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CASO CLÍNICO/CASE REPORT

Nitrous Oxide-Induced Psychosis: Case Report
Psicose Induzida por Óxido Nitroso: Relato de Caso

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ABSTRACT
Nitrous oxide (N_2O), has seen a troubling rise in recreational use. While its hematological and neurological toxicities are well documented, its psychiatric effects remain underrecognized. Chronic or high-dose exposure can result in vitamin B12 deficiency, exacerbating neuropsychiatric manifestations. We report the case of a 27-year-old male with a recent onset of daily N_2O inhalation, who was admitted for a first-episode psychosis. Laboratory findings revealed vitamin B12 and folic acid deficiencies. Treatment included antipsychotic medication and vitamin supplementation, leading to full symptom remission. Establishing a formal longitudinal diagnosis during the first psychotic episode is a challenge. This case highlights the potential of N_2O to trigger acute psychosis, especially in vulnerable individuals. Considering the rising prevalence of N_2O misuse, targeted public health strategies and clinician education are essential for timely diagnosis and effective intervention.

RESUMO
O consumo recreativo de óxido nítrico (N_2O) tem aumentado de forma preocupante. Apesar da sua toxicidade hematológica/neurológica estar bem documentada, os efeitos psiquiátricos permanecem subvalorizados. A exposição crónica ou em altas doses pode causar défice de vitamina B12, potenciando estas manifestações. Apresentamos o caso de um homem de 27 anos, com consumo recente de N_2O, internado por primeiro episódio psicótico. Os exames laboratoriais revelaram défice de vitamina B12 e ácido fólico. O tratamento com antipsicótico e suplementação possibilitou a completa remissão de sintomas. A determinação de um diagnóstico formal aquando de um primeiro episódio psicótico constitui um desafio clínico. Este caso evidencia o potencial do N_2O para desencadear quadros psicóticos, sobretudo em indivíduos vulneráveis. Face ao aumento do consumo recreativo, é essencial definir estratégias de saúde pública e promover a formação dos clínicos para diagnóstico precoce e intervenção eficaz.

Keywords: Nitrous Oxide/adverse effects; Psychoses, Substance-Induced

Palavras-chave: Óxido Nitroso/efeitos adversos; Psicoses Induzidas por Substâncias

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INTRODUCTION

Nitrous oxide (N_2O), commonly known as "laughing gas," was discovered in 1772 by British scientist Joseph Priestley and later popularized by Humphry Davy, who documented its euphoric and anesthetic properties in a book published in 1800. However, it was not until 1844 that American dentist Horace Wells introduced its use as an anesthetic in clinical practice[1].

Currently, N_2O is legally used in medical and dental settings for its anxiolytic, analgesic, and anesthetic effects, as well as in the food and automotive industries.[2] Nevertheless, its recreational use has been rising globally in recent years, particularly among young individuals.[3] Although national data from Portugal remain limited, international surveys reflect growing concern regarding its use. For instance, the 2022 Global Drug Survey reported an increase in N_2O consumption from 10% in 2015 to 20% in 2021,[4] and in the United Kingdom, it is now the third most commonly used drug among young individuals, after cannabis and cocaine. While some recent surveys suggest a slight decline in overall use,[5] changing patterns of consumption — shifting from occasional use at social events to more frequent or heavier use in private settings[6] — alongside rising hospital admissions related to inhaled anesthetics, including N_2O, point to riskier and more harmful patterns of use.[3]This growing misuse is largely driven by the substance's easy accessibility, low cost, rapid onset of euphoria (typically within 10 seconds), and short duration of action, despite increasing evidence of significant neurotoxicity and neuropsychiatric complications.[2,7] Emerging clinical evidence suggests a correlation between chronic or high-dose use and the onset of acute psychotic symptoms.[8,9]

CASE REPORT

We report the case of a 27-year-old man originally from Lisbon, Portugal, where he lived with his wife and two children. He had completed six years of formal education, marked by multiple grade retention in the context of behavioral and learning difficulties. He had no regular employment since 2022, when the restaurant where he had worked for several years closed, taking short-term jobs since then, his most recent in construction, which he quit due to low pay, as confirmed by his family. Family reports indicated preserved peer-level functioning, with active participation in household tasks and family dynamics. His family history was notable for a mother diagnosed with schizophrenia, with multiple hospitalizations reported. His past medical history included meningitis at the age of 7, which required hospitalization but resulted in no apparent residual deficits. No prior psychiatric symptomatology identifiable in longitudinal assessment, with no follow-up in Psychiatry or primary healthcare. The patient reported occasional social use of cannabinoids between the ages of 19 and 25, typically weekly, with no associated psychiatric symptoms. He had one recent episode of use in the week prior to presenting to the Emergency Department.

In April 2024, he was brought to the Psychiatric Emergency Department by police, presenting with a 15-day history of sudden behavioral disorganization, wandering the streets, episodes of hetero-aggressiveness directed at reference family members, soliloquies, and suspiciousness, with progressive worsening over the previous two days. The mental status examination revealed delusional ideation of harm and persecution with increased affective and behavioral drive, behavior suggestive of hallucinatory activity, dysphoric mood, total insomnia, and complete lack of insight. No other abnormalities were noted on the mental status and brief neurological examination.

It was also found that, beginning three weeks before his emergency visit, he had started inhaling N_2O recreationally with increasing frequency, eventually daily during the week preceding his presentation. Apart from the single reported use of cannabinoids, no other substance use was identified in the period before admission. Laboratory tests revealed deficiencies in vitamin B12 (167 pg/mL; Normal range 195-770 pg/mL) and folic acid (4.4 ng/mL; Normal range 4.6-18.7 ng/mL). Urine screening tested positive for cannabinoids. Cranial magnetic resonance imaging (MRI) was performed, revealing no significant abnormalities. No other abnormalities were found on laboratory tests. After discussion with the Internal Medicine team, no additional investigations were recommended. A diagnosis of a first-episode psychosis comorbid with substance use disorder was established, and the patient was subsequently admitted to the Psychiatry Department for involuntary inpatient treatment.

Treatment with risperidone was initiated and gradually titrated to 6 mg/day, followed by a switch to the long-acting monthly injectable formulation in the days prior to discharge, to ensure treatment adherence. The plan was discussed with the patient, who agreed, considering it easier to ensure adherence than with oral medication. No adverse effects were reported. Oral vitamin B12 supplementation was also administered, following a multidisciplinary discussion, with subsequent laboratory evaluation demonstrating normalization of serum levels within two weeks.

Full symptom remission was achieved within two weeks, with the patient showing progressive insight into the symptomatology that prompted hospitalization, but limited insight into the impact of substance uses on the course of his clinical condition. He was voluntarily discharged on day 23 of hospitalization, prescribed quetiapine 100 mg at bedtime and long-acting risperidone 100 mg monthly.

Following this episode, he was placed under outpatient follow-up, exhibiting fluctuating symptoms that appear to be directly influenced by his ongoing use of N_2O, for which he demonstrates minimal motivation to cease. These episodes, with a duration of less than 24 hours, are mainly characterized by psychomotor agitation and suspiciousness. They are managed in the Emergency Department with oral therapy with olanzapine 10 mg, without the need for hospitalization, and with full recovery between episodes. Urine toxicology tests have been negative for other substances during these periods. The patient's family has been actively involved in his care to provide additional support; however, despite their efforts, adherence remains inconsistent, and he has not accepted referral for specialized addiction treatment.

DISCUSSION

Establishing a formal longitudinal diagnosis with high accuracy during first-episode psychosis represents a significant challenge, especially when multiple risk factors coexist. In this case, the main DSM-5 differential diagnostic hypotheses are a substance-induced psychotic disorder (primarily N_2O, possibly in combination with cannabis), strongly supported by the close temporal link with heavy N_2O use and rapid remission after cessation and B12 replacement, although chronic cannabis use may have acted synergistically; a brief psychotic disorder, compatible with the less-than-one-month duration and full remission, but rendered less likely by family history and long-standing cannabis use; schizophreniform disorder/schizophrenia, which remain possible given the patient's family history, low premorbid functioning and chronic cannabis use, yet are currently unlikely due to complete remission without maintenance antipsychotics; and schizoaffective disorder, which can be ruled out by the absence of a full mood episode. Only long-term follow-up and sustained substance abstinence can clarify the diagnosis, as is common practice in psychiatry. At present, the most likely hypothesis is a substance-induced psychotic disorder in which heavy N_2O use appears to have acted as the main precipitant, while chronic cannabis use represented an important vulnerability or co-precipitating factor. The potential role of cannabis therefore cannot be dismissed — even though its consumption had reportedly been low or absent for several years without previous psychotic symptoms, cannabis remains one of the strongest environmental risk factors for psychosis and may interact synergistically with acute N_2O exposure in vulnerable individuals. We therefore consider that daily N_2O use very probably played a major precipitating role in the development of the psychotic symptomatology, either as the principal trigger or as a precipitant of the first manifestations of a primary psychotic disorder in a vulnerable individual.[8-10] This case illustrates the potential of N_2O use to induce psychotic symptoms. Additionally, the patient presented with a vitamin B12 deficiency. This deficiency can, in itself, contribute to or exacerbate neuropsychiatric symptoms, ranging from cognitive impairment to psychiatric manifestations.[11,12] In this context, the vitamin B12 deficit — most likely induced or aggravated by the use of N_2O — may have contributed to the clinical picture, and its prompt replacement appears to have played an important role in the observed rapid clinical improvement.

Although the hematological and neurological toxicity of N_2O is well established — particularly its association with subacute combined degeneration of the spinal cord, peripheral neuropathy, ataxia, limb weakness, and gait disturbances[2,3] — its psychiatric manifestations remain underrecognized and are often underdiagnosed. Described psychiatric effects include paranoia, delusions (often persecutory), hallucinations (visual, auditory, or kinesthetic), psychomotor agitation, hypervigilance, confusion, delirium, and, in rare cases, catatonia.[9,13,14] Affective and behavioral symptoms such as depression, mania, anxiety, emotional instability, personality changes, suicidal ideation, and violent behavior have also been reported.[7,8,15,16] Cognitive deficits and chronic neurocognitive impairment may also occur.[2,9] Of particular concern is the onset of acute psychosis, which has been increasingly reported in association with N_2O use,[8,9,17] especially among young individuals. Notably, psychiatric symptoms may present in isolation, as the sole or initial manifestation of toxicity, without overt neurological signs,[9] thereby complicating the differential diagnosis from other causes of psychosis.

N_2O acts predominantly as a non-competitive antagonist of NMDA receptors, interfering with glutamatergic neurotransmission and potentially triggering dissociative and psychotic symptoms.[18] Additionally, N_2O oxidizes the cobalt ion in vitamin B12, functionally inactivating the vitamin and leading to vitamin B12 deficiency, even in individuals with normal serum levels. This inactivation compromises key enzymes (methionine synthase and methylmalonyl CoA mutase), resulting in the accumulation of homocysteine and methylmalonic acid[19] — useful diagnostic biomarkers.

The increasing prevalence of recreational N_2O use is reinforced by the widespread misperception of its safety and represents an emerging public health concern. Greater awareness among healthcare professionals of its metabolic and neuropsychiatric effects is therefore essential, and N_2O use should be considered in the differential diagnosis of acute psychiatric presentations, particularly in young individuals. This is especially important given the lack of formal screening tools and the compound's short half-life.[2] In these circumstances, serum levels of vitamin B12, homocysteine and methylmalonic acid remain valuable indirect markers of N_2O exposure.[7]

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MMD, MR: Revisão da literatura, redação do manuscrito.
RS, RC: Redação e revisão crítica do manuscrito. Todos os autores aprovaram a versão final a ser publicada.
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CONTRIBUTORSHIP STATEMENT

MMD, MR: Literature review, writing of the manuscript.
RS, RC: Writing and critical review of the manuscript. All authors approved the final version to be published.
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