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Research Article

Establishing a Link between Duration of Nitrous Oxide (N_20) Abuse and Recovery Time from Functional Demyelination: A Systematic Review

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Abstract

Background: Nitrous Oxide (N_20) is widely used as an adjunctive anesthetic agent with analgesic properties. Unfortunately, owing to the euphoric properties experienced by users, the abuse and addiction of N_20 is becoming a global problem. Surprisingly, in England and Wales alone, nitrous oxide was the third most used drug in 2018, 2019, and 2020, after cannabis and cocaine. Several cases have been reported in the past, but there have been limited efforts to draw a comprehensive conclusion on the relationship between the duration of N_20 abuse and the recovery time from such neurological impairments, which is crucial for developing effective treatment strategies and providing accurate prognostic information.

Method: This systematic review was conducted by comprehensively searching five electronic databases, including PubMed, CINAHL, MEDLINE, Cochrane, and Web of Science, with data spanning from 2010 to 2023. The retrieved studies were independently and collectively screened by both authors and represented using a Prisma Flowchart.

Result: The outcomes emerged from 27 studies comprising 32 participants. Patients were young, between the ages of 18 and 53 years, with a common presentation of neurological symptoms. Laboratory markers, such as MMA and homocysteine, were elevated despite normal or low serum B12 concentrations. The duration of N_2O use also showed a strong positive relationship with the duration of recovery ($r=0.675$, $p=0.0003$).

Conclusion: This review significantly contributes to our understanding of N_20 abuse-induced neurological injuries by providing valuable insights into clinical presentations, diagnostic markers, and treatment outcomes. A notable finding of this study is the positive association between the duration of N_20 abuse and recovery time, indicating that individuals with prolonged abuse may experience prolonged recovery periods and potentially poorer prognoses.

Keywords: subacute combined degeneration or functional demyelination, nitrous oxide or N_20, vitamin B12, cobalamin, abuse or recreational use, case report or case series, treatment or intervention or therapy.

Introduction

Nitrous oxide (N_20) is widely used as an adjunct anesthetic agent with analgesic properties [1]. It performs its functions by acting on multiple targets. To function as an analgesia, it acts on opioid receptors by stimulating endogenous opioids receptors. The anxiolytic effects are potentiated by GABA-A activation, and lastly, the anesthetic effect is via non-competitive inhibition of N-Methyl-D-Aspartate (NMDA) in the central nervous system [1]. Unfortunately, due to its euphoric properties experienced by users [2], the abuse and addiction of N_20 is becoming a global problem. In England and Wales alone, N_20 was the third most used drug in 2018, 2019, and 2020, after cannabis and cocaine [3]. The availability of N_20 and ease of purchase by young people are other reasons for concern. Grocery stores and online retailers sell them in boxes with numerous metal canisters that contain inhalational N_20 [4].

Vitamin B12 (cobalamin) is a critical vitamin necessary for optimum functioning of the nervous system. Specifically, it helps in the maintain the myelin sheath. Any disturbances in vitamin B12 metabolism resulting in deficiency could lead to demyelination of the spinal cord matter, resulting in Subacute Combined Degeneration (SCD) [5]. Vitamin B12 can be indirectly depleted when N_20 is inhaled at high concentrations, which can change vitamin B12 from its active, bivalent form to its inactive, monovalent form [6]. The precise mechanism by which N_20 leads to neural damage remains unclear and various models have been proposed to explain this phenomenon. These models include reduced methylation of phospholipids in the myelin sheath [7], downregulation of Erk1/2 and upregulation of myelin basic protein [8], increased production of myelinotrophic cytokines and growth factors, such as IL-6 and EGF [9], increased expression of neurotrophic gene factors [10], and control of the normal prion protein concentration in the nervous system [11]. Regardless how this happens the treatment goal has been to restore vitamin B12 levels in these individuals.

Several cases of N_20 induced functional demyelination have been reported in the past, but there have been limited efforts to draw a comprehensive conclusion on the relationship between the duration of N_20 abuse and recovery time from such neurological impairments. The objective of this research is twofold: (1) to perform a systematic review of the existing literature to outline the investigations of reported cases of N_20 induced SCD, and (2) to assess how the duration of N_20 abuse affects the recovery time following therapy.

Methods

Eligibility Criteria

A summary of the eligibility criteria is presented Table 1. The extracted data provided answers as they related to the aims and objectives of this research.

Inclusion and Exclusion Criteria

Inclusion	Exclusion
· Patients who experience sub-acute degeneration of spinal cord after excessive recreational ingestion of nitrous oxide.	· Patient who experiences sub-acute degeneration of spinal cord after nitrous oxide anesthesia or analgesia or any other source apart from recreational use.
· Case series or case reports	· Review articles
· Studies in English Language	· Studies in foreign language
· Human studies	·Animal studies

Table 1: Showing eligibility summary.

Database search: This systematic review was conducted by comprehensively searching five electronic databases, including PubMed, CINAHL, MEDLINE, Cochrane, and Web of Science, with data spanning from 2010 to 2023.

Search Strategy and Study Selection

The search identified 97 articles, and both the authors screened the retrieved studies independently and collectively. Relevant keywords and synonyms were used, including functional demyelination (subacute combined degeneration), Nitrous Oxide (N_2O), and overdose (abuse). Endnotes were used to remove duplicates [18]. After titles and abstract review, 45 articles were excluded because they did not meet the inclusion criteria. Furthermore, after full text review, seven articles were excluded because they described anesthesia use of nitrous oxide rather than recreational abuse, and they reported sub-acute degeneration due to conditions other than N_2O abuse. The search strategy is expressed in the prismatic flowchart shown in Figure 1.

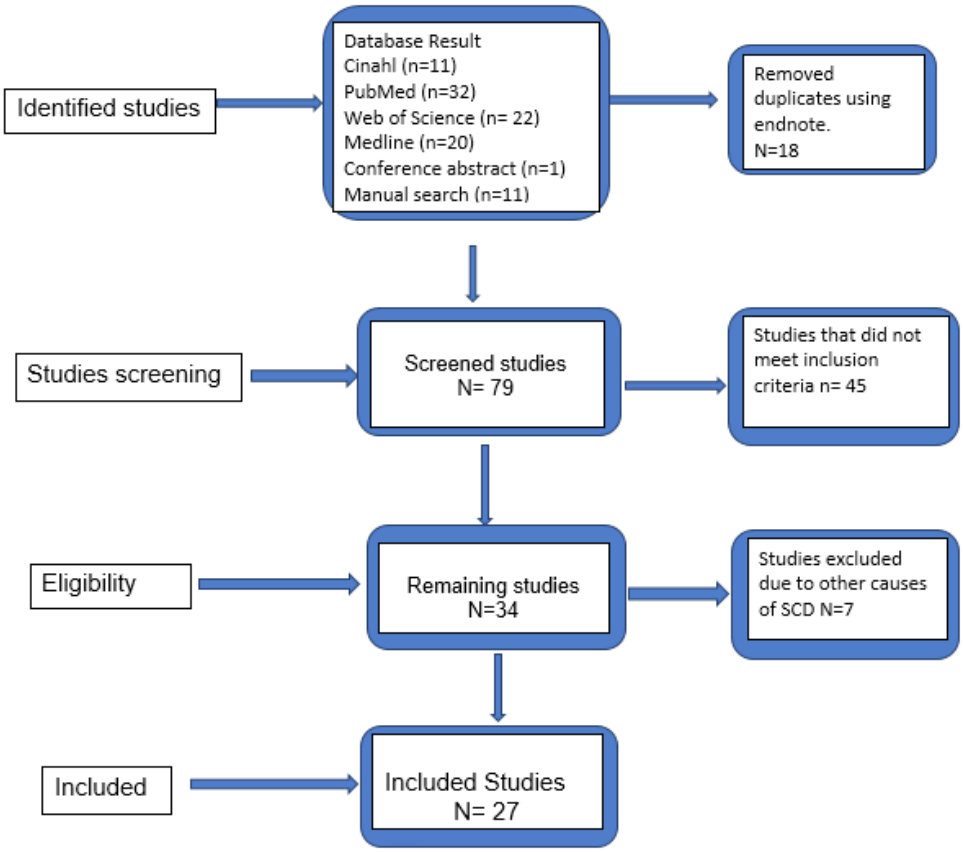

Figure 1: PRISMA flowchart, which illustrates the selection process.

Quality Assessment/ Risk of Bias

Study Characteristics

Twenty-seven studies were selected for the systematic review [12-38] with studies characteristics shown in Table 2 below. The studies had a total of 24 case reports and three case series emerging from the USA, United Kingdom, China, Korea, Australia, Belgium, the Netherlands, and Canada. The outcome considered was subacute combined spinal cord degeneration, also called demyelination of the spinal cord. It is defined as neurological symptoms and abnormal cord signals associated with N_2O abuse, with or without laboratory or radiological manifestations [39].

Research Author, year	Location	Study design	No. of Participant, Age/ sex	Duration of N_20 abuse	Recovery time with therapy
Agarwal, et al., 2021 [12]	USA	Case-Report	1 19/M	100-500 N_2O catridges weekly for 12months	not specified
Attri and Janian, 2020 [13]	Carlifonia, USA	Case-Report	1 49/M	24-whippits of N_2O daily for several months	6 weeks
Charters, et al., 2021 [14]	United Kingdom	Case-Report	1 18/M	over 30-whippits of N_2O one off use	24 weeks
Chen, et al., 2022 [15]	China	Case-Report	1 18/F	N_2O use every week for 36months	19 days

Cheng, et al., 2013 [16]	Australia	Case-Report	1 22/F	N_2O use 3 times a week for 2 months	72 weeks
Chin, et al., 2015 [17]	USA	Case-Report	1 38/M	60 months of N_2O abuse	3 weeks
Choi, et al., 2019 [18]	Korea	Case-series	2 24/M 22/F	daily recreational use for 5 months and 3months respectively	6 weeks and 12 weeks respectively
Duque, et al., 2015 [19]	USA	Case-Report	1 20/F	not specified	4 weeks
Khan, et al., 2023 [20]	United Kingdom	Case-Report	1 28/F	not specified	4 weeks
Kingma et al., 2022 [21]	USA	Case-Report	1 21/F	50 whippets of N_2O daily	signed out of treatment after 3 weeks
Marotta and Kesserwani, 2020 [22]	USA	Case-Report	1 41/M	8-30 canisters of N_2O per day for 12months	2 weeks
McArdle and Gaillard, 2020 [23]	Australia	Case-series	4 24F 19/F 19/F 18/F	N_2O use 200times per day for 9months/ N_2O use for few weeks/ not specified/N_2O use for over 6months	Persistent moderate sensorimotor neuropathy after 2 weeks/ not specified for 3 cases
Nadal Bosch, et al., 2023 [24]	USA	Case-Report	1 23/M	12 months use of N_2O	continuous recovery after 5 days
Omotosho, et al., 2022 [25]	USA	Case-Report	1 32/M	chronic recreational use of N_2O	6 weeks
Onrust and Frequin, 2019 [26]	Netherland	Case-Report	1 30/F	50 whippets a day for 2 months	8 weeks
Pugliese, et al., 2015 [27]	USA	Case-Report	1 27/F	100-200 whippets per day, 3-4 days a week for 36 months	discharged after 3 days despite unresolved neurologic symptoms
Samia, et al., 2020 [28]	USA	Case-Report	1 53/M	daily use of N_2O multiple times for 1 month	8 weeks
Seed and Jogia, 2020 [29]	United Kingdom	Case-Report	1 22/M	120-288 canisters of N_2O weekly for 36months	8 weeks

Shariff, et al., 2023 [30]	United Kingdom	Case-Report	1 19/M	1-2 cylinder of N_2O every day for 3-4months	4 weeks
Shoults, 2016 [31]	British Columbia, Canada	Case-Report	1 34/F	10-12 whippits of N_2O daily for 6months	lost to follow up
Simpson and Mukherji, 2023 [32]	USA	Case-Report	1 44/M	50-100 canisters per day for several months	continuous rehabilitation after 6weeks
Srichawla, 2022 [33]	USA	Case-Report	1 44/M	80-100 canisters of N_2O daily for 3months	continuous recovery after 10days
Strauss and Qadri, 2021 [34]	USA	Case-Report	1 45/M	not specified	24 weeks
Van Berkel, et al., 2021 [35]	Belgium	Case-Report	1 40/M	not specified	20 weeks
Wu, et al., 2022 [36]	USA	Case-Report	1 32/M	N_2O us for several months	continuous recovery after 5days
Wu, et al., 2023 [37]	China	Case-Report	1 18/M	3-4 times a week N_2O use for 6 months	12 weeks
Zhao, et al., 2020 [38]	China	Case-series	2 21/M 18/F	16-24 canisters 5 times a week for 1 month/ 40 canisters per day for 1 month	16 weeks and 36 weeks respectively

Table 2: Showing Study characteristics.

Data Extraction, Synthesis, and Analysis

The authors extracted the data. The extracted data included patient characteristics, clinical presentation, N_2O abuse duration, treatment duration, and recovery duration. Data analysis was performed using SPSS version 22. Pearson's correlation coefficient was calculated on the data-sets to demonstrate the relationship between the duration of N_2O and other parameters.

Results

Clinical Presentation

The duration from symptom initiation to hospital presentation ranged from one day to four months. Patients exhibited various clinical manifestations, including limb weakness (predominantly affecting the lower and upper limbs), paresthesia or tingling sensation, abnormal gait, and poor balancing effort which occasionally result in falls [12-38]. Other less recurring symptoms include voiding difficulties [18,23,27,32,34], abdominal or back pain [19,27,37], and, infrequently, cognitive impairment accompanied by insomnia, confusion, memory loss, and visual and auditory hallucinations [17,23,33,37]. Erectile dysfunction was reported in one of the studies [35]. These symptoms collectively delineate the clinical presentation of patients upon admission to the hospital, manifesting after variable durations of N_2O abuse. The mean age of the patients was 22.8 years with a range of 18 to 53 years, and a male-to-female ratio of 9:7.

Length of N_2O use and duration of recovery

Parameter	Duration of N_2O abuse (Months)	Duration of recovery or complete resolution of symptoms (Weeks)
Mean	14.5	17
Median	9	12
Range	3.0-36	3.0-72.0

Table 3: Descriptive Value of the Length of N_2O use and the Duration of Recovery.

The average length of nitrous oxide use in the included studies was 14.5 months a median value of 9.0 months; the shortest length of use was 3 months and the longest 36 months. The results of the included studies showed that the duration of recovery from signs and symptoms associated with nitrous abuse showed an average value of 17 weeks and a median value of 12 weeks, with the earliest complete resolution of symptoms occurring in 3 weeks and the longest occurring in 72 weeks. This recovery occurred after cessation of N_2O abuse, and initial treatment with intramuscular hydroxocobalamin and rehabilitation therapy was noted in many cases. Use of extra therapy such as intravenous immunoglobulin, large doses of folic acid, and vitamin D supplements were noted in some case report [19,22,24,36]. However, their role in recovery could not be ascertained.

Laboratory Investigation

Parameter	Folate Level (>4ng/mL n=7)	MMA level (87-318 mmol/L n=16)	Homocysteine (2.0-15.0 umol/L) n=17	MCV (80-100fL) n=16	B12 (200-900pg/mL) n=31	Hb (g/dL) n=15
Mean	12.23	3157.53	69.62	97.41	361.09	11.77
Median	11.9	2920	58.9	96.8	178	11.75
Range	6.5-20	324-10739	10-213	87.6-108.4	70-2000	7.5-15.1

Tables 4: Descriptive Values of the Various Parameters Determined in the Included Studies

The mean and median values of the Folate Level of the included studies were 12.23 and 11.9 ng/mL respectively with the Folate Level ranging from 6.5 minimum to 20 maxima. Equally, the MMA level had a mean and median value were 3157.53 and 2920 mmol/L with a 324-10739 range. The homocysteine level of the included studies had a mean value of 69.62 µmol/L and a median value of 58.9 µmol/L within a range of 10-213 µmol/L. The Mean Cell Value (MCV) of the included studies had mean and median values of 97.41 and 96.8fL with a range value of 87.6-108.4 fL. The B12 values of the included studies had mean and median values of 361.09 and 178 pg/mL, respectively, with a range value of 70-2000 pg/mL. The mean and median Hb of the included studies were 11.77 and 11.75 g/dL with a range Hb value of 7.5-15.1.

Parameter	**Folate Level (>4ng/mL n=32 n (%)**	**MMA level (87-318nmol/L) n=32n (%)**	**Homocysteine (2.0-15.0 µmol/L) n=32 n (%)**	**MCV (80-100fL) n=32 n (%)**	**B12 (200-900pg/mL) n=32 n (%)**	**Hb (g/dL) n=32 n (%)**
Normal	14 (43.75)	1(3.12)	5(15.62)	15(46.88)	10(31.25)	13(40.62)
Low	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	18(56.25)	8(25.00)
High	0 (0.0)	15 (46.88)	15 (46.88)	4(12.5)	3(9.38)	0(0.0)
N/A	18 (56.25)	16 (50.00)	12 (37.50)	13(40.62)	1(3.12)	11(34.38)

Table 5: Frequency of the State of the Various Parameters from the Included Studies

Parameter	r-value	p-value	Remark
Folate Level	0.844	0.034	Statistical insignificant
MMA level	-0.51	0.06	Statistical insignificant
Homocysteine	-0.25	0.389	Statistical insignificant
B12	0.086	0.672	Statistical insignificant
MCV	0.202	0.471	Statistical insignificant
HB	-0.223	0.424	Statistical insignificant
Duration of recovery	0.675	0.003	Statistical significant

Table 6: Correlation between the length of N_2O and some parameters.

N/A=Not available, r-value=correlation coefficient, p-value=statistical significance level, $p<0.005$=statistical significance, while $p>0.05$, is statistically insignificant.

The results showed that folate levels increased with increasing length of N_2O use (r-value=0.844, p=0.034), which demonstrated a very strong positive (direct) correlation between the length of N_2O abuse and folate level of the patients. In addition, the duration of N_2O use also showed a strong positive relationship with the duration of recovery (r=0.675, p=0.0003). This means that increasing the duration of N_2O increases the duration of recovery. However, an inverse relationship was observed between MMA, homocysteine, and Hb levels, although the relationship was not statistically significant.

Imaging and other investigations:

Of the 32 patients included in this study, 31 underwent Magnetic Resonance Imaging (MRI) at some point during the evaluation for N2O induced SCD [12-38], while only 6 considered a lumbar puncture [13,24,28,30,32,37]. Spine MRI reports revealed a range of abnormalities that were predominantly related to spinal cord degeneration. Notable findings include abnormal cord signals in the posterior columns at the T11-T12 level [13]; abnormal T2 signals within the cervical spinal cord from C2-C6 extending to the thoracic spinal level [12,14,16,20,21,23,24,26-28,30-33,35,38]; and diffuse high signals in the T2W1 sequence of the spinal cord [37]. A consistent observation across several cases was the presence of abnormal cord signal intensity in the bilateral dorsal columns, from C1-C2 through C6-C7 and T4-T5 through T9-T10, and a characteristic inverted V-shaped or triangle-shaped signal [14,15,18-20,22,23,25,29,30,31,36] indicative of subacute degeneration. Additionally, mild disc protrusion or attenuation in the cervical and lumbar regions was reported in two studies [14,17] and a normal MRI scan in another study [34].

Lumbar puncture was performed for Cerebrospinal Fluid (CSF) analysis primarily to rule out infectious etiologies such as meningitis and encephalitis as potential differential diagnoses. The results indicated normal CSF findings [13,30,37], with CSF protein elevated in one study [24], and an incidental observation of disc protrusion was reported in two patients [28,32].

Discussion

The case reports and case series emerged from high impact countries, where the availability of N_2O is relatively easier. The studies were carefully recruited and appraised following the use of the JBI's critical appraisal tool for quality of case series and reports. See appendix 1.

The finding of this review supports previous evidence ascertaining neurological presentation as the most common presentation encountered in patients with N_2O abuse [40,5,41,40]. Neuropsychiatric presentation is rare, apart from one case report where visual and auditory hallucinations were described [17]. Difficulties in passing urine were also described in five of the included studies [18,23,27,32,34]. The findings are similar to those of other studies [41-43]. Moreover, these symptoms occurring in the younger age group further increased the diagnostic likelihood of N_2O-induced neurological injury.

As discussed earlier, vitamin B12 depletion plays a central role in N_2O-induced SCD. This review predominantly showed low-to-normal levels of serum B12 (Table 5). This pattern is consistent with a systematic review by Garakani, et al. [5]. In contrast, review by Marsden, et al. [40] showed that patients predominantly had normal levels of B12. This could be due to the self-administration of vitamin B12 supplements prior to hospital admission. Furthermore, normal B12 levels reflect the consequence of N_2O abuse being functional, rather than an absolute deficiency of B12 vitamin [43]. Thus, regardless of serum B12 levels, intramuscular hydroxocobalamin (vitamin B12) remains the drug of choice. MMA and homocysteine are strong indicators of serum vitamin B12 levels. The MMA concentration has an inverse relationship with the concentration of active B12 [44]. Hence, MMA tends to increase with depleted serum B12 levels. Increased homocysteine levels can indicate a lack of vitamin B12, but they can also be high in cases of folate deficiency, kidney failure, and individuals with genetic variations such as polymorphisms [45]. Therefore, it is crucial to assess folate levels alongside homocysteine levels to accurately interpret the findings. Our study showed significantly

increased levels of MMA and homocysteine, but normal folate levels (Table 5). This is consistent with the results of previous studies [43,46]. Recent treatment guideline for N_20 induced SACD only require MMA and homocysteine in individuals with normal serum B12 concentrations [47]. The MRI findings of abnormal cord signalling in the dorsal column or a characteristic inverted V-shaped affecting the cervical and thoracic were consistent with other findings [42,43,48].

Limited research has examined the duration of N_20 abuse in relation to recovery. This study found a positive correlation between the duration of N_20 abuse and recovery time with treatment, including B12 replacement ($r=0.675$, $p=0.0003$). The longer the duration of abuse, the longer the recovery time; in most cases, patients never completely record the resolution of symptoms. Slow recovery can also be attributed to the patients being lost to follow-up. In a comprehensive analysis of documented cases, it was found that out of 59 patients with available follow-up data, symptoms completely disappeared in only 17% of cases, showed partial improvement in 78%, and remained unchanged in 5% of patients with no signs of improvement [5].

This study aligns with cognitive-behavioural theory, which emphasizes the interplay between thoughts, feelings, and behaviors and how they influence each other [49,50]. Regardless of the treatment modality, abstinence from further use of N_20 is necessary to kick-start the recovery process. The behavior of patients in adopting new practices of abstinence is crucial to their recovery. The finding of a positive association between the duration of N_20 abuse and recovery time reflects the behavioral component of the theory, highlighting the impact of behavioral patterns (*i.e.*, prolonged substance abuse) on treatment outcomes. This underscores the importance of addressing and modifying maladaptive behaviours associated with substance abuse to improve recovery trajectories and patient outcomes. Overall, the study's findings align with the cognitive-behavioural theory in clinical practice by emphasizing the importance of understanding cognitive processes, recognizing maladaptive behaviors, and implementing tailored interventions to optimize treatment outcomes for individuals with N_20 abuse-induced neurological injury. However, it is important to note that this connection may be more speculative than scientific, as the authors did not have information on the beliefs of the patients included in this study.

Limitation

Many of the included studies did not record parameters in a single unit. The error associated with the conversion rate may impede the results. The authors are aware of the pre-analytical and analytical differences specific to each laboratory. Hence, there was a likelihood of laboratory bias in the collected data. Second, because our study relied on case or series reports, it is susceptible to information or publication bias. Disparity in reporting varied greatly among studies that lacked sufficient data to assess the resolution of symptoms and treatment modalities.

Conclusion

This review contributes significantly to our understanding of N_20 abuse-induced neurological injury by providing valuable insights into clinical presentations, diagnostic markers, and treatment outcomes. This underscores the importance of conducting thorough assessments and implementing tailored interventions to improve patient outcomes.

Moreover, this review highlights the typical clinical presentations of N_20 abuse-induced neurological injury, emphasizing its recognition in clinical settings, particularly among younger patients. Laboratory markers such as MMA and homocysteine are frequently elevated even in the presence of normal or elevated serum B12 concentrations, suggesting their utility in diagnosis.

A notable finding of this study was the positive association between the duration of N_20 abuse and recovery time, indicating that individuals with prolonged abuse may experience prolonged recovery periods and potentially poorer prognoses. This underscores the need for further research to investigate the impact of prolonged N_20 abuse on recovery trajectories and inform therapeutic strategies accordingly.

Contributions by authors

This study was conducted in collaboration with the two authors. Both authors (Author A – Emmanuel Ojeabuo Oisakede and Author B – Olawunmi Oluwakemi Oyedeji) contributed to this work. Author A wrote all the chapters. Author B extracted the data, read, and contributed to all chapters, providing extra insight and accuracy checks to all chapters especially the search strategy and outcome. Both authors have read and approved the final manuscript.

Declaration

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Data availability statement: Secondary data were used for this study, which were clearly reproducible upon request.

Consent and Ethical Approval: It is not applicable.

Competing Interests: Authors have declared that no competing interests exist. All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Appendix 1: JBI's critical appraisal tool [51,52].

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Agarwal, et al., 2021 [12]	Y	U	Y	Y	Y	Y	N	Y
Attri and Janian, 2020 [13]	Y	Y	Y	Y	Y	Y	U	Y
Charters, et al., 2021 [14]	Y	Y	Y	Y	Y	Y	N	Y
Chen, et al., 2022 [15]	Y	U	Y	Y	Y	Y	N	Y
Cheng, et al., 2013 [16]	Y	U	Y	Y	Y	Y	N	Y
Chin, et al., 2015 [17]	Y	Y	Y	Y	Y	Y	N	Y
Choi, et al., 2019 [18]	Y	Y	Y	Y	Y	Y	N	Y
Duque, et al., 2015 [19]	Y	Y	Y	Y	Y	Y	N	Y
Khan, et al., 2023 [20]	Y	U	Y	Y	Y	Y	N	Y
Kingma, et al., 2022 [21]	Y	N	Y	Y	Y	Y	N	Y
Marotta and Kesserwani, 2020 [22]	Y	Y	Y	Y	Y	Y	N	Y
McArdle and Gaillard, 2020 [23]	Y	U	Y	Y	Y	N	N	Y
Nadal Bosch, et al., 2023 [24]	Y	U	Y	Y	Y	Y	N	Y
Omotosho, et al., 2022 [25]	Y	Y	Y	Y	Y	Y	N	Y
Onrust and Frequin, 2019 [26]	Y	U	Y	Y	Y	Y	N	Y
Pugliese, et al., 2015 [27]	Y	Y	Y	Y	Y	Y	N	Y
Samia, et al., 2020 [28]	Y	Y	Y	Y	Y	Y	N	Y
Seed and Jogia, 2020 [29]	Y	Y	Y	Y	Y	Y	N	Y
Shariff, et al., 2023 [30]	Y	Y	Y	Y	Y	Y	N	Y
Shoults, 2016 [31]	Y	Y	Y	Y	Y	U	N	Y
Simpson and Mukherji, 2023 [32]	Y	Y	Y	Y	Y	Y	N	Y
Srichawla, 2022 [33]	Y	U	Y	Y	Y	Y	N	Y
Strauss and Qadri, 2021 [34]	Y	U	Y	Y	Y	Y	N	Y
Van Berkel et al., 2021 [35]	Y	Y	Y	Y	Y	Y	N	Y
Wu et al., 2022 [36]	Y	Y	Y	Y	Y	Y	N	Y
Wu et al., 2023 [37]	Y	Y	Y	Y	Y	Y	N	Y
Zhao et al., 2020 [38]	Y	Y	Y	Y	Y	Y	N	Y

Yes – Y

No- N

Unclear-U.

Not Applicable-NA

1. Were patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?
4. Were diagnostic tests or assessment methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?