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Case Study: Naltrexone for the Treatment of Nitrous Oxide Use

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Abstract

Background: Using a clinical case example, we describe and discuss the use of oral naltrexone as a novel treatment strategy for nitrous oxide use. Nitrous oxide is an inhalant drug that is readily available and legally obtained. Though frequency of reported cases of substance use disorder for nitrous oxide is low, previous case reports have described severe neurological and psychiatric harms associated with chronic use. Despite this, evidence for pharmacotherapy is currently lacking. Clinical studies have shown variable efficacy for naltrexone across a number of substances including alcohol, nicotine, and stimulants.

Case: We present here a case of a 41 year old man with a substance use disorder for nitrous oxide who was reportedly using of up to four hundred 8g canisters of nitrous oxide per day. Oral naltrexone was initiated at 50mg daily in an attempt to decrease cravings. The dose was subsequently titrated to 100mg daily, resulting in a decrease in nitrous oxide use to less than sixty 8g canisters per week over a one-month timeframe.

Discussion: Previous literature surrounding naltrexone provides both a plausible mechanism of action for craving reduction as well as a precedent for its use across a number of substances. To our knowledge, use of naltrexone for nitrous oxide use has not been previously described. While clinical studies are currently lacking, this case highlights naltrexone as a possible treatment strategy for nitrous oxide use, with potential to reduce significant harms associated with chronic use.

Keywords

nitrous oxide; substance use; addiction treatment; naltrexone

Introduction

Nitrous oxide was first discovered to have euphoric and analgesic properties in the late 1700s[1]. Because nitrous oxide inhibits bacterial growth, it has been adopted in the commercial food industry as a propellant for cooking sprays and whipped cream canisters. It can be obtained legally and at low cost from commercial retailers or the internet in the form

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Consent

Written informed consent was obtained from the subject for the publication of this case study.

of small metal canisters containing 8L of compressed nitrous oxide gas that are used to charge whipped cream dispensers, referred to colloquially as 'whippets'[2]. When used recreationally, nitrous oxide is inhaled from a whipped cream dispenser or from balloons filled via larger tanks. There are currently no restrictions on the purchase of nitrous oxide canisters in the Canadian market. A package of 100 canisters for use in whipped cream dispensers can be purchased for less than one hundred Canadian dollars[3].Though 'whippets' are the most commonly described source of nitrous oxide in the case literature, some case reports describe inhalation from larger tanks used for anaesthetic gas, commercial food applications, or even fuel tanks[4,5].

More than ninety examples in the case literature describe recreational nitrous oxide use[1]. Unfortunately, there is little data available regarding the prevalence of recreational nitrous oxide use over time. Several case reports from the 1970's and 1980's described recreational use within the dental community, though the available data, consisting only of small surveys, suggests that frequency of recreational use among dental professionals at that time was less than 5%[6]. The past two decades have seen a resurgence of nitrous oxide use in the club and festival scene, particularly in the United Kingdom[7]. In 2014, The Global Drug Survey, an international internet-based anonymous survey of drug use, revealed that 18.8% of participants globally and 38.6% of participants in the UK had ever tried nitrous oxide, with a median of two days of use in the past month for both groups[7]. While the majority of individuals who use nitrous oxide do so infrequently, a small minority of individuals who report daily use are at increased risk of severe adverse effects.

A systematic review of the case literature by Garakani et al in 2016 described 91 cases of nitrous oxide-related complications, of which 72 had neurological symptoms at presentation, most commonly numbness, paraesthesias and weakness, and 11 involved primarily psychiatric symptoms, most commonly delusions[1]. Notably, the majority of symptomatic cases were associated with a low serum B12 level[1]. Though there is significant debate in the literature regarding the mechanism through which nitrous oxide exerts its neuropsychiatric effects, inactivation of methylcobalamin is hypothesized to be an important common step in the biochemical cascade[1]. Reported cases of death from nitrous oxide inhalation have been associated with evidence of asphyxia on autopsy, attributed to hypoxia caused by rapid displacement of oxygen[5]. Despite significant morbidities associated with chronic nitrous oxide use, there is a critical lack of evidence-based treatment options. To our knowledge, previous reports have not described the use of pharmacotherapy. We report here on the use of daily oral naltrexone for craving reduction in a case of substance use disorder for nitrous oxide.

Case Presentation

A 41 year-old man was brought to the emergency room by police after endorsing suicidal ideation in the context of an argument with his spouse. His past medical history was significant for major depression and unspecified anxiety disorder. At the time of presentation, the patient was receiving venlafaxine extended-release 150mg daily for anxiety, and zolpidem 10mg sublingually for sleep. He had no known drug allergies. His social history revealed that he lived in private rental housing with his spouse and was

financially independent. Substance use history was significant for daily nitrous oxide inhalation. The patient also had a previous history of gamma-hydroxybutyrate use in a binge pattern primarily on weekends, with no use in the preceding three years. The patient denied use of any other substances.

The patient reported purchasing nitrous oxide in large packages of up to six hundred individual canisters, either online or from commercial retailers. The nitrous oxide was inhaled using a whipped cream dispenser. The patient gave a history of gradually escalating use over four years from less than ten 8g canisters per weekend initially up to more than four hundred 8g canisters per day. There were previous attempts to cut down and periods of abstinence ranging from one to eight weeks over the preceding two years. Attempts to cut down were associated with frequent and severe cravings for nitrous oxide and ultimately relapse. The patient had educated himself regarding potential complications and had self-initiated oral supplementation with 1000 micrograms of Vitamin B12 most days of the week. Negative consequences from his nitrous oxide use included excessive financial resources spent on nitrous oxide, as well as strained relationships with his spouse and business partner. The patient had attended substance use counselling sessions and recovery meetings in the two months leading up to initial assessment, though self-reported attendance was inconsistent. He had not received any previous pharmacotherapy for his substance use disorder.

At the time of presentation to the emergency department, the patient's vital signs were normal. Physical examination revealed a well-appearing man with normal speech and gait. A full neurological exam revealed no abnormalities. The physical examination remained unchanged on subsequent visits. Investigations revealed a complete blood count (including mean corpuscular volume), electrolytes, and liver enzymes that were within the normal range. The serum B12 level was within the normal range at >128 pmol/L. On further assessment, the patient denied active suicidal ideation though he endorsed a sense of hopelessness surrounding his substance use as a result of multiple relapses. The patient reported being motivated for abstinence from nitrous oxide. Accordingly, oral naltrexone 50mg daily was prescribed in an attempt to reduce the patient's cravings for use.

Three weeks later, the patient was once again brought to the emergency department under similar circumstances, reporting acute suicidal ideation following an argument with his business partner. Following psychiatric assessment, he was felt not to be at risk of self-harm. At the time of reassessment, he reported a significant reduction in the intensity of cravings and in overall nitrous oxide use, from four hundred canisters per day down to two hundred, which he attributed to naltrexone. Furthermore, the patient reported several periods of three to four days of abstinence. He was interested in having the naltrexone increased further. On reassessment, liver enzymes remained within the normal range. Accordingly, the patient's oral naltrexone was increased to 100mg daily.

At clinic follow-up visit two weeks later, the patient reported a further reduction of nitrous oxide use down to less than sixty 8g canisters being consumed per week. He reported reduced intensity of cravings. At the time, he had not received any additional counselling

services and was not attending recovery meetings. The venlafaxine had been increased to 225mg daily. There had been no change to his work or relationships status.

Discussion

We have presented here a case of a 41 year-old man with severe substance use disorder for nitrous oxide, with compulsive use of up to four hundred 8g nitrous oxide canisters per day. Following initiation of oral naltrexone, there was a clinically significant reduction in nitrous oxide use, down to less than sixty 8g nitrous oxide canisters per week. In the current case example, the patient did not experience neurological adverse effects of chronic nitrous oxide use, possibly due to self-administration of vitamin B12. To our knowledge, use of pharmacotherapy for craving reduction in nitrous oxide use has not been previously described.

Though several examples of daily nitrous oxide use have been reported in the literature, the mechanism through which nitrous oxide interacts with the reward pathway of addiction is not well understood. Nitrous oxide is believed to exert its analgesic effects through activation of opioidergic neurons in the periaqueductal grey matter of the brainstem, the primary pain modulator of the central nervous system[8]. Endogenous opiate release in the brainstem inhibits gamma-aminobutyric acid-releasing neurons, in turn activating descending noradrenergic pathways that inhibit pain[8]. Researchers have postulated that the euphoric effects of nitrous oxide may be related to inhibition of N-methyl D-aspartate receptors[9], a pharmacodynamic property that also mediates its anaesthetic effects. It may be postulated that administration via inhalation leads to rapid bioavailability within the central nervous system, potentially leading to more marked euphoria and therefore a greater reinforcing effect[10]. A body of evidence supports the use of naltrexone for relapse prevention in alcohol use disorder and opioid use disorder[11,12]. In addition, a number of randomized placebo-controlled trials have also shown some degree of efficacy for nicotine and stimulant use, suggesting that endogenous opiates may play an important role in the pathophysiology of addiction across different substances[13].

We recognize that factors other than naltrexone may have contributed to the outcome of this case. Changes in personal and professional relationships as well as improved connection with health care providers during clinic follow up visits may have affected his substance use. In addition, the status of his underlying anxiety disorder and interval adjustment of the venlafaxine dosage could have contributed to the outcome. While mental health and addiction are frequently interconnected, it is difficult to say with certainty whether the underlying mood disorder would have triggered changes in nitrous oxide use or vice versa.

Notably, neurologic symptoms were not evidence in this case. We are aware of one case report that described the development of neurologic symptoms despite B12 supplementation[14]. In addition, there are several case reports describing development of psychiatric complications without neurologic symptoms. While intensity and chronicity of use seem to be predictive factors for development of complications in general, there is no clear set of risk factors to predict the type and severity of complications that will develop. In

addition, cases of nitrous oxide use without complications are likely to be missing from the literature due to publication bias, making it difficult to develop predictive tools.

To our knowledge, use of naltrexone for nitrous oxide use has not been previously described. Previous studies have demonstrated safety of naltrexone in doses up to 100mg daily, allowing for dose escalation as needed[15]. Though this case represents a single example of possible efficacy, given the potential for significant harms associated with chronic nitrous oxide use, consideration of treatment options is warranted. Further work is needed to explore the potential of naltrexone in this regard. Though frequency of reported cases of substance use disorder for nitrous oxide is low, screening is warranted for those at risk, particularly for individuals who work in industries where nitrous oxide is readily available, or for those who frequent the club and festival scene.

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References

1. Garakani A, Jaffe RJ, Savla D, et al. Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: A systematic review of the case literature. Am J Addict. 2016;25(5):358–369. [PubMed: 27037733]
2. van Amsterdam J, Nabben T, van den Brink W. Recreational nitrous oxide use: Prevalence and risks. Regul Toxicol Pharmacol. 2015;73(3):790–796. [PubMed: 26496821]
3. CTV News. Doctors issue warning after "whippits" misuse lands B.C. woman in hospital. CTV News. 12 2019.
4. Suruda AJ, McGlothlin JD. Fatal abuse of nitrous oxide in the workplace. J Occup Med. 1990;32(8):682–684. [PubMed: 2401921]
5. Wagner SA, Clark MA, Wesche DL, Doedens DJ, Lloyd AW. Asphyxial deaths from the recreational use of nitrous oxide. J Forensic Sci. 1992;37(4):1008–1015. [PubMed: 1506823]
6. Yagiela JA. Health hazards and nitrous oxide: a time for reappraisal. Anesth Prog. 1991;38(1):1–11. [PubMed: 1809046]
7. Kaar SJ, Ferris J, Waldron J, Devaney M, Ramsey J, Winstock AR. Up: The rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. J Psychopharmacol. 2016;30(4):395–401. [PubMed: 26912510]
8. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology. 2008;109(4):707–722. [PubMed: 18813051]
9. Maze M, Fujinaga M. Recent advances in understanding the actions and toxicity of nitrous oxide. Anaesthesia. 2000;55(4):311–314. [PubMed: 10781114]
10. Bearn J, O'Brien M. "Addicted to Euphoria": The History, Clinical Presentation, and Management of Party Drug Misuse. Int Rev Neurobiol. 2015;120:205–233. [PubMed: 26070759]
11. Lee JD, Nunes EVJ, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet (London, England). 2018;391(10118):309–318.
12. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. 2018;320(8):815–824. [PubMed: 30167705]
13. Aboujaoude E, Salame WO. Naltrexone: A Pan-Addiction Treatment? CNS Drugs. 2016;30(8):719–733. [PubMed: 27401883]

14. Pugliese RS, Slagle EJ, Oettinger GR, Neuburger KJ, Ambrose TM. Subacute combined degeneration of the spinal cord in a patient abusing nitrous oxide and self-medicating with cyanocobalamin. Am J Health Syst Pharm. 2015;72(11):952–957. [PubMed: 25987690]

15. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295(17):2003–2017. [PubMed: 16670409]