

# Acute psychotic and vitamin B12 deficiency in patient with nitrous oxide misuse: A case report

SAGE Open Medical Case Reports  
Volume 12: 1–4  
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DOI: 10.1177/2050313X241269577  
journals.sagepub.com/home/sco



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## Abstract

Nitrous oxide, also called nitrous monoxide, or nitrous oxide, is a colorless and odorless gas, without toxicological effect, but it can be asphyxiating at high concentration, its misuse is increasing especially among young people. Chronic use of N<sub>2</sub>O may cause psychiatric complications, including depression, hypomania, and paranoid psychosis with visual and auditory hallucinations. We present a case of nitrous oxide abuse “laughing gas” in 25 years old woman with bizarre behavior delusions and hallucinations with a normal neurological examination. The patient had low levels of vitamin B12 (135 pmol/L). Treatment with antipsychotics and vitamin B12 (cobalamin) resolved her psychosis. In addition to the hematological and neurological effects, rare cases of acute psychosis, especially in young people with or without psychiatric history, use varies from 1 month to years. Clinicians are increasingly in need of knowledge regarding the misuse of nitrous oxide.

## Keywords

Acute psychosis, nitrous oxide, misuse, vitamin B12

Date received: 13 March 2024; accepted: 25 June 2024

## Introduction

Nitrous oxide, also known as dinitrogen monoxide and with the chemical formula N<sub>2</sub>O, was first discovered by Joseph Priestley in 1772.<sup>1</sup> Under normal conditions of temperature and pressure, this gas is colorless and odorless, and it is non-toxic. However, in high concentrations, it can cause asphyxiation. Since the late 18th century, nitrous oxide has been used for recreational purposes, often referred to as “laughing gas,” as well as for medical applications as an anesthetic.<sup>2</sup>

Nitrous oxide, a gas with a slightly sweet taste, can be readily available for purchase in some countries. It is sometimes sold in consumable cartridges found in supermarkets. Unfortunately, there has been a significant increase in the misuse of nitrous oxide in Morocco, especially among secondary school pupils, students, and young adults. In the United States, it ranks among the top five inhalants frequently used by teenagers due to its euphoric effects.<sup>3</sup> Evidence of its misuse can sometimes be observed in public areas, indicated by the presence of discarded metal cartridges containing the gas.

Nitrous oxide may induce psychiatric symptoms, including hallucinations, rapidly reversible confusion, delusions, and bizarre behavior, often accompanied by neurological

manifestations.<sup>4–6</sup> In severe cases, hospitalization in a psychiatric facility may be necessary.<sup>6</sup> Generally, treatment with vitamin B12 leads to the resolution of these symptoms. Although rare, there have been reported instances of nitrous oxide-induced psychosis in the medical literature.<sup>6</sup> In this article, we present a case of an isolated psychotic episode resulting from the misuse of nitrous oxide.

## Case presentation

This case concerns a 25-year-old Moroccan female who presented at the psychiatric emergency department accompanied by her mother, exhibiting behavioral disturbances concomitant with delusional ideation. Up to this point, the

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patient had no prior medical or psychiatric record, and she does not have any documented family history of psychiatric disorders.

One year ago, after attending a party with her friends, the patient began using nitrous oxide recreationally. She found the euphoric effects of the substance appealing, leading her to progressively increase her consumption to 100 nitrous oxide balloons per day. Approximately 4 months before her hospitalization, her family and friends began to observe significant social and professional consequences. She withdrew from social activities and faced multiple work interruptions.

A month ago, the patient began experiencing paranoid thoughts, hallucinations, insomnia, increased anxiety, and a reluctance to leave her home. She also reported seeing distorted faces of people on the street. Mrs. M endorsed occasional use of alcohol but denied using any other psychoactive substances.

Upon initial psychiatric assessment, the patient appeared calm and well-oriented in time, space. She demonstrated good memory and concentration, and her attire was clean and appropriate. Notably, the patient exhibited significant anxiety despite a neutral mood. Her affect was congruent with her mood, and her thought processes were continuous without any mental blocks or fading.

The patient endorsed delusions of persecution, believing that those around her are conspiring against her. Specifically, she is convinced that someone has implanted a “chip” in her head to monitor her. Additionally, she presented delusions of reference, believing that people are discussing her on social media and in the media.

Furthermore, the patient reported experiencing visual hallucinations, and difficulty in recognizing her loved ones. Moreover, she described auditory hallucinations with unclear content. Importantly, she denied any current suicidal ideation.

General and neurological examinations revealed no abnormalities. Biological examinations showed mostly normal hematological cell count and morphology, except for a slight increase in neutrophils. All electrolyte levels, as well as hepatic, renal, and thyroid functions, were within the normal range. The toxicology screen came back negative. The immunometric vitamin B12 level was 135 pmol/L (normal range: 156–672 pmol/L), the urinary methylmalonyl acid was 42 mmol/L (normal range: <20 mmol/L), and the homocysteine level was 44.42  $\mu$ mol/L (normal range: 5–15  $\mu$ mol/L).

A magnetic resonance imaging of the brain showed no abnormalities.

Following consultation with an internist, a treatment plan was initiated consisting of administering 1000 mcg of vitamin B12 intramuscularly for 1 week, followed by weekly oral supplementation for 1 month. The patient was prescribed risperidone 4 mg, diazepam 30 mg daily, with a gradual tapering plan for the diazepam. Additionally, she received vitamin B1 and B6 therapy and was advised to consume 3 L of water daily for hydration.

Progressive improvement was noted in the patient’s psychiatric condition. Hallucinations disappeared during the

first week, and the patient began to exhibit self-criticism of delusions at the beginning. Her delusions disappeared during the third week, and there was an improvement in her sleep pattern. Prior to discharge, laboratory evaluation revealed vitamin B12 levels of 231 pmol/L, urinary methylmalonic acid level of 27 mmol/L, and homocysteine level of 23.1  $\mu$ mol/L. Unfortunately, attempts to follow up with the patient were unsuccessful.

## Discussion

In recent years, the consumption of nitrous oxide has seen a dramatic increase, gaining attention worldwide. In a recent study by the Global Drug Survey, which included 74,864 participants, nitrous oxide was among the most widely used substances, especially in the United Kingdom and United States of America, with lifetime prevalence rates of 38.6% and 29.4%, respectively.<sup>7</sup> Reinforcing this concern, a 2020 Dutch general population survey among adults aged 18 and over found that nitrous oxide use in the past 12 months was highest among young adults aged 18–19 (14.5%) and 20–24 (12.1%). This percentage is six times higher than in the entire adult population (2.1%). Meanwhile, past-year use among 12–16-year olds was 6.7%, with 11.7% of 15–16-year olds using the gas.<sup>8</sup> These findings are concerning, as research from other countries also suggests a rise in nitrous oxide use among young people. For example, a study conducted in France investigated psychoactive substance use among individuals aged 18–25 years. This study included 46,203 respondents, mostly in universities (>60%) and mostly women (63.4%), with an average age of 21.4 years. The overall prevalence of nitrous oxide use was around 6% for males and 3% for females.<sup>9</sup> More recently, the use of nitrous oxide has also been reported among teenagers, including middle and high school students.<sup>10</sup> Unfortunately, in Morocco, we lack official figures regarding the number of nitrous oxide consumers.

Although the exact mechanism of the neurological changes caused by nitrous oxide leading to psychosis is still a topic of debate,<sup>2</sup> one of the hypotheses leading to neurological damage involves the oxidation of vitamin B12 by nitrous oxide, leading to a deficiency of vitamin B12, which plays an important role in the formation of red blood cells and the maintenance of a healthy nervous system.<sup>11</sup> Vitamin B12 deficiency results in the inhibition of methionine synthase and impaired conversion of homocysteine to methionine and 5-methyl-tetrahydrofolate to tetrahydrofolate, irreversible inactivation of methionine synthase lead to demyelination of neurons.<sup>12</sup> Other hypothesis suggests that the increase in dopamine levels induced by N<sub>2</sub>O may explain the hallucinogenic effects of the substance, aligning with the N-methyl-D-aspartate (NMDA) receptor hypo-function hypothesis of schizophrenia.<sup>11</sup> In an investigation conducted by Piazza et al., including three studies from the same research lab (study 1: Das et al., 2018; study 2: Kamboj et al., 2021) were combined with unpublished data from their laboratory (study 3), they

**Table 1.** Literature review on psychotic episodes induced by nitrous oxide.

Authors/year	Age (years)	Gender	Duration of N <sub>2</sub> O use	Psychiatric symptoms	Vitamin B12 level
Chin et al. <sup>19</sup> 2015	38	M	Not applicable	Visual and auditory hallucinations, delusions	193 pg/mL
Cousaert et al. <sup>20</sup> 2013	24	M	Not applicable	Bizarre behavior, delusions, and confusion	171 pg/mL
Garakani et al. <sup>21</sup> 2014	24	M	Two years	Persecutory delusions, bizarre behavior	144 pg/mL
Sethi et al. <sup>22</sup> 2006	33	M	One month	Agitation, delusions	202 pg/mL
Wong et al. <sup>17</sup> 2014	30	M	Few days	Verbal aggression, delusions, mood lability	148 pmol/L
Chen et al. <sup>23</sup> 2018	19	M	Six months	Auditory hallucinations, emotional instability, delusions	602.1 pmol/L
Kwok et al. <sup>24</sup> 2019	21	F	Not applicable	Agitation, auditory and visual hallucinations	Normal
Our case	25	F	One year	Visual hallucinations, delusions	135 pmol/L

found that nitrous oxide (N<sub>2</sub>O) reliably produced dissociative and psychotomimetic effects of similar magnitude to those reported with ketamine.<sup>13</sup>

At present, there is no clearly defined toxic dose for long-term exposure. Nitrous oxide is a depressant of the central nervous system.<sup>14</sup> Moreover, inhaling it gradually replaces oxygen, leading to asphyxia or even respiratory arrest, which can result in death, especially when used without medical supervision or at high concentrations. However, if used correctly and in the absence of contraindications, the side effects of inhalation are rare and immediately reversible upon cessation. These side effects may include euphoria, dreaming, paresthesias, restlessness, nausea, and vomiting. The first two effects are the ones that have led to its misuse.<sup>15</sup>

Although the exact mechanism of the neurological changes caused by nitrous oxide leading to psychosis is still a topic of debate,<sup>2</sup> chronic use of N<sub>2</sub>O may cause psychiatric complications, including depression, hypomania, and paranoid psychosis with visual and auditory hallucinations.<sup>5,6,16</sup> Although these psychiatric complications are typically observed alongside neurological manifestations, they rarely occur in isolation.<sup>17</sup> Indeed, in a narrative review, out of 25 patients, 16 had neurological symptoms associated with psychiatric manifestations.<sup>18</sup>

It should be noted that Mrs. M had no other known exposures that could contribute to her psychotic illness, although the possibility of a spontaneous psychotic episode should not be ruled out. The patient's use of N<sub>2</sub>O directly preceded her psychotic symptoms, suggesting that her psychotic episode was induced by voluntary inhalation of N<sub>2</sub>O.

Most of the cases reported in the literature involve adolescents or young adults who use multiple drugs. They have used N<sub>2</sub>O for a duration ranging from a few days to several years and often have a history of mood disorders. Hospitalization was not always necessary, and most of

their urine drug screens were negative for other toxic substances, suggesting a direct causal relationship between N<sub>2</sub>O use and psychiatric symptoms (Table 1).

In a survey study summarized, the psychiatric presentations associated with N<sub>2</sub>O use, the most common of which were delusions, hallucinations, and confusion.<sup>7</sup> The management of psychosis induced by N<sub>2</sub>O involves a two-pronged approach, abstinence from N<sub>2</sub>O inhalation and short-term (1 week) intramuscular or oral cobalamin supplementation, typically at a dosage of 1000 µg daily.<sup>18</sup> An antipsychotic is often prescribed until psychiatric symptoms subside. The prognosis is generally favorable, with complete resolution of most, if not all, psychiatric abnormalities. Mild neurological sequelae, if present, may persist.<sup>6,18</sup>

## Conclusion

Nitrous oxide is very familiar to teenagers and young adults in many countries. The low cost and rapid onset of desired effects may encourage frequent use, potentially leading to excessive consumption.

Therefore, there is a need to introduce stricter measures for its sale. N<sub>2</sub>O can rarely induce an acute psychotic episode, in addition to potentially causing serious somatic pathologies. Clinicians need to be increasingly aware of the misuse of nitrous oxide.

## Acknowledgements

None.

## Author contributions

H.M. and E.S. were responsible for the diagnostic evaluation and management of the patient. M.H. managed the literature review and wrote the first draft of the manuscript. O.B. provided critical revisions to the manuscript and helped with framing.

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed consent

Written informed consent was obtained from a legally authorized representative (the parents) for anonymized patient information to be published in this article.

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