# The dangers of recreational inhalation of nitrous oxide


## Abstract

Nitrous oxide, also known as 'laughing gas', is one of the most widely used recreational drugs among teenagers in the UK. Copious inhalation of nitrous oxide may increase intra-alveolar pressure, resulting in barotrauma secondary to alveolar rupture. Pneumomediastinum and subcutaneous emphysema are common clinical findings in nitrous oxide-associated barotrauma. Prolonged nitrous oxide misuse may inactivate vitamin $B_{12}$ through the alteration of its metabolism, causing demyelination of the central and peripheral nervous system. A spectrum of neurological manifestations has been reported, including peripheral neuropathy, myelopathy and subacute combined degeneration of the spinal cord. Medical therapies and psychosocial interventions aiming at nitrous oxide cessation are important treatment steps to achieve partial or complete recovery from the adverse effects associated with inhalation of nitrous oxide.



**Key words: Homocysteine; Nitrous oxide; Pneumomediastinum; Radiology; Subcutaneous emphysema; Subacute combined degeneration; Vitamin $B_{12}$ deficiency**

**Submitted: 30 May 2021; accepted following double-blind peer review: 6 August 2021**



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## Introduction

At standard temperature and pressure, nitrous oxide exists as a colourless and odourless gas (Becker and Rosenberg, 2008). As a result of its solubility and anxiolytic and analgesic effects, nitrous oxide is largely used as an inhalation anaesthetic and analgesic adjunct for medical and dental procedures (Thompson et al, 2015). It is these anaesthetic and analgesic properties that caused Humphrey Davey to coin the term 'laughing gas' (Hardman et al, 2019).

The antibacterial properties of nitrous oxide mean it is also widely used in the food preparation industry, mainly as an aerosol canister propellant in foods such as whipped cream dispensers and cooking oil sprays (Garakani et al, 2016). As a result of the ease of access and low cost, nitrous oxide has become a popular recreational drug choice in entertainment venues, particularly among teenagers and young adults aged 16–24 years, with 8.7% having used it between 2018 and 2019 in England and Wales (Home Office, 2019).

Recreational nitrous oxide products are readily available online and from local corner shops and street vendors. These products are sold as small but highly pressurised metal canisters (Figure 1) (Randhawa and Bodenham, 2016), typically containing 8 g nitrous oxide, which is equivalent to 8 litres of gas at room temperature and atmospheric pressure (Wagner et al, 1992).

The recreational consumption of nitrous oxide typically involves discharging the gas contents from a high-pressure canister into a balloon or a whipped cream dispenser, where the gas is then inhaled. For this reason, nitrous oxide is also called by its street names: 'balloon' and 'whippets'. Once the gas is inhaled, it increases the pressure within the pulmonary alveoli which causes the gas to be rapidly absorbed into the systemic circulation, producing the desired neuropsychiatric effects (Garakani et al, 2016).

While nitrous oxide is considered a safe and effective agent in the medical and dental settings, abuse and unsupervised inhalation of nitrous oxide may have serious health consequences, including acute barotrauma and chronic neurological sequelae. Owing to its increasing prevalence in the community as a recreational drug, it is vital to review the limited evidence of the adverse events associated with nitrous oxide inhalation.

## Acute barotrauma from nitrous oxide misuse

Pneumomediastinum can be characterised by the presence of extraluminal gas within the mediastinal cavity and can be spontaneous or secondary to an underlying condition.




**How to cite this article:**
Wong J, Viyasar T, Layton B, Lauder J. The dangers of recreational inhalation of nitrous oxide. Br J Hosp Med. 2021. https://doi.org/10.12968/hmed.2021.0322

**Figure 1.** Eight pressurised canisters containing nitrous oxide for commercial and recreational use.

Spontaneous pneumomediastinum is a rare condition that results from a raised intra-alveolar pressure (for example, short periods of intense coughing or breath holding) leading to the rupture of the marginal pulmonary alveoli (Jeddy et al, 2016). Although spontaneous pneumomediastinum is considered a benign condition, secondary causes should be excluded in the assessment of patients presenting with pneumomediastinum and subcutaneous emphysema.

Secondary pneumomediastinum is caused by blunt or penetrating chest injuries (Storz et al, 2017), alveolar rupture from pre-existing respiratory conditions (such as asthma), gastrointestinal tract disruption (such as iatrogenic or spontaneous oesophageal perforation), tracheobronchial perforation (for example, secondary to neck and thoracic surgery, intubation and poorly inserted chest drains) and barotrauma (most commonly as a result of positive pressure generated from excessive manual ventilation) (Banki et al, 2013).

Pneumomediastinum is a rare occurrence, with an incidence of about 1 in 25 000 people aged between 5 and 34 years old (Jougon et al, 2003). The incidence of pneumomediastinum is believed to be more frequent than reported, as it is often underdiagnosed because its clinical manifestations resemble other more common respiratory pathologies (Talwar et al, 2013). Furthermore, pneumomediastinum may be missed from the chest radiograph and the presenting symptoms attributed to anxiety, musculoskeletal pain and other insignificant pathologies, especially in younger people. In the literature, the individual incidences of spontaneous and secondary pneumomediastinum are not well described. This is possibly because of the differences in the diagnostic methods used and the varying clinical presentations in the populations studied, making it difficult to classify the patient into one of the two types of pneumomediastinum.

## Pathophysiology

Mechanical ventilation is a recognised iatrogenic cause of barotrauma, which presents as pneumomediastinum and subcutaneous emphysema. However, cases of barotrauma have also been reported following the extensive recreational inhalation of nitrous oxide. The incidence of nitrous oxide-induced pneumomediastinum is significantly lower than pneumomediastinum of other causes listed above. As far as the authors are aware, only six case reports of nitrous oxide-induced pneumomediastinum have been published to date (McDermott et al, 2015; Garakani et al, 2016; Jeddy et al, 2016; Tavare et al, 2018).

The repetitive use of a nitrous oxide-filled balloon or direct inhalation of the gas from highly pressurised canisters can generate a strong positive intra-alveolar pressure, almost as much as the positive airway pressure from excessive mechanical ventilation. This can lead to the rupture of marginal alveoli, resulting in barotrauma (McDermott et al, 2015; Jeddy et al, 2016; Tavare et al, 2018).

In addition, because of the increased relative solubility of nitrous oxide, it has been proposed that inhalation of the gas may contribute to spontaneous pneumomediastinum via the Macklin effect (McDermott et al, 2015). The Macklin effect proposes that a small alveolar rupture releases gas which then tracks along the bronchial tree and causes pneumomediastinum (Hsu et al, 2012b). Alternatively, the high lipid solubility of nitrous oxide causes an increased gas exchange from the alveolus to the alveolar cavity. The blood solubility of nitrous oxide is relatively low, so as the concentration of nitrous oxide decreases, it causes rapid expansion of the alveolar cavity. This contributes to an increase in pneumothorax size and suggests the use of nitrous oxide as analgesia is contraindicated in patients with pneumothoraces (Brown and Sneyd, 2016). Hence, excessive nitrous oxide inhalation may cause pneumomediastinum via one or both of these mechanisms. As the free air passes along the visceral pleura, surgical emphysema occurs when the air travels from the chest cavity along the fascia of the chest, neck and face (Storz et al, 2017).

### Clinical presentations

The clinical severity of pneumomediastinum and subcutaneous emphysema correlates with the extent of gas leakage and degree of organ involvement. The most common presenting complaints include pain, swelling and crepitation over the affected sites, most frequently the chest and neck. Dyspnoea, odynophagia and dysphagia have also been reported in several cases (Macia et al, 2007; Iyer et al, 2009). The classic Hamman's sign, a crunching and clicking sound that is synchronous with the heartbeat, is only detected in about 18% of patients (Hamman, 1945; Talwar et al, 2013; Mansella et al, 2014).

Nitrous oxide misuse is most common in teenagers. In a young patient with no prior medical history, who presents with acute chest and neck discomfort, nitrous oxide misuse should be considered as one of the differential diagnoses. As nitrous oxide is not detected on routine drug screening panels, a thorough clinical history, including recreational drug use, is essential to establish any potential triggers causing the presentation of the symptoms of pneumomediastinum.

### Investigations

An initial diagnostic workup includes a chest radiograph to reveal the extent of pneumomediastinum and subcutaneous emphysema. If the anterior chest wall is affected, subcutaneous emphysema can outline the pectoralis major muscle, giving rise to the ginkgo leaf sign (Chimutengwende-Gordon et al, 2010). Moreover, the plain film is crucial in excluding any overt pneumothorax and traumatic changes, for example rib fractures (Figure 2).

An oral, water-soluble, contrast-enhanced computed tomography scan of the neck and thorax can be performed if there is suspicion of oesophageal perforation, especially in patients with a history of vomiting. It is worth noting that the radiation dose for a computed tomography scan of the neck and chest is significant and these patients are often young. Therefore, this examination should be considered with caution.

### Management

Patients with pneumomediastinum undergo observation and are treated with supportive measures including low-dose oxygen therapy and analgesics. Regular monitoring is key to prevent or promptly treat complications from pneumomediastinum, such as tension pneumothorax and infections, and intravenous or oral antibiotics are often prescribed as a prophylactic measure against mediastinitis and sepsis (Mansella et al, 2014). Patients with nitrous oxide-induced pneumomediastinum generally make a complete recovery within 4 weeks (McDermott et al, 2015; Jeddy et al, 2016; Tavare et al, 2017). A repeat chest radiograph should be performed to ensure a complete recovery.

## Neurological sequelae from longstanding nitrous oxide misuse

In the UK, vitamin $B_{12}$ deficiency occurs in approximately 6% of people younger than 60 years old (Hunt et al, 2014). Although vitamin $B_{12}$ deficiency is rarely detected in young

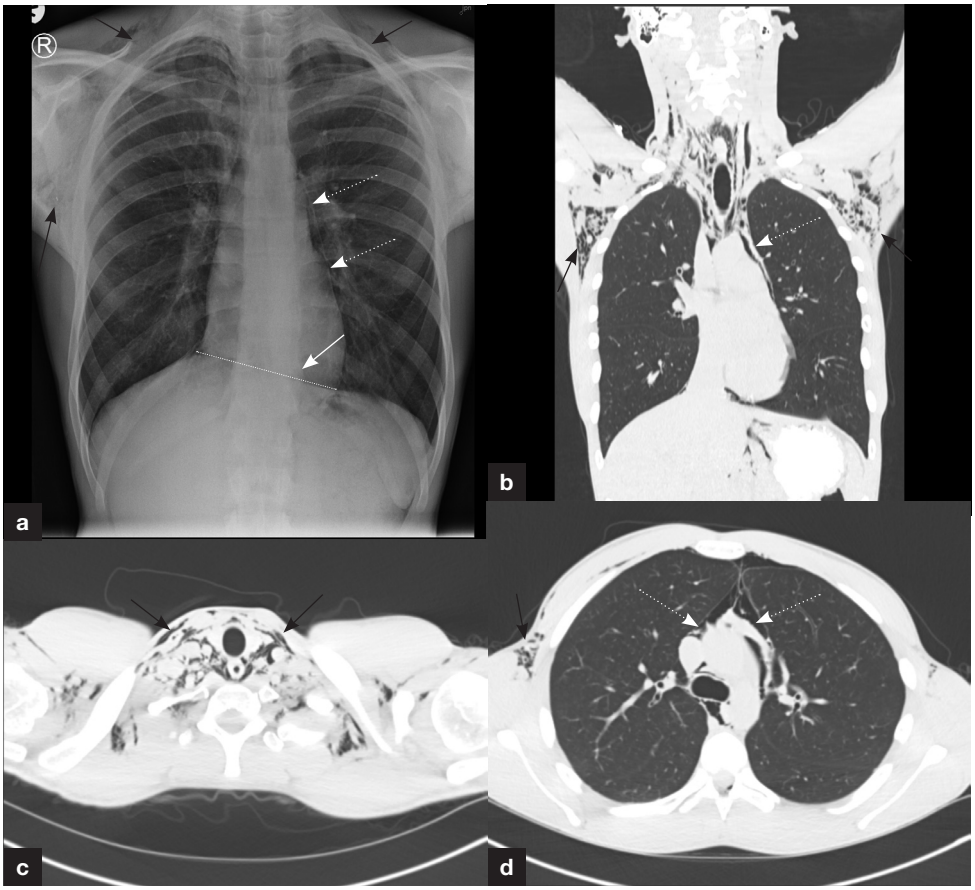


**Figure 2.** a. A chest radiograph, (b) coronal computed tomography and (c and d) axial computed tomography showing diffuse subcutaneous emphysema (black arrows) and pneumomediastinum (white dashed arrows). The continuous diaphragm sign of pneumomediastinum is seen on the chest radiograph (white arrow). Note the absence of pneumothorax.

and well-nourished adults, nitrous oxide misuse is a leading cause of vitamin $B_{12}$ abnormality in this age group (Chiang et al, 2013). To the authors' knowledge, cases of nitrous oxide-induced vitamin $B_{12}$ inactivation are rare. A systematic literature review from 1900 to 2016 found 45 reported cases of nitrous oxide-induced vitamin $B_{12}$ inactivation (Garakani et al, 2016). Prolonged recreational use of nitrous oxide is associated with adverse neurotoxicity secondary to the inactivation of vitamin $B_{12}$ (cobalamin). These neurological symptoms are seen in about 4% of people who use nitrous oxide (Williamson et al, 2019; Campdesuner et al, 2020). The most recognised physical manifestations are paraesthesia, numbness, weakness and gait disturbances (Singer et al, 2008; Massey et al, 2016; McArdle and Gaillard, 2020).

## Pathophysiology

The neurological complications associated with nitrous oxide misuse have been attributed to the inactivation of vitamin $B_{12}$ or a functional vitamin $B_{12}$ deficiency, despite normal serum $B_{12}$ concentrations. Active vitamin $B_{12}$ functions as a cofactor that converts methymalonyl-coenzyme A to succinyl-coenzyme A, and homocysteine to methionine. These processes are catalysed by vitamin $B_{12}$-dependent enzymes, known as methylmalonyl-coenzyme A mutase and methionine synthase (Jameson et al, 1999). Even during short exposures, nitrous oxide toxicities interfere with DNA synthesis and oxidises cobalt ions in vitamin $B_{12}$, ultimately inactivating it (Makdsi and Kadrie, 2009; Hsu et al, 2012a). In its inactive form, vitamin $B_{12}$ is unable to produce methionine synthase and methylmalonyl-coenzyme A mutase and is therefore unable to convert methymalonyl-coenzyme A to succinyl-coenzyme A, and homocysteine to methionine (Garakani et al, 2016). Ultimately, this results in a reduced production of myelin sheath proteins leading to a loss of axon fibres and the subsequent demyelination of the central and peripheral nervous system (Figure 3) (Campdesuner et al, 2020; McArdle and Gaillard, 2020).

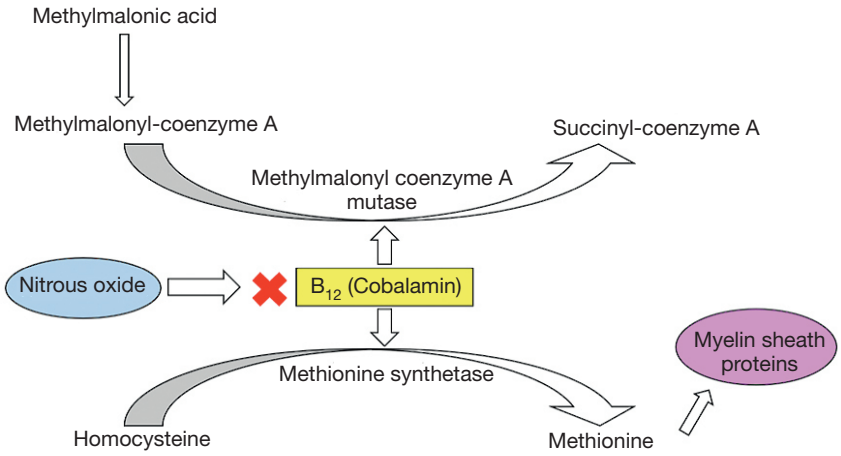


**Figure 3.** The effects of nitrous oxide on the metabolism of vitamin $B_{12}$ (cobalamin).

The risk of vitamin $B_{12}$ inactivation is increased in individuals with a preexisting $B_{12}$ deficiency, such as vegans, those suffering from pernicious anaemia and those who have previously had a small bowel resection. Additionally, vitamin $B_{12}$ deficiency can occur in those who have used nitrous oxide for a long time, particularly when the gas is consumed in poorly ventilated environments (Randhawa and Bodenham, 2016; Egan et al, 2018).

## Clinical presentations

The demyelination of the central and peripheral nervous system may be manifested as a spectrum of neurological sequelae ranging from peripheral neuropathy, polyneuropathy, myelopathy and sub-acute combined degeneration of the cord (Williamson et al, 2019; Samia et al, 2020). When examining patients suspected of chronic nitrous oxide use, glove-and-stocking ascending loss of distal vibratory sensation, reduced proprioception, impaired reflex, diminished grip strength and ataxia could be signs of early stage involvement of the nervous system (Banks and Hardman, 2005; Zhao et al, 2019). The ultimate consequence of nitrous oxide neurotoxicity resembles vitamin $B_{12}$ deficiency subacute combined degeneration of the cord (Jiang and Shang, 2020). Patients with nitrous oxide-induced subacute combined degeneration of the cord may present with limb paraesthesia, severe weakness and spasticity, gait disturbances and even urinary and fecal incontinence (Makdsi and Kadrie, 2009; Hsu et al, 2012a; Massey et al, 2016).

In addition to the neurological symptoms, reports have also suggested a link between longstanding vitamin $B_{12}$ inactivation and systemic manifestations such as skin hyperpigmentation and vascular diseases (Banks and Hardman, 2005; Chiang et al, 2013). The accumulation of homocysteine is closely associated with endothelial injury and thrombotic deposits, thus patients with hyperhomocysteinaemia are at high risks of vascular events, such as myocardial ischaemia (Edirisinghe, 2004).

## Investigations

Laboratory tests in patients with a vitamin $B_{12}$ deficiency (for example, individuals with pernicious anaemia) show high mean corpuscular volume, low vitamin $B_{12}$ concentrations and low haemoglobin concentrations (known as macrocytic anaemia). However, these haematological changes are not consistently found in patients with nitrous oxide-associated vitamin $B_{12}$ inactivation. In these patients, normal mean corpuscular volume, vitamin $B_{12}$ and haemoglobin concentrations may be found.

While the cause of such a discrepancy is still not known, the use of other sensitive markers is recommended in the diagnosis of nitrous oxide-associated vitamin $B_{12}$ inactivation, and the differentiation from organic vitamin $B_{12}$ deficiency. The reduced recycling of homocysteine to methionine in nitrous oxide-induced vitamin $B_{12}$ inactivation results in increased homocysteine substrates (Jameson et al, 1999). Similarly, the reduced recycling of methylmalonyl-coenzyme A to succinyl-coenzyme A increases serum methylmalonic acid levels (Wagner et al, 1992;

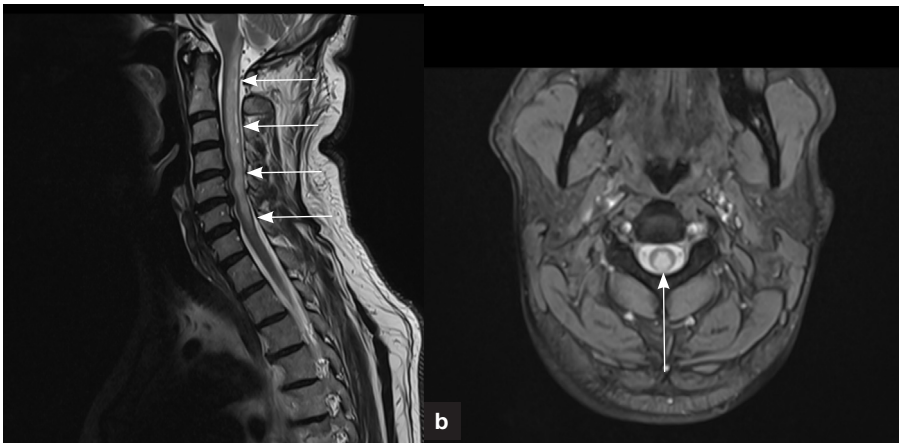


**Figure 4.** (a) Sagittal T2 and (b) axial T2-weighted fat-saturated magnetic resonance imaging sequences of the cervical spine. There is high T2 signal within the dorsal columns with an 'inverted V' morphology.

Thompson et al, 2015). Therefore, a laboratory test with normal vitamin $B_{12}$ and haemoglobin concentrations may exclude vitamin $B_{12}$ deficiency. However, in chronic nitrous oxide users, serum homocysteine and methymalonic acid levels should be analysed to exclude vitamin $B_{12}$ inactivation. 'Functional vitamin $B_{12}$ deficiency' can be diagnosed when there are high levels of methymalonic acid and homocysteine (Vashi et al, 2016).

In patients with chronic vitamin $B_{12}$ inactivation, magnetic resonance imaging studies have demonstrated specific changes. The magnetic resonance images of the spinal cord show that in $B_{12}$ deficiency associated sub-acute combined degeneration of the cord, there is a high T2-signal and long segmental hyperintensity in the dorsal, but rarely lateral, columns of the spinal cord in the axial window, resembling an 'inverted V' sign (Figure 4) (Kumar and Singh, 2009; Zhao et al, 2019).

### Management

Patients with nitrous oxide-associated vitamin $B_{12}$ inactivation should be treated promptly with intramuscular and subsequent oral high-dose vitamin $B_{12}$ and folate supplements. Clinical signs and symptoms, and biochemical markers (for example, vitamin $B_{12}$, homocysteine and methymalonic acid levels) should be assessed to monitor the patient's response to treatment. It is important to note that vitamin $B_{12}$ replacement should be performed before the folate treatment to prevent sub-acute degeneration of the cord (Hunt et al, 2014). Physiotherapy is also advised in patients with reduced mobility.

Medical therapy should be combined with psychosocial strategies to discourage further nitrous oxide consumption and optimise long-term outcomes in people who are chronic users of nitrous oxide. Cessation of nitrous oxide use, along with good compliance with vitamin $B_{12}$ supplementation, may result in an improvement of the neurological symptoms, but this may take up to 2 years. However, in some individuals, these symptoms may persist and become permanent if the treatment is delayed. A study of 18 published cases of nitrous oxide-induced neurotoxicity demonstrates only 25% of cases result in complete resolution of symptoms after vitamin $B_{12}$ replacement (Singer et al, 2008).

## Conclusions

Inhalation of large quantities of nitrous oxide may cause alveolar rupture and trigger pneumomediastinum. Prolonged nitrous oxide misuse may alter vitamin $B_{12}$ metabolism, resulting in a series of neurological sequelae including peripheral neuropathy, polyneuropathy, myelopathy and sub-acute combined degeneration of the cord.

Nitrous oxide misuse should be investigated in a young and otherwise fit patient presenting with pneumomediastinum or neurological complaints. A thorough drug history is vital to establish any nitrous oxide associated triggers.

Medical therapies and psychosocial interventions aiming to stop the use of nitrous oxide are important treatment steps to achieve partial or complete recovery from nitrous

## Key points

- Nitrous oxide inhalation should be considered as a potential cause of pneumomediastinum and neurological complaints, especially in a young and otherwise healthy patient. In these patients, a thorough clinical history of recreational drug use should be conducted.
- Although spontaneous pneumomediastinum is a benign condition, secondary causes of pnemomediastinum should be excluded, and potential complications (such as, infection or pneumothorax) should be monitored.
- Conducting a whole spine magnetic resonance imaging scan in young patients with new-onset neurological signs is important.
- To rule out nitrous oxide-induced vitamin $B_{12}$ inactivation, serum homocysteine and methymalonic acid levels should be investigated.

oxide-associated adverse effects. Through education, it is also important to raise public awareness of the short- and long-term harmful effects of nitrous oxide.

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**Conflicts of interest**

The authors declare that they have no conflicts of interest.

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