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Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment

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ABSTRACT

Recreational use of nitrous oxide (N_2O) has increased rapidly in recent years and is now the second most commonly used recreational drug among young people in the UK. There has been a corresponding rise in cases of nitrous oxide-induced subacute combined degeneration of the cord (N_2O-SACD), a pattern of myeloneuropathy usually associated with severe vitamin B_{12} deficiency. This can cause serious and permanent disability in young people but, if recognised early, may be effectively treated. All neurologists should be aware of N_2O-SACD and its treatment; however, there are currently no agreed guidelines. Based on our experience in East London, an area of high N_2O use, we provide practical advice on its recognition, investigation and treatment.

INTRODUCTION

Nitrous oxide-induced subacute combined degeneration of the cord (N_2O-SACD) was first described in 1978 in 14 dental practitioners abusing nitrous oxide (N_2O).[1] Vitamin B_{12} inactivation was soon established as the likely mechanism of toxicity, as N_2O oxidises the cobalt atom integral to vitamin B_{12} function.[2 3] N_2O-SACD was subsequently reported as an infrequent complication of N_2O anaesthesia in patients with pre-existing subclinical B_{12} deficiency.[4–6] However, the exponential rise in recreational N_2O use in the last decade has made it now the second most commonly used drug among 16–24 year olds in the UK.[7 8] Around 3.4% of N_2O users experience neurological symptoms consistent with subacute combined degeneration (SACD)[9]—but this may be an underestimate—and there has been a rapid rise in reports of N_2O-SACD both in the UK and worldwide.[10–14] Despite this, there is no consensus or guideline on how best to diagnose and treat N_2O-SACD in practice.

At the Royal London Hospital, we diagnose and treat one case of N_2O-SACD on average every 9 days. Since 2021, we have run a quality improvement project to improve its diagnosis and treatment and now share practical advice on its recognition, investigation and treatment to help other clinicians seeing similar rises in cases. The flowchart in figure 1 summarises our pathway.

Challenges in N_2O-SACD

- Recognising the disease.
- Choosing and interpreting investigations.
- Starting intramuscular B_{12} injections promptly and deciding on the duration of treatment.
- Maximising treatment adherence and follow-up attendance.
- Coordinating care between the emergency department, ambulatory medical care and neurology services.

RECOGNITION AND DIAGNOSIS

N_2O-SACD is commonly misdiagnosed and so inappropriately treated.[15] Awareness and recognition of the disease are crucial to preventing long-term harm. This can be helped by considering the local availability of N_2O, the clinical features of the case, enquiring carefully about N_2O use and maintaining a high index of suspicion (as patients may not always disclose N_2O use).

Epidemiology

Most patients developing N_2O-SACD are young (16–30 years). Around 75% are male,[9 13 16] but women may be more

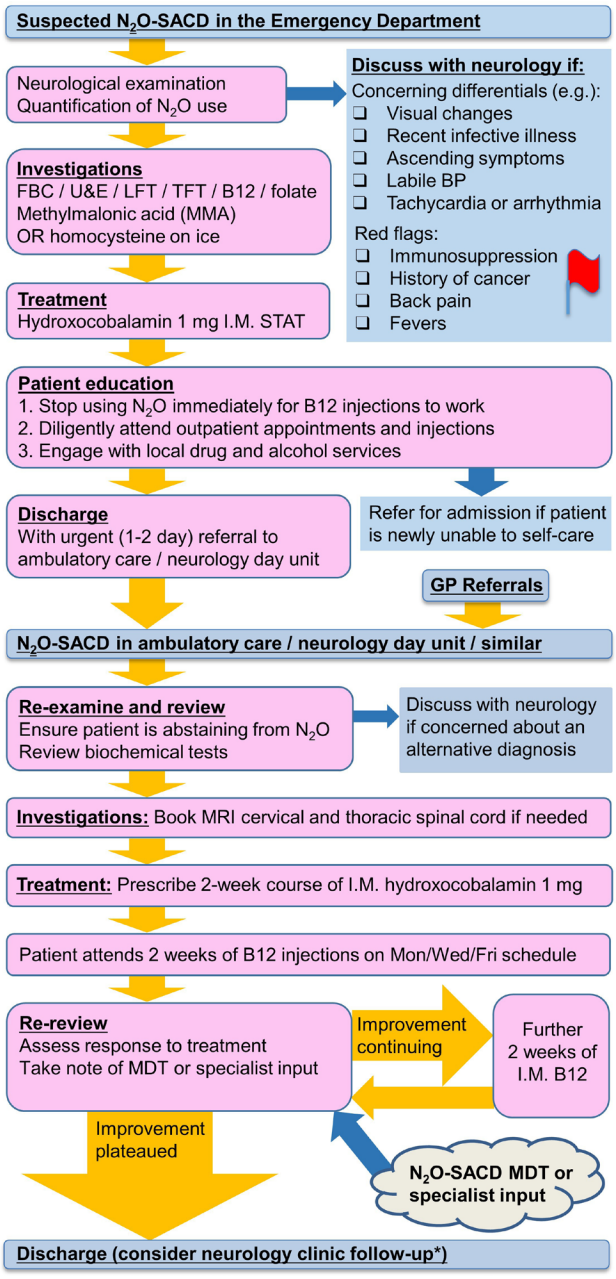

Figure 1 Pathway for patients with suspected N_2O-SACD. In the Emergency Department, the focus is on immediate treatment with I.M. hydroxocobalamin, time-critical investigations, and patient education. Due to subsequent non-attendance, the Emergency Department is occasionally the only point of patient contact. In our practice, methylmalonic acid (MMA) is preferred compared to homocysteine, as it is more specific and does not need to be transported on ice. However, the choice of test will be determined by local preference, availability, and turnaround time. In ambulatory care, the focus is on continuing treatment and repeated assessment of progress, and guided by the N_2O-SACD multi-disciplinary team (MDT) meeting or specialist input. *In our practice, we arrange neurology follow-up if the final diagnosis remains uncertain, there are outstanding investigations to interpret or if there is significant disability.

susceptible to N_2O-SACD at higher doses of N_2O (>20 canisters per session).[9] In different geographical regions, members of different communities are more likely to use N_2O and hence to develop N_2O-SACD. In East London, most patients presenting to the hospital with N_2O-SACD are of Bangladeshi descent[13]; in the Netherlands, Moroccan–Dutch men appear to be more affected[17]; and in Australia, harmful use is highest among university students.[18]

The risk of developing SACD symptoms increases with greater N_2O use: those using one canister per session have around a 1.9% risk of experiencing distal paraesthesia compared with 8.5% in people who use over 100 canisters per session.[9] In general, people presenting to the hospital with N_2O-SACD report heavy recreational use over months to years.[16 19–21] In our clinical practice over the past 5 years, patients have reported using an average of 580 canisters per week (IQR 147.5–1012.5), which is in keeping with other reports.[20] However, those with pre-existing subclinical B12 deficiency are much more susceptible at lower doses of N_2O.[6 22–24] In this scenario, one-off use in anaesthesia can cause N_2O-SACD,[6] and anecdotally some of our patients who have come to harm through recreational use reported using only 5–10 canisters on one occasion.

Clinical features

The clinical features of N_2O-SACD closely resemble those of classical SACD. Symptoms can present over a varying time course, from several days to 6 months.[16 25] Where there has been only a single exposure to N_2O, the time delay to symptoms is 2–6 weeks.[5] The initial presenting complaint is often distal paraesthesia involving the lower and/or upper limbs. If the patient ignores this or if N_2O-SACD is not diagnosed at presentation, patients may then develop gait ataxia (worse in low lighting), falls or inability to walk independently.[1 13] Figure 1 shows features to prompt consideration of an alternative diagnosis.

On direct questioning, a large majority of patients have distal paraesthesia, mainly in the feet but often also the hands.[13 16] Many report unsteadiness on walking.[24] Less common symptoms are weakness,[16 19] Lhermitte's phenomenon,[1] bladder or bowel urgency or incontinence,[1 19 20] impotence or other sexual dysfunction,[1] segmental myoclonus[1 13] or psychiatric complaints.[16] Some patients have urinary retention on presentation, and clinicians should consider arranging a bladder scan.[20] Note there may also be symptoms suggesting pulmonary embolism or deep vein thrombosis, as N_2O-induced hyperhomocysteinaemia can cause a hypercoagulable state.[26] Additionally, clinicians should ask patients about risk factors for low serum B_{12} levels, which would increase their vulnerability to N_2O-SACD. These include dietary preferences, previous gastric or small bowel resections, or chronic intestinal conditions such as Crohn's disease

Table 1 Forms of N_2O used for recreational use and their current online cost

Container	Example brands	Quantity	Canister equivalent	Price per item online
Standard canister	ProWhip, Liss, iSi, Mosa, iSi-Sparkwhip, Best Whip	8 g	1	£0.20–£0.60
Double canister (less common form)	Best Whip	16 g	2	£0.60–£1.80
Standard cylinder	Smartwhip, Fastgas, Cream Deluxe, Greatwhip	580–640 g	72.5–80.0	£25–£35
Entonox (50% N_2O, 50% O_2)	BOC Ltd	350 L≈350 g N_2O	~44	£24*
		500 L≈500 g N_2O	~62.5	£33.50*

*Entonox is not for sale to the general public and is sold to healthcare facilities. The street value of Entonox is unclear.

or coeliac disease. Several common drugs can also decrease serum B_{12} concentrations, including gastric acid suppressants, metformin, potassium supplements and the contraceptive pill.

On examination, the physical findings are generally symmetrical. Common signs are distal loss of vibration and joint-position sense,[1 16 27] and a positive Romberg's sign or ataxic gait.[1 13 16 21] Pseudoathetosis may occur through loss of joint-position sense.[11] There may be hyporeflexia or (less commonly) hyper-reflexia at the knee or ankle, and this pattern may reflect the relative contributions of myelopathy and neuropathy to the clinical picture.[1 16 19] In more severe cases, the plantar responses may be extensor.[19 21 25] Muscle weakness is usually relatively mild but can become severe in advanced cases.[1 21]

Quantification of N_2O use

Patients often do not spontaneously report N_2O use. They may also not connect N_2O use with their neurological symptoms, although those living in areas where use is common do increasingly recognise its possibility of harm.[28] It is important to enquire specifically and to record the quantity, duration, pattern and type of N_2O container used. Most patients in our experience purchase N_2O online, where it is readily available to the general public and is marketed for use in whipping cream. Commonly, patients use 8 g canisters (known as 'whippits' or 'chargers' in the UK and 'nangs' in Australia), but cylinder use—which make it easier to consume large amounts of N_2O—is becoming more common. Occasionally, patients report using medical-grade N_2O, which is not available for sale to the general public but may have been stolen from healthcare facilities and sold.[29] We recommend quantifying N_2O use in 'canister equivalents', with one cylinder approximately equal to 75 canisters (table 1). In general, N_2O abusers use containers of the gas to inflate balloons, which are then inhaled. Using a mask or releasing N_2O into enclosed spaces is less common and particularly dangerous, as there is a risk of death by asphyxiation without preceding dyspnoea.[30]

CHOOSING AND INTERPRETING INVESTIGATIONS

Investigations in suspected N_2O-SACD may support the clinical diagnosis, but there should be no delay in starting treatment promptly (with intramuscular B_{12} injections) while undertaking results. We take blood on all patients and arrange MRI of the cervical and thoracic cord on most patients, except for those with minor symptoms and a clear diagnosis. Nerve conduction studies and electromyography are optional tests to undertake if the history or examination are inconsistent, or if improvement is suboptimal with treatment.

Blood testing

Active vitamin B12 is essential for the enzymatic conversion of homocysteine to methionine and of methylmalonic co-enzyme A to succinyl co-enzyme A. Thus, vitamin B12 deficiency or B12 inactivation tends to increase plasma homocysteine and methylmalonic acid (MMA). Tests for assessing B12 status include serum B12, homocysteine, MMA and holotranscobalamin (table 2).

On first suspecting N_2O-SACD, we take blood for serum B_{12} and MMA. The laboratory processes the serum B_{12} concentration routinely; the MMA is processed in all patients except those in whom the B_{12} concentration is below the reference range, where it would not change the diagnosis or management. Homocysteine is an alternative to MMA, but it must be transported to the laboratory on ice, which in practice places a barrier to its use. Serum B_{12} has relatively low sensitivity (~20% to 50%) for SACD, but MMA and homocysteine are both significantly raised in over 80% of reported cases.[13 19 21 31] However, both homocysteine and MMA normalise with B_{12} treatment and with abstinence from N_2O, and it is likely that MMA and homocysteine testing may be normal if delayed, although the exact time frame is unclear.[32] Ideally therefore, all blood samples for biochemical tests should be drawn before starting treatment with B_{12} injections, but treatment should not be delayed for testing to occur.

In addition to these diagnostic blood tests, we test full blood count, urea and electrolytes, liver function tests and thyroid function tests in all patients as part of the routine medical workup (figure 1). In N_2O-SACD, the mean corpuscular volume and haemoglobin are usually normal,[13 16 21] in contrast to traditional SACD.[33] Folate should be measured in all patients to identify codeficiencies. We offer HIV and syphilis testing to

Table 2 Biochemical tests for N_2O-SACD

Test (approximate reference range)	Comment	Approximate sensitivity for N_2O-SACD
Vitamin B_{12} (190–950 pg/mL)	Serum vitamin B_{12} measurement is the standard first test. However, as N_2O-SACD is a functional deficiency of B_{12}, serum B_{12} concentrations are often within the reference range,[13 16 19 27] as opposed to SACD due to pernicious anaemia or dietary deficiency where they are usually low.[19] A lower B_{12} predisposes to N_2O-SACD with smaller, shorter exposures to N_2O.[5 6 24 45] In our practice, serum B_{12} is normally in the lower third of the reference range or below; however, N_2O-SACD can reportedly occur with high normal and even above normal B_{12} concentrations, including in patients who try to prevent N_2O-SACD by taking oral or injectable B_{12} alongside recreational N_2O.[13 21]	20–50%[16 19 21 31]
MMA (<0.28 µmol/L)	MMA concentrations rise with falling concentrations of active B_{12}[46]; an MMA above 0.75 µmol/L is highly suggestive. Other causes of raised MMA include renal disease, hypovolaemia and small bowel overgrowth. Analysis of MMA is complex and so tends to be performed only in specialist laboratories. While all hospitals should have access to these services, the return of results may take several days.	80–90%[13 24 31]
Homocysteine (<15 µmol/L)	Elevated homocysteine concentrations can reflect B_{12} deficiency but may also occur in folate deficiency, renal failure and in patients with genetic polymorphisms.[47] Hence, concurrent folate measurement is essential for interpretation of results. Samples for homocysteine measurement must be placed on ice after collection and transported to the laboratory promptly, which represents a significant barrier to its use.	80–90%[16 19 21 31]
Holo-transcobalamin	Holotranscobalamin is the ~25% of circulating B_{12} that binds to transcobalamin and is the form that can be transported into cells. Thus, holotranscobalamin is known as 'active' B_{12}. Although there are no data on its use in N_2O-SACD, its concentration is not changed by the presence of N_2O,[47] and it is likely to have similar sensitivity to standard B_{12} assays.	Unknown

MMA, methylmalonic acid; N_2O, nitrous oxide; N_2O-SACD, nitrous oxide-induced subacute combined degeneration; SACD, subacute combined degeneration.

all patients, as both can cause treatable myelopathy that can present similarly to N_2O-SACD. In addition, serum copper and zinc concentrations can be tested if the history of N_2O use is not classical or if copper deficiency myeloneuropathy is a possibility; some patients anecdotally have multiple deficiencies simultaneously.[23] In addition to the above tests, clinicians should consider the possibility of coexisting B_{12} malabsorption, which may have been unmasked by N_2O use. This is particularly pertinent in those patients with an initial B_{12} concentration below the reference range or N_2O-SACD after only modest N_2O use. In these cases, clinicians should test serum anti-intrinsic factor and antigastric parietal cell antibodies to investigate for pernicious anaemia, and consider testing for coeliac disease and markers of generalised malabsorption (eg, ferritin and vitamin D).[34]

MRI

MR scans of the cervical and thoracic cord may both confirm the diagnosis and exclude alternative causes. In 50%–100% of patients with N_2O-SACD, MRI

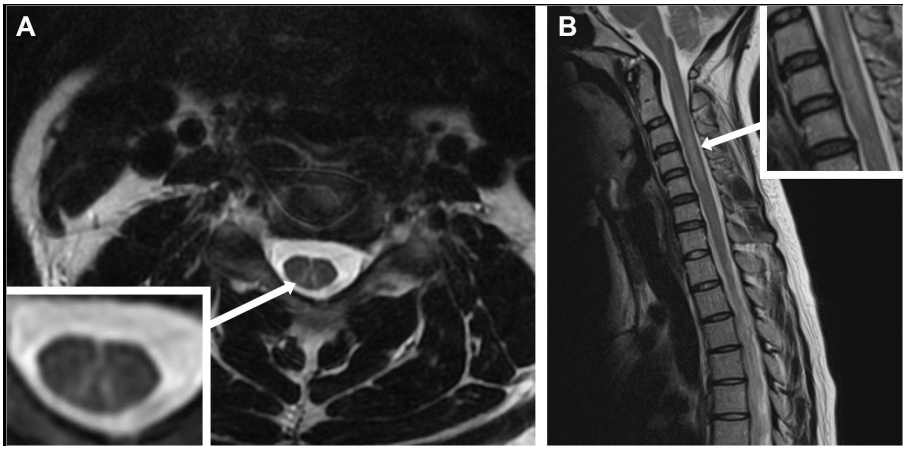

Figure 2 Classical MRI findings in nitrous oxide-induced subacute combined degeneration of the cord. The T2 axial image (A) shows hyperintense signal in the dorsal columns of the cervical spinal cord, creating an 'inverted V' sign. The sagittal image (B) shows the commonly found pattern of hyperintensity extending longitudinally over several cervical spinal segments.

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shows dorsal column T2 hyperintensity in the cervical spinal cord with C3–C5 most commonly affected (figure 2B).[13 16 21] Axial slices are particularly useful to see the classical 'inverted V' or 'rabbit ears' sign (figure 2A).[35]

Given the currently high prevalence of N_2O use, clinicians should be aware that N_2O users may have an alternative cause for a spinal cord syndrome, including inflammatory processes, cervical cord compression and hereditary syndromes. MRI is particularly useful to look for these other causes, since each has a distinct MRI appearance (described elsewhere).[36] However, N_2O-SACD cannot be distinguished solely by imaging, as several other conditions exactly share its MRI findings; these include myelopathy caused by HIV infection, copper deficiency, vitamin E deficiency and methotrexate toxicity.[37] MRI also cannot differentiate traditional SACD from N_2O-SACD, although N_2O-SACD may have less involvement of the thoracic cord, wider lesions on sagittal MRI, fewer spinal segments with lesions and a higher rate of the inverted V sign.[19]

We request MRI of the cervical cord on most patients with suspected N_2O-SACD. The exception is for patients with a very clear history of recently heavy N_2O use and mild symptoms that resolve with B_{12} therapy and who have stopped N_2O; for such cases, imaging may not be necessary. We do not recommend routine brain MRI, unless suspecting an alternative disease process. Brain imaging in case series has either been universally normal,[16] or it has shown T2/fluid attenuated inversion recovery (FLAIR) hyperintense white matter lesions in the frontal, periventricular and centrum semiovale regions.[21]

Further investigations

In general, patients with N_2O-SACD do not need further investigation. In patients undergoing peripheral neurophysiology studies, the most common finding is a mixed axonal and demyelinating sensorimotor neuropathy, with the axonal component being more common than the demyelinating.[16 21 38]

TREATMENT AND ORGANISATION OF B_{12} INJECTIONS

Patient education and support

Patient education is the most important aspect of N_2O-SACD management. All patients should be warned that N_2O has caused their symptoms and that treatment with B_{12} will not work if they continue to use N_2O, since this would inactivate the B_{12} supplements. However, relapse following return to N_2O use is relatively common,[19] and so we encourage all patients to contact their local drug and alcohol service to support their abstinence.

Standard treatment regimen

As soon as N_2O-SACD is suspected in the emergency department, patients should start alternate daily intramuscular injections of 1 mg hydroxocobalamin without delay, continued for at least 2 weeks.[39 40] This treatment regimen is derived from the standard B_{12} course for traditional SACD.[39] In practice, we give the first injection in the emergency department, and subsequent injections as an outpatient on Mondays, Wednesdays and Fridays (figure 1). It is often difficult to organise vitamin B_{12} injections in primary care, especially at short notice, with real risk of treatment delay or incomplete treatment. In rare cases where a patient needs admission due to loss of functional independence, alternate day injections can start as an inpatient and switch to outpatient after discharge.

When to stop injections

It is often difficult to decide when to stop injections. Standard practice in traditional SACD is to continue alternate day injections until there is no further neurological improvement. We base N_2O-SACD treatment similarly on clinical progress. We therefore perform a standardised neurological examination at baseline and at 2 weeks, to track clinical improvement accurately (figure 1). Ideally, this includes an objective measure such as a 10 m walk test.

If the patient's condition has improved and then plateaued, we consider stopping the acute course of injections. However, if there is ongoing improvement at 2 weeks, we continue for a further 2 weeks (six more injections) and re-review each fortnight with the same standardised neurological examination until improvement has plateaued, at which point we stop the acute course of injections. In patients where N_2O is probably the sole cause of SACD and the serum B_{12} concentration was normal at first presentation, we do not continue B_{12} supplementation every 3 months long-term. Where coexisting B_{12} deficiency has probably contributed to a patient's vulnerability to N_2O-SACD, they should continue long-term supplementation with either B_{12} injections every 3–6 months or oral supplementation, depending on whether the deficiency is dietary or non-dietary.[34]

If there is no clinical improvement at all at 2 weeks, we rediscuss the diagnosis and scrutinise the patient's reported abstinence from N_2O. This is relatively rare, but it is reasonable to continue the injections for up to 8 weeks, as occasionally there is a delayed clinical improvement. Serum folate should be checked and replaced if low. Methionine or folic acid may also be possible treatment adjuncts[41 42]; however, there is no clinical evidence to support their routine use, and we do not do this in practice.

Consideration of oral supplementation

Intramuscular B_{12} supplementation is strongly preferable to oral supplements. However, a small minority of patients find injections unacceptable (eg, severe needle phobia). A potential alternative—but only in

preference to no supplementation—is oral cyanocobalamin 1000–2000 mcg once a day.[43]

MAXIMISING ADHERENCE AND ATTENDANCE

Patients with substance abuse issues are at higher risk of missing follow-up appointments and investigations[44]; our experience with N_2O-SACD suggests that heavy recreational N_2O users are no exception. However, several of our local interventions have improved follow-up attendance. First, a clear handover pathway between the emergency department, ambulatory care and neurology has helped to minimise the time between appointments and to clarify a standard point of contact for patients (figure 1). Second, standardising B_{12} injection days to Monday, Wednesday and Friday, at the same location, makes the injections schedule easy to remember. Third, we explicitly warn patients that two or more episodes of unannounced non-attendance may lead to discharge from the clinic. These interventions have improved attendance to appointments in our practice and reduced average time per B_{12} injection.

COORDINATION OF CARE

Where the first point of patient contact is in the emergency department, the initial injection, investigations and education occur at that time (figure 1), as patients sometimes do not attend further appointments. When the first point of contact is at the general practice, the first injection and investigations usually occur at the first hospital visit. Such patients often do not require admission but do need an urgent course of regular intramuscular injections and specialist input. This is relatively unique and does not fit easily into existing care delivery structures. Different centres seeing patients with N_2O-SACD naturally choose different pathways to deliver this care, which could be centred on neurology day units or on medical ambulatory care. In our practice, we treat patients in medical ambulatory care with close neurology input via a weekly N_2O-SACD multidisciplinary team meeting (figure 1). This meeting forms the crux of the patient pathway and consists of a neurologist, ambulatory care consultant and senior ambulatory care nurse. We complete several important steps to aid the overall delivery of care:

- We review cases and investigations and confirm the diagnosis.
- We determine the level of further investigation required (eg, MRI, nerve conduction studies/electromyography, testing for alternative causes of B_{12} deficiency such as pernicious anaemia).
- We decide how long to continue treatment.
- We clinically code N_2O -SACD to facilitate tracking of cases using the appropriate SNOMED codes: (subacute combined degeneration of the spinal cord due to use of N_2O (disorder)–SCTID: 1105051000000102 and N_2O misuse (finding)–SCTID: 1104931000000109).
- We book outpatient neurology follow-up for patients who have completed a treatment course, particularly for those with ongoing symptoms or with an uncertain diagnosis. Patients with classical presentations that have completed the diagnostic workup and recovered may not need further outpatient follow-up.

Medical ambulatory care is often well set up to deliver more intensive outpatient treatment. With close neurology input, we can effectively manage N_2O-SACD in this setting. Depending on available resources, other centres may wish to develop similar pathways, assign a dedicated consultant or create new settings to deliver care for this condition.

Key points

- Serum B_{12} is often normal in N_2O-SACD; functional B_{12} testing with methylmalonic acid or homocysteine can help to establish the diagnosis.
- Intramuscular B_{12} injection is a low-risk, high-impact treatment and should be given as promptly as possible once N_2O-SACD is suspected.
- B_{12} injections should continue until improvement reaches a plateau; abstinence from N_2O is crucial to recovery and allows B_{12} injections to work.
- Successful treatment of this condition requires a clear and smooth set of connections between the emergency department, ambulatory care and outpatient neurology.

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Contributors AJN, RMA, JW and AW conceived of the pathway and project. AJN led and supervised the project. RMA provided expert advice on biochemical testing. AJ, AP and LL collected recommendations for the pathway and conducted the Royal London Hospital audit. AP collated and wrote the manuscript. TH, NE, JBL and DN reviewed the manuscript, provided feedback on the pathway and gave expert opinions.

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