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Recreational N₂O use: Just laughing or really bad news?

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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. Recently, recreational N₂O use is emerging world-wide [1] with increasing rates in Australia, U.S.A., Denmark, the Netherlands, China and elsewhere [2, 3] often in the context of poly-drug use [4]. The UK reported the highest rate of last year N₂O use of 8.7% of youngsters aged 16–24 years in 2019/20, though it stabilized over the past few years [5]. According to the 2019 Global Drug Survey (GDS), N₂O is the 10th most popular drug in the world with 91% using N₂O once monthly or less [6]. The apparent upsurge of N₂O use has created a panic in the media although N₂O is generally regarded as a relatively safe drug. Legislative measures aiming to remove N₂O from the legal circulation are considered in some countries 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. Instead, N₂O users should be approached with credible information to limit their use, raise awareness of early symptoms (persistent numbness and tingling in feet mouth tongue fingers) and seek help [7].

In a recent issue of The N.Y. Times, it was concluded that the COVID-19 pandemic lockdown has resulted in increase in the use of drugs including N₂O [8], because of COVID-19 related mental stress and boredom due to economic uncertainty and social isolation. The pandemic has disturbed drug trafficking and shifted national drug consumption trends [9], because shortage of drugs, like cocaine and heroin may have facilitated the consumption to locally produced, more accessible and cheaper substances, like nitrous oxide and cannabis. Interestingly, cancellation of festivals during the lockdown was responsible for the decreased use of ecstasy, a typical party drug (Nabben, personal communication).

The typical recreational N₂O user takes ≤ 5 hits (whippets) in a single session [10-12]. Within seconds euphoria and sometimes visual hallucinations are induced which dissipate within several minutes. Most recreational N₂O users believe that the substance is safe [10]. However, the numbers of patients reporting to specialists and emergency departments with neurological issues are growing [4, 13] and neurologic complications became more common following prolonged N₂O use at high dose of 10-100 hits/session [2]. GDS reported that 3% of 17,000 recent N₂O users reported dose-dependent “persistent numbness/tingling (paraesthesia)” [12].

In high doses, N₂O inactivates vitamin B₁₂ (cyanocobalamin) which in turn can cause deep vein thrombosis, pulmonary embolism, psychosis and neurological damage such as paraplegia, and very occasionally death [7]. Demyelination in the spinal cord can result in permanent paraplegia, if not timely supplemented with vitamin B₁₂. Most clinical N₂O presentations were on neurologic sequelae, including myeloneuropathy and subacute combined degeneration [13]. Between 2017-2019, an increasing number of young patients (mean age: 21 yrs.) was treated in the Netherlands following prolonged N₂O use, and the number of cases has steadily increased since then (Bruijnes 2020; RTL News 2020). Commonly reported complaints were tingling and numbness in the hands and legs and weakness in the lower limbs. According to the Dutch Association of Neurologists, 64 young patients (mean age: 22 yrs.) had been hospitalised in the Netherlands over the past two years due to problematic N₂O use [14] resulting in paraplegia; some of them will be permanently confined to a wheelchair. The actual number is probably higher, because only 42 of 78 hospitals participated in the survey. It is remarkable, that many patients waited too long before seeking medical assistance. One of the reasons is shame. This became specifically apparent in a small subgroup of young Muslim heavy N₂O users [15]. Moreover, their use of N₂O in high quantities for prolonged periods suggests that N₂O may have some dependence liability. Alarmingly, there is an increased use of 2 kg-tanks (cannisters) allowing continuous inhalation of large amounts of N₂O: in the Netherlands from 9% in 2018 to 22% in 2019 [16].

Inquiries about N₂O adverse health incidents received by National Poison Information Centers (NPIC) also steadily increased in the last five years. For example, the Dutch NPIC received 13 inquiries in 2015, mainly related to N₂O use by young adults (≤ 30 yrs.), while it received 67 inquiries in the first half of 2019 [17] of which 52% referred to prolonged use. Similarly, in the U.S., the number of N₂O related cases reported to the FDA (FAERS data) increased from 25 in 2012-2015 to 99 in 2016-2019 with 70% of the cases aged 13-29 years [18]. The FAERS cases (n=128) comprised hospitalization (34%), disabling and life-threatening events (both 7%) and fatalities (25%). Most frequently reported symptoms were subacute combined cord degeneration, vitamin B₁₂ deficiency, myelopathy, hypoaesthesia and cardiac arrest [18]. It should be noted that improved registration of the N₂O-related events (e.g., coding) may partly explain the increase in N₂O related adverse events.

A specific harm, observed in the Netherlands, was the increased number of N₂O related traffic accidents (from 130 in 2017 to 960 mid 2019), because drivers were either using N₂O or busy filling balloons while driving. Drivers were mostly unaware of impaired driving while under influence of N₂O, but on the other hand, one is capable to drive well again within 15 minutes after the last N₂O inhalation because of its rapid degradation.

Of special concern is the high rate of N₂O use among youngsters. N₂O is attractive because it is legal, cheap, easy-available and has a relatively low toxicity. In addition, there are no residual effect, like red eyes or a hang-over, that may attract the attention of parents when the substance is used. Personal and contextual risk factors will largely determine whether young adolescents will progress to using additional drugs, but from a neurobiological and a moral perspective, it is advocated that youngsters refrain from using psychoactive substances. Here we propose prevention and harm reduction initiatives to limit problematic N₂O use with special attention directed at (potential) young users using social media and influencers to raise awareness regarding the potential risks.

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