NITROUS OXIDE USE DISORDER IN ADOLESCENTS:
THE SERIOUS SIDE EFFECTS OF "WHIPPITS"

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A 17-year-old male with a history of attention-deficit/hyperactivity disorder (ADHD) was brought by the police to the emergency room from his school for bizarre behavior. According to the reports, the patient had been observed talking to himself during class, laughing inappropriately, and making odd statements. The patient initially denied illicit substance use, and his urine toxicology and volatile screens were negative. His physical exam was notable for diffuse hyperreflexia and decreased sensation to light touch of his hands and feet. Additional laboratory data was requested and included a normal B12 level, mildly elevated methylmalonic acid, and significantly elevated homocysteine. On further questioning, the patient endorsed recent frequent inhalation of nitrous oxide, which he minimized, pointing out that nitrous oxide "is just laughing gas."

History

Nitrous oxide (N_2O) is a non-flammable, colorless gas with a somewhat sweet odor that has been used as a volatile anesthetic in dentistry for nearly 200 years. Discovered in 1793 by the English chemist Joseph Priestly, nitrous oxide entered the mainstream in 1799 when Sir Humphrey Davy administered the gas at the Pneumatic Institute and, given its anxiolytic and euphoric effects, coined the term "laughing gas." Nitrous oxide was primarily used recreationally to induce altered states of consciousness until the early 1840s. In 1844, American dentist Horace Wells helped demonstrate the analgesic and anesthetic effect of nitrous oxide after volunteering to have his tooth extracted while inhaling the gas. In addition to its widespread use as an anesthetic, nitrous oxide also has several nonmedical applications, including manufacturing of semiconductors, increasing horsepower of car engines to improve performance, preventing decompression sickness in divers, and as a propellant in food processing.[1,2]

Nitrous Oxide as an Anxiolytic

In addition to its analgesic and anesthetic effects, nitrous oxide also has anxiolytic properties. Animal models of anxiety have shown nitrous oxide to produce patterns of behavior similar to those elicited by benzodiazepines, and these responses are inhibited by flumazenil, a benzodiazepine antagonist. Furthermore, mice that have been made tolerant to benzodiazepines through daily chlordiazepoxide administration develop cross tolerance to nitrous oxide-mediated anxiolysis. It has been hypothesized that this anxiolytic effect is mediated by indirect or direct activation of the benzodiazepine binding site on the gamma-aminobutyric acid (GABA) receptor, leading to chloride ion influx and downstream signal transduction.[3]

Nitrous Oxide as a Neurotoxin

It is theorized that the neurotoxicity of nitrous oxide is mediated through at least three mechanisms, including functional vitamin B12 deficiency, increased dopaminergic activity in the mesolimbic area, and N-methyl-D-aspartate (NMDA) receptor antagonism.

Functional Vitamin B12 Deficiency

Nitrous oxide produces functional vitamin B12 (cobalamin) deficiency by oxidizing cob(I)alamin to cob(III)alamin, rendering B12 ineffective. The loss of function of B12 as a cofactor leads to inactivation of methionine synthase, which usually catalyzes the conversion of homocysteine to methionine via intermediaries S-adenosyl-homocysteine (SAH) and S-adenosyl-methionine (SAM).[4-6] As a result, serum methylmalonyl-CoA and homocysteine levels rise and serve as markers of functional B12 deficiency. Accumulation of homocysteine leads to increased formation of reactive oxygen species, NMDA agonism, and cell apoptosis.[7] Furthermore, SAM is normally intimately involved in myelination, and its deficiency results in abnormal myelin sheath formation and can cause subacute combined degeneration.

Increased Dopaminergic Activity in the Mesolimbic Area

Nitrous oxide has been shown to increase dopaminergic activity in the mesolimbic pathway, with rat models demonstrating neuronal damage in the retrosplenial and posterior cingulate cortices. Of note, this neurotoxic effect can be inhibited by the addition of a dopamine antagonist such as haloperidol.[8,9]

NMDA Antagonism

Although NMDA antagonism can be protective under certain circumstances, in excess it can be toxic, especially in the vulnerable developing brains of children and adolescents, where it can lead to vacuolization of neurons.[7]

Nitrous Oxide Use Disorder

Reports of nitrous oxide abuse began to surface as early as in the 1960's. For example, a 1964 article reports "a

young female patient who...described some rather interesting events pertaining to an addition activity" after inhaling the gas at parties.[10] Nitrous oxide intoxication produces a euphoric, often dissociative high that can be accompanied by hallucinations, delusions, agitation, and neurological findings.[11] Nitrous oxide is found in whipped cream propellant cartridges (sold under the brand name "Whip-It," but also known as "whippits") that can be easily purchased online, at smoke shops, or even at the grocery store.[2] A package of 50 "whippits" sells for about $25, and although typical use amounts to 10–20 cartridges, it is not atypical for a user to consume hundreds of cartridges in a single setting. The gas can be captured in a container or inflatable object after puncturing the end of a cartridge, making a larger volume of nitrous oxide ready for inhalation.

Table 1: Neuropsychiatric Manifestations of Nitrous Oxide Abuse

Neurological
- Optic neuropathy
- Opthalmoplegia
- Ataxia
- Spastic clonus
- Hyperreflexia
- Motor-sensory polyneuropathy
- Decreased proprioception
- Paralysis
- Subacute combined degeneration of the spinal cord
- Reduced intellectual function
- Cerebrovascular disease

Psychiatric
- Psychosis
- Depression
- Hypomania
- Agitation
- Personality changes
- Dementia

Nitrous oxide's euphoric, psychedelic high and easy accessibility make it prime for abuse among youth. In fact, according to data from the 2000 and 2001 National Household Surveys on Drug Abuse, nearly one in ten children aged 12–17 had used inhalants, and over 20% of these endorsed lifetime nitrous oxide use.[12] Use is even more frequent among incarcerated youth, with one study estimating a lifetime prevalence of nitrous oxide use of 15.8% in a population of 13–17 year olds in a residential Midwest facility.[2] It is estimated that nitrous oxide is the fifth most commonly abused inhalant in the young, trailing gasoline, Freon, butane lighter fluid, and glue.[5]

Neuropsychiatric Manifestations

Nitrous oxide abuse leads to a variety of neuropsychiatric presentations that can develop after weeks to months of regular use (see Table 1).[13] Neurologic symptoms can be profound and may include optic neuropathy and ophthalmoplegia, spastic tonus, hyperreflexia, motor-sensory polyneuropathy, cerebrovascular disease, and paralysis. There are multiple reports of nitrous oxide abuse leading to subacute combined degeneration of the posterior and lateral columns of the spinal cord.[14] Psychiatric symptoms following prolonged nitrous oxide use are diverse and can include dementia, depression, florid psychosis, hypomania, violent behavior, reduced intellectual function, and more subtle personality changes.[5,6,15-17]

Screening and Diagnosis

Nitrous oxide abuse is often omitted from the differential of an evaluating psychiatrist. Given its wide accessibility, child and adolescent psychiatrists should routinely screen for nitrous oxide abuse, especially in patients presenting with new neuropsychiatric symptoms. Nitrous oxide use may be rapidly assessed using just three items from the Volatile Solvent Screening Inventory, an interview developed by Howard *et al* in 2008 (see Box 1).[18] If there is concern for nitrous oxide abuse, a full neurological exam should be performed, paying special attention to check for hyperreflexia, signs of peripheral neuropathy, and ataxia. Laboratory findings may include macrocytic anemia, low–normal vitamin B12, high–normal methylmalonic acid (MMA), and high–normal homocysteine.

Treatment

As with other drugs of abuse, providers should consider referring patients abusing nitrous oxide to a specialist. Acute treatment involves replenishing vitamin B12, even if levels are normal, as they may be functionally deficient. This can be accomplished by administering parenteral (intramuscular or subcutaneous) vitamin B12 using a dose of 1,000 mcg daily for one week, followed by 1,000 mcg weekly for one month, then, if necessary, 1,000 mcg monthly until the patient is no longer deficient and stops using nitrous oxide. Although restoring vitamin B12 levels may improve psychiatric symptoms, psychosis may also be managed with adjunct antipsychotics, usually with doses lower than used in primary psychotic disorders. There is no data to suggest favoring a particular antipsychotic; however, studies have demonstrated both haloperidol and quetiapine are effective.

Conclusion

Nitrous oxide, or laughing gas, is widely available and frequently abused by youth due to its euphoric, dissociative high. The gas has been shown to be neurotoxic through at least three mechanisms, including functional vitamin B12

deficiency, increased dopaminergic activity in the mesolimbic area, and NMDA antagonism. Chronic use may lead to profound neuropsychiatric symptoms. Child and adolescent psychiatrists should consider routinely screening for nitrous oxide abuse, especially in patients presenting with new neuropsychiatric symptoms. If nitrous oxide abuse is suspected, it is important to check a complete blood count and levels for vitamin B12 level, MMA, and homocysteine. Treatment includes addressing the substance use disorder, correcting vitamin B12 deficiency, and administering low-dose antipsychotics if necessary.

Take Home Summary

Nitrous oxide is widely available, and its abuse in youth is growing increasingly common. If you suspect nitrous oxide abuse, complete a full neurological exam, check a complete blood count and levels for vitamin B12 level, MMA, and homocysteine, and treat by replenishing B12, administering low-dose antipsychotics if necessary; refer to substance rehabilitation treatment.

Box 1: Screening and Diagnosis

History:

- "Have you ever inhaled or 'huffed' nitrous oxide ('laughing gas') through your nose or mouth in an effort to get high?"
- "Have you ever inhaled or 'huffed' whippets (i.e. carbon dioxide canisters containing nitrous oxide) through your nose or mouth in an effort to get high?"
- "Have you ever inhaled or 'huffed' gas from whipping cream cans through your nose or mouth in an effort to get high?"

Exam:

- Full neurological exam, findings may include:
  - Hyperreflexia
  - Peripheral neuropathy
  - Ataxia

Laboratory Data:

- Macrocytic anemia
- Low/normal B12
- High/normal MMA
- High/normal homocysteine

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