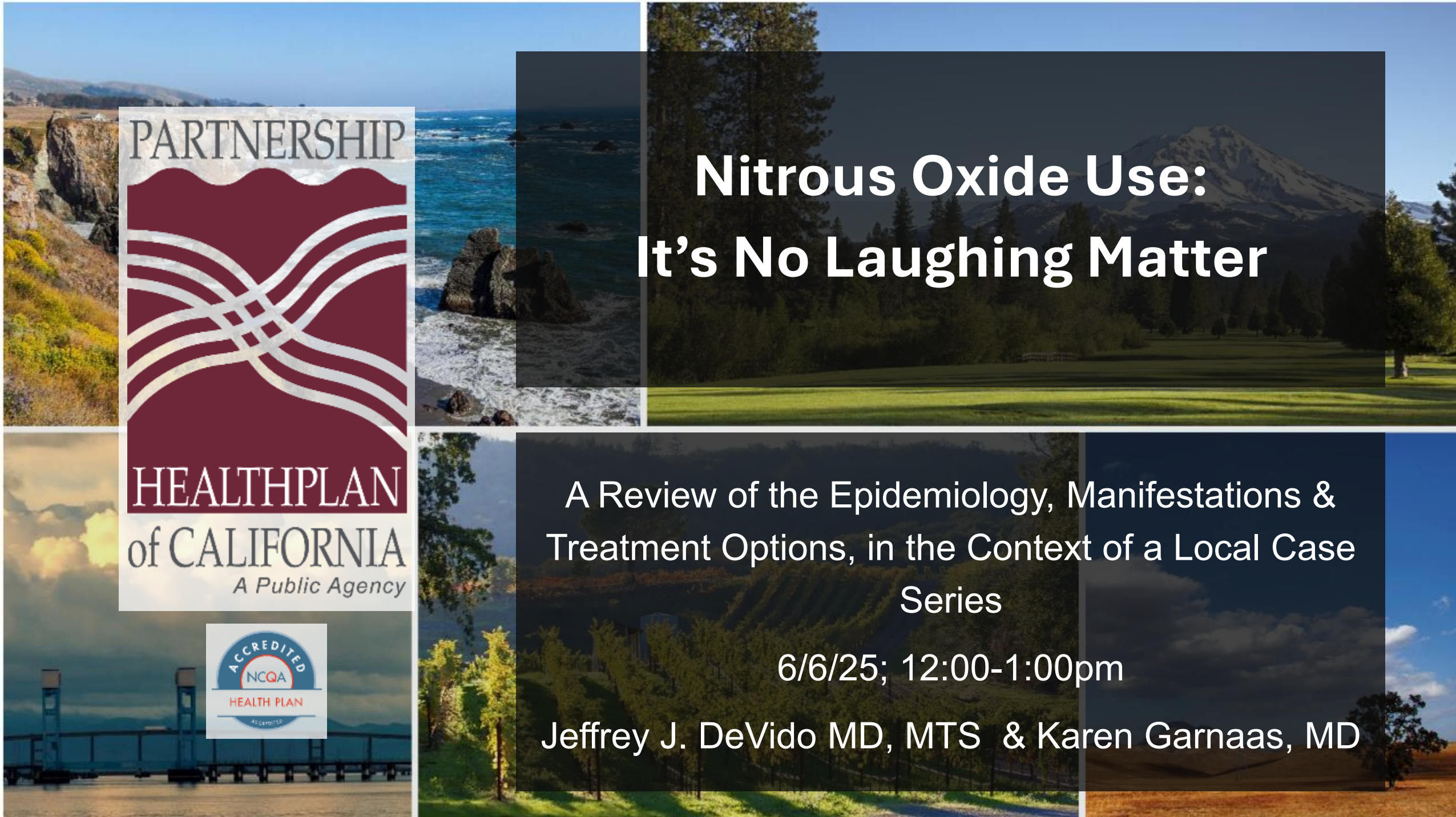


Nitrous Oxide Use: It's No Laughing Matter

A Review of the Epidemiology, Manifestations & Treatment Options, in the Context of a Local Case Series

6/6/25; 12:00-1:00pm

Jeffrey J. DeVido MD, MTS & Karen Garnaas, MD

Jeffrey DeVido, MD, MTS

- Behavioral Health Clinical Director, Partnership HealthPlan of California
- Chief, Addiction Services, Marin County HHS
- Assistant Clinical Professor—Volunteer, Dept of Psychiatry and Behavioral Sciences, Weil Institute for Neurosciences & University of California, San Francisco
- Disclosures: No financial disclosures relevant to this talk. Equity shareholder Phillip Morris/Altria/Merck. The opinions expressed herein are my own and do not reflect the opinions of my employing agencies/institutions.

CATALYST
NEUROMEDICAL CENTER

Karen Garnaas, MD

- Board Certified Adult Neurologist with Neuromuscular Fellowship training
  - Career focused on addressing healthcare inequity of access in rural America
  - 30 year career practicing in North Dakota, South Dakota and now Northern California
  - Various academic appointments as clinical teaching faculty member
- Founder of Catalyst Neuromedical Center, Redding CA
  - Serving the Northstate with Outpatient neurologic care since 2020
  - Large geographic catchment area of over 700,000 patients

- Disclosures: No financial disclosures relevant to this talk.

Partnership: Who we are

Mission:

To help our members, and the communities we serve, be healthy

Vision:

To be the most highly regarded managed care plan in California

About Us:

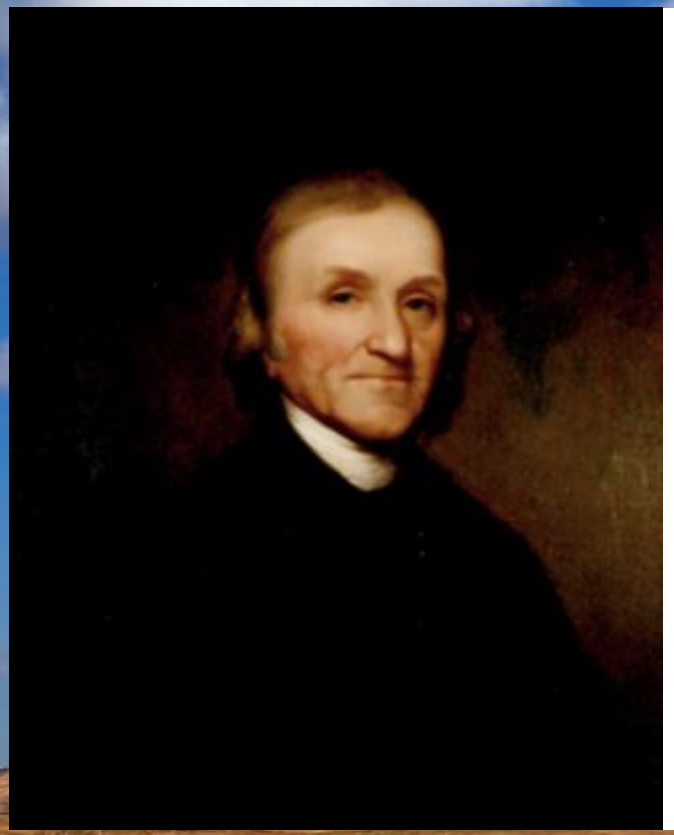
Non-profit community-based health care organization

Beginning in Solano Co in 1994, now 24 counties in NorCal

Objectives

- History & Epidemiology (industrial and recreational use)
- Pharmacology of action
- Clinical manifestations of use
- Detection/diagnosis approach
- Treatment and management considerations
- Bringing it all together: a local case series

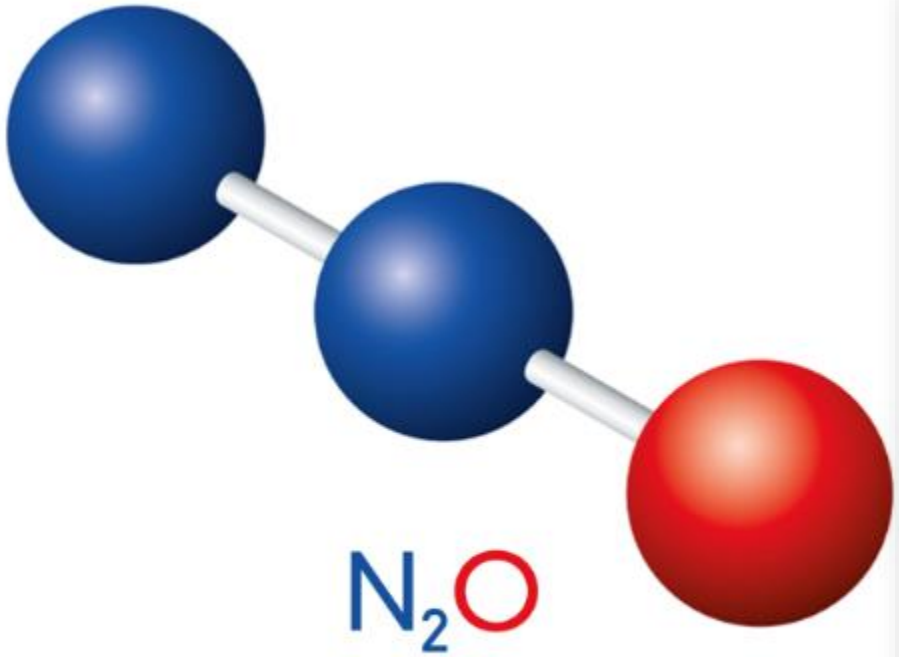
What is Nitrous Oxide?



- Joseph Priestly—1772 “Phlogisticated Nitrous Air”
- Horace Wells—1844 First dental extraction using N2O
  - But public demonstration went… er… BAD
  - Ether demonstrated the next year
- By 1930s, commonly used in dentistry and labour anesthesia

Lew, V., et al, Past, Present, and Future of Nitrous Oxide. British Medical Bulletin, 2018, 125:103–119

Industrial and Medical Uses of Nitrous Oxide



Nitrous oxide

- Gas at room temperature
- Relatively impotent as anesthetic, requiring concentrations 15-20%
- Unlike other vaporous anesthetics, it is more analgesic
- Highly lipophilic, more dissolvable in water than oxygen, crosses BBB rapidly but doesn't dissolve in tissue→rapid off
- Blocks post-synaptic NMDA and AMPA-Kainate subtype Glutamate receptors; $GABA_A$ receptor agonism
- May also cause transient hypoxia

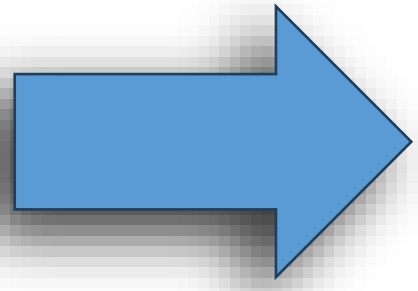
Lew, V., et al, Past, Present, and Future of Nitrous Oxide. British Medical Bulletin, 2018, 125:103–119

Industrial and Medical Uses of Nitrous Oxide

- WHO List of Essential Medications
- Oxidizer in rocket propellants, and motor racing fuels
- Greenhouse gas (increasing)
  - Agriculture→nitrogen fertilizers converted by micro-organisms
- Aerosol propellant for foods

Subanesthetic Acute Effects

- Intoxication
- Euphoria/dysphoria
- Spatial disorientation
- Temporal disorientation
- Reduced pain sensitivity



Often only for a minute or two = repeated use

- Analgesia
- Anxiolysis

Jay M (1 September 2008). "Nitrous oxide: recreational use, regulation and harm reduction". *Drugs and Alcohol Today*. **8**(3): 22–25

Subanesthetic Acute Effects

- Respiratory irritation
- Pneumomediastinum
- Interstitial emphysema
- Rarely will it cause acute death via asphyxiation→esp if not in open space

Jay M (1 September 2008). "Nitrous oxide: recreational use, regulation and harm reduction". *Drugs and Alcohol Today*. **8**(3): 22–25

As a Treatment for Depression?

Newsweek

New study may have found a fast depression treatment, but experts urge caution

A new study may have found a fast-acting treatment for depression, but experts say there is reason for concern.

By Thomas Westerholm

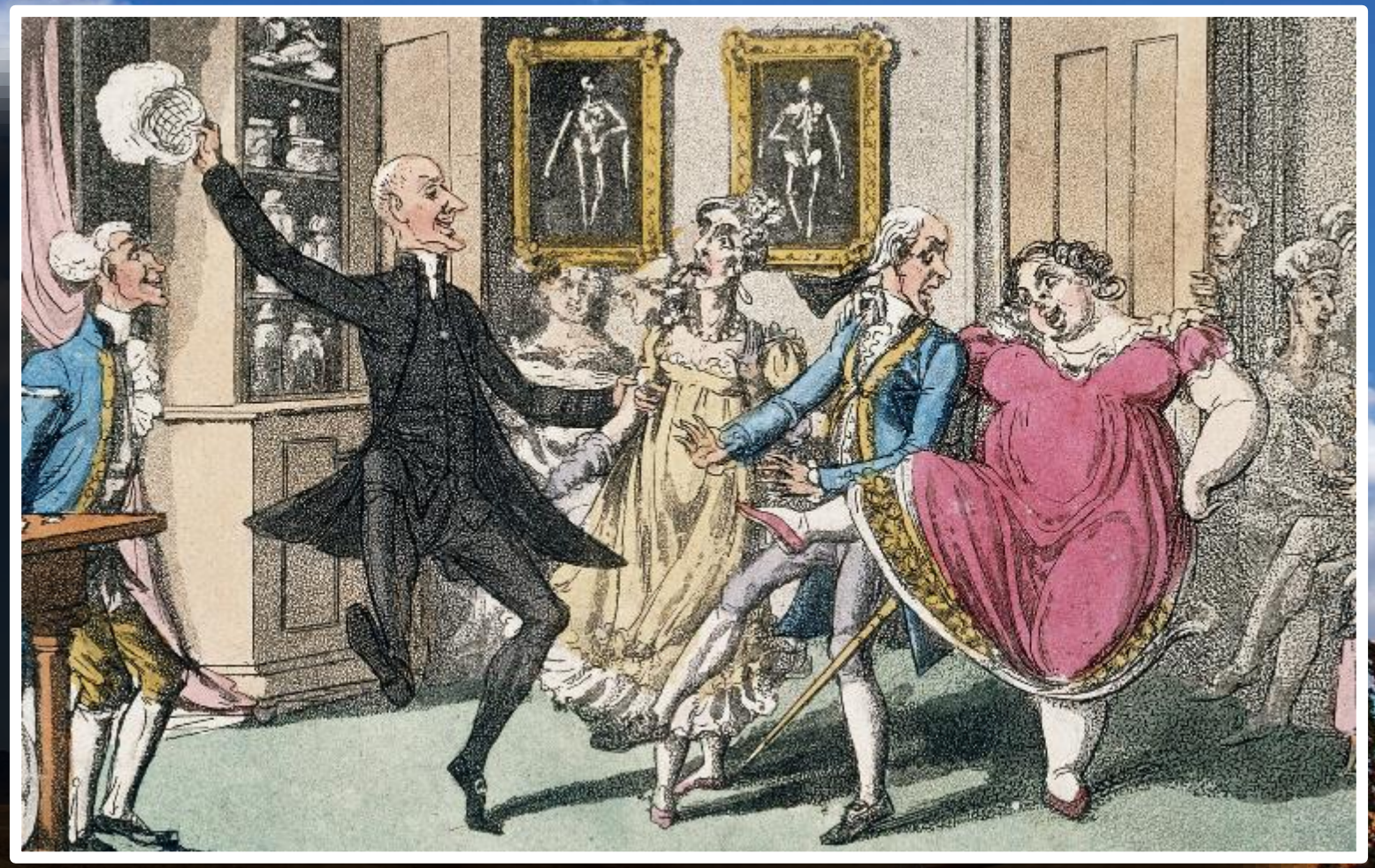
Published April 7, 2025

A new study might have found a fast-acting treatment for depression, but experts have urged caution regarding the treatment.

- In "Stressed" Mice
- Increased activity shown in prefrontal layer 5 (L5) pyramidal neurons (underactive in depression)→persists after acute phase
- SK2 potassium channel blockade (not NMDA-related)
- Prior human studies have shown some antidepressant effects, too

Cichon, J., Joseph, T.T., Lu, X. *et al.* Nitrous oxide activates layer 5 prefrontal neurons via SK2 channel inhibition for antidepressant effect. *Nat Commun* **16**, 2999 (2025).

How is Nitrous Oxide Misused?



Doctor and Mrs Syntax, with a party of friends, experimenting with laughing gas. Coloured aquatint by T. Rowlandson after W. Combe. Avaiable on: https://commons.wikimedia.org/wiki/File:Doctor_and_Mrs_Syntax,_with_a_party_of_friends,_experimentin_Wellcome_L0022227.jpg

How e Misused?

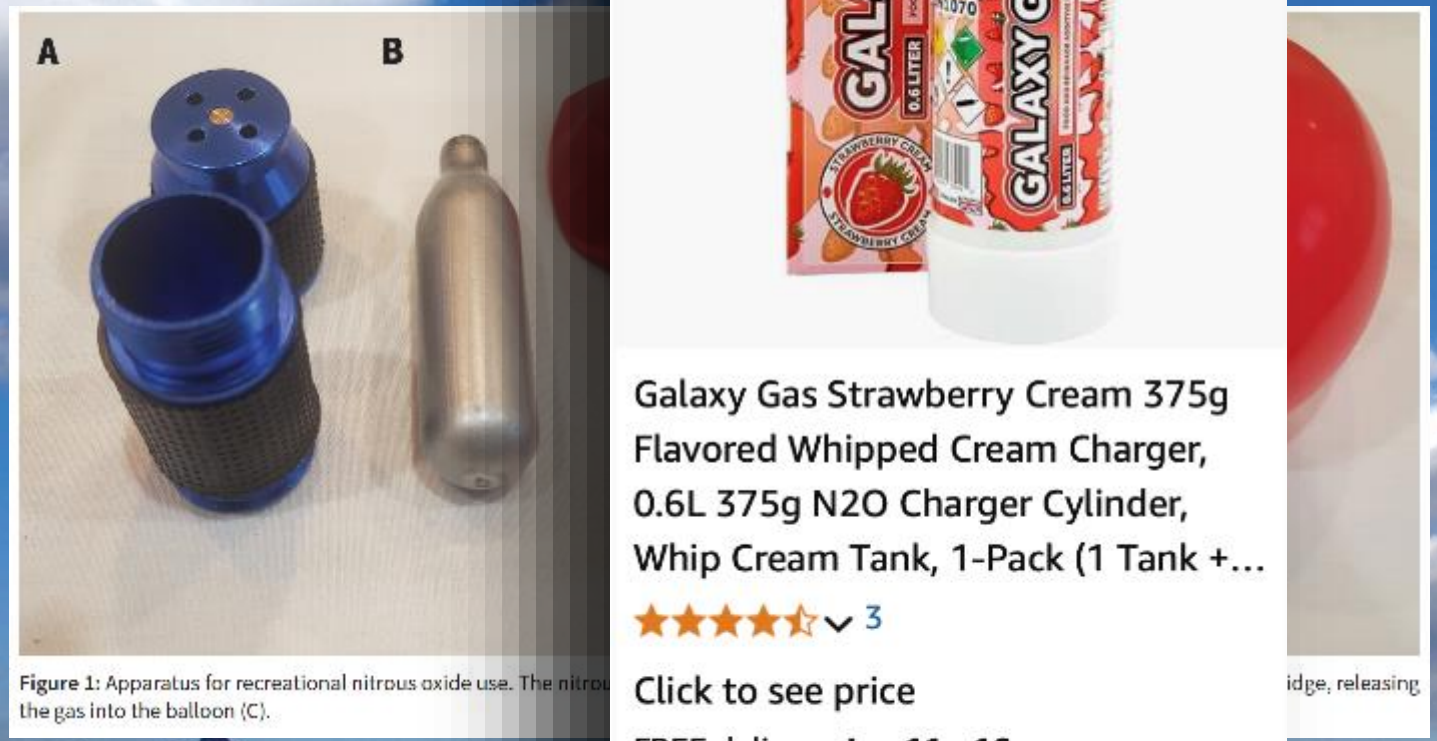


Figure 1: Apparatus for recreational nitrous oxide use. The nitrou… the gas into the balloon (C).

idge, releasing

Galaxy Gas Strawberry Cream 375g Flavored Whipped Cream Charger, 0.6L 375g N2O Charger Cylinder, Whip Cream Tank, 1-Pack (1 Tank +…

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$145.99

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De Halleux, C. Diagnosis and manag… the recreational use of nitrous oxide. CMAJ 2023 August 21;195:E1075-81.

How is Nitrous Oxide Misused?

"Nitrous"

"Hippie Crack"

"Whippets"

"Laughing Gas"

"Nitro"

Back, S., et al. Does nitrous oxide addiction exist? An evaluation of theevidence for the presence and prevalence of substance use disorder symptoms in recreational nitrous oxide users. Addiction. 2024;119:609–618.

Epidemiology of Nitrous Oxide Use

- Not a lot is known for certain
- Use of inhalants, in general, peaks around 13-14 years old, but N_2O use seems to peak in early adulthood
- No toxicology screens/hard to detect
- Prevalence:
  - Increasing over the last 20 years, globally
  - The Global Drug Survey estimated lifetime prevalence to be 23%
  - Last year prevalence doubling from 6.5% to 11.9% between 2014 and 2019

Back, S., et al. Does nitrous oxide addiction exist? An evaluation of theevidence for the presence and prevalence of substance use disorder symptoms in recreational nitrous oxide users. Addiction. 2024;119:609–618.

Epidemiology of Nitrous Oxide Use

- 2023 UK Review
  - East London→Bangladeshi
  - Netherlands→Moroccan-Dutch
  - Australia→University students

  - In clinical practice, average of 580 cannisters/week for folks who report to hospital with sxs
  - Pre-existing B12 deficiency = more susceptible to much lower doses of N_2O

Paris A, Lake L, Joseph A, Workman A, Walton J, Hayton T, Evangelou N, Lilleker JB, Ayling RM, Nicholl D, Noyce AJ. Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment. Pract Neurol. 2023 Jun;23(3):222-228.

Chronic Use of N_2O

- Psychosis
- Mood disorders
- Vitamin B12 Megaloblastic Anemia
- Peripheral Neuropathy
- Thrombotic events
- Asphyxiation = death

77% of chronic users not aware of negative physiological and psychiatric potential consequences

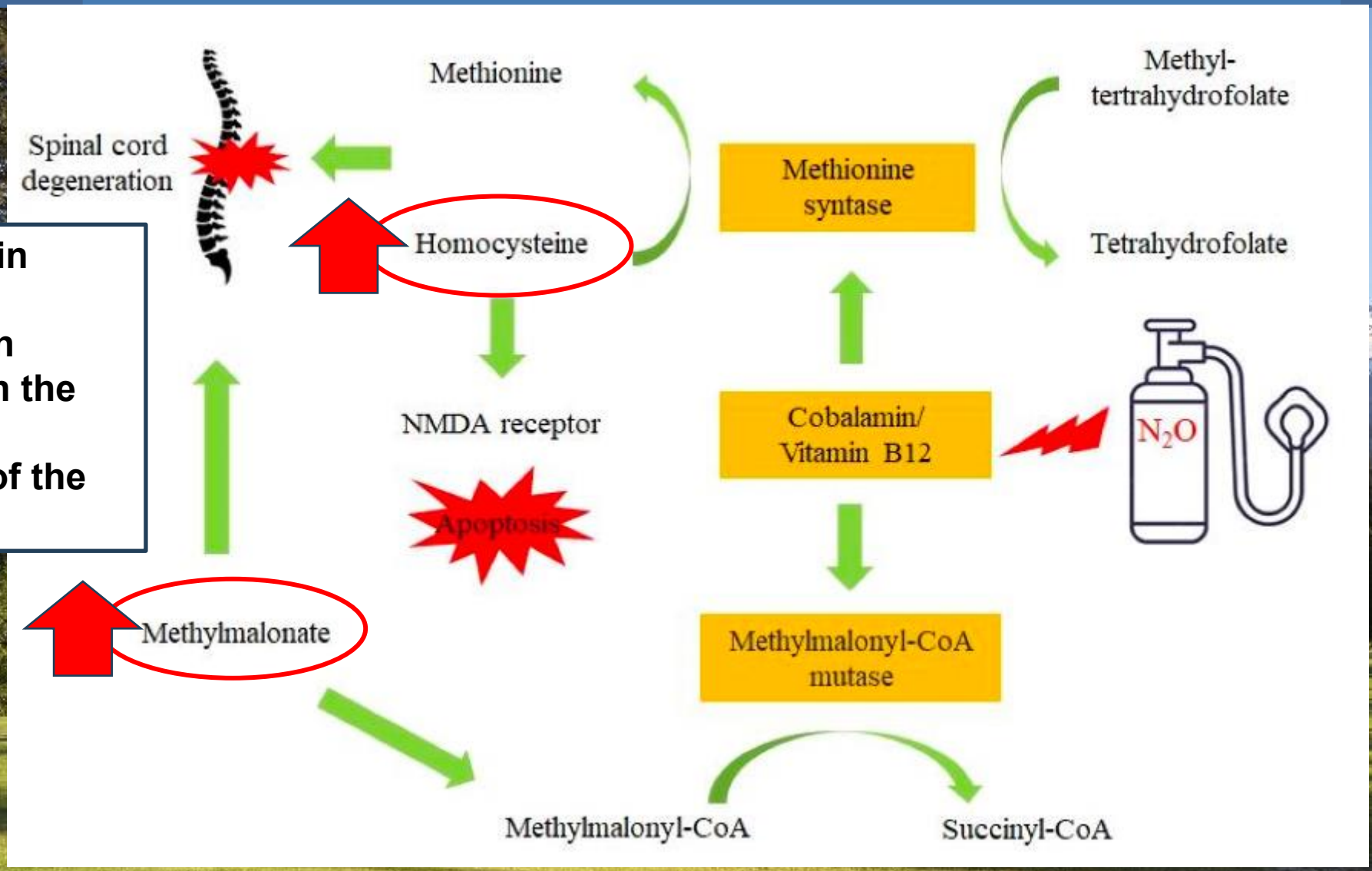
Chronic Use of N_2O

- Nitrous oxide-Induced Subacute Combined Degeneration of the Cord (N_2O-SACD)
  - First described 1978: 14 Dental Practitioners
  - Tied to B12 inactivation
  - Symptoms develop over several days to 6 months
  - Typical starts with distal parasthesias
  - Gait ataxia (worse in low lighting)/Falls/Inability to walk
  - Hypercoagulable state (hyperhomocysteinaemia)
  - Less common:
    - Impotence or other sexual dysfunction, bladder incontinence and/or urgency, weakness

Paris A, Lake L, Joseph A, Workman A, Walton J, Hayton T, Evangelou N, Lilleker JB, Ayling RM, Nicholl D, Noyce AJ. Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment. Pract Neurol. 2023 Jun;23(3):222-228.

Chronic Use of N_2O

DNA/RNA/protein methylation by methionine is an essential step in the production of phospholipids of the myelin sheath



Brunt, TM., et al. Mechanisms Involved in the Neurotoxicity and Abuse Liability of Nitrous Oxide: A Narrative Review. Int. J. Mol. Sci. 2022, 23, 14747

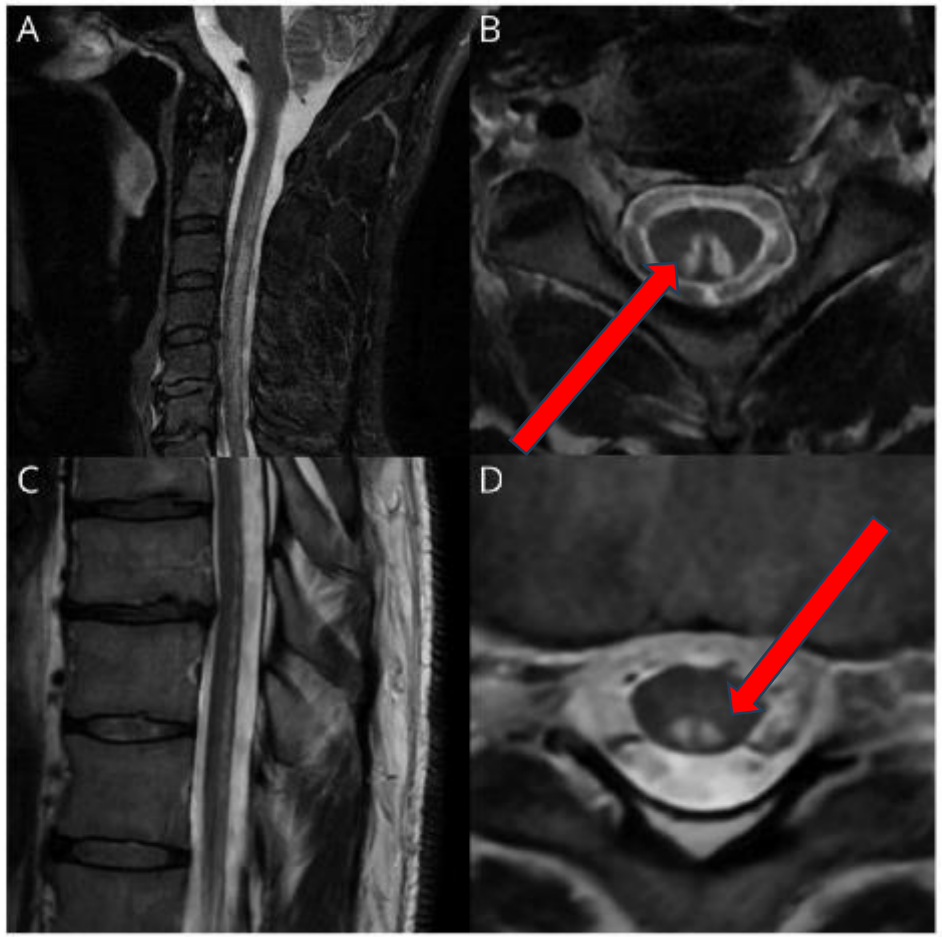
Chronic Use of N_2O

- Ask about:
  - Crohn's/Celiac
  - Diet
  - Bariatric surgery
  - Bowel resections
  - Meds: gastric acid suppressants, metformin, potassium supplements, OCPs

Paris A, Lake L, Joseph A, Workman A, Walton J, Hayton T, Evangelou N, Lilleker JB, Ayling RM, Nicholl D, Noyce AJ. Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment. Pract Neurol. 2023 Jun;23(3):222-228.

Chronic Use of N_2O

Figure MRI of the Cervical and Thoracic Spine, With Sagittal and Axial T2-Weighted Imaging Showing Longitudinal Hyperintensity Throughout the Dorsal Columns



- B12: >2,000 pg/mL (nl=232-1245)
- MethylImalonic acid level normal
- Homocysteine 84umol/L (nl=0-14)
- Wide based gait
- Decreased light tough, pinprick, vibration and proprioception
- Increased LE DTRs w/o spasticity or clonus

DiPane, J. Nitrous Oxide Toxicity With Subsequent Recovery. Neurology: 2023;101:674-675.

Summary of Potential Impacts of N_2O Use

Table 1: Complications of recreational nitrous oxide use

Type of complication	Clinical consequences
Acute	Altered cognition Hypoxemia Death by asphyxia (rare) Cold-related injury: e.g., mouth, hands
Chronic	Peripheral neuropathy • Bilateral paresthesia and weakness, gait disturbances, hyporeflexia Myelopathy (subacute combined degeneration) • Bilateral numbness, weakness, gait disturbances, hyperreflexia, urinary retention, incontinence Encephalopathy (rare) • Behavioural changes, paranoia, delusions, hallucinations and other psychiatric symptoms Anemia Skin hyperpigmentation (rare) Thrombosis (rare)

De Halleux, C. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. CMAJ 2023 August 21;195:E1075-81.

Detection/Diagnosis

Table 2: Investigations for patients suspected of having nitrous oxide toxicity

Investigation type	Finding
Vitamin B_{12}	Low (50%–75%) or normal (25%–50%) in patients with neurologic symptoms
Homocysteine	Increased
Methylmalonic acid	Increased
MRI spine	If myelopathy is present: hyperintensities in T_2, often at the C3–C4 with caudal extension in severe cases
Nerve conduction studies	Abnormal in most patient with symptoms • Axonal degeneration with or without demyelination (common) • Isolated demyelination without axonal degeneration (rare)

Note: MRI = magnetic resonance imaging.

- In differential: anyone with peripheral neuropathy, myelopathy, encephalopathy, esp if young
- h/o N_2O exposure
- Labs
- MRI
- Nerve conduction studies

De Halleux, C. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. CMAJ 2023 August 21;195:E1075-81.

Treatment

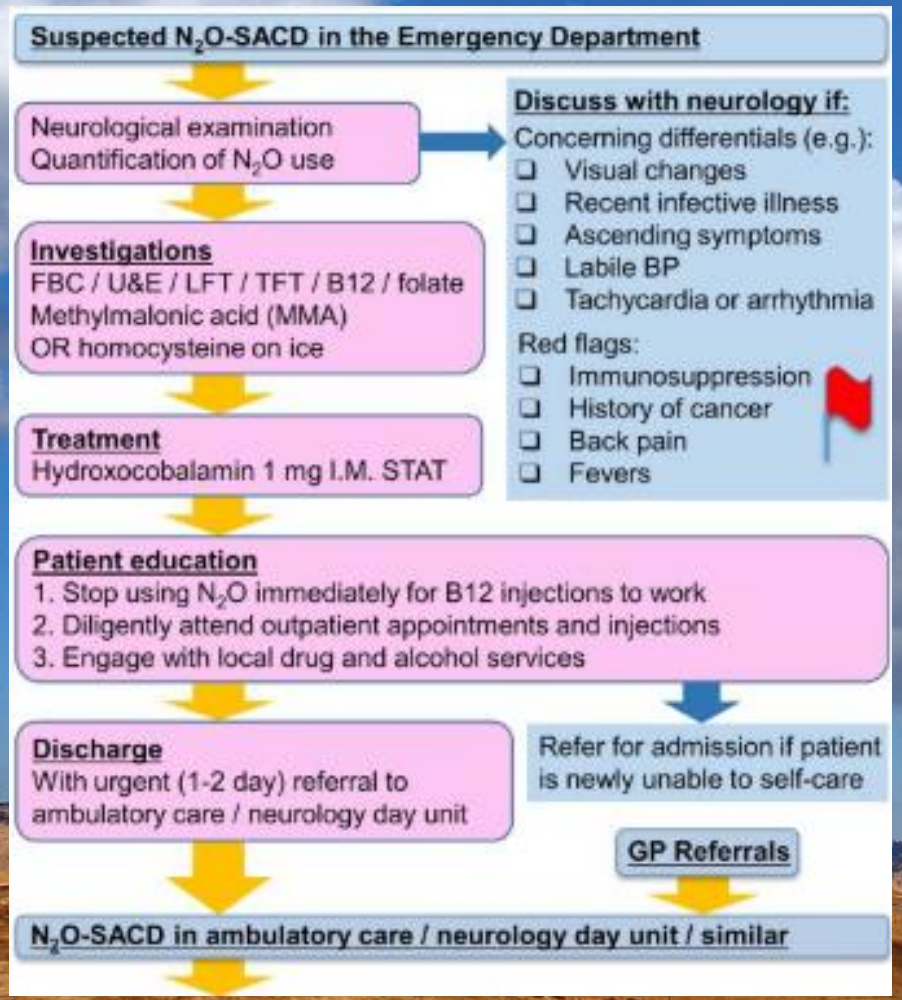
- No official guidelines
- Cessation of N_2O use
- B12 Supplementation
  - Varies, but one approach = IM B12 1000ug daily or every other day x 1 week, then once a week x 4-8 weeks, then monthly thereafter
  - Or, oral 1000-2000ug daily until sxs resolve
- Some authors posit oral methionine as helpful as well

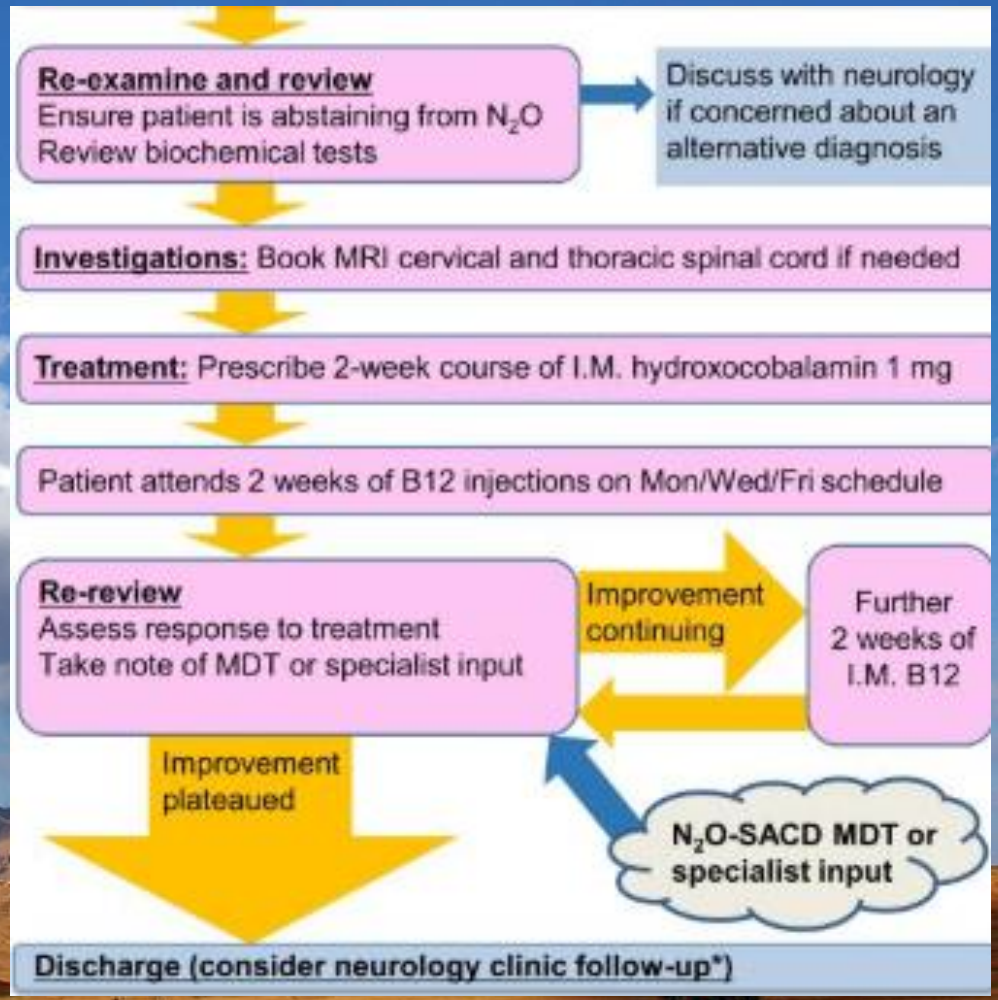
- Reticulocyte count comes back in one week
- Megaloblastic anemia resolves in 6-8 weeks
- Most neurologic symptoms and lesions will disappear in time, but not for everyone
- 98% see some improvement, 1/3rd with residual sxs

De Halleux, C. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. CMAJ 2023 August 21;195:E1075-81.

Xiang, Y., et al. Recreational Nitrous Oxide Abuse: Prevalence, Neurotoxicity, and Treatment. Neurotoxicity Research (2021) 39:975–985

One Approach…





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Regulation of N_2O

- Federal:
  - Food, Drug and Cosmetic Act→possession is legal and can be sold for culinary and medical reasons, but it cannot be marketed for the purpose of producing a high
- State:
  - Michigan (2024): criminalizes sale for non-medical, non-culinary purposes
  - Louisiana: outright ban on recreational sales
  - California: misdemeanor (6mos in jail) to possess with intent to inhale to get high; illegal to sell to anyone under 18

First Case: July 2024

- 56-year-old male prior history of polysubstance abuse including alcohol, prediabetes with underlying progressive neuropathy despite being clean and sober > 1 year
  - Small fiber sensory PN with evolving hyperreflexia and Babinski's
  - Normal B12/folate but homocysteine >171
- Discovered to be using 3-4 large canisters/week of Nitrous Oxide to manage his pain, anxiety and lack of detectability
  - B12 deficiency masked by oral B12 supplemation
- Neurologic deficits persisted but homocysteine normalized and DTR's improved w/cessation

Case series of 6 patients with NO-induced Subacute Degeneration of the Spinal Cord Shasta Co 2024

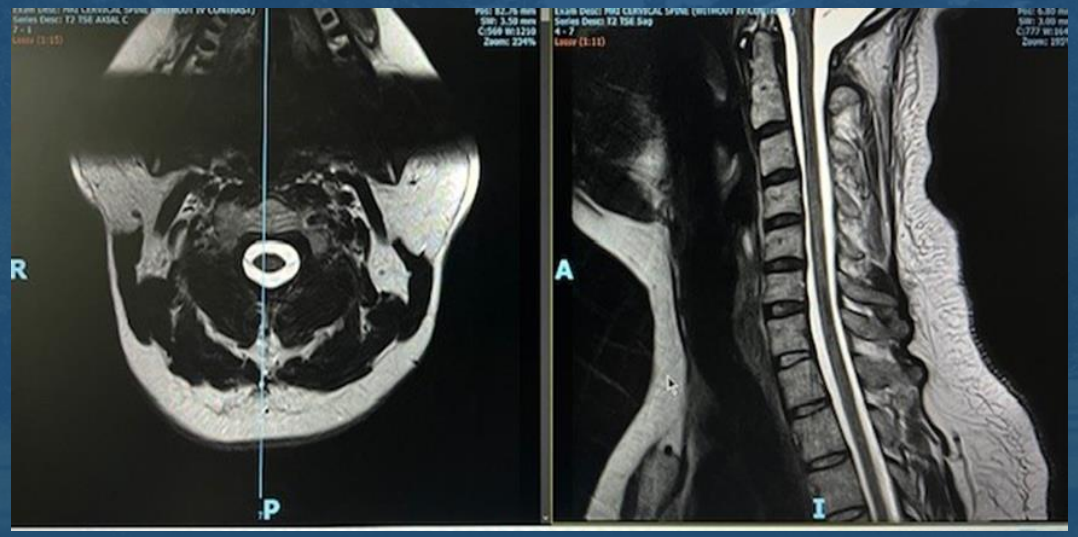
- 6 patients presented to my outpatient neurology practice over 2 month interval
- Ages 26-38 years
- 5 male, 2 female
- All had initially presented with subacute progressive ascending paresthesias, weakness and ataxia
  - None had cognitive complaints
  - All had stocking sensory loss and gait ataxia
  - Some loss of DTR's, misinterpreted as GBS
  - Others hyperreflexia, Babinski's
  - 2 had profound bilateral foot drop (also alcoholics)

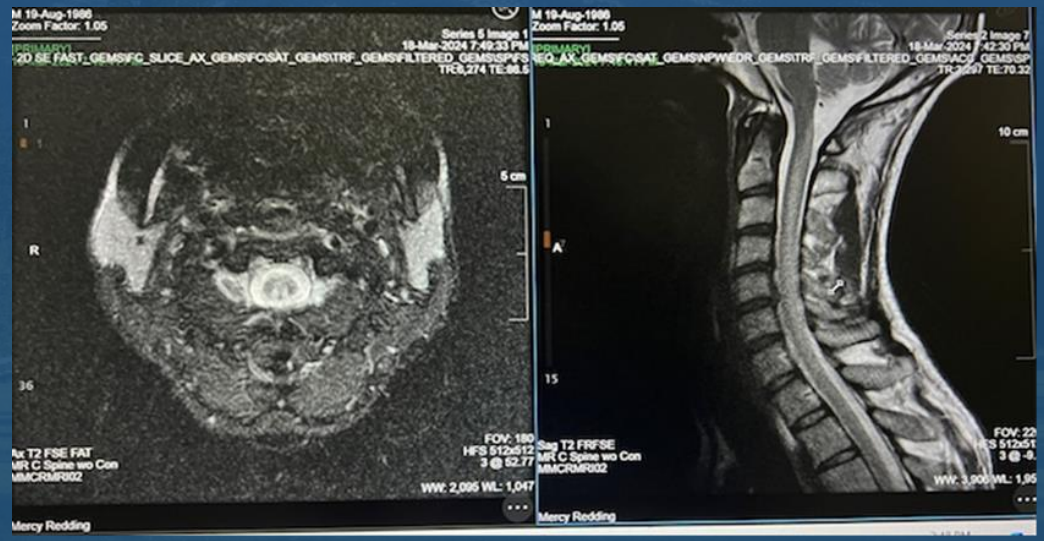
Clues for diagnosis

- Vitamin B12 levels at presentation
  - Very low levels ranging from 109-193 (5 pts<150)
  - 1 patient didn't have low B12 but MCV >117
  - Macrocytosis
- All patients had history of some form of substance abuse
  - 4 alcohol, 3 cocaine, 2 cannabis, 1 polysubstance
- Those with coexistent alcohol abuse had the most profound weakness
- NONE had volunteered that they were using nitrous until specifically asked.
- Duration of use ranged from 3 weeks to 6 months

MRI findings

- **5/6 had MRI studies**
- **ALL (not all reported by radiology) had faint signal in C spine and classic inverted V sign as seen with combined subacute degeneration**
- **2 patients demonstrated faint enhancement**





R. Dabby et al NO-induced myeloneuropathy Due to Recreational Abuse, Isr Med Assoc 2024 May: 26(5):294-298

Other diagnostic studies

- **EMG/NCS performed in 4/6 patients**
  - **3 had evidence of an axonal predominant, length dependent peripheral neuropathy**
  - **1 had evidence of additional polyradicular features consistent with a polyradiculoneuropathy**

- **CSF available on 4/6 patients**
  - **ALL had elevated CSF protein**
  - **None had positive oligoclonal bands**
  - **1 patient with enhancement of C spinal cord also had AQP4 antibodies checked, which were negative**

Qin, Acute Nitrous oxide-induced neuropathy mimicking Guillian Barre Syndrom, J Peripheral Nervous System 2022
Fortanier et al, How to distinguish GBS from Nitrous Oxide-induced neuropathy, Eur Jof Neurology 2023

Treatment and Outcome

- **Inpatient:**
  - 2 had been treated with full course of IVIG for presumed Guillian Barre Syndrome
  - 2 had been treated with IV Solumedrol for cervical myelitis
  - As their B12 levels came in, started parenteral B12 variable protocol
- **Outpatient:**
  - Many lost to followup with variable compliance with B12 supplementation and abstinence of nitrous use
  - Limited education and understanding of dangers
- **Outcome:**
  - All patients presenting to my clinic months later had persistent paresthesias, gait ataxia
  - Some profound distal weakness requiring AFO's, cane, walker

Take aways

- Recreational Nitrous Oxide use is an increasing epidemic in our substance abuse culture with devastating long-term effects on one's nervous system
- Specifically think about and ask about use in all patients with substance abuse history and presentation of paresthesias, ataxia particularly think of it in subacute presentations
- Educate your patients as to the dangers of nitrous use and how supplementation alone doesn't protect
- Increase suspicion/detection of Vitamin B12 deficiency, with macrocytosis and checking MMA and Homocysteine
- Early detection and treatment is critical. Consider starting IM B12 while waiting for results
- More intentional education and close follow up is required to ensure compliance with supplementation and abstinence

Paris A, NO induced subacute combined degeneration of the cord: dx and treatment Pract Neurology 2023 Feb 22;23(3):222-228

Questions