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just laughing or really bad news?

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Recreational N₂O use: just laughing or really bad news?

There is evidence of a global increase in N₂O use among young people, along with a low level of awareness about the risks of prolonged/heavy use and late presentation to treatment after experiencing side effects. We advocate a combined effort of legislation and better education about side effects to limit problems associated with excessive N₂O use.

Nitrous oxide (N₂O; laughing gas) has been inhaled by hundreds of millions of patients in medical settings for acute pain control mainly in surgery and dentistry since 1844. N₂O also has a long history of recreational use, but recently, there has been an increase in recreational N₂O use in many countries, including Australia, United Kingdom, United States, the Netherlands, and China [1–3]. The highest rate of last year N₂O use was found in the United Kingdom in 2019/2020 with 8.7% of youngsters age 16 to 24 years [4] using N₂O in the past year, although it has stabilized over the past few years. In the United Kingdom, N₂O use is the second most popular drug among 16- to 24-year-olds, following cannabis [5]. In Australia, an increase of 8% in 2003 to 67% in 2020 was reported among recreational drug users in New South Wales [6]. The apparent upsurge of N₂O use and the related public nuisance (empty balloons, canisters and bulbs) have led to an increased coverage in the media demanding legislative measures aiming to take N₂O out of legal circulation in some countries [7], although some experts are warning that criminal drug runners will then control the market and young minors will be exposed to a myriad of more harmful controlled drugs. They propose instead that youngsters should be approached with credible information to limit their use, raise awareness of early symptoms (persistent numbness and tingling in feet, mouth, tongue and fingers) and seek help [8].

Although general prevalence data are lacking for most countries and N₂O use is usually not included in general population surveys, there are some indications that problematic N₂O use is on the rise [1,2,9]. In the United States, the number of N₂O related cases reported to the Food and Drug Administration (FDA) (FDA Adverse Event Reporting [FAERS] data) increased from 25 in 2012 to 2015 to 99 in 2016 to 2019 [10], which referred in 70% of cases to subjects age 13 to 29 years. The FAERS cases (*n* = 128) comprised hospitalization (34%), disabling events (7%), life threatening events (7%) and fatalities (25%). Improved registration of the N₂O-related events (e.g. coding) may partly explain the increasing trends in N₂O related adverse events, but several studies from other countries have shown a similar gradual increase in clinical cases [2,9,11,12].

It has been noted that some patients wait too long before seeking medical assistance [1,11]. One of the reasons is shame. This became specifically apparent in a small subgroup of young Muslim heavy N₂O

users [13]. Moreover, their use of N₂O in high quantities for prolonged periods suggests that N₂O may have some dependence liability. In addition, a shift was noted in the Netherlands from using standard cartridges (8 g) to using 2-kg tanks. A specific harm, observed in the Netherlands, was the increased number of N₂O related traffic accidents (from 130 in 2017 to 960 mid-2019) [14]. However, no distinction was made between accidents because of N₂O intoxication and accidents because of filling balloons while driving.

Based on hospital data, it was concluded that the COVID-19 lockdown may have generated a further increase in the abuse of N₂O and more neurological hospital admissions [2,3]. The pandemic may have disturbed drug trafficking and shifted national drug consumption trends, because of shortage of drugs, like cocaine and heroin, may have facilitated the increased consumption of locally produced or more accessible and cheaper substances, like N₂O and cannabis. For example, the use of ecstasy, a typical party drug, decreased during the lockdown [15]. However, a report from the Netherlands noted a decrease in ecstasy and N₂O use during the COVID-19 lockdown because of a lack of social opportunities [16].

The typical recreational N₂O user takes ≤5 hits (whippets) in a single session [8] and is unaware of its side-effects [17]. Although incidental N₂O use is indeed associated with little or no harm, prolonged use of high doses may lead to neurological damage [8], including generalized demyelinating polyneuropathy, resulting in paraesthesia, unsteady gait, weakness and even paralysis because of spinal cord injury [1,2,8,11]. In almost all clinical cases, N₂O-related neurological symptoms were accompanied by vitamin B₁₂ (cyanocobalamin) deficiency [1,8,9,18]. In the absence of timely supplement with vitamin B₁₂, excessive N₂O use causes increases in homocysteine and methylmalonic acid, which attributes to demyelination of the spinal cord. Some reports explicitly stated that patients presented too late to hospital for adequate treatment [1,11].


In conclusion, there is evidence of a global increase in N₂O use and N₂O-related harm and concerns are raised about the specific popularity of N₂O use among young subjects (16–24 years.), the low level of awareness about the risks to prolonged and/or heavy N₂O use, and the late presentation to treatment after experiencing side-effects. Therefore, we advocate a combined effort of legislation (reducing availability of N₂O) and better education of potential users (including N₂O information in existing prevention strategies) and medical professionals about side-effects to limit problems associated with (excessive) N₂O use. In addition, hospital doctors and neurologists should take into account homocysteine, methylmalonic and

vitamin B₁₂ levels when dealing with young, otherwise healthy, patients with neurological symptoms.

DECLARATION OF INTERESTS

None.

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