Nitrous oxide-induced myeloneuropathy: a case series

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ABSTRACT

Background Nitrous oxide (N₂O) is the second most common recreational drug used by 16- to 24-year-olds in the UK. Neurological symptoms can occur in some people that use N₂O recreationally, but most information comes from small case series.

Methods We describe 119 patients with N₂O-myeloneuropathy seen at NHS teaching hospitals in three of the UK’s largest cities: London, Birmingham and Manchester. This work summarises the clinical and investigative findings in the largest case series to date.

Results Paraesthesia was the presenting complaint in 85% of cases, with the lower limbs more commonly affected than the upper limbs. Gait ataxia was common, and bladder and bowel disturbance were frequent additional symptoms. The mid-cervical region of the spinal cord (C3–C5) was most often affected on MRI T2-weighted imaging. The number of N₂O canisters consumed per week correlated with methylnitrosalicylic acid levels in the blood as a measure of functional B₁₂ deficiency (rho (p)=0.44, p=0.04).

Conclusions Preventable neurological harm from N₂O abuse is increasingly seen worldwide. Ease of access to canisters and larger cylinders of N₂O has led to an apparent rise in cases of N₂O-myeloneuropathy in several areas of the UK. Our results highlight the range of clinical manifestations in a large group of patients to improve awareness of risk, aid early recognition, and promote timely treatment.

INTRODUCTION

Nitrous oxide (N₂O), also known as laughing gas, is an anaesthetic commonly used in medical and dental settings. Since its discovery, N₂O has also been inhaled recreationally for its euphoric and dissociative effects. In recent years, use among young people in the UK has risen and it is now the second most used drug, with over 8% of 16- to 24-year-olds reporting use in 2018–19, although this is likely an underestimate.¹ Some countries, such as the Netherlands, have implemented legislation to ban N₂O for recreational use.⁴

N₂O-myeloneuropathy due to recreational N₂O use was first reported following illicit use by dentists in 1978.¹ In recent years, an increased number of N₂O-myeloneuropathy cases have been reported. N₂O-myeloneuropathy results from functional vitamin B₁₂ deficiency, which leads to a failure in the production of myelin, notably damaging the dorsal columns of the spinal cord through subacute combined degeneration (SACD), identifiable on MRI.⁶ Neuropathy on nerve conduction studies (NCS) has also been described.⁷ Low pre-exposure B₁₂ levels increase susceptibility to SACD, with shorter exposures to N₂O.⁵

The mainstay of treatment currently available for N₂O-myeloneuropathy is the cessation of use and parenteral B₁₂ supplementation.⁹ Prophylactic B₁₂ administration while continuing N₂O use is unlikely to mitigate neurological damage.¹¹ Recovery and prognosis have been variably reported.¹² ¹³ Although cases have been reported from iatrogenic use of N₂O, recreational use is the cause of the current N₂O-myeloneuropathy ‘epidemic’.¹⁴ Thromboembolic complications have also been described from recreational use.¹⁵ It has not yet been determined if there is a minimum amount of N₂O necessary to consume before reaching a threshold for SACD or neuropathy.

This work aims to characterise the demographic, clinical and investigative findings in a large series of patients with N₂O-myeloneuropathy, to inform
further research on the topic and raise awareness of the issue both in scientific and public domains.

METHODS
Case identification
Data from 119 patients were collated from hospital trusts in three major UK cities: East London (Barts Health NHS Trust), Greater Manchester (Northern Care Alliance NHS Foundation Trust and Manchester University NHS Foundation Trust), and Birmingham (University Hospitals Birmingham NHS Foundation Trust, Royal Wolverhampton NHS Trust and University Hospitals Coventry and Warwickshire NHS Trust). Presentations occurred between 1 September 2014 and 26 October 2022, with 57 cases arising from the last 12 months. Patients were identified for data collection from referral to neurology or ambulatory care and are therefore likely to represent only a proportion of patients seen with N2O-myeloneuropathy over this period.

Case definition
Three definitions were used to triage inclusion in this case series (online supplemental figure 1). Individuals presenting with a history of N2O exposure, supportive clinical features and biochemical evidence (abnormal serum B12, methylmalonic acid (MMA) and/or homocysteine levels) were included in the study. Definite cases were those with abnormalities on MRI demonstrating dorsal column pathology indicative of SACD, and/or NCS showing either axonal or demyelinating patterns. Probable cases satisfied the inclusion criteria without additional MRI or NCS support. Possible cases were those with symptoms of N2O-myeloneuropathy, but without clinical signs, MRI, NCS or biochemical evidence, and these cases were excluded from the study.

Data collection
Follow-up of patients was generally poor due to non-attendance. Electronic patient records were used to gather demographic and clinical data on each patient (online supplemental table 1). Information regarding neurological status at follow-up was gathered from electronic patient records, including letters from follow-up appointments. This work was undertaken in a framework of clinical service development, rather than research. Consent to report these data was not obtained from patients. All data reported has been fully anonymised and aggregated, and these data are being reported in the public interest.

Analysis
Descriptive analysis was undertaken on all 119 definite and probable cases to generate results for demographics, presenting complaint(s), details of N2O use, neurological examination findings, and additional findings. Six ‘possible’ cases were excluded from the study. Although 92 patients had MRI scans, only 82 of these were 10 days before or 90 days after initial diagnosis and were used for analysis. NCS findings were available in only 32 individuals (all from Manchester and Birmingham). Where available, blood results for B12, MMA, and homocysteine were recorded for all patients regardless of location; blood results for haemoglobin and mean corpuscular volume (MCV) were recorded for patients at Manchester and London hospitals. Blood results taken closest to the time of presentation were recorded, while results taken outside of the time window of 21 days before to 21 days after the initial presentation were excluded. For analysis of biochemical tests, those with known or suspected B12 supplementation before blood sampling were separated from those without known or suspected B12 supplementation. B12 supplementation before blood sampling was known to have occurred if patients reported self-supplementation before presentation or the first B12 injection was given prior to testing. Furthermore, a B12 level above the maximum range of analysis (≥1500 or ≥2000 ng/L) at presentation was taken as evidence of prior B12 supplementation. Reference ranges varied slightly between hospital sites and testing laboratories (online supplemental table 2). For haemoglobin, the reference range was set as 115–165 g/L for women and 130–170 g/L for men regardless of the location of testing, due to multiple reference ranges at each hospital varying by age and sex. To test the correlation between the degree of N2O used and biochemical tests, Spearman’s rank test of correlation was used in R version 2021.09.1 + 372.

RESULTS
Demographics
A total of 119 patients were included in the case series, of which there were 80 ‘definite’ cases. MRI evidence of SACD (n=68), or NCS findings of neuropathy (n=29) classified these cases. Seventeen cases had evidence on both MRI and NCS, and 12 cases had NCS findings alone without MRI findings. Thirty-nine cases of N2O-myeloneuropathy were classified as ‘probable’. Cases had a median age of 22 years (range 14–39 years) (table 1). The majority of patients were male (n=89, 75%) and the majority were of Asian or Asian British ethnicity, which was particularly evident in East London; 49% were documented as cigarette smokers, while only 36% of cases drank alcohol (13 were recorded as drinking excessively); 31% had reported the use of other recreational drugs such as cocaine and cannabis; 41% were documented as either being in education or employment at the time of presentation; B12 supplementation before the presentation was recorded in 13 patients (11%).

Presenting symptoms
Paraesthesia was the most common presenting complaint observed overall (n=101, 85%). When accounting for symptoms presenting simultaneously, paraesthesia alone remained the most common presenting complaint (n=48, 40%) (figure 1). In some cases, paraesthesia presented alongside unsteadiness (n=17, 14%) or weakness (n=16, 13%). Eight individuals (7%) presented with all three symptoms of paraesthesia, unsteadiness, and weakness. Less common presenting symptoms included an inability to walk unassisted, bladder and bowel disturbance, and pain.

Nitrous oxide use
N2O use was recorded in all 119 patients (table 2). The amount of use was documented in 78 individuals (66%). Twenty individuals reported using larger cylinders of ~600g. The ~600 g cylinders were taken to be ~75 times the amount of a single ~8 g canister. Of the 78 patients in whom quantity was documented, the median weekly amount was 318 canisters. Weekly use ranged from one canister to 35 cylinders (equivalent to roughly 2800 canisters). The use pattern was regular in 91 individuals (76%) and 14 reported sporadic use (12%).

Examination findings
Initial examination of sensation was performed in the upper limbs for 117 individuals and the lower limbs for 118 individuals (figure 2A,B). Sensory loss was evident in the lower limbs more frequently than in the upper limbs. Loss of joint position sense in the lower limbs was the most reported sensory finding (n=61,
51%). Other sensory findings common in the lower limbs were loss of vibration sense (n=46, 39%), loss of light touch sensation (n=42, 35%) and loss of pinprick sensation (n=41, 34%). The most frequent co-occurrent impairment in sensory modalities was seen in lower limb joint position sense and vibration sense (n=17, 14%) reflecting dorsal column involvement. Neurological examinations at the time of presentation revealed 67% of patients had gait ataxia (n=80) (figure 2C). Lower limb power was reduced in a greater number of patients compared with upper limb power, (n=67 and n=30, respectively) (figure 2D). Findings when testing deep tendon reflexes were mixed (figure 2E).

Further symptoms and signs documented from the history and examination of patients were described (table 3). Urinary (n=21, 18%) and bowel disturbances (n=18, 15%) were frequently described. Erectile dysfunction, Lhermitte’s sign and pseudoathetosis were also described, but all of these symptoms were likely under-reported.

Investigations

Results from biochemical tests were available for B₁₂ (99/119 patients, 83.2%), MMA (n=41, 34.5%), homocysteine (20/119 patients, 16.8%), haemoglobin (66/119, 55.4%), and MCV (64/119, 53.7%). MMA was tested more commonly (26/46 cases, 56.5%) when B12 was determined as normal or high than when B₁₂ was low (14/53 cases, 26.4%). Homocysteine was tested with equal frequency regardless of whether B₁₂ was determined as normal (8/46 cases, 17.4%) or low (10/53 cases, 18.8%). Median values and the percentage of tests outside of the reference range are shown in table 4. A graphical display of biochemical values in those with no previous supplementation and previous supplementation is shown in online supplemental figure 2. Biochemical testing frequencies likely reflect local hospital testing procedures.

The results of biochemical tests taken before any B₁₂ supplementation were analysed in relation to the quantity of N₂O used (figure 3). The quantity of N₂O consumed per week was associated with increased MMA levels at presentation (Spearman’s ρ (ρ)=0.44, p=0.04, n=22). There was no correlation between increasing N₂O and homocysteine levels (Spearman’s ρ=0.29, p=0.33, n=13), B₁₂ levels (Spearman’s ρ=−0.02, p=0.86, n=60), or MCV (Spearman’s ρ=−0.09, p=0.54, n=44).

Imaging and nerve conduction studies

A total of 98 out of 119 (82.4%) patients had an MRI, and 82 of these patients had an MRI either within 10 days before or 90 days after the initial date of diagnosis, with a median delay of 5 days from initial contact date (IQR 2–20). Among these 82 patients, 60 (73.2%) had appearances consistent with SACD. Sixteen (19.5%) were normal, and six (7.3%) were inconclusive due to image quality or non-specific findings. In those with imaging findings consistent with SACD, the levels of the spinal cord affected were available in 54 patients. In these patients, the
Spinal cord injury

The median number of spinal cord levels affected was 5 (IQR 4–7) with the C3–C5 spinal segments most affected (figure 4).

NCS were conducted in 32 cases across the hospitals from the Manchester and Birmingham areas. Findings were suggestive of N₂O-myeloneuropathy in 29 of these cases (90.6%), with 21 studies describing axonal damage (65.6%), and eight describing conduction velocity slowing indicative of demyelination (25.0%). In the remaining three (9.4%) patients, no damage was described.

Treatment

Of the 119 patients, 70 (59%) were admitted for inpatient management. However, this varied between centres, with inpatient management in 32/35 (91%) cases in Birmingham, 18/28 (64%) cases in Manchester, and 20/56 (36%) cases in London. Only the London centre had an outpatient ambulatory care pathway in place for patients with N₂O-myeloneuropathy, which may have caused the decreased admission rate relative to other centres. This pathway involved a 2-week course of intramuscular B₁₂ injections, with further B₁₂ if clinically improving. However, it was not possible to collect data accurately on the number of B₁₂ injections received. Data regarding the length of the treatment course were available for a subset of 26 patients at this site, where the median duration of treatment was 34.5 days (IQR 17.25–41.75).

Outcomes

Information regarding follow-up neurological status more than 28 days after initial presentation was available in 38/119 patients, with a median time to follow-up examination of 183 days (IQR 54.25–404.75). Among those with a follow-up examination, only four (10.5%) had no ongoing symptoms. The most common ongoing symptoms documented were subjective or objective ongoing sensory change (32 patients, 84.2%), followed

Table 2

<table>
<thead>
<tr>
<th>Pattern and amounts of N₂O use by patients</th>
<th>London</th>
<th>Birmingham</th>
<th>Manchester</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with documented N₂O use</td>
<td>56</td>
<td>35</td>
<td>28</td>
<td>119</td>
</tr>
<tr>
<td>Number with documented amount of use</td>
<td>51 (91%)</td>
<td>14 (40%)</td>
<td>13 (46%)</td>
<td>78 (65.5%)</td>
</tr>
<tr>
<td>Median weekly N₂O amount in 8g canisters</td>
<td>560</td>
<td>200</td>
<td>75</td>
<td>318</td>
</tr>
<tr>
<td>Range weekly N₂O amount in 8g canisters</td>
<td>5 to 2800</td>
<td>21 to 2100</td>
<td>1 to 1680</td>
<td>1 to 2800</td>
</tr>
<tr>
<td>Individuals with documented use of larger –600g cylinders</td>
<td>10 (17.9%)</td>
<td>7 (20%)</td>
<td>3 (10.7%)</td>
<td>20 (16.8%)</td>
</tr>
<tr>
<td>Median weekly larger N₂O cylinder amount</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Range weekly larger N₂O cylinder amount</td>
<td>1 to 35</td>
<td>1 to 28</td>
<td>1 to 13</td>
<td>1 to 35</td>
</tr>
<tr>
<td>N₂O use pattern (regular/sporadic/unknown)</td>
<td>43/9/4 (77%/16%/7%)</td>
<td>29/4/2 (83%/11%/6%)</td>
<td>19/1/8 (68%/3%/29%)</td>
<td>91/14/14 (76%/12%/12%)</td>
</tr>
</tbody>
</table>

Values are displayed as the number in relation to each column, displaying N₂O use across hospitals in these cities. Where relevant, percentages of that value for the total column are given in parentheses. Where documented, consumed amounts of N₂O taken from electronic patient records enabled classification of use amounts and patterns of use. One large ~600g N₂O cylinder was taken to be equivalent to 75 of the smaller ~8g canisters and incorporated into the median 8g canister amount.

N₂O, nitrous oxide.
Spinal cord injury

by abnormal power in the upper or lower limbs (18 patients, 47.3%) and gait abnormality (18 patients, 47.3%), with ongoing continence issues also documented (eight patients, 21.1%).

DISCUSSION
This multicentre series of patients with N₂O-myeloneuropathy characterises the neurological manifestations and patterns of use. Most cases were young, in keeping with previous reports. Individuals of Asian or Asian British ethnicity made up a large proportion of cases in East London (73%), Birmingham (54%) and Manchester (29%). The latest National Census data from 2021 revealed that the proportion of the population that is Asian or Asian British in Tower Hamlets (East London), Birmingham and Manchester were 45%, 31% and 21%, respectively. As such, Asian or Asian British individuals presenting with N₂O-related harm appear to be over-represented relative to the proportion of the population that is Asian or Asian British in each region.

We and others have speculated that N₂O is a drug of choice for individuals not engaging with other substances for cultural or religious reasons. This study does not necessarily support this idea, with the consumption of N₂O along with other substances demonstrated across ethnic groups. However, the predominance of cases with Asian ethnicity may highlight genetic, dietary, or nutritional predispositions to neurological damage from N₂O exposure, but also may indicate social circumstances predisposing use. The possibility that genetic variation affects proteins in relevant metabolic pathways and predisposes individuals to adverse outcomes has been previously raised and should be further investigated.

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Figure 2  Initial neurological examination findings. (A) Upper limb (UL) sensory examinations mostly revealed no objective sensory abnormalities. The upper graph denotes co-occurrences of losses in sensory modalities, the left graph describes total losses in each sensory modality. (B) Lower limb (LL) sensory examinations revealed notable losses in various modalities. (C) Gait ataxia was described frequently. (D) Power in both upper and lower limbs was documented using the MRC power grading system. (E) Reflexes were graded from brisk to absent. HA, hyperaesthesia; JPS, joint position sense; LT, light touch; MRC, Medical Research Council, ND, not documented; PP, pinprick sensation; Temp, temperature sensation; Vib, vibration sense.
While the quantity of N₂O used varied widely, most individuals used it regularly. There are several instances of relatively few canisters being consumed. While this could suggest that very little N₂O is needed to cause myeloneuropathy, this is unlikely given the decades of medical use of the substance without widespread iatrogenic harm. N₂O used for anaesthesia has been reported to cause SACD, but this is thought to mainly arise in the postoperative period is important. It is worth noting that the use of N₂O in the context of administering anaesthesia is generally considered to be safe. N₂O-myeloneuropathy occurring with relatively low exposure is more likely to suggest individual risk factors are present that may predispose to neurological damage (see above). The number of N₂O canisters used weekly correlated with MMA levels, suggesting that greater consumption may contribute to greater inactivation of B₁₂ and a higher risk of myeloneuropathy. As such, the danger of the larger cylinders is amplified, as it is easier to consume large amounts of gas with these compared to the smaller canisters.

Paraesthesia was the most common presenting symptom, highlighting the importance of N₂O-myeloneuropathy as a differential diagnosis for sensory disturbance in both primary and secondary care. Sensory abnormalities were more common in the lower limbs than the upper limbs, particularly loss of joint position sense and vibration sense. N₂O-myeloneuropathy has both a myelopathic and a neuropathic element. We theorise that the neuropathic component of N₂O-myeloneuropathy first affects the longest peripheral nerves. Combined with evidence of predominant involvement in the cervical white matter tracts of the posterior cord, this may explain why the lower limbs are more affected. The high occurrence of gait ataxia is likely to be due to sensory ataxia. Additional symptoms described the varying effects of N₂O-myeloneuropathy. Bladder dysfunction, bowel disturbance, and erectile dysfunction were reported in this series, which are likely under-recognized as a component of N₂O-myeloneuropathy by both patients and clinicians. We recommend enquiring about these symptoms during history-taking of patients suspected of N₂O-myeloneuropathy.

N₂O-myeloneuropathy should be considered in the differential diagnosis of cervical myelopathy, particularly in those under the age of 30 years. However, it is also essential to consider other common causes of cervical myelopathy pathology, including degenerative cervical myelopathy (particularly in older persons) and other causes of cord compression, as well as inflammatory or infective lesions, vascular pathology, or other nutritional deficiencies. The tempo of symptom onset and evolution, and clinical investigations will help to rule out alternative pathology.

There was a lack of correlation between N₂O quantity and B₁₂ levels, mirroring previous studies. This emphasises the value of further testing MMA or homocysteine levels, beyond only serum B₁₂ levels when exploring N₂O-myeloneuropathy as a differential. The proportion of cases in this series with MMA measurements was low (34%, n=41/119). This could be due to the high cost of the test, the limited laboratory availability to process samples, as well as limited standardisation of operating protocols. However, MMA is preferred to the measurement of homocysteine because of the simultaneous contributions of vitamin B₁₂ and B₉ to the metabolism of homocysteine. Furthermore, plasma separation and storage on ice create challenges when measuring homocysteine.

MRI imaging revealed that the cervical posterior cord is commonly affected, with abnormal findings at C3–5 in >90% of MRI reports where the cord regions were specified. In cases with

<table>
<thead>
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<th>Table 3</th>
<th>Additional clinical findings</th>
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<tr>
<td>Proportion (out of n=119)</td>
<td>Additional findings</td>
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<tr>
<td>&gt;10%</td>
<td>Urinary disturbance (n=21)</td>
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<td></td>
<td>Bowel disturbance (n=18)</td>
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<td></td>
<td>Pseudooasthenia (n=13)</td>
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<tr>
<td>5–10%</td>
<td>Lhermitte’s sign (n=10)</td>
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<tr>
<td></td>
<td>Erectile dysfunction (n=7)</td>
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<tr>
<td>≥1%, &lt;5%</td>
<td>Intention tremor (n=4)</td>
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<td></td>
<td>Extensor plantars (n=4)</td>
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<td></td>
<td>Memory issues (n=3)</td>
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<td></td>
<td>Vision disturbance (n=3)</td>
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<tr>
<td></td>
<td>Nausea/vomiting (n=3)</td>
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<tr>
<td></td>
<td>Increased lower limb tone (n=3)</td>
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<td></td>
<td>Numb perineum (n=2)</td>
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<td></td>
<td>Dysdiadochokinesia (n=2)</td>
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<td></td>
<td>Past pointing (n=2)</td>
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<td></td>
<td>Syncope (n=2)</td>
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<td></td>
<td>Floaters (n=2)</td>
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<td></td>
<td>Chest pain (n=2)</td>
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<td></td>
<td>Alloodynia (n=2)</td>
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<tr>
<td></td>
<td>Speech difficulty (n=2)</td>
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<tr>
<td>&lt;1%</td>
<td>Nystagmus (n=1)</td>
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<tr>
<td></td>
<td>Low mood (n=1)</td>
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<tr>
<td></td>
<td>Drenching sweats (n=1)</td>
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<td>Spastic paraparesis (n=1)</td>
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<td>Clubbing (n=1)</td>
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<td>Uhthoff’s sign (n=1)</td>
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<tr>
<td></td>
<td>Low amplitude tremor (n=1)</td>
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<td></td>
<td>Hypoalgesia (n=1)</td>
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</tbody>
</table>

Additional symptoms and signs documented on history and examination are outlined. Groupings based on the proportion of the whole cohort (n=119) who presented with each finding.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Biochemical findings in patients with N₂O-myeloneuropathy</th>
</tr>
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<tbody>
<tr>
<td>Test (units) (reference range)</td>
<td>Among all patients</td>
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<tr>
<td></td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>B₁₂ (pg/mL) (187–911)</td>
<td>191 (150–246.5, n=99)</td>
</tr>
<tr>
<td>MMA (µmol/L) (0–0.42)</td>
<td>2.98 (0.62–5.84, n=41)</td>
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<tr>
<td>Homocysteine (µmol/L) (0–16)</td>
<td>77.5 (21.6–95.3, n=20)</td>
</tr>
<tr>
<td>Hb (g/L) (women 115–165; men 130–170)</td>
<td>139.0 (130.5–149.8, n=66)</td>
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<tr>
<td>MCV (FL) (80–101)</td>
<td>91.8 (89.5–94.6, n=64)</td>
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</tbody>
</table>

Biochemical tests in patients with N₂O-myeloneuropathy in all patients as well as in patients with no documented prior B₁₂ supplementation. The reference ranges displayed in the table are the broadest reference ranges used between centres; full details of reference ranges are in online supplemental table 2.

Hb, haemoglobin; MCV, mean corpuscular volume; MMA, methylmalonic acid; N₂O, nitrous oxide.
a normal MRI, SACD may not be fully excluded because imaging was often not done immediately at presentation, and often after B12 regimens which may have improved SACD to a level which is not visible on MRI. The NCS performed provide evidence of mixed axonal and demyelinating nerve damage. Preclinical research has demonstrated impaired neuron regeneration due to N2O in rats.24 Further research is needed to investigate the degree of degeneration and remyelination seen on follow-up in those with axonal and demyelinating features. The presence of demyelination highlights the need to consider N2O-myeloneuropathy as a differential diagnosis for Guillain-Barré syndrome.9 Of the cases followed up with neurological examinations in this study (n=38, 32%), only four had no ongoing symptoms. Residual sensory disturbances were common, with power and gait disturbances present in just under half of those examined. However, there is potential for bias in that patients with residual symptoms were more likely to attend follow-up than patients whose symptoms had resolved.

Bias in case identification is likely because moderate to severe cases are more likely to present to healthcare services than milder cases. Consequently, both the total number of patients and patients presenting within the last 12 months are thought to incompletely capture the true number of cases in this period. Furthermore, the investigative and treatment pathways are not standardised, resulting in some cases displaying greater documentation of tests and interventions than others both within and between sites. Inconsistent documentation on electronic patient records also applied to data about N2O use, and the number of B12 injections received. Furthermore, neurological examinations were not performed by the same individual. Similarly, MRI reporting was not performed by the same neuroradiologist as this was a multicentre study. The industrial processes generating N2O used recreationally may lead to the integration of other unknown substances with a biological effect, which cannot be accounted for in this study. Finally, an assumption that each larger cylinder was roughly equivalent to 75 smaller canisters was made, based on manufacturers reporting of the volumes within cylinders.25

This public health issue urgently requires more research into the threshold quantity of N2O necessary to consume to cause neurological damage, the natural history of N2O-myeloneuropathy, and optimal treatment. Awareness among young people is increasing through media coverage and public health campaigns. Local guidelines at Barts Health Trust are helping to guide a wider national approach to creating effective

**Figure 3** Blood tests according to the quantity of N2O used per week. (A) There was no correlation between B12 levels and the quantity of N2O canisters used per week. (B) There was a significant correlation between MMA and the number of N2O canisters used per week (Spearman’s Rank p=0.04) in those with no previous supplementation. (C) There was no correlation between homocysteine levels and the quantity of N2O used weekly. (D) Most patients with modest use of N2O (<100 canisters per week) tended to have MCVs on the upper end of the reference range. Green shaded areas denote reference ranges, with dark green areas representing reference ranges common to all laboratories and light green shaded areas denoting values within the reference range for only some laboratories. MCV, mean corpuscular volume; MMA, methylmalonic acid; N2O, nitrous oxide.

**Figure 4** Distribution of affected spinal cord segments in cases of N2O-SACD. Fifty-four cases had MRI reports denoting specifically affected regions of the spinal cord within 10 days before or 90 days after diagnosis. Affected regions are summarised above, along with the percentage of the cases with changes in each region. Note that MRI reports described spinal cord regions in relation to spinal vertebrae, so this nomenclature has been continued here. N2O, nitrous oxide; SACD, subacute combined degeneration.
treatment pathways.25 Manufacturers of N2O urgently need to be informed of this risk and regulated accordingly.

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DM: collating manuscript, data collection (East London), formulating results (clinical presentation, nitrous use, MRI findings, NCS), guarantor for overall content; AP: identification of patients, formulating results (investigations, treatments, outcomes), data collection (East London), review of manuscript; SAZ: data collection (East London), formulating results (clinical presentation, demographics), data collection, review of manuscript; FS: data collection (East London), review of manuscript; SJ: data collection (Manchester region), review of manuscript; LMW: data collection (Manchester region), review of manuscript; JBL: identification of patient and data collection (Manchester region), review of manuscript; DG: identification of patient and data collection (Manchester region), review of manuscript; CE: identification of patients, data collection (Birmingham region), review of manuscript; TH: identification of patients, data collection (Birmingham region), review of manuscript; DL: data collection (Birmingham region), review of manuscript; HA: identification of patients (Birmingham region), review of manuscript; MP: identification of patients (Birmingham region), review of manuscript. AIN is the guarantor of the work.

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