



Short report

Alarming increase in poisonings from recreational nitrous oxide use after a change in EU-legislation, inquiries to the Dutch Poisons Information Center



A.J.H.P. van Riel*, C.C. Hunault, I.S. van den Hengel-Koot, J.J. Nugteren-van Lonkhuyzen, D.W. de Lange, L. Hondebrink

Dutch Poisons Information Center (DPIC), University Medical Center Utrecht, Utrecht University, PO box 85500, 3508 GA, Utrecht, the Netherlands.

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ABSTRACT

Background: After the change in EU-legislation in 2014, recreational use of nitrous oxide (N₂O) increased in the Netherlands from 2015 onwards. We studied the effect on N₂O poisonings during an 11 year period.

Methods: A retrospective observational study was performed on the incidence rate of N₂O poisonings, relative to all recreational drug poisonings reported to the Dutch Poisons Information Center (DPIC) from 2010-2020. Secondary outcomes were the frequency of heavy use, frequent use, co-exposures, and toxicity in 2019 and 2020.

Results: 433 N₂O poisonings were included. The incidence rate increased exponentially from 0.12% in 2010 to 11% in 2020, with an average monthly rate of 3.8%. In 2019 and 2020, 79% of the patients indicated heavy use, frequent use or both, and 42% used from large cylinders. Chronic toxicity (signs of peripheral neuropathy) was reported in 38% of the patients.

Conclusion: The rate of N₂O poisonings increased alarmingly in the Netherlands. An increasing proportion of patients reported problematic heavy or frequent use, accompanied by chronic toxicity.

Introduction

Nitrous oxide (N₂O) is commonly used as an anaesthetic in medical and dental procedures, as a power booster in the automotive industry and as a whipped cream propellant. It is also used as a recreational drug causing brief derealization, anxiolysis, analgesia, and euphoria (Garanaki et al., 2016; Kaar et al., 2016). In July 2014, the European Court of Justice ruled that products without apparent therapeutic effect cannot be classified as medicines (European High Court, 2014). Since this verdict, the sales and use of N₂O are regulated under the Commodities Act in the Netherlands. Although other regulations and EU directives for vending, storage, transport and labelling of hazardous chemicals apply to the intended uses of N₂O, the unintended recreational use by consumers is not covered, leaving N₂O trade for recreational use difficult to prosecute. In various countries different national regulations apply for N₂O sales and use (Forrester, 2021; Harper et al., 2020; Randhawa & Bodenham, 2016; Zheng et al., 2020).

Recently, concerns have been raised by several countries about the increasing recreational use of N₂O. In the Global Drug Survey of 2019, 24% of the participants reported ever using N₂O as a recre-

ational drug and 12% used it in the last 12 months (Global Drug Survey, 2019). In addition, Australia, China, Denmark, the US, the Netherlands and the UK reported increases in health incidents related to N₂O use (Forrester, 2021; Harper et al., 2020; Hoegberg et al., 2020; National Drug Monitor, 2020; Randhawa & Bodenham, 2016; Zheng et al., 2020). Occasional recreational use of a few balloons is considered harmless (Kaar et al., 2016). Heavy use, however, is harmful. Case reports from several countries describe severe adverse health effects following heavy N₂O use. Neurological damage, both in the peripheral (neuropathy) and central nervous system (degeneration of the spinal cord resulting in permanent paralysis) have been reported, due to functional vitamin B12 deficiency (Garanaki et al., 2016; Micallef et al., 2020; Randhawa & Bodenham, 2016; Zheng et al., 2020).

Data on the epidemiology of N₂O poisonings can contribute to toxicovigilance and support preventive measures. Therefore, we retrospectively queried the database of the Dutch Poisons Information Center (DPIC) to study the rates of N₂O poisonings in the Netherlands between 2010 and 2020. In addition, we systematically collected additional data on packaging, heavy use and frequent use in 2019 and 2020.

* Corresponding author.

E-mail address: A.vanRiel@umcutrecht.nl (A.J.H.P. van Riel).

Methods

Design

In this retrospective observational study the database of the Dutch Poisons Information Center (DPIC) was queried for the number of N₂O poisonings and recreational drug poisonings between 2010 and 2020, using dedicated software (QlikView, v12).

The DPIC provides a 24/7 telephone service on the management of acute poisonings to healthcare professionals only, serving a population of 17.5 million. During all inquiries, an electronic case report form (eCRF) is completed and stored in the centers' database. Anonymous data is routinely collected on patient (e.g., age and gender) and exposure characteristics (e.g., substance(s), reason for exposure), as well as on toxicity (symptoms present before or during the inquiry). From January 2019 onwards, additional questions on patterns of use were asked by the Specialists in Poison Information to the medical professionals during all telephone inquiries on N₂O poisoning. The questions concerned details on frequency of use, amount of use and packaging (bought in balloons, cartridges or cylinders from which the user fills balloons prior to inhaling). The collected details were registered in the eCRF and were extracted manually from the electronic case report forms (eCRF) for 2019 and 2020.

Participants

All patients for whom an inquiry on intentional recreational N₂O use was made to the DPIC between January 1st, 2010 and December 31st, 2020 were included.

Measures

For 2010-2020 the primary studied variables included the number of inquiries on intentional N₂O poisoning and on poisonings with all recreational drugs. To correct for general increases in call volume about recreational drugs, rates of N₂O poisoning were calculated, relative to the total number of recreational drug poisonings. Heavy use of N₂O was defined as use from a cylinder or the use of 50 balloons or more in one session, equivalent to ≥ 400 g or ≥ 200 L of N₂O gas. Frequent use was scored if confirmed by the treating physician during the inquiry, based on the patient history, (e.g., 'uses frequently', 'uses daily', 'weekly use'). If the amount or frequency of use were unknown, "not heavy" and "not frequent" were assumed, to avoid overestimation. Signs of peripheral neuropathy were defined as the presence of ataxia (gait abnormalities) or paresthesia (perception of abnormal sensations, e.g. tingling, numbness, prickling, mostly in the extremities). Signs of peripheral neuropathy are considered an early sign of neurological damage.

Analyses

The monthly incidence rates of N₂O poisonings were calculated by dividing the number of inquiries on N₂O poisonings by the number of inquiries on all recreational drug poisonings. First, we plotted the observed incidence over time. We then decomposed the observed time series in three components ("trend", "seasonal" and "random"). The trend line was subsequently fitted to an exponential function (detailed description in the Supplementary Material). Statistical analyses were performed with SPSS (version 26.0.01) and R software (R version 4.0.3 with R Studio version 1.3.1093).

Before analysis, the study data was cleared of any potential person identifying information, including exact dates, treatment facilities and health care worker information. The data was considered anonymous and in agreement with GDPR regulations.

Results

Epidemiology of N₂O poisonings

From January 1st, 2010 until December 31st, 2020, 433 N₂O poisonings and 11,483 recreational drug poisonings were reported to the DPIC. From 2010-2015 an average of 6 N₂O poisonings were recorded annually, increasing to 144 N₂O poisonings in 2020 (Fig. 1A). Poisonings with recreational drugs also increased from an average of 903 poisonings a year in 2010-2015 to 1325 in 2020.

The average monthly incidence rate of N₂O poisonings (relative to recreational drug poisonings) increased from 0.12% in 2010 to 10.6% in 2020, with an average of 3.2% for the whole study period. Fig. 1B shows the observed incidence and the trend component of the time series. The incidence rate of inquiries on N₂O poisoning increased exponentially (model parameters in the Supplementary Material).

Patterns of use (details of poisonings in 2019 and 2020)

In this period, a total of 272 N₂O poisonings was reported: 128 in 2019 and 144 in 2020. The median age was 22 years (IQR 25%-75%: 20-26,3 years) and most patients were male (64%).

Overall, 79% of the patients indicated heavy use, frequent use or both. The frequency of heavy use was 59% (50% in 2019, 67% in 2020), the occurrence of frequent use was 64% (59% in 2019, 69% in 2020), and the frequency of both heavy and frequent use (by one patient) was 44% (33% in 2019, 53% in 2020). Use from cylinders (2 to 10 kilogram) was reported in 42% of the inquiries (31% in 2019, 51% in 2020).

Toxicity (details of poisonings in 2019 and 2020)

All patients (N=272) reported adverse health effects, most often signs of peripheral neuropathy (38%, 32% in 2019, 43% in 2020, Fig. 1A), gastro-intestinal distress (28%) and dizziness (15%). Patients who used N₂O only (no concomitant exposures, N=192), reported comparable symptoms in similar frequencies.

Discussion

We observed an exponential increase of the incidence rate of N₂O poisonings between 2010 and 2020. Heavy use of N₂O is associated with peripheral neuropathy and neurological damage (Garanaki et al., 2016; Micallef et al., 2020; Zheng et al., 2020). This is further supported by our data, showing signs of peripheral neuropathy in 38% of all patients in 2019 and 2020. The observed patterns of heavy and frequent use, increasingly from cylinders, are worrying. To compare, one cylinder can fill several hundreds of balloons, while one small cartridge (for whipped cream) only fills one balloon. Notably, the easy availability of cylinders can facilitate heavy use, resulting in more frequent adverse neurological effects. The change to less strict EU legislation in 2014 may have influenced the availability of N₂O for recreational purposes, gradually leading to more problematic use and more poisonings, although such increases were also observed outside the EU. In the UK, however, recreational use of N₂O appears unaffected by more strict legislation, with similar prevalences of use being reported before and after the introduction in 2016 (Rough & Brown, 2020).

From March 15th 2020 onwards, several measures to control the COVID-19 pandemic were in place in the Netherlands. To investigate whether the pandemic affected our findings, we reanalyzed the time trend, while excluding the 2020 data. This still resulted in an exponential curve, supportive of our main conclusion. Furthermore, the use of incidence rates (relative to all recreational drug poisonings) to analyze the time trend, also corrects for COVID-19 related effects on recreational drug poisonings in general. The COVID-19 pandemic and subsequent

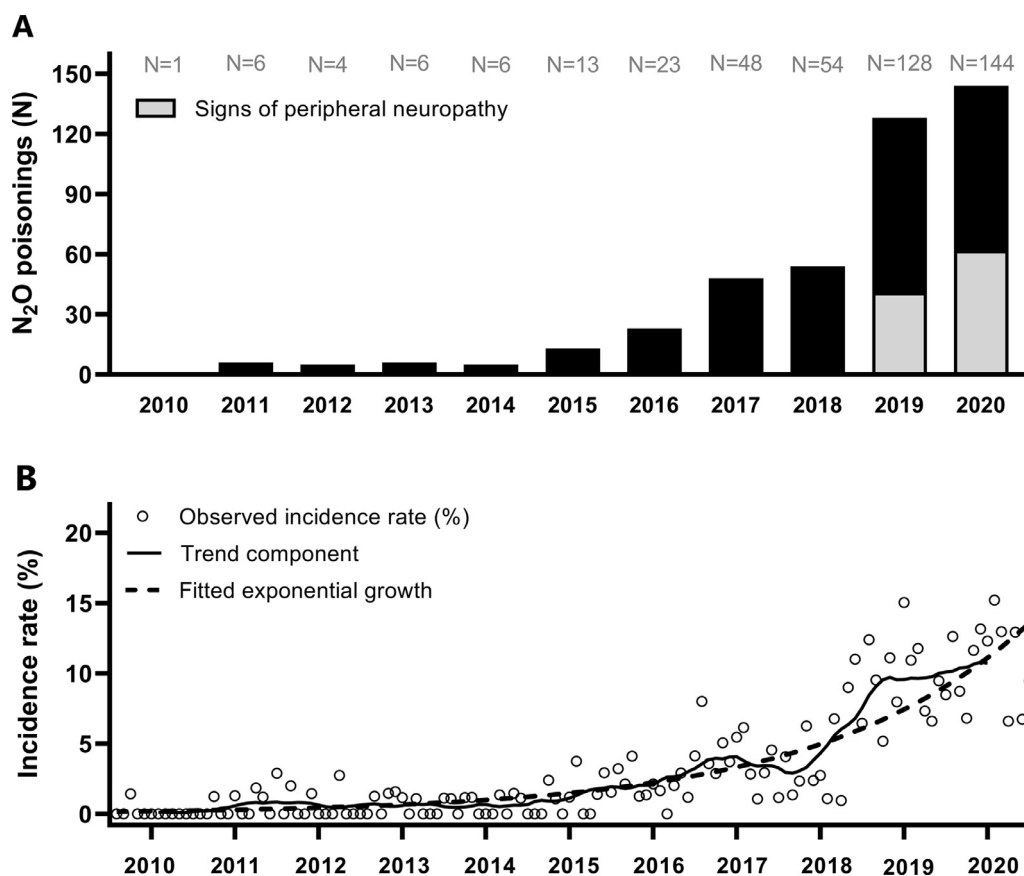


Fig. 1. Epidemiology of nitrous oxide (N₂O) poisonings reported to the DPIC between 2010-2020.

A. Number of N₂O poisonings. B. Observed monthly incidence rates (relative to all recreational drug poisonings) with trend component and fitted exponential growth.

lockdowns apparently did not prevent (heavy) users from obtaining N₂O and using it. In the Netherlands some companies even provide 24/7 delivery. Possibly, the extreme patterns of use have been exacerbated by the COVID-measures.

Previously, N₂O was considered non addictive (Kaar et al., 2016; Van Amsterdam et al., 2015), but recently several reports indicate that it may lead to substance use disorder. A review identified 59 published cases meeting two or more DSM-V criteria of abuse or dependence to N₂O (Fidalgo et al., 2019). In addition, seven cases of severe N₂O use disorder have been identified in Taiwan (Chien et al., 2020). Although we did not collect details on the addictive properties of N₂O, the high occurrence of heavy and frequent use in our study, the massive amounts used by some patients, and the sometimes daily use of N₂O, are suggestive of addictive potential. Possibly, N₂O's interaction with opioid and NMDA-receptors underlie this potential (Kaar et al., 2016). Quantitative studies, such as animal studies with drug choice paradigms or human studies applying DSM-V criteria, are needed to establish the addictive properties of N₂O.

Users perceive N₂O as fairly harmless, and some do not even perceive it as a drug of abuse (National Drug Monitor, 2020). Presumably, the legal status and the unregulated sales, even in retail stores, contribute to this perception. Also, many users are unaware that the possible adverse health effects can be severe and can include irreversible neurological damage (National Drug Monitor, 2020). Raising awareness on the health risks of N₂O in user groups and in the medical community can contribute to prevention. Early recognition of symptoms and correct laboratory diagnostics of N₂O related vitamin B12 deficiency, followed by early intervention and treatment, are pivotal to prevent permanent neurological damage (Garanaki et al., 2016; Randhawa & Bodenham, 2016).

A limitation of this study is selection bias due to the voluntary nature of reporting to our poisons center. Consequently, we lack denominator data on all (N₂O) poisonings in the Netherlands and selection towards symptomatic (more severe) cases will occur, leading to an overestimation of the health risk. Selection bias also occurred because inquiries to the DPIC are usually done in a (sub)acute intoxication setting. Most inquiries on N₂O originated from general physicians, ambulance staff and emergency physicians. Patients who gradually develop neurological problems are more likely to consult a neurologist or a rehabilitation doctor, and thus would be absent in our population. This could lead to an underestimation of the incidence rate. Two other limitations are the retrospective data collection, resulting in missing variables and the lack of follow up data on the persistence and reversibility of signs of peripheral neuropathy.

Conclusion

We observed an exponential increase in the number of N₂O poisonings, including those with signs of neurological damage, in the Netherlands. The frequency and amounts of N₂O used, suggest that N₂O has potential to cause substance use disorder. The Dutch experience demonstrates the importance of educating users on the health risks. Monitoring and considering a ban on the sales of large amounts of N₂O to consumers, in whipped cream cartridges and especially in larger cylinders, is strongly recommended to help prevent increases in recreational use and subsequent problematic use with damage to public health.

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Ethical approval

No.

Declarations of Interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.drugpo.2021.103519](https://doi.org/10.1016/j.drugpo.2021.103519).

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