ABSTRACT: A 34-year-old female with a history of alcohol and crystal methamphetamine abuse presented to the emergency department with limb paresthesia and difficulty walking. At a primary care visit a week earlier her progressive neurological compromise had been viewed in the context of anemia and she was started on daily B12 injections. Further investigations in hospital revealed diminished proprioception, hyperalgesia with pinprick and temperature tests, a wide-based high-steppage gait, elevated levels of B12 and homocysteine, and normocytic anemia. Magnetic resonance imaging revealed abnormal cord signal intensity in bilateral dorsal columns C1-C2 through C6-C7 and T4-T5 through T9-T10. Eventually the patient was diagnosed with subacute combined degeneration neuropathy secondary to nitrous oxide abuse that had affected B12 activation. The patient was continued on B12 therapy, neurology follow-up was arranged, and addiction counseling services were recommended. Unfortunately, the patient was lost to follow-up after discharge from the hospital. Physicians should be aware that nitrous oxide is easy to acquire in the form of commercially available cartridges or whipped cream canisters called “whippits” and abuse of nitrous oxide is increasingly common. Physicians should also be aware that a high B12 level is difficult to interpret because nitrous oxide inhibits B12 activation yet does not lower B12 levels. Patients presenting with limb paresthesia, sensory loss, and B12 deficiency should be asked about nitrous oxide use. Abstinence is key to treatment.

Case report:
Neurological complications of nitrous oxide abuse

A patient who presented with limb paresthesia and B12 deficiency was eventually diagnosed with subacute combined degeneration neuropathy secondary to nitrous oxide abuse.

Case data
A 34-year-old female presented with a 2-week history of progressive bilateral limb paresthesia and tenderness, as well as an inability to balance. She had been well previously, although she did have a history of alcohol and crystal methamphetamine abuse. She had abstained from crystal methamphetamine for 5 years and from alcohol for 2 months. She was working as a care aid and denied using illegal drugs currently, but reported she had been inhaling nitrous oxide (“laughing gas”) for 6 months, with an escalation of use over the previous 2 months. She reported using 10 to 12 nitrous oxide cartridges (“whippits”) a day. A week earlier, she had visited a primary care clinic where her progressive neurological compromise was viewed in the context of anemia related to a low B12 level of 114 pmol/L. She was diagnosed with B12 deficiency of unknown cause and started on daily B12 injections. Unfortunately, she did not refrain from nitrous oxide use following this preliminary diagnosis and her symptoms continued.
In the emergency department her physical examination revealed diminished proprioception, diminished vibration perception, and diminished light touch perception in the hands and lower limbs, with sensory loss in a glove and stocking pattern. She had hyperalgesia with pinprick and temperature tests. She had extensor plantar reflex responses bilaterally and a wide-based high-steppage gait. Her Romberg test result was positive. Her motor strength, reflexes, and cranial nerve findings were normal.

The patient’s blood work revealed an elevated B12 level of 1069 pmol/L (normal range 150 to 600 pmol/L) and an elevated homocysteine level of 14.5 µmol/L (normal range less than 12.9 µmol/L). Methylmalonic acid levels were not measured. A normocytic anemia was also identified, with normal iron and ferritin levels but a low transferrin saturation and a red cell distribution width (RDW) in the upper range of normal (14.4%). Test results for infectious diseases considered in the differential diagnosis, including HIV, hepatitis, and syphilis, were negative. Autoimmune conditions and demyelinating conditions were also considered. Guillain-Barré and multiple sclerosis were excluded based on history, physical examination, and imaging. Magnetic resonance imaging revealed abnormal cord signal intensity in bilateral dorsal columns C1-C2 through C6-C7 and T4-T5 through T9-T10 consistent with subacute degeneration (Figure). The patient continued on daily 1000-µg B12 injections for a total of 10 days and then transitioned to weekly injections for 2 months. A plan was made to transition to monthly injections depending on clinical response, and neurology follow-up was arranged. The patient was counseled on the importance of abstaining from nitrous oxide and provided with information on addiction services in the community. Unfortunately, the patient was lost to follow-up after discharge from the hospital.

Discussion
Nitrous oxide use can result in a subacute combined degeneration of the spinal cord and a peripheral neuropathy by converting B12 from an active monovalent to an inactive bivalent. Active B12 is a coenzyme for methionine synthase in the production of methionine. Methylmalonic acid is also a precursor and can likewise be elevated.

Postoperative subacute combined degeneration and peripheral neuropathy in susceptible patients treated with nitrous oxide anesthesia have been reported in the literature for over 2 decades. For example, Holloway and colleagues described neurological deterioration after nitrous oxide anesthesia in 1990. Multiple cases since have described patients with subclinical B12 deficiency for reasons such as pernicious anemia, irritable bowel disease, or dietary restrictions who experience neurological symptoms immediately following surgery until about 2 months after surgery. In these cases, duration of nitrous oxide exposure (40% to 66% concentrations)
ranged from 1 to 11 hours. A recent systematic review analyzed adverse effects associated with nitrous oxide use in labor and delivery. Maternal adverse effects to the drug included nausea, vomiting, and dizziness. The study sizes were inadequate to assess more rare and serious effects such as neurological compromise. However, it may be that pregnant women experience fewer serious side effects than the general population because the B12 and folic acid they consume in prenatal supplements are protective.

Neurological effects related to recreational nitrous oxide abuse have also been described in case reports. Like our patient, most patients in these cases have subclinical B12 deficiency and symptoms that only develop after 1 to 6 months of heavy use. They typically consume nitrous oxide by puncturing the ends of commercially available cartridges or whipped cream canisters and breathing in the escaping gas or collecting it in a balloon and inhaling it from there. Patients in various case reports describe using 1 to 20 cartridges a day.

Given that nitrous oxide is easy to acquire and believed by many to be harmless, the number of nitrous oxide abusers could increase in years to come. The Canadian Addiction Survey found that 1.3% (CI 1.0-1.6) of Canadians 15 years of age and older reported lifetime use of inhalants in 2004, compared with 0.8% (CI 0.6-1.0) in 1994. There are no recent data on the prevalence in Canada of nitrous oxide abuse specifically, but it is estimated that 40% of people who claim to use inhalants concomitantly abuse nitrous oxide. Interestingly, 90% of nitrous oxide users also use other inhalants. Adolescents with psychiatric disorders and adolescents from vulnerable populations are at high risk for nitrous oxide abuse. Health care workers with chronic exposure to nitrous oxide, including dentists and anesthesiologists, have also been identified as being at increased risk for misuse, abuse, and dependence on nitrous oxide.

Abstinence is key in treatment. Our patient did not abstain from use and perceived no improvement in her symptoms with B12 supplementation alone. In the majority of cases, patients improve with abstinence and B12 supplementation, although symptoms can be slow to resolve and patients are not always deficit-free at the end of treatment. Serum B12 level does not seem to correlate with treatment response.

Physicians should be aware that patients may fail to mention nitrous oxide when asked about drug use, and many seek medical attention a few times before a diagnosis of neuropathy related to abuse of nitrous oxide is made. Physicians should become familiar with the effects of nitrous oxide and think to ask about this drug when patients present with neurological and other symptoms that suggest abuse of “laughing gas.”

Summary
The case of a 34-year-old female shows how nitrous oxide abuse can cause subacute combined degenerative neuropathy secondary to B12 inactivation. The case also shows that nitrous oxide is easy to acquire and abuse of it is increasingly common. This is unfortunate because recovery is slow and long-term deficits can result.

Treatment includes abstinence from nitrous oxide and B12 supplementation.

Patients presenting with limb paresthesia, sensory loss, B12 deficiency, and other clinical findings described here should be asked about nitrogen oxide use.

Competing interests
None declared.

References