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Treatment Seeking Nitrous Oxide Users in Addiction Care: A Comparison with Cocaine Users on Clinical and Treatment Characteristics

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Keywords
Nitrous oxide · Laughing gas · Substance-related disorders · Addiction

Abstract

Introduction: Over the past decade, frequent use of large quantities of nitrous oxide (N_2O) has become more common in the Netherlands. Although N_2O poses several negative health consequences for a subgroup of problematic N_2O users, there is a lack of knowledge on what characterizes these intensive users. This study therefore aims to provide the demographic and substance use characteristics and experiences during treatment of treatment seeking problematic N_2O users and to compare this with a matched group of treatment-seeking problematic cocaine users. ***Methods:*** A retrospective chart review was performed of patients who were referred for treatment of problematic N_2O use at a large Dutch addiction care facility from January 2020 to September 2022, extracting demographics, pattern of use and follow-up data. Additionally, a subgroup of N_2O users was propensity-score matched (1:1) with a subgroup of treatment seeking problematic cocaine users, both groups excluding users with substance use disorders or frequent use of substances other than N_2O and cocaine, respectively. ***Results:*** 128 patients with a N_2O use disorder were included in the total sample and a subgroup of 77 N_2O-only users was propensity-score matched on age and sex to 77 cocaine-only users. N_2O users were typically young (mean age 26.2 years), male (66.4%), unmarried (82.9%), with a low education level (59.0%) and born in the Netherlands (88.2%), with parents born in Morocco (45.3%). N_2O was used intermittently (median 10 days/month, IQR 4.0–17.5 days) and often in very large quantities (median 5 kg [ca. 750 balloons] per average using day, IQR 2–10 kg). Compared to the patients with a cocaine use disorder, matched N_2O users were lower educated, more often from Moroccan descent, and less likely to be alcohol or polysubstance users. Despite receiving similar treatments, N_2O users were twice as likely to discontinue treatment before completion compared to cocaine users (63 vs. 35%, $p = 0.004$). ***Conclusion:*** Treatment-seeking problematic N_2O users are demographically different from treatment-seeking problematic cocaine users and are much more likely to dropout from psychological treatment. Further research is needed into the needs and other factors of problematic N_2O users that relate to poor treatment adherence in problematic N_2O users.

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Introduction

Nitrous oxide (N_2O) has been used in dentistry and other medical practices for its anesthetic, analgesic and anxiolytic properties since the late 18th century. Due to its ability to induce euphoria, relaxation, and psychedelic effects, N_2O is also used recreationally [1]. The effects of N_2O occur quickly after inhalation (peaking at 10–20 s) and dissolve within 1–5 min [2]. For over 100 years, N_2O use was considered safe and to be without any side effects. However, it is currently known that frequent or prolonged N_2O exposure can induce a functional vitamin B12 deficiency, resulting in potentially severe neurological, psychiatric, hematological, and vascular complications [3].

In recent years, there has been an increase in the recreational use of N_2O among young adults in the Netherlands and a sharp increase in reported N_2O related health incidents, mainly resulting from heavy and frequent use [4]. From 2010 to 2015, an annual average of 6 of these health incidents was recorded by the Dutch Poisoning Information Centre (DPIC), while in 2020 144 incidents were reported. The improved accessibility and popularity of N_2O for recreational use in the Netherlands appears to have played a major role in the increase of recreational use and the substantial number of N_2O-related health incidents [5].

For over 40 years, N_2O has been readily available in small canisters of whipped cream charges (containing an average of 8 g N_2O, equivalent to 4 L of gas, i.e., the volume of one balloon). However, when in 2014 N_2O became subjected under the Commodities Act (due to a change in European legislation) larger canisters of N_2O (up to 10 kg, equivalent to 5,000 L of gas and the volume of ca. 1,250 balloons) also became available on the recreational market in the Netherlands which enabled recreational use in much larger quantities [2, 4, 6].

In parallel with an increase in health incidents reported by the DPIC, there was an increase in the number of patients seeking treatment for problematic N_2O use at Dutch addiction care facilities [7]. Although it is still debated in scientific literature to what extend a "N_2O use disorder" exists [8, 9], as we show here, numerous patients have now requested help control their N_2O use. Very little is known about the characteristics of this new treatment seeking population, about the pattern and level of N_2O use, and the experiences with standard treatments provided at addiction care facilities. This study aims to provide more insight into these aspects. Furthermore, in our clinical experience, we have observed patients with a "N_2O use disorder" to be a particularly difficult group of patients to treat. Treatment dropout and subsequent relapse in use have appeared more frequent among N_2O users compared to users of other substances. Additionally, we therefore objectively compare patients with a "N_2O use disorder" with patients with a cocaine use disorder. This allows for determining in what respect the N_2O users are in fact similar or dissimilar on clinical characteristics and treatment results to patients with other substance use disorders, such as patients with cocaine use disorder. Patients with a cocaine use disorder were chosen as comparator because of a similar ability to use this substance in a binge-like pattern, as we see frequently in our population of N_2O users, allowing for discontinuation of use without major withdrawal symptoms [10].

Methods

Description of the Treatment Seeking N_2O Group

This study is a descriptive retrospective digital chart review of patients who were referred for treatment for problematic use of N_2O to Jellinek, the largest addiction care facility in the region of Amsterdam, the Netherlands, from January 2020 to September 2022. Patients were included in the analysis if (1) N_2O was registered as the primary substance of abuse according to the Measurement of Addiction for Triage and Treatment (MATE) module 1 during intake, (2) a substance use disorder was diagnosed using the patients history according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by trained psychologists (without use of MATE module 4 due to time-constraints), and (3) participants were >18 years of age at the time of treatment enrollment [11, 12].

The MATE is a structured interview covering the use of psychotropic substances in the past 30 days and throughout life [12]. The frequency of use and amounts used (if applicable in standardized units) are systematically recorded for each patient and each substance. Since there is no specific classification in the DSM-5 for a N_2O use disorder, problematic use of N_2O was classified as "other (or unknown) substance-related use disorder (304.90)." In practice, also some other classifications were used for these patients, including: "sedative, hypnotic, or anxiolytic use disorder (304.10)," "other hallucinogen use disorder (304.50)," or "inhalant use disorder (304.60)." These four classifications were seen as appropriate to classify a "N_2O use disorder" in this study. Although module 4 of the MATE includes a standardized assessment of the DSM-5 substance use disorder criteria, this assessment is unfortunately not routinely performed at the intake procedure due to time restraints. Data regarding which items of the substance use disorder (e.g., presence or absence of craving) were present in the patients at time of intake were, therefore, not available.

Depending on the required treatment intensity, treatment took place in an outpatient, inpatient or outreaching setting and generally consisted of cognitive behavioral therapy, a community reinforcement approach, or a psychosocial treatment according to the Minnesota model (a group-based psychosocial intervention program, based on the twelve steps of the Anonymous Alcoholics

program [13]). Treatment outcome data were collected from a standardized treatment cessation form where the treating psychologist enters the reason for treatment cessation (e.g., completion or premature termination) and – if available – information on whether the patient was abstinent at the time of treatment cessation.

Data were automatically extracted from patient charts (e.g., demographics, MATE module data, and follow-up data) and anonymized before analysis. Since data were anonymized before analysis, a waiver for ethical review was obtained from the Medical Ethical Research Committee of the Amsterdam University Medical Center and patients did not have to provide consent for participation.

Subgroup Analysis: N_2O versus Cocaine Use Disorder

In a subgroup analysis, we selected patients with only a N_2O use disorder (i.e., no other substance use disorders and no frequent (>7 days/month during the month prior to intake) use of other substances, with the exception of tobacco use disorder) and compared this group with a control group of patients with only a cocaine use disorder. These exclusion criteria were chosen to allow for more appropriate comparison regarding treatment results, as comorbid substance use disorders among cocaine users are more frequent compared to N_2O users. Cocaine use disorder was considered to be present if cocaine was registered as the primary substance of abuse in the MATE module 1 and trained psychologists had confirmed the DSM-5 diagnosis. Similarly, patients having other substance use disorders or using other substances >7 days per month were excluded, with the exception of tobacco use disorder.

To further increase comparability, patients with a N_2O use disorder were 1:1 propensity-score matched with patients with a cocaine use disorder on age (as N_2O are typically younger compared to cocaine users) and gender using the propensity-score matching functionality in SPSS (Fig. 1). Tolerance was set at 0.39, as this was the lowest tolerance with no index-cases lost. Unpaired *t* tests and Mann-Whitney U tests were used to compare the means of normally and non-normally distributed continuous variables, respectively. The Fisher's exact test and χ^2 test were used to compare dichotomous and categorical variables, respectively. Since these analyses were exploratory, a correction for multiple testing was not performed and statistical significance ($p < 0.05$) should be interpreted with caution. Analyses were performed using IBM SPSS statistics, version 27.

Results

Of the 16,517 patients referred to our institution for substance use disorder treatment during the 21 months inclusion period, 128 patients (0.8%) were registered with N_2O as the primary substance of abuse in the MATE module 1 and with a DSM-5 substance use disorder diagnosis for this substance. Among these 128 included participants (total sample), 77 (60.2%) participants had a primary N_2O use disorder without additional substance use disorders or frequent use of other substances (with the exception of tobacco). Cocaine was registered as primary substance of abuse in 3,365 patients (20.4%), including 278 (8.3%) patients without a disorder in the use of other substances or frequent use of other substances (with the exception of tobacco), from which 77 control cases were selected using propensity-score matching with the 77 primary N_2O participants without additional substance use disorders or frequent use of other substances.

Participant Characteristics

Demographic characteristics of included patients are shown in Table 1. N_2O users were typically young (mean age: 26.2 years, 78.9% was below 30 years of age), male (66.4%), unmarried (82.9%) and born in the Netherlands (88.2%). Participants frequently reported a Moroccan cultural background: 45.3% of the parents of the N_2O users were born in Morocco and 46.8% of the N_2O users reported to belong to the Moroccan culture. Only few patients had completed a university or university of applied sciences level education (4.9%). Most N_2O users had completed a vocational training (59.0%) or had only finished secondary education (i.e., high school) (28.7%). Nearly half was employed or self-employed (46.1%), while the other half was not financially self-supporting, with the largest group dependent by on social assistance benefits (32.8%).

Propensity-score matching of the N_2O-only group with the cocaine-only control group resulted in a comparable control group of cocaine users with regard to gender distribution, however, a significant difference in age remained (mean age: 24.9 vs. 31.0 years, *p* value <0.001) despite our aim to create a comparable control group. In addition, index and control groups differed significantly with regard to almost all other demographic variables: N_2O users were more often unmarried than cocaine users (86.1 vs. 58.3%) and had a lower education than cocaine users (having completed an university of applied sciences or research university education: 6.6 vs. 25.7%). Less N_2O users were employed or self-employed than cocaine users (44.2–62.2%), and they were more often not financially independent due to having no income (14.3 vs. 2.7%) or being dependent on a student loan (14.3 vs. 5.4%). Almost all N_2O and cocaine users were born in the Netherlands (94.9 and 89.7%), but a Moroccan background was much more common among N_2O users compared to cocaine users: 58.7% and 10.0% of parents of N_2O users were born in Morocco, respectively; and 57.7% and 11.1% of N_2O users reported belonging to the Moroccan culture, respectively.

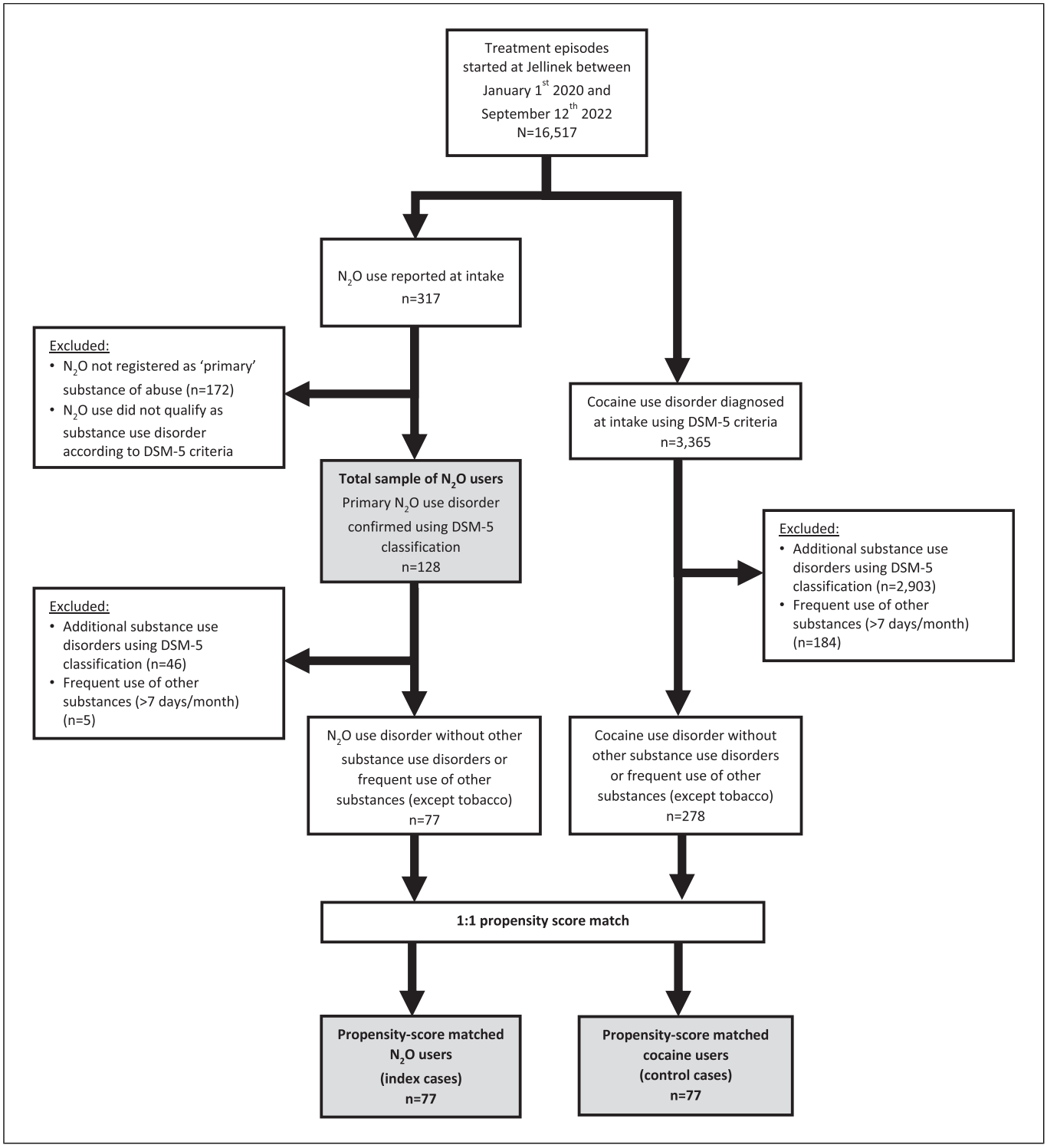

Fig. 1. Flowchart of participant selection.

Table 1. Participant characteristics

	Total sample		Propensity-score matched samples				
	N_2O users (n = 128), mean (SD) or n (%)		N_2O users (n = 77), mean (SD) or n (%)		cocaine users (n = 77), mean (SD) or n (%)		p value[2]
Mean age, years	n = 128	26.2 (6.0)	n = 77	24.9 (4.4)	n = 77	31.0 (8.3)	<0.001
Age under 30 years	n = 128	101 (78.9)	n = 77	66 (85.7)	n = 77	45 (58.4)	<0.001
Gender	n = 12		n = 77		n = 77		0.1
Male		85 (66.4)		54 (70.1)		63 (81.8)	
Female		43 (33.6)		23 (29.9)		14 (18.2)	
Missing, n (% of total sample[1])		0 (0)		0 (0)		0 (0)	
Marital status	n = 123		n = 72		n = 72		0.003
Unmarried		102 (82.9)		62 (86.1)		42 (58.3)	
Unmarried, living together		6 (5.9)		4 (5.6)		15 (20.8)	
Married		8 (6.5)		3 (4.2)		9 (12.5)	
Divorced		7 (5.7)		3 (4.2)		5 (6.9)	
Widow		0 (0)		0 (0)		1(1.4)	
Missing, n (% of total sample[1])		5 (3.9)		5 (6.5)		5 (6.5)	
Highest education level attained	n = 122		n = 76		n = 70		0.007
Primary education		9 (7.4)		4 (5.3)		4 (5.7)	
Secondary education[3]		35 (28.7)		22 (28.9)		22 (31.4)	
Lower tertiary education[4]		72 (59.0)		45 (59.2)		36 (37.1)	
Higher tertiary education[5]		6 (4.9)		5 (6.6)		18 (25.7)	
Missing, n (% of total sample[1])		6 (4.7)		1 (1.3)		7 (9.1)	
Source of income, n (%)	n = 128		n = 77		n = 74		0.01
Employed/self-employed		59 (46.1)		34 (44.2)		46 (62.2)	
Social assistance benefit		42 (32.8)		21 (27.3)		22 (29.7)	
No income		14 (10.9)		11 (14.3)		2 (2.7)	
Scholarship		13 (10.2)		11 (14.3)		4 (5.4)	
Missing, n (% of total sample[1])		0 (0)		0 (0)		3 (3.9)	
Country of birth	n = 102		n = 59		n = 68		0.3
The Netherlands		90 (88.2)		56 (94.9)		61 (89.7)	
Other		12 (11.8)		3 (5.1)		7 (10.3)	
Missing, n (% of total sample[1])		26 (20.3)		18 (23.4)		9 (11.7)	
Country of birth of parents (n × 2)[6]	n = 190		n = 104		n = 130		<0.001
The Netherlands		59 (31.1)		26 (25.0)		92 (70.8)	
Morocco		86 (45.3)		61 (58.7)		13 (10.0)	
Other		45 (23.7)		17 (16.3)		25 (19.2)	
Missing, n (% of total sample[1])		66 (25.8)		50 (32.5)		24 (15.6)	
Cultural origin[7]	n = 94		n = 52		n = 63		<0.001
Dutch		24 (25.5)		11 (21.2)		44 (69.8)	
Moroccan		44 (46.8)		30 (57.7)		7 (11.1)	
Other		26 (27.7)		11 (21.2)		12 (19.0)	
Missing, n (% of total sample[1])		34 (26.6)		25 (32.5)		14 (18.2)	

Percentages of outcomes are calculated per variable over non-missing data. Total number of patients per sample is reported in the first row of each sample. The number of patients with available data is noted for each variable in the first column. [1]The percentages of the missing numbers are calculated as percentages of the total number of patients of the samples. [2]Comparing propensity-score matched samples of N_2O and cocaine users, p values are calculated using unpaired t tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. [3]Referring to preparatory vocational secondary education, senior general secondary education and university preparatory education. [4]Vocational education and training. [5]University of applied sciences and research university. [6]Two parents per participant. [7]Culture to which patient has reported to feel belonging to.

Table 2. Substance use of primary substance

	Total sample		Propensity-score matched samples				
	N_2O users (n = 128), median (IQR)		N_2O users (n = 77), median (IQR)		cocaine users (n = 77), median (IQR)		p value[1]
Using days in the last 30 days	n = 108	10 (4–18)	n = 69	10 (4–19)	n = 63	8 (2–16)	0.5
Use on an average using day	n = 95	5.0 (2.0–10.0) kg	n = 68	5.0 (2.0–10.0) kg	n = 71	1.0 (1.0–2.0) g	
Years of regular use[2]	n = 84	2.0 (1.2–4.0)	n = 64	2.0 (1.5–4.0)	n = 65	3.0 (2.0–7.0)	0.019

Values are calculated using participants with non-missing data for each variable. The number of patients with a reported outcome for the variable is noted in the first column of each sample. [1]Comparing propensity-score matched samples of N_2O and cocaine users, p values are calculated using Mann-Whitney U tests. [2]Regular use is defined as use at least 1 or more times a week.

Substance Use Characteristics

An overview of the substance use characteristics of the primary substance is shown in Table 2. The total sample of N_2O users used N_2O during a median (IQR) of 10 (4–18) days in the last 30 days, a median (IQR) of 5.0 kg (2.0–10.0 kg) N_2O on an average using day and had a history of a median (IQR) of 2.0 (1.2–4.0) years of regular use. In the propensity-score matched groups, number of using days in the last 30 days was similar: N_2O users median 10 days, IQR: 4–19; cocaine users median 8 days, IQR 2–16. The history of regular use was shorter among N_2O only users (median: 2.0 years, IQR: 1.2–4.0) than for the cocaine-only users (median: 3.0 years, IQR: 2.0–7.0). Figure 2 displays the distribution of kilogram N_2O used on a typical using day by patients with a N_2O use disorder.

An overview of the use characteristics of other substances in all subgroups is presented in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539860). Patients of the total sample of N_2O users also used nicotine (74.4%), alcohol (49.2%), cannabis (29.7%), sedatives (17.2%), MDMA (14.1%), cocaine (12.5%), GHB (9.4%), and stimulants (6.3%). Within the propensity-score matched subgroups concomitant use of other substances was overall less frequent among N_2O users compared to cocaine users: nicotine (62.3 vs. 80.5%, p = 0.02), alcohol (35.1 vs. 71.4%, p < 0.001), and cannabis (6.5 vs. 28%, p < 0.001). When using other substances, N_2O users typically used these substances less frequently and in lower doses compared to cocaine users (e.g., median number of cigarettes smoked daily: 10 vs. 15 in N_2O vs. cocaine users).

Treatment and Follow-Up Data

Therapy setting and type of therapy received by patients who had started treatment is listed in Table 3. No significant differences were found in the type and intensity of treatment provided between N_2O and matched cocaine users. Treatment follow-up data comparing matched N_2O and cocaine users are presented in Table 4. N_2O users were significantly less likely to complete their treatment than cocaine users (36.7 vs. 65.4%, p = 0.004). To allow for appropriate comparison, all further follow-up data were stratified over patients having completed their treatment or those having quit treatment prematurely. Over these strata, no differences were found in duration of treatment between N_2O and cocaine users. N_2O users were more often using N_2O at treatment initiation compared to cocaine users using cocaine (100 vs. 73.5%, p = 0.02). Although data about use at the time of treatment cessation for most patients was missing, no differences were found in substance used at these time points.

Discussion

This is the first study characterizing a population of addiction treatment seeking patients with problematic N_2O use. Moreover, we were able to compare patients with solely "N_2O use disorder," i.e., without other substance use disorders, with patients having solely a cocaine use disorder, using propensity-score matching.

Patient Characteristics

N_2O users were more frequently male than female, which is similar to the overrepresentation of men in other substance use disorders [14]. However, there was a substantial number of women requesting treatment in our study, which may be due to women being more susceptible to the adverse health effects of N_2O use [15]. N_2O users were typically quite young, with 78.9% being younger than 30 years of age. This is in accordance with recreational N_2O usage data from the general adult

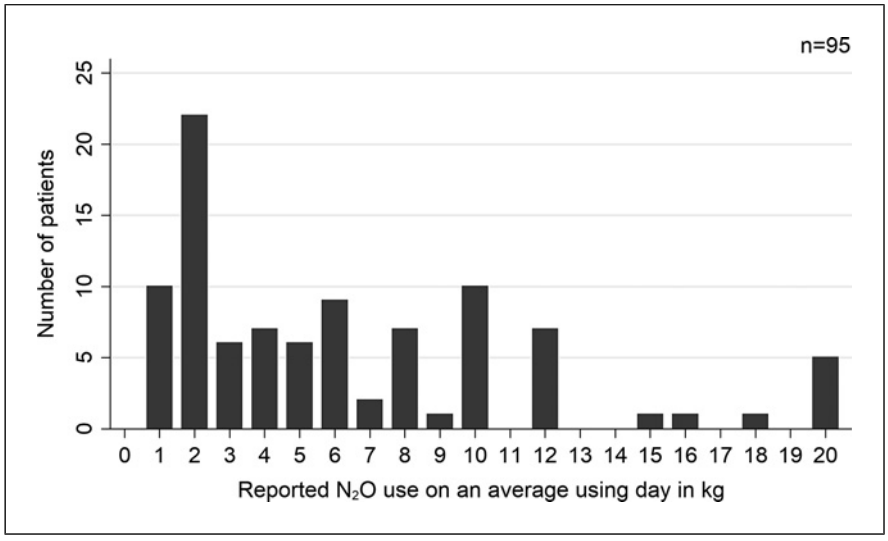

Fig. 2. Reported N_2O use on an average using day.

Table 3. Type of treatment received

	Total sample	Propensity-score matched samples		
	N_2O users, *n* (%)	N_2O users, *n* (%)	Cocaine users, *n* (%)	*p* value[3]
Primary setting of therapy, *n* (%)[1,2]				
Clinical treatment	10 (8.9)	4 (6.0)	8 (11.1)	0.3
Outpatient treatment	80 (71.4)	49 (73.1)	49 (68.1)	
Outreaching treatment	4 (3.6)	2 (3.0)	6 (8.3)	
No treatment initiated after intake	18 (16.1)	12 (17.9)	9 (12.5)	
Missing (% of total sample)	16 (12.5)	10 (12.9)	5 (6.5)	
Primary form of therapy, *n* (%)[1,2]				
Cognitive behavioral therapy	84 (77.8)	53 (79.1)	48 (71.6)	0.2
Acceptance and commitment therapy (ACT)	0 (0.0)	0 (0.0)	1 (1.5)	
Community-reinforcement approach	4 (3.7)	2 (3.0)	6 (9.0)	
Minnesota model	2 (1.9)	0 (0.0)	3 (4.5)	
No treatment initiated after intake	18 (16.7)	12 (17.9)	9 (13.4)	
Missing (% of total sample)	20 (15.6)	10 (13.0)	10 (13.0)	

[1]Concerns the first type of therapy received after intake. [2]Percentages are calculated over non-missing values. [3]Using χ^2 tests.

population, with 24.8% of people of 18–29 years of age having ever used N_2O compared to only 7.5% among people aged 30–49 years old [16]. Of note is that only participants 18 years of age or older were included in this analysis; however, a substantial number of patients below 18 years of age have also received treatment for an N_2O use disorder in our clinic, which for logistical reasons could not be included in this analysis.

Having a Moroccan cultural background was in our study more common among N_2O users compared to cocaine users. This association may also be due to less frequent use of cocaine among people with a Moroccan background or may be a chance finding resulting from the large amount of statistical tests performed. However, a similar association between N_2O use and having a Moroccan background in the Netherlands was reported by Nabben et al. [7] Several potential underlying causes for this association have been proposed: (1) the taboo on substance use among people within the Muslim faith where N_2O is sometimes perceived as less sinful (i.e., less "haram") thereby replacing use of other drugs or alcohol, (2) N_2O can easily be used "covertly" (i.e., hidden from parents or other caretakers), due to its short effects and lack of odor, and (3) a cultural taboo surrounding mental

Table 4. Treatment outcomes

	Total sample	Propensity-score matched samples		
	N_2O users (n = 128), mean (SD) or n (%)	N_2O users (n = 77), mean (SD) or n (%)	Cocaine users (n = 77), mean (SD) or n (%)	p value[1]
Treatment outcome	n = 79	n = 49	n = 52	0.004
Treatment completed	32 (40.5)	18 (36.7)	34 (65.4)	
Treatment discontinued before completion	47 (59.5)	31 (63.3)	18 (34.6)	
Excluded from analyses (% of total sample)	n = 49	n = 28	n = 25	
Treatment ongoing	23 (18.0)	14 (18.2)	10 (13.0)	
Treatment never started after intake	18 (14.1)	12 (15.6)	9 (11.7)	
Missing data	8 (6.3)	2 (2.6)	6 (7.8)	
Median number of treatment days per treatment outcome group (IQR)				
Treatment completed	n = 32 168 (129–199)	n = 18 187 (148–205)	n = 34 222 (154–373)	0.1
Treatment discontinued before completion	n = 47 175 (115–231)	n = 31 162 (115–215)	n = 18 200 (123–254)	0.3
Number of patients reporting ongoing use of substance at the start of treatment per treatment outcome group				
Treatment completed	n = 32 31 (97)	n = 18 18 (100)	n = 34 25 (73.5)	0.02
Treatment stopped before completion	n = 47 37 (79)	n = 31 25 (80.7)	n = 18 16 (88.9)	0.5
Number of patients reporting ongoing use of substance at treatment cessation per treatment outcome group				
Treatment completed	n = 10 3 (30.0)	n = 4	n = 20	
Missing data	n = 22	n = 14 1 (25.0)	n = 14 4 (20.0)	0.6
Treatment stopped before completion	n = 14 8 (57.1)	n = 12 7 (58.3)	n = 7 4 (57.1)	0.6
Missing data	n = 33	n = 19	n = 11	

Percentages of outcomes are calculated per variable over non-missing data. [1]Comparing propensity-score matched samples of N_2O and cocaine users, p values are calculated using unpaired Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables.

health disorders (including substance use disorders) resulting in less knowledge about self-regulatory behaviors regarding substance use, and an aversion toward mental healthcare [7]. In our study, N_2O users used N_2O more frequently as their only substance of use or used other substances less frequently or in lower quantities, which supports these hypotheses regarding the unique cultural position that N_2O has acquired in our N_2O users' population. Finally, a lower education level of Moroccan-Dutch youths may add to the vulnerability associated with developing a substance use disorder [17].

Patterns of Use

The most notable N_2O use characteristic found in our study was the large amount of N_2O inhaled by participants on an average day of use, which was up to 20 kg per day. Recreational use typically involves less than 10 balloons per session, while 20 kg represents an equivalent of 2,500 balloons. Such use requires an almost continuous inhalation of N_2O during prolonged periods of time (e.g., more than 12 h). This high-volume pattern of use may be more addictive compared to the low-volume recreational type of use as described earlier, which could explain why only since the availability of large canisters of N_2O patients have been reporting a loss of control over their N_2O use. Another characteristic was that the use of N_2O was typically intermittent; most likely in a binge-like pattern (not represented in our data, but known from user reporting). This suggests that physical dependency does not play a significant role in the persistence of problematic N_2O use, as users are able to regularly quit their N_2O use [18].

Recent studies have reported inconsistent findings regarding the existence of a "N_2O use disorder," mostly due to the lacking data on whether DSM-5 substance use disorder criteria are met in published case-reports and

case-series [8]. Although we were also unable to provide data regarding these DSM-5 criteria among our patients, treatment seeking at addiction care facilities and the presence of a high-volume use suggest the presence of a moderate/severe N_2O use disorder with loss of control over use of this substance. Pharmacologically, this addictive potential may be explained by N_2O mediated endogenous opioid release. Released opioids interact with GABAergic neurons in the midbrain and cause dopamine release through which reward and craving properties can develop. Interaction with NMDA receptors might also be involved in the reward mechanism of N_2O by disinhibiting dopamine release in the nucleus accumbens and ventral tegmental area [19].

The fewer reported years of regular use of N_2O versus cocaine before seeking treatment is striking since qualitative research reported a delay in help-seeking by Moroccan-Dutch problematic N_2O users [7]. In part, this delay was purported to be due to low confidence of Moroccan-Dutch in the Dutch healthcare system. However, N_2O users may suffer from serious physical adverse health effects in an earlier stage, due to an induced functional vitamin B12 deficiency, perhaps prompting them to seek addiction care treatment relatively early. Although we were unable to provide data regarding such adverse physical health consequences of the N_2O use in our sample, the frequency and amounts of N_2O used are known to be accompanied with somatic complications [20].

Treatment Outcomes

Cocaine users completed their treatment approximately twice as often compared to N_2O users. As discussed previously, sociocultural factors regarding substance use and mental health disorders may similarly play a role in the difficulty retaining patients in care for a N_2O substance use disorder. Little is known about the physiological addictive properties of N_2O when used in the quantities described in the current study; these may also play a role in the difficulty to treat a N_2O use disorder [19, 21]. Moreover, potential cognitive impairments resulting from long-term vitamin B12 deficiency might negatively influence psychological treatment effectiveness [22, 23].

Strengths and Limitations

Strengths of this study include the fact that the sample was drawn from a large, regular addiction treatment sample, and included routinely collected information, thus the data are representative of the studied population. On the other hand, this also resulted in some limitations, as the ability to only include retrospective and routinely collected data from automated forms in digital patient charts, which resulted in incomplete data, especially for the treatment outcome measures. This also includes the lack of the MATE module 4 with standardized questions regarding DSM-5 criteria for substance use disorders. This causes some uncertainty whether patients were correctly diagnosed. However, patients voluntarily requested help for their problematic N_2O use from our institution and indicated that their primary problem was N_2O use, suggesting that there was at least a significant impact on their health and/or their daily functioning due to their substance use. Moreover, the psychologists of our institution are specialized in addiction care and highly trained to diagnose substance use disorder in daily practice. It can therefore be assumed that all patients included in this study had a substance use disorder. A statistical limitation of our subgroup analysis was that we were unable to sufficiently match on age which has likely influenced outcomes such as the disparity in attained education levels, relationship status, employment, education, and the shorter duration of regular use as N_2O users were younger. Furthermore, as this study was exploratory, we did not account for multiple comparisons in our study, which greatly increased the likelihood of a type I error. Noteworthy is also a potential for selection bias in our control group by selecting only patients with a cocaine disorder without other substance use disorders. Since this is rare, we may have selected a relatively easy-to-treat control-population, overestimating the relatively poor treatment outcomes among patients with a N_2O user disorder.

Conclusion

This study describes a population of treatment seeking problematic N_2O users, typically in their mid-twenties, more male than female, with generally a low level of education. A large group of N_2O users was Moroccan-Dutch, in accordance with previous studies which have provided several explanatory sociocultural factors for this trend. The pattern of use in these problematic N_2O users was intermittent, most likely in binge cycles. The very large amounts of N_2O used by participants in our study may be a key factor in the development of a N_2O use disorder. Dropout rates during addiction treatment were high among patients with N_2O use disorder. Further research is needed to reveal the areas on which current standard therapeutic approaches do not match needs of people with a "N_2O substance use disorder." A tailored and individualized approach may be crucial, considering the unique sociodemographic characteristics of this "new" population of people with a substance use disorder.

Statement of Ethics

In this study, data were retrospectively collected and anonymized before analysis, therefore the Medical Ethical Research Committee of the Amsterdam Medical Centers (Amsterdam UMC) confirmed our study was exempted from requiring an ethical review by the committee. In the waiver letter provided by the Medical Ethical Research Committee, it was confirmed that when data are retrospectively collected and anonymized before analysis consent for participation is not required according to Dutch regulations.

Conflict of Interest Statement

S.O.V., J.d.B., J.A., T.N., and A.G. have no conflicts of interest to declare. In the last 3 years, WvdB has been a consultant to Takeda, Kinnov Therapeutics, Camurus, Janssen, and Clearmind Medicine. None of these consultancies are related to the topic of the current paper.

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Author Contributions

S.O.V. designed the lay-out of the study, analyzed the data and prepared the manuscript. J d. B. analyzed data and prepared the manuscript. J.A., T.N., W.d.B., and A.E.G. aided in designing the lay-out of the study, reviewed the manuscript, and provided commentary. All authors approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to restrictions by the European General Data Protection Regulation but are available from the corresponding author.

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