



Nitrous Oxide (N₂O)

A briefing for professionals

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1. Background to current situation: Nitrous oxide (N₂O for short) is a colourless, slightly sweet smelling, non-flammable gas, first discovered in 1772. N₂O became a popular recreational drug because of its euphoric effects and much later came to be widely used in dentistry and during childbirth for its mild anaesthetic and analgesic effects (Gilman, 2019; Ruston, 2022).

The contemporary resurgence in recreational use of N₂O has predominantly revolved around the sale of single-use finger-length steel cartridges containing 8 grams of pressurised gas, disingenuously sold from shops and websites for making whipped cream (fig 1). The recent availability and popularity of much larger 600+ gram tanks containing 80+ times the amount of N₂O, along with reports of an increase in neurological and other problems are currently causing concern. Although supply was previously covered by the *Psychoactive Substances Act* (PSA), in light of these concerns N₂O became a controlled drug on **November 8th 2023**: Class C, Schedule 5 (Misuse of Drugs Regulations (amendment) regulations 2023).

2. Common names: Nitrous oxide is commonly known as *Laughing Gas*. When mixed 50/50 with air and used medically (*Entonox*) it is commonly known as *Gas and Air*. When used as an additive in drag racing engines it is commonly known as *NOS (Nitrous Oxide System)*. *NOS* or *Noz* are also nicknames for it as a street drug, although it is also known by other street names such as *balloons* and (mainly by journalists) as *Hippy Crack*.

3. Pharmacology: N₂O is classed as a dissociative, putting it in the same drug class as ketamine (Adley/ DrugWatch, 2021). Despite its long-term medical use, the pharmacology of N₂O is not fully understood. It has been suggested that *opioid receptors* are responsible for its analgesic properties (Savage, Ma, 2014) while its dissociative effects are believed to be caused by preventing the normal action of the *NMDA receptor* (NEPTUNE, 2015). Its anti-anxiety effect is produced by the blocking *GABA(A) receptors*, while euphoria felt when the drug is taken is due in part to the release of *dopamine*. N₂O's effects occur at low concentrations and may be produced by alterations in brain blood flow similar to those produced when sniffing poppers (Drug Science, 2019; Sasajima, Zako, Ueta & Murotani, K., 2022).

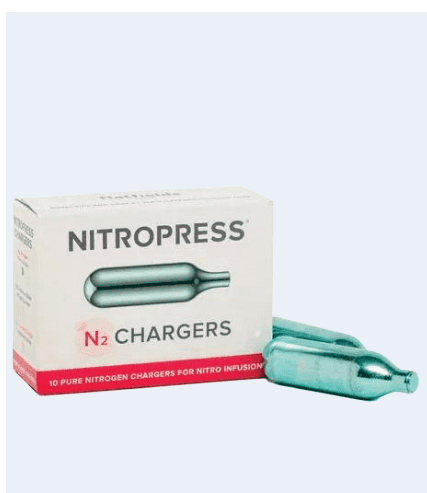
4. Effects: A single inhalation will result in effects starting almost immediately, peaking about 10-30 seconds after inhalation and then rapidly diminishing. It produces a euphoric, pleasant, joyful,

empathogenic and sometimes hallucinogenic effect, and causes a deep ‘silly’ voice. If the dose is repeated, effects reach a plateau about 30-60 seconds after the first breath. Whilst the user often feels back to ‘normal’ within about 1-5 minutes after the last inhalation, some users report effects such as a sense of wellbeing for up to 30 minutes after last use. Short term temporary side effects include pins and needles, numbness, dizziness, dissociation, disorientation, loss of balance, impaired memory and cognition and weakness in the legs (van Amsterdam, Nabben, & van den Brink, 2015; The Vaults of EROWID, 2022; PsychonautWiki, 2022; NEPTUNE, 2015).

4.1 N₂O use with other drugs: Anecdotal reports suggest an increase in the effects of N₂O when combined with alcohol, and it may briefly enhance the effects of psychedelic drugs like LSD and ketamine. When used at the same time as stimulant drugs it may additionally impact blood pressure and heart rate. As it is not metabolised by the liver, the potential for drug interactions with other agents, including antiretrovirals, is very low (NEPTUNE, 2015). Anecdotal reports suggest when combined with alcohol, GHB/GBL or opioids there is greater loss of co-ordination and balance and increased sedation leading to unexpected loss of consciousness at high doses (PsychonautWiki, 2022).

5. Methods of recreational N₂O use: In order to produce its effects N₂O must be inhaled. Serious damage can be done to the lungs by inhaling any pressurised gas directly from cylinders or the nozzle of a whipped cream dispenser. Additionally, when discharged N₂O is freezing cold and can cause ice burns (LiPuma, Wellman, & Stern, 1982). Inhaling through a mask, respirator, via a bag over the head or in an enclosed space such as a car, runs the risk of asphyxia as the N₂O displaces oxygen in a closed space (Wagner, Clark, Wesche, Doedens, & Lloyd, 1992). Users will likely drop a balloon filled with N₂O if they are getting too **hypoxic** (a deficiency of oxygen) or lose consciousness, so inhaling from balloons is the least risky way of using N₂O for recreational purposes. Balloons come in both standard and extra-large sizes.

6. Small chargers and larger tanks: The single-use finger-length steel whipped cream chargers containing 8 grams of N₂O, are known as *whippets*, *chargers* or *nangs* etc. (fig 1). An 8g charger is inserted into a device called a *cracker* (fig 2) and a balloon is attached and filled with N₂O. Alternatively, an 8g charger is fitted into a whipped cream dispenser and when the lever is pressed the balloon fills with N₂O [fig 3] (The Vaults of EROWID, 2022; Drug Science, 2019).



(Fig 1). 8g chargers or ‘Whippets’



(Fig 2). An 8g charger is fitted inside a device called a ‘Cracker’



(Fig 3). An 8g charger can also be used with a whipped cream dispenser

6.1 Larger sized tanks: Although the UK recreational N₂O market has been dominated by 8g chargers (*whippets*), the market appears to have recently changed with the advent and widespread availability from mainstream and specialist websites, social media vendors and other retail outlets of much larger 600+ gram tanks. According to a VICE article the two largest companies supplying the UK are Dutch and were formed in 2018/2019 (Hiller, 2022). It is unclear exactly when this market change first occurred in the UK, but a recent Dutch study indicates that the large tanks first appeared in Amsterdam around 2017/2018 (Nabben, Weijs, & van Amsterdam, 2021). The larger 640g sized tanks (fig 4) come with a small nozzle for directly filling the balloon (fig 5). Even larger tanks containing 2,000 grams (equal to 250 x 8g chargers) are now also being used in the UK [fig 6] (Creme Deluxe (a), MMU/GMCA (a) 2023). There is currently no UK data on the volume of N₂O sales for catering/recreational use or for the market share of larger tanks.



(fig 4) 640g tanks



(fig 5) A small release nozzle



(fig 6) 2,000g tank

7. Prevalence: N₂O use by young adults in England in Wales was first recorded in 2013-14 when 7.6% of those aged 16-24 reported use in the past year. Prevalence peaked at 9.0% in 2016-2017, and despite N₂O's inclusion in the *Psychoactive Substances Act (PSA)*, estimated use of N₂O by young adults aged 16–24 years was 8.7% in the year ending March 2020, making it the second most prevalent drug after cannabis. However the latest ONS data from 2021 shows that nitrous oxide use has decreased from 2.4% to 1.3% for people aged 16 to 59 years and from 8.7% to 3.9% for young adults aged 16 to 24 years (Home Office, 2018; ONS, 2022).

Despite media coverage of discarded 8g N₂O chargers leading to a short-lived moral panic and a parliamentary debate (Hansard, 2020), there was little evidence of an increase in N₂O use during lockdown. In 2021 the use of N₂O was reported by 1.8% of pupils aged 11-15 in England in the last year, down considerably from 4.1% in 2018 (ONS (a), 2022). However, in contrast to national data, the GM-TRENDS survey of young people in contact with services, together with reporting from professionals, suggests that in Greater Manchester at least, there has been a notable post-lockdown increase in N₂O use: increasing from 2.1% (2021) to 14.5% of respondents to the online young peoples survey in 2022. Almost a quarter (23.1%) of these young people who took part reported using for the first time during the past year (MMU/GMCA (a), 2023).

8. **Prices:** According to advertising by one supplier the 640g of N₂O in a large tank (equal to 80 single 8g chargers) is sold at a price equivalent to 50 x 8g chargers, representing a cost saving (Creme-deluxe (b), 2022). Prices of large tanks vary and they are also sold in bulk at a discount. Prices for one of the leading brands ‘Smart Whip’ on the UK supplier ‘Smart Chef Store’ website (based in Bolton) are below (Smart Chef Store, 2022). As with any ‘heavy’ drug habit, (see section 10.1) cost and debt are likely to be an issue and debt problems have been reported in Dutch research with heavy users (Nabben, Weijs, & van Amsterdam, 2021).

Brand and size	Price	Total of N ₂ O	Price per gram of N ₂ O
Smartwhip 8g x 24 pack	£10.99	192g	5.8p per g
Smartwhip 8g x 120 pack	£50.99	960g	4.2p per g
Smartwhip 640g x 1 pack	£29.99	640g	4.6p per g
Smartwhip 640g x 6 pack plus free gift of 24 x 8g pack	£139.99	3,840g + 192g Total = 4,032g	3.5p per g

9. **Risk and harms of infrequent recreational use:** It is commonly thought that the vast majority of those people who use N₂O are infrequent, episodic users. Infrequent use of lower doses of N₂O is considered lower risk compared to that of other illicit substances, with few short-term adverse effects other than headaches (NEPTUNE, 2015; ACMD, 2015; Winstock & Ferris, 2020). A recent paper compared N₂O to 20 well-know drugs, with N₂O scoring as the second least harmful drug. However, the authors acknowledge that in their model:

“Drugs with low scores may on occasion cause significant harm to a small minority of users, but when considering policy and regulation the factor that carries the most weight should be harm on a population-based level” (Ferreira, et al., 2022).

Most commonly, harms from N₂O use are likely to result from falling over and accidental injury. However, accidental injury is dose related (Kaar, et al., 2016), so if the widespread use of larger tanks has led or leads to an increase in the amount used in a session, a corresponding increase in accidental injury may occur. There is no available data on falling over or accidental injury as a result of N₂O use.

9.1. **Accidental asphyxiation as a result of method of use:** When N₂O is inhaled it displaces the air in the lungs, thus temporarily preventing oxygen from entering the bloodstream and causing the side effects described in section 4. Deaths associated with N₂O use are often attributed to its method of use, and accidental asphyxiation leading to **arrhythmias** (abnormal heart beat) and **seizures**. Although N₂O does not depress the respiratory drive significantly, the normal physiological response to **hypoxia** (deficiency of oxygen) is blunted when N₂O is taken. Deaths are often associated with bags being put over the head in order to facilitate inhalation, or inhalation in cars, as N₂O displaces oxygen in a closed space (NEPTUNE, 2015; Winstock & Ferris, 2020; Wagner, Clark, Wesche, Doedens, & Lloyd, 1992; Knuf & Maani, 2022).

9.2. **Fatalities:** There were 56 N₂O deaths registered in England and Wales between 2001 and 2020; 45 of those having been registered since 2010 [4½ per year between 2010 to 2020] (ONS (b), 2022).

9.3. **Arrhythmia:** People with heart conditions or abnormal blood pressure may be at higher risk of harm as the drop in oxygen levels caused by inhaling N₂O raises the heart rate and can cause arrhythmias. This could lead to cardiac arrests in susceptible people (Drug Science, 2019).

9.4. **Ice burns:** N₂O canisters become ice cold as the gas is discharged and may cause ice burns when coming into contact with skin. Sometimes these ice burns may not be noticed due to the anaesthetic effect of N₂O. Some users get blisters in the mouth and on the tongue, arms and legs (Nabben, Weijs, & van Amsterdam, 2021). According to the GM-TRENDS study, these ice burns tend to result in minor injuries to the fingers that typically do not lead to the need for medical attention (MMU/GMCA (a), 2023).

“A lot of the young people say to me they’ve had ‘freeze burns’ as they call it. Often not too serious where they need to go to A & E or anything, but frequent reports of burns to their fingers or mouth and lips through doing balloons. I don’t think they realise that it’s compressed and freezing when it comes out and what the risks are.” (Young Person’s Outreach Worker. MMU/GMCA (a), 2023)

However, some of these wounds can be very deep, requiring multiple surgeries and resulting in scars. Burns may look superficial, but can rapidly develop into third-degree burn wounds (Quax, Van Der Steenhoven, Bronkhorst, & Emmink, 2022; Stone, Roberts, & Anwar, 2021). There are recent local anecdotal reports suggesting the valves of larger tanks can burst, causing gas to leak and ice burn injury (MMU/GMCA (a), 2023). *The British Burn Association* has reported an increase in deep cold burns following the use of N₂O canisters held between the legs, however no detail or additional data are available (British Burn Association, 2022). For minor ice burns it is recommended to immerse the area in warm water, but as more serious burns can appear superficial, medical assistance or advice should be sought by dialling **NHS 111** (NHS, 2022).

10. **Amount used per session and frequency of use:** Although the practice of putting two 8g chargers into a single balloon (known as *double ballooning*) is widely known, the introduction of 640g tanks means it is far harder to regulate the amount in an individual balloon, particularly with the introduction of XL balloons, which are even sold as a package with N₂O *crackers* on mainstream websites such as Amazon (Amazon, 2022). 8g chargers are usually purchased in packs of 10 or more, with multiple doses are often used in a session. Although data is limited and the typical amount reportedly used in a single session varies, it is generally thought most people use N₂O less than 10 times per year with less than 10 balloons per session. Whilst it has long been acknowledged that there is a sub-population of N₂O users who are heavy users, there is a paucity of information on the percentage of the overall population of N₂O users frequently using very large amounts. One survey showed 14% of respondents using N₂O more than 100 times and 17% using more than 25 whippets in an average session (van Amsterdam, Nabben, & van den Brink, 2015; NEPTUNE, 2015; Ferreira, et al., 2022). Although there are no quantitative data or large-scale studies, according to a recent Greater Manchester study, the use of larger tanks has led to an increase in the amounts used both in single balloons and in sessions (MMU/GMCA (a), 2023).

“You definitely use more with the big canister because it’s easier to use. They’re quicker. You don’t need to use a cracker. It’s less messing about.” (17-year-old male N₂O user. MMU/GMCA (a), 2023)

“I think now yeah, people use a lot more innit? It’s so easy with the big ones to fill it up and you don’t know yeah. But I think you just keep going ‘til it’s full so I think a lot more gets put into it [a balloon].” (16 year-old male N₂O user. MMU/GMCA (a), 2023)

10.1. Amounts used by chronic, heavy users: There is no definition of what constitutes heavy or chronic use. *Marsden et al* suggest that from a diagnostic perspective, a rough guide is the daily use of 100 x 8g cartridges for at least a month would constitute chronic toxicity (Marsden, Sharma, & Rotella, 2022). This equates to daily use of 1.25 x 640g tanks per day for a sustained period. One medical case study reported the daily use of 400 x 8g cartridges of N₂O per day (Ickowicz, Brar, & Nolan, 2020), however by their nature medical case studies report on extremes, or unusual cases.

A recent study of 119 patients (median age 22) with **N₂O-myeloneuropathy** (damage of the tracts of the spinal cord and peripheral nerves in the lower limbs) seen at NHS teaching hospitals in the UK’s three largest cities: London, Birmingham and Manchester, suggests that the cause of (a reported) rise in cases is related to the use of larger canisters. However, of the 78 whose amount used was recorded, only 20 were using large (600+gm) canisters. Most, but not all, were using very large amounts, with the median weekly amount being 318 x (8g) canisters (2,544g). Weekly use ranged from one canister to 35 cylinders - equivalent to roughly 2,800 (8g) canisters (Mair D, Paris A, Zaloum SA, et al. 2023). Dutch research into heavy street users, suggests that chronic use inevitably becomes an isolated solo activity, with binges of 2 to 3 x 2,000g tanks at least 3 times a week, with one reportedly using 8 x 2,000g tanks in a day-long session.

“A considerable group of unsuspecting users gradually inhale themselves longer and deeper into an unknown world without a bottom, ceiling, and perspective. Some of them increasingly get lost in hypnotically repetitive and long-lasting nitrous oxide sessions starting from once a week, to a few times a week to sometimes every day. Compared to other substances, nitrous oxide is different in that it can be used for hours and sometimes even days (binge) and the user is not aware when he/she has to stop”. (Nabben, Weijs, & van Amsterdam, 2021, page 13)

11. Dependency and chronic, heavy use: There is no evidence of significant withdrawal symptoms apart from cravings to use more, and little evidence of physical dependence to N₂O. However there is anecdotal evidence of psychological dependence and tolerance developing with heavy use, and a subpopulation of heavy users *‘who may be using in a dependent pattern’* (van Amsterdam, Nabben, & van den Brink, 2015; Malamed & Clark, 2003; NEPTUNE, 2015; Kaar, et al., 2016). Anecdotal reports from treatment services occasionally mention heavy N₂O use but no adults or young people in treatment during 2020-21 were recorded as having a problem¹ with N₂O (OHID, 2021; OHID, 2022). However, if N₂O use is taking place within populations where its use is taboo, access to treatment may be limited, and treatment numbers may not accurately reflect problems associated with the drug.

¹ When young people enter treatment, they can record up to 3 substances that they have a problem with. The absence of N₂O mentions may be a result of the numbers being so low that they were recorded under ‘other/NPS’ and/or they did not see their use of N₂O as a problem.

12. Acute intoxication: The toxic dose of N₂O is not established. Advice on occupational exposure limits ranges from 25 to 100 parts per million. This is thought to be far below the level of common heavy use, however may provide an indication of the level at which harms can occur in recreational users (NEPTUNE, 2015). According to NEPTUNE the evidence of acute harms associated with recreational use is limited, consisting mainly of case reports, with occasional experimental studies into acute effects. NEPTUNE provides a summary chart [below] (NEPTUNE, 2015).

Features of acute intoxication with nitrous oxide (NEPTUNE, 2015)		Simple definition of medical terms
Respiratory effects	Asphyxia and Hypoxia	<i>Hypoxia</i> : a term used to indicate a deficiency of oxygen. <i>Asphyxia</i> : refers to the physiological results of hypoxia.
Neurological and psychiatric effects	CNS depression Convulsions Psychiatric symptoms Headache Polyneuropathy Myeloneuropathy Dizziness, Excitement, Paraesthesia Paralysis Psychosis	<i>Myeloneuropathy</i> : damage of the tracts of the spinal cord and peripheral nerves in the lower limbs. <i>Polyneuropathy</i> : the simultaneous malfunction of peripheral nerves throughout the body. <i>Paraesthesia</i> : refers to a burning or prickling, tingling sensation or numbness that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body.
Cardiovascular effects	Hypertension Cardiac dysrhythmias Megaloblastic anaemia Leukopenia Anoxia	<i>Hypertension</i> : raised blood pressure. <i>Cardiac dysrhythmias</i> : irregular heartbeats. <i>Megaloblastic anaemia</i> : a type of vitamin B12 deficiency. <i>Leukopenia</i> : lower than normal white blood cells. <i>Anoxia</i> : when your body or brain completely loses its oxygen supply. Anoxia is usually a result of hypoxia
Metabolic features	Thrombocytopenia	<i>Thrombocytopenia</i> : deficiency of platelets in the blood. This causes bleeding into the tissues, bruising, and slow blood clotting after injury.
Gastrointestinal symptoms	Nausea and vomiting	

12.1 B12 deficiency and neuropathic damage: The toxicity of N₂O is based on its interaction with **vitamin B12** and was first reported in 1968 (Banks, Henderson, & Pratt, 1968). The inactivation of vitamin B12 as a result of heavy N₂O use manifests as the respiratory, psychiatric, cardiovascular, metabolic and neurological features outlined in the chart above. N₂O-induced damage to the nerves (**neuropathy**) was first recognized in the 1970s (Layzer, Fishman, & Schafer, 1978). While infrequent, episodic users are not at risk, a minority of heavy users are at dose-dependent risk of developing these serious neurological consequences (Marsden, Sharma, & Rotella, 2022; Winstock & Ferris, 2020). Vegans, dependent drinkers and patients with pernicious anaemia are more susceptible to B12 deficiency (Society of Hospital Medicine, 2015, Fragasso, Mannarella, Ciancio, & Sacco, 2009).

N₂O-induced vitamin B12 deficiency can manifest as **myeloneuropathy**. Myeloneuropathy is characterized by simultaneous damage of the tracts of the spinal cord and peripheral nerves in the lower limbs. The earliest symptoms are usually the presence of tingling or numbness, in hands and legs (starting in fingers and toes, usually on both sides at same time), skin crawling, or itching, numbness in hands and legs and later staggering uncoordinated walk, lower limb weakness, muscles stiffening or tightening, overactive or overresponsive bodily reflexes such as twitching, etc. Standard treatment is cessation of N₂O use, along with vitamin B12 supplementation. This can result in improvement and, in some cases, complete resolution of symptoms, although this can take months (Campdesuner, Teklie, Alkayali, Pierce, & George, 2022; NEPTUNE, 2015; Eftimova, Sholjakova, Mirakovski, & Hadzi-Nikolova, 2017; Nabben, Weijs, & van Amsterdam, 2021).

It has been suggested in some online user forums that taking vitamin B12 supplements may mitigate against B12 deficiency for those using large amounts of N₂O (reddit forum, 2020). There is no evidence that taking over the counter oral supplements works. One paper suggests this is futile as B12 has very low oral absorption, so severely deficient people need B12 intramuscular injections (Blair, Tremonti, Edwards, Haber, & Halmagyi, 2019).

12.2 Reproductive risks: Before health exposure limits were introduced, data from professionals working in dental and midwifery practices exposed to high levels of N₂O, indicated reproduction effects that included congenital anomalies, spontaneous abortion and reduced fertility rates in females. Recreational users of N₂O, may repeatedly expose themselves to (very) high doses of N₂O, greatly exceeding the health exposure limits. There is therefore a potential risk, especially in heavy N₂O users, pregnant users or those who intend to become pregnant (van Amsterdam & van den Brink, 2022).

12.3 Psychiatric symptoms: Current literature suggests that psychosis associated with N₂O use is transient, and resolves upon cessation of use and treatment of vitamin B12 deficiency. However, in a recent review approximately half of the cases that presented with N₂O-induced psychiatric complaints did not show neurological symptoms, and their vitamin B12 concentration was often within the hospital's reference range (Paulus, Wijnhoven, Maessen, Blankensteijn, & van der Heyden, 2021; Roberts, Farahmand, & Wolkin, 2020).

12.4. Clinical guidelines: UK clinical guidelines were produced by NEPTUNE in 2015 and advice is available from TOXBASE for medical professionals (NEPTUNE, 2015). An Australian review paper suggested a guide for diagnosis of chronic N₂O toxicity (see chart below):

A suggested approach for the diagnosis of chronic nitrous oxide toxicity (Australia) (Marsden, Sharma, & Rotella, 2022).	
Clinical	<ul style="list-style-type: none"> • Young patient (usually in 20s). • Reported use of >100 'bulbs' (8g cartridges aka 'whippets') per day. • At least months of use. • Presence of neurological disturbances such as sensory changes and gait ataxia weakness.
Biochemical	<ul style="list-style-type: none"> • Elevated serum homocysteine and/or methylmalonic acid prior to commencement of any treatment. • Serum total and active Vitamin B12 may be normal.
Imaging and other tests	<ul style="list-style-type: none"> • Dorsal column abnormalities (diagnostic). • Peripheral neuropathy on nerve conduction studies (supportive).

Note: A suggested approach to diagnosis is offered but requires validation in prospective studies (Marsden, Sharma, & Rotella, 2022).

In 2023 new clinical practice guidelines for the management of patients with *nitrous oxide-induced subacute combined degeneration of the spinal cord* (N2O-SACD) were published by the *Association of British Neurologists*. These were written by experts from Manchester, Birmingham, Nottingham and the Queen Mary University of London (Paris A, Lake L, Joseph A, et al, 2023) following a rise in cases of N2O-SACD, a pattern of myeloneuropathy usually associated with severe vitamin B12 deficiency. The pathway for patients from the guidelines is shown opposite (fig 7).

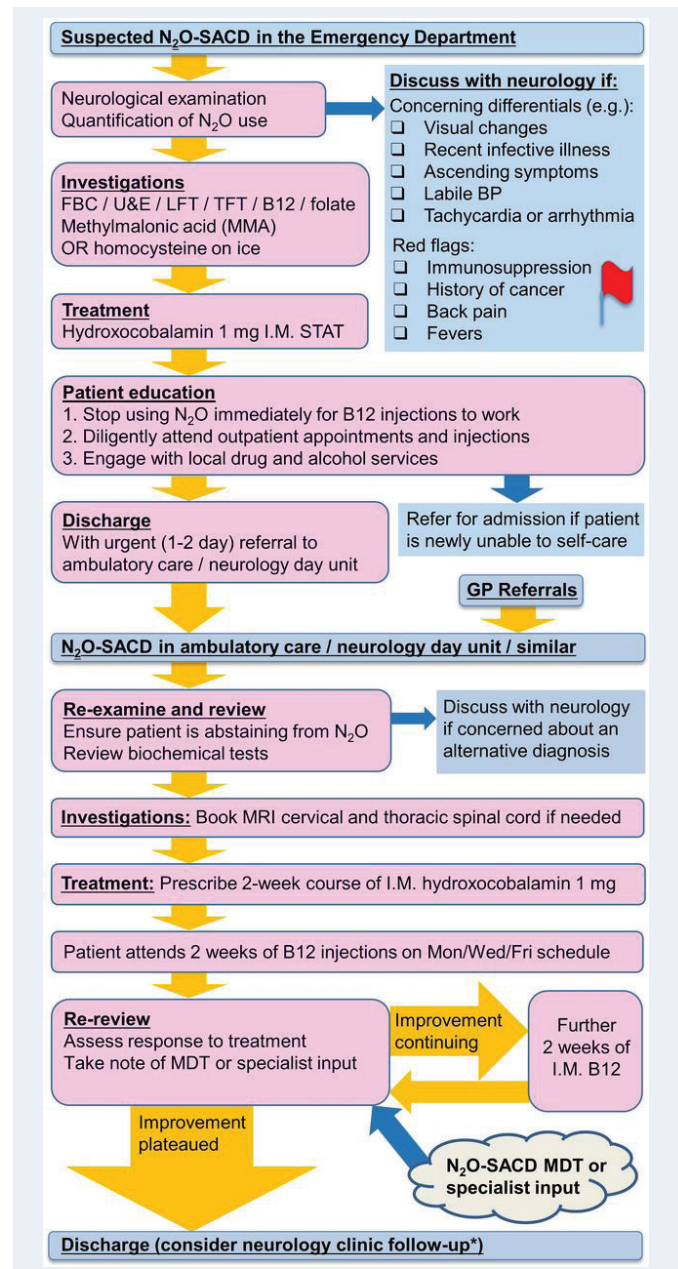
12.5. Prevalence of acute intoxication

presentations: Although there is a lack of available data, there is enough anecdotal evidence to suggest there has been a rise in cases seen by hospitals. Some UK neurologists have claimed that the common availability of larger tanks have been responsible for the ‘epidemic’ of young people seen with neurological injuries (The Independent, 2022). Doctor David Nicholl, a consultant neurologist at Queen Elizabeth Hospital in Birmingham, has stated that he and his colleagues are seeing ‘large numbers of young people’ coming into hospital after taking N₂O (Sky News, 2022; Hussain, 2022). However, as no data is available from the NHS on the number of incidents involving chronic use of N₂O, quite what ‘large numbers’ or ‘epidemic’ equates to is unclear.

Local data was sought by the 2022 *GM-TRENDS* study. In one area, a young person’s substance use service reported an increase in N₂O-related hospital admissions over the past year: from 0 in the previous year to 2 in the first 7 months of 2022. Another hospital reported an increase from 4 in the last financial year to 5 in the first 5 months of 2022/23. No other Greater Manchester areas reported data (MMU/GMCA, 2023 (a)).

The Dutch Poisons Information Centre reported an annual average of 6 poisonings per year between 2010-2015, which rose to 144 in 2020. They associated this increase with a shift from heavy and frequent use of 8g cartridges to large canisters and cylinders (van Riel, et al., 2022). According to the 2021-2022 UK *National Poisons Information Service* (NPIS) annual report, they received 36 enquiries relating to recreational N₂O misuse representing a 257% increase since the 2011 to 2012 reporting year (NPIS, 2022).

13. Driving: Although N₂O is very short-acting it negatively affects coordination, awareness and psychomotor skills, thereby increasing the likelihood of road traffic accidents (NEPTUNE, 2015; Moyes,



(Fig 7). Pathway for patients with suspected N2O-SACD

Cleaton-Jones, & Lelliot, 1979). Unlike alcohol there are no national statistics on road traffic deaths involving drugs. However, experimental data indicates that in Great Britain in 2019 'Drugs of abuse' were detected in 117 deceased drivers (compared to 143 involving alcohol). There is no breakdown of the types of 'Drugs of abuse' involved (Dept for Transport, 2022). Reports from Dutch police indicate that between 2019-2021, 63 people were killed in road traffic accidents involving N₂O (NL Times, 2021).

There have been a number of local media reports of people inhaling balloons while in or driving cars, and of N₂O-related road traffic accidents (MEN (a), 2022; MEN (b), 2022). Data from City Centre Manchester indicates that there were 71 reported incidents in 2021/2022 of drivers inhaling from balloons (sometimes while in the act of driving), an increase from 31 reported incidents during 2020/2021 (GMP, October 2022).

14. Use by young men of Asian or Asian British ethnicity: A number of respondents in the 2022 GMTRENDS study also shared reports of people inhaling balloons while in or driving cars. Additionally, this was thought to a particular trend in some areas among young Asian men:

"You see it especially with the young Asian lads. If you walk around the street where we live you will see them parked up in their cars doing balloons and you can see where they've been using in the cars and just dumped a load of empty cannisters by the roadside." (Manager, Young Person's Substance Use Service. MMU/GMCA (a), 2023)

This issue was also raised as a concern by a number of health professionals within the study, one of whom compared the cases of two people who had both presented with similar side effects and noted:

"As for the other young man, the 17-year-old. These falls, pins and needles to feet/legs and loss of sensation to legs seemed to be as a direct consequence of long-term nitrous oxide use. What both cases have in common for me are ethnicity, age and gender. It might be that they don't see nitrous oxide as a drug and therefore acceptable to use in their culture/religion. My concern is that there may be groups of Asian young men/young adults that are not known to services and therefore unaware of the risks associated with nitrous oxide use." (Alcohol Nurse Specialist, MMU/GMCA (a), 2023)

Heavy use of nitrous oxide reported in the case studies of patients with N₂O-myeloneuropathy seen at NHS teaching hospitals the UK's three largest cities was also disproportionately common among males of Asian or Asian British ethnicity. The majority of the 119 patients were male (n=89, 75%) and of Asian or Asian British ethnicity (n=68, 57%). Individuals of Asian or Asian British ethnicity made up a large proportion of cases in East London (73%, n=41), Birmingham (54%, n=19) and Manchester (29%, n=8) (Mair D, Paris A, Zaloum SA, et al. 2023).

"We and others have speculated that N₂O is a drug of choice for individuals not engaging with other substances for cultural or religious reasons. This study does not necessarily support this idea, with the consumption of N₂O along with other substances demonstrated across ethnic groups. However, the predominance of cases with Asian ethnicity may highlight genetic, dietary, or nutritional predispositions to neurological damage from N₂O exposure, but also may indicate social circumstances predicating use." (Mair D, Paris A, Zaloum SA, et al. 2023)

15. Aggression and violence: The association of N₂O with aggression and violence is not new. A wood engraving from 1840 entitled 'An Exhibition of the Laughing Gas' states:

"It is named Laughing Gas on account of the very exhilarating emotions produced in those who respire it for a short time; laughing, dancing, jumping, acting, reciting and (last but not least) fighting are amongst the prominent effects displayed by persons under its influence." (Ruston, 2022)

Although there are reports of *"high tension, quarrels and sometimes violence between users or toward friends, partners and parents"* among heavy users (Nabben, Weijs, & van Amsterdam, 2021, p. 10), these are also widely reported among people who use commonly-used drugs such as alcohol and cocaine, and are typically reported when new drugs or drug trends appear. Given the large numbers of people who use N₂O, there is little evidence to suggest that the majority are likely to become aggressive or violent, any more than they are likely to start *acting* or *reciting*. However, researchers involved in fieldwork cautioned against disturbing people who are under the influence of the drug, describing them as being *"in their self-created time capsule... a rough disturbance can lead to aggressive behaviour"* (Nabben, Weijs, & van Amsterdam, 2021, p. 10).

15. Enviromental impact: Abandoned nests of empty 8g chargers are a common sight on UK streets, although as with many N₂O related issues, there is no national prevalence data. One recycling and waste management company claims to have seen *"...an extraordinary increase in the number of gas canisters being thrown out as general waste"* (Vaclavova, 2022).

N₂O depletes the ozone layer, and while it may have a significant impact on global warming, this overwhelmingly involves its use in agriculture (Shankman, 2019). Although non-flammable, N₂O will support combustion to the same extent as oxygen does. Used chargers and tanks should never be thrown into fires as they may explode (Knuf & Maani, 2022). Smaller 8g chargers and larger tanks, are often put into mixed recycling bins [often your neighbours] (MEN (c), 2022) but may explode when going through an 'Energy from Waste facility' [EfW] (Vaclavova, 2022). Recycling advice is often conflicting and confusing. Although not all recycling centres accept smaller 8g chargers, they are recyclable and some specialist recycling centres will accept them. Larger tanks should be placed with the other large gas cylinders at local recycling centres (Recycle for Greater Manchester, 2020).

Several local authorities have tried to tackle the N₂O anti-social/litter issue with initiatives involving education, public reporting, street cleaning, enforcement and dispersal (Middlesbrough Council, 2022), but there are no available evaluations for the effectiveness of their effectiveness.



16. N₂O legislation: In 2015 the Advisory Council for the Misuse of Drugs (ACMD) concluded that N₂O was not sufficiently harmful to warrant it becoming a controlled drug (ACMD, 2015). In 2016 N₂O was included within the *Psychoactive Substances Act* (PSA). It could be sold legally, for instance as a propellant in whipped cream, but it was an offence under the PSA to supply N₂O for the purpose of intoxication. Under the PSA, possession of N₂O was not an offence unless in a custodial institution. However, including N₂O in the PSA had little impact on prevalence (Home Office, 2018). On September 3rd 2021, the then Home Secretary asked the ACMD to again review the legal status of N₂O (ACMD, 2021).

In March 2023 the ACMD reported back to the government that there was no substantive evidence of links between N₂O use and crime or anti-social behaviour, although they had received some responses suggesting an association with nuisance behaviour. However, their review was hampered by evidence gaps, so much so that the original version of this briefing was cited twice as evidence by the ACMD (ACMD, 2023). They recommended monitoring the prevalence of neurological and other harms, road traffic accidents, deaths and anti-social behaviour including the environmental impact of littering. They advised that N₂O should remain under the PSA, but that the government should explore restrictions on direct-to-consumer sales, canister sizes, volume of sales, online sales and paraphernalia (e.g. crackers) and that there should be increased health warning information on packaging (ACMD, 2023).

The government are obliged to seek the advice of the ACMD before enacting drugs legislation. However, they are under no obligation to take this advice. In June 2023, the government announced that despite advice from the ACMD advice, N₂O was to become Class C drug (ACMD (a), 2023). As part of the statutory framework the government then had to return to the ACMD and ask for advice on scheduling. The ACMD advised that none of the existing schedules would allow the legitimate medical, industrial and catering uses of N₂O. The closest, Schedule 5, would have needed to be amended and they recommended that the government adopt a *'legally robust definition of legitimate use'* (ACMD (b), 2023). The government once again ignored this advice in favour of a *"broad definition"* (ACMD, (c), 2023).

"...we have decided to take a broad approach and make uses of nitrous oxide lawful except where the drug is likely to be inhaled by humans. All other legitimate uses that do not involve inhalation by a human will be considered lawful. There will be exemptions for inhalation for legitimate medical uses and secondary inhalation (e.g. gases in the atmosphere)." (ACMD (c), 2023)

16.1 Legal status of N₂O: Nitrous Oxide became a Class C, Schedule 5 (amended) drug under the Misuse of Drugs Act (MDA) on November 8th 2023.

16.2 Supply: As it was already an offence under the PSA to supply N₂O if it was likely to be used for its psychoactive effects, there are few changes now it has become a Class C drug, other than an increase in maximum sentences from 7 years under the PSA to 14 years under the MDA. Production, import, export, supply, offer to supply N₂O are legal, except where they *"intend, know or are reckless as to whether the substance is likely to be **wrongfully inhaled**³ by a person"* (Home Office, 2023; Misuse of Drugs (Amended) Regulations 2023). The Home Office do not expect an increase in the number sentenced to immediate custody from between 4 to 11 per year that currently occurs under the PSA (Home Office (b), 2023).

³ "Wrongful inhalation" means any inhalation which is not for a medical or dental purpose (for example, recreational inhalation for psychoactive effect) or is not of nitrous oxide which has been released into the atmosphere (for example, directly from a canister or a balloon) (Misuse of Drugs Regulations (amendment) regulations 2023).

16.3 Possession: Possession of N₂O was not an offence under the PSA, but from 8th November 2023 it became a criminal offence to be found in possession of the drug where *“its intended use is to be inhaled for psychoactive effects, or ‘to get high’”* (Home Office , 2023). The legislation does not define how ‘intent’ is proven, but the Home Office *Media Fact Sheet* states that;

“This will be a matter for police to investigate, however it is right to expect individuals to put forward a robust case and evidence to prove they have legitimate plans to use the nitrous oxide in their possession” (Home Office 2023).

It will still be legal to possess and inhale N₂O for medical or dental purposes. Large medical grade hospital tanks are classed as medicinal products, and supply or administration without MHRA authorization is already a criminal offence under the *Human Medicines Regulations 2012* (UK Statutory Instruments, 2012). Possession, supply and production of N₂O for industrial or scientific education purposes will also be legal.

You won’t need a license to be in possession of any size of canister provided you don’t intend to inhale it ‘for psychoactive effects’. So for instance it is still legal for ‘hobbyists’ to possess N₂O in large tanks designed for modified car engines³ (NOS) or if to be used in ‘model rocketry’. As was the case under the PSA, it is also permitted to supply and possess N₂O for *“catering, as a whipped cream propellant”*. The 600g+ tanks are not classed as medicinal products so (as was the case under the PSA) they can still be legally supplied and possessed for *‘catering purposes’* (Home Office , 2023).

The Home Office estimate up to an extra 62,200 offences of possession of N₂O could per year. Maximum penalties for possession are up to 2 years in prison and/or an unlimited fine, although most cases of possession of N₂O are expected to receive conditional cautions, diversionary activity, community resolutions etc. However, it is estimated up to an extra 2,000 children and 9,900 adults per year will be charged. The Home Office do not expect any children to be sent to prison, but they estimate that up to 500 adults per year will be sent to prison for possession of N₂O (6% of those convicted) (Home Office (b), 2023).

18. Harm reduction advice: The following advice may be useful to those using N₂O.

The Law

- Be aware that possession of nitrous oxide is now an offence where *‘its intended use is to be inhaled for psychoactive effects, or ‘to get high’*.
- Unless you can provide evidence of legitimate use, i.e. you have a whipped cream machine at home or you use it for model rockets, you will be arrested. It is less likely any whipped cream type evidence will be believed if you are caught with your mates with a half used crate of 600g canisters in a park late at night.
- In most cases of possession, provided you have no previous offences, you will be offered a conditional caution, diversionary activity or community resolution. However, it is possible you will be charged and have to appear in court.

³ Nitrous Oxide used as a fuel in drag racing engines is not suitable for human use because it contains sulphur dioxide and other impurities (The Vaults of EROWID, 2022).

Burns

- Nitrous oxide tanks can become freezing cold when the gas is released and there has been a rise in ice burns when people hold the large tanks between their legs.
- Nitrous oxide released directly from the tank can cause ice burns, sometimes these are not noticed due to the anaesthetic effect of nitrous oxide. Some of the burns can be very deep, require multiple surgeries and result in scars. Burns can look superficial, but can rapidly develop into third-degree burn wounds. If you get nitrous oxide on your skin, rinse it in cold water. If you get an ice burn, seek medical attention from a doctor or at a hospital.

Asphyxiation (suffocation)

- Do not inhale directly from the tank, cracker or whipped cream dispenser, it's so cold that it could seriously damage the throat and lungs. Always inhale nitrous oxide through a balloon.
- Do not use nitrous oxide with a bag over your head or with a mask attached to cylinders. About five people a year die as a result of breathing nitrous oxide continuously without breathing air. People suffocate as the body becomes starved of oxygen.
- Do not continuously breathe nitrous oxide in a confined space such as a car. Nitrous oxide pushes the air out of confined spaces, cutting off the supply of oxygen. Several deaths have been linked to this.

Accidents

- Driving under the influence of nitrous oxide is an offence and has resulted in a number of fatal car crashes.
- When using nitrous oxide, use in a safe location (for example sitting on a sofa or the floor). This is to prevent you falling or having other accidents because of temporary loss of balance or consciousness. Do not smoke or hold drinks or anything sharp when inhaling nitrous oxide. The more nitrous oxide you use, the higher the risk of falls or accidents.

Effects on physical health

- 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, which could cause problems in these individuals.
- Avoid mixing nitrous oxide with other drugs, especially stimulants, as effects on blood pressure and heart rate could be unpredictable.

Mental Health

- Use of nitrous oxide may induce psychotic symptoms in people with underlying mental ill health.

Pregnancy

- If pregnant, breast-feeding or planning on becoming pregnant then you should avoid nitrous oxide as this can harm the baby.

Addiction

- There has been an increase in the use of larger 640g tanks and extra-large balloons. This has led to some people using very large amounts on a regular basis. Some people are using compulsively and may have become dependent on nitrous oxide. There are confidential services who can help you.

Nerve Damage

- Because of the increased use of larger tanks and extra-large balloons, there has been a significant increase in people being seen at hospitals with nerve damage as a result of using large amounts of nitrous oxide on a regular basis.
- Using large amounts of nitrous oxide on a regular basis can lead to vitamin B12 deficiency, which can cause serious damage to the nerves and spine, resulting in some people being unable to walk. In some cases, this can last for months or years, or may even be permanent.

- Taking B12 supplements will not prevent B12 deficiency as a result of heavy prolonged nitrous oxide use. You may be treated with B12 supplements at hospital or your GP, but this is given by injection. You also have to stop using nitrous oxide for this treatment to be effective.
- The earliest symptoms of B12 deficiency are usually persistence of tingling, skin crawling or itching, numbness in hands and legs and later a staggering uncoordinated walk, lower limb weakness, muscle stiffness or twitching. If you have been using large amounts of nitrous oxide and are experiencing any of these symptoms, please see your doctor or go to the A&E department of the hospital as soon as possible.

Poisons

- Because they are both gases used to fill balloons, nitrous oxide is sometimes confused with helium. Helium causes a high 'silly' voice, whereas nitrous oxide causes a deep 'silly' voice. The two gases are not related.
- Nitrous oxide is not the same as nitric oxide. Nitric oxide is a poisonous gas.

What to do in emergency?

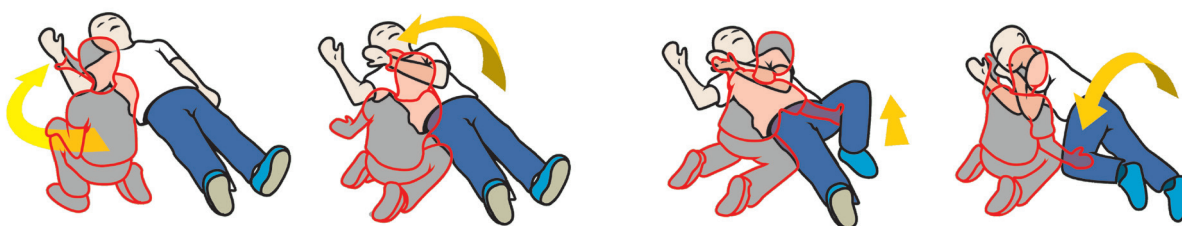
- If there are serious adverse effects call 999 and tell emergency services what has been taken.
- Seek medical attention if experiencing any negative side effects.
- Always place an unconscious person in the **recovery position** (see illustration below).

1. Put the right hand by the head (as if they were waving)

2. Put the left arm across the chest, so that the back of the hand rests against the cheek

3. Hold the hand in place and lift up the left knee

4. Turn them on their side by pushing down on the knee



Recycling: Dispose of empty containers responsibly. Whippets can be recycled and larger tanks can be placed with other large gas cylinders at a recycling centre.

Where to get help: Anyone experiencing issues from nitrous oxide or other substances should seek medical support via their GP or the NHS. There are a wide range of young people's services who can offer confidential support and help, for example:

England: <http://www.talktofrank.com/need-support>

Scotland: <https://www.scottishdrugservices.com/>

Wales: <http://dan247.org.uk>

Northern Ireland: <http://www.publichealth.hscni.net/publications/drug-and-alcohol-directories-services>

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