



Association of British Neurologists

Clinical Practice Guide: Nitrous Oxide-Induced Subacute Combined Degeneration of the Cord

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Purpose: To improve management of all patients with nitrous oxide-induced subacute combined degeneration of the cord (N₂O-SACD). This guideline is intended for use by neurologists, emergency clinicians, and general and acute physicians in the UK.

Method: These guidelines have been developed following an audit of N₂O-SACD care at the Royal London Hospital conducted by AP, LL, AJ, AW, JW, RMA and AJN. Feedback from patients with N₂O-SACD was gathered informally during the course of clinical care and was used to optimise the treatment pathway.

Evidence Base: Several very recent systematic reviews have summarised clinical findings and investigations in N₂O-SACD [1,2]. Guidance regarding recognition and

investigation are based on these reviews, the largest individual case series [3–7], and expert opinion. No prospective studies or clinical trials have been conducted in the treatment of N₂O-SACD. Hence, guidance regarding treatment is based on expert opinion.

External Review: The guidelines were sent out and reviewed by the ABN-affiliated acute neurology special interest group including CE, TH, NE, JBL and DN to improve their quality and national applicability and to identify regional barriers to implementation.

Updating Procedure: These guidelines will be reviewed once yearly by the Royal London Hospital N₂O-SACD audit group, taking into account newly published evidence.

Funding: Barts Charity. The funding body did not influence the content of these guidelines.

Conflicts of Interest: No financial or non-financial conflicts of interest declared by any author.

Background

The use of nitrous oxide (N₂O) has increased during the last decade and it is now the second most commonly used drug amongst people aged 16-24 in the UK [8,9]. In parallel to this, there has been a rise in cases of N₂O-SACD, a pattern of myeloneuropathy usually associated with severe vitamin B12 deficiency. It is recognised that 3.4% of N₂O users experience neurological symptoms consistent with SACD [10], but this may be an underestimate and cases of N₂O-SACD presenting to hospitals in the UK are increasing. This document aims to disseminate a combination of evidence-based and expert-recommended guidelines for the assessment and management of N₂O-SACD for the benefit of patients with N₂O-SACD and of clinicians seeing a rise in cases.

Guidance

1. Assessment and management of N₂O-SACD

Evidence regarding common clinical features and results of investigations in N₂O-SACD have been based on systematic reviews of case reports [1,2] and from specific case series where required [3–7] (Oxford CEBM level 4 evidence) along with expert clinical experience.

a. Recognition

- N₂O-SACD should be suspected in any patient presenting with gait disturbance, paraesthesia, weakness, numbness or ataxia and a history of N₂O use [1,2].
- Be aware that the history of N₂O use may not be forthcoming and if there is a high index of suspicion then biochemical tests and imaging should be undertaken with consent.

- Most patients presenting with N₂O-SACD are young (median age 22), male, and have used large amounts of N₂O regularly for weeks to months [1,2].
- In those with pre-existing B12 deficiency, N₂O-SACD can occur following relatively low exposure to N₂O. This includes during a single episode of anaesthesia or following modest recreational use [2,11]. Several patients have reported relatively low and “one-off” use of N₂O (e.g. 5-10 canisters) [7].
- Co-deficiencies (e.g. copper) may also decrease the threshold of N₂O use required to precipitate N₂O-SACD [12].
- Where the cause of N₂O-SACD is a single exposure to N₂O, symptoms appear to begin approximately 2-6 weeks after exposure [13].
- The diagnosis of N₂O-SACD is based on clinical judgement, and treatment should not be delayed whilst waiting for investigations to return.

b. Initial clinical assessment

- At initial emergency assessment (i.e. in the emergency department, same day emergency care, or ambulatory emergency care), a standardised assessment and treatment pathway for patients (shown in **Appendix 2**) should be followed.
- When patients with suspected N₂O-SACD present to primary care, patients may undergo the initial urgent assessment and treatment in primary care or via local ambulatory care or acute assessment units depending on availability of resources.
- Enquire specifically about bowel, bladder and sexual function. Urinary retention is reported in approximately 5% of N₂O-SACD [2]. Consider the need for a bladder scan or urinary catheter.
- Symptoms that should prompt careful consideration of other diagnoses include back pain, fevers, visual changes, progressively ascending weakness, labile blood pressure, and tachycardia or arrhythmia. Features in the medical history that should prompt consideration of alternative diagnoses include a history of cancer or immunosuppression (**Appendix 2**).

c. Quantification of N₂O use

- N₂O use should be quantified in terms of pattern (one-off use or regular), time period, and quantity.
- Use is best quantified in 8 gram canister-equivalents. Most canisters bought online are 8 grams (rarely 16 grams) and are known as “whippits”, “chargers”, or “nangs”.
- One cylinder (e.g. Smartwhip) is approximately equivalent to 75 canisters, and each £1 spent on use will buy approximately 3 canisters.

- The general public is able to buy nitrous for culinary use legally online. Patients occasionally also report using Entonox which is not for sale to the general public but may be stolen from healthcare facilities.
- Usually, patients inflate balloons using the container and inhale the gas from balloons. Filling enclosed spaces with N₂O or the use of masks poses a high risk of asphyxiation and this can occur without preceding dyspnoea [14].

d. Investigations

i. Blood testing

- All patients with suspected N₂O-SACD should have the following basic bloods tested at presentation as part of the routine medical workup: FBC, U&Es, LFTs, TFTs, B12, and folate.
- All patients with suspected N₂O-SACD should have blood taken for functional B12 testing as soon as possible. This can be with methylmalonic acid (MMA) or homocysteine, depending on local preference.
- For MMA, the blood sample should be conveyed to the laboratory as soon as possible after being drawn. For homocysteine, the blood sample should be placed on ice before being taken to the laboratory.
- MMA and homocysteine should first be stored by the laboratory whilst B12 levels are tested. If B12 levels are below the reference range, it is usually not necessary for the laboratory to process the MMA or homocysteine as they would not alter the diagnosis or management. However, if B12 levels return in the reference range (as is the case in approximately 50% of cases [1]), the MMA or homocysteine samples should be processed.
- B12, MMA and homocysteine normalise after abstinence from N₂O and treatment with hydroxocobalamin, and blood samples should be drawn taken at initial presentation (however, treatment with hydroxocobalamin treatment should not be delayed for testing).
- An MMA concentration above 0.75 µmol/L is highly suggestive of functional B12 deficiency. 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. Whilst all hospitals should have access to these services, return of results may take several days.
- Elevated levels of homocysteine can reflect B12 deficiency, but may also be elevated in folate deficiency, renal failure, and patients with genetic polymorphisms [15]. Hence, concurrent folate measurement is essential for interpretation of results.
- MCV and haemoglobin are usually normal in N₂O-SACD patients, unlike in traditional SACD [1,2].
- Zinc and copper testing is optional depending on the clinical certainty of N₂O-SACD, but co-deficiency of copper has been found in some patients.

- All patients should be offered testing for HIV and syphilis as they can cause treatable myelopathy which presents similarly.
- Do not wait for blood results to return prior to starting urgent treatment (below).

ii. Spinal cord imaging

- Most patients should have outpatient imaging with an MRI of the cervical and thoracic spine to confirm the diagnosis and exclude alternative pathology. Axial images should be taken in order to establish the presence or absence of the “inverted V” sign seen in N₂O-SACD [5].
- The urgency of MRI should be guided by the severity of the clinical case and the level of uncertainty in the diagnosis.
- In 50-100% of N₂O-SACD patients, MRI shows dorsal column T2-hyperintensity in the cervical or upper thoracic spinal cord with C3-5 most commonly affected [1,4,6,7].
- Patients where there is clear history of N₂O use and mild classical symptoms that completely resolve with treatment may not require an MRI.

iii. Nerve conduction studies and electromyography

- Nerve conduction studies and electromyography are not required to make a diagnosis of N₂O-SACD, but should be considered if/when coexistent neuropathy is suspected.
- In N₂O-SACD, the most common finding is a mixed axonal and demyelinating sensorimotor neuropathy, with the axonal component being more common than the demyelinating [4,6,16].

a. Management

No studies exist regarding best treatment options in N₂O-SACD. Hence, treatment guidance has been adapted from the treatment of subacute combined degeneration in those with B12 deficiency due to pernicious anaemia or dietary deficiency. This guidance regarding management of N₂O-SACD is based on expert opinion, mechanism-based reasoning, and usual clinical practice (Oxford CEBM Level 5 Evidence).

i. Emergency management

- Early treatment may be critical and should not be delayed.
- Intramuscular hydroxocobalamin 1 mg should be given as soon as possible following assessment [17].

- Hydroxocobalamin solution for injection should be stocked in emergency and acute medical settings or in a location easily accessible to staff from these areas.
- Intramuscular injections with hydroxocobalamin 1 mg should be given once every two days for at least 2 weeks [17].
- Patients should be educated that total abstinence from N₂O together with continued engagement with follow-up B12 injections is crucial for optimum recovery.
- Hydroxocobalamin injections are generally very safe and well tolerated with a minimal side effect profile [17], and so benefits of treating suspected cases generally outweigh the suspected risks of delaying treatment.
- Patients should be advised that continued use of N₂O may lead to continued worsening of neurological function and that this may not be reversible.
- All patients should be explicitly warned that B12 injections and supplementation will likely not be successful if they continue to use N₂O.
- Consider referring patients to the local drug and alcohol service to aid abstinence from N₂O.
- Consider referring patients with N₂O-SACD to physiotherapy and occupational health when necessary.

ii. Organisation of follow-up hydroxocobalamin injections

- In most cases, patients will be suitable for outpatient management with "safety-netting" if their condition worsens.
- Patients should be referred to a hospital medical ambulatory care, same day emergency care (SDEC), neurology day unit, or equivalent department for ongoing B12 injections and follow-up.
- In general, management of N₂O-SACD patients may be risky in primary care, as access to injections can be difficult to organise at short notice and patients often require further specialist input.
- Patients may need to be admitted to hospital if they have lost their functional independence or where symptom management is not possible as an outpatient. When patients are admitted, hydroxocobalamin injections should continue as an inpatient once every two days.

iii. Continued management and injections as an outpatient

- An appointment in an outpatient department, such as medical ambulatory care, SDEC, or neurology day unit, should be organised within 2 days of the initial presentation and treatment.

- At the first appointment, the patient should be assessed in a standardised manner that is as objective as possible and includes quantitative tests such as a timed ten metre walk, in order to allow serial monitoring of neurological function. An example examination proforma is shown in **Appendix 1**.
- An intramuscular injection of hydroxocobalamin 1 mg should be given at the first appointment and continue once every two days for at least 2 weeks. A suggested regimen for injections would be Monday, Wednesday and Friday each week in order to simplify the logistics of treatment at the weekend.
- Patients with substance abuse issues attend less follow-up appointments than those without [18]. Explain the importance of compliance to the patient and consider the use of compliance aids such as appointment cards, text message reminders, and patient contracts.

iv. Determining when to stop injections

- There is uncertainty regarding the optimum treatment length for N₂O-SACD and no studies have compared different lengths of treatment.
- After a treatment course of 2 weeks (6 injections):
 - Re-review patients using the standardised neurological assessment and objective measures (**Appendix 1**).
 - If clinical improvement is ongoing at 2 weeks, book 2 further week of injections (Mon/Wed/Fri).
 - If there has been no improvement whatsoever, abstinence from N₂O should be scrutinised and the patient should be re-discussed with the N₂O-SACD MDT or lead consultant for N₂O-SACD (see below). In this scenario, which is relatively rare, delayed improvement has been anecdotally reported and it is reasonable to continue B12 injections for up to 8 weeks.
- Continue to assess once every two weeks using the standardised neurological assessment, and book two further weeks of injections until improvement has plateaued.
- When improvement plateaus, the patient may be discharged from medical ambulatory care / SDEC / neurology day unit.
- Patients with incomplete recovery or with any diagnostic uncertainty should be prioritised for follow-up in outpatient neurology clinics. Those with complete recovery and firm diagnoses may not need outpatient neurology follow-up.

2. Establishment of a N₂O-SACD MDT / lead for N₂O-SACD

- Where a centre or NHS trust has a significant number of N₂O-SACD cases, a N₂O-SACD MDT should be considered. This can consist of a neurology

consultant, medical consultant, and nurse. Alternatively, an interested clinician can be identified as an N₂O-SACD lead.

- The N₂O-SACD lead clinician or MDT can provide the following services:
 - Review patients and their investigations (e.g. MRI), and the need for further investigations (e.g. nerve conduction studies, electromyography, additional/interval imaging or further tests for co-deficiencies or alternative vitamin B12-related pathologies such as pernicious anaemia).
 - Check that the correct clinical coding (i.e. SNOMED) term has been used in the electronic record. The SCTID numbers for the conditions are as follows:
 - Subacute combined degeneration of the spinal cord due to use of nitrous oxide (disorder) – **SCTID: 1105051000000102**
 - Nitrous oxide misuse (finding) – **SCTID: 1104931000000109**
 - Discuss 'edge cases', such as those that warrant further duration of treatment despite limited improvement.

3. Concurrent B12 deficiency

- Patients with low pre-exposure B12 are more vulnerable to N₂O-SACD at shorter, smaller exposures to N₂O [2]. In these cases, consider the possibility that N₂O use may have unmasked previously asymptomatic B12 deficiency [11].
- In the clinical history, screen for risk factors and symptoms associated with low B12 levels. This includes certain dietary preferences (e.g. a diet low in animal products); previous gastric or small bowel operations; symptoms of gastrointestinal malabsorption; or alcohol excess.
- Be aware that several common drugs can decrease B12 levels, including proton pump inhibitors (PPIs), H₂-receptor antagonists, biguanides (e.g. metformin), potassium supplements, and the oral contraceptive pill [19].
- If the B12 level is below the reference range on presentation or the patient has developed N₂O-SACD after only modest exposure to N₂O:
 - Test for pernicious anaemia using anti-intrinsic factor antibodies and anti-gastric parietal cell antibodies.
 - Consider testing for coeliac disease and markers of generalised malabsorption (e.g. ferritin and vitamin D).

4. Continuation of long-term B12 supplementation

- Where SACD is clearly related to N₂O use and B12 levels were within the reference range on presentation, patients do not necessarily need long term B12 supplementation after the acute parenteral course is completed as above.

- In patients with B12 below the reference range at presentation, continue B12 supplementation after the initial course is completed according to whether the deficiency is thought to be diet or non-diet related [20].
- If the deficiency is thought to be diet related, advise patients to either take cyanocobalamin tablets 50-150 mcg daily or have a twice-yearly 1 mg hydroxocobalamin injection. If the dietary B12 content improves through dietary modification then this may not need to be continued life-long.
- If the B12 deficiency is **not** thought to be diet related (e.g. pernicious anaemia) patients should continue 1mg hydroxocobalamin injections every 2-3 months lifelong.

5. Oral B12 supplementation

- Intramuscular supplementation according to the protocol above is **strongly** preferable compared to oral supplementation.
- In cases where a patient refuses ongoing B12 injections (e.g. the patient is severely needle-phobic), offer oral B12 supplementation in preference to no supplementation. Potential oral B12 options include cyanocobalamin 1000 – 2000 mcg once daily, which may be as effective as parenteral supplementation [21].
- Patients receiving oral supplementation should receive regular reviews at the same frequency as those receiving injections.

6. Adjuncts to B12 therapy

- Folic acid and methionine have been suggested as adjuncts in the treatment of N₂O-SACD [22,23], however, there is no evidence regarding their effectiveness and no recommendation can currently be given regarding their use.
- Folate should be tested and replaced if low.

7. Relapse

- If patients re-present with new symptoms of N₂O-SACD following previous N₂O-SACD treatment, reassess N₂O use and consider alternative diagnoses
- When relapse occurs, treatment via the above pathway should be re-instituted.

8. Monitoring / auditing criteria

- Prospective studies, along with randomised trials, are needed to assess recovery and how treatment can be optimised (e.g. treatment length, treatment adjuncts).

- For auditing logistical success in the treatment pathway, we recommend conducting a yearly audit measuring days taken per B12 injection, percentage of patients who receive functional B12 testing and MRI, and percentage of missed appointments.

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Appendix 1: Examination proforma – Designed to standardise repeated examinations outpatient ambulatory care / SDEC / neurology day unit and neurology follow-up to track clinical progress.

Gait description (Do they require walking aids?):			
Romberg's test:		Time for ten metre walk test:	
Note that findings are generally symmetrical in N ₂ O-SACD			
Right side:		Left side:	
Joint position sense loss to:		Joint position sense loss to:	
UL:	LL:	UL:	LL:
Pinprick sensory loss to:		Pinprick sensory loss to:	
UL:	LL:	UL:	LL:
Power (MRC flex/extend 0-5):		Power (MRC flex/extend 0-5):	
Hip f: e:	Shoulder - f: e:	Hip - f: e:	Shoulder - f: e:
Knee f: e:	Elbow - f: e:	Knee - f: e:	Elbow - f: e:
Foot d: p:	Grasp -	Foot - d: p:	Grasp -
Reflexes (0 to ++++):		Reflexes (0 to ++++):	
Biceps:	Knee: Ankle:	Biceps:	Knee: Ankle:
Plantar:		Plantar:	
Other possible findings in N ₂ O-SACD			
Lhermitte's:		Psychiatric disturbance:	
Pseudo-athetosis:		Vision change:	
Bowel and bladder disturbances (do they need a bladder scan?):			

Appendix 2: Pathway infographic for a suggested pathway for N₂O-SACD. This figure also appears in Paris et al. (2023) [24].

