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ADDICTION OPINION AND DEBATE

ADDICTION SSA

Does nitrous oxide addiction exist? An evaluation of the evidence for the presence and prevalence of substance use disorder symptoms in recreational nitrous oxide users

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Abstract

Background: Prevalence of nitrous oxide (N_2O) use appears to be increasing in numerous countries worldwide, and excessive use has been associated with physical and mental problems. Because there currently is no consensus whether N_2O has addictive potential, we aimed to evaluate the evidence for the presence and prevalence of DSM-5 substance use disorder (SUD) symptoms in N_2O users.

Analysis: A literature search was conducted to assess the evidence for the presence of any of the 11 DSM-5 SUD symptoms in N_2O users and the prevalence experiencing those symptoms. A substantial part of the studied N_2O users use more than intended (i.e. 46% to 98%) and spend a substantial amount of time using N_2O. At least some of the studied N_2O users experience interpersonal problems (i.e. 13% to 80%) and use N_2O in risky situations, such as driving under the influence. Evidence for the other criteria is either insufficient or inconclusive.

Conclusions: The literature base for the presence and prevalence of DSM-5 substance use disorder (SUD) symptoms in nitrous oxide (N_2O) users is limited and largely consists of qualitative studies and case studies, but it provides consistent evidence for the presence of at least four SUD criteria in heavy N_2O users. N_2O could well be addictive and should be treated as a potentially addictive substance until systematic assessments can provide evidence-based guidance to users, healthcare professionals and legislators.

KEYWORDS
addiction, DSM-5, laughing gas, nitrous oxide, substance use disorder, symptoms

INTRODUCTION

Nitrous oxide (N_2O), also known as ‘laughing gas’, ‘hippy crack’, ‘nitro’, ‘whippits’ or ‘nangs’, is a chemical compound of nitrogen and oxygen. Animal research has shown that N_2O can have both analgesic effects through stimulation of endogenous opioid release [1] and anesthetic effects through inhibition of glutamatergic neurotransmission [2]. Aside from the use of N_2O in the medical [3] and food industry [4, 5], the gas is increasingly used as a recreational drug [6]. The rising use of recreational N_2O use has caused concern because of its negative health effects, including the potential development of addictive behaviors. However, there is little to no consensus regarding the addictive potential of N_2O and research on the matter is scarce [7–9]. In a recent report, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) highlighted the lack of understanding of the addictive potential of N_2O and called for better classification and coding systems as well as standardized case definitions to improve diagnosis, treatment, quantification and understanding of the issue [10]. In this narrative review, the potential of N_2O addiction will be evaluated in the context of the evidence for the presence and prevalence of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for substance use disorder (SUD) [11] in N_2O users.

Recreationally, N_2O is most often inhaled using balloons, or bulbs that are regularly used in the food industry in whipped cream dispensers—both referred to as 'shots' [12]—inducing pleasurable effects such as mild euphoria, behavioral disinhibition, dissociation and heightened consciousness [5]. The subjective effects of N_2O do not appear to differ between males and females [13]. One shot corresponds to one bulb of ~8 g, containing 10 mL of liquid N_2O [14]. N_2O has the fastest onset of all inhalation drugs: effects peak 1 minute after inhalation, disappear rapidly and are mostly invisible to observers [15]. The drug cannot be detected by common drug screens and hangover effects appear absent [4]. In addition to this, N_2O is legally and easily available through wholesalers, some supermarkets and round-the-clock delivery services in many countries [16], contributing to its popularity.

The prevalence of recreational use of N_2O has been rising for the last 20 years [6]. The Global Drug Survey estimated lifetime prevalence to be ~23% [17]—varying across regions [18]—with last year prevalence doubling from 6.5% to 11.9% between 2014 and 2019 [17]. Among N_2O naïve young adults in England, 79.2% indicated they would likely use within the following 3 months [19].

Most N_2O users inhale less than five shots per session and report less than 10 sessions in the last year [18], indicating that most N_2O users do not exhibit problematic use. However, ~3% of users inhale at least once a week, with the heaviest users inhaling 10 or more shots a day [18]. In extreme instances, hundreds of shots—emptying several 2-kg tanks on one's own—are inhaled during one binge [20]. Although no direct adverse consequences of modest use (<10 shots a day) are to be expected [15], heavier use has been associated with vitamin-B12-deficiency-induced megaloblastic anemia and peripheral neuropathy, in a dose-dependent manner [14, 21, 22]. In severe cases, this can lead to N_2O induced paralysis [14, 23] that leaves some patients permanently impaired [24, 25]. The steep increase in N_2O-related admissions to emergency rooms [20, 26] is indicative of an increase in risky N_2O use, particularly in men [27]. Furthermore, heavy N_2O use has been associated with mental health problems, including psychotic symptoms and mood disorders [28]. There are also instances of serious thrombotic events following recreational N_2O use [29] and N_2O-related deaths, most commonly caused by asphyxiation [15].

Despite the available evidence, 77% of users report to be unaware [30] of the potential harmful effects of N_2O use. Furthermore, experts in the field have not reached a consensus on the existence of N_2O addiction [15, 31, 32]. Because of the lack of clarity on the addictive potential of N_2O, N_2O use disorder remains currently unrecognized [28] despite the alarming increase in prevalence of heavy N_2O use and N_2O poisoning. N_2O-related representations in emergency rooms in New South Wales, Australia, increased fivefold over the course of 2 years [33], the Dutch national poison information center reported a 267% rise in cases over a 2-year period (2017–2019) [34], whereas the United Kingdom's national poison information service reported an increase from 1 to 37 cases in a single year (2019–2020) [35]. Hence, it is crucial to provide clarity on the current evidence for the addictive potential of N_2O. We aimed to evaluate the existence of N_2O addiction by reviewing the available evidence for the presence and prevalence of each of the 11 DSM-5 SUD symptoms in N_2O users. We explicitly focused on samples that used N_2O for recreational purposes (i.e. excluding exposure during anesthesia or occupational or accidental exposure), but also considered animal studies when relevant. Table S1 provides an overview of the individual studies that were considered in our evaluation of the evidence.

EVALUATION OF THE EXISTENCE OF DSM-5 SUD SYMPTOMS IN N_2O USERS

Loss of control

Criterion 1: Taking N_2O in larger amounts or over a longer period than intended

A systematic review of case reports of heavy N_2O use showed that 98% (of 61) of individuals reported using N_2O in larger amounts or for longer durations than intended [7]. Further evidence for the presence of this symptom is provided by a survey conducted by Nugteren-Van Lonkhuyzen *et al.* [8] as part of a prospective observational cohort study on neuropathy and self-reported SUD in Dutch patients intoxicated with N_2O. Nine of 10 users reported using N_2O in larger amounts or for longer durations than intended. Furthermore, a qualitative study by Nabben *et al.* [20] showed that 6 of the 13 heavy N_2O using interviewees explicitly mentioned that their heavy use started with recreational use in significantly smaller amounts than their present use. Only one of the subjects reported initiating N_2O use in large quantities. The authors describe a general pattern of starting with an experimental phase, which develops into a party phase that escalates into a peak phase in some heavy users. Although these studies point toward the potential presence of this criterion in N_2O users, current evidence is based on (small sample) case studies and systematic analysis of this symptom in larger samples is lacking.

Criterion 2: Persistent desire or unsuccessful efforts to cut down or control N_2O use

Although unsuccessful efforts to cut down or control N_2O use can be operationalized in many ways, we will focus on the presence and prevalence of relapse in N_2O users. Layzer [36] studied 13 patients with self-administered N_2O-induced neurological symptoms, of which three reported relapse (time window not reported). A qualitative study by Nabben *et al.* [20] also described a patient who was admitted to emergency care with N_2O-induced paralysis, who resumed N_2O use within weeks after finishing treatment. Similar cases of multiple unsuccessful attempts to control use resulting in varying periods of abstinence and relapse are reported [37–39], with one relapse case known to have resulted in death [40].

Although these findings suggest the presence of relapse in a non-negligible minority of heavy users, results are inconsistent across studies. For example, a large study of 110 Chinese N_2O users reported only one relapse case (only 46% follow-up rate) [41] and another study focusing on hospital admitted Chinese N_2O users reported no incidences of relapse among 61 subjects [42]. However, follow-up durations were no longer than 4 months, which could limit the generalizability to longer abstinence periods.

Two studies specifically investigated the prevalence of unsuccessful efforts to cut down or stop N_2O use, rendering contradicting results. Although Nugteren-Van Lonkhuyzen *et al.* [8] concluded that 8 of 10 heavy N_2O users reported having tried to control their use unsuccessfully, Fidalgo *et al.* [7] found that only two of 59 case reports documented evidence for criterion 2.

Evidence for unsuccessful efforts to cut down or control N_2O use is mixed and suggests that although relapse is not the standard, it is present in a minority of heavy N_2O users. More research with longer follow-up periods is necessary to confirm this conclusion.

Criterion 3: A great deal of time is spent in activities necessary to obtain or use N_2O or to recover from its effects

Time spent on obtaining and using a substance can be influenced by a variety of factors, including legal status, availability and price. As N_2O is widely available in most countries [16], time needed to obtain it is limited compared to other drugs and rapid onset and absence of hangover effects are indicators of fast recovery times [4]. However, although most users reported <10 sessions a year [18], Nabben *et al.* [20] described several cases of heavy N_2O use up to 250 shots daily, and Chen *et al.* [43] reported heavy users using four to five times per day. Such binges might last multiple hours and are potentially stimulated by the quick offset of the effects of N_2O, prompting users to keep using to preserve the desired effects. In the only systematic studies on this topic, Fidalgo *et al.* [7] and Nugteren-Van Lonkhuyzen *et al.* [8] both reported substantial time spent on obtaining or using N_2O in over 90% of cases. Hence, the evidence regarding time spent obtaining N_2O seems equivocal, but there is sufficient evidence that heavy N_2O users spend a great deal of their time using N_2O. Time spent recovering from the effects of N_2O appears limited.

Criterion 4: Craving or a strong desire to use N_2O

Research shows that the use of N_2O can ameliorate alcohol, tobacco, cannabis [44] and cocaine [45] craving, but research on craving for N_2O itself is limited, potentially affected by the absence of craving as a SUD symptom in the DSM-IV [7]. However, several lines of research can be used to gather evidence on the matter. Self-administration paradigms are frequently used to study craving in animals [46] as craving often signifies an intention to use [47]. However, self-administration studies provide limited evidence for self-administration [48] and animal studies seem to collectively point toward a low reinforcing value of N_2O [9].

Two human experimental studies used the motivation to use N_2O compared to a placebo as a measure of the reinforcing value of N_2O, which could affect craving [47]. Walker and Zacny [49] exposed 20 non-drug using individuals to various doses of N_2O (Agent A) and O_2 (Agent B) for 10 minutes. Subjects could choose to inhale agent A or agent B to assess preference, resulting in 80% having a relative preference for N_2O in a dose-dependent manner. Dohrn *et al.* [50] used a similar paradigm, but reported seemingly contradicting results: N_2O was preferred over placebo in 22% of the cases. These studies were conducted in N_2O-naive individuals, in which the reinforcing value of N_2O might not reflect craving. Looking at craving in heavy N_2O users, Ickowicz *et al.* [37] described a man experiencing intense cravings, which were ameliorated by admission of Naltrexone, and an interviewee of the Nabben *et al.* [20] (p. 10) study reported that his 'desire for nitrous oxide was stronger than his mind'.

There is mixed evidence for a dose-dependent reinforcing effect of N_2O that could trigger craving. However, there is only limited evidence from case studies for self-reported N_2O craving in heavy N_2O users, highlighting the need for additional studies focusing on self-reported craving as well as cue-reactivity or physiological responses potentially indicative of craving.

Social consequences

Criterion 5: Recurrent use of N_2O resulting in a failure to fulfill major role obligations at work, school or home

Evidence for the presence of failures to fulfill obligations at school, work or home in heavy N_2O users is scarce, although nine of 10 users in the study by Nugteren-Van Lonkhuyzen *et al.* [8] reported interference of N_2O with work, school or home. Looking at heavy N_2O users, Nabben *et al.* [20] found that all 13 interviewees reported social isolation because of their drug use as they could not hold on to jobs or dropped out of school. However, van den Toren *et al.* [51] found no association between truancy and N_2O use in a general sample of 555 secondary school students. Hence, results suggest that heavy N_2O use can affect school and work performance, but studies are warranted to confirm these results and establish the prevalence of this criterion in N_2O users.

Criterion 6: Continued use of N_2O despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use

Fidalgo *et al.* [7] showed that eight of 59 case study reports indicate interpersonal or social problems in heavy N_2O users. Nugteren-Van

Lonkhuyzen *et al.* [8] more specifically studied continued N_2O use despite experiencing interpersonal problems caused by the substance and concluded that eight of 10 users reported the presence of this symptom. In the case report study by Redmond *et al.* [52], the four of 13 patient sample with N_2O-induced neurological disorders experienced social isolation. Furthermore, a case study by Ickowicz *et al.* [37] was indicative of serious interpersonal problems in a heavy N_2O user: the man continued use despite strained relationships with his wife and business partner. There is consistent evidence from case reports that heavy N_2O users might experience severe interpersonal problems associated with N_2O use. However, large-scale studies have not been conducted to assess the prevalence of these problems in N_2O users.

Criterion 7: Important social, occupational or recreational activities are given up or reduced because of use of N_2O

In the observational study by Nugteren-Van Lonkhuyzen *et al.* [8], six of 10 reported giving up important or pleasurable activities because of N_2O use. Although there are no further studies specifically focused on changes in social, occupational or recreational activities in heavy N_2O users, the qualitative study by Nabben *et al.* [20] reported that each of the 13 interviewees lost their job or dropped out of school. One of the interviewees stated that he gave up almost all activities: 'For me it was eat, work, call the dealer, use it and sleep. Every day for five months.' (p. 9) [20]. There is substantial overlap between the three social criteria (criteria 5, 6 and 7) and more research is warranted to establish the prevalence of negative social consequences of heavy N_2O use.

Risky use

Criterion 8: Recurrent use of N_2O in situations in which it is physically hazardous

Experimental research showed that exposure to N_2O significantly reduced performance on a drive simulator up to 30 minutes after use [53], potentially because of unwanted side effects such as dizziness [15], disorientation, blurred vision and impairment of general judgment [54]. According to the authors, the simulated driving task was less complex than real-life driving, suggesting even larger potential N_2O-induced impairments in real-life driving. Furthermore, because of the fast onset of N_2O effects [15], the effects might be significantly greater if used while driving compared to pre-driving, indicating the potential risk of driving under the influence of N_2O.

In the Netherlands alone, there have been 1800 car accidents involving N_2O between 2019 and 2021 [55], of which 63 had lethal consequences. Incidents of aggressive driving behavior and driving without a license involving N_2O seem to be rising, with over 3500 incidents in 2021 in the Netherlands. According to a Belgian survey that reached over 6000 respondents, 6% of respondents drive after N_2O use at least monthly [56]. Among male drivers ages 18 to 24, this percentage increases to 20%. There is reason to assume this percentage is higher among heavy users, as field research by Nabben *et al.* [20] suggested that heavy N_2O users often isolate themselves in a car to use N_2O. Research on the topic of driving under the influence of N_2O appears highly localized in specific regions, as statistics are limited to the Netherlands and Belgium.

Other examples of high-risk N_2O use include administration through methods that increase the risk of asphyxiation, the most common cause of death because of N_2O [15]. Administration methods such as masks [57], or bags placed over the head [32], increase the risk of asphyxiation, as the user remains exposed to N_2O even after losing consciousness [5]. Over 82% of individuals who died with N_2O as primary cause used N_2O through one of the above-mentioned methods [32]. These methods carry the highest risks; however, it should be noted that some cases could also be intentional suicide attempts rather than cases of recreational use.

Furthermore, the majority of heavy users use tanks instead of whippits to fill balloons, often holding the tank between their legs [8]. Contact with skin during discharge of N_2O can cause third-degree frostbite injuries, as the tank cools down drastically when N_2O is released [58]. Seeking to speed up the administration process, users might inhale directly from the tank, risking frostbite of the mouth and the lips [8]. A related risk is lung barotrauma, which can be caused by inhaling directly from the tank [59].

Although there is consistent reporting of risky N_2O use, there is virtually no systematic research evaluating the prevalence of this symptom among heavy N_2O users. Fidalgo *et al.* [7] reported that 87% of case studies lack data on this criterion, but that there were indications of risky use in the majority of cases that did report on this. Additionally, in the study by Nugteren-Van Lonkhuyzen *et al.* [8], five of 10 reported using N_2O in physically hazardous situations.

Criterion 9: Continued use of N_2O despite knowledge of having a persistent or recurrent physical or psychological problem caused or exacerbated by the substance

The majority of N_2O users, ~77% [30], seem to have limited awareness of the causal or exacerbating role of N_2O in physical and mental problems. Nevertheless, nine of 10 of the N_2O users included by Nugteren-Van Lonkhuyzen *et al.* [8] reported presence of this criterion. Furthermore, there are case reports on continued N_2O use despite knowledge of its effect on recurrent physical problems. For example, Nabben *et al.* [20] reported on a man treated for N_2O induced paralysis who started using again after discharge and needed to be readmitted with similar symptoms. Additionally, Layzer [36] reported about three heavy N_2O users of a sample of 13, who relapsed after being treated for myeloneuropathy caused by N_2O despite being aware of the direct link between N_2O use and their

TABLE 1 The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition substance use disorder criteria and current evidence for their presence and prevalence in N_2O-users.

Criterion		Description	Evidence strength		Evidence description	Literature
Loss of control						
1	Using more than intended	The substance is often taken in larger amounts or over a longer period than was intended	Consistent but limited evidence for taking more than intended	+	Most heavy N_2O users reported using more than intended. The number of studies is limited, but results are consistent and future studies should focus on establishing prevalence of using more than intended.	[7,8,20]
2	Unsuccessful reduce or quit attempts	There is persistent desire or unsuccessful efforts to cut down or control use of the substance	Inconclusive evidence for unsuccessful reduce or quit attempts	+/−	Estimated relapse rates vary from 0.1% to 23%, suggesting unsuccessful reduce or quit attempts in a minority of heavy N_2O users. The number of studies is limited, prevalence estimates are variable, and longer follow-up timeframes are needed to establish the potential presence and prevalence of unsuccessful reduce or quit attempts.	[8,20,36–41]
3	Substantial time investment	A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects	Consistent but limited evidence for substantial time investment	+	Time spent recovering from use appears limited because of the absence of hangover effects. Widespread legal availability results in limited time spent obtaining N_2O. However, most heavy N_2O users meet the substantial time investment criterion because of the substantial time spent on N_2O use itself. The number of studies is limited, but results are consistent and future studies should focus on establishing prevalence of substantial time investment.	[7,8,20,43]
4	Craving	Craving or a strong desire to use the substance	Inconclusive evidence for craving	+/−	One experimental study suggested potential dose-dependent reinforcement effects in N_2O-naïve participants. A limited number of cases reported N_2O craving. Additional studies are needed to establish the potential presence and prevalence of N_2O craving.	[20,37,48–50]
Social consequences						
5	Failure to meet obligations	Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school or home	Inconclusive evidence for failure to meet obligations	+/−	A qualitative study suggested failure to meet obligations in most heavy N_2O-users. Questionnaire results do not show associations between N_2O-use and truancy as a measure of the failure to meet obligations. Studies are limited in number, heterogeneous in methods and results. Additional studies are needed to establish the potential presence and prevalence of failure to meet obligations.	[8,20,51]

(Continues)

TABLE 1 (Continued)

Criterion		Description	Evidence strength		Evidence description	Literature
6	Social or interpersonal problems	Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use	Consistent but limited evidence for social or interpersonal problems	+	Evidence from case studies suggested social or interpersonal problems in 13% to 80% of heavy N_2O-users. The number of studies is limited and future studies should focus on establishing the prevalence of social or interpersonal problems.	[7,8,37,52]
7	Giving up activities	Important social, occupational or recreational activities are given up or reduced because of use of the substance	Insufficient evidence for giving up activities	−	Only one qualitative study reported on the presence of giving up activities in heavy N_2O-users. More studies are needed to establish the presence and prevalence of giving up activities.	[8,20]
Risky use						
8	Hazardous use	Recurrent use of the substance in situations in which it is physically hazardous	Consistent but limited evidence for hazardous use	+	Most case studies (>87%) do not report on hazardous use. Those that do suggest hazardous use is common in heavy N_2O users. Epidemiological studies suggested evidence for administration with risk of asphyxiation and driving under the influence. The number of studies is limited and future studies should focus on establishing the prevalence of hazardous use.	[8,20,32,53,56–58]
9	Use despite health effects	Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.	Insufficient evidence for use despite health effects	−	Awareness of the potential negative health effects of N_2O-use appears limited. Hence, most evidence for use despite health effects is indirect and more research is needed to establish its potential presence and prevalence.	[8,20,28–32,36, 38,60–62]
Pharmacological consequences						
10	Tolerance	Tolerance, as defined by either of the following: a need for markedly increased amounts of the substance to achieve intoxication or desired effect. A markedly diminished effect with continued use of the same amount of the substance	Inconclusive evidence for tolerance	+/−	Experimental studies confirmed the possibility of tolerance to the effects of N_2O. Case studies showed limited evidence for self-reported tolerance, even in heavy N_2O-users. More studies are needed to establish the potential presence and prevalence of tolerance.	[7,8,20,63–71]
11	Withdrawal	Withdrawal, as manifested by either of the following: the characteristic withdrawal syndrome for other (or unknown) substance. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms	Insufficient evidence for withdrawal	−	The limited number of studies, including animal studies and case studies, show only anecdotal evidence for N_2O-withdrawal. More studies are needed to establish the potential presence and prevalence of withdrawal.	[8,73–75]

complaints. Similarly, den Uil *et al.* [38] reported on a patient who relapsed after experiencing N_2O-related aortic arch thrombus and Hirvioja *et al.* [40] reported on a patient who relapsed after experiencing recurrent N_2O-related paraparesis.

In general, it appears that heavy N_2O users worry less about psychological consequences than physical consequences [30], potentially because of limited availability of data and information on these consequences. Although causality remains to be determined, heavy N_2O use has been associated with psychosis [60–62], personality changes [61], aggressive-impulsive behavior [60] and mood disorders [28]. Furthermore, hallucinations or delusions related to N_2O use are experienced by almost a third of last year N_2O users [28, 32], although for some these experiences might be part of the desired effects of N_2O [30]. Altogether, there is only limited indirect evidence of continued use despite knowledge of physical and mental health problems because of N_2O.

Pharmacological consequences

Criterion 10: Tolerance

The DSM-5 defines tolerance in two ways: the need for an increased amount of the substance to achieve the desired effect or a reduced effect with continued use of the same dose of the substance. A distinction should also be made between acute and chronic tolerance [63], with the former developing within a single exposure, whereas the latter refers to a reduction of the effects of a drug over multiple administrations of the same quantity. Although there is evidence on acute tolerance in humans in response to N_2O when it comes to its anesthetic [64], analgesic [65, 66] and hedonic [66] effects, the DSM-5 definitions of tolerance largely focus on chronic tolerance.

Tolerance is most often studied using rodent models, which provided evidence for a 50% reduction of analgesic effects (16–18 hour exposure to 75% N2O) [67] and the development of tolerance after 2 to 3 weeks of continued exposure to 50% N_2O [68], which diminished after a week of abstinence. An intermittent exposure paradigm by Ramsay *et al.* [69] also showed that exposure affects N_2O-induced body temperature reductions. Rats repeatedly exposed to 60% N_2O demonstrated a significantly smaller drop in bodily temperature than control rats, indicative of chronic tolerance to N_2O hypothermic effects.

Only one study assessed these effects in humans, intermittently (six sessions) exposing 64 participants to 35% N_2O (placebo-controlled, controls: n = 16, total: n = 80) and measuring tolerance to analgesic effects as detection and pain thresholds during electrical stimulation of the teeth [63]. Results showed evidence for acute tolerance after 7 to 12 min and chronic tolerance over the sessions with pain and detection threshold dropping by over 39%. Several non-experimental studies support the presence of self-reported tolerance in recreational N_2O users [8, 20], but most case studies (98%) do not report on tolerance effects [7].

In their assessment of recreational use of N_2O, Nabben *et al.* [20] concluded that tolerance may occur in the long term in heavy N_2O users. For example, one subject mentioned that 'We started with 2 kg (75 balloons each), but that slowly increased to 8 to 10 kg. You are building up tolerance, you know, which makes you want to use more and more each time' (p. 9) [20], which could be interpreted as an indication of tolerance. Furthermore, Marotta and Kesserwani [70] describe a case in which dental anesthesia had no effect on a patient who used up to 30 canisters of N_2O daily, indicative of potential tolerance. Similarly, another single case study by Berger-Vergiat *et al.* [71] demonstrates tolerance as well, with another case study showing similar results. Although these results seem to imply that chronic tolerance to N_2O is possible, there is also evidence that puts its frequency up for debate. Fidalgo *et al.* [7] found that 98% of literature cases provide no data on the presence of tolerance. To conclude, experimental studies suggest the potential for both acute and chronic tolerance in laboratory settings in rodents [67–69] as well as humans [63–66]. However, there is only limited evidence for self-reported tolerance in heavy N_2O users.

Criterion 11: Withdrawal

Drug withdrawal can be defined as the combination of averse mental and physiological effects experienced after cessation of drug use [72]. Although N_2O is frequently used to ameliorate withdrawal symptoms from other drugs [44, 45], research into N_2O withdrawal is limited. The majority of N_2O users in the study by Nugteren-Van Lonkhuyzen *et al.* [8] reported experiencing unpleasable aftereffects after N_2O wears off. However, looking at experimental studies in rodents, there appears to be no evidence for N_2O withdrawal [73, 74] after prolonged exposure. Similarly, case studies of withdrawal symptoms in humans show only limited anecdotal evidence for N_2O withdrawal [71, 75].

CONCLUSIONS

Although heavy recreational use of N_2O is increasingly common, there is very limited research into the addictive potential of N_2O. Our evaluation of the evidence for DSM-5 SUD criteria in N_2O users showed that although there is limited, but consistent evidence that a substantial number of heavy N_2O users use more than intended (criterion 1), spend a substantial amount of time using (criterion 3), experience social or interpersonal problems (criterion 6) and show potentially physically hazardous use (criterion 8), there is insufficient or inconclusive evidence for the other SUD criteria (Table 1). Although population statistics and case studies show that heavy N_2O users engage in use in risky situations (e.g. while driving; criterion 8), the awareness of the potential risk for N_2O is low and there is only anecdotal evidence for the conscious continuation of use when faced with negative mental or physical consequences of use (criterion 9). Evidence for a failure to cut down or quit use (criterion 2) is mixed, potentially only being present in a subset of heavy N_2O users. Similarly, there is mixed evidence for N_2O craving (criterion 4). Dose-dependent reinforcement effects, that might indicate craving, are consistently reported. However, self-reported craving is under-investigated. Although most heavy N_2O users report social or interpersonal problems (criterion 6), there is only anecdotal evidence for potential other social consequences of N_2O use (criteria 5 and 7), with a subset of heavy users reporting the inability to hold on to jobs or finish school and indirect evidence for reduced time spent on social, occupational and recreational activities because of N_2O use. Looking at the pharmacological consequences of use, there is limited and inconsistent evidence for N_2O tolerance (criterion 10). Although laboratory studies show evidence for tolerance to at least the analgesic effects of N_2O, studies on real-life tolerance in heavy N_2O-users is largely lacking. Currently, there is no evidence for the presence of N_2O-withdrawal symptoms, although the presence of craving and relapse in a subset of heavy users could be indicative of psychological withdrawal.

In general, research into symptoms of N_2O addiction is limited. Very little experimental research has been conducted on humans and large cohort studies are lacking. Most of the evidence comes from qualitative studies, case studies and reviews of those studies, providing largely anecdotal evidence. Current evidence is, therefore, insufficient to identify potential moderators (e.g. gender, age, socioeconomic and cultural background) of the association between N_2O use and the presence or prevalence of any of the DSM-5 SUD symptoms. Furthermore, none of the included studies were tailored to the assessment of DSM-5 SUD symptoms—the presence of these criteria is seldom explicitly specified—limiting the evaluation to constructs that could be indicative of symptom presence. Importantly, there is also no systematic evaluation of the effect of heaviness of N_2O use on symptom presence and most studies include a wide range of users including polydrug users and individuals with comorbid mental disorders. It is key that future studies assess the presence of these symptoms in groups of heavy N_2O users to clarify to what extent their use should be classified as a SUD, to encourage appropriate treatment. Although decades of research have provided estimates of the addictive potential of other substances—the addictive potential of cannabis and alcohol for ever-users is estimated at 8% and 5.8%, respectively [76]—the current literature base is insufficient to provide these important statistics and leaves an important direction for future research.

Our results suggest that N_2O use disorder—based on the DSM-5 SUD criteria—might exist in the heaviest N_2O users and that the addictive potential of N_2O should not be underestimated. However, the evidence base is limited, and large-scale research is necessary to corroborate and extend on our findings. As high-risk N_2O use is on the rise [6, 26, 77], it remains crucial to extend our knowledge to better inform treatment, encourage public health campaigns and provide arguments for the debates regarding N_2O legislation. This narrative review provides a starting point for future research, showing that N_2O could well be addictive and should be treated as a potentially addictive substance while we build on the existing evidence.

AUTHOR CONTRIBUTIONS

Sammie Back: Conceptualization (equal); writing—original draft (lead); writing—review and editing (equal). **Emese Kroon:** Supervision (supporting); writing—review and editing (equal). **Karis Colyer-Patel:** Writing—review and editing (equal). **Janna Cousijn:** Conceptualization (equal); writing—review and editing (equal); supervision (lead).

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DECLARATION OF INTERESTS

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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