

High Incidence of Signs of Neuropathy and Self-Reported Substance Use Disorder for Nitrous Oxide in Patients Intoxicated with Nitrous Oxide

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Keywords

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Abstract

Introduction: The number of patients with excessive nitrous oxide (N₂O) use and neurological disorders has been rising, indicating an addictive potential of N₂O. We studied the incidence of self-reported substance use disorder (SUD)-related symptoms, signs of neuropathy, and the patterns of use in N₂O-intoxicated patients. **Methods:** The Dutch Poisons Information Center (DPIC) provides information by telephone on the management of intoxications to healthcare professionals. Retrospective data on signs of neuropathy and patterns of use were collected for all N₂O intoxications reported to the DPIC in 2021 and 2022. Frequent and heavy use were self-reported as “often/frequent/weekly use” and as “use of tanks or >50 balloons/session,” respectively. From this cohort, we included patients with excessive N₂O use or signs of neuropathy in a prospective observational cohort study. Online surveys were sent 1 week, 1 month, and 3 months after DPIC consultation. The survey included

the drug use disorder questionnaire (validated to measure self-reported substance abuse [SA] and substance dependence [SD] based on Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV-TR criteria) and questions on patterns of use and signs of neuropathy. DSM-IV-TR criteria were translated to DSM-V criteria to score for mild, moderate, or severe SUD, with 2–3, 4–5, or ≥6 symptoms, respectively. **Results:** We included 101 N₂O-intoxicated patients in the retrospective study. Of these, 41% showed signs of neuropathy (N = 41), 53% used N₂O tanks to fill balloons (N = 53), 71% used them frequently (N = 72), and 76% used them heavily (N = 77). We included 75 patients in the prospective study and 10 (13%) completed the first survey. All 10 patients fulfilled the criteria for SA and SD (DSM-IV-TR, median number of questions answered “yes” = 10/12), all used N₂O tanks to fill balloons, and 90% (N = 9) experienced signs of neuropathy. After 1 and 3 months, 6/7 and 1/1 patients, respectively, continued to fulfill SA and SD criteria. Translating to DSM-V criteria, 1/10 patients fulfilled the

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criteria for (self-reported) mild SUD, 1/10 patients for moderate SUD, and 8/10 patients for severe SUD, 1 week after consultation. **Conclusion:** The high proportion of N₂O-intoxicated patients reporting frequent and heavy use of N₂O indicates an addictive potential of N₂O. Although follow-up rate was low, all patients fulfilled self-reported SA, SD (DSM-IV-TR), and SUD (DSM-V) criteria for N₂O. Somatic healthcare professionals treating patients with N₂O intoxications should be aware of possible addictive behavior in patients. The screening, brief intervention, and referral to treatment approach should be considered to treat patients with self-reported SUD symptoms.

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Introduction

Nitrous oxide (N₂O) is a gas traditionally used in medical practice for its anesthetic effects. It also has legitimate uses in the automotive industry to power boost engines and in the culinary industry in whipped cream dispensers [1]. Since a change in European legislation, sales to consumers increased dramatically [1], and a subsequent rise in the recreational use of N₂O in The Netherlands has been observed [2]. While in 2015, 20% of Dutch students had ever used N₂O, this percentage rose to 29% in 2019 [1]. Data from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) suggest that the use of N₂O in other European countries may also be increasing among young people, based on an increase in reports of poisonings to poison centers and a rise in emergency department presentations involving N₂O use [3]. Notably, the number of N₂O intoxications has increased exponentially in The Netherlands during the last decade [1].

N₂O usually comes in whippets or tanks and is recreationally inhaled using a balloon. Inhalation can cause hallucinogenic effects and a momentary euphoric high, hence its alternative name, “laughing gas” [4]. The lifetime prevalence of recreational N₂O use seems to be slightly higher among Dutch males than among Dutch females, while their last year or last month prevalence of N₂O use is comparable [2]. Until recently, controlled and infrequent use of N₂O was not associated with significant adverse health effects [4–6]. However, a subgroup of users consumes N₂O frequently and in large amounts [1, 4, 5, 7]. In a Dutch cohort of N₂O-intoxicated patients, 79% indicated heavy use (>50 balloons per session) and 42% used N₂O tanks to fill balloons [1]. Tanks containing up to 15 kg N₂O – enough to fill 1,200 balloons – can be legally purchased online [8].

The recreational use of N₂O can cause symptoms of acute and/or chronic intoxication. Acute symptoms comprise dizziness, headache, unconsciousness, or chest pain [9]. Inhaling N₂O directly from the tank can cause freezing of the lips, mouth, and the airways or can cause barotrauma in the lungs [10, 11]. Additionally, holding the tank between the thighs can result in burn injuries [12]. Chronic toxicity of N₂O comprises mostly neurological symptoms, caused by the inactivation of vitamin B12 [13]. This can lead to demyelination of peripheral and central nerves and can therefore cause polyneuropathy or, in extreme cases, myelopathy [13]. Moreover, several cases of severe thromboembolic events caused by N₂O have been reported [14]. Psychiatric manifestations such as psychosis, self-harm, suicidal attempts, or violent behavior can also occur in N₂O users [15].

A Dutch study in patients intoxicated with N₂O reported that 38% of the patients showed signs of neuropathy [1]. The literature showed that 36–98% of patients who presented in the hospital with N₂O abuse showed signs of neuropathy [16, 17]. Supplementation with vitamin B12 could reverse damage, provided that N₂O use is discontinued [18, 19].

Neuropathy due to N₂O use is mainly seen in users who use N₂O frequently or in large amounts [5]. In studies of patients with neurological disorders caused by inhaling N₂O, patients reported the use of excessive amounts [16, 20, 21]. Also, some N₂O users met at least 2–3 out of 11 Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria for substance use disorder (SUD), which suggests the presence of mild SUD [22]. In addition, published case reports describe addictive behavior among N₂O users, such as continuous use of large amounts (>100 whippets per day) [23], the presence of withdrawal symptoms, and difficulties quitting N₂O use [24, 25]. These signs could indicate that N₂O use is addictive. While Dutch addiction specialists have reached out to mass media to express their concerns regarding the addictive potential of N₂O use [J. Weijts, Vereniging Verslavingsgeneeskunde Nederland (VVGn), RTL Nieuws, November 14, 2020], scientific evidence to support this claim remains limited [26]. As such, there are no studies that examined the association between the excessive use of N₂O and the incidence of N₂O addiction. The aim of this study was to investigate the incidence of, and the association between, self-reported symptoms related to SUD, signs of neuropathy, and the patterns of use in patients with N₂O intoxication as reported to the Dutch Poisons Information Center (DPIC).

Method

Setting

The DPIC provides information on the clinical course and the management of intoxications to healthcare professionals. Professionals can access information on intoxications on the DPIC's website or by telephone 24/7. During this study, information on N₂O was not available on the DPIC website. During a telephone inquiry to the DPIC, a standardized electronic case report form (eCRF) is filled in for each reported intoxication by a trained Specialist in Poisons Information (SPI) and stored in the DPIC's database. eCRFs include anonymous patient data such as age, weight, gender, exposure characteristics, co-exposures, and symptoms (observed before or during inquiry) as reported by the healthcare professional. The exact reason of consultation is not registered but generally concerns the clinical management of patients. The DPIC relies on information provided by intoxicated patients to healthcare professionals (e.g., self-reported exposures) and is often consulted in an early, acute phase of intoxications. Chronic intoxications are reported occasionally. Follow-up is not routinely performed by the DPIC for every case. Therefore, the outcome of most cases is unknown, and essential information may be missing.

Study Design

This study contains two parts.

1. The first part is a retrospective observational study, using the data from eCRFs concerning all, acute or chronic, N₂O intoxications reported to the DPIC during a 1-year period.
2. The second part is a prospective observational cohort study in which patients from the retrospective study with signs of neuropathy or usage of excessive amounts of N₂O were asked to participate in an online survey including questions on self-reported symptoms related to SUD.

Patients

Retrospective Observational Study – Analysis of Electronic Case Reports (2021–2022)

For every patient with, acute or chronic, N₂O intoxication for whom the DPIC was consulted, an eCRF was created and stored in the database. Cases reported between January 16, 2021, and January 15, 2022, were included in the study. Occasionally, the DPIC was consulted more than once about the same intoxication in 1 patient and multiple eCRFs were created. In such cases, data from all eCRFs were combined. Cases with concomitant exposures (medication, alcohol, or other recreational drugs) were also included.

Prospective Observational Cohort Study (2021–2022)

Patients from the retrospective observational study were included in the prospective observational cohort study if they were ≥16 years of age and fulfilled the following criteria: (1) they used an excessive amount of N₂O (>50 balloons/>200 L/>450 g N₂O) and/or (2) they indicated the presence of signs of neuropathy (see Measures section). These two criteria were combined to include as many relevant cases as possible since information on patterns of use is not always available during the telephone inquiry to the DPIC, while information on symptoms usually is. When physicians consulted the DPIC and the patient met the inclusion criteria, the SPI requested the physician to ask the patient if they

would be willing to participate in the study. When patients accepted to participate, the physician provided the DPIC with the patient's email address. Within a week after consultation, patients were invited to fill in an online survey. Each survey started with obtaining (written) informed consent. When patients finished the survey, they were asked for permission to receive a second survey 1 month after the first survey. After the second survey was completed, patients were asked for permission to receive a third survey 3 months after the first survey (shown in online suppl. material A; for all online suppl. material, see www.karger.com/doi/10.1159/000530123).

Data Collection

Retrospective Observational Study – Analysis of Electronic Case Reports

The SPIs are trained to fill in a standardized eCRF for every consultation. Standardized eCRFs include anonymous patient data such as age, weight, gender, exposure characteristics (i.e., amount, timing, intention, co-exposures), and symptoms (observed before or during inquiry). For N₂O intoxications, additional questions were added to the standardized eCRF, including the packaging of N₂O used (balloons, tanks, whippets), the duration of the exposure, frequency of use, whether the patient experienced addictive behavior, the patient's diet, the presence of specific neurological symptoms related to neuropathy, and the duration of symptoms. Anonymous patient data and answers on the specific N₂O questions may be missing and, in that case, the corresponding specific variable was considered unknown. Data from eCRFs were exported to SPSS. All telephone inquiries were voice recorded and stored in the database. Recordings were used for data checks on the eCRFs and supplemented in SPSS, if necessary.

Prospective Observational Cohort Study

Data management platform Castor (v. 2022.2.2.1) was used to create a survey to send it to patients and to collect data from completed surveys. The survey consisted of three topics: the validated drug use disorder (DUD) questionnaire (12 questions, [27]), patterns of use (2 questions), and signs of neuropathy (4 questions) (shown in online suppl. material A). Using Castor, data from the surveys were exported to SPSS. Incomplete surveys were excluded from data analysis.

Outcomes

The primary outcomes of the retrospective part of this study were the incidence of signs of neuropathy and the patterns of use in patients with N₂O intoxication. The secondary outcome of the retrospective part of this study was the association between signs of neuropathy and patterns of use. For the prospective part of this study, the primary outcome was the presence of self-reported SUD-related symptoms. The secondary outcomes of the prospective part of this study were signs of neuropathy, patterns of use, and their association.

Measures

Definitions and measures in this study are in line with previous definitions published by the DPIC on N₂O intoxications [1]. Signs of neuropathy include symptoms related to peripheral neuropathy and myelopathy such as paresthesia, sensory issues in extremities, ataxia, fine motor difficulties, loss of strength in extremities, or paralysis of extremities. The patterns of use include the frequency

of N₂O use, the amount of N₂O used, the route of administration, and co-exposures. Heavy use of N₂O was defined as using a tank to fill balloons or the use of >50 balloons per session (equivalent to ≥400 g or ≥200 L of N₂O gas). Frequency of use was scored as “frequent” if patients told their physician that they used “often/frequent/weekly.” If no information was reported about the pattern of use, “not heavy” and “not frequent” use were assumed. Co-exposures included exposures other than therapeutic doses of medication and ≥2 glasses of alcohol.

SUD-related symptoms were assessed using the DUD questionnaire that has been validated for research purposes [27]. The questionnaire is based on criteria of SUD as described in the DSM-IV-TR, the psychiatric handbook to classify and diagnose psychiatric illnesses. In the DSM-IV-TR, SUD is categorized into two subtypes: substance abuse (SA) and substance dependence (SD). Questions 1–4 in the validated questionnaire used in this study correspond to the criteria for subtype SA. If ≥1 of these questions were answered with “yes,” patients met the criteria for SA (shown in online suppl. material A). Questions 5–12 of the validated questionnaire correspond to the criteria for subtype SD. If ≥3 questions were answered with “yes,” patients met the criteria for SD. If patients met criteria for both subtypes, subtype SD was scored, as the subtype SD is considered more severe than SA [27]. During the study design, this was the only validated questionnaire available for research purposes to measure SUD-related symptoms. Since currently DSM-V is used in clinical practice, we also applied DSM-V criteria to the DUD questionnaire results to score for mild, moderate, or severe SUD, defined as 2–3, 4–5, or ≥6 questions being answered “yes,” respectively. The questions in our survey on the patterns of use and signs of neuropathy were not validated and are only used for descriptive purposes and not to measure additional diseases or disorders.

Data Analysis

Retrospective Observational Study

Patient characteristics were analyzed using descriptive statistics in SPSS. Variables were tested for normal distribution. If the data were not normally distributed, variables were expressed as medians. Using descriptive statistics, the frequency of patients with signs of neuropathy was determined, and the patterns of use were analyzed. Incidence of signs of neuropathy was calculated by dividing the number of N₂O intoxications in which users showed signs of neuropathy by the total number of N₂O intoxications. Association between signs of neuropathy and patterns of use was assessed using Pearson χ^2 test for independence ($p < 0.05$) in SPSS. The phi coefficient was calculated to indicate the strength of the association.

Prospective Observational Cohort Study

Baseline characteristics for the patients in the prospective observational cohort study were compared between patients in the group with and without follow-up using the Pearson χ^2 test or Fisher’s exact test (if expected number <5 in >25% of cells) for categorical variables and using Mann-Whitney test for continuous non-normally distributed variables in SPSS ($p < 0.05$).

For every patient, the presence of self-reported SUD-related symptoms was determined, followed by the potential presence of N₂O dependence according to DSM-IV-TR and DSM-V criteria. Patient characteristics, presence of signs of neuropathy, and the patterns of use were analyzed using descriptive statistics in SPSS.

Results

From January 16, 2021, till January 15, 2022, the DPIC received 120 reports on N₂O intoxications concerning 101 patients, of whom 75 met the inclusion criteria for the prospective part of the study (shown in Fig. 1).

Epidemiology

Of the 101 patients with N₂O intoxication, the majority were young adults with a median age of 23 years (IQR 20–28). The gender distribution was approximately equal (shown in Table 1).

Characteristics of N₂O Intoxications

Of the 101 patients, the majority stated frequent or heavy N₂O use ($N = 72$, 71%, and $N = 77$, 76%, respectively). Most patients used N₂O tanks to fill their balloons ($N = 53$, 53%), varying in content from 2 to 20 kg. N₂O was mainly used as a solitary drug ($N = 71$, 70%) (shown in Table 1). In case of co-exposures, N₂O was combined with other recreational drugs ($N = 14$, 14%), alcohol and recreational drugs ($N = 6$, 6%), or alcohol only ($N = 4$, 4%). Of all patients ($N = 101$), 41 patients (41%) reported the presence of neurological symptoms related to neuropathy such as paresthesia ($N = 30$, 30%), muscle weakness of the extremities ($N = 13$, 13%), ataxia ($N = 9$, 9%), pain in the extremities ($N = 7$, 7%), and tremor ($N = 1$, 1%). Most patients experienced multiple signs of neuropathy. Signs of neuropathy were significantly associated with frequent N₂O use ($p = 0.002$, $\phi = 0.302$), while no significant association was observed with heavy N₂O use ($p = 0.08$, $\phi = 0.177$).

Prospective Observational Cohort Study – Analysis of Surveys

Inclusions

From all 101 N₂O intoxications, 75 patients met the inclusion criteria of the prospective study. Ten patients gave informed consent and completed the first survey (shown in Fig. 1). Reasons for lost to follow-up included “participation not requested by DPIC” ($N = 21$), “participation not agreed by patient” ($N = 32$), and “participation agreed, but survey not filled in” ($N = 12$). The median age of patients was 23 years (IQR 18–24; range 16–26), and the majority was female ($N = 8$, 80%). Patients in the group with and without follow-up did not differ in age, method of use, proportions of frequent and heavy use, co-exposures, or signs of neuropathy. However, in the group with follow-up, more females were present (shown in Table 1).

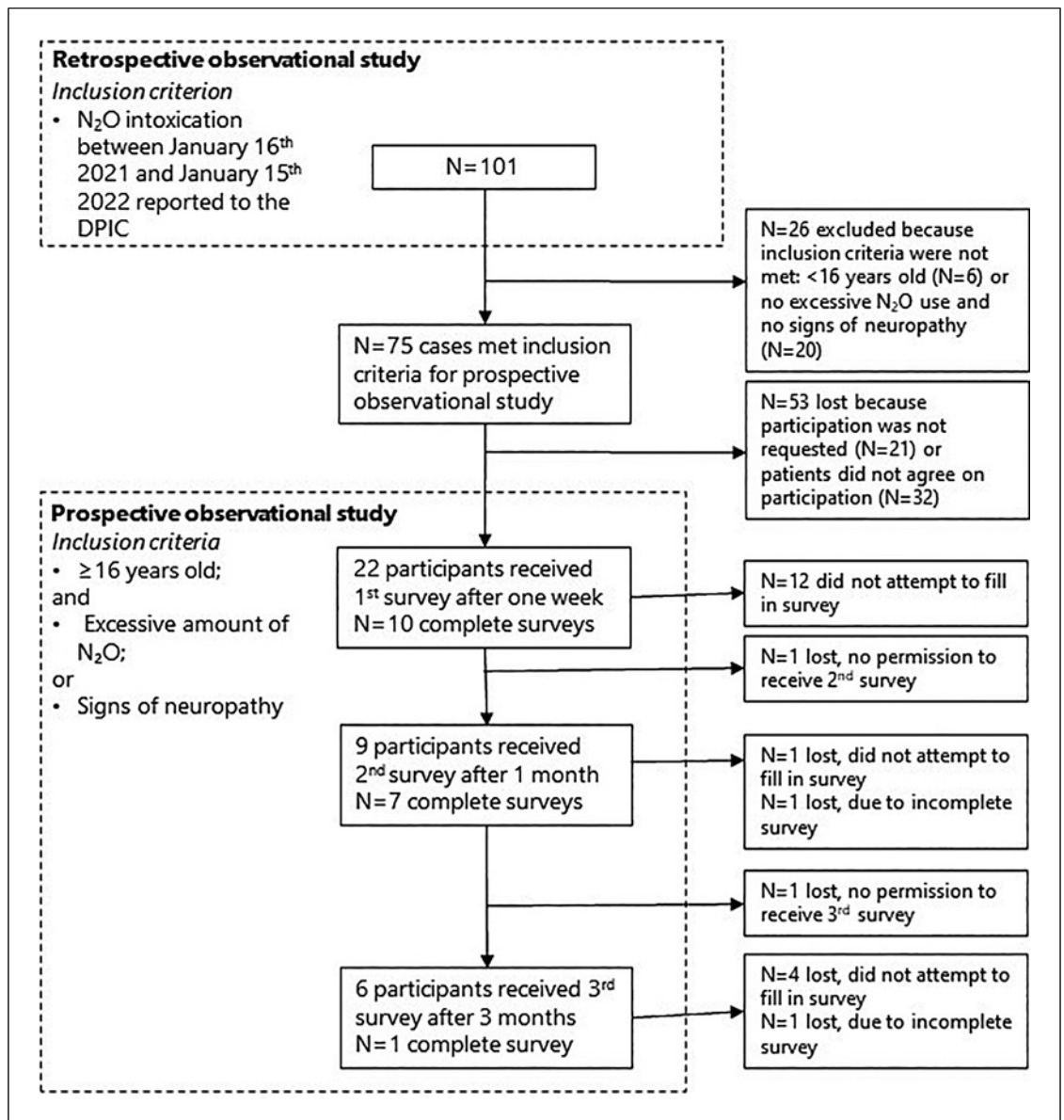


Fig. 1. Flow chart of the inclusions in the retrospective observational study and the prospective observational cohort study on (acute or chronic) nitrous oxide (N₂O) intoxications reported to the Dutch Poisons Information Center (DPIC) in 2021 and 2022.

SUD, Signs of Neuropathy, and Patterns of Use

All patients who completed the first survey ($N = 10$, 100%) scored positive on self-reported SA and SD. The median number of SA questions scored with “yes” was 3/4 (range 2–3). The median number of SD questions scored with “yes” was 7/8 (range 3–8). As SA and SD are a (research) measure for self-reported SUD according to DSM-IV-TR criteria, all patients classified as having self-reported SUD-related symptoms (shown in Table 2, 3). Most patients

stated that N₂O had a negative influence on their relation with friends and family and that it interfered with their education ($N = 9$, 90%). Patients needed to use more N₂O to experience the same effects ($N = 8$, 80%) and suffered from adverse aftereffects like anxiety and headaches ($N = 10$, 100%). Eight patients (80%) tried to quit using N₂O but failed to do so. Detailed survey results are shown in Table 2 and Table 3. Translating to DSM-V criteria, 1/10 fulfilled the criteria for (self-reported) mild, 1/10 for moderate, and

Table 1. N₂O intoxications reported to the DPIC: patient characteristics and patterns of use

Patient characteristics	Retrospective observational study		Prospective observational cohort study ¹			Significance ($p < 0.05$) ²
	all intoxications ($N = 101$) N (%)	patients with signs of neuropathy ($N = 41$) N (%)	included patients ($N = 75$) N (%)	patients with follow-up ($N = 10$) N (%)	patients lost to follow-up ($N = 65$) N (%)	
Age, years Median (IQR; range)	23 (20–28; 14–50)	23 (20–27; 18–38)	23 (20–28; 16–45)	23 (18–24; 18–26)	23 (16–45; 20–28)	$p = 0.217$
Gender						
Male	53 (52)	22 (54)	40 (53)	2 (20)	38 (59)	$p = 0.023$
Female	48 (48)	19 (46)	35 (47)	8 (80)	27 (42)	
Use						
From tank	53 (53)	25 (61)	47 (63)	8 (80)	39 (60)	$p = 0.429$
From whippet	17 (17)	5 (12)	10 (13)	–	10 (15)	
Unknown	31 (31)	10 (24)	18 (24)	2 (20)	16 (25)	
Frequent use ³	72 (71)	36 (88)	61 (81)	8 (80)	53 (82)	$p = 0.907$
Heavy use ⁴	77 (76)	35 (86)	69 (92)	9 (90)	60 (92)	$p = 0.802$
Co-exposures ⁵						
None	71 (70)	32 (78)	57 (76)	8 (80)	49 (75)	$p = 0.750$
Co-exposures	30 (30)	9 (22)	18 (24)	2 (20)	16 (25)	
Signs of neuropathy ⁶	41 (41)	41 (100)	41 (55)	8 (80)	33 (51)	$p = 0.084$

¹Note that the prospective cohort was included from the retrospective cohort, based on excessive N₂O use or signs of neuropathy. ²Patients with and without follow-up (lost) were compared. ³Frequent use was scored when physicians stated that patients used “often, frequent, or weekly.” ⁴Heavy use was defined as using “>50 balloons in one session or the use from a tank.” ⁵Co-exposures are any concomitant exposures other than prescribed medication (therapeutic dose) or ≤ 2 glasses of alcohol. ⁶Data from the retrospective observational study (the moment of phone consultation with the DPIC) were used to determine signs of neuropathy. In 1 patient, signs of neuropathy were only reported during follow-up (not during consultation). This patient was included in the prospective observational cohort study based on excessive use.

8/10 for severe SUD, 1 week after consultation (shown in online suppl. material B, Table 4).

Nine patients reported signs of neuropathy (90%) such as paresthesia ($N = 9$, 90%), sensory issues in extremities ($N = 9$, 90%), muscle weakness of the extremities ($N = 9$, 90%), ataxia ($N = 7$, 70%), fine motor disabilities ($N = 6$, 60%) and 2 patients reported paralysis of their feet (20%). Most patients used N₂O at least weekly ($N = 7$, 70%). All 10 patients used N₂O tanks to fill balloons, varying in content from 2 to 20 kg.

Follow-Up

Nine out of 10 patients (90%) who completed the first survey consented for receiving the follow-up survey after 1 month. This survey was completed by 7 patients (78%). Six out of seven (85%) continued to fulfill the self-reported criteria for SA and SD (DSM-IV-TR) and severe SUD (DSM-V)-related symptoms. All 6 patients still experienced signs of neuropathy. One patient no longer fulfilled the self-reported criteria for SA and SD (DSM-IV-TR) and

SUD (DSM-V)-related symptoms, did not experience signs of neuropathy anymore, and the frequency of use was lowered from monthly to yearly. Six out of seven patients (85%) who completed the second survey consented for receiving the third and final survey after 3 months. Only 1 patient completed the final survey. The patient continued to fulfill the self-reported criteria for SA and SD (DSM-IV-TR) and severe SUD (DSM-V)-related symptoms. The patient still experienced signs of neuropathy.

Discussion

This study showed that a large proportion of patients with N₂O intoxication – as reported to the DPIC – experienced signs of neuropathy ($N = 41$, 41%). As anticipated, patients with these signs more often reported frequent use of N₂O compared to those without. In contrast to the traditional use of N₂O from whippets by recreational users, the patients in our study often used N₂O tanks to fill

Table 2. Results from survey in the prospective study per patient

Patient (#)	Time of survey after DPIC consultation	Subtype SUD (n criteria met) ¹	Frequency of use	Use of tanks (weight)	No. of balloons used (per session)	Presence of neurological signs (duration)
1	1 week	SD (7/8)	Weekly	Yes (2–4 kg)	Unknown	Paresthesia ² , ataxia ³ , muscle weakness of upper legs (120 days)
2	1 week	SD (7/8)	Daily	Yes (10 kg)	70	Paresthesia, sensory issues in extremities, ataxia, muscle weakness of feet, legs, hands, pain in the abdomen and back (60 days)
	1-month follow-up	SD (6/8)	Unknown	Yes (2 kg)	50	Paresthesia, sensory issues in extremities, ataxia, fine motor difficulties ⁴ , muscle weakness of feet and legs
3	1 week	SD (4/8)	Monthly	Yes (2 kg)	100	No signs
	1-month follow-up	No SUD	Yearly	Yes	10	No signs
4	1 week	SD (7/8)	Weekly	Yes (2–6 kg)	Unknown	Paresthesia, sensory issues in extremities, ataxia, fine motor difficulties, muscle weakness of legs and arms (3 days)
5	1 week	SD (8/8)	Monthly	Yes (10 kg)	Unknown	Paresthesia, sensory issues in extremities, ataxia, muscle weakness of hands (14 days)
	1-month follow-up	SD (8/8)	Monthly	Yes	500	Paresthesia, sensory issues in extremities, muscle weakness of hands
6	1 week	SD (7/7)	Weekly	Yes (2–4 kg)	Unknown	Paresthesia, sensory issues in extremities, muscle weakness of arms
	1-month follow-up	SD (7/7)	Weekly	Yes (4 kg)	Unknown	Paresthesia, sensory issues in extremities, muscle weakness of arms
7	1 week	SD (3/8)	Yearly	Yes	2	Paresthesia, sensory issues in extremities, ataxia, muscle weakness of legs (5 days)
8	1 week	SD (8/8)	Weekly	Yes (2–6 kg)	Unknown	Paresthesia, sensory issues in extremities, ataxia, fine motor difficulties, muscle weakness of feet and legs (60 days)
	1-month follow-up	SD (6/8)	Monthly	Yes (2–4 kg)	Unknown	Paresthesia, sensory issues in extremities, ataxia, fine motor difficulties, muscle weakness
9	1 week	SD (7/8)	Weekly	Yes	Unknown	Paresthesia, sensory issues in extremities, ataxia, fine motor difficulties, muscle weakness of feet, legs, and hands
	1-month follow-up	SD (5/8)	Weekly	Yes	Unknown	Paresthesia, sensory issues in extremities, muscle weakness of hands
10	1 week	SD (8/8)	Weekly	Yes (20 kg)	500 balloons	Paresthesia, sensory issues in extremities, ataxia, fine motor difficulties, muscle weakness (3 days)
	1-month follow-up	SD (7/8)	Unknown	Yes	Unknown	Paresthesia
	3-month follow-up	SD (8/8)	Weekly	Yes	1,000 balloons	Paresthesia, ataxia, fine motor difficulties

¹The numbers in this column represent the number of self-reported SUD (substance use disorder)-related symptoms as reported by patients of the prospective cohort study ($N = 10$). Substance abuse (SA) and substance dependence (SD) were scored positive if ≥ 1 and ≥ 3 questions were answered as “yes,” respectively, based on DSM-IV-TR criteria [27]. As SA and SD are a (research) measure for self-reported SUD according to DSM-IV-TR criteria, all patients classified as having self-reported SUD-related symptoms 1 week after consultation. ²Paresthesia is a prickling or burning sensation of the skin. ³Ataxia is defined as problems with walking, falling, or shaking. ⁴Fine motor difficulties include miss-reaching, difficulties buttoning your shirt, or tying shoelaces.

Table 3. Group data on the response to the drug use disorder (DUD) questionnaire

SUD-related symptoms (according to DSM-IV-TR criteria)	<i>n</i> patients answered “yes”
<i>Substance abuse</i>	
1. In the past year, did your N ₂ O use interfere with taking care of your home or family or cause you problems at work or school?	9/10
2. In the past year, did you more than once get into a situation while using or after using N ₂ O that increased your chances of getting hurt-like driving a car or other vehicle or using heavy machinery?	5/10
3. In the past year, did you get arrested, held at a police station, or have legal problems because of your N ₂ O use?	2/10
4. In the past year, did you continue to use N ₂ O even though it was causing you trouble with your family or friends?	8/10
<i>Substance dependence</i>	
5. In the past year, have you found that you have to use more N ₂ O than you once did to get the effect you wanted?	8/10
6. In the past year, did you find that your usual amount of N ₂ O had less effect on you than it once did?	8/10
7. In the past year, when the N ₂ O effects were wearing off, did you experience some of the bad after effects-like trouble sleeping, feeling nervous, restless, anxious, sweating, or shaking, or did you have seizures or sense things that were not really there?	9/10
8. In the past year, did you end up using more N ₂ O or using for a longer period than you intended?	9/10
9. In the past year, did you more than once want to try to stop or cut down on your N ₂ O use but could not do it?	8/10
10. In the past year, did you spend a lot of time using N ₂ O or getting over the bad aftereffects of use?	10/10
11. In the past year, did you give up or cut down on activities that were important to you or gave you pleasure in order to use N ₂ O?	6/10
12. In the past year, did you continue to use N ₂ O even though it was causing you to feel depressed or anxious or causing a health problem or making one worse?	9/10

Data represent the response to questions included in the DUD questionnaire, based on DSM-IV-TR criteria for substance abuse (questions 1–4) and dependence (questions 5–12) in the first survey (1 week after contact with the Dutch Poisons Information Center [DPIC]). Indicated is the number of patients who marked “yes” on the specific question, with a total of 10 patients. Questionnaire originates from Scherer et al. (2013) [27].

balloons and used N₂O as a solitary drug. The high prevalence of heavy use in the retrospective part already provided an indication of possible addictive properties of N₂O. Stronger evidence was obtained in the prospective study, where all patients met the self-reported criteria of SUD-related symptoms and thereby scored positive for N₂O dependence. The majority of these patients (*N* = 9, 90%) also reported heavy use and signs of neuropathy, demonstrating an association between these aspects and self-reported SUD-related symptoms.

While initially no addictive potential of N₂O was expected [4, 6], a study demonstrating possible SUD in N₂O users based on case reports in the literature has recently been published. However, the available data were not sufficient to score separate SUD criteria, likely resulting in underrepresentation of (the severity of) SUD [22]. Our study is the first that prospectively demonstrates the presence of self-reported SUD-related symptoms in N₂O users. Remarkably, all patients in our prospective cohort reported a sufficient number of SUD-related symptoms to

score positive for N₂O dependence according to DSM-IV-TR and DSM-V criteria. Four patients fulfilled all criteria (8/8) for SD, illustrating the potential severity of SUD-related symptoms. The overall increasing proportion of patients with symptoms of N₂O addiction is possibly related to the misconception among users that N₂O is nonaddictive [28].

The patterns of use observed in this study showed that the majority of the study population used N₂O from tanks to fill their balloons. Tanks are likely to facilitate heavy use because they contain more gas, are cheaper, and balloons can be filled quicker [1, 28, 29]. Selling and buying N₂O tanks was legal in The Netherlands until recently but will be banned from January 1, 2023 [30]. Notably, we observed that the majority of patients with N₂O intoxication used solely N₂O, without concomitant drug or alcohol exposures, which has also been observed in other studies [1, 28, 31]. This is remarkable because most recreational drug intoxications reported to the DPIC concern poly-drug intoxications [32]. There could be several explanations for this phenomenon. Qualitative research on N₂O use among

Dutch adolescents showed that users consider N₂O as a relatively safe drug. They believe that only combining N₂O with alcohol or hard drugs could cause serious harm [28]. Furthermore, unlike alcohol, cannabis, or other drugs, N₂O is odorless, the visible effects only last seconds to minutes, and no lasting visible signs are present, which makes N₂O use easier to hide from friends or parents [8, 28].

In this study, patients with signs of neuropathy mostly reported paresthesia and loss of strength in their extremities, in line with other studies [17, 33–35]. In our cohort, signs of neuropathy were positively associated with frequent N₂O use. Other studies also reported an increased risk of developing neuropathy or severe neurological symptoms with increasing N₂O doses or longer periods of use [16, 36]. However, also low-intermittent exposure to N₂O can cause neurological damage due to individual variation in pre-existing vitamin B12 serum concentrations [16]. Therefore, an exact toxic dose of N₂O is difficult to determine.

In our experience, patients often present themselves to professionals with a variety of N₂O-related symptoms such as headache, chest pain, or dyspnea, fairly shortly after N₂O exposure. However, physicians should also be aware of signs of chronic intoxication. This includes vitamin B12 deficiency, which can best be diagnosed via measurement of serum concentrations of homocysteine and methylmalonic acid, as the serum vitamin B12 concentration can have normal values in excessive N₂O users, despite being inactive [35, 37].

The main limitations of this study are the possibility of selection bias and self-reporting bias. Selection bias can arise because health professionals mainly contact the DPIC when patients experience adverse effects following N₂O use and because consultation is optional. Likely, the proportion of patients with neurological symptoms and with self-reported SUD-related symptoms is an overestimation for the general population of N₂O users. In addition, not all N₂O intoxications are reported to the DPIC. However, in our population of intoxicated patients, the proportion of patients with frequent or heavy use could also be underestimated since data were not available in every case due to self-reporting bias. For the prospective study, the main limitation was the high percentage of cases lost to follow-up. However, characteristics during inquiry of the group with and without follow-up were largely similar. Therefore, the high incidence of self-reported SUD-related symptoms that we observed in the group with follow-up could also be present in our whole sample. In the follow-up group, a higher percentage of females were present. This is remarkable as the prevalence of recreational N₂O use seems to be comparable between both sexes or even slightly higher among males than among females [2]. Several studies have

shown that women are more likely to participate in surveys than men [38–40]. A minor limitation is that we used a validated DUD questionnaire that was based on the DSM-IV-TR criteria, while currently DSM-V criteria are used in diagnosing psychiatric illnesses. However, it was the only validated questionnaire for research purposes at the time of study design. Most SUD criteria overlap in both DSM editions, and comparable results for SUD have been obtained in other study populations [41], as well as in our study population (shown in online suppl. material B). Like Scherer et al. [27] indicated, the validated DUD questionnaire cannot be used to diagnose patients with SUD but can provide an indication for risk of SUD.

Although poison center data have their limitations, our study on health problems related to N₂O (ab)use is not the first example to show that toxicovigilance by poison centers is usually one of the first sources to identify a substance-related public health threat [1, 42–45]. This monitoring role of poison control centers is further corroborated in the report on N₂O by the EMCDDA [26].

In summary, we observed a high incidence of self-reported SUD-related symptoms in our cohort of N₂O-intoxicated patients. As these symptoms were associated with frequent use, availability of N₂O should be restricted, e.g., by prohibiting the purchase of tanks and large quantities of whippets by the general public. Legal measures are urgently required and will be in place from January 1, 2023, in The Netherlands [30]. Education on the health risks of excessive recreational N₂O use is needed to protect frequent and/or heavy users. From a physicians' perspective, awareness is required not only to treat symptoms of acute N₂O intoxication but also of chronic intoxication and abuse, both on a somatic (vitamin B12 deficiency and signs of neuropathy) and psychiatric level (SUD or other psychiatric manifestations). In addition, collaboration between general practitioners, neurologists, and addiction care specialists is recommended to increase awareness of the adverse effects related to N₂O use and to create clinical guidelines on how to manage patients suspected of excessive N₂O use. Physicians treating patients with N₂O intoxications should consider the screening, brief intervention, and referral to treatment approach to provide early intervention and treatment services for patients with self-reported SUD symptoms and collaborate with addiction care specialists [46].

Statement of Ethics

This study protocol was reviewed and approved by the accredited Medical Research Ethics Committee of the University

Medical Center Utrecht (approval number 20/831). The committee decided that the Dutch Medical Research Involving Human Subjects Act did not apply to this study.

Written informed consent from participants was obtained in the prospective part of the study before access to the survey was granted. Participants <16 years were not included in the prospective study.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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