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Evaluation of an ambulatory care pathway for patients with nitrous oxide-induced myeloneuropathy

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ABSTRACT

Introduction Cases of nitrous oxide (N_2O)-induced myeloneuropathy are increasing at UK hospitals. At our centre, a dedicated ambulatory care pathway, endorsed nationally, was established to treat and monitor patients with N_2O-myeloneuropathy in 2021 and refined through three audit cycles. We analysed the outcomes of patients on this pathway to better understand factors associated with non-engagement. Alongside, a novel approach using WhatsApp for questionnaire delivery was trialled in an attempt to improve engagement with treatment.

Methods Patients on the N_2O ambulatory care pathway were identified from MDT meeting lists from 9 September 2022 to 25 April 2023. Clinical data were collected via electronic clinical records, including the most recent neurological examination and reason for discharge from the pathway. Patients identified from MDT lists from 27 January 2023 to 14 March 2023 were approached to participate in weekly 12-item surveys, delivered via WhatsApp. This was approved as a service development project with approval for WhatsApp use given by the chief clinical information officer.

Results 35/56 (62.5%) patients were discharged from ambulatory care due to non-attendance and 17/56 (30.4%) completed their treatment course. The median time from initial presentation to discharge was 49 days. 24/40 (60.0%) of patients with a final neurological examination documented had a residual deficit, with objective sensory deficits most common. 12 patients were approached to receive weekly questionnaires via WhatsApp. 5/8 who expressed interest returned a consent form. All participants were withdrawn due to non-response or participant choice. 1/5 returned more than two surveys.

Conclusion Despite poor participation in surveys delivered via WhatsApp, novel approaches are needed to improve engagement with patients on the N_2O ambulatory care pathway.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with nitrous oxide-induced myeloneuropathy have poorly documented follow-up in the literature, despite often having residual neurological deficits at the point of last contact with healthcare. This patient group is reported to be difficult to engage with their treatment.

WHAT THIS STUDY ADDS

⇒ A novel approach using a widely used method of communication was trialled in this patient group. Despite initial interest, engagement was poor, indicating that new initiatives to engage patients with their healthcare are essential.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study should inform future approaches, including national long-term follow-up of these patients. The route to the approval of the widely used communication app could be used for other studies requiring two-way communication with patients.

INTRODUCTION

Nitrous oxide (N_2O) has been increasing in popularity as a recreational drug in recent years[1] with 230 000 16–24 year olds in England and Wales estimated to have taken N_2O in 2021–2022.[2] N_2O-induced myeloneuropathy was first reported in dentists in 1978[3] and followed by relatively few reports until a sharp rise in published case reports in recent years.[4] Patients experience a range of neurological syndromes from peripheral neuropathy to subacute combined degeneration of the cord.[5] N_2O is widely thought to cause myelopathy through the inactivation of vitamin B_{12}, preventing the formation of myelin.[6] Despite many cases resulting from chronic and heavy use of N_2O, there are reports of patients with 'one-off' use of only several balloons.[7 8] The predictors of a poor outcome and the susceptibility to sustaining neurological damage remain undetermined. Permanent disability has been reported, often in those continuing to use N_2O.[9]

Until recently, there was no consensus on treatment guidelines for suspected N_2O-induced myeloneuropathy. In response to a rising number of cases, a dedicated N_2O-myeloneuropathy pathway was established at the Royal London Hospital in September

2021, which formed the basis of the current national guidelines[4 10] aiming to standardise investigations and treatment. Following its inception, the pathway was further optimised using quality improvement methodology in three further cycles. Briefly, cycle one established the pathway, aimed to rationalise biochemical testing, reduce hospital admissions, and increase the number of patients that had B_{12} injections in ambulatory care rather than being referred to primary care. It included 10 patients from July 2021 to September 2021 and 13 patients from September 2021 to July 2022. Cycle two included 27 patients from August 2022 to October 2022 and aimed to increase in-hospital awareness through internal promotion of the pathway and to add recommendations to improve documentation of N_2O abstinence. Cycle three included 23 patients from December 2022 to March 2023 and aimed to establish an objective measure (a 10 m walk test) of patient function to aid treatment decisions regarding B_{12} discontinuation. Successive audit cycles led to improvements to the pathway over time.[11]

Patients with N_2O-myeloneuropathy often do not attend follow-up appointments, similar to those with other substance abuse issues.[12] The eventual clinical outcome of patients with N_2O-myeloneuropathy is often unavailable due to loss to follow-up.[5 13–16] Whether high rates of non-attendance persist despite a structured N_2O treatment pathway is unclear. We evaluated the reasons for discharge from the ambulatory care pathway. Furthermore, whether attendance can feasibly be improved using novel methods of patient engagement is unclear.

METHODS

Patients on the N_2O ambulatory care pathway at the Royal London Hospital were identified from multidisciplinary team (MDT) lists between 9 September 2022 and 25 April 2023. N_2O MDT meetings consisted of a neurology consultant, an acute medicine consultant, and an ambulatory care nurse. Clinical data were collected via Millenium PowerChart (Oracle Health), the electronic clinical records system at Barts Health National Health Service (NHS) Trust. Demographic data on age at presentation, sex, N_2O use, smoking, other drug use, alcohol use, ethnicity, religion, and indices of multiple deprivation calculated from postcode were collected. Clinical data were collected on initial presentation, including duration of symptoms and initial symptoms, number of B_{12} injections, the number of clinical reviews, discharge outcome, and final neurological examination. On the Royal London Hospital N_2O ambulatory care pathway, patients are discharged after two consecutive non-attendances for either B_{12} injections or clinical review, if no reason or warning was provided. Patients could re-engage with the pathway after a period of non-attendance and were restarted on treatment and had clinical reviews scheduled if necessary. B_{12} injections were continued until the patient recovered or plateaued, according to national guidelines.[4]

To improve attendance and engagement of users with the Ambulatory Care treatment pathway, a 12-item questionnaire was devised with input from a consultant neurologist consisting of questions that were answerable with a numbered option or a binary yes/no response (table 1). This aimed to remind patients about their ongoing condition and the importance of treatment, with the secondary aim of gathering more granular data on the impact of treatment on a week-to-week basis. The questionnaires were sent via WhatsApp to patients who had consented, once per week, with up to three reminder messages every few days before participants were no longer contacted. The questionnaire was sent as text, that could be copied and pasted, or as a Portable Document Format (PDF) according to participant preference. WhatsApp was selected as the mode of communication as response to email and phone calls in this patient group had been noted by staff to be low, and WhatsApp has been used to successfully conduct health systems research in settings with highly mobile and difficult-to-contact participants.[17] Patients from the MDT lists from 27 January to 14 March were approached to be enrolled on the weekly WhatsApp survey project. Patients who had presented to the emergency department more than 2 weeks prior were not approached, as any data collected may have missed initial improvement on commencing B_{12} injections. Patients were approached either in ambulatory care when attending for intramuscular B_{12} injections as part of the treatment pathway or over the phone. Patients were required to return a consent form in order to participate (online supplemental appendix 1).

WhatsApp was decided on as the most suitable mode of communication as the majority of young people already have the app installed on their phones for regular use. This allowed for two-way messaging and the app is end-to-end encrypted, meaning the data were not accessible by WhatsApp or any third parties. The consent form included advice for patients such as having a passcode lock on their phone and deleting messages after they had been received by the team to increase personal security of potentially sensitive health data. Overall, it was decided that the risk of not trying novel ways of engaging with patients with N_2O-induced myeloneuropathy outweighed the potential data protection concerns over the use of WhatsApp. SNOMED CT codes were added to the clinical records of all cases used for analysis, as requested by the Chief Clinical Information Officer. SNOMED code "2765991000000115—subacute combined degeneration of the spinal cord due to the use of N_2O" was added for any patient with confirmed or clinically probable SACD as confirmed by the MDT. SNOMED code "2765741000000111—N_2O misuse" was added to all clinical records of those confirmed to have used N_2O recreationally. Statistical tests and graph creation were performed using RStudio V.2023.03.1+446 'Cherry Blossom' release for Windows.

Table 1 Survey questions sent via WhatsApp to participants. These were sent as a message that participants could send back with the appropriate number or yes/ no for each question, or as a Portable Document Format (PDF) as per participant preference.

Questions	Answer options
How often do you have tingling or numbness in your hands and/or arms?	► 1—never ► 2—some of the time ► 3—around half of the time ► 4—most of the time ► 5—all of the time
How often do you have tingling or numbness in your feet and/or legs?	
How often do you have issues with going to the toilet? (such as being unable to pass stool or urine, or becoming incontinent)	
How often do you have issues with your sexual performance?	
Do you have difficulty texting/ typing on a laptop/using a video game controller?	► 1—no difficulty doing it ► 2—some difficulty doing it ► 3—cannot do it ► N/A—I don't do this activity
Do you have difficulty doing your hair/makeup?	
Do you have difficulty walking heel-to-toe in a straight line?	
Do you have difficulty standing with your eyes closed?	
Have you got any problem with your walking?	► 1—No problem ► 2—Feel unsteady or weak when walking ► 3—Need to hold onto furniture or other people when walking or using crutches ► 4—Need a wheelchair
How have your employment and/or activities of daily life been affected?	► 1—No change at all ► 2—Some change ► 3—Can no longer do my previous employment/ activities of daily living
Do you feel your mental health and well-being have been affected by your condition?	► Yes ► No
Have you managed to stop using nitrous oxide?	
If there is anything further you would like to tell us please type here:	

RESULTS

Attendance patterns and discharge of patients on the N_2O ambulatory care pathway

62 patients were reviewed between September 2022 and April 2023 in the Royal London Hospital N_2O MDT. Three were excluded from the analysis as presentations were not reported as being due to or related to N_2O use. Three were excluded due to the treatment and clinical course being incomplete at the time of data capture. Of the 56 patients included, 4 had previously presented to services for neurological symptoms for N_2O use, and 1 patient had two separate attendances and treatment courses within the time frame. Initial attendances to the emergency department occurred between June 2022 and March 2023.

A total of 35/56 (62.5%) patients were discharged from ambulatory care due to non-attendance. Of the remaining patients, 17 (30.4%) were discharged due to completion of treatment, including 3 patients under long-term neurology follow-up after completion of B_{12} treatment. In four cases (7.1%), the outcome was unclear, with no formal discharge letter. Patient demographics are outlined in table 2.

The median time from initial presentation to discharge was 49 days for 56 patient presentations. Quantified data on N_2O use was available for 44 patients. The median number of canisters used per month was 600, with 1 SmartWhip, a 600 g canister, being approximated as 70 small 8 g canisters. The median of 2.5 months of use reflects that many patients used N_2O in binges, often once or twice with no chronic use. The longest reported history of use was 10 years. The length of time from presentation to discharge was not significantly different (p=0.50; t-test) between the group that was discharged due to completion of treatment and those who were discharged due to non-attendance. The symptom duration prior to presentation was shorter (p=0.029; t-test) for the group that was discharged due to completion of treatment compared with those who were discharged due to non-attendance. Sex was not associated with discharge due to non-attendance (p=0.54; Fisher's exact test), however, age at presentation was associated, with older patients less likely to be discharged due to non-attendance (p=0.029; t-test).

The median length of time from presentation to the emergency department to the final neurological exam was 42 days for those who attended clinical reviews. Table 3 indicates the number of clinical reviews attended. Of the 40 patients who had a final neurological examination available, 24/40 (60.0%) had some deficit remaining at discharge. Of those patients, 12/24 (50.0%) had a

Table 2 Cohort characteristics of those who were discharged from the N_2O ambulatory care pathway due to non-attendance and discharged due to completion of treatment.

	Discharged due to non-attendance (n=35)	Discharged due to completion of treatment (n=17)
Median age at presentation	22 (17–32)	25 (18–40)
Gender		
Male	24 (68.6%)	10 (58.8%)
Female	11 (31.4%)	7 (41.2%)
Symptom duration prior to presentation (median days)	7 (1–90)	4 (1–42)
Average time from presentation to discharge (median days)	53 (6–205)	49 (22–153)
Remaining deficit on final examination		
Yes	16 (45.7%)	8 (47.1%)
No	8 (22.9%)	8 (47.1%)
Examination not done	11 (31.4%)	1 (5.9%)
Ethnicity		
Black	4 (11.4%)	1 (5.9%)
South Asian	25 (71.4%)	12 (70.6%)
White	3 (8.6%)	3 (17.6%)
Mixed/other	3 (8.6%)	1 (5.9%)
Religion		
Islam	21 (60.0%)	10 (58.8%)
Church of England	3 (8.6%)	0 (0.0%)
Other	0 (0.0%)	1 (5.9%)
Unknown	11 (31.4%)	6 (35.3%)
IMD decile of deprivation (median)	3 (1–6)	2 (1–4)
N2O use		
Median number of canisters per month	600 (7–25200)	840 (1–4200)
Length of use history in months	3 (0.1–96)	1.5 (0.03–96)
Smoking		
Yes	20 (57.1%)	9 (52.9%)
No	3 (8.6%)	4 (23.5%)
Not documented	12 (34.3%)	4 (23.5%)
Alcohol consumption		
Yes	11 (31.4%)	6 (35.3%)
No	13 (37.1%)	10 (58.8%)
Not documented	11 (31.4%)	1 (5.9%)
Other recreational drug use		
Yes	9 (25.7%)	5 (29.4%)
No	16 (45.7%)	10 (58.8%)
Not documented	10 (28.6%)	2 (11.8%)
Employment status		
Employed or in education	14 (40.0%)	11 (64.7%)
Unemployed	8 (22.9%)	4 (23.5%)
Not documented	13 (37.1%)	2 (11.8%)

IMD, Index of Multiple Deprivation; N2O, nitrous oxide.

remaining reduction in power, 22/24 (91.7%) had a sensory deficit, 9/24 (37.5%) had reduced or absent reflexes, 13/24 (54.2%) had not returned to their baseline walking ability and 1/24 (4.2%) had a reported coordination issue. Compared with the group of patients who were discharged following the completion of treatment, the group that was discharged due to non-attendance had higher rates of deficit in all domains. 8/16 (50.0%) of patients discharged following the completion of treatment had no remaining deficit at discharge compared

Table 3 Number of clinical reviews attended in patients discharged due to completion of treatment and discharged due to non-attendance

Clinical reviews attended	Patients discharged due to completion of treatment (n=16)	Patients discharged due to non-attendance (n=35)
0	0 (0.0%)	5 (14.3%)
1	1 (6.25%)	8 (22.9%)
2	1 (6.25%)	9 (25.7%)
3	4 (25.0%)	7 (20.0%)
4	4 (25.0%)	3 (8.57%)
5	4 (25.0%)	2 (5.71%)
6	1 (6.25%)	0 (0.0%)
7	0 (0.0%)	1 (2.86%)
8	1 (6.25%)	0 (0.0%)

with 8/24 (33.3%) of those discharged due to non-attendance, however, this was not significant (p=0.34; Fisher's exact test).

Survey participants

Of the 12 patients approached to receive weekly questionnaires via WhatsApp, 8 expressed an interest in participating and 5 returned a consent form (online supplemental appendix 1). All five participants were withdrawn due to non-response after three reminder messages (4/5) or participant choice (1/5) (figure 1).

DISCUSSION

Patients with N_2O-related neurological harm in this cohort had high rates of discharge due to non-attendance, despite the implementation of the dedicated ambulatory care pathway. The pathway has undergone multiple cycles of quality improvement; however, novel approaches are

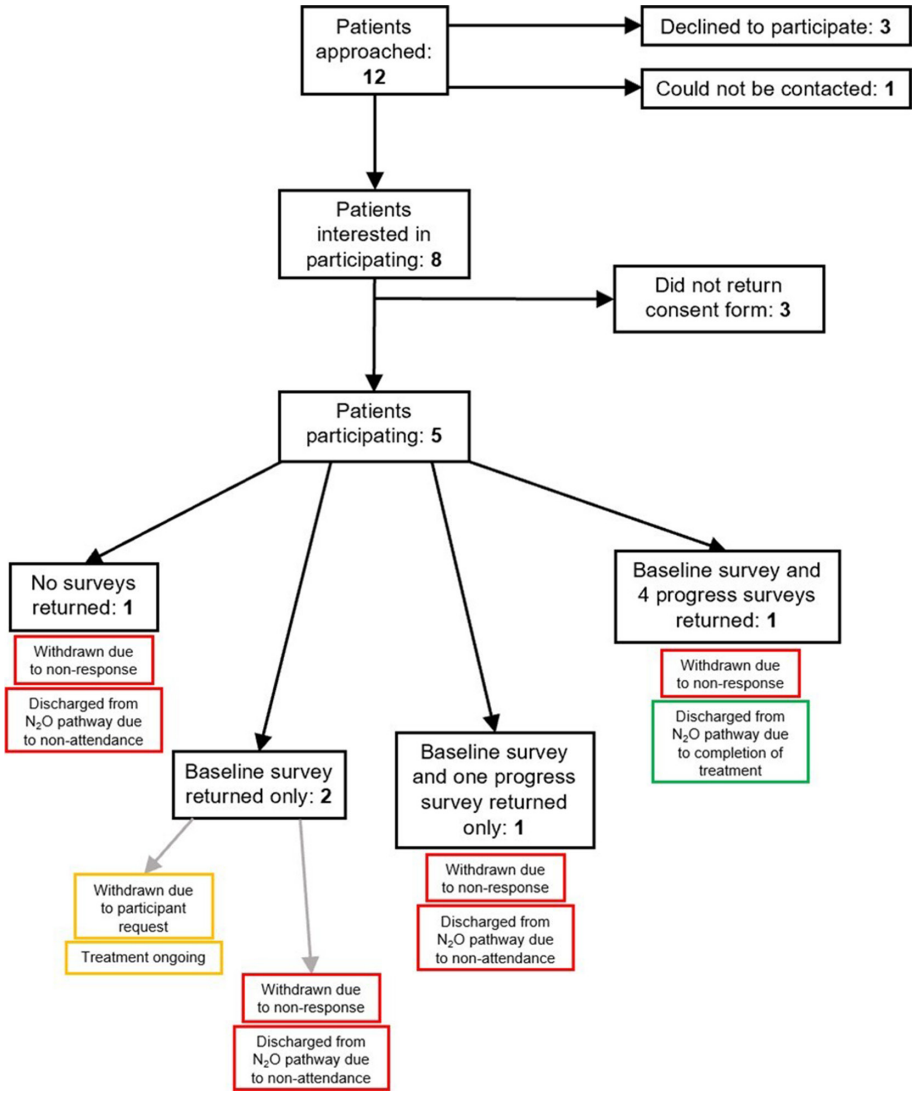

Figure 1 Flow chart of participants approached to participate in the survey project. The number of surveys returned, the reason for withdrawal and outcome of treatment on the N_2O ambulatory care pathway are shown. N_2O, nitrous oxide.

still needed to improve access and adherence for N_2O patients. The high rate of non-attendance is in concordance with a large multicentre case series, in which only 32% of patients had a neurological exam reported 28 days or more after initial presentation, indicating that non-attendance has been an ongoing issue since at least 2016.[8] In our centre, on this pathway, 62.5% of patients being discharged for non-attendance highlights the scale of the issue faced in providing effective treatment to this population. Loss to follow-up rates have varied in small case series of 3–20 patients from 15% to 60%.[5 14–16 18] There is no way of knowing if these non-attendances were due to clinical improvement, frustration at lack of apparent improvement, patient choice, or difficulty accessing healthcare in this way. Disability resulting from N_2O use or social factors such as being unable to afford public transport to attend appointments may play a role in non-attendance. Residual neurological deficit was not associated with non-attendance in this cohort, but the sample size is relatively small. Younger patients were less likely to complete their treatment course, which may indicate further issues accessing and engaging with the pathway. Patient-led initiatives, considering the self-reported needs of this group, will be essential in creating effective and lasting initiatives to improve outcomes. Although this will be challenging, given the high rate of non-attendance and oftentimes an unwillingness to stay in the department, it is necessary to continue to develop new initiatives to engage with patients and coproduce future projects. This may improve participation and help to improve healthcare for patients with N_2O-induced myeloneuropathy in the future.

The length of symptom duration prior to presentation was significantly longer in the group that was discharged for non-attendance. This may indicate a reluctance to seek help from healthcare and a similar reluctance to engage once on a treatment pathway. The high rate of non-attendance means it is difficult to effectively evaluate the impact of treatment on final outcomes. Many of the unknowns in the pathogenesis, clinical course and long-term outcomes of N_2O-induced myeloneuropathy will require collaboration with patients to determine. The predictors of both a full recovery and poorer outcomes are yet to be determined, with B_{12} status and metabolism suspected to play a role in susceptibility to neurological sequelae.[14] 60% of patients had some neurological deficit remaining at their final neurological examination prior to discharge, with this percentage likely higher given many patients did not attend any clinical reviews thus their level of deficit is unknown. This high proportion, as well as sensory issues being the most common, is consistent with other findings.[8 19] Accurate and consistent SNOMED coding of N_2O-induced myeloneuropathy cases is hoped to build a database of patients. In the future, this group data could help with determining predictors of outcomes and help inform future treatment guidelines.

The lack of participation in the WhatsApp survey project was disappointing but in line with wider difficulties in engaging this patient population. Given the high rates of non-attendance of patients with N_2O-induced neurology, low rates of participation in an optional survey were to be expected. There is no obvious incentive for participants to participate in a service development project such as this one. This led to a high non-response rate even among those who consented. This may reflect several aspects. N_2O users were already identified as having high rates of non-attendance for treatment and clinical reviews. Rather than representing an easier method of engaging with healthcare via a familiar method of communication, this likely represented another task that added to the existing B_{12} injection appointments and clinical reviews. The user experience of returning surveys via WhatsApp may have contributed to the lack of engagement. The participant had to copy and paste the survey, adding their answer to each question, or write on a PDF version of the survey. In the future, using an app already optimised for patient use, such as 'Patients Know Best' which provides personal records to patients, may provide a more user-friendly experience. Communicating with patients via an app specifically for healthcare information and communication may improve participation, as all of their healthcare-related information and tasks would be in one place with the added benefit of increased data safety.

This project had multiple limitations, aside from the low participation. Although a potential way of tracking participants' symptoms over time, it was difficult to establish an accurate baseline. The identification of the participants at biweekly MDTs and the time taken to gain consent meant most were contacted a minimum of a week after they first presented to the emergency department. Identification and enrolment in a study would ideally be carried out at the first presentation in future to establish an accurate baseline. With the implementation of regular MDT meetings and a dedicated clinical fellow, undertaking a similar project in future would be less susceptible to these issues. Additionally, participants could respond to messages at any time and often waited many days before returning surveys. This provided a level of uncertainty as to when in their clinical course the response correlated. Using an app in future to allow participants to enter data at a time of their choosing, with automated reminders may eliminate some of the difficulty in recording timely data. Codesigning future initiatives with patients may aid in improving participation and ultimately attendance at ambulatory care pathway appointments. Exploration of the underlying reasons for non-attendance is needed, and appropriate social care provided where necessary to address barriers to accessing healthcare.

Despite the limitations, valuable lessons were learnt from this study. It is important to continue to devise novel ideas for engaging patient groups in their care. The population that presents with N_2O-induced myeloneuropathy is generally young, less than 30 years of age, and well-versed with technology. Utilising methods of communication that patients are already familiar with and regularly use may improve engagement with healthcare services. Given

the reported low attendance at appointments made via email or letter, these methods of communication were not suitable to distribute the questionnaires. The trust uses AccuRx messaging to notify patients of appointments which was considered for this project, however, this only allows for one-way messaging. WhatsApp is widely used by young people, and although not commonly used in the healthcare setting, in this case, with a population at risk of permanent disability due to disengagement with treatment, the risk of not trying a new method of communication was deemed to outweigh the risks around the use of WhatsApp to receive clinical information. Integrating an app for symptom tracking or communication with healthcare teams may be a successful step in the future. Ultimately, it is up to the individual as to whether they engage with their healthcare and the tools available to them. Hence, education is vital about the health risks of N_2O and the potentially permanent disability that can result from misuse to motivate patients to engage with their treatment.

It has been suggested that certain populations may have a higher likelihood of using N_2O, with those from Asian British backgrounds overrepresented in this cohort and others.[8] Misunderstanding surrounding religious and cultural permissibility of N_2O as a drug exists in Asian communities.[20] 31/56 (59.6%) of patients identified their religion as Islam according to their demographic data on Millenium PowerChart. This proportion may be higher, with no data on religion for a further 17 patients. Although N_2O is not permissible in most mainstream interpretations of Islam, misunderstanding combined with the odourless, inconspicuous nature of the drug may lead to prevalence in young people from this community. Religious and youth groups are key audiences to empower with knowledge of the neurological risks of N_2O.[21]

More needs to be done to engage patients with N_2O-induced myeloneuropathy with the treatment pathway to improve outcomes. This is even more essential as the UK government reclassified N_2O as a Class C drug under the Misuse of Drugs Act 1971 in November 2023.[22] Criminalisation risks further preventing engagement with healthcare for those with disability caused by N_2O use.[23] It is essential that those with symptoms due to N_2O feel able to seek help from healthcare providers and engage fully with their treatment.

CONCLUSION

Patients with N_2O-related neurological symptoms had high rates of non-attendance to follow-up appointments, and the majority continued to be symptomatic at the time of last clinical contact. WhatsApp represents a communication method already commonly used by young people that may be able to be used for healthcare purposes. Despite the poor engagement with the surveys via WhatsApp, high rates of discharge for non-attendance indicate it is necessary to develop new initiatives to facilitate the engagement of patients on the N_2O ambulatory care pathway with their treatment. In the future, the co-creation of initiatives with patients would aid in developing avenues that help patients to fully attend their care and maximise recovery.

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Contributors SAZ and AJN conceptualised the project. SAZ collected the data and distributed the surveys. SAZ drafted the initial manuscript. SAZ, AP and DM contributed to the writing of the manuscript. BO, JW, AW, NV and AJN contributed to running the ambulatory care pathway and maintaining the patient list. SAZ, AP, DM, CG, RMA, BO, JW, AW, NV and AJN reviewed and edited the manuscript. AJN is the guarentor for the overall content of this work.

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Competing interests DM leads the educational campaign N2O: Know the Risks. AJN reports grants from the Queen Mary Impact Fund and Tower Hamlets Council related to nitrous oxide educational programmes and clinical service development and sits on the ACMD advisory council.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this project was approved as a service development project on 29 November 2022 by the Clinical Effectiveness Unit at Barts Health NHS Trust, ID 13125. The approval specifically for the use of WhatsApp to distribute surveys for the project was given by the Chief Clinical Information Officer of Barts NHS Health Trust on 9 December 2022. Participants gave informed consent to participate in the study before taking part.

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