant environment to reduce stress. The aim is for the patient to experience the treatment as safe and meaningful.

o Treatment rooms should have

- Soundproofed/ soundproofed room
- Possibility of dimming
- Be equipped with a bed/lounger
- Single or heavy duvet, pillow if needed • Eye mask • Noise-canceling headphones
- Access to adequate music; it is recommended to use instrumental and calm music

o Treatment implementation

- Initial conversation before all ketamine infusions
- Clarify what form of reassurance and support the patient wants and allows during and after treatment, with verbal consent for any physical contact.
- Patient is encouraged to go to the toilet before treatment
- Measurement of blood pressure, pulse and oxygen saturation, which is documented in the medical record
- Insertion of a peripheral venous catheter, which is flushed with NaCl before the ketamine pump connected
- Music selection
- Breathing/relaxation techniques before infusion starts

Typically, patients begin to notice the effects 5-10 minutes after starting the infusion.
After the infusion is finished, it usually takes up to half an hour for the patient to feel most of the effects wear off.
Healthcare professionals are present throughout the treatment.

o After treatment

- Inform the patient that the infusion is complete
- Measurement of blood pressure, pulse and oxygen saturation. Documented in the medical record
- It takes up to 20-30 minutes before the patient is ready to leave the treatment room
- The patient is verbally prohibited from driving on all treatment days and offered telephone follow-up the following day
- In connection with ketamine infusions, it is recommended that patients are offered conversations with a focus on integration. This involves reflection on the patient's experience during the ketamine infusions, and how these can be understood and integrated into further therapy.

- It also includes discussing any insights or emotional reactions that arise during treatment, as well as exploring how the patient can continue to work toward their therapeutic goals.

3.2 Administration and dosage

Ketamine is mixed with NaCl 9 mg/ml and administered as an intravenous infusion over 40 minutes.
The ketamine dose is adjusted individually in the range between 0.5 to 1.5 mg/kg. Dose increases are made in 0.25 mg/kg steps, for example, at the 1st infusion 0.5 mg/kg is given, at the 2nd infusion the dose can be increased to 0.75 mg/kg and from the 3rd infusion 1.0 mg/kg can be given. The aim is to find the individual dose that gives the best possible effect with the least possible side effects. The total dose of 150 mg ketamine per treatment should not be exceeded.

Exceptionally, ketamine can be given intramuscularly, for example if the patient has difficult venous conditions.
The disadvantage of IM administration is that the entire dose is given at once, so it cannot be adjusted in the event of panic attacks, nausea, etc. This exception must be approved by the responsible physician.

Since intramuscular ketamine has similar bioavailability (95%), the same dosage can be used. With intramuscular administration, a longer monitoring period must be considered. The maximum amount of fluid for IM injection in the upper arm should not exceed 3 ml.

3.3 Quality control and drug handling

Ketamine infusions are prescribed by a doctor. Preparation should be double-checked.

For storage and shelf life, refer to the joint catalogue: Joint catalogue Ketamine

In this protocol, ketamine in racemic form is referred to as Ketalar and Ketamin Abcur.
This is an A-preparation and is subject to strict documentation and storage requirements that must be followed.
Prepared ketamine mixtures should be stored as safely as the original packaged ampoule until the medication is used. Unused pre-mixed ketamine should be destroyed, the action documented and countersigned by a staff member.

3.4 Psychotherapy

The use of ketamine in the treatment of depression is understood as part of a comprehensive treatment program in combination with psychotherapy. The patient should be psychotherapeutically anchored by a local DPS, contracted specialist, private practicing psychiatrist or psychological specialist. There are no requirements regarding the type of psychotherapy to be used and it can be both individual or group therapy.

It is recommended that the patient has started psychotherapeutic treatment before starting treatment, where preparatory conversations are offered before starting treatment and integrative conversations during and after ketamine treatment. Together with their psychotherapist, the patient can identify strategies and resources to maintain positive changes and cope with any challenges that arise after treatment.

Dialogue is sought between the treatment facility and the psychotherapist.

3.5 Treatment response and psychometrics

Treatment response is assessed based on clinical picture, subjective experience, psychometrics and possibly

the psychotherapist's feedback in a separate conversation two weeks after the 6th treatment. If possible with a psychotherapist and/or next of kin. In principle, treatment response is considered achieved if the patient shows a 50% reduction in depression symptoms.

Psychometric tests are sent digitally to the patient. Before the first treatment, the following are sent to the patient for self-completion: MADRS-S, PHQ-9, GAD-7, AUDIT, DUDIT and KSET. 14 days after the 6th infusion, the following are sent to the patient as a basis for response evaluation: MADRS, PhQ9 and KSET. In the maintenance phase, the MADRS-S, PHQ-9, GAD-7 and KSET are sent the day before and 14 days after each ketamine infusion.

3.6 Side effects

During treatment with ketamine, mainly psychological, neurological, cognitive, hemodynamic and urogenital side effects may occur, which are most often mild, transient and dose-related.
Serious side effects are rare.

The most common side effects include anxiety and confusion, increased heart rate and blood pressure, visual disturbances, sedation, headache, dizziness, and nausea (2,3).

o Psychological side effects

The most common acute psychological side effects reported with ketamine treatment are perceptual disturbances, anxiety, panic, agitation, euphoria, derealization and depersonalization (2).

Dissociation during ketamine treatment is generally considered part of the drug's therapeutic mechanism, but may be experienced as difficult or confusing for some patients (5,6,7).
Psychological side effects as mentioned above can be reduced by administering ketamine in a controlled setting, in a calm atmosphere and by using music, an eye mask and offering the supportive presence of staff with whom the patient feels safe.

In case of severe anxiety attacks, 1mg midazolam can be given intravenously after consultation with a doctor. It is important to closely monitor the status of sedation and any subsequent respiratory depression.

o Psychosis

All psychoactive drugs, including ketamine, have been associated with the potential to induce psychosis in both users and patients, and particularly in individuals predisposed to psychotic disorders. Patients with current or past psychotic symptoms are therefore excluded from ketamine treatment due to the risk of temporary exacerbation (8). Ketamine, however, can be safely used in patients with severe depression with affect-congruent psychotic symptoms (9).

o Cardiovascular side effects

Ketamine has cardiostimulatory effects via central mechanisms. At subanesthetic doses, ketamine can cause an acute, but transient, increase in blood pressure and heart rate. For this reason, untreated hypertension is contraindicated for ketamine treatment (2).

Increases in systolic and diastolic blood pressure are reported in 10–50% of patients and usually resolve within 2–4 hours. Blood pressure changes are often small, dose-related, clinically insignificant, and are

well tolerated (2, 10).

Isolated increased blood pressure is not clinically relevant in patients with good cardiovascular health.

Asymptomatic blood pressure below 180/110 mmHg can be followed with repeated checks until normalization. Secondary blood pressure increase due to anxiety in patients without known hypertension does not need to be excluded from ketamine treatment.

Acute hypertensive crises have not been observed in ketamine studies and are therefore thought to occur extremely rarely. For patients without cardiovascular disease who are medically stable, frequent or continuous measurements of the patient's vital parameters are not generally indicated (11).

Symptoms of hypertensive crisis	Symptoms of non-acute high blood pressure
• Chest pain • Reduced level of consciousness (GCS < 8) • Severe stomach pain • Shortness of breath • Fainting, syncope • Clock • Visual disturbances • Possible symptoms of stroke	• Headache or head pressure, possibly eye pressure • Rarely dizziness • Nosebleed • Palpitations • Most people do not experience any discomfort

o Neurological

The most common neurological side effects are dizziness, drowsiness and lightheadedness (2). In patients treated with ketamine for treatment-resistant depression, no persistent reduction in cognitive function has been reported (12).

o Urogenital side effects

Chronic abuse of high-dose ketamine has been associated with a syndrome called ketamine bladder . This includes cystitis (bladder infection with painful urination, polyuria, incontinence, and hematuria) with upper urinary tract obstruction and papillary necrosis (13). There are few reports of this syndrome or serious urinary tract symptoms in placebo-controlled or long-term studies of the use of ketamine for treatment-resistant depression (1,14,15).

If the patient discovers blood in the urine (hematuria) or other signs of cystitis after treatment, the dose frequency can be reduced or treatment paused, and the cystitis will usually improve without further action or treatment.

Category	Symptoms	Occurrence	Measures
Anaphylactic	• Urticarial rash • Tachycardia • Hypotension • Takypne • Hvesing	Extremely rare. Case reports only. Note: Erythema and morbilliform rash without The above symptoms are a common reaction, and not anaphylaxis.	• Call the doctor • Make breathing easier: raise the chair/bed 45 degrees. • If hypotension, lay the patient flat with legs elevated. • EpiPen
Pulmonary	• Increased secretion • Laryngospasme • Respiratory depression • Hypoxia • Apne	Rare in doses used to treat depression, but possible.	• Call the doctor If persistent hypoxia or apnea: • Raise the chair/bed to 45 degrees • Stimulate the patient verbally and with touch • Head-tilt/Chin-lift/Jaw-thrust maneuver • Ventilation with mesh bag • CPR if necessary with AED
Cardiovascular	• Hypertension • Tachycardia • Bradycardia • Arrhythmia	Transient (<a few hours) • Asymptomatic blood pressure below 180/110 mmHg can only be followed with repeated checks until normalization. • If BT > 180/110 + symptoms of hypertensive crisis: call the doctor • Cardiac arrest: Call the doctor. CPR with AED	
Gastrointestinal • Nausea • Vomiting		Can be avoided by fasting four hours before treatment	• Ondansetron: IV maximum 16 mg per day • Prophylactic use: up to 4 mg ivper day
Urogenital	• Urination • Polyurea • Hematuria • Incontinence	Transient	Reduce frequency or pause treatment
Muscular	• Muscle stiffness • Spasms • Tonic-clonic movements	Transient	No treatment necessary
Ophthalmological	• Diplopia • Nystagmus	Transient	No treatment necessary
Psychiatric	• Angst • Confusion • Agitation • Disorientation • Dysphoria.	Transient	In case of severe anxiety attacks or agitation midazolam iv/im 1 mg/ml is given after consultation with a doctor

3.7 Interactions

Antidepressants, mood stabilizers, and other psychotropic drugs are generally safe to use in combination with subanesthetic doses of ketamine as in the treatment of therapy-resistant depression.

Combination of ketamine and other drugs that can cause CNS depression may potentiate this effect or increase the risk of respiratory depression. Reduction of the ketamine dose may be necessary when used concomitantly with anxiolytics, sedatives and hypnotics. CYP3A4 inhibitors may increase and CYP3A4 inducers may decrease plasma concentrations of ketamine.
See also:
https://www.interaksjoner.no/results.html?PreparatNavn=ketamin%0D%0A
https://www.legemiddelhandboka.no/L22.3.1.4/Ketamin
https://www.felleskatalogen.no/medisin/ketalar-pfizer-560507#interaksjon

3.8 Emergency medication

Emergency medication
All medications are prescribed by a doctor.
In cases of severe anxiety, benzodiazepines with a short half-life can be given either before or after treatment, such as 1-2 mg of midazolam iv.
In case of nausea and vomiting, ondansetron (1 ampoule iv. with 4 mg) can be given either prophylactically before or after the infusion.

3.9 Safeguard

Data from clinical studies over the past 20 years show that ketamine in subanesthetic doses has a good safety and tolerability profile (1).
However, ketamine treatment may increase blood pressure and heart rate in some patients, so providers administering ketamine must be prepared to manage possible cardiovascular events (2).

Patient safety when administering ketamine is regularly assessed through systematic monitoring of adverse reactions. For example, an adverse reaction scale (attached) can be used and sent to all patients before initiation, after the 6th infusion and 24 hours after each maintenance treatment.

3.10 Abuse

Ketamine is also abused as a drug. Chronic abuse of high doses of ketamine has been associated with potentially serious and persistent toxic side effects including urological, hepatological and cognitive damage.

Although no increased risk of addiction has so far been documented when using ketamine in the treatment of depression within the therapeutic framework described in this protocol, the risk of abuse and addiction must be part of the assessment of whether the patient is suitable for treatment or not (1,14).

The withdrawal period after using illegal drugs should be at least 6 months before starting treatment.
In cases of previous serious abuse of ketamine (or other drugs), it may be appropriate to generally exclude patients from treatment.

3.11 Emergency preparedness

In general, an on-site anesthesiologist is not required when administering sub-anesthetic doses of IV ketamine to low-risk patients. However, ketamine infusions should be administered in a facility where equipment to maintain vital functions is available and is suitable for managing behavioral side effects. Facilities should have on-site personnel qualified to perform advanced cardiopulmonary resuscitation in the event of acute cardiovascular or respiratory failure.

A standby physician with specialist training in psychiatry or relevant medical specialist training should be physically available if needed while ketamine treatment is being administered to patients.

o Emergency equipment

- Bag-valve mask
- automated external defibrillator (AED)
- EpiPen

o In case of emergency:

- Call for rear guard
- Call the emergency response team (if available) or call 113.

o Necessary measures include:

- Prepared procedures for emergency situations
- All employees must be trained in emergency procedures, CPR protocol, use of AED and other necessary resuscitation equipment
- All employees must be familiar with where the emergency equipment is located.
- The patient is observed until their vital and mental parameters have normalized, usually within an hour of ketamine infusion
- Patients with complex health conditions and increased risk of side effects are assessed individually considering the frequency and duration of monitoring

o Treatment equipment

- Blood pressure and heart rate monitor
- Oxygen saturation meter
- Infusion pump
- Equipment for inserting peripheral venous catheters/PVK
- Bed, deck chair or lounge chair
- Duvets (or heavy duvet) and pillows
- Eye mask against light
- Music player with headphones, possibly with noise reduction
- Workplace for therapist

4 Consent, data collection and research

Consent to research projects and ketamine treatment is voluntary. No patient should receive ketamine treatment without consent. Consent competence is a requirement for receiving ketamine treatment and participating in research projects. Consent competence is assessed according to the same standards as for other medical treatments, procedures or interventions.
If doubts arise during the assessment interview or upon presentation that a patient understands, can acknowledge and reason about, and is able to make an informed choice, a thorough assessment of the patient's consent competence to receive ketamine treatment and participate in associated research projects is carried out before any inclusion and initiation of treatment.

Some patient groups may be at increased risk for somatic or psychiatric conditions that may lead to a lack of consent to receive ketamine treatment or participate in associated research projects. This could include, for example, patients with developmental disabilities, cognitive impairment, or neurodegenerative diseases. It is also important to remember that some of these conditions that may lead to a lack of consent may have an increased incidence with age.

o Physical contact

Some patients may become frightened or anxious during treatment and may therefore request physical contact in the form of being held in the hand, on the arm or on the shoulder for a short period. Physical contact beyond this is usually not necessary. In such a case, the patient must have consented to physical contact before the start of the infusion, so that the patient's wishes during treatment can be complied with by the therapist, as the patient is not considered competent to consent to physical contact under the influence of ketamine. It is recommended that this be clarified at the first appointment and the patient must be informed that consent to physical contact can be withdrawn at any time.

o Informed consent

Patients receiving ketamine treatment must sign an informed consent. This is a confirmation that the patients have understood that the treatment involves the use of a drug outside of an approved indication and that they have been adequately informed about possible somatic and especially psychological side effects associated with the treatment.

Because ketamine treatment is of an experimental nature, all patients must sign an informed project-specific consent for ongoing research projects related to ketamine treatment. In addition, patients are invited to contribute to research by signing a broad consent form for the NORSMI general biobank and registry.

5 Training

Clinicians who administer ketamine infusions are doctors or nurses. New employees receive training from experienced colleagues in the implementation of treatment. Healthcare professionals who administer ketamine should have a basic understanding of ketamine's mechanisms of action and how these can affect the patient's psychotherapeutic progress.

Clinicians should keep themselves updated at all times. In addition, it is recommended that regular professional days be organized for development and progress.

6 Appendix

6.1 Inclusion and exclusion criteria

o Inclusion criteria

- Age from 18 years
- Treatment-resistant depression
- Within the diagnostic spectrum bipolar depression F31, depressive episode F32, recurrent depressive disorder F33, persistent affective disorders F34
- Postpartum depression F53 and organic affective disorders F06.3 are assessed individually
- Ongoing depression with a MADRS score of at least 20
- At least two different antidepressants of different classes were tried, which either had insufficient effect or intolerable side effects in the current episode.
- Psychotherapeutically rooted
- Somatic examination with blood pressure and pulse measurement as well as ECG before starting that does not reveal relevant pathology

o Exclusion criteria

- Lack of consent competence to receive ketamine treatment
- Subject to compulsory mental health care
- Lack of ability or willingness to cooperate
- Primary psychotic disorders ICD-10 F2x
- Mania or ongoing manic or hypomanic symptoms
- Current harmful use or dependence on alcohol and/or illegal drugs, a- and b-preparations. Current medications taken as prescribed are assessed individually. Withdrawal period from drugs of 6 months before any assessment of treatment
- Women: Pregnancy is considered an absolute contraindication
- Women: Breastfeeding is considered a relative contraindication. Studies have shown minimal transfer of ketamine and ketamine metabolites into breast milk and consider breastfeeding after ketamine infusion to be safe. However, breastfeeding is not recommended until 48 hours after infusion. A separate treatment plan should be developed for nursing patients.
- Severe eating disorder with a current BMI <16
- Cardiovascular diseases:
  - o Essential hypertension > 150 mm Hg systolic and/or 95 mm Hg diastolic despite treatment. This does not apply to short-term hypertension due to anxiety or stress
  - o Heart attack or stroke in the last three months
  - o In case of a recent myocardial infarction, known or unstable arrhythmia, heart failure or prolonged QTc interval, the patient must be cleared by a cardiologist before starting ketamine treatment.
  - o In the event of a previous stroke or hemorrhage further back in time, the patient must be cleared by neurologist before starting ketamine treatment
  - o Central aneurysm
- Untreated/unresolved hyper- or hypothyroidism

- Severe kidney, bladder, liver or lung disease, unless an individual risk-
  The benefit assessment is carried out by a specialist in the Ketamine Unit in consultation with a specialist for the underlying somatic disease.
- Increased risk of violence
- Imminent or acutely elevated suicide risk
- If it is suspected that the patient's depressive syndrome is due to a somatic illness or side effects of medication, the primary disorder should be investigated and treated first.
- If unclear conditions are discovered in preliminary examinations, they are individually assessed as to whether they are relevant and should be clarified before any initiation of ketamine treatment.
- Rare or unclear conditions are assessed individually and in consultation with a specialist for the underlying condition.

6.2 Template for application for use of a medicinal product outside of an approved indication

Application for use of a drug outside of an approved indication for individual patients
To: Director
From: Treating institution
Responsible physicians:
The application concerns: Single patient
Which drug does the application apply to: Ketamine Abcur 50 mg/ml injection solution given intravenously over 40 minutes in doses of 0.5 to 1.5 mg/kg
Indication for use of the drug: (diagnose and situation) Must be completed by the applicant for the individual patient
Scientific background for the desired treatment choice and effect on the current indication: Many relevant research reports from abroad, as well as our own clinical experience (> 200 patients) show significant symptom relief and response and complete remission in a significant number of patients. Thus, we see great potential as part of the treatment of patients with therapy-resistant depression.
How is the safety (side effects) of the treatment assessed? Ketamine has been known as a safe drug for many years. Ketamine has a large therapeutic window, the risk of serious side effects is minimal with the regimen used in the treatment of treatment-resistant depression. More frequent side effects such as dizziness, nausea or increased anxiety are treated symptomatically and are most often of short duration (up to 30 minutes after the end of the infusion). There is little/no evidence that the use of ketamine in a therapeutic setting, such as when used for treatment-resistant depression, can lead to addiction. The dose is adjusted to the patient's body weight and is very low compared to doses at which ketamine is used for other indications, such as anesthesia or as an analgesic. Our inclusion and exclusion criteria for receiving treatment are strict and we follow the protocol of the National Institute of Mental Health (NIMH) and consensus guidelines for the use of ketamine in the treatment of depression published by the American Psychiatric Association (APA) in 2017. The patient is examined by a GP before starting treatment and both an ECG and blood tests are performed to detect any underlying somatic conditions. Patients with cardiovascular disease must be assessed by a cardiologist. Patients with substance abuse problems are excluded from treatment. Before and after each infusion, blood pressure, pulse and oxygen saturation are measured. A nurse or doctor is present during treatment. Overall, the safety of the treatment is generally considered to be very high. The patient meets all requirements according to our inclusion and exclusion criteria. There are no special conditions in the patient that indicate that he has an increased risk by receiving ketamine treatment. The patient has been informed that there is an oral driving ban on the days of treatment. Overall, the safety of the treatment in this patient is considered very high.

What are the consequences of not offering the patient the experimental treatment?
Must be completed by the applicant for the individual patient

Treatment plan: The (including clinical control, e.g. X-ray examination, blood sampling, etc.)
patient is initially offered 6 initial treatments over 3 weeks, i.e. 2 treatments per week. 2 hours are set aside per treatment day. The infusion itself takes approximately 40 minutes. Blood pressure, pulse and oxygen saturation are measured before and after the infusion. A doctor or nurse is present during treatment.
Before starting, the patient is examined by a GP and a blood test and ECG are taken.
It is a requirement that the patient is locally anchored in psychotherapy, either in the local DPS or with an agreed specialist, because ketamine treatment has the best effect in combination with psychotherapy with a focus on depression treatment.

The patient is informed that the treatment is of an experimental nature and must sign informed consent before any start. The patient is also asked to sign broad consent for future research.
Digital measurement tools and clinical assessment are used to document any effect. In case of response, the patient is offered up to 6 further maintenance treatments, starting with one per month, but the interval can be adjusted according to the patient's needs.

Treatment should normally be terminated after 12 infusions and the patient cannot be re-referred until a waiting period of 6 months has passed.
All treatments are provided at: treating institution

Describe stopping criteria if the treatment does not have the intended effect or has undesirable side effects:
(when, how, consequence)
Before the 6th treatment, a response evaluation is performed. It is based on digital measurement tools and clinical assessment.
In the event of a lack of response (decrease in MADRS-S and/or PHQ-9 less than 50% plus clinical assessment), treatment is terminated and the patient is not offered maintenance treatments. This assessment is made in consultation with the consultant.

Treatment is terminated at any time during the course if the patient wishes to terminate, experiences serious side effects, loses the ability to consent, experiences psychotic or manic episodes, or no longer meets our requirements according to our exclusion criteria.

It is planned to end the treatment after 12 infusions.

Special conditions: (e.g. rare condition or special circumstances of the individual patient)
Must be completed by the applicant for the individual patient

Patient/relative's wish for the treatment and information provided that the current treatment is experimental: The patient has received information about the treatment and wishes to receive ketamine as an experimental treatment for therapy-resistant depression.

Cost of treatment: Under (drug cost, assessment of personnel load)
investigation:
- Nyemetoder.no
- Norwegian Directorate of Health/Helfo

(For medicines without a marketing authorization (unregistered medicines), please is there is no maximum profit, price may be changed, and provide the price that applies at the time of application.)

Is the drug approved by the Decision Forum or the Blue Receptor Council for other indications: Ketamine has an approved indication as a medicinal product for the induction and maintenance of anaesthesia in children and adults as the sole anaesthetic or in combination with other anaesthetics.

References:

Intravenous ketamine for treatment-resistant depression and suicidal ideation: a single technology assessment – mapping

Published by the Norwegian Institute of Public Health

Responsible Camilla Stoltenberg, Director

Authors Martin S. Larsen, Jose F. Meneses-Echavez, Hege Kornør
ISBN 978-82-8406-315-7

Publication type Method assessment

Is the patient resident (registered) in _____recording area?
Yes/no

Decision for ketamine treatment

The application

Approved by the subject director

Not approved by the subject director

Datum:

Possible justification if not approved:

The application form is saved in the patient record/DIPS of data controller. Sent to the director of

review, assessment decision. The form is considered approved if "Not approved" is deleted and and as not approved, if "Approved" is deleted by then inserting today's date approves the

director of studies and that the subject director justifies the decision

and and

6.3 Necessary investigations before start-up

- ECG with results
- Somatic examination with blood pressure and pulse
- Blood test:
  - Inflammation: CRP
  - Extended hematology: Hb, leukocytes, platelets, erythrocytes, MCV
  - Chemistry: Electrolytes
  - Kidney: Creatinine, estimated GFR
  - Liver: ALT, GGT, ALP
  - Vitamins/miscellaneous: Vit. B12, vit. D, folic acid, ferritin, HbA1c, cholesterol, LDL/HDL
  - Hormones: TSH, fT4
  - Alcohol: PEth
- Possible clearance/examinations from other fields
- Mapping of previous and current somatic diseases with allergies
- Mapping of stimulants
- Medications in use

6.4 Screening for adverse reactions

Modified KSET

(Basert på Ketamine Side Effect Screening Tool Short, Brooke, et al. "Development of the ketamine side effect tool (KSET)." *Journal of affective disorders* 266 (2020): 615-620.)

Har du opplevd en eller flere av følgende symptomer i løpet av den siste måneden?

Hvis «JA», hvor alvorlig var de? (sett sirkel rundt tall)

0= Aldri
1= Mildt
2= Moderat – forårsaket ubehag og/eller var forstyrrende
3= Alvorlig – forårsaket betydelig ubehag og /eller var sterkt forstyrrende

Dissosiasjon (f.eks. følte deg frakoblet fra selvet, kroppen, tanker, omgivelser, rar følelse og /eller fjern)	**0 1 2 3**
Hallusinasjoner (f.eks. ser, hører, lukter eller smaker ting som ikke finnes)	**0 1 2 3**
Problemer med hukommelse og/eller konsentrasjon	**0 1 2 3**
Angst	**0 1 2 3**
Rastløshet/Uro/Agitasjon	**0 1 2 3**
Forhøyet/irritert humør (eufori, uforsiktighet, økt energinivå, økt selvtillit)	**0 1 2 3**
Tar lett til tårene	**0 1 2 3**
Døsighet, utmattelse, kroppslig svakhet	**0 1 2 3**
Svimmelhet, «susete/rar» i hodet, følelsen av å skulle besvime (følelsen av at det spinner, snurrer, svinger)	**0 1 2 3**
Hodepine	**0 1 2 3**
Nummenhet og/eller prikking i deler av kroppen	**0 1 2 3**
Unormale bevegelser (f.eks. skjelving, ukoordinerte bevegelser, kramper)	**0 1 2 3**
Synsforstyrrelser/endringer (f.eks. uklart syn)	**0 1 2 3**
Hørselsendringer (f.eks. nedsatt hørsel eller tinnitus)	**0 1 2 3**
Tørr i munnen, mer spytt enn ellers, metallisk/uvanlig smak i munnen	**0 1 2 3**
Kardiovaskulært (f.eks. kortpustethet, brystsmerter og/eller hjertebank)	**0 1 2 3**
Kvalme og/eller oppkast	**0 1 2 3**
Forandringer i huden (f.eks. utslett, kløe, gul misfarging)	**0 1 2 3**
Følelsen av å være uvanlig varm, svett eller kald	**0 1 2 3**
Urinveisproblemer, hurtig/smerte/blod ved vannlating	**0 1 2 3**

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