PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

PERSPECTIVE

Laughing gas: nothing to laugh about

André Costa e Silva

Hospital Santa Luzia, Viana do Castelo, Portugal

Abstract

Trends in substance abuse are constantly evolving and therefore our awareness and knowledge as health professionals should too. Nitrous oxide (N_2O), also known as "laughing gas", "nangs", "whippits" or "hippie crack" has been used in a recreational context for almost 250 years, with a few periods of exponential growth in its use during that time, the latest occurring in the last 10 years. There is, however, a significant difference when comparing recent years to the 1970s or the Victorian era. Nowadays, N_2O is not only widely available, it is also cheap and easy to use. Adolescents who abuse N_2O are seeking quick sensations such as euphoria, relaxation, or hallucinations, unaware of, or disregarding, the potential serious adverse effects and chronic consequences. In 2014, the Global Drug Survey confirmed that N_2O had become increasingly popular as a recreational drug and Portugal, unfortunately, is no exception. In 2021, Portuguese law enforcement authorities seized nearly 400 units of canisters (N_2O containers) and 2022 followed the same trend, which led to a proposal to the Portuguese Ministry of Health to regulate N_2O sales and consumption. In September 2022, that proposal was approved and ever since, N_2O has been classified as a prohibited psychoactive substance.

Keywords: Drugs. Nitrous oxide. Adolescents. Vitamin B12. Neurotoxicity.

Gás do riso: sem razões para rir

Resumo

O forma de uso e abuso de substâncias ilícitas está em constante mutação pelo que os profissionais de saúde devem ter essa consciência e acompanhar a evolução do conhecimento nessa área. O óxido nitroso (N_2O), também conhecido como "gás do riso", "nangs", "whippits" ou "hippie crack", tem sido usado em contexto recreativo há quase 250 anos, com alguns períodos de crescimento exponencial, o mais recente ocorrendo nos últimos 10 anos. No entanto, existe uma diferença significativa ao comparar os anos recentes com os anos 1970, ou da era vitoriana. Atualmente, o N_2O não só está amplamente disponível, como também é barato e fácil de usar. Os adolescentes que abusam do N_2O procuram sensações rápidas como euforia, relaxamento ou alucinações, ignorando ou desconsiderando os potenciais efeitos adversos graves e consequências crónicas. Em 2014, o Global Drug Survey confirmou que o N_2O se tinha tornado cada vez mais popular como uma droga recreativa e Portugal, infelizmente, não é exceção. Em 2021, as autoridades portuguesas apreenderam quase 400 unidades de cartuchos (recipientes de N_2O), sento que 2022 seguiu a mesma tendência, o que levou a uma proposta ao Ministério da Saúde Português para regular as vendas e o consumo de N_2O. Em setembro de 2022, essa proposta foi aprovada e, desde então, o N_2O foi classificado como uma substância psicoativa proibida.

Palavras-chave: Drogas. Óxido nítrico. Adolescentes. Vitamina B12. Neurotoxicidade.

Correspondence:
André Costa e Silva
E-mail: andrecostaesilva1@gmail.com

Received: 25-02-2023
Accepted: 27-11-2023
https://pjp.spp.pt

Available online: 01-04-2024
Port J Pediatr. 2024;55(2):113-116
DOI: 10.24875/PJP.M24000437

Keypoints

What is known

- N_2O mixed with oxygen has been a valuable tool in pediatric emergency departments for managing pain during procedures. Its anesthesiological properties and side-effect reduction are well-documented.
- N_2O has a history of recreational use dating back to the 19th century, including "laughing gas parties" among the British upper class and usage among university students in the 1970s for euphoria.

What is added

- This paper outlines recent trends in the recreational use of N_2O, including its growing popularity among adolescents and the legislative actions taken in Portugal and other countries to address this issue. This includes the classification of N_2O as a prohibited substance in Portugal as of September 8, 2022.
- It emphasizes the need for education on the health hazards of inhalants for children, adolescents, parents, and teachers. Furthermore, it advocates for referring patients with N_2O abuse issues to specialized institutions for drug dependence treatment.

Nitrous oxide (N_2O) and its psychotropic effects have been known to the scientific community for over two centuries. In 1772, Joseph Pristley firstly synthesized N_2O and a few years later Humphry Davy investigated, by personally inhaling N_2O, the chemistry of the gas and its psychotropic properties[1]. 1844 was the year when Horace Wells, a dentist, discovered its anesthesiologic properties and used it for the first time to extract his own molar teeth[1]. From then on, several milestones followed, including the discovery that using a mixture of N_2O and oxygen helped prevent or reduce side effects such as hypoxia and nausea/vomiting. Nowadays, a mixture of N_2O and oxygen is a very useful tool in several pediatric emergency departments in managing/sedating children and adolescents who require painful procedures (fracture reductions, minor surgery, suturing or venous access, etc.).

On a different note, and following medicinal use, N_2O also began to be used recreationally. During the 19th century, members of the British upper class engaged in a peculiar form of entertainment, known as laughing gas parties, where N_2O was inhaled from silk bags[2]. Those who inhaled N_2O did so to lose their inhibitions and dance/sing. In the 1970s, the gas grew in importance as university students sourced N_2O from canisters (cylinders) for making whipped cream and used it for a quick sensation of euphoria[3]. From a cohort of 500 medical and dentals students, a study performed in 1976 found that 16% had used N_2O recreationally in the past[4].

Since then and up until 2010, other drugs attracted more attention and nitrous oxide lost its appeal to the younger generation as a recreational drug. However, the truth is that in recent years a new trend is emerging, showing a growing consumption/abuse of this gas among adolescents. In the "streets", N_2O has been nicknamed "laughing gas", "hippie crack," "whippets", and "chargers". Teenagers usually inhale it through a balloon or bulb, known as "nagging" or "nanging".

Ever since 2010, many countries around the world have documented this increase in the recreational use of N_2O. The problem became increasingly concerning from 2017, when both the supply and consumption of the gas grew[4]. The market adjusted for this substance and suppliers began to sell larger cylinders of the gas, deliberately targeting this recreational market. As a result, N_2O is now easily available and cheap. It is not only easy to find and order online, but social media has also helped encourage the use of this gas at parties, festivals, and raves, making N_2O a very common drug.

In 2014, a Global Drug Survey involving 74,864 participants from 17 countries confirmed that N_2O had gained interest among teenagers as a popular recreational drug[5]. The same group conducted another survey in 2019 involving 30 countries (including Portugal), which confirmed the popularity of this drug[6]. A survey conducted in 2020 in England, aimed at 16- to 24-year-olds, found that nine percent had used N_2O in the previous year, making the drug second only to cannabis[7].

In recent years in Portugal, a number of newspaper articles have been warning of the recent popularity of N_2O among the younger population. Unlike nearly all other drug classes, it is most-commonly used among younger adolescents with use peaking between the seventh and ninth grades[8]. In 2021, 93 confiscations of nitrous oxide (bottles or balloons) were recorded, namely in Lisbon, Setúbal and Faro[4]. Around 300 to 400 units of varying sizes of canisters and bottles were seized[4].

In 2022, up until the conclusion of the report entitled 'Recreational use of nitrous oxide: a growing concern for Europe', 35 confiscations of nitrous oxide (bottles or balloons) had already been documented by Portuguese law enforcement authorities. Following these events, the

General Directorate for Intervention on Addictive Behaviors and Dependencies (SICAD) submitted a proposal to the Ministry of Health to regulate sales and consumption of nitrous oxide[9]. The proposal was approved and ever since September 8, 2022, nitrous oxide has been classified as a prohibited psychoactive substance[9]. Despite legislative action and these regulations, N_2O remains easily accessible online and even in some convenience stores.

When inhaling the gas, users seek certain symptoms/sensations such as relaxation, a giggly mood, sound or visual distortions, and euphoria. All of these are immediate upon inhalation and disappear in a matter of 1 to 2 minutes usually, depending on the dose and concomitant drugs[2]. However, adverse effects can also occur: headache, dizziness and intense feelings of paranoia[1,2,3].

To date, the mechanisms of N_2O toxicity have not been fully elucidated. Clinically, its toxicity can be divided into acute toxicity and chronic toxicity[5,10]. In terms of acute toxicity, N_2O, once inhaled, diffuses across the basement membrane of the alveoli faster than oxygen and then rapidly enters the bloodstream, diluting the volume of oxygen in the alveoli. Decreased oxygen tension in the alveoli then leads to decreased oxygen delivery to the brain, and it is this hypoxia that is responsible for the sensations sought by consumers. Healthy individuals can tolerate this hypoxia in a well-ventilated space, but individuals with comorbidities such as epilepsy or heart diseases may develop seizures, arrhythmias, or even respiratory or cardiac arrest[3].

Chronic toxicity is mainly dependent on vitamin B12 deficiency. N_2O causes oxidation of the cobalt ion in vitamin B12, thereby rendering it inactive, and leading to functional vitamin B12 deficiency, even with normal stores. Without vitamin B12, homocysteine cannot be converted to methionine, thus preventing methylation of myelin proteins and ultimately promoting demyelination in the peripheral and central nervous systems. In the spinal cord, there is a predilection for demyelination in the dorsal columns, leading to a myelopathy due to 'subacute combined degeneration' of the spinal cord[10].

N_2O neurotoxicity can present with varying degrees of upper and lower motor neuron involvement. Spinal cord involvement manifests as spasticity, pyramidal pattern weakness and dorsal column sensory loss. Peripheral nerve involvement results in length-dependent large- and small-fiber sensory loss and symmetrical distal weakness. Some patients also develop visual disturbance due to optic neuropathy. Also, hyperhomocysteinemia induced by the enzymatic inhibition of methionine synthase is known to cause increased rates of thrombosis, and ischemic strokes have been linked to the recreational use of nitrous oxide in the past[11].

Some studies also suggest transient elevations in plasma homocysteine play a role in the pathogenesis of acute myocardial infarctions, via endothelial dysfunction, oxidative stress, and vascular inflammation[12]. When it comes to chronic elevations of homocysteine, these are often associated with the development of coronary artery disease via accelerated atherosclerosis[12]. A contribution of nitrous oxide on the etiology of pneumothorax and pneumomediastinum was also described[13,14].

Other complications include: mental symptoms (such as delusion, delirium, and depression), megaloblastic anemia, skin changes, and immune disorders[3]. This means that the abuse of N_2O should constitute one of the differential diagnoses in subacute-onset myeloneuropathy to explore metabolic (folic acid and copper deficiency), infectious (syphilis and HIV), vascular (spinal cord ischemia), neoplastic (compressive tumor), and autoimmune/inflammatory (Guillain-Barre syndrome and multiple sclerosis) causes.

When it comes to managing acute inhalant intoxication, maintaining cardiorespiratory function and removing the child from the source of the toxin (bottle or bag) are of primary importance. When hypoxic, supplemental 100% oxygen by a non-rebreather face mask should be administered. As to treatment in cases of neurotoxicity, this involves cessation of N_2O and immediate administration of vitamin B12. Current guidelines suggest intramuscular, rather than oral, treatment, at a dose of 1 mg on alternating days for two weeks, although it is reasonable to continue with this replacement schedule while there is ongoing neurological improvement[4,15,16].

Given the fact that adolescents will often conceal their N_2O exposure history, abuse of this gas is likely to be missed as a possible cause in emergency or medical departments, leading to misdiagnosis. Physicians, especially pediatricians, should be aware of the increasing prevalence of N_2O abuse and its potential complications. When suspected, laboratory assessments should include blood testing for vitamin B12, homocysteine, methylmalonic acid, and folic acid. Close contact with Centro de Informação Antivenenos (CIAV) should be established when nitrous oxide intoxication is suspected.

Education focused on the health hazards of inhalants and aimed at children, adolescents, parents, and teachers should be carried out in order to try and keep abreast of trending drugs. Finally, patients with either chronic or acute abuse of nitrous oxide should be referred to institutions/organizations specifically

designed to help patients dealing with drug dependence, such as the Gabinete de Prevenção Seletiva e Indicada (CLICK) and the Gabinete de Atendimento a Jovens e Envolventes (GAJE).

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Gillman MA. Mini-Review: A Brief History of Nitrous Oxide (N2O) Use in Neuropsychiatry. Curr Drug Res Rev. 2019;11(1):12-20. doi: 10.2174/1874473711666181008163107. PMID: 30829177; PMCID: PMC6637098.
2. Evans EB, Evans MR. Nangs, balloons and crackers: Recreational nitrous oxide neurotoxicity. Aust J Gen Pract. 2021 Nov;50(11):834-838. doi: 10.31128/AJGP-10-20-5668. PMID: 34713284.
3. Xiang Y, Li L, Ma X, Li S, Xue Y, Yan P, et al. Recreational Nitrous Oxide Abuse: Prevalence, Neurotoxicity, and Treatment. Neurotox Res. 2021 Jun;39(3):975-985. doi: 10.1007/s12640-021-00352-y. Epub 2021 Mar 26. PMID: 33770366.
4. European Monitoring Centre for Drugs and Drug Addiction (2022), Recreational use of nitrous oxide: a growing concern for Europe, Publications Office of the European Union, Luxembourg.
5. 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 Apr;30(4): 395-401. doi: 10.1177/0269881116632375. Epub 2016 Feb 24. PMID: 26912510.
6. Barratta MJ, Hughes CE, Ferris JA, Global Drug Survey (2019). The GDS Core Research Team, London, UK. Available online at: https://www.globaldrugsurvey.com/wp-content/themes/globaldrugsurvey/results/GDS2019-Exec-Summary.pdf (accessed May 19, 2019).
7. Office for National Statistics. Drug misuse in England and Wales: year ending March 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/articles/drugmisuseinenglandandwales/yearendingmarch2020 (Accessed on January, 2023).
8. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future National Results on Adolescent Drug Abuse: Overview of Key Findings, 2010. 2011. http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2010.pdf (Accessed on November 30, 2011)
9. Diário da República n.º 173/2022, Série I de 2022-09-07, pp. 4-8 (September 7, 2022).
10. Evans EB, Evans MR. Nangs, balloons and crackers: Recreational nitrous oxide neurotoxicity. Aust J Gen Pract. 2021 Nov;50(11):834-838. doi: 10.31128/AJGP-10-20-5668. PMID: 34713284.
11. 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 Dec 21;10(12):e3761. doi: 10.7759/cureus.3761. PMID: 30820381; PMCID: PMC6389023.
12. Pushpakumar S, Kundu S, Sen U. Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. Curr Med Chem. 2014;21(32):3662-72. doi: 10.2174/0929867321666140706142335. PMID: 25005183; PMCID: PMC5539954.
13. McDermott R, Tsang K, Hamilton N, Belton M. Recreational nitrous oxide inhalation as a rare cause of spontaneous pneumomediastinum. BMJ Case Rep. 2015 Sep 21;2015:bcr2015209750. doi: 10.1136/bcr-2015-209750. PMID: 26392441; PMCID: PMC4577686.
14. Garbaz L, Mispelaere D, Boutemy M, Jounieaux V. Pneumothorax et inhalation volontaire de protoxyde d'azote [Pneumothorax following recreational inhalation of nitrous oxide]. Rev Mal Respir. 2007; 24(5): 622- 624. French. https://doi.org/10.1016/s0761-8425(07)91130-4
15. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ 2014;349:g5226. doi: 10.1136/bmj. g5226.
16. Expert Group for Gastrointestinal Guidelines. Vitamin, mineral and trace element deficiencies. In eTG complete [Internet]. Melbourne, Vic: Therapeutic Guidelines Limited, 2016.