

## **Nitrous oxide: smart legislation, prevention, and harm reduction activities are required to reduce the risks of heavy use**

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Nitrous oxide (N<sub>2</sub>O) has been used non-medically since the early 19<sup>th</sup> century, but it has only been over the last 20 years that it has become established in the recreational pharmacopeia (1). It is not regularly included in national substance use surveys, and so it is difficult to assess global prevalence. In England and Wales, 9% of 16-24 year olds reported use in 2019/20, which has been stable since 2016, but makes N<sub>2</sub>O the second most popular controlled substance after cannabis (2). In Australia N<sub>2</sub>O is grouped with other inhalants, and use by those aged 14+ gradually increased from 0.4% in 2001 to 1.7% in 2019 (3). In the US 4.5% of the population aged 12+ reported a lifetime use episode in 2020, and this has been relatively stable over the past 20 years (4).

N<sub>2</sub>O is typically consumed through inhalation from small balloons containing around 10ml gas, and produces a short lasting euphoria and mild perceptual changes (0.5-1 minute). Occasional recreational use is considered less harmful than many other types of substance use (5), but there is still the risk of cold burns to the lips, larynx or exposed skin and asphyxiation through administration practices (6). Recent UK media reports have suggested an increase in the number of clinical presentations related to N<sub>2</sub>O neurological symptoms (7). It is unclear whether this is a genuine trend, or partly related to more consistent enquiries about N<sub>2</sub>O use and a correction of otherwise misattributed conditions.

There are no routinely reported data on nitrous oxide presentations. Historically, occupational exposure to N<sub>2</sub>O was of most concern, but recreational users represent around half of patients in the literature (8). Patients present with conditions associated with myeloneuropathy and peripheral neuropathy caused by functional vitamin B-12 deficiency. International case-study reviews suggest patients are typically males in their 20s, using a median of 25 cartridges (containing approximately 10 mL/ 8000 mg of N<sub>2</sub>O under pressure) per day over at least 6 months, although some have reported using in excess 100 cartridges per day (8). Heavy use is atypical, but one study of recreation users

suggested that the probability of reporting paraesthesia increased by 3.5% for every 10% increase in N<sub>2</sub>O dose per episode (9).

Increased availability of larger volumes of N<sub>2</sub>O may underlie clinicians' concerns. Whilst the Dutch Poisons Information Center reported an annual average of 6 poisonings between 2010 and 2015, this rose to 144 in 2020 (10). This was associated with a shift from heavy and frequent use of 8g cartridges, to large cannisters (up to 1kg) and cylinders (between 2-10kg). Data from other countries is sparse, but N<sub>2</sub>O appeared in the top 10 information-seeking telephone enquiries to the UK National Poisons Information Service for the first time in 2020/21 (11). Larger N<sub>2</sub>O canisters (0.6-2kg; containing up to 250 times more volume of gas) are sold as 'catering supplies', and easily available online in most global markets. Many retailers offer price promotions and market their products through the cost savings of purchasing large volume containers. Thus, consumers can be potentially exposed to the large volumes of N<sub>2</sub>O typically associated with clinical presentations through a single canister purchase.

As N<sub>2</sub>O is not included in the United Nations drug control conventions, few countries have introduced national controls, although local bylaws prohibiting possession may be in place. Whilst still subject to medicinal product regulations, N<sub>2</sub>O status as an approved foodstuff in many territories has meant that as long as it is not sold for its psychoactive properties, prosecutions are difficult. In light of health concerns the Netherlands plans to introduce formal control in 2023, and the UK government is currently considering a similar ban. However, such legislation poses challenges. Legitimate uses will need to be protected, and low level supply and possession is unlikely to be a police priority. Drug laws are a blunt instrument and are not an effective health improvement tool (12). With high levels of N<sub>2</sub>O demand, legal controls may encourage diversion of medicinal and industrial supplies, a shift to darkweb sales, sourcing from countries where the drug is not controlled, substitution with more harmful substances, or inhibition of help seeking. Smart legislation that focuses on suppliers may be more advantageous. Age restrictions on purchase, regulation of canister size, bans on bulk sales to individuals and licensing of buyers may potentially reduce consumers' exposure to large volumes of gas. However, this would be resource intensive and difficult to implement. Recreational drugs are subject to fashions and natural cycles of consumption like other goods, and prevention and education activities may help to support a decline in use. In the meantime, public awareness activities to improve self-identification of neurological symptoms, and encourage self-referral is important. More radically, but reflecting developments in cannabis policy, regulation that permits limited recreational use, but restricts the market on the basis of public health principles may provide a long-term solution to some of the problems associated with use.

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