Novel Psychoactive Treatment UK Network

NEPTUNE

Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances

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Inspiring Improvement

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Chapter 5

Nitrous oxide

Drug group: depressant/dissociative/inhalant

5.1. Street names

Street names at the time of publication include: Laughing Gas, Hippie Crack, Whippets (cartridges of nitrous oxide), Chargers, Bulbs.

Other names may be used locally.

5.2. Legal status

In the UK it is legal to sell nitrous oxide to people aged over 18 but not under if may be assumed that they are likely to be inhaling it. The sale of nitrous oxide for catering and other legitimate reasons is legal, although its sale in gas-filled balloons or canisters intended for human recreational use violates the Medicines Act.[1]

5.3. Quality of the research evidence

The evidence on the management of the acute and chronic harms associated with the recreational use of nitrous oxide is limited, consists mainly of case reports, with occasional experimental studies into acute effects. There are few findings on acute harms and interventions relating to the use of the drug, but consistent findings on the chronic effects of prolonged nitrous oxide use.

5.4. Brief summary of pharmacology

Nitrous oxide is a gas whose pharmacology is not well studied and existing evidence is not conclusive. It has been suggested, however, that opioid receptors may be responsible for its analgesic properties[2] and a study has shown that naloxone inhibits its analgesic effects.[3] Furthermore, nitrous oxide may act as an N-methyl-D-aspartate (NMDA) antagonist, similar in nature to ketamine, another anaesthetic (Chapter 4).[2] It works primarily via the opiate system, mediating the release of beta-endorphins and directly binding to mu, delta and kappa opiate receptors.[4] Nitrous oxide is used clinically as an anaesthetic gas with pain-relieving properties.

It is also a 'dissociative' drug. Although the effects of the drug on the brain are not fully understood, its dissociative effects are probably caused by preventing the normal action of the NMDA receptor.

Nitrous oxide is rapidly absorbed via pulmonary circulation.[4] Due to high lipid solubility it passes easily through the blood–brain barrier and has a rapid onset of action; it is cleared from the body within a few hours.[5]

The use of nitrous oxide leads to vitamin B12 depletion, which is believed to be due to its effect on cobalt in vitamin B12, whereby the vitamin is converted from an active, monovalent form to an inactive, bivalent form.[6]

5.5. Clinical and other legitimate uses of nitrous oxide

Nitrous oxide has been used as a medical anaesthetic for over 150 years and continues to be widely used for medical, dental and veterinary purposes. It is also used for analgesia and can help relieve anxiety. It is used in various settings, including ambulances, emergency departments, relief for women in labour and in dentistry, where its short duration of action is an advantage.[1] The use of nitrous oxide in anaesthesia, however, has long been challenged because of the hazards posed to both clinicians through unintended occupational exposure and patients by its haematological, neurological, myocardial and immunological effects, and because it can lead to postoperative nausea and vomiting and expansion of air-filled spaces.[7]

Nitrous oxide has been shown to ameliorate craving and withdrawal symptoms from alcohol, opioid, nicotine, cocaine and cannabis.[8–13]

Outside of human and animal applications, nitrous oxide is used as a fuel additive, as an oxidising agent to increase the power of cars, as a component of rocket fuel, as an aerosol dispersant and in the catering industry in the dispensing of whipped cream. This forms the basis of its legal sale on websites in the form of small canisters or larger tanks, which are labelled with 'approved for food use' and not intended for recreational use.[1]

5.6. Prevalence and patterns of use

The use of nitrous oxide for recreational purposes is not new, as 'laughing gas parties' were popular in Victorian times, mostly in the context of variety performances in music halls, theatres and carnivals. There is anecdotal evidence that nitrous oxide is currently popular for use in some clubs and music festivals, where it is bought as gas-filled balloons. This has led to moves by the Medicines and Healthcare Products Regulatory Agency (MHRA) to control the drug's supply under section 52 of the 1968 Medicines Act.[14]

The use of nitrous oxide for recreational use was recorded in the Crime Survey for England and Wales (CSEW; formerly the British Crime Survey) for the first time in 2012/13. The 2013/14 CSEW found that:

- 2.3% of adults aged 16–59 had taken nitrous oxide in the last year;

- 7.6% aged 16–24 had taken nitrous oxide in the last year.

This prevalence was not significantly different from that in the previous year.

The 2011/12 *MixMag* Global Drug Survey reported lifetime recreational use by 49.6% of UK respondents and past-year use by 27.2%, and past-year use by 43% of UK regular clubbers.[15] The 2011 report from the UK Advisory Council on the Misuse of Drugs (ACMD) on novel psychoactive substances presented anecdotal evidence of widespread use at the Glastonbury Festival in 2010.[1]

Wood et al. investigated the use of nitrous oxide among 330 men who have sex with men (MSM) in gay-friendly London clubs. Levels of use reported were lower than those reported in the Global Drug Survey, with 28.1% reporting lifetime use and 11.9% use in the previous year.[16]

5.7. Routes of ingestion and frequency of dosing

Nitrous oxide is used for its euphoric effects. The onset of the effects is immediate and they last for approximately two minutes; users may take many 'hits' over a few hours.

Nitrous oxide is a colourless gas that is slightly sweet smelling and tasting. It is typically inhaled, sometimes referred to as 'nagging', commonly from balloons or steel bulbs. The latter (sometimes called chargers) are small cartridges containing highly pressurised nitrous oxide that are available from catering suppliers and used for whipped cream. These containers or cylinders are sometimes referred to as whippet/whippit. Cylinders vary by brand, but are approximately 6 cm long, 1.8 cm wide and have a wall approximately 2 mm thick to withstand the pressure of the gas. Most contain approximately 8 g of nitrous oxide under pressure and are non-refillable.

These 'bulbs' are supplied with a dispenser into which, when fitted, they release their compressed gas. If the dispenser is not filled with cream, the nozzle simply releases the gas only. A balloon can be placed over the nozzle to capture the nitrous oxide.[14] Alternatively, 'whippets' can be opened with the 'cracker' on the cream dispenser and the nitrous oxide again released into a balloon, from which it then can be inhaled.

Both whippets and crackers can be obtained from online suppliers and in 'head shops'. The quality (purity) of the nitrous oxide depends on its source. Products intended for food use are of higher quality, especially if they originate from the UK. Products for industrial use may be adulterated or impure. Regular and long-term users of nitrous oxide in particular should be aware of impurity. The typical cost at the time of writing is £3 for a balloon-full, but it seems to be common to buy in bulk, for parties, at around 24 chargers for £10, which is less than 50p a balloon.*

* This was ascertained by searching a listing of small advertisements for the London area (http://www.gumtree.com/other-kitchen-appliances/london/nitrous+oxide).

Nitrous oxide is also available in much larger gas cylinders intended for medical or industrial use. The use of these, for purposes other than those intended, can be dangerous. Unsafe methods include breathing directly from a cylinder using a face mask, opening a cylinder tank in a car or small room or filling a bag with the gas and putting it over the head. Cylinder tanks of nitrous oxide intended for cars can contain harmful contaminants like sulphur dioxide.

Case studies have shown that the average number of containers/whippets inhaled in a session is usually fewer than 5;[17] for example, a survey of students in Auckland found that recreational use typically amounted to 2–5 containers in a session.[18] However, other studies report a range of 10–100 bulbs used in one session.[17–28] Recreational users will typically inhale a number of small, imprecise doses from small containers and consequently it may be difficult to assess the quantity of nitrous oxide.

An experimental study testing the effects of nitrous oxide in 12 volunteers found that the primary effects were found only at the inhalation of 20% to 40% concentrations.[29] At the inhalation of 40% nitrous oxide (the highest concentration tested), subjects were confused, sedated, high, dysphoric and stimulated, but fatigue and depression were observed once the effects had worn off.

As nitrous oxide is used as an anaesthetic, official advice has been issued on the short-term occupational exposure limit, to avoid harms. The advice on this ranges from 25 parts per million (ppm) to 100 ppm,[7] and may provide an indication of the level at which harms can occur in recreational users. The harms resulting from nitrous oxide are largely determined by its mode of use rather than its direct physiological effects. Inhalation through balloons or canisters is relatively safe, whereas the use of airtight bags, masks or respirators carries a high risk of asphyxiation.[14]

5.8. Desired effects of nitrous oxide for recreational use

Nitrous oxide is used recreationally to induce euphoria. Its effects are very short-lasting and typically include a rush of dizziness, relaxation, laughing fits, auditory distortions and sometimes hallucinations. As an anaesthetic gas, it affects coordination and awareness. It is reported that some people use it to self-manage pain and anxiety. Nitrous oxide consumption also reduces psychomotor performance.[30]

There is variability in the subjective effects of the drug. In one study, 12 individuals (under controlled, blinded conditions) were given a choice between oxygen and nitrous oxide after a sampling period for both. There was significant individual variability in the reported effects of the drug. Those who reported feelings of 'tingling', 'drunk', 'dreamy', 'coasting', 'floating' and 'having pleasant bodily sensations' during the nitrous oxide sampling period chose nitrous oxide more often during the choice period.[30]

There is disagreement in the literature as to whether there are gender differences in the effects of nitrous oxide.[29,31]

5.9. Mortality

A number of cases of death by asphyxiation are reported among individuals who were using nitrous oxide at the time. Although nitrous oxide does not depress the respiratory drive significantly, the normal physiological response to hypoxia is blunted when 50% nitrous oxide is given and deaths are often in relation to bags put over the head in order to facilitate inhalation[32] or inhalation in cars.

5.10. Acute harms

5.10.1. Acute toxicity

The 2011 ACMD report on novel psychoactive substances suggested that nitrous oxide typically has few short-term adverse effects, other than headache for some.[1] Harms are likely to result from disorientation and unsteadiness caused by inhalation (e.g. falling down[29]). There are also isolated instances in the literature of hypothermic skin trauma resulting from contact with chilled canisters.[33]

Nonetheless, acute exposure to nitrous oxide may irritate the respiratory tract and acute use of inhalants in general can result in sneezing, coughing, excess salivation and conjunctival erythema.[4] It can also cause asphyxia, headache, nausea, vomiting,

Box 5.1. *Features of acute intoxication with nitrous oxide*

Respiratory effects
Asphyxia
Hypoxia

Neurological and psychiatric effects
CNS depression
Convulsions
Psychiatric symptoms
Headache
Myeloneuropathy
Polyneuropathy
Dizziness
Excitement
Paraesthesias
Paralysis
Psychosis

Cardiovascular effects
Hypertension
Cardiac dysrhythmias
Megaloblastic anaemia
Leukopenia
Anoxia

Metabolic features
Thrombocytopenia

Gastrointestinal symptoms
Nausea and vomiting

dizziness and excitement, and to central nervous system (CNS) depression, convulsions and death. Hypertension and cardiac dysrhythmias are possible. Patients can present with altered mental state, paraesthesias, ataxia and weakness or spasticity of the legs.[7] Nausea, cyanosis and fainting have been reported as a result of nitrous oxide.[34] The features are summarised in Box 5.1.

When nitrous oxide is inhaled from a balloon it displaces the air in the lungs, thus temporarily preventing oxygen from entering the bloodstream and potentially causing tachycardia and transient peripheral neurological symptoms. There have been reports of fatalities after acute exposure, due to asphyxiation.[35,36]

Nitrous oxide is insoluble in blood, and therefore rapidly clears into the alveoli from the blood once inhalation has ceased.[37] At the high concentrations (e.g. >70%) used in anaesthesia there is the potential for hypoxia if a high concentration of oxygen is not then provided. Nitrous oxide may have effects on immune function, but the evidence is unclear on this issue.[7]

There is a risk that users may confuse the much more toxic or potent gases or volatile substances, such as butane, with nitrous oxide. If a patient requires admission to an emergency department, there is a chance that he or she has used butane, which does not only have different effects but also different harms. The use of nitrous oxide is not as life-threatening as the use of butane, which can cause arrhythmia and increases the risk of sudden cardiac arrest. Life-threatening risks of nitrous oxide are linked to mode of use, which may lead to hypoxia or anoxia.

5.10.2. Acute withdrawal

For withdrawal see section 5.12.1.1.

5.10.3. Poly-drug use and drug interactions

There may be some increase in the effects of nitrous oxide when it is combined with alcohol.[38] It is possible that nitrous oxide ingested at the same time as stimulants has a greater effect on blood pressure and heart rate. There is anecdotal evidence that nitrous oxide can briefly enhance the effects of psychedelics like LSD, or bring the effects back strongly when the drug is wearing off, which could be very frightening if unexpected.

As it is not metabolised by the liver, the potential for drug interactions with other agents, including antiretrovirals, is very low.

5.11. Clinical management of acute toxicity

5.11.1. Identification and assessment of acute toxicity

The diagnosis of acute nitrous oxide toxicity should be made by clinical assessment. There are no rapid urine or serum field tests, so analytical assessment should not be

For up-to-date guidance on the management of nitrous oxide acute toxicity, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.toxbase.org/Poisons-Index-A-Z/N-Products/Nitrous-oxide/

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

considered a component of routine diagnosis. Assessment should be based on the recognition of the clinical toxidrome associated with nitrous oxide and the potentially harmful modes of use.

5.11.2. Clinical management of acute toxicity

The management of acute harms resulting from nitrous oxide include removal from exposure and providing symptomatic treatment for any resultant problems. TOXBASE® recommends observation for at least one hour after exposure and a need to perform a 12-lead ECG and a full blood count in symptomatic patients. Where there is chronic use of nitrous oxide, it is recommended that B12 concentration is checked in symptomatic patients (see section 5.12.2).

5.12. Harms associated with chronic use and dependence

5.12.1. Dependence

There are currently no reported instances of nitrous oxide dependence in the literature, and it has been suggested that its addictive potential is low as it is only a partial opiate agonist and its euphoric effects fade rapidly. [20] However, as the effects are short-lasting and pleasurable, people may use it re-dose frequently. There is anecdotal evidence of psychological dependence, and daily use of nitrous oxide should be avoided in particular by people with mental health problems or other psychological vulnerability. [39]

5.12.1.1. Withdrawal

Nitrous oxide is sometimes used in a compulsive way by some individuals, possibly explaining one of its street names, 'hippie crack'. There are no significant withdrawal symptoms aside from the desire to use more nitrous oxide.

5.12.2. Other harms – vitamin B12 deficiency

The harms caused by nitrous oxide tend to stem from heavy usage and specifically the depletion of vitamin B12 by oxidising the cobalt moiety of the vitamin.[23,40,41] By inactivating vitamin B12, a critical cofactor in haematopoiesis and lipid membrane formation, nitrous oxide can cause anaemia and neuropathy; severe myeloneuropathy is one complication of nitrous oxide use.[23]

Regular or long-term use of nitrous oxide has been associated with leukopenia, thrombocytopenia, myeloneuropathy[23] and vitamin B12 deficiency leading to severe megaloblastic anaemia.[42] It can also lead to neurological complications and psychiatric symptoms, including psychosis, paralysis, paraesthesiae and sensory loss, though these can respond to vitamin B12 replacement. One case report has described peripheral neuropathy[43] and a number of others have given details of myelopathy[5,17,23,24,26,44–49] and polyneuropathy[43] as a result of sustained nitrous oxide misuse and associated vitamin B12 deficiency. This has been seen to present with paralysis[21] and ataxia,[23] and may be confused with Guillain–Barré syndrome.[26] A case report of cardiac arrest has been published.[21]

Although the evidence is limited, it is possible that nitrous oxide can worsen some mental health problems, and its use has been linked to manic relapse.[50] One case report describes a psychotic episode occurring in a patient with no history of psychosis who had been regularly using nitrous oxide.[42]

There is a growing body of evidence, mainly from animal studies, that nitrous oxide may have some neurotoxic effects. Rat studies suggest long-term developmental issues such as memory impairment, but the long-term cognitive outcomes in humans remain unknown.[2]

5.13. Management of harms related to chronic use

Suggested treatment for the chronic harms related to the use of nitrous oxide resulting from vitamin B deficiency include parenteral folinic acid,[23,44] intramuscular vitamin B12 injection[17,23,43,45,47] and intravenous methylprednisolone.[5] A number of studies have shown that stopping exposure and introducing vitamin B supplementation may result in either partial or complete recovery, although this can take months.[45] A case report suggests that where symptoms persist, methionine treatment has been successful where B12 treatment alone has failed.[51]

One case report has highlighted the need to consider vitamin B12 deficiency in patients who arrive at a hospital with psychiatric manifestations who report a history of nitrous oxide exposure or misuse in the recent or remote past.[42]

5.13.1. Psychosocial and pharmacological support

There is no relevant pharmacological support. For psychosocial support, see Chapter 2.

5.14. Harm reduction and public health

The inhalation of nitrous oxide through the balloon method may carry less risk than other methods and minimises the risk of anoxia. Users will drop the balloon if they are getting too hypoxic or lose consciousness. Other methods may carry more risk, in that the user may become unconscious through anoxia and continue to have insufficient access to oxygen.

The following harm reduction measures have been identified:[14]

- Users should always inhale nitrous oxide from a balloon – never from a tube or mask, or directly from a dispenser or compressed air tank.
- Users must be careful not to confuse nitrous oxide with other gases and volatile substances, which have far greater risks.
- Users should avoid inhaling while standing up and should be aware of their immediate surroundings (e.g. steep drops, fires, rivers).
- The use of nitrous oxide should be avoided in particular by people with problems with low blood pressure or any mental health issues.
- Users should stop inhaling if they feel any physical discomfort, such as 'pins and needles' or numbness.
- Regular and long-term users of nitrous oxide in particular should be aware of the purity of the products they use and of the impact of any impurities.

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