



Tackling the growing burden of nitrous oxide-induced public health harms

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Nitrous oxide has been increasing in popularity as a recreational drug in the past decade, and with this an increase in health harms related to nitrous oxide use, particularly nitrous oxide-induced myeloneuropathy. In response, governments in many countries have adopted new laws that either target the end user, by criminalising possession, or target suppliers. The effect of these measures remains to be seen, but the potential to exacerbate harm by targeting the user and thus affecting health-care-seeking behaviour is a concern. Education around the preventable harm from recreational use of nitrous oxide and tightening regulations on suppliers are essential in mitigating the increase in nitrous oxide-related health harms.

Introduction

Nitrous oxide, commonly known as laughing gas, is an anaesthetic used in medical and dental settings. When recreationally inhaled it causes a 5–20 s euphoric effect.¹ Recreational use of nitrous oxide is increasing² and, with this, reports of the serious harms from use.³

The Global Drug Survey, a voluntary survey of more than 32 000 participants in 22 countries (mostly European) found that 22·5% of respondents had used nitrous oxide in their lifetime, and almost 10% had used it in the past year.⁴ 7-year trends indicate a global increase in nitrous oxide use from 10% in 2015 to 20% in 2021.² Nitrous oxide is the third most commonly used drug after cannabis and cocaine in the UK.⁵ Use is highest among people aged 16–24 years, although prevalence estimates could be inaccurate due to the voluntary nature of surveys. Among people aged 16–24 years, a self-reported survey of 592 000 people globally estimated 24% used nitrous oxide in 2021,² whereas the national crime survey in England and Wales estimated 4·2% used it in this age group in 2022–23, falling from a peak of 9% in 2016–17.⁵ Despite this apparent decline, these data do not necessarily equate to a reduction in harm, as a shift in use at festivals and nightclubs (ie, occasional users), to use at home or in public spaces (ie, heavy users), could represent a shift from sporadic nitrous oxide use to heavy, frequent use. Increased hospital admissions in 2022 due to solvents and inhaled anaesthetics, including nitrous oxide, might indicate an increase in people using it heavily, contrary to overall national trends.⁶ Nitrous oxide users who progressively increase consumption could even meet criteria for addictive disorders.^{7,8} Additionally, concurrent drug use with nitrous oxide is common.⁹

Most surveys focus on people older than 16 years, neglecting an important demographic group known to use nitrous oxide. A 2016 survey found that 9% of people aged 11–15 years had been offered nitrous oxide¹⁰ and in 2021, 1·8% of people aged 11–15 years in the UK admitted to using nitrous oxide.⁶ There is no data at population level on nitrous oxide use stratified by ethnic groups. South Asians made up 57% of patients in

one large case series, according to self-reported demographics on electronic patient records, although the demographics of the urban areas where cases arose could have contributed to this.⁹

Nitrous oxide is perceived by many in the population to be a relatively safe drug. Among 140 young adults surveyed in London, almost 80% of non-users reported that they were very likely to try nitrous oxide in the next 3 months.¹ In a 2016 survey, only 23·5% of nitrous oxide users were worried about the effect of nitrous oxide use on their physical health and 22·5% were worried about their mental health.¹¹ Some people perceive nitrous oxide as preferable to other drugs due to its shorter duration of effect, absence of a commonly reported hangover effect, and a misconception of no perceived executive impairment.¹² Nitrous oxide is relatively accessible, sold in shops and widely over the internet. Almost a quarter of people believe it would be very or fairly easy to obtain nitrous oxide within 24 h, according to a UK survey.⁵

Three main factors are thought to be causing the increase in nitrous oxide use (and related health harms) within the UK. First, nitrous oxide is cheap to purchase online. Second, larger cylinders containing roughly 70 times the amount of nitrous oxide of traditional canisters have become available since 2017. Manufacturers are now producing 2000 g cylinders and in various flavours, such as pineapple and coconut. Companies acknowledge that the gas is scented, not flavoured.¹³ There is no legitimate use for scented propellant gas in the catering industry. Third, despite being now classified as a Class C drug in the UK, ease of online purchasing continues without a need to provide any form of licence. With no distinct odour and minimal overt drug-related paraphernalia, it might be easier to conceal nitrous oxide use than other popular recreational drugs.

Harms associated with nitrous oxide

Reports of health harms due to recreational use of nitrous oxide have increased since 2000 (figure 1, appendix p 2), with sparse reports in the decades before. Neurological harms due to nitrous oxide are most commonly reported, with an increase in other harms

See Online for appendix

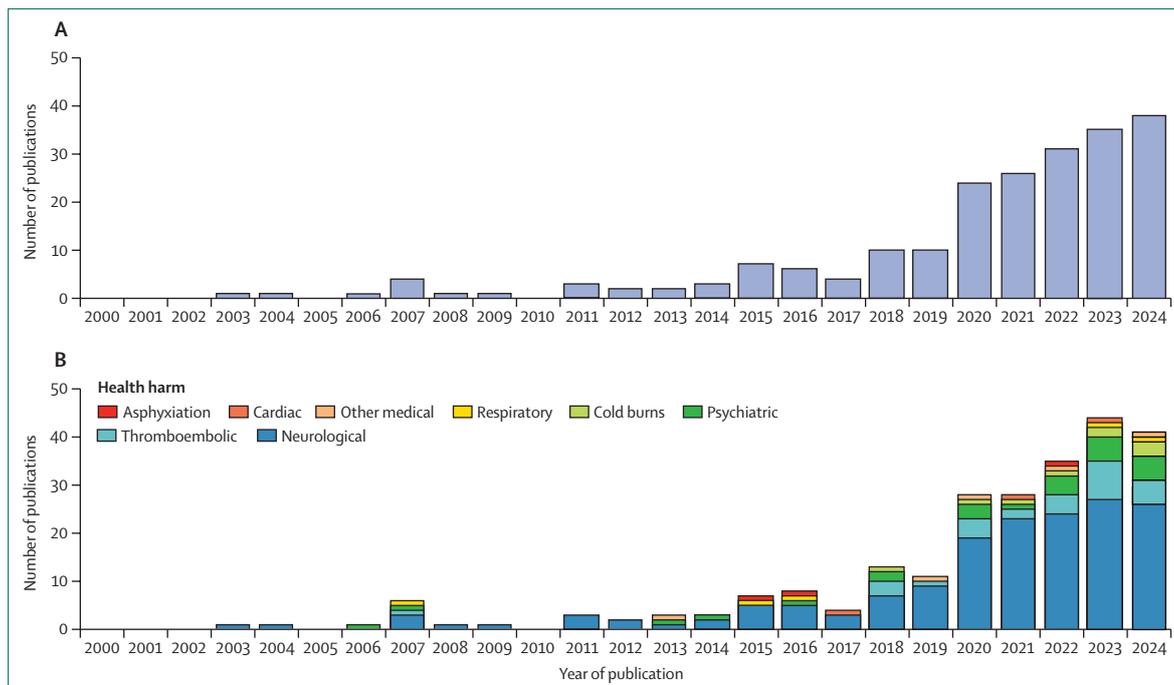


Figure 1: Number of PubMed-indexed case reports and case series on health harms due to recreational use of nitrous oxide since 2000

(A) Case reports and series per year since 2000. (B) Case reports and series per year since 2000 categorised by health harm due to nitrous oxide. Case series and reports can have more than one health harm primarily reported on and could be classified under up to three health harm categories. Other medical harms included acute pancreatitis (n=1), acute liver injury (n=1), papilloedema (n=1), and skin hyperpigmentation (n=2).

(particularly thromboembolic and psychiatric) in the past 5 years.

Neurological harm

Nitrous oxide-induced myeloneuropathy is an umbrella term for the neurological harm caused by nitrous oxide, encompassing subacute combined degeneration of the spinal cord, a pattern of myelopathy, and a nitrous oxide-induced peripheral neuropathy. Nitrous oxide-induced myeloneuropathy is associated with an absolute or functional B₁₂ deficiency, in which serum B₁₂ concentrations are within the reference range. The most common presenting symptom is paraesthesia,¹⁴ with other symptoms including gait disturbance, ataxia, weakness, and bladder and bowel dysfunction.^{9,15} The true prevalence of neurological symptoms in nitrous oxide users is unknown, as many might not seek help or report milder symptoms. A dose–response effect has been reported,¹⁴ with many cases in the literature associated with long-term nitrous oxide use or large amounts of nitrous oxide in a short time, with high average consumption seen in large case series.^{3,9,16} The threshold for sustaining neurological harm is poorly understood, with some users having symptoms after using very few canisters.^{9,17}

Nitrous oxide-induced myeloneuropathy is caused by an underlying functional vitamin B₁₂ (cobalamin) deficiency. Nitrous oxide irreversibly binds to the cobalt ion in cobalamin, leading to inactivation and thus preventing

the conversion of homocysteine to methionine.^{18,19} There has been suggestion that prophylactic B₁₂ supplementation while misusing nitrous oxide does not necessarily prevent functional deficiency.²⁰

Until recently, there was no consensus on treating nitrous oxide-induced myeloneuropathy. National guidelines published in the UK in 2023 suggest treating nitrous oxide-induced subacute combined degeneration of the cord with intramuscular B₁₂ on alternate days for 2 weeks, with a neurological review after this time. Intramuscular B₁₂ is continued in 2-week courses, with periodic clinical review, provided there is an objective ongoing improvement.²¹ Despite many people showing improvement or complete recovery with treatment, some sustain permanent disability, typically those with continued nitrous oxide use.²² The predictors of recovery are not yet known. Almost 90% of people in one case series had ongoing symptoms at a median of 183 days after presentation,⁹ whereas only 33% of people followed up in another study had persistent neurological deficits.²³ High loss to follow-up rates probably mask the true prevalence of lasting deficits, with high rates of non-attendance for treatment found.²⁴ Methionine has been used as an adjunct to treatment with B₁₂ and could represent a future avenue for treatment.^{21,25}

Psychological harm

Nitrous oxide can trigger psychological symptoms and primary psychiatric presentations. These presentations

include delusions, hallucinations, paranoia, and depression.¹⁷ Psychiatric disturbances can be the first presenting symptoms of nitrous oxide misuse and can occur in the absence of neurological or other physical health issues.²⁶ Nitrous oxide could precipitate acute psychosis in some cases.^{27,28} A history of psychiatric conditions can also predispose nitrous oxide use in the first instance.²⁹ Addiction to nitrous oxide is not well understood. There is probably a psychological element to the addiction. It is now known that the opioid system is involved in addiction, and that nitrous oxide binds directly at opioid receptors and produces typical opioid behavioural effects in humans.^{30,31} There is also evidence that nitrous oxide stimulates the GABA system.³⁰

Nitrous oxide has addictive potential, with a large proportion of cases reporting use of nitrous oxide in larger quantities and for longer than intended, and spending a great deal of time obtaining, using, and recovering from nitrous oxide.⁷ Cravings have also been shown.³² One small study of ten nitrous oxide users showed that all of them met the criteria for substance abuse and dependence as outlined by the Diagnostic and Statistical Manual of Mental Disorders fifth edition, of which most used only nitrous oxide.⁸ Humans might develop a tolerance to nitrous oxide,³³ although evidence in recreational users is scarce. Anecdotally, withdrawal might also occur.^{28,34} One study of more than 400 patients found that 55% had relapsed 6 months after first presentation.³⁵ Comorbid mental health disorders are typically associated with poor treatment outcomes and high service use among people who use substances.³⁶ There is an important role for mental health services and referral to drug and alcohol services could be required, particularly if nitrous oxide is part of polydrug misuse.^{7,8}

Other health harms

The range of adverse health outcomes related to nitrous oxide is yet to be fully elucidated. Unlike neurological and psychological health harms of nitrous oxide, which are more likely to affect regular users of nitrous oxide, some harms affect both occasional and regular users. Nitrous oxide inhalation has been reported to acutely cause pneumomediastinum and pneumothorax.³⁷ Death during nitrous oxide use is generally linked to asphyxiation.³⁸ Nitrous oxide use has been associated with thromboembolic events, including deep vein thrombosis, pulmonary embolism, and central venous sinus thrombosis,^{39,40} probably mediated via hyperhomocysteinaemia.⁴¹ Also potentially mediated via hyperhomocysteinaemia are myocardial infarction⁴² and stroke,⁴³ both of which have been reported in rare cases after nitrous oxide use. Cold burns, also known as frostbite injuries, due to recreational nitrous oxide use have been reported, especially from the use of larger cylinders.⁴⁴ Cold burns can occur via two mechanisms: direct spillage of the liquified gas onto the skin or by contact from the metal canister as it rapidly cools when the liquid nitrous

oxide turns into gas.⁴⁴ Cold burns to the medial thighs, usually bilaterally, are the most commonly reported. Eight of 16 patients in one case series had full-thickness burns, with four patients requiring excision and split-thickness skin grafts.⁴⁴

Social harms

Social context underpins both the use and the legislation of nitrous oxide. Although use of nitrous oxide and related harms have been described across a range of demographics, use is most prevalent among young people, with three large case series of patients with nitrous oxide myeloneuropathy reporting high average consumption of nitrous oxide and a median age of 21–23 years.^{8,9,23} In two large case series, one reported 37% of users were not currently employed nor in education,¹⁶ while the other reported 59% were not employed nor in education.⁹ These data suggest that markers of social deprivation are associated with nitrous oxide and criminalisation of use risks propagating the poverty–disability cycle.⁴⁵ There has been speculation that the absence of smell, easy online access, and misinformation about religious permissibility have led to high amounts of use among some ethnic groups.⁴⁶

Individuals have been reported to recreationally use nitrous oxide in their cars and while driving.⁶ Whether this car-based use is a socially influenced behaviour is unknown. Nitrous oxide has been associated with driving-related road traffic incidents and deaths. Users might incorrectly assume that the short-lived high means that cognitive faculties are unaffected during driving. Dutch road traffic incidents involving nitrous oxide increased by 80%, from 2652 incidents in 2019 to 4860 in 2021.⁶ As of 2020, 1 in 50 adults in the Netherlands used nitrous oxide and the drug was involved in almost 1800 road traffic incidents during a 3-year period, including 63 fatal incidents.⁴⁷ Driving is not advised for 30 min after nitrous oxide inhalation as impairment has been shown up to 30 min after exposure.⁴⁸ Better quality data collection is required in the UK to quantify traffic-related harm from nitrous oxide, and minimising avoidable harm through awareness is warranted.

The public health approach to nitrous oxide

The public health approach in the UK

The UK Government reviewed their legislation on nitrous oxide in 2023. Before 2023, legislation under the 2016 Psychoactive Substances Act meant that nitrous oxide was illegal to supply, produce, and carry with the intent to supply but not illegal to possess.⁴⁹ From January, 2018, to September, 2021, the Metropolitan Police in London recorded 84 nitrous oxide-related offences under the Psychoactive Substances Act.⁵⁰ In the 2 years after the 2016 Psychoactive Substances Act, there did not appear to be a change in the use of nitrous oxide, and there were at least 202 seizures of nitrous oxide by

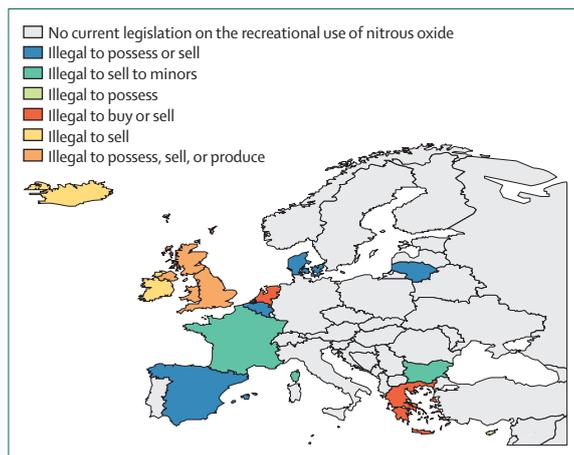


Figure 2: Legislation on the recreational use of nitrous oxide in Europe
Map accurate as of May, 2024.

police.¹⁰ Public Spaces Protection Orders for anti-social behaviour linked to nitrous oxide use have been in place in some areas of the UK, including the London Borough of Tower Hamlets since 2021.⁵¹ Between May, 2021, and the end of November, 2022, Tower Hamlets Enforcement Officers, under the nitrous oxide Public Spaces Protection Orders, gave 86 anti-social behaviour warnings and 70 enforcements.⁵²

The Advisory Council on the Misuse of Drugs (ACMD) was commissioned by the UK Home Office in September, 2021, to review the health and social implications of nitrous oxide use. This effort was expedited in January, 2023. The ACMD recommended additional measures to tackle the non-legitimate supply of nitrous oxide and advocated for more education for the public and health-care professionals on the harms associated with nitrous oxide (appendix p 1). The ACMD advised against adding nitrous oxide to the 1971 Misuse of Drugs Act on the grounds that it would not be proportionate to the harms, would criminalise young people, and would affect sectors that use nitrous oxide legitimately.⁶ The UK Government nonetheless decided to control nitrous oxide under the 1971 Misuse of Drugs Act, classifying it as a Class C drug, and cited reasons of anti-social behaviour, littering, and health harms.⁵³ Possession can now result in a 2-year prison sentence along with an unlimited fine, whereas supply and production can result in a 14-year sentence.⁴⁹

Nationally, no public health programme or intervention (ACMD recommendation 3) has accompanied the change in legislation. Several small-scale local campaigns have been initiated to provide local education and awareness. For example, N₂O: Know The Risks in east London was launched in 2021 in response to increasing numbers of people presenting to London hospitals with nitrous oxide-related harm. This initiative provides interactive workshops to young people in Tower Hamlets

to empower them with knowledge about the risks of nitrous oxide.⁵⁴ Neurologists and other medical professionals have taken to social media to dissuade young people from consuming nitrous oxide.⁵⁵

Public health approaches in Europe

A total ban on nitrous oxide is not widely supported by experts given it would be difficult to enforce due to the legitimate uses of nitrous oxide.⁵⁶ Although most countries have not introduced measures specifically targeting nitrous oxide, some have introduced laws in response to the rising popularity of nitrous oxide (figure 2) and health concerns.³ France, Ireland, and Denmark have prohibited the sale of nitrous oxide to people younger than 18 years, although this is probably easily circumvented given the ease of access to nitrous oxide via the internet. France is in the process of putting information about the harms of inhaling nitrous oxide on the packaging of all forms of nitrous oxide.³ Lithuania banned nitrous oxide except for medical and industrial purposes in 2020.³ Ireland prohibits sale under the Criminal Justice (Psychoactive Substances) Act 2010, using similar legislation to the UK before 2023.⁵⁷ In 2023, Denmark prohibited the possession of nitrous oxide in a public place and made sale illegal for the purpose of intoxication.⁵⁸

The Netherlands banned nitrous oxide as of 2023 by adding it to Schedule II of the Dutch Opium Act, prohibiting the import, export, and trade of nitrous oxide. This legislation prohibits sale rather than use, although sale as a food additive will still be allowed. This approach was taken to not discourage individuals from seeking help should they experience health issues, a concern shared by health-care professionals in many countries.^{45,56} Belgium banned the possession, transportation, and sale of nitrous oxide both physically and online unless intended for medical, technical, or catering purposes.⁵⁹

We could not identify any EU-wide legislation on the sale, possession, or consumption of nitrous oxide.

Public health approaches globally

Outside of Europe, fewer countries have laws regulating the recreational use of nitrous oxide. In Australia, laws relating to nitrous oxide vary by state. For example, in the state of South Australia, the sale of nitrous oxide is restricted under the Controlled Substances Act 1984, which prohibits the sale of nitrous oxide to people younger than 18 years and making nitrous oxide visible and accessible in retail stores,⁶⁰ whereas in Western Australia, new stricter legislation introduced in late 2024 restricts the sale of nitrous oxide to registered food and beverage businesses and restricts the sale to 10 g canisters only, with larger canisters banned.⁶¹ In Canada, it is prohibited to sell or advertise the sale of nitrous oxide to the general public.⁶² There is no federal law in the USA on nitrous oxide; however, state-level regulations differ. In California,

a person can be found guilty of a misdemeanour if they inhale nitrous oxide for recreational purposes.⁶³ Additionally, a person who knowingly dispenses nitrous oxide for intoxication is liable for a fine of up to US\$1000 or imprisonment for up to 6 months.⁶⁴ In 2020, Taiwan tackled rising recreational nitrous oxide use by regulating suppliers. Taiwan listed nitrous oxide as a controlled substance, which meant that unlicensed operators involved in the supply of nitrous oxide could be fined and nitrous oxide manufacturers have since had to record every transaction and submit a monthly report of these to the Government.⁶⁵

The inconsistent legislation on nitrous oxide might be due to many factors. Nitrous oxide is difficult to regulate due to its legitimate uses in health care and industrial sectors. The enforcement of any laws targeting the sale or possession of nitrous oxide becomes difficult as it requires distinguishing recreational from legitimate use. The sparse legislation indicates variable popularity of nitrous oxide. Although nitrous oxide is popular in western Europe and some parts of southeast Asia as a recreational drug, this might not be the case in other countries, due to cultural, social, and economic factors.

Policy effects

The effect of the UK Government passing legislation to make nitrous oxide a Class C drug remains to be seen. Neither decriminalisation nor punishments for drug possession are correlated with rates of drug use for other drugs.⁶⁶ Most research and policy focuses on adults, people older than 16 or 18 years, but adolescents as young as 14 years have sustained neurological damage due to nitrous oxide use.⁹ There could be safeguarding issues for some minors who use nitrous oxide, and it is important that a punitive approach is not taken with these young people. One study in Paris, France, showed that the most socially disadvantaged suburbs were the most affected by cases of nitrous oxide-induced neurological damage.¹⁶

In 2001, Portugal changed legislation to consider possession of any illicit drug illegal, but with no resulting criminal proceedings if the amount of drug possessed is less than the amount an average user would use during 10 days. People found in possession of drugs are referred to a panel that signposts them to appropriate services. The decriminalisation policy in Portugal has not led to an increase in drug use, rather rates for most drugs are lower than levels before 2001. Drug-related harm has also decreased, probably due to harm-reduction and treatment implementation.⁶⁷ Decriminalisation could make it easier to access support that users need to reduce or stop their drug use, should they wish to do this.

The main reason cited for scheduling nitrous oxide as a Class C drug in the UK was due to anti-social behaviour and littering. Before the decision to criminalise, the ACMD called for evidence on littering, anti-social

behaviour, and violence. Littering was anecdotally recorded; however, the ACMD found no substantive evidence to associate nitrous oxide with anti-social behaviour. The ACMD found little evidence of association with violence in the majority of users,⁶ whereas the European Crime Prevention Network described a low risk of organised crime from nitrous oxide, although they mentioned that making nitrous oxide illegal could propagate such networks.⁵⁶

For some nitrous oxide users, especially young people, comprehensive support in multiple areas of their life might be required, such as support with housing, employment, and education, not just for nitrous oxide cessation. Young people, particularly from disadvantaged backgrounds with regular use of high volumes of nitrous oxide, might require additional support beyond the purely legislative approach. Criminalisation could pose an additional barrier to accessing this support. Public and community education has a role in reducing preventable harm. Accessing regular treatment for neurological symptoms due to nitrous oxide use is essential for potential recovery and rarer medical emergencies (eg, pneumothorax or pulmonary embolism) require immediate attention and not seeking help could be fatal. However, compared with other Class C drugs, such as benzodiazepines, the annual deaths from nitrous oxide in the UK are low at 56 deaths compared with more than 2000 deaths for benzodiazepines during a 19-year period.⁶ It remains to be seen if the recent policy change will lead to delayed diagnosis and treatment and worse long-term outcomes.

The European Crime Prevention Network advocates forging community partnerships to tackle nitrous oxide misuse. For example, working with local vendors to reduce the visibility of nitrous oxide in shops or introducing the need for ID when purchasing nitrous oxide. Locally targeted awareness campaigns are key for reducing harm.⁵⁶ In the UK, there are indications that many vendors sell nitrous oxide for non-legitimate purposes, at times packaging B12 supplements, balloons, or other gas dispensing equipment.⁶ For Winstock and Ferris¹⁴ (who run the Global Drug Survey), nitrous oxide use is unlikely to decrease in response to increased enforcement, but instead health promotion campaigns that raise awareness of neurological risks are likely to be the most effective approach.¹⁴

Health and social harms associated with nitrous oxide use are increasing in UK cities and across Europe, and several other parts of the world. Further research is needed to better understand the full range of health and social effects of nitrous oxide, and more action is needed to educate those most at risk of nitrous oxide use and targeted campaigns for heavy users of nitrous oxide most at risk of health sequelae. Although laws could reduce use, education to prevent harm and interventions that target sellers, not the end user, are necessary. Health policy will play a crucial role in determining the trajectory of nitrous oxide-induced

Search strategy and selection criteria

We searched MEDLINE via PubMed from database inception on April 24, 2024, to ascertain the health harms reported in case reports and series relating to nitrous oxide. We used the search string (“nitrous oxide” OR N2O) AND (recreational OR misuse OR abuse) AND (“case report” or “case series” OR cases OR patient OR patients). A secondary search was conducted in January, 2025, to obtain any further reports from Jan 1 to Dec 31, 2024. We included papers written in English and chose papers based on quality and breadth of information covered, with a preference for case reports over singular case reports. Due to the nature of governmental health policy and the necessity of grey literature to understand this topic, a systematic search was not carried out to examine the health policies.

presentations, and how the population that uses nitrous oxide responds.

Prevention is key to reducing the harm that young people come to through nitrous oxide use. Targeted strategies to educate those most at risk are essential. The use of social media and community initiatives to reach those most at risk of coming to harm should be continued, while also making nitrous oxide harder to obtain. Holding vendors, both physical and online, to account will be essential in reducing the accessibility and use of nitrous oxide and the harms caused by it.

Contributors

SAZ, DM, AP, and AJN conceptualised the Health Policy. SAZ drafted the initial manuscript. DM contributed to the writing of the manuscript. SAZ and DM created the figures. SAZ, DM, AP, LJS, MP, BLO, and AJN reviewed the manuscript. AJN was responsible for overall supervision.

Declaration of interests

DM leads the educational campaign N₂O: Know the Risks. AJN reports grants from the Queen Mary University London Impact Fund and Tower Hamlets Council related to nitrous oxide educational programmes and clinical service development; and sits on the ACMD advisory council. All other authors declare no competing interests.

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References

- Ehirim EM, Naughton DP, Petróczy A. No laughing matter: presence, consumption trends, drug awareness, and perceptions of “hippy crack” (nitrous oxide) among young adults in England. *Front Psychiatry* 2018; 8: 312.
- Winstock A, Munksgaard R, Davies E, Ferris J, ZhuParris A, Barratt M. 2022 Drug Trend Report: Time, Music, Clubbing, Age, and Diet. https://www.globaldrugssurvey.com/wp-content/uploads/2022/02/2022WowReport_Final.pdf (accessed Jan 14, 2025).
- European Monitoring Centre for Drugs and Drug Addiction. Recreational use of nitrous oxide: a growing concern for Europe. 2022. https://www.emcdda.europa.eu/system/files/media/publications/documents/14934/20225054_PDF_TD0922561ENN_002.pdf (accessed April 10, 2023).
- Global Drug Survey. GDS 2021 Global Report. 2021. https://www.globaldrugssurvey.com/wp-content/uploads/2021/12/Report2021_global.pdf (accessed May 28, 2024).
- UK Office for National Statistics. Drug misuse in England and Wales: year ending March 2023. 2023. <https://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/articles/drugmisuseinenglandandwales/yearendingmarch2023> (accessed June 14, 2024).
- UK Advisory Council on the Misuse of Drugs. Nitrous oxide: updated harms assessment. 2023. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1140251/ACMD_Nitrous_Oxide_Report_06_March.pdf (accessed May 28, 2024).
- Fidalgo M, Prud'homme T, Allio A, et al. Nitrous oxide: what do we know about its use disorder potential? Results of the French Monitoring Centre for Addiction network survey and literature review. *Subst Abus* 2019; 40: 33–42.
- Nugteren-Van Lonkhuyzen JJ, van der Ben L, van den Hengel-Koot IS, de Lange DW, van Riel AJHP, Hondebrink L. High incidence of signs of neuropathy and self-reported substance use disorder for nitrous oxide in patients intoxicated with nitrous oxide. *Eur Addict Res* 2023; 29: 202–12.
- Mair D, Paris A, Zaloum SA, et al. Nitrous oxide-induced myeloneuropathy: a case series. *J Neurol Neurosurg Psychiatry* 2023; 94: 681–88.
- UK Home Office. Review of the Psychoactive Substances Act 2016. 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/756896/Review_of_the_Psychoactive_Substances_Act_2016_web_.pdf (accessed April 10, 2023).
- Kaar SJ, Ferris J, Waldron J, Devaney M, Ramsey J, Winstock AR. Up: the rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. *J Psychopharmacol* 2016; 30: 395–401.
- DrugScience, The Global Drug Survey, Release, Transform Drug Policy. House of Commons debate briefing for MPs: tackling the misuse of nitrous oxide. 2020. https://drugscience.org.uk/wp-content/uploads/2020/07/Briefing-House-of-Commons-Debate-NitrousOxide_21072020.pdf (accessed April 10, 2023).
- Goldwhip. How do N2O flavours work? <https://www.goldwhip.com/post/how-do-n2o-flavours-work> (accessed May 27, 2024).
- Winstock AR, Ferris JA. Nitrous oxide causes peripheral neuropathy in a dose dependent manner among recreational users. *J Psychopharmacol* 2020; 34: 229–36.
- Oussalah A, Julien M, Levy J, et al. Global burden related to nitrous oxide exposure in medical and recreational settings: a systematic review and individual patient data meta-analysis. *J Clin Med* 2019; 8: 551.
- Dawudi Y, Azoyan L, Broucker TDE, et al. Marked increase in severe neurological disorders after nitrous oxide abuse: a retrospective study in the greater Paris area. *J Neurol* 2024; 271: 3340–46.
- Garakani A, Jaffe RJ, Savla D, et al. Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: a systematic review of the case literature. *Am J Addict* 2016; 25: 358–69.
- Savage S, Ma D. The neurotoxicity of nitrous oxide: the facts and “putative” mechanisms. *Brain Sci* 2014; 4: 73–90.
- Gernez E, Deheul S, Tard C, Joncquel M, Douillard C, Grzych G. Plasma methionine and clinical severity in nitrous oxide consumption. *Toxics* 2022; 11: 12.
- Pugliese RS, Slagle EJ, Oettinger GR, Neuberger KJ, Ambrose TM. Subacute combined degeneration of the spinal cord in a patient abusing nitrous oxide and self-medicating with cyanocobalamin. *Am J Health Syst Pharm* 2015; 72: 952–57.
- Paris A, Lake L, Joseph A, et al. Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment. *Pract Neurol* 2023; 23: 222–28.
- Thompson AG, Leite MI, Lunn MP, Bennett DL. Whippits, nitrous oxide and the dangers of legal highs. *Pract Neurol* 2015; 15: 207–09.
- Yu M, Qiao Y, Li W, et al. Analysis of clinical characteristics and prognostic factors in 110 patients with nitrous oxide abuse. *Brain Behav* 2022; 12: e2533.
- Zaloum SA, Paris A, Mair D, et al. Evaluation of an ambulatory care pathway for patients with nitrous oxide-induced myeloneuropathy. *BMJ Neurol Open* 2024; 6: e000737.
- Scott JM, Dinn JJ, Wilson P, Weir DG. Pathogenesis of subacute combined degeneration: a result of methyl group deficiency. *Lancet* 1981; 2: 334–37.

- 26 Paulus MC, Wijnhoven AM, Maessen GC, Blankensteijn SR, van der Heyden MAG. Does vitamin B12 deficiency explain psychiatric symptoms in recreational nitrous oxide users? A narrative review. *Clin Toxicol* 2021; **59**: 947–55.
- 27 Sood R, Parent T. Peripheral polyneuropathy and acute psychosis from chronic nitrous oxide poisoning: a case report with literature review. *Medicine* 2022; **101**: e28611.
- 28 Brodsky L, Zuniga J. Nitrous oxide: a psychogenic agent. *Compr Psychiatry* 1975; **16**: 185–88.
- 29 Chien WH, Huang MC, Chen LY. Psychiatric and other medical manifestations of nitrous oxide abuse: implications from case series. *J Clin Psychopharmacol* 2020; **40**: 80–83.
- 30 Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. *Anesth Prog* 2007; **54**: 9–18.
- 31 Gillman MA. Analgesic (sub anesthetic) nitrous oxide interacts with the endogenous opioid system: a review of the evidence. *Life Sci* 1986; **39**: 1209–21.
- 32 Ickowicz S, Brar R, Nolan S. Case study: naltrexone for the treatment of nitrous oxide use. *J Addict Med* 2020; **14**: e277–79.
- 33 Davy H. Researches chemical and philosophical: chiefly concerning nitrous oxide or dephlogisticated nitrous air and its respiration. 1800. <https://wellcomecollection.org/works/wtdr8dvd> (accessed June 14, 2024).
- 34 Back S, Kroon E, Colyer-Patel K, Cousijn J. Does nitrous oxide addiction exist? An evaluation of the evidence for the presence and prevalence of substance use disorder symptoms in recreational nitrous oxide users. *Addiction* 2024; **119**: 609–18.
- 35 Xu J, Zhang Y, Lei C, Sun P, Chen R, Yuan T. Using machine learning to identify factors related to nitrous oxide (laughing gas) relapse among adolescents. *Gen Psychiatr* 2023; **36**: e101003.
- 36 Rand K, Arnevik EA, Walderhaug E. Quality of life among patients seeking treatment for substance use disorder, as measured with the EQ-5D-3L. *J Patient Rep Outcomes* 2020; **4**: 92.
- 37 Davidson LT. Recreational use of nitrous oxide causes seizure, pneumothorax, pneumomediastinum, and pneumopericardium: nitrous oxide and its harm, a case report. *Ups J Med Sci* 2023; **128**: 128.
- 38 Bäckström B, Johansson B, Eriksson A. Death from nitrous oxide. *J Forensic Sci* 2015; **60**: 1662–65.
- 39 Patyjewicz M, Mair D, Zaloum SA, et al. Recreational nitrous oxide and thrombotic events: a case series. *BMJ Neurol Open* 2024; **6**: e000619.
- 40 Oulkadi S, Peters B, Vliegen AS. Thromboembolic complications of recreational nitrous oxide (ab)use: a systematic review. *J Thromb Thrombolysis* 2022; **54**: 686–95.
- 41 Caris MG, Kuipers RS, Kiestra BE, et al. Nitrous oxide abuse leading to extreme homocysteine levels and thrombosis in young adults: a case series. *J Thromb Haemost* 2023; **21**: 276–83.
- 42 Oomens T, Riezebos RK, Amoroso G, Kuipers RS. Case report of an acute myocardial infarction after high-dose recreational nitrous oxide use: a consequence of hyperhomocysteinaemia? *Eur Heart J Case Rep* 2021; **5**: ytaa557.
- 43 Bajaj D, Agrawal A, Gupta S, Bajaj S. Recreational nitrous oxide abuse causing ischemic stroke in a young patient: a rare case report. *Cureus* 2018; **10**: e3761.
- 44 Chen JHC, Eriksson S, Mohamed H, Bhatti S, Frew Q, Barnes D. Experiences of frostbite injury from recreational use of nitrous oxide canisters in a UK burns center: not a laughing matter. *J Plast Reconstr Aesthet Surg* 2023; **83**: 282–88.
- 45 Paris A, Mair D, Zaloum S, Onen B, Noyce AJ. Nitrous oxide and its neurological harms. *Lancet Neurol* 2023; **22**: 882.
- 46 Nabben T, Weijts J, van Amsterdam J. Problematic use of nitrous oxide by young Moroccan–Dutch adults. *Int J Environ Res Public Health* 2021; **18**: 5574.
- 47 Rankin J. Dutch to ban laughing gas over fears for health and road safety. *The Guardian*. 2022. <https://www.theguardian.com/society/2022/nov/15/dutch-to-ban-laughing-gas-over-fears-for-health-and-road-safety> (accessed April 10, 2023).
- 48 Moyes D, Cleaton-Jones P, Lelliot J. Evaluation of driving skills after brief exposure to nitrous oxide. *S Afr Med J* 1979; **56**: 1000–02.
- 49 UK Government. Drug penalties. 2023. <https://www.gov.uk/penalties-drug-possession-dealing> (accessed May 28, 2024).
- 50 Metropolitan Police. Nitrous oxide incidents from January 2018 to September 2021. 2022. <https://www.met.police.uk/foi-ai/metropolitan-police/d/february-2022/nitrous-oxide-incident-january2018-september2021/> (accessed May 28, 2024).
- 51 Tower Hamlets. Public Space Protection Order to tackle use of nitrous oxide linked to antisocial behaviour. 2021. https://www.towerhamlets.gov.uk/News_events/2021/May-2021/Public-Spaces-Protection-Order-to-tackle-use-of-nitrous-oxide-linked-to-antisocial-behaviour.aspx#:~:text=On%20Wednesday%2028%20April%20the,out%20in%20a%20specified%20area (accessed April 9, 2023).
- 52 Tower Hamlets Borough Council. Public Space Protection Order enforcement. 2022. https://www.whatdotheyknow.com/request/public_space_protection_order_en_41 (accessed May 4, 2024).
- 53 Philp C. Government response: ACMD nitrous oxide review. 2023. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1145963/Nitrous_Oxide_letter_to_ACMD_-_March_2023_-_FINAL_003_003_.pdf (accessed April 10, 2023).
- 54 Mair D, Zaloum SA, Patel F, Noyce AJ. Effectiveness of interactive workshops to raise awareness of the neurological harms associated with nitrous oxide use: a cross-sectional study. *Lancet* 2023; **402** (suppl 1): S65.
- 55 Hussain Z. Nitrous oxide: doctors warn of “epidemic” of use by young people. *BMJ* 2022; **378**: e0155.
- 56 European Crime Prevention Network. Recommendation paper: preventing the misuse of nitrous oxide. 2021. https://eucpn.org/sites/default/files/document/files/2101_Preventing%20the%20misuse%20of%20nitrus%20oxide_ENG_LR_0.pdf (accessed April 10, 2023).
- 57 Mongan D. Nitrous oxide use in Ireland. 2023. https://www.drugsandalcohol.ie/38441/1/Drugnet_84.pdf (accessed Jan 14, 2025).
- 58 Danish Safety Technology Authority. Carrying nitrous oxide in public places or selling it to others will be prohibited. 2023. <https://via.ritzau.dk/pressemeddelelse/13702039/det-bliver-forbudt-at-medbringe-lattergas-pa-offentlige-steder-eller-saelge-det-til-andre?publisherId=90703> (accessed Jan 28, 2024).
- 59 Walker L. Belgium officially bans laughing gas as intoxicant becomes widespread. 2023. <https://www.brusselstimes.com/840552/belgium-will-officially-ban-laughing-gas-as-intoxicant-becomes-widespread> (accessed Jan 14, 2024).
- 60 Government of South Australia. Nitrous oxide regulations. <https://www.agd.sa.gov.au/law-and-justice/legislation/nitrous-oxide-regulations> (accessed Jan 28, 2024).
- 61 Government of Western Australia Department of Health. Nitrous oxide. 2024. https://www.health.wa.gov.au/Articles/N_R/nitrous-oxide (accessed Jan 14, 2025).
- 62 Government of Canada. Drugs (continued). 2023 https://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/page-67.html (accessed Jan 28, 2024).
- 63 Legislative Council of California. Part 1 of crimes and punishments of crimes against the public health and safety. https://leginfo.ca.gov/faces/codes_displaySection.xhtml?sectionNum=381b.&lawCode=PEN (accessed Jan 28, 2024).
- 64 Legislative Council of California. AB-1735 nitrous oxide: dispensing and distributing. 2014. https://leginfo.ca.gov/faces/billTextClient.xhtml?bill_id=201320140AB1735 (accessed Jan 28, 2024).
- 65 Taipei Times. Nitrous oxide added to controlled substances list. 2020. <https://www.taipetimes.com/News/taiwan/archives/2020/10/31/2003746098> (accessed April 5, 2024).
- 66 Eastwood N, Fox E, Rosmarin A. A quiet revolution: drug decriminalisation across the globe. 2016. <https://www.release.org.uk/sites/default/files/pdf/publications/A%20Quiet%20Revolution%20-%20Decriminalisation%20Across%20the%20Globe.pdf> (accessed April 10, 2023).
- 67 UK Home Office. Drugs: international comparators. 2014. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/368489/DrugsInternationalComparators.pdf (accessed April 10, 2023).

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