Nitrous oxide (N₂O) is used in the food industry as a mixing and foaming agent (E942) in the production of whipped cream, and as a fuel booster in the motor industry. It is also a familiar agent in obstetric, dental, emergency, and anaesthetic practice, where its use is made of its analgesic and anaesthetic properties. However, nitrous oxide was used recreationally long before its medical potential was realized. Joseph Priestly is accredited with synthesizing the gas in 1772, and by the late 18th century inhalation was realized. Joseph Priestly is accredited with synthesizing the gas in 1772, and by the late 18th century inhalation was realized. Nitrous oxide became a popular public entertainment. The product is freely available from catering outlets, street vendors, and even via home-delivery service through the Internet. For recreational use, nitrous oxide is commonly sold in pre-filled balloons (at point of use) or small pressurized metal canisters or mobile vans advertising nitrous oxide for sale in UK cities. A standard catering canister containing 8 g of nitrous oxide in a volume of 10 cm³ can be refilled. Although the routine use of nitrous oxide in anaesthesia is declining in both the UK and internationally, there has been a recent resurgence of recreational use of the gas. Its presence is now commonplace at festivals and university parties, with a surprisingly high 7.6% of 16- to 24-yr-olds responding to the 2013/14 Crime Survey for England and Wales reporting nitrous oxide use in the preceding year. This is a greater proportion than had used cocaine, ecstasy, or ketamine. Despite this, it is our impression that many anaesthetists and emergency department doctors are unaware of the scale of nitrous oxide use in the community.

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pressure of nitrous oxide increases in the lungs and subsequently in the bloodstream, producing the desired neurological effects.

**An ideal agent for recreational use?**

The first time I inspired the nitrous oxide, I felt a highly pleasurable sensation of warmth over my whole frame . . . The only motion which I felt inclined to make, was that of laughing at those who were looking at me. My eyes felt distended, and towards the last, my heart beat as if it were leaping up and down. On removing the mouth-piece, the whole sensation went off almost immediately.

Samuel Taylor Coleridge, poet, letter to Sir Humphrey Davy, 1799

Nitrous oxide fulfills many of the desirable properties of an ideal agent for the food industry in that it is non-flammable, bacteriostatic, colourless, tasteless, and odourless. It also has properties that attract recreational drug users. It is legal, cheap, readily available, and undetectable on routine drug screens. It has a very rapid onset of action, such that the physiological effects (behavioural disinhibition, analgesia, and euphoria) begin within seconds of inhaling the gas. Its rapid offset of action and lack of hangover effect mean that the user may safely resume normal activities within a short time of exposure. As one university student described the experience: ‘it came on fast and totally wipes you out . . . and in five minutes you are ready to do your homework.’

The gas produces minimal cardiorespiratory disturbance in fit patients and is rapidly and completely eliminated from the body after exposure, so is generally considered to be safe. However, it may pose significant risks in certain population groups, and with particular methods of administration. There were 17 deaths related to nitrous oxide misuse reported between 2006 and 2012.3 The true figure could be much higher, with intoxication falsely attributed to other drugs.

**Dangers of recreational nitrous oxide use**

Nitrous oxide has a number of specific adverse effects of relevance to patient selection for general anaesthesia involving the agent,11 12 but also poses risks to fit subjects engaged in recreational use.

High concentrations of inhaled nitrous oxide constitute a hypoxic inspired mixture. The dangers of such mixtures in the dental chair will be familiar to older generations of anaesthetists, and contributed to the Department of Health banning general anaesthesia by non-anaesthetists outside the hospital setting.13 The likelihood and severity of resultant hypoxaemia will depend on the effectiveness of nitrous oxide delivery, air entrainment, depth of respiration, and breath-holding to alter washout of nitrogen, oxygen, and carbon dioxide from the lungs. Such hypoxaemia should be well tolerated by a fit person but could give rise to seizures, arrhythmias, or even respiratory or cardiac arrest in patients with epilepsy, cardiac disease, or other co-morbidities, especially if combined with other centrally acting or arrhythmogenic drugs.

Vomiting in patients who are obtunded by co-ingestion of other drugs carries an aspiration risk, and the disorientation and loss of motor control caused by nitrous oxide can result in trauma, particularly if used while driving or operating machinery. Although there is said to be no physiological addiction, like any drug, nitrous oxide can be habit forming, with the associated financial and social implications. A handbill from 1845 advertising a public demonstration of the effects of laughing gas proclaimed ‘those who inhale the Gas once are always anxious to inhale it a second time.’

**Problems from chronic use**

Chronic or intensive nitrous oxide abuse carries serious risks. Nitrous oxide interferes with DNA synthesis during even relatively short exposures,11 by directly inhibiting the enzyme methionine synthase and inactivating its cofactor, vitamin B12, resulting in reduced synthesis of methionine and tetrahydrofolate. A few hours of exposure can cause megaloblastic changes in the bone marrow, and days of exposure can cause agranulocytosis.11 10 The likelihood of vitamin B12 inactivation is increased in individuals abusing the gas in poorly ventilated environments and in those with pre-existing low vitamin concentrations, such as vegans or those with pernicious anaemia. Habitual abuse inhibits the synthesis of new methionine synthetase.

Chronic vitamin B12 inactivation can present with symptoms ranging from mild paraesthesia10 to a neurological condition resembling subacute degeneration of the cord.11 14 15 Impairment of methylation of myelin sheath proteins results in axonal loss, causing myelopathy and peripheral neuropathy. Instances linked to chronic or intensive nitrous oxide abuse have presented with ascending or intermittent distal numbness, ataxia, impaired proprioception, and reduced grip strength.15 16 Investigations in these patients have revealed increased mean cell volume despite normal haemoglobin concentrations, low or low-normal vitamin B12 concentrations, high homocysteine (methionine precursor) concentrations, and long segmental hypertensity changes in the posterior columns on magnetic resonance imaging.15 Some of these patients have been treated successfully with vitamin B12 and folate supplementation alongside cessation of nitrous oxide use, but others have suffered permanent neuronal damage.15 16

In addition to neurological symptoms, functional vitamin B12 deficiency causes megaloblastic anaemia, skin hyperpigmentation, and vascular disease from hyperhomocysteinaemia, and is teratogenic.1 12 17

**Problems from unregulated methods of administration**

In medical practice, nitrous oxide is available as a piped supply of pure gas, which is delivered to the patient via a breathing circuit with a controlled supply of oxygen to avoid hypoxic mixtures, or as Entonox, a 50:50 mixture of N₂O and oxygen, which is delivered to the patient via tubing containing a demand valve.11 The
demand valve forms a crucial inherent safety feature in that the
patient must be capable of exerting sufficient inspiratory effort to
release any Entonox from the supply, so that no further Ento-
ox can be released to a patient obtunded by hypoxia. In this
scenario, the rapid offset of action of the gas means that con-
sciousness is rapidly restored, and breathing room air reverses
the hypoxia.

In recreational use of nitrous oxide, inhaling the gas from a
balloon has similar safety features. Air, and therefore oxygen,
may be entrained alongside the gas on inhalation, and if the
user is rendered hypoxic and loses consciousness, manual grip
on the balloon will fail, propelling the balloon away. Assuming
the airway remains patent, hypoxic drive will cause the user to
start to breathe room air again, reversing the hypoxia. Permanent
harm could occur if the user is obtunded with other drugs, or as-
pirates vomit, or is prone to seizures or cardiac dysrhythmias in
the presence of hypoxia.

More dangerous effects have been recorded when alternative
methods of nitrous oxide administration have been used. Some
users dispense the nitrous oxide canisters into whipped cream
dispensers (‘whippets’) and inhale the gas directly from the noz-
ble. The lack of a reducing valve means that this inhaled gas is
under considerable pressure, and instances of pneumomediasti-
um and subcutaneous emphysema have been attributed to intra-alveolar rupture from this practice.12

Through lack of available equipment, or through seeking to
achieve higher concentrations of inspired gas, users may breathe
nitrous oxide directly from canisters. When a compressed gas ex-
ceeds rapidly, it undergoes significant cooling as a result of adia-
batic change of state (this is the physical principle underlying
the mechanism of the cryoprobe used in therapeutic rapid freezing of
tissues).13 There is further cooling as a result of loss of latent heat
of vaporization.12 The anaesthetic effects of the gas may make
users initially unaware of the tissue damage being caused by in-
halation of such cold gas or freezing of metal components of the
delivery system, and frostbite of the mouth, nose and vocal cords
is a recognized complication.13

The rapid offset of effects may cause abusers of the gas to ex-
plor methods of continuous inhalation of higher concentrations
to enhance and prolong the effects, such as rebreathing in an
enclosed container, such as a bag over the head, or opening cylin-
ders in a small enclosed space, such as a car. This increases the
ratio of N₂O to oxygen. Once there is significantly less than 20% oxygen in the inhaled gas, there is potential for irreversible hyp-
oxic brain damage or death by asphyxiation.13 19 Simulations have
confirmed the dangerous hypoxic environment that can be cre-
ated inadvertently. When a standard 8 g nitrous oxide canister is
punctured in an enclosed bag, such as that which has been
found tied over the head of a fatality from nitrous oxide abuse,
the percentage of nitrous oxide rapidly increases to 59%, while
the oxygen concentrations decrease to 13% in 10 s, and only
10% within a minute.6 Adding the effects of respiration within
this enclosed environment would reduce the available oxygen
even further as oxygen is used. At 50% inspired nitrous oxide,
the normal response to hypoxia is blunted, making death from
asphyxia even more likely.6

Problems from unregulated manufacture and storage

Industrial manufacture of nitrous oxide involves heating ammo-
nium nitrate to 250°C and then removing impurities, such as NH₃,
N₂, NO, NO₂, and HNO₃, by passage through a series of washers
and scrubbers.11 12 Unregulated manufacturing of the gas for rec-
reational abuse is like to have less stringent quality-control
processes, and resultant inhaled impurities can cause harm.21
Deaths have been reported after contamination of nitrous oxide
balloons with butane,7 and older anaesthetists will have learnt
about patient fatalities in the UK in 1966 reported in a special
BJA editorial.22

Improper storage of the gas also creates the potential for
harm. Nitrous oxide for medical use is stored in cylinders below
its critical temperature, so it exists as a vapour above a volume
of nitrous oxide in its liquid phase.12 These cylinders are intention-
ally under-filled to accommodate increases in pressure as the va-
pour phase expands. Overfilling of the cylinders and storage
above the critical temperature carries an explosion risk.11

Regulation of nitrous oxide

Nitrous oxide is not a controlled drug and therefore not subject to
the Misuse of Drugs Act 1971.7 The large cylinders of nitrous oxide
seen in hospitals are classed as medicinal products, and
supplying or administering these without MHRA (Medicines
and Healthcare products Regulatory Agency) authorization is a
criminal offence under the Human Medicines Regulations 2012.
However, the small canisters designed for the catering industry
are not classed as medicinal products and therefore not subject
to this Act.7

Until very recently, it was not illegal to sell or possess nitrous
oxide, given its legitimate uses. Possession of nitrous oxide with
the intent to inhale is a misdemeanour in most states in the
USA,1 and in the UK the Intoxicating Substances (Supply) Act
1985 prohibits the sale, to those under the age of 18 yr, of sub-
stances which the seller has reason to believe may be inhaled
for the purposes of intoxication.21 Similar to glue, petrol, knives,
and other legal substances that may cause harm through misuse,
regulation of sale of this gas to adults is fraught with difficulty.
In recognition of the resurgence of the recreational use of nitrous
oxide and the difficulties in restricting its availability, the Advisory
Council on the Misuse of Drugs recently issued public health
safety advice and recommendations to the Government, local
councils, and the Department of Health to increase awareness
of this issue.24 In response to this, in May this year, the Home Of-

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fice released new legislation, the Psychoactive Substances Bill
2015,23 which makes it an offence to ‘produce or supply any sub-
stance intended for human consumption that is capable of pro-
ducing a psychoactive effect.’ Although medicinal nitrous oxide
is exempt from this legislation, it does give the police and local
authorities new powers to enforce civil sanctions against the
supply of nitrous oxide for recreational use. It remains to be
seen how effective such legislation will be, with the danger that
resulting covert manufacture may lead to unforeseen conse-
quences, such as increased concentrations of dangerous impur-
ities in supplied nitrous oxide gas, while restrictions on supply of
canisters and balloons may shift recreational abuse toward the
more hazardous larger cylinders and airtight bags.20

Relevance to anaesthetists and other medical professionals

Perceptions of relative safety of usage coupled with cheapness
and ease of procurement of this gas make it an increasing public
health issue.

Patients who suffer complications of acute nitrous oxide
abuse (e.g. hypoxia, aspiration, cardiac arrhythmias, seizures,
trauma, pneumomediastinum) may present to the emergency
department, and recreational abuse should be considered as a
differential diagnosis in these patients.
Chronic nitrous oxide abuse should be considered in the differential diagnosis of patients presenting with atypical neurological symptoms and signs, particularly where these resemble subacute degeneration of the cord. With increasing popularity of this recreational drug, particularly among young adults, consideration should be given to counselling pregnant women against the teratogenic risks of chronic nitrous oxide use, alongside advice about other drugs, tobacco, and alcohol.

Increasing usage and documented complications of this gas may give insight into further potential hazards of medical use and exposure in health-care workers.

In conclusion, in most people, inhalation of nitrous oxide gas from balloons produces little or no adverse effect. However, intense or chronic abuse can cause permanent neurological damage, while rebreathing in an enclosed space can cause hypoxia and asphyxial death. Fatalities can also occur through contaminated supplies, or through trauma or aspiration, particularly when co-ingested with other drugs or alcohol. There should be increasing awareness among the clinical staff of the various presentations and dangers of this increasingly popular drug of abuse.

Authors’ contributions
Co-wrote the manuscript: G.R., A.B.

Declaration of interest
A.B. is on the editorial board of British Journal of Anaesthesia and Journal of the Intensive Care Society.

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