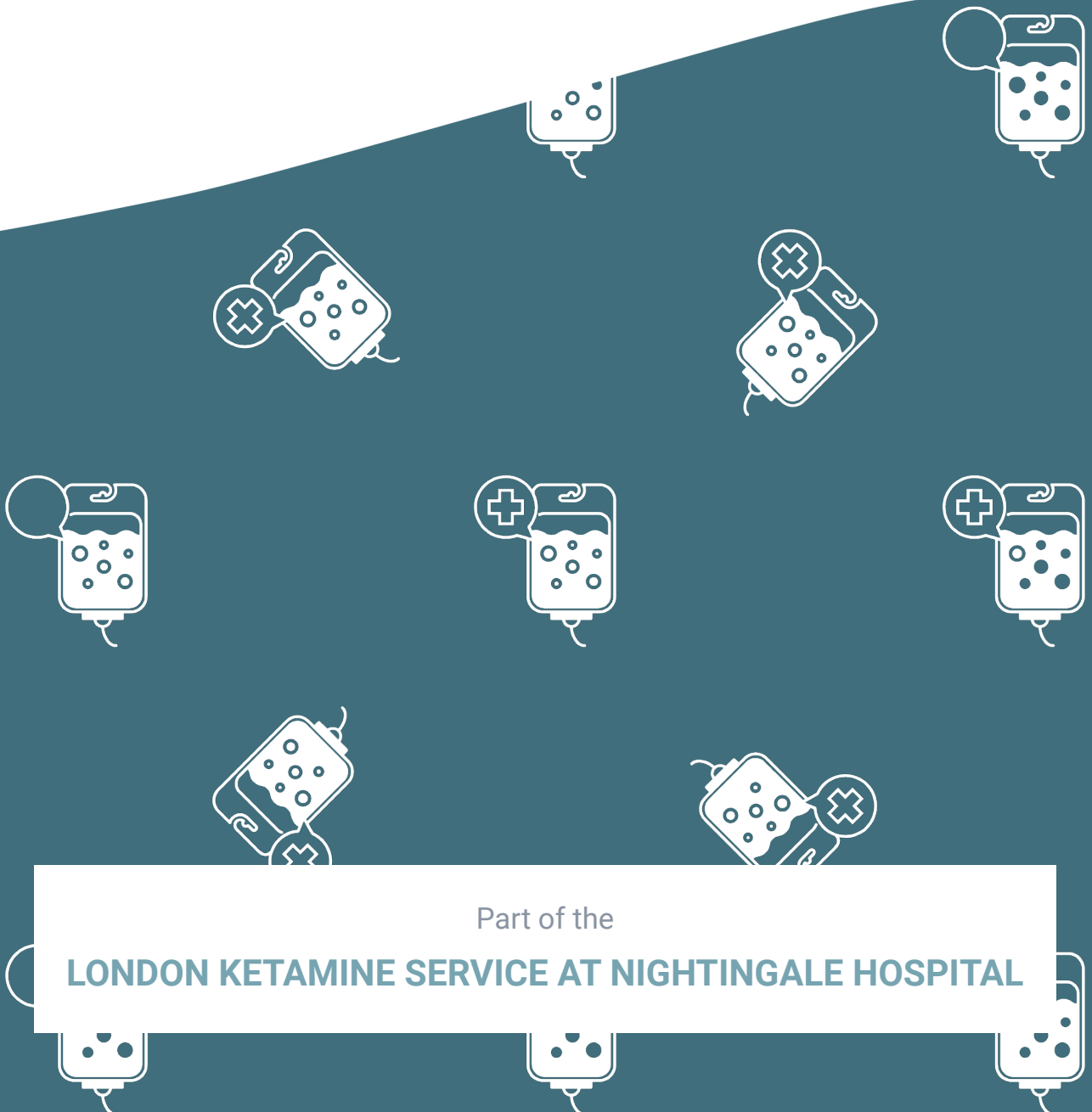


LOW-DOSE KETAMINE INFUSIONS

For depression, including treatment-resistant depression



Part of the

LONDON KETAMINE SERVICE AT NIGHTINGALE HOSPITAL

The London Ketamine Service at Nightingale Hospital offers a number of different pathways for ketamine treatment for depression, one of them being low-dose ketamine infusions.

► What is ketamine?

Ketamine was first developed as an anaesthetic medication. However in the early 2000s, researchers observed its antidepressant properties and began studying the use of ketamine to treat depression. Since this discovery, ketamine's rapid, yet brief, antidepressant effect and safety has since been established in numerous clinical trials.¹

Unlike traditional antidepressants, which work by affecting certain brain chemicals like serotonin, dopamine, and noradrenaline (known as monoamines), ketamine works in a completely different way. It targets a specific brain receptor called NMDA, which is part of the brain's glutamate system. This difference is thought to be why it is an effective treatment for depression unresponsive to other traditional antidepressants.

Ketamine can either be taken as an intravenous infusion, by intranasal administration or ingestion. The strongest evidence is for low-dose ketamine infusions closely followed by prescription nasal spray.

► How do ketamine infusions work?

The unique mechanism of action of ketamine sets it apart from traditional antidepressants.

While most antidepressants work by modulating the levels of serotonin, norepinephrine, or dopamine in the brain, ketamine targets the NMDA receptors and influences the release of glutamate. This action promotes the growth and repair of neural connections, ultimately leading to improvements in mood and overall mental health.²

► Is ketamine a licensed treatment?

Ketamine is licensed as an anaesthetic medication and for pain relief. However, despite good evidence to support its safety and effectiveness, it is not a licensed treatment for depression, and it is therefore prescribed as an 'off-label' treatment for depression.

Prescription nasal spray, which contains esketamine (the S-enantiomer of ketamine), has a licence for treatment-resistant depression in combination with an SSRI or SNRI antidepressant. It has not been approved for use in the NHS as it was not deemed cost effective by the National Institute for Clinical Evidence.

Nightingale Hospital provides prescription nasal spray for treatment-resistant depression and around 60% of people who have had this treatment at Nightingale Hospital have had a good response.

► Benefits of ketamine infusions

For patients with treatment-resistant depression, low-dose ketamine infusions can be a very beneficial option.

A recent study found that for people without psychotic symptoms, ketamine was as effective as ECT.³ Suitability for treatment is always discussed with your consultant first but this means that there are now other effective options that might be more tolerable than traditional ECT.

► Potential side effects and risks of ketamine infusions

Like any intervention, there are potential risks and side effects associated with ketamine treatment.

About 45% of individuals who have a ketamine infusion have a pleasant experience with another 45% describing their experience as neutral, neither pleasant nor unpleasant. The other 10% of individuals who have a ketamine infusion find the experience very difficult, with some people reporting worse depressive symptoms and suicidality that can persist for up to two weeks after treatment. Because of this, some people will choose not to continue with ketamine infusions.

As with all treatments for treatment-resistant depression, ketamine commonly causes brief side effects. These are more common at higher doses, but the relationship between dose and side effects is variable, even within the same patient. Studies into the side effects of ketamine are ongoing so there may be unusual side effects or long-term effects which have not yet been reported.

If you experience any side effects as a result of ketamine infusions, please speak with your ketamine clinician or consultant.

Side effects which occur during or shortly after treatment may include:

- **Dissociation:** You may experience a sensation which feels like your mind and body are disconnected. This may escalate to an 'out of body' experience or a floating sensation.
- **Ego dissolution:** Ego dissolution is a temporary state in which the boundaries between your sense of self (or 'ego') and the external world blur or disappear. While some describe this experience as one of awe, others describe it as incredibly frightening. Similarly, some describe feeling extremely small, like an atom, or vast, as if expanding into the universe.
- **Dizziness:** A feeling of unsteadiness or light headedness, similar to being mildly intoxicated.
- **Fatigue:** It is common to feel tired for the remainder of the day following treatment.
- **Altered perception:** Things 'look peculiar' or sound different.
- **Nausea or vomiting:** Some people can experience nausea during or after ketamine treatment. If you experience nausea in your treatment, anti-nausea medication can be provided at subsequent appointments if needed. We also recommend limiting your food intake for 4 hours prior to your appointment.
- **Anxiety or panic:** Anxiety and panic during infusions can occur 'out of the blue', even in people who have had previous ketamine treatments. However, anxiety typically subsides quickly as ketamine is rapidly metabolised by the body. The infusion can be turned off if necessary and anxiety usually subsides within 5-10 minutes after switching it off.
- **Headaches:** If you experience headaches during or after your treatment, these are usually manageable with paracetamol.

▶ **Tinnitus:** Tinnitus means hearing a ringing or buzzing noise that comes from inside your ear. For those who already have tinnitus, this may worsen with ketamine infusions, but it can also appear in individuals who don't have tinnitus. Experiencing tinnitus as a result of ketamine infusions is more likely if you are taking other medications which list tinnitus as a side-effect. Tinnitus usually resolves when ketamine treatment is stopped, but please speak with your consultant or ketamine clinician if you currently experience tinnitus or if you start to experience it during your treatment.

▶ **Temporary bruising:** There may be slight bruising at the site where the infusion needle was inserted.

▶ **Increased blood pressure or heart rate:** Any changes in blood pressure or heart rate are generally mild and comparable to everyday fluctuations.

As mentioned, side effects can occur with any treatment and the following table provides a comparison summary of potential side effects of the different treatments.

Side effect	ECT	Low-dose ketamine infusions	Prescription nasal spray
Dissociation	+/-	+	+
Ego dissolution	+/-	+	+
Dizziness	+	+	+
Fatigue	+	+	+
Altered perception	+/-	+	+
Memory loss	+	+/-	+/-
Nausea or vomiting	+	+	+
Anxiety or panic	+	+	+
Headaches	+	+	+
Tinnitus	+	+	+
Increased blood pressure or heart rate	+/-	+	+
Muscle pain	+	+/-	+/-

+ indicates a likely side effect

+/- indicates a rarely experiences side effect

► Criteria for treatment

Patients must:

- Currently be suffering from depression
- Have tried at least 2 different types of antidepressants for at least 6 weeks each at an adequate treatment dose
- Have tried at least one type of psychological treatment
- Have a consultant at Nightingale Hospital supervising treatment (this could be in collaboration with a psychiatrist or therapist outside Nightingale Hospital)
- Be able to travel safely to Nightingale Hospital for treatment and appointments
- Be willing and able to complete regular questionnaires online (for instance depression ratings), or have someone who can help them do this if needed
- Be able to understand the nature and purpose of the treatment, its benefits and possible side effects

Normally you should not take ketamine if you have:

- Raised intra-cranial pressure (your doctor will know if this is the case)
- Severe hypertension
- Glaucoma
- Recent history of epilepsy
- Current or recent history of psychosis
- History of drug induced manic episodes
- Used illicit substances in the last two years
- Cannot abstain from alcohol for at least three days
- Are undergoing IVF or may conceive

► The London Ketamine Service team

The London Ketamine Service at Nightingale Hospital is led by Dr Christopher Muller-Pollard, Consultant Psychiatrist.

Dr Muller-Pollard is supported by a team of doctors and nurses who administer the low-dose ketamine infusions.

► The process of ketamine infusions

An overview of the process to receive ketamine infusions is shown below with more details discussed further in this brochure.

Assessment with a consultant psychiatrist to discuss suitability (remote or in person)

Physical health assessment which includes blood tests and an ECG (in person at Nightingale Hospital)

Engage in an initial series of treatment: This is generally 3 to 6 ketamine infusions over 3 to 6 weeks

Take a break from treatment for 3 to 4 weeks

Follow up appointment with your consultant psychiatrist to discuss response and if relevant, any benefit

Consultant psychiatrist will prescribe further treatment, if appropriate

► Assessment

If you would like to be assessed for your suitability for ketamine infusion treatment, our Patient Services Team will match you with a Nightingale Hospital consultant psychiatrist who will conduct the assessment. When the assessment appointment is arranged, we will send details of the appointment along with some questionnaires which we would kindly ask you to complete prior to the appointment. Assessment meetings are usually online but can be in person if preferred.

You will then have separate appointment in the hospital which will involve a physical health check including taking your blood pressure, weight, conduct a blood tests and an ECG to ensure the treatment is safe for you to receive. You will also do a urine test to screen for any illicit substances. Blood tests will also help us establish whether there may be any metabolic or endocrine factors contributing your depression (thyroid function, folate or B12 vitamin deficiencies).

► Treatment

The initial treatment generally consists of 3 to 6 ketamine infusions over 3 to 6 weeks, usually followed by a break of 3 to 4 weeks.

Before each of your ketamine infusion appointments, we will send you a link to a brief questionnaire to complete. This questionnaire is to understand your symptoms, medications and will allow you the opportunity to advise of any changes in risk.

On the day of your treatment, please minimise your food intake within four hours of your appointment. Do not take benzodiazepines or alcohol the night before or on the day of your treatment as this may reduce the benefit.

Infusions are given by a clinician at Nightingale Hospital's ketamine suite and the whole treatment session lasts around one hour. When you arrive to the hospital, the specialist nurse will come collect you from reception. The person accompanying you will be asked to wait in the recovery area for you to complete the treatment.

During the infusion, you will be sitting on a treatment chair. A needle will be placed into a vein on the back of your hand an infusion of low dose ketamine will be given over 40 minutes. The nurse will be present throughout the infusion and will check on how you are feeling before, during and after the infusion, recording any symptoms or side affects you may experience.

During your treatments, you will be required to arrange for someone to escort you to the appointment and stay with you in the hospital for one hour after treatment. While you are in the hospital during the recovery period, we recommend that you eat and drink something before leaving.

On the day of receiving your infusions you should NOT:

- ▶ drive a vehicle or ride a bicycle
- ▶ drink alcohol
- ▶ sign any legal documents
- ▶ be responsible for looking after dependents

An improvement in mood is seen in more than 50% of patients to the extent they choose to continue receiving low-dose ketamine infusions. Meanwhile, the majority relapse at some point but then respond again with further treatment. As with conventional antidepressants, regular treatment over several years is often needed.⁴

Please note, filming, recording or photography of any kind is not permitted.

▶ What happens after the initial series of treatment?

Most people who initially benefited to ketamine relapse during the 3 to 4 week break because the average duration of benefit of ketamine is 10 days. The reason we recommend the break from treatment is to better understand whether ketamine has resulted in a benefit, as well as the size and duration of the benefit. If you responded to the initial course of ketamine, you are very likely to respond when you resume treatment.

▶ Follow up

After the initial series of 3 to 6 treatments, around four weeks after your last infusion, you will have a 30-minute follow-up appointment by telephone or video with your consultant psychiatrist to review your response and to discuss the next steps for treatment.

Further treatment includes either:

- ▶ Infusions every 4-8 weeks (this is the most common initial pattern)
- ▶ Infusions as-and-when required

For those who have not responded to ketamine infusions, further ketamine treatment is not indicated and other options such as other pharmacotherapy, rTMS, ECT, or bright light therapy will be explored.

The decision about these options will depend on a wide range of factors and will be discussed in the light of your response to ketamine.

▶ Further follow up

After every sixth intravenous infusion, your consultant psychiatrist prescribing treatment will review your treatment. These appointments will last 30 minutes and can be in person or by video.

▶ If you are worried

If you are worried about your treatment or any side effects you are experiencing, please speak to the Ketamine Team. The Ketamine Team can be contacted Monday – Friday between 9am and 4pm on ketamine@nightingalehospital.co.uk.

Please note, we will endeavour to get back to you as soon as possible, but outside of these times and in the case of an emergency, please contact emergency services on 999 or your local A&E.

References

- ¹ McIntyre, R.S., et al. (2021). Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation, *American Journal of Psychiatry*, 178(5), 383–399. doi: 10.1176/appi.ajp.2020.20081251.
- ² Shinohara, R., Aghajanian, G.K. and Abdallah, C.G. (2021). Neurobiology of the Rapid Acting Antidepressant Effects of Ketamine: Impact and Opportunities. *Biological Psychiatry*, Volume 90, Issue 2P85-95, doi: 10.1016/j.biopsych.2020.12.006.
- ³ Anand, A., et al., (2023). Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. *The New England Journal of Medicine*, 388(25), 2315-25. doi: 10.1056/nejmoa2302399.
- ⁴ Murrugh, J.W., et al., (2013). Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression. *Biological Psychiatry*, 74(4), 250–256. doi: 10.1016/j.biopsych.2012.06.022.
O'Brien, B., et al., (2023). Replication of distinct trajectories of antidepressant response to intravenous ketamine. *Journal of Affective Disorders*, 321, 140–146. doi: 10.1016/j.jad.2022.10.031.

Referral and treatment commencement

To access low-dose ketamine infusions, you must be under the care of a Nightingale Hospital consultant psychiatrist, and they must assess your suitability before you can be referred for treatment.

If you are already under the care of a Nightingale Hospital psychiatrist, please contact their practice to discuss your suitability and if appropriate, a referral for low-dose ketamine infusion treatment.

If you are not under the care of the Nightingale Hospital psychiatrist, please contact our Patient Services Team who will organise an assessment for you with one of our consultants.

For more information, or if you have any questions about this treatment, please contact the London Ketamine Service Team via email or telephone.

London Ketamine Service Team
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Patient Services Team
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