

The Royal College of Emergency Medicine

Best Practice Guideline

**Suspected nitrous
oxide toxicity in
Emergency
Departments**

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Summary of recommendations

1. Patients presenting with neurological abnormalities without obvious cause should have nitrous oxide considered as a potential cause for their symptoms.
2. Systems should be in place to allow samples for homocysteine and methylmalonic acid analysis to be obtained in Emergency Departments. It is acknowledged that the result may take several days to return, and clear local protocols for ownership of these delayed results by whichever specialty is providing ongoing care are required.
3. Emergency Medicine clinicians have a role to play in promoting consideration of nitrous oxide toxicity and can support diagnosis by ordering the correct investigations early in the patient's journey.
4. The majority of Emergency Medicine investigation is likely to focus on exclusion of other causes of neuropathy.
5. If a diagnosis of nitrous oxide toxicity is suspected, treatment should be initiated before the return of definitive diagnostic results.
6. Patients presenting with potential consequences of drug use should have a full drug and alcohol history taken, and be offered referral to drug/alcohol liaison services. Nitrous oxide should be specifically asked about as patients may not consider it a 'drug'.

Scope

This scope of this guideline is limited to unregulated nitrous oxide (N₂O) use. It does not relate to use of Entonox or delivery of anaesthesia, and is not applicable in settings other than Emergency Departments (EDs).

The process of creating this guideline has included contemporaneous literature reviews for high-level evidence in the medical literature on all aspects of N₂O toxicity, as well as searches for consensus agreement publications where they exist. The guideline group have formed consensus on areas lacking clear answers.

Background

N₂O is a short-acting anaesthetic agent, with a history of recreational use preceding any use in anaesthesia.ⁱ

The UK has historically seen some of the highest rates of N₂O use amongst people who use drugs.ⁱⁱ In the year ending Mar 2020, use in the last 12 months was reported by 2.4% of adults age 16-59, and 8.7% of adults age 16-24.ⁱⁱⁱ The most recent data (June 2022) has seen significant reductions in reported use, but these estimates are based on a smaller sample and reduced data collection period. The lag period in reporting national statistics means it is challenging to understand the current landscape of drug use in the UK.

The National Poisons Information Service has seen a rise in enquiries related to N₂O over the last decade, but the total number of enquiries remains low.^{iv} Reflecting this signal of relatively low harm compared to many other drugs, in the last 20 years, N₂O has been responsible for 56 deaths in England and Wales. While every death is a tragedy, these numbers are small in the context of all England and Wales drug misuse deaths (3060 to year end Mar 2021 alone).^v

It is likely that rates of use are higher in younger people who use drugs (age 16-24) and there is a male:female user ratio of approximately 3:2.ⁱⁱ

More recently, anecdotal evidence suggests an increase in hospital admissions related to N₂O chronic toxicity, with suggestions of a link to heavier use and/or the availability of significantly larger N₂O canisters.^{vi}

There are a number of mechanisms by which N₂O use may result in presentations to EDs and this guideline has been written to bridge the current gap between evidence and the need for emergency clinicians to provide quality care and advice to patients suffering consequences of use.

Acute toxicity/harm

Acutely, the following have been reported:

1. injuries secondary to intoxication or syncope
2. hypoxia and asphyxiation (leading to arrhythmias, seizures, hypoxic brain injury, or death)
3. barotrauma (pneumothorax, pneumomediastinum, tympanic membrane rupture)
4. confusion, hallucinations
5. vomiting with aspiration
6. cold injuries to the lips or mucosa

Typically, there is no specific toxicological management, and as the assessment and management of these harms does not require modification of core Emergency Medicine skill sets, they are not discussed further in this guidance.

Chronic toxicity/harm

Presentations related to chronic harms are typically associated with long-term high-frequency use, though some patients can present following use of high amounts of N₂O over a shorter period of time.

Consequences of chronic N₂O toxicity are classically either neurological (sensory, motor, or co-ordination deficits) or haematological (megaloblastic anaemia).

The toxicity from chronic N₂O use relates to oxidation of the cobalt ion within cobalamin (vitamin B12), which renders it functionally inactive. This inactivation leads to a reduction in methionine synthase activity which:

1. prevents the conversion of homocysteine to methionine by methionine synthase (MS), reducing myelin production.
2. prevents the conversion of 5-methyl-tetrahydrofolate to tetrahydrofolate impacting on DNA synthesis.

Additionally, inactivation of cobalamin reduces the activity of the mitochondrial enzyme, methylmalonyl-CoA mutase (MMCoAM), leading to increased methylmalonic acid (MMA) concentrations, which can lead to demyelination.

Greater exposure to N₂O, being female, and younger age have been associated with an increased risk of symptoms.^{vii} There is also a suggestion that those potentially at risk of low vitamin B12 levels (e.g., people following a vegan diet) may be at higher risk.

Signs & symptoms

Patients presenting with neurological abnormalities without obvious cause should have N₂O considered as a potential cause for their symptoms. Patients may present with any of:

- sensory deficits (either in a classic peripheral neuropathy pattern, or with isolated areas of numbness or paraesthesia)
- motor deficits (classically described as predominantly lower limb, or with issues relating to fine motor control)
- ataxia
- urinary retention
- erectile dysfunction
- non-specific symptoms such as confusion, or personality change (including low mood or irritability)^{viii}

Patients presenting with haematological abnormalities consistent with vitamin B12 deficiency should have N₂O considered as a potential cause for their symptoms:

- anaemia
- macrocytosis
- agranulocytosis or pancytopenia

Investigation

The majority of investigation is likely to focus on exclusion of other causes of neuropathy. However, Emergency Medicine clinicians have a role to play in promoting consideration of N₂O toxicity, and can support diagnosis by ordering the correct investigations early in the patient's journey.

It is important to understand that because N₂O oxidises cobalamin rather than destroying it, vitamin B12 levels may be normal, even if cobalamin is not functional.^{ix}

It is therefore important to look for other indications of poor cobalamin function:

- The reduced function of MS leads to increased homocysteine levels.
- The reduced function of MMCoAM leads to increased methylmalonic acid levels.

<p>Available immediately</p>	<ul style="list-style-type: none"> • Full neurological examination of central and peripheral nervous system • FBC* • Renal function, electrolytes, LFT • Thyroid function tests • Vitamin B12* • Folic acid* • ECG <p>*While these tests may demonstrate features of folate/B12 deficiency (anaemia, macrocytosis, etc.), they may be falsely reassuring.</p>
<p>Need to be taken prior to treatment in Emergency Dept. as diagnostic (but may take several days)</p>	<ul style="list-style-type: none"> • Homocysteine** • Methylmalonic acid** <p>**These tests should be sent from the Emergency Department, as tests undertaken after treatment has commenced may have normalised. However, if the patient is not being admitted to hospital, there should be a clear local protocol for specialty ownership of results. It is suggested that the biochemistry laboratory are consulted prior to obtaining these, as sampling procedures may vary between providers.</p>
<p>Not always needed in Emergency Dept. and may be normal</p>	<ul style="list-style-type: none"> • CT head • MRI brain/spine⁸

Management

This patient group may be candidates for Same Day Emergency Care (SDEC), acute neurology, or similar ambulatory pathways, but the patient should be discussed with the appropriate specialty if there is a concerning differential, or red flag symptoms:

<ul style="list-style-type: none"> • Vision changes • Recent infective illness • Ascending symptoms • Labile blood pressure • Tachycardia or arrhythmia • Immunosuppression • History of cancer • Back pain • Fever • Features of cauda equina syndrome <p><i>Symptoms adapted from Paris et al.¹</i></p>
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If a diagnosis of N₂O toxicity is suspected, treatment should be initiated before the return of definitive diagnostic results. A suggested regime is given below.

- Vitamin B12 1mg intramuscular once daily
- Folic acid 5mg orally once daily

There will be a spectrum of severity in presentations and the certainty regarding diagnosis. Hospital admission may be required.

Some Emergency Departments have established outpatient pathways for the care of these patients.

If it is felt that the patient can be safely discharged for follow-up, the following are suggested (for adaptation to local services as required):

1. Appropriate urgent follow-up clinic within 7 days for review of baseline investigations, review of need for ongoing treatment and consideration of alternative diagnoses if not improving (e.g., SDEC return clinic, hot acute medical clinic, hot neurology clinic).
2. A way of contacting the follow-up service if an appointment is not received as expected. (e.g., a telephone number or email address)
3. Clear advice to stop using N₂O immediately, and to return to the Emergency Department if there is any deterioration in symptoms.
4. A method of administering intramuscular vitamin B12 injections (patients may be able to receive training in self-administration).
5. Appropriate supply of medication to cover out-of-hours periods.
6. A full drug and alcohol history, and an offer of referral to drug liaison services.

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Endorsements

None

Review

Usually within three years or sooner if important information becomes available.

Declarations of interest

David Wood: Member of UK Advisory Council on the Misuse of Drugs (ACMD) and the ACMD Nitrous Oxide Working Group.

Disclaimers

The College recognises that patients, their situations, Emergency Departments and staff all vary. This guideline cannot cover all possible scenarios. The ultimate responsibility for the interpretation and application of this guideline, the use of current information and a patient's overall care and wellbeing resides with the treating clinician.

Appendix 1: Patient information

Specific safety-netting advice regarding cessation of N₂O use and to return in case of deterioration in symptoms should be offered to patients with suspected N₂O toxicity if being managed as outpatients.

However, as with any Emergency Department presentation following drug use, it is important that the consultation be seen as an opportunity to educate and reduce future harms, rather than stigmatise or criticise.

The below text is offered for inclusion in departmental advice leaflets for all patients who report use of nitrous oxide, reproduced and adapted with permission from Drug Science (www.drugscience.org.uk):

What is nitrous oxide?

Nitrous oxide (N₂O), commonly known as 'laughing gas' or 'nos', is an anaesthetic gas with pain-relieving and anti-anxiety properties. It has been used recreationally and in medicine for over 200 years. It has become widely and easily available for recreational use as it can be legally bought and sold for the purpose of making whipped cream. However, as of 2016, it is illegal to possess nitrous oxide with the intent to sell for use of its psychoactive properties.

What are the effects of nitrous oxide?

When someone inhales nitrous oxide, the gas rapidly dissolves into the bloodstream, and reaches the brain within seconds. A rush of dizziness and euphoria is commonly reported, and people often burst into laughter. Sound distortion also occurs.

Hallucinations are possible, from simple moving bright dots to complete detailed dreamscapes, although most users do not experience complex hallucinations. Due to the anaesthetic properties of the gas, coordination and awareness are strongly affected, and users may fall over if they are not sitting or lying down. The effects are short lasting, wearing off within two minutes. Nitrous oxide also reduces anxiety and pain.

Additionally, when purely nitrous oxide is inhaled recreationally, the gas displaces air in the lungs, temporarily preventing much or any oxygen from reaching the blood. This may cause the heart to beat faster, and limbs to feel tingly or heavy.

What are the risks of using nitrous oxide? Can they be avoided or reduced?

Using nitrous oxide is relatively low risk, however, it is still very important to be aware of the risks involved, and what you can do to avoid or reduce them.

Oxygen starvation

Inhaling nitrous oxide prevents oxygen from entering the lungs and therefore the bloodstream. This can lead to oxygen starvation which can be fatal when extreme. Some methods of inhaling nitrous oxide can increase the risk of experiencing extreme oxygen starvation. For example, inhaling directly from a canister; inhaling in an enclosed space; placing a bag over one's head to inhale; filling a room with the gas; or using a medical mask to inhale.

Frostbite

When the gas is released from its highly pressurised container, the gas and metal briefly become very cold (around -40°C). Exposure of tissue to this extreme cold can result in frostbite. Therefore, it is important to take care when opening a canister, and important to not inhale directly from the canister, as this can cause frostbite of internal tissues.

Injury from falling

As inhaling nitrous oxide causes dizziness, it is possible that people may lose balance and fall after inhalation, leading to injury. To prevent this, nitrous oxide should only be inhaled when sitting or lying down.

Heart problems

People with heart conditions or abnormal blood pressure may be at higher risk as the drop in oxygen levels caused by inhaling nitrous oxide raises the heart rate and can cause arrhythmias (skipped heartbeats). This could lead to cardiac arrests in susceptible people.

Addiction

Due to the short-lasting effects of nitrous oxide, people are often tempted to take multiple doses over a short period of time. It is possible for people become psychologically addicted to nitrous oxide and find it difficult to resist taking it every day. Those with existing mental health conditions may be at additional risk of addictive behaviours.

Nerve damage or problems with the blood

Regular heavy use of the drug can lead to vitamin B12 deficiency. As vitamin B12 is essential for maintaining the nervous system, abuse of nitrous oxide can lead to nerve damage. Symptoms of nerve damage include tingling and numbness in fingers and toes and weakness of the arms and legs. Treatment with high doses of B12 is effective, but some damage can be irreversible. It is likely that less severe vitamin B12 deficiencies caused by nitrous oxide overuse can go undiagnosed, but cause other symptoms, such as depression, forgetfulness, and tiredness.

Harm reduction advice when using nitrous oxide

Avoid mixing drugs

As with all drugs, mixing nitrous oxide with other substances increases the risks. Therefore, it is not advised to mix nitrous oxide with any other drugs, especially alcohol. It is possible that risks could be greater with stimulants and any other drugs that put pressure on your heart, as effects on blood pressure and heart rate could be unpredictable.

Nitrous oxide can, allegedly, briefly multiply the effects of psychedelics like LSD (acid) and psilocybin (magic mushrooms) or bring the effects back strongly when the drug is wearing off, which could be very frightening if unexpected.

Using a balloon

Using a balloon, with caution, is the least risky way to use nitrous oxide. Here, the gas is dispensed into a balloon from which a user inhales and exhales repeatedly until they have inhaled enough, or the gas runs out.

If oxygen levels in the body drop to the degree where the user is close to losing consciousness, they will be unable to hold the balloon to their lips and will automatically begin to breathe air again. This safety mechanism minimises the risk of death by suffocation. Paying attention to any discomfort and not resisting the urge to breathe normal air will minimise the chances of harm of any kind.

Choosing the right setting

The risks of getting hurt if you fall or lose coordination and awareness when taking nitrous oxide can be minimised by sitting down away from hard edges and other hazards.

Never try to fill a space with the gas

Never attempt to fill a room, car, bag over someone's head, or any enclosed space with nitrous oxide. This can lead to fatal oxygen starvation.

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