'Self-anesthetizing' to cope with grief

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Mr. M, age 51, stops eating and develops delusions after his wife dies. He has been using increasing amounts of *Cannabis* and nitrous oxide. What could be causing his symptoms?

CASE Grieving, delusional

Mr. M, age 51, is brought to the emergency department (ED) because of new-onset delusions and decreased self-care over the last 2 weeks following the sudden death of his wife. He has become expansive and grandiose, with pressured speech, increased energy, and markedly reduced sleep. Mr. M is preoccupied with the idea that he is "the first to survive a human reboot process" and says that his and his wife's bodies and brains had been "split apart." Mr. M has limited his food and fluid intake and lost 15 lb within the past 2 to 3 weeks.

Mr. M has no history of any affective, psychotic, or other major mental disorders or treatment. He reports that he has regularly used *Cannabis* over the last 10 years, and a few years ago, he started occasionally using nitrous oxide (N_2O). He says that in the week following his wife's death, he used N_2O almost daily and in copious amounts. In an attempt to "self-anesthetize" himself after his wife's funeral, he isolated himself in his bedroom and used escalating amounts of *Cannabis* and N_2O, while continually working on a book about their life together.

At first, Mr. M shows little emotion and describes his situation as "interesting and fascinating." He mentions that he thinks he might have been "psychotic" the week after his wife's death, but he shows no sustained insight and immediately relapses into psychotic thinking. Over several hours in the ED, he is tearful and sad about his wife's death. Mr. M recalls a similar experience of grief after his mother died when he was a teenager, but at that time he did not abuse substances or have psychotic symptoms. He is fully alert, fully oriented, and has no significant deficits of attention or memory.

What could be causing Mr. M's symptoms?

a) acute grief
b) psychotic depression
c) mania
d) substance-induced psychosis

The authors' observations

Grief was a precipitating event, but by itself grief cannot explain psychosis. Psychotic depression is a possibility, but Mr. M's psychotic features are incongruent with his mood. Mania would be a diagnosis of exclusion. Mr. M had no prior history of major affective illness. Mr. M was abusing

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Cannabis, which might independently contribute to psychosis[1]; however, he had been using it recreationally for 10 years without psychiatric problems. N_2O, however, can cause symptoms consistent with Mr. M's presentation.

In a patient who has been abusing N_2O, what metabolic abnormalities should be considered?

a) thiamine deficiency
b) cobalamin (vitamin B_{12}) deficiency
c) pyridoxine deficiency
d) vitamin D deficiency

EVALUATION Laboratory tests

Mr. M's physical examination is notable only for an elevated blood pressure of 196/120 mm Hg. Neurologic examination is normal. Toxicology is positive for cannabinoids and negative for amphetamines, cocaine, opiates, and phencyclidine. Chemistries are normal except for a potassium of 3.4 mEq/L (reference range, 3.7 to 5.2 mEq/L) and a blood urine nitrogen of 25 mg/dL (reference range, 6 to 20 mg/dL), which are consistent with reduced food and fluid intake. Mr. M shows no signs of anemia. Hematocrit is 42% and mean corpuscular volume is 90 fL. Syphilis screen is negative; a head CT scan is unremarkable.

Further workup reveals a cobalamin (vitamin B_{12}) level of 82 pg/mL (reference range, 180 to 900 pg/mL) and a methylmalonic acid level of >5 (reference range, <0.3). Mr. M's folate level is normal (>22 ng/mL). Because the acute onset of symptoms corresponded with a sudden increase in N_2O use, further workup for other causes of vitamin B_{12} deficiency (***Table 1***[2]) is not pursued.

The authors' observations

N_2O, also known as "laughing gas," is routinely used by dentists and pediatric anesthesiologists, and has other medical uses. Some studies have examined an adjunctive use of N_2O for pain control in the ED and during colonoscopies.[3,4]

Table 1

Causes of vitamin B_{12} deficiency

Folate deficiency
Malnutrition
Gastric bypass surgery
Pernicious anemia
Nitrous oxide use
Alcohol use
HIV
Helicobacter pylori

Source: Reference 2

In the 2013 U.S. National Survey on Drug Use and Health, 16% of respondents reported lifetime illicit use of N_2O.[5,6] It is readily available in tanks used in medicine and industry and in small dispensers called "whippits" that can be legally purchased. Acute effects of N_2O include euphoric mood, numbness, feeling of warmth, dizziness, and auditory hallucinations.[7] The anesthetic effects of N_2O are linked to endogenous release of opiates, and recent research links its anxiolytic activity to the facilitation of GABAergic inhibitory and *N*-methyl-D-aspartic acid (NMDA)-mediated transmission.[8] Abuse of N_2O has been the presumptive cause of death in 29 cases.[9]

N_2O may cause neurologic and psychiatric dysfunction by 2 main routes: direct toxic CNS effects and inactivating vitamin B_{12}. Putative mechanisms of action of vitamin B_{12} deficiency–induced neuronal dysfunction include dysregulation of cytokine and growth factor levels in the CSF.[10] By irreversible oxidation of its cobalt ion, N_2O inactivates vitamin B_{12} and causes functional deficiency.[11] Vitamin B_{12} deficiency can cause various signs and symptoms, including macrocytosis, depression, and hallucinations (***Table 2, page 50***).[2,12] Several case reports have linked abuse of N_2O with vitamin B_{12} deficiency and reported

Clinical Point

N_2O may cause neurologic and psychiatric dysfunction via toxic effects on the CNS or by inactivating vitamin B_{12}

Table 2

Vitamin B_{12} deficiency: Signs and symptoms

Signs	Anemia, macrocytosis (mean corpuscular volume >100 fL), hypersegmented neutrophils, idiopathic pancytopenia, elevated methylmalonic acid levels,[a] elevated homocysteine levels
Symptoms	Weakness, ataxia, paresthesia, memory loss, depression, hypomania, psychosis, hallucinations

[a]Common in patients with renal insufficiency

Source: References 2,12

Clinical Point

Vitamin B_{12} deficiency can cause various signs and symptoms, including macrocytosis, depression, and hallucinations

psychotic symptoms as the sole presenting abnormalities, with an absence of other signs and symptoms.[13-16]

Beginning with a 1960 report of a series of patients with "megaloblastic madness,"[17] there have been calls for increased awareness of the potential for vitamin B_{12} deficiency–induced psychiatric disorders, even in the absence of other hematologic or neurologic sequelae that would alert clinicians of the deficiency. In a case series of 141 patients with a broad array of neurologic and psychiatric symptoms associated with vitamin B_{12} deficiency, 40 (28%) patients had no anemia or macrocytosis.[2]

Vitamin B_{12}-responsive psychosis has been reported as the sole manifestation of illness, without associated neurologic or hematologic symptoms, in only a few case reports. Vitamin B_{12} levels in these cases ranged from 75 to 236 pg/mL (reference range, 160 to 950 pg/mL).[18-20] In all of these cases, the vitamin B_{12} deficiency was traced to dietary causes. The clinical evaluation of suspected vitamin B_{12} deficiency is outlined in the ***Figure***[21] (***page 51***).

Mr. M had used *Cannabis* recreationally for a long time, and his *Cannabis* use acutely escalated with use of N_2O. Long-term use of *Cannabis* alone is a risk factor for psychotic illness.[22] Combined abuse of *Cannabis* and N_2O has been reported to provoke psychotic illness. In a case report of a 22-year-old male who was treated for paranoid delusions, using *Cannabis* and 100 cartridges of N_2O daily was associated with low vitamin B_{12} and elevated homocysteine and methylmalonic acid levels.[23]

Cannabis use may have played a role in Mr. M's escalating N_2O use. In a study comparing 9 active *Cannabis* users with 9 non-using controls, users rated the subjective effects of N_2O as more intense than non-users.[24] In our patient's case, *Cannabis* may have played a role in both sustaining his escalating N_2O abuse and potentiating its psychotomimetic effects.

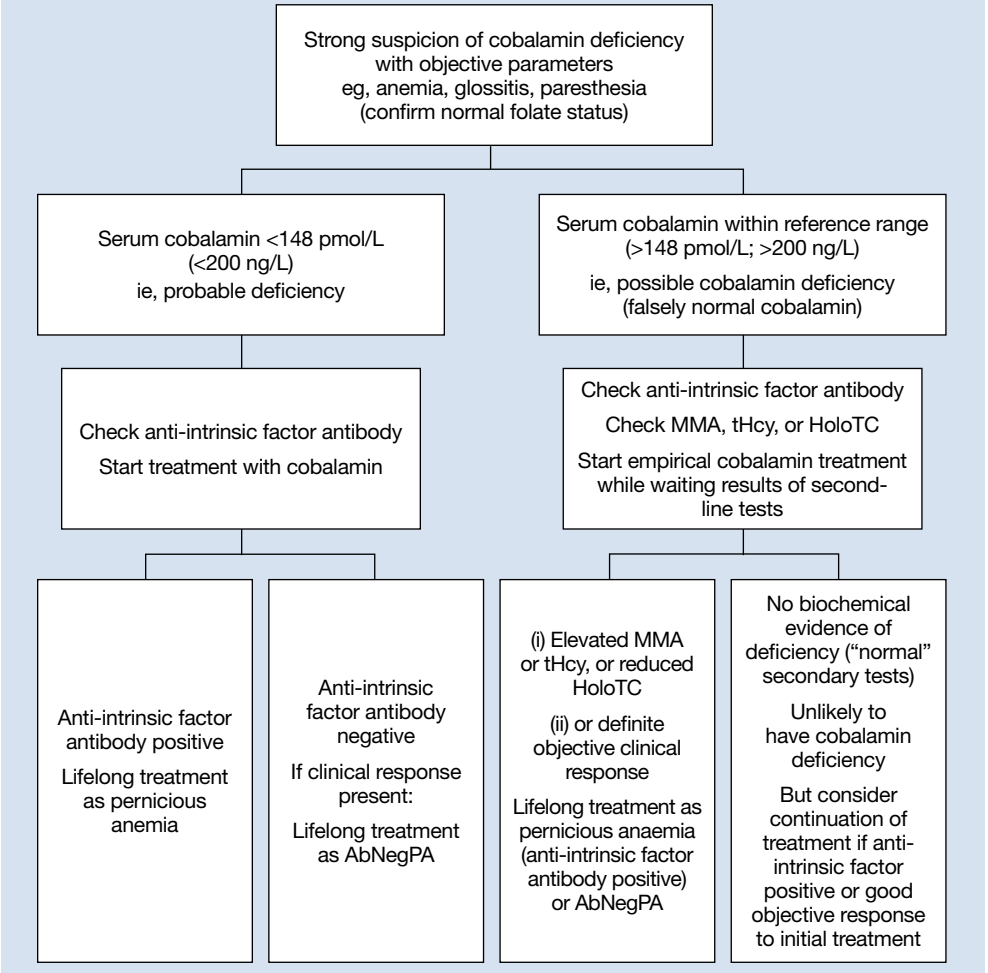
It also is possible that Mr. M may have been "self-medicating" his grief with N_2O. In a recent placebo-controlled crossover trial of 20 patients with treatment-resistant depression, Nagele et al[25] found a significant rapid and week-long antidepressant effect of subanesthetic N_2O use. A model involving NMDA receptor activation has been proposed.[25,26] Zorumski et al[26] further reviewed possible antidepressant mechanisms of N_2O. They compared N_2O with ketamine as an NMDA receptor antagonist, but also noted its distinct effects on glutaminergic and GABAergic neurotransmitter systems as well as other receptors and channels.[26] However, illicit use of N_2O poses toxicity dangers and has no current indication for psychiatric treatment.

TREATMENT Supplementation

Mr. M is diagnosed with substance-induced psychotic disorder. His symptoms were precipitated by an acute increase in N_2O use, which has been shown to cause vitamin B_{12} deficiency, which we consider was likely a primary contributor to his presentation. Other potential contributing factors are premorbid hyperthymic temperament, a possible propensity to psychotic thinking under stress, the sudden death of his wife, acute grief, the potentiating role of *Cannabis*, dehydra-

Figure

Identifying vitamin B_{12} deficiency



ABNegPA: antibodynegative pernicious; HoloTC: holotranscobalamin; MMA: methylmalonic acid; tHcy: total homocysteine

Source: Reference 21

tion, and general malnutrition. The death of a loved one is associated with an increased risk of developing substance use disorders.[27]

During a 15-day psychiatric hospitalization, Mr. M is given olanzapine, increased to 15 mg/d and oral vitamin B_{12}, 1,000 mcg/d for 4 days, then IM cyanocobalamin for 7 days. Mr. M's symptoms steadily improve, with normalization of sleep and near-total resolution of delusions. On hospital Day 14, his vitamin B_{12} levels are within normal limits (844 pg/mL). At discharge, Mr. M shows residual mild grandiosity, with limited insight into his illness and what caused it, but frank delusional ideation has clearly receded. He still shows some signs of grief. Mr. M is advised to stop using *Cannabis* and N_2O and about the potential consequences of continued use.

The authors' observations

For patients with vitamin B_{12} deficiency, guidelines from the National Health Service in the United Kingdom and the British Society for Haematology recommend treatment with IM hydroxocobalamin, 1,000 IU,

Clinical Point

Combined abuse of *Cannabis* and N_2O has been reported to provoke psychiatric illness

Related Resource

- Tips for teens on inhalants. https://store.samhsa.gov/shin/content/PHD631/PHD631.pdf.

Drug Brand Names

Olanzapine • Zyprexa
Cyanocobalamin • Nascobal
Hydroxocobalamin • Cyanokit

3 times weekly, for 2 weeks.[21,28] For patients with neurologic symptoms, the British National Foundation recommends treatment with IM hydroxocobalamin, 1,000 IU, on alternative days until there is no further improvement.[21]

This case is a reminder for clinicians to screen for inhalant use, specifically N_2O, which can precipitate vitamin B_{12} deficiency with psychiatric symptoms as the only presenting concern. Clinicians should consider measuring vitamin B_{12} levels in psychiatric patients at risk of deficiency of this nutrient, including older adults, vegetarians, and those with alimentary disorders.[29,30] Dietary sources of vitamin B_{12} include meat, milk, egg, fish, and shellfish.[31] The body can store a total of 2 to 5 mg of vitamin B_{12}; thus, it takes 2 to 5 years to develop vitamin B_{12} deficiency from malabsorption and can take as long as 20 years to develop vitamin B_{12} deficiency from vegetarianism.[32] However, by chemically inactivating vitamin B_{12}, N_2O causes a rapid functional deficiency, as was seen in our patient.

Clinical Point

By chemically inactivating vitamin B_{12}, N_2O causes a rapid functional deficiency

OUTCOME Improved insight

At a 1-week follow-up appointment with a psychiatrist, Mr. M has no evident psychotic symptoms. He reports that he has not used *Cannabis* or N_2O, and he discontinues olanzapine following this visit. Two weeks later, Mr. M shows no psychotic or affective symptoms other than grief, which is appropriately expressed. His insight has improved. He commits to not using *Cannabis*, N_2O, or any other illicit substances. Mr. M is referred back to his long-standing primary care provider with the understanding that if any psychiatric symptoms recur he will see a psychiatrist again.

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Bottom Line

When consumed for recreational purposes, nitrous oxide (N_2O) can rapidly cause vitamin B_{12} deficiency. N_2O can precipitate a broad array of psychiatric symptoms, including psychotic syndromes, and although rare, psychosis related to vitamin B_{12} deficiency has been reported as the sole manifestation of illness, without associated neurologic or hematologic symptoms.

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Clinical Point

Screen for vitamin B_{12} levels in psychiatric patients at risk for deficiency, including older adults, vegetarians, and those with alimentary disorders