

# Inhaled Nitrous Oxide ‘Whip-Its!’ Causing Subacute Combined Degeneration of Spinal Cord

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**Abstract** The opioid prescription drug epidemic is not the only challenging drug abuse that the United States is facing. Over the past decade, the prevalence of another substance of abuse has dramatically increased that is nitrous oxide, also known as ‘Whip-its’. As per the Substance Abuse and Mental Health Administration, there were twelve million users reported in 2012. Whip-its has become a popular trend among teenagers and young adults, as it is easily accessible. ‘Whip-Its!’ canisters containing nitrous oxide are available for purchase at grocery stores, on the internet, and various retailers without any age limit, warning or regulations. Reported cases of ‘Whip-its’ use have been linked to loss of consciousness, anoxic brain injury, cardiac arrest, and death. Yet, another result of chronic nitrous oxide abuse is that of spinal cord myelopathy due to vitamin B 12 deficiency. In this report we present a case of a 22-year-old male with daily abuse of inhaled nitrous oxide in the form of ‘Whip-its’, who presented with initial symptoms of presumed drug induced psychosis and gradually developed neurological focal deficits, and findings of sensorimotor peripheral neuropathy with myelopathy of the cervical spine and vitamin B12 deficiency.

**Keywords:** *substance abuse, whip-its, subacute combined degeneration of spinal cord*

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## 1. Introduction

While much attention has been given to the opioid prescription drug epidemic, this is not the only challenge in terms of drug abuse that United States is facing; Abuse of nitrous oxide also known as ‘Whip-its’ has emerged as another epidemic over the past decade. As per the Substance Abuse and Mental Health Administration, there were a reported twelve million users 2012 and it has become a popular trend among teenagers and young adults largely because of easy access. ‘Whip-its’ are sold as canisters containing nitrous oxide and are available for purchase at grocery stores, on the internet, and other various retailers without any age limit, warning or regulations. Reported cases of ‘Whip-its’ abuse have been linked to loss of consciousness, anoxic brain injury, cardiac arrest, and death. Yet, another result of chronic nitrous oxide abuse is that of spinal cord myelopathy due to vitamin B 12 deficiency. Here we present a case of a 22-year-old man with daily abuse of inhaled nitrous oxide in the form of ‘Whip-its’, who presented with initial symptoms

of presumed drug induced psychosis and gradually developed neurological focal deficits, and findings of sensorimotor peripheral neuropathy with myelopathy of the cervical spine and vitamin B12 deficiency.

## 2. Report of the Case

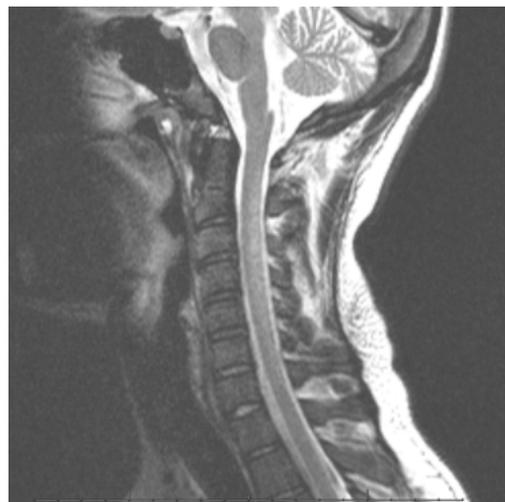
Our patient was a 22-year-old male with no past medical history who began recreational inhalational use of nitrous oxide 4 months prior to presentation. Within the first week of starting the drug, his use quickly escalated to one hundred 8-ounce canisters daily. The craving for a ‘relaxed and happy’ euphoric sensation, which he felt the drug provided fueled his continued use, eventually becoming a dependency. The patient presented to our emergency department with complaints of fornication after a fight with his wife and mother. He had otherwise no abnormal neurological or other physical findings. Urine toxicology screening (amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, and oxycodone) and blood alcohol were negative. He denied use of tobacco or other substance abuse.

Initially the patient was brought into the emergency department with complaints of a three day history of formication and was admitted to the psychiatry service for twenty-four hours. Over the subsequent two days, he developed mild lower limb weakness, and progressive unsteady gait with worsening sensory deficits. The patient was transferred to the medical service for further evaluation. Clinical examination revealed decreased sensation to sharp and light touch in a glove and stocking distribution (Lower Limb > Upper Limb), impaired proprioception and coordination, upper limb weakness +4/5 bilaterally, lower limb weakness 3/5 bilaterally with hypertonicity and hyperreflexia 3+, very unsteady gait, scissoring posture and urinary retention. Upon admission, a texas catheter was placed, with no output noted in the first 12 hours. After the insertion of a foley catheter an output of 1800 ml amber urine was obtained. The initial CT brain showed no hydrocephalus, no cerebral or cerebellar edema; no evidence of intra-or extra-axial hemorrhage, midline shift or mass effect, or herniation. Due to patient's reported dependency of nitrous oxide and concerns of myelopathy and B12 deficiency, the initial diagnostic blood work consisted of Free thyroxine (Free T4) 1.23 ng/dl (0.8-2.7), thyroid stimulating hormone (TSH) 5.185 uIU/ml (0.350-5.550), thiamine 145.3 nmol/L (66.5-200), red blood cells 3.29/uL (4.5-6), hemoglobin 11.4g/dL (13-18), hematocrit 33.9% (40-52), mean corpuscular volume 103 fL (80-95), red cells distribution width 16.2% (11.5-14.5), platelets 255K/cmm (150-450), folate 12.73ng/ml (2.8-13.5), homocysteine 22.4 umol/l (0.0-15.0), Methylmalonic acid 2491nmol/L (73-376), vitamin B12 252 pg/ml (210-920).

In summary, the patient was found to have borderline low vitamin B12 levels, macrocytic anemia, elevated methylmalonic acid and homocysteine levels. HIV testing and VDRL were negative. The patient was started on high dose vitamin B12 at 1mg intramuscular daily for treatment of presumed subacute combined degeneration of the spinal cord secondary to nitrous oxide (NO) toxicity. With concern for autonomic dysfunction in the setting of acute urinary retention, the patient required telemetry monitoring.

On Day 2 of admission under the medical service, with the concern of subacute combined degeneration giving the history of NO abuse and diagnostic work-up, an MRI of the brain and whole spine was performed. The MRI showed no acute intracranial pathology with minimal nonspecific supratentorial periventricular T2 FLAIR hyperintensity; abnormal increased signal in V-shape within the spinal cord extending posteriorly at the C1-2 level to the C6 level, cervical spine revealed abnormal signal in keeping with demyelinating disease extending from C1-C6; and no definite abnormal spinal cord signal in thoracic or lumbar regions (Figure 1).

By Day 4 of admission, the patient developed sinus bradycardia which was initially episodic and infrequent but became continuous within 24 hours with his heart rate falling to the 30s for prolonged periods, means of 44 beats per minute (range 31-55 beat per minute) with short sinus pauses (Figure 2, Figure 3). He remained hemodynamically stable and asymptomatic. He demonstrated appropriate chronotropic response to a heart rate range of 60 beat per minute with exercise in the bed (limited by motor weakness). Telemetry monitoring continued with no acute events.



**Figure 1.** Magnetic resonance image of cervical region without contrast, T2 weighted Diagnostic MRI image from our patient presented: Abnormal signal within the spinal cord starting from C1-2 through C6 level. Mild multilevel disc bulging. Mild central canal stenosis at C6-7. No evidence of spinal cord compression.

From Days 1 to 7, his neurological deficits gradually worsened, in that the sensory level gradually rose to the level of thoracic spine, with weakness of abdominal wall muscles and inability to stand or sit upright without assistance. Namely, on day 4, neurological exam revealed 4/5 in upper limbs bilaterally, 3/5 lower limbs bilaterally, hypertonic lower limbs, hyperreflexia 3+ at knees, ankle clonus >4 beats bilaterally; proprioception at first toes and ankles to light and sharp touch were impaired. Foley's catheter was in with light yellow clear urine in bag. On day 7, neurological exam showed 4/5 upper limbs bilaterally with poor grip and reduced dexterity, 4-/5 lower limbs bilaterally, hypertonic lower extremities bilaterally but less than previously, hyperreflexia at knees has decreased in both sides more at right one, ankle clonus decreased 3 beats bilaterally. Daily Vital Capacity and Negative Inspiratory Force were monitored during the period of worsening weakness and ascending sensory neuropathy; no respiratory abnormalities were detected at rest. We persisted with the course of daily 1g intramuscular Vitamin B12 supplementation.

The patient showed some improvement in his neurological exam by day 7 with the help of aggressive physiotherapy. He was able to stand with one person assistance. Despite having a scissoring gait, he was able to walk several feet with the use of a rolling walker. At the time the neurological exam showed power 4/5 upper limbs bilaterally, 4-/5 lower limbs bilaterally, hypertonic bilateral lower extremities, hyperreflexia at knees in the right more than left, ankle clonus 3-4 beats bilaterally.

Over the following several days, with intensive physiotherapy and vitamin B12 therapy, his ability to walk with a rolling walker improved further. The bradycardia had also resolved. The first trial of void of urine was successful on day 10. He completed 10 days of 1mg IM vitamin B12, and then started weekly injections. B12 levels rose, initially to above normal limits, then normalized. Homocysteine, 9.97 umol/l (0.0-15.0), and Methylmalonic acid level, 118 nmol/L (73-376), levels also normalized.

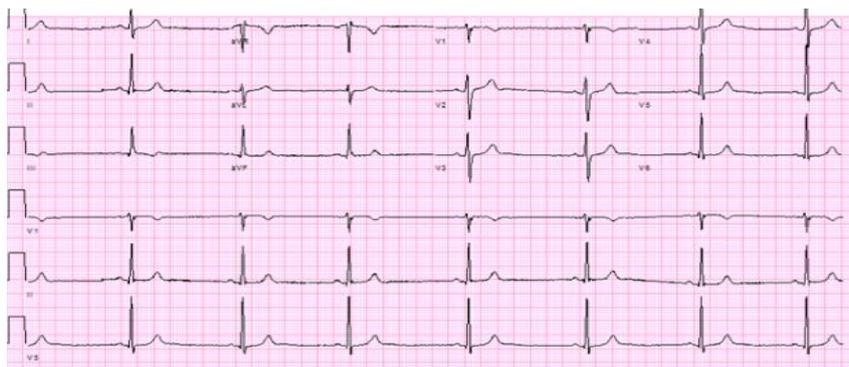


Figure 2. 12 leads EKG showing sinus bradycardia

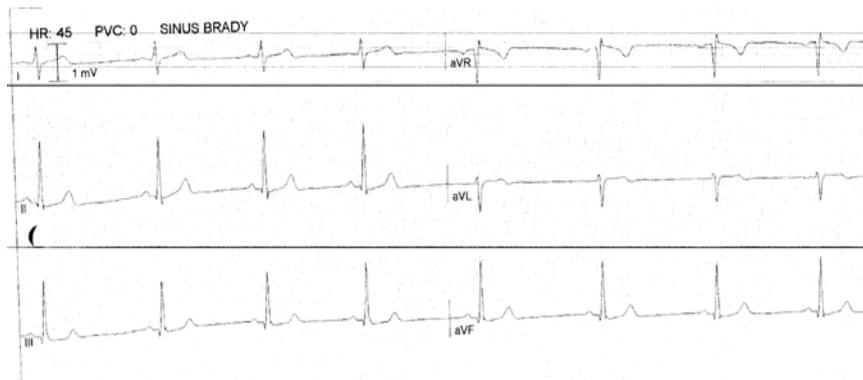


Figure 3. Telemetry of the patient during hospitalization

With the clinical improvement, he was transferred to an Acute Inpatient Rehabilitation Facility, on Day 12, where he received intensive therapy for 10 days. Upon discharge from the acute rehabilitation setting, he was able to walk independently but had residual deficits with grip and dexterity and complaints of residual paresthesia of the fingertips. He was sent home on oral Vitamin B12 at 1mg per week and to continue outpatient occupational therapy, and with neurology and cardiology follow-up care. After 2 weeks, a Zio-patch showed normal sinus rhythm and sinus bradycardia at night. However, the patient did not follow up with cardiology service after the results.

At follow-up 6 weeks later, the patient admitted to continued use of nitrous oxide, in decreased quantities, and complained of paresthesia of the distal fingers of both hands.

He had no neurological deficits on examination and expressed interest in exploring admission to a detoxification program but later declined to follow through with the program.

### 3. Discussion

Nitrous oxide was first synthesized in the eighteenth century and used for internal combustion in engines, rockets, aerosol spray propellant in food manufacture, and is widely used in dental and surgical procedures [1]. In the last two decades, nitrous oxide misuse increased exponentially, especially among young adults and medical professionals [2], likely due to easy accessibility, low cost and pleasurable side effects.

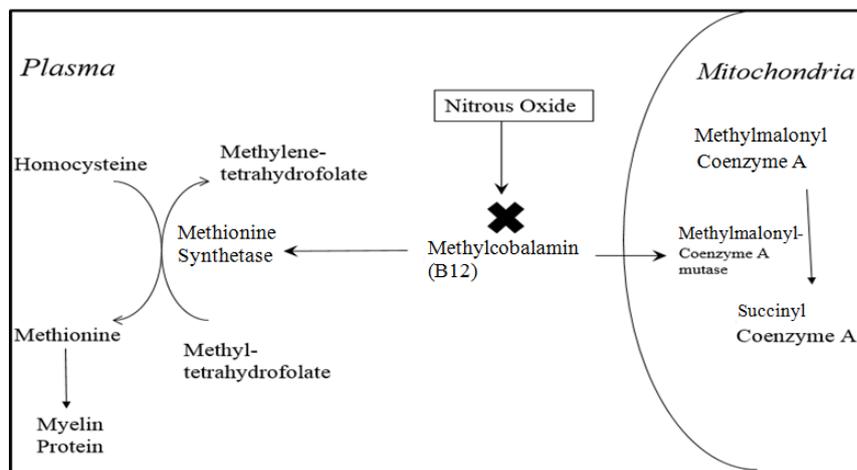


Figure 4. Methylcobalamin (vitamin B12) works as an enzyme cofactor for converting methylmalonyl coenzyme A to succinyl coenzyme A and homocysteine to methionine. Nitrous oxide causes permanent oxidation of cobalt ions in vitamin B12 and thus inhibits the conversion of methylmalonyl coenzyme A and homocysteine.

The toxic effect of nitrous oxide is mainly a neurological and occurred through interference of vitamin B12, cobalamin, and its metabolism in the nervous system. Normally vitamin B12 works as an enzyme cofactor for converting methylmalonyl coenzyme A to succinyl coenzyme A and homocysteine to methionine. Succinyl coenzyme A and methionine are important for methylation of myelin protein. Nitrous oxide causes permanent oxidation of cobalt ions in vitamin B12 and thus inhibits the conversion of methylmalonyl coenzyme A and homocysteine. (Figure 4) This results in demyelination of the central and sometimes peripheral nervous system [3].

Nitrous oxide inhalation resulting in neurological deficits is more likely to occur when used at high doses and for prolonged durations. The patient usually presents with symptoms of subacute combined degeneration of spinal cord, which manifest with peripheral sensorimotor neuropathy and spastic paraparesis with autonomic dysfunction. On physical examination, the physician often elicits signs of decrease upper and lower motor neuron function. The diagnosis can be confirmed with MRI of the central nervous system, which shows abnormal signal. In our case, the abnormal signal was observed mainly in T2 weighted imaging due to edema and decrease in motor conduction velocities in peripheral nerve conduction studies. The serum level of vitamin B12 is usually normal and the level of methylmalonic acid is increased [4].

The treatment of loss of myelin and neuropathological manifestations of nitrous oxide toxicity is to stop nitrous oxide use, high doses of vitamin B12 therapy and physiotherapy. In one reported case of vitamin B12 treatment failure, methionine therapy was reported to be successful [5].

Neurological symptoms were previously reported in cases of repeated nitrous oxide use in patients with sickle cell disease and vaso-occlusive crisis [6]. Prognosis and resolution of neurological manifestations is variable but may be slow and incomplete [7].

#### 4. Conclusion

Nitrous oxide abuse is an underestimated cause of neurotoxicity and subacute combined degeneration manifestation and should be considered as an etiology especially in young adults. It is diagnosed by low/normal vitamin B12 and high methylmalonic acid levels with demyelinating changes on MRI as outlined. The treatment of the condition involves stopping the offending agent, vitamin B12 supplementation and physiotherapy. The

prevalence of neuropathological disease caused by nitrous oxide misuse is under-recognized and our case highlights the need to maintain a high degree of suspicion in young adults presenting with this.

Nitrous oxide abuse can cause significant neurologic manifestations such as subacute combined degeneration as shown in our case. An increased prevalence of substance abuse and dependency is one of the biggest challenges that health care providers are encountering in medicine today. Nitrous oxide, or 'whip its' are being abused very often due to their lack of regulation and easy accessibility. Nitrous oxide induced neurotoxicity, subacute combined degeneration manifestation, autonomic dysfunction and arrhythmias poses high risk of morbidity and mortality for the population and thus, warrants more awareness in order to include in the differential diagnoses in people with history of nitrous oxide exposure or abuse presented with neurologic manifestations that does not fit with localized insult of central nervous system.

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