Provide diagnostic strategies using biochemical markers (e.g., elevated homocysteine, methylmalonic acid).

# Recognizing Nitrous Oxide Toxicity: Key Neuropsychiatric symptoms and Diagnostic Clues

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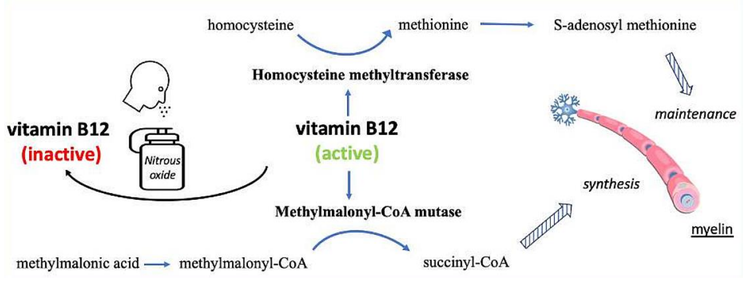
## Objectives

1. Describe nitrous oxide ($N_2O$) mechanism of action
2. Identify key laboratory that may indicate chronic $N_2O$ use if substance use is not initially disclosed
3. Review management of $N_2O$ toxicity
4. Raise awareness among healthcare professionals regarding the risks of $N_2O$ misuse and its potential for long-term disability

## Introduction

- **Background:**
  - $N_2O$ is an inhaled gas used in anesthesia but is also used recreationally for euphoria
  - Nicknamed “whippits,” $N_2O$ is available in 8g, 640g, and 2000g cannisters
- **Mechanism of toxicity:** With chronic use, $N_2O$ inactivates vitamin B12 → causing functional and then absolute B12 deficiency --> megaloblastic anemia and nerve demyelination
- **Symptoms:** Neuropathy, ataxia, cognitive decline, and hallucinations
- **Prevalence**: Lifetime U.S. prevalence is 4–5%.
- **Challenges**: $N_2O$ is undetectable on routine drug screens, and self-supplementation can mask deficiency.
- **Key lab values**: Elevated homocysteine and methylmalonic acid (MMA) are key markers of functional B12 deficiency
- **Key imaging:** CT imaging of the brain can show chronic anoxic damage, MRI can show subacute combined degeneration of the spinal cord




Vitamin B12 as a cofactor in multiple enzymatic reactions. $N_2O$ toxicity leads to disrupted B12 metabolic functions.

## Case Description

*Patients seen and treated by University of Virginia Toxicology for B12 deficiency secondary to chronic $N_2O$ use. Patients were followed outpatient by both Toxicology and Psychiatry*

**Case One:**
A 48-year-old male was hospitalized in May 2020 after being found unconscious, surrounded by hundreds of $N_2O$ canisters. He presented with excessive drowsiness, confusion, bilateral lower extremity numbness, weakness, ataxia, and delusions. He was noted to be reaching into the air, attempting to grasp imaginary objects.
Laboratory tests revealed:
- Elevated vitamin B12 levels (due to self-supplementation),
- Elevated homocysteine levels
- Normal methylmalonic acid.

An MRI of the brain exhibited cortical atrophy markedly greater than expected for his age. The patient admitted to using up to 1200 whippits daily. Despite B12 supplementation and reported abstinence from $N_2O$, his condition worsened. Three months post-hospitalization, he experienced persistent ataxia and significant short-term memory deficits. By September 2022, he remained unable to return to work.

**Case Two:**
A 40-year-old male was hospitalized in February 2024 with ataxia, recurrent falls, confusion, bilateral numbness and weakness in the lower extremities and hands, and memory loss.
Laboratory tests revealed:
- Low vitamin B12 levels,
- Elevated homocysteine,
- Elevated methylmalonic acid.

The patient reported escalating use to 12–18 canisters daily since starting to use $N_2O$ the summer of 2023. Notably, he had been hospitalized in December 2023 for a pulmonary embolism, likely related to elevated homocysteine levels, which is a risk factor for thrombosis development, from $N_2O$ use. Treatment included intramuscular B12 injections followed by oral supplementation with some improvement. By May 2024 he returned to work despite persistent weakness.

**Case Three:**
A 49-year-old male presented in September 2024 with three weeks of confusion, difficulty completing sentences, and visual hallucinations, including objects appearing to pulsate or crawl up walls. He reported extreme anxiety accompanied by auditory hallucinations of indecipherable whispers.
Medical history included heavy tianeptine use, recent buprenorphine/naloxone taper, and kratom use.
Initial tests revealed:
- Cortical volume loss greater than expected for his age,
- Low vitamin B12
- Elevated homocysteine and methylmalonic acid.

Despite initial denial, he later admitted to heavy $N_2O$ use over six months. Treatment involved B12 supplementation, thiamine, sertraline for mood, and gabapentin. He declined methionine supplementation. By October 2024, he experienced significant motor and cognitive improvements and was able to return to work.

## CONCLUSION

- These cases collectively highlight the often underrecognized but serious neuropsychiatric and functional consequences of chronic nitrous oxide ($N_2O$) use.
- Beyond isolated vitamin B12 deficiency, $N_2O$ misuse disrupts essential neurochemical and neurotrophic pathways, leading to persistent psychiatric symptoms, sensorimotor deficits, and cognitive dysfunction.
- Diagnostic delays are common, especially when use is undisclosed, emphasizing the importance of clinical suspicion in patients with unexplained neuropsychiatric presentations and low B12 levels.
- While vitamin B12 supplementation may offer partial recovery, ongoing use undermines treatment efforts. Early identification, patient education, and harm-reduction strategies are essential to prevent long-term morbidity in this emerging public health issue.

### Implications for Practice

- **Screen for $N_2O$ use** in patients with unexplained neuropsychiatric or hematologic findings, especially when B12 is low or borderline.
- **Do not rely on B12 levels alone**—functional B12 deficiency may exist despite normal serum levels.
- **Include $N_2O$ use in differential diagnoses** of myelopathy, peripheral neuropathy, and new-onset psychiatric symptoms.
- **Multidisciplinary management** needed for optimal recovery.

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