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The Ventilatory Management of Paediatric Central Sleep Apnoea: A Systematic Review

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Abstract

Purpose: Paediatric central sleep apnoea (CSA) occurs more frequently in the presence of another medical condition. This systematic review aimed to determine the effectiveness of oxygen therapy and non-invasive ventilation (NIV) for children with CSA and additional underlying comorbidities. **Method**: A search was undertaken of CINAHL Complete, Emcare, Scopus, MEDLINE, and PubMed with forward and backward citations for studies published between database inception and the 5th of May 2022. Articles of any study design or quality were included, excluding systematic reviews, letters, or study protocols. Articles had to involve only paediatric patients with a diagnosis of CSA with another underlying pathology and incorporate a detailed treatment protocol involving oxygen therapy or NIV to be eligible for inclusion. Relevant articles selected for the review were thoroughly analysed and appraised using the Crowe Critical Appraisal Tool. Using the Synthesis Without Meta-analysis (SWiM) reporting guideline, a narrative synthesis was utilised due to heterogeneity in the populations, interventions, outcomes, and designs of included studies. **Results**: Of 3295 identified articles, 13 were eligible, with critical appraisal detecting common weaknesses in the areas of ethical matters, results, and discussion sections of articles (mean total score of 69%). Nocturnal oxygen therapy and NIV positively impacted polysomnography results. A wide range of underlying diagnoses were associated with CSA, however, definitive conclusions surrounding the interventions' effectiveness and applicability to specific presentations could not be drawn. **Conclusions**: Research quality was generally poor, with studies' external validity, strengths/limitations, and suggestions for future research rarely described. The presence of reporting bias and a lack of analysis, integration, and interpretation methods were also limitations. Future research should include larger samples through the organisation of multi-centred trials to increase the generalisability and validity of the results. The impact of patient adherence to interventions should also be explored.

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ABSTRACT

Purpose: Paediatric central sleep apnoea (CSA) occurs more frequently in the presence of another medical condition. This systematic review aimed to determine the effectiveness of oxygen therapy and non-invasive ventilation (NIV) for children with CSA and additional underlying comorbidities. **Method**: A search was undertaken of CINAHL Complete, Emcare, Scopus, MEDLINE, and PubMed with forward and backward citations for studies published between database inception and the 5th of May 2022. Articles of any study design or quality were included, excluding systematic reviews, letters, or study protocols. Articles had to involve only paediatric patients with a diagnosis of CSA with another underlying pathology and incorporate a detailed treatment protocol involving oxygen therapy or NIV to be eligible for inclusion. Relevant articles selected for the review were thoroughly analysed and appraised using the Crowe Critical Appraisal Tool. Using the Synthesis Without Meta-analysis (SWiM) reporting guideline, a narrative synthesis was utilised due to heterogeneity in the populations, interventions, outcomes, and designs of included studies. **Results**: Of 3295 identified articles, 13 were eligible, with critical appraisal detecting common weaknesses in the areas of ethical matters, results, and discussion sections of articles (mean total score of 69%). Nocturnal oxygen therapy and NIV positively impacted polysomnography results. A wide range of underlying diagnoses were associated with CSA, however, definitive conclusions surrounding the interventions' effectiveness and applicability to specific presentations could not be drawn. **Conclusions**: Research quality was generally poor, with studies' external validity, strengths/limitations, and suggestions for future research rarely described. The presence of reporting bias and a lack of analysis, integration, and interpretation methods were also limitations. Future research should include larger samples through the organisation of multi-centred trials to increase the generalisability and validity of the results. The impact of patient adherence to interventions should also be explored.

Keywords: sleep-disordered breathing, central sleep apnoea, children, non-invasive ventilation, oxygen therapy

INTRODUCTION

Central sleep apnoea (CSA) is a sleep-related respiratory syndrome characterised by a diminished or absent ventilatory effort.[1] Central apnoeas are common during sleep in both neonates and infants.[1] They decrease over time with the maturation of the central nervous system theorised as being a significant contributor.[1] The prevalence of CSA is four percent in children, occurring more frequently in the presence of another medical condition.[2] The retrospective chart review by Felix et al found an underlying neurological disorder was the most typical cause of paediatric CSA in patients who were not preterm.[2] A review by McLaren et al effectively classified paediatric CSA into three main categories: physiologic, idiopathic, and CSA with specific medical conditions.[3] These are illustrated in Table 1.

Table 1. Paediatric Classification of Central Sleep Apnoea[3]

Physiologic central sleep apnoea	Sleep onset, post-arousal, post-sigh, phasic rapid eye movement sleep, body movement, sleep-wake transition.	
Idiopathic central sleep apnoea	There are polysomnographic features and symptoms of sleep-disordered breathing without an underlying medical condition, hypoventilation, or Cheyne-Stokes breathing.	
Central sleep apnoea with specific medical conditions	CSA with possible hypoventilation	Arnold–Chiari malformations, central nervous system tumours, neuromuscular disorders, thoracic cage disease, chronic renal failure and dialysis patients.
	CSA with genetic conditions	Achondroplasia, congenital central hypoventilation syndrome, Down syndrome, Rett syndrome, Vici syndrome, Smith–Magennis syndrome.
	CSA with other sleep-disordered breathing conditions	Obstructive sleep apnoea, continuous positive airway pressure emergent central sleep apnoea.
	CSA with heart conditions	Heart failure, idiopathic pulmonary arterial hypertension.
	CSA with congenital craniofacial abnormalities	Craniosynostosis, Pierre–Robin sequence.
	CSA with neurogenetic/neurological conditions	Prader–Willi syndrome, Joubert syndrome.
	CSA with endocrine conditions	Obesity, hypothyroidism.
	CSA with upper airway abnormalities	Laryngomalacia, Choanal Atresia.
	CSA with other medical conditions	Gastroesophageal reflux, prematurity, bronchopulmonary dysplasia, Tetralogy of Fallot.
	CSA with miscellaneous conditions	Behavioural hyperventilation, high altitude.

The gold standard test for diagnosis of CSA is a full-night in-laboratory polysomnography with a sleep technician who carefully monitors the parameters.[4] Polysomnography measures physiological factors, including airflow, electro-oculography, electroencephalography, electrocardiogram, body position, chin and leg electromyography, pulse oximetry, and measurements of thoracic and abdominal respiratory effort.[4] The central apnoea index (CAI), which is the number of apnoeic events of central origin during each hour of sleep, is the measure used to identify CSA.[3] Five or more central events per hour is considered clinically significant.[3] In addition, it is crucial to consider congenital central hypoventilation syndrome (CCHS), where genetic investigations may be commenced.[5] A rare neurocristopathy, CCHS is characterised by a decreased sensitivity to hypoxia and hypercapnia, which occurs mainly during sleep, and an absence of automatic control of respiration.[5] An autosomal dominant disease, it occurs due to frameshift mutations in the paired like homeobox 2B gene and heterozygous polyalanine expansions.[5]

The clinical presentation for paediatric CSA can vary, meaning that it cannot be reliably identified based on a specific set of signs and symptoms or history.[3] In some cases, CSA has been found incidentally in children with Down syndrome, achondroplasia, and Arnold–Chiari malformations following polysomnographic recordings.[2] On the other hand, sleep complaints are common in children with idiopathic CSA.[6] These include gasping, daytime sleepiness, respiratory pauses, frequent night-time awakenings, snoring, and restless sleep.[6]

Intervention strategies for CSA in adults aim to prevent sleep-related oxygen desaturations and normalise the disordered breathing. The severity/degree of sleep symptomatology determines treatment urgency, with management of underlying medical conditions abolishing symptoms in mild CSA cases.[7] Non-invasive ventilation (NIV) is the first-line treatment modality for more severe cases.[7]

Given the various devices and modes, there are several considerations before initiating NIV. Although current evidence provides little guidance on optimal treatment strategies for individual CSA subtypes, continuous positive airway pressure (CPAP) is generally chosen initially, due to its efficacy amongst heart failure patients, a population group where contemporary CSA treatment evidence is largely focussed.[7]

The therapeutic management for paediatric CSA is poorly analysed, with little evidence surrounding the preferred treatment for specific conditions.[3,8] Surgically, cervico-occipital decompression can correct CSA in patients with Arnold Chiari malformations, with ear, nose and throat surgery improving CSA in patients with a combination of CSA and obstructive sleep apnoea (OSA).[3,8] Watchful waiting, individualised on a clinical basis, is selected for patients who may display a growth-related improvement due to anatomical changes, in conditions such as Pierre Robin sequence, achondroplasia, Arnold Chiari type 1 malformation (ACM1), Down syndrome, or with a disorder that may improve with growth, for example, Prader Willi syndrome.[8,9] Weight management is commonly utilised, in addition to either nocturnal oxygen therapy or NIV, depending on the contribution/presence of OSA.[3,8] Overall, the treatment direction is dependent on the tolerance and clinical symptoms of CSA, nocturnal gas exchange anomalies, the underlying medical condition, and the polysomnography results.[8]

Therefore, the systematic review aimed to explore the effectiveness of oxygen therapy and NIV, due to their frequency of use in adult populations, while also exploring treatment applicability to specific paediatric CSA presentations. The quality of available evidence was also analysed, to judge its value and relevance to clinical practice.

METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was adhered to during the formulation of this systematic review.[10] This guideline recommends utilising the Population, Intervention, Comparators, and Outcomes (PICO) structure to format the overarching research question: “what is the effectiveness of oxygen therapy and NIV for children with CSA and additional underlying comorbidities?”

Eligibility Criteria

Articles of any study design or level of evidence were included, excluding systematic reviews, meta-analyses, letters, or study protocols, published from electronic database establishment to the literature search date. In addition to satisfying the above criteria, studies were also deemed eligible if they were published in a peer-reviewed journal, in English, with access to the full text.

Population

Articles had to involve only paediatric patients (< 18 years of age) with a diagnosis of CSA to be eligible for inclusion. An underlying pathology was also required due to a higher likelihood of physiotherapeutic involvement amongst these patients. Articles were excluded if the study population primarily consisted of participants with apnoea of prematurity, CCHS, rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation syndrome, or Haddad's syndrome diagnoses. Finally, studies were also excluded if they involved neonatal/preterm participants (< 28 days old or born before 37 weeks of pregnancy).[11]

Intervention

To be included, a study had to incorporate a detailed (i.e., including parameters) rehabilitation/treatment protocol involving oxygen therapy or NIV, specifically addressing CSA. Only these two interventions were deemed eligible due to their known applicability to adult presentations and an aim of identifying treatment interventions for children with CSA that may fall under the scope of practice of a physiotherapist.

Comparators

The presence of comparators did not influence eligibility for inclusion, as the efficacy of NIV and oxygen therapy were being evaluated in isolation and restricting this component may have unintentionally excluded relevant articles.

Outcome

Reporting of the effectiveness of the intervention/s on patient outcomes was required to warrant eligibility. Relevant outcomes included polysomnographic data (specifically the CAI) and observed/reported symptoms, such as gasping, daytime sleepiness, respiratory pauses, frequent night-time awakenings, snoring, and restless sleep.[6]

Design

Multiple systematic reviews registered with the International Prospective Register of Systematic Reviews (PROSPERO) examine the efficacy and safety of pharmacological management and NIV for CSA, but they only include studies that involve adult cohorts. Furthermore, the only systematic reviews which involve paediatric sleep-disordered breathing focus on OSA. With no registered

reviews investigating the therapeutic management of paediatric CSA, this presented a unique opportunity to explore where current knowledge may be lacking and guide future research.

Protocol and Registration

This systematic review was registered on PROSPERO under the registration number: CRD42021286555.

Funding, Supports and Conflicts of Interest

No financial or non-financial supports were sourced for this review. The authors have no conflicts of interest to disclose.

Information Sources

On the 5th of May 2022, a systematic electronic literature search was conducted, utilising CINAHL Complete (EBSCOhost, 1937 to present), Emcare (Ovid, 1995 to present), Scopus (1788 to present), MEDLINE (Ovid, 1946 to present), and PubMed (1946 to present). On the 30th of May 2022, reference lists of eligible articles were manually screened, and the Scopus interface was utilised to perform a forward citation search to identify further potentially eligible articles.

Search Strategy

Relevant search terms were combined with Boolean operators to devise the search strategy, which was approved by both authors and an assisting librarian. An extension of the PRISMA statement, the PRISMA-S guideline, was utilised to assist with reporting the literature search components of this systematic review.[10] Congruent with the research question and eligibility criteria, the PICO framework was applied to develop the search strategy.[10] As the databases chosen for the review were a mix of subject-heading and keyword databases, the strategy was individualised to ensure a comprehensive literature search. Consistent with the eligibility criteria and aims, no date, study design, or language limitations were applied to the search strategy. These strategies are outlined in Appendix A, with an example also displayed below:

CINAHL Complete (EBSCOhost) Strategy

1. (MH "Sleep Apnea, Central+")
2. (MH "Infant+") OR (MH "Child+") OR (MH "Adolescence+")
3. (MH "Respiration, Artificial+")
4. (MH "Oxygen Therapy+")
5. (MH "Ventilators, Mechanical") OR (MH "Oxygen Delivery Devices+")
6. (MH "Oxygen Therapy Care (Saba CCC)") OR (MH "Pulmonary Care (Saba CCC)+")
7. (MH "Oxygen Therapy (Iowa NIC)") OR (MH "Mechanical Ventilation (Iowa NIC)") OR (MH "Ventilation Assistance (Iowa NIC)")
8. (MH "Physical Therapy+")
9. S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. S1 AND S2 AND S9

Selection Process

The PRISMA 2020 guidelines were utilised to assist two reviewers when screening the articles obtained from the electronic literature search.[10] EndNote 20 was employed to manage relevant studies following identification. After removing duplicates, two reviewers independently screened titles and abstracts of all articles retrieved. Full-text copies were then acquired for articles deemed pertinent, which were then further analysed to establish eligibility. Discussion between reviewers occurred in a situation where they disagreed, reviewing the eligibility criteria to reach a consensus on whether an article should be included or excluded.

Data Collection

Two researchers (KH and AJ), working independently, completed the extraction of relevant data from articles deemed eligible for inclusion in a table specifically created to suit the project's aims. The extracted information was compared, with a discussion resolving discrepancies between reviewers. For missing or unclear data, any assumptions made were documented and explained. Essential items of the data extraction table included study details, methodology (participant sample and demographics, intervention/s, statistical analyses), outcomes, and results.

Critical Appraisal

Relevant articles selected for the review were thoroughly analysed and appraised using the Crowe Critical Appraisal Tool (CCAT).[12] The CCAT facilitates appraisal by allowing a wide range of research designs to be directly compared.[12] The CCAT was primarily chosen due to evidence surrounding its high inter-rater reliability, obtaining consistency intraclass correlation coefficients from 0.91 to 0.64.[13]

Two researchers independently determined the quality of a study using the CCAT, assigning a score from zero to five for eight categories containing 22 items based on satisfaction of item descriptors.[12] The appraisers had to consider the weighting of each descriptor, as they are not all of equal significance.[12] To summarise the overall quality of the study, a total score out of 40 and a percentage score were calculated and documented.[12] Regarding the single categories, scores of 4-5 were considered high quality, 2-3 moderate quality, and 0-1 low quality. Regarding the overall score, percentages ≥75% were considered high quality, 51%-74% moderate quality, and ≤50% low quality. Again, disagreements between researchers were resolved through discussion and comparison of CCAT scores.

Synthesis Methods

Due to heterogeneity in the populations, interventions, outcomes, and study designs highlighted in a preliminary scoping review, a meta-analysis of effect estimates was not an appropriate data synthesis method.[14] Therefore, a narrative synthesis was the most viable approach. One researcher organised the included studies into groups based on the type of intervention they employed. Following this, the details of the management strategies, their efficacy, and sample populations were summarised. Serious shortcomings of this method have been identified, including a lack of transparent links between study-level data, the synthesis, and the conclusions; an inadequate description of the methods used; and insufficient documentation of the synthesis's limitations.[15] The Synthesis Without Meta-analysis (SWiM) reporting guideline was utilised to limit the impact of these deficiencies.[15]

In addition to the narrative synthesis, pertinent data was tabulated to display each study's main findings and characteristics. Data was abstracted on the intervention/management strategy addressing CSA, characteristics and size of the sample population, and study results. A separate table detailed the score obtained in every category of the CCAT.

RESULTS

Three thousand two hundred ninety-five articles were identified from the electronic literature search. Of these, 447 were discovered to be duplicates and were subsequently removed using Endnote 20. The titles, key terms, and abstracts of 2848 articles were then screened, resulting in the exclusion of 2747 records. Eighteen articles could not be retrieved, meaning 83 full-text articles were assessed for eligibility. Seventy-one were deemed ineligible for this review as they did not meet the inclusion and exclusion criteria, leaving 12 eligible articles. Using these chosen articles, citing reference searching was then performed, discovering 71 potentially relevant publications. Eight could not be retrieved, and after analysis of the remaining 63, one was deemed eligible. As a result, a total of 13 articles were selected and synthesised. Reasons for full-text record exclusion and study flow are depicted in Figure 1. Record characteristics pertinent to the research question and aims of the review were extracted and summarised and are displayed in Table 2.

Figure 1. PRISMA Flow Chart[10]

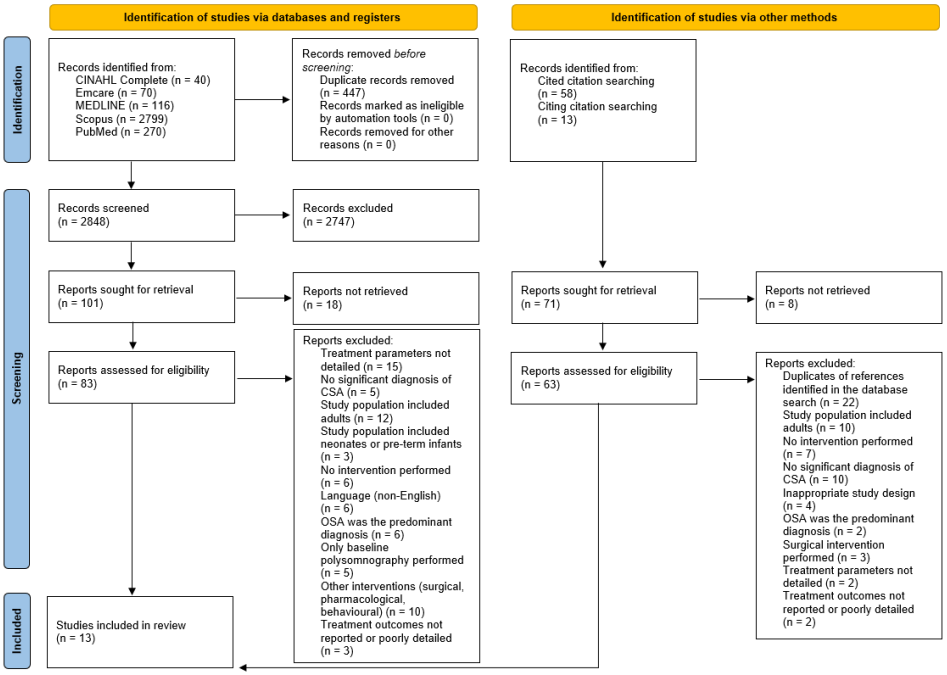


Table 2. Characteristics of Included Studies

Study	Intervention/s Delivered	Sample Size and Characteristics	PSG Results
Bin-Hasan et al[16]	Supplementary O2 via NP (3 L/min). Treprostinil via subcutaneous infusion.	Total sample size: 1 10-year-old female, new diagnosis of IPAH.	Room air: CAI=6.3; SpO2 nadir=57%. Oxygen therapy: CAI=5.7; SpO2 nadir=72%. Oxygen therapy and Treprostinil: CAI=0.5; SpO2 nadir=90%.
Campbell et al[17]	All patients received supplementary oxygen via NP. Patient 1: 1L/min. Patient 2: 1L/min. Patient 3: 1L/min.	Total sample size: 3 All patients had mutations in NALCN. Patient 1: female, aged 3 years. Patient 2: male, aged 2 years. Patient 3: female, aged 8 months.	*Patient 1:* Baseline study: apnoeas at a frequency of 39 events per hour. Oxygen therapy: no drop in SpO2 and markedly fewer respiratory pauses. *Patient 2:* Baseline study: complete cessation of respiratory effort and associated drop in SpO2 at a frequency of 37 per hour. Oxygen therapy: respiratory pauses were less frequent and not associated with a drop in SpO2. *Patient 3:* Baseline study: a mixture of central and obstructive episodes, obstructive events were resolved via T&A. Oxygen therapy: almost complete abolition of the central events.
Cohen et al[9]	Nocturnal supplemental low flow oxygen (0.25–1.0 L/min) trialled during a PSG. Interface for oxygen delivery not detailed.	Total sample size: 44 Size of intervention group: 9 The median age was 1.9 years (range 0.3–15.6 years). PWS diagnoses.	Baseline study: median CAI=14 (range 5, 68); median SpO2 nadir=70% (range 52,92); maximum TcCO2=47mmHg (range 44, 51). Oxygen therapy: median CAI=1 (range 0, 6; p=0.008); median SpO2 nadir=82% (range 64, 95; p=0.080); maximum TcCO2=45mmHg (range 36, 53; p=0.121).
Er et al[18]	CPAP (titration) – 6cmH2O. BiPAP without a backup respiratory rate – 14.3/7.8cmH2O. BiPAP with backup respiratory rate of 12 - 19/10cmH2O. ASV.	Total sample size: 1 TECSA developed after standard T&A for OSA.	Under CPAP titration: AHI=6, 85.2% central events. CPAP treatment for 3 months (nasal mask): AHI=30, 54.9% central events. CPAP treatment for 19 months (full-face mask): AHI=40.9, 73.2% central events. BiPAP without a backup respiratory rate: AHI=28.1, 90.4% central events. BiPAP with a backup respiratory rate: smooth breathing with no central apnoeas. ASV: AHI=3.8, 98.3% central events.
Hong et al[19]	Patient 1: S/T mode, 16/6cmH2O, backup rate of 20 breaths/min, supplemental O2 (1 L/min) through the circuit via a small nasal mask. Patient 2: timed mode, 8/4cmH2O, backup rate of 20 breaths/min, I-time 0.8 seconds, via a small nasal interface.	Total sample size: 2 Patient 1 (8-year-old male): diagnosis of pathogenic UNC80 mutation. Patient 2 (20-month-old female): diagnosis of KCNJ11 mutation.	*Patient 1:* Baseline study: CAI=213.5. BiPAP: successful resolution of central apnoea and desaturations. *Patient 2:* Baseline study: CAI=131.1; SpO2 nadir=74%. BiPAP: improvement in respiratory status, died before follow-up PSG.

Huang et al[20]	BiPAP: S/T mode, 11/7 cmH2O, backup rate=18. Minimum time the driver spends in IPAP, and rise time=200 milliseconds, maximum time in IPAP=1.5 seconds.	Total sample size: 1 4-year-old male, diagnosis of diffuse midline glioma. Presented with CSA, PH, syncopal episodes.	Baseline study: CAI=14.7; SpO2 nadir=71%. Post-intervention: CAI=5.7; SpO2 nadir=78%.
Joseph et al[21]	Nocturnal oxygen therapy (0.1L/min). Suboccipital craniectomy + cervical laminectomy.	Total sample size: 1 57-day-old male infant, new diagnosis of ACM1.	Baseline study: AHI=9.5; CAI=7.7. Oxygen therapy: resolution of desaturations, apnoeas persisted. Post-surgery: AHI=2.3; CAI=0.9.
Martirosyan and Malhotra[22]	Posterior fossa decompressive surgery. BiPAP – S/T mode with a setting of 10/6 cmH2O and a backup rate of 12 breaths/min.	Total sample size: 1 9-year-old male with diagnosis of KFS and new ACM1 finding.	Baseline study: CAI=4.81; SpO2 nadir=89%. 7 weeks post-surgery: CAI=41.6; SpO2 nadir=81%. NIV: CAI=0; SpO2 nadir=93%.
Morelli et al[23]	Corticosteroid therapy (methylprednisolone). Immunosuppression (azathioprine). Prophylactic AB therapy. BiPAP - spontaneous mode (no backup rate), 11/7cmH2O.	Total sample size: 1 14-year-old-female admitted to ED with respiratory distress. New diagnoses of NMOSD.	Baseline study: CSA observed with intermittent hypoxia and a respiratory rate of 3. BiPAP: no apnoea was observed. Intervention maintained after 3 years as PSG without NIV revealed a CAI of 110.
Quera-Salva and Guilleminault[24]	Nasal CPAP (increased from 5 to 15cm/H2O). Doxapram hydrochloride infusion. PNPV trialled at 14, 12, and 10 breaths/min. Nasal CPAP + PNPV at 10 breaths/min (pressures +2 to -30cmH2O).	Total sample size: 1 11-year-old male, presenting 1.5 years post-TBI.	Baseline study: RDI, REM sleep=99; RDI, non-REM sleep=75; SpO2 nadir=75%. Nasal CPAP: RDI, REM sleep=91; RDI, non-REM sleep=68; SpO2 nadir=79%. Doxapram hydrochloride: no change in number of apnoeic episodes or SpO2. PNPV: RDI, REM sleep=86; RDI, non-REM sleep=72; SpO2 nadir=59%. Nasal CPAP + PNPV: RDI, REM sleep=0; RDI, non-REM sleep=0; SpO2 nadir=95%.
Strang and Katwa[25]	BiPAP with backup respiratory rate of 12 – 12/6cmH2O. Posterior fossa decompressive surgery.	Total sample size: 1 10-year-old male with new diagnosis of ACM1.	Pre-surgery: CAI=53; SpO2 nadir=54%. 4 months: CAI=9; SpO2 nadir=83%. 15 months: CAI=26; SpO2 nadir=88%. 36 months: CAI=9.6; SpO2 nadir=87%. 48 months: CAI=9; SpO2 nadir=89%. 68 months: CAI=13; SpO2 nadir=80%. 88 months: CAI=1.1; SpO2 nadir=92%.
Taytard et al[26]	Supplementary oxygen via NP (1 L/min). BiPAP - S/T mode, 11/4cmH2O, and breathing frequency of 14 breaths/minute.	Total sample size: 1 12-year-old female, new diagnosis JSRD. Known history of CSA.	Room air: CAI=10; SpO2 nadir=87%. Oxygen therapy: CAI=12; SpO2 nadir=88%. BiPAP: CAI=0; SpO2 nadir=91%.
Yosunkaya and Pekcan[27]	CPAP – automatic titration, 10cmH2O and 95th percentile pressures. BiPAP – S/T mode, 14/8 cmH2O, backup rate of 15 via an oronasal mask.	Total sample size: 1 13-year-old female with new ACM1 diagnosis, developed CSA from PAP therapy.	Baseline study: CAI=32.4; SpO2 nadir=63%. CPAP therapy: CAI=83.2; SpO2 nadir=75%. BiPAP for 3 months: CAI=2; SpO2 nadir=79%.

Note. In studies utilising bilevel positive airway pressure, inspiratory and expiratory positive airway pressures are displayed as a fraction (IPAP/EPAPcmH2O). The central apnoea index is reported in events/hour.

Abbreviations: AB, antibiotic; ACM1, Arnold Chiari malformation type 1; AHI, apnoea-hypopnoea index; ASV, adaptive-servo ventilation; BiPAP, bilevel positive airway pressure; CAI, central apnoea index; CPAP, continuous positive airway pressure; CSA, central sleep apnoea; ED, emergency department; IPAH, idiopathic pulmonary arterial hypertension; IPAP, inspiratory positive airway pressure; JSRD, Joubert syndrome and related disorders; KFS, Klippel Feil syndrome; NIV, non-invasive ventilation; NMOSD, neuromyelitis optica spectrum disorder; NP, nasal prongs; OSA, obstructive sleep apnoea; PAP, positive airway pressure; PH, pulmonary hypertension; PNPV, portable negative pressure ventilator; PSG, polysomnography; PWS, Prader-Willi syndrome; RDI, respiratory disturbance index; REM, rapid eye movement; S/T, spontaneous/timed; SpO2, oxygen saturation; T&A, adenotonsillectomy; TBI, traumatic brain injury; TcCO2, transcutaneous carbon dioxide; TECSA, treatment-emergent central sleep apnoea.

Table 3. Crowe Critical Appraisal Results

Study Authors (Year)	Crowe Critical Appraisal Tool Results									
	Individual Categories (/5)								Total Scores	
	Prelim	Intro	Design	Samp	DC	EM	Results	Disc	0-40	%
Cohen et al[9]	5	5	3	3	4	4	4	4	32	80
Er et al[18]	5	5	4	4	3	3	4	3	31	78
Morelli et al[23]	5	4	3	4	4	4	3	3	30	75
Strang and Katwa[25]	5	4	4	4	3	2	4	4	30	75
Taytard et al[26]	5	5	3	4	4	2	4	3	30	75
Bin-Hasan et al[16]	5	4	3	4	3	3	3	3	28	70
Hong et al[19]	5	5	3	4	3	2	2	4	28	70
Huang et al[20]	5	2	4	4	4	2	4	3	28	70
Martirosyan and Malhotra[22]	4	5	4	4	3	2	3	3	28	70
Quera-Salva and Guilleminault[24]	3	1	4	3	4	3	4	3	25	63
Yosunkaya and Pekcan[27]	4	2	3	4	4	1	4	3	25	63
Campbell et al[17]	4	1	2	4	3	4	2	4	24	60
Joseph et al[21]	2	0	3	3	2	2	2	3	17	43

Note. The table highlights the individual category scores for each article using the CCAT and the total overall score (last two columns on the right-end side). For both single category and total overall scores, high, moderate, and low quality are represented by green, yellow, and red cells, respectively.
Abbreviations: DC, data collection; Disc, discussion; EM, ethical matters; Intro, introduction; Prelim, preliminaries; Samp, sampling.

Narrative Synthesis of Evidence

Critical Appraisal Results

Of the 13 included records, there was one retrospective cohort study, nine case studies, two case series, and one clinical pearl.[9,16-27] It is important to note that all included studies were either descriptive or observational.[9,16-27] As highlighted in Table 3, the CCAT identified an amount of variability in the quality of the included studies, with total scores ranging from 43% to 80%. The mean total CCAT score was 69%.

The intervention or outcome measures were not precisely detailed in six and five studies, respectively, potential confounding variables were present in five studies, and there was potential reporting bias in five studies.[9,16-19,21,23,26,27] Maturation, attrition, and observation biases were potentially present in one study each, and there was possible information bias in four studies.[9,17,19,23,26,27] In seven separate studies, the data collection protocol was inadequately detailed, omitting details regarding exactly how data was collected.[16-19,21,22,25] The CCAT identified ethical concerns in a vast majority of the included studies, with articles commonly neglecting to state if informed consent was gained, potential subjectivities, sources of funding, and if ethical approval was sought. The main concern identified in the results category was that raw data, specifically polysomnography findings, were not present in six studies.[16,17,19,21-23] No studies described their generalisability/external validity, and nine studies were missing an important aspect of their concluding remarks, either highlighting strengths/limitations or suggesting future studies.[16,18,20-24,26,27]

Oxygen Therapy

Five studies involved using supplementary oxygen as an intervention strategy for paediatric CSA.[9,16,17,21,26] Underlying diagnoses included idiopathic pulmonary arterial hypertension, ACM1, cerebellar dysplasia affecting the vermis (with none of the usual clinical features associated with Joubert syndrome and related disorders), growth hormone naïve Prader Willi Syndrome, and compound heterozygous mutations in NALCN associated with facial dysmorphism, developmental delay, and hypotonia.[9,16,17,21,26]

Intervention Characteristics

The oxygen flow applied was similar in four of the studies, ranging between 0.1-1 litres/minute.[9,17,21,26] The only outlier was Bin-Hasan et al, who implemented a much higher flow rate titrated at three litres/minute.[16] Four studies provided supplementary oxygen therapy through a nasal cannula.[16,17,21,26] Cohen et al failed to detail the interface for oxygen delivery.[9] A common flaw amongst these articles was poor reporting of the duration of the intervention. After initiating oxygen therapy, Campbell et al do not detail whether it was continued after polysomnography testing.[17] Similarly, it was unable to be determined if the intervention was continued during/after the study period in two separate studies.[16,26] Joseph et al do not specify how long supplementary oxygen was trialled before a neurosurgical intervention was pursued and the time that surgery was performed compared to the initial diagnosis of CSA.[21] Finally, no study commented on the patient's adherence/tolerance to initiating supplementary oxygen therapy during sleep.

Effectiveness of Interventions

A commonality across four of the studies was that they utilised polysomnography data as primary outcomes, measuring and calculating variables such as sleep efficiency, mean sleep oxygen saturation (SpO2), oxygen desaturation index (ODI), CAI, obstructive apnoea index (OAI), apnoea-hypopnoea index (AHI), mean periodic breathing cycle length, mean apnoea length, and mean transcutaneous carbon dioxide measurements (TcCO2). Supplementary oxygen therapy displayed mixed success in managing CSA amongst the varying patient populations. The CAI was significantly decreased to a median of 1 (range 0, 6; $p = 0.008$) for patients in Cohen et al's study.[9] There was no corresponding hypercapnic response with oxygen treatment: maximum TcCO2 (mmHg) was 45 (range 36–53) with supplemental oxygen and 47 (range 44–51) on room air ($p=0.121$).[9] Only a trend towards significant improvement in the SpO2 nadir was seen, from 70% to 82% (range 64, 95; $p = 0.080$).[9] The study did not discuss the association between effective oxygen therapy and anthropometric data.[9] Campbell et al reported similar effects of oxygen therapy; however, the stated results do not include raw polysomnography data and are unspecific.[17] After initiation of oxygen therapy in two patients, oxygen desaturations ceased, and markedly fewer respiratory pauses were observed.[17] Subsequent studies showed a marked periodicity of the events, which can likely be associated with the effect of different stages of sleep.[17] For the third patient, there was an almost complete abolition of the apnoeic events, and at ten years of age, there was no evidence of any change in sleep breathing abnormality.[17] The impact of supplementary oxygen therapy on non-respiratory related symptoms and social/behavioural development was not explored.[17]

Bin-Hasan et al reported that following the initiation of supplementary oxygen therapy, the frequency of the SpO2 desaturations and periodic breathing events did not significantly change in their patient (CAI=5.7).[16] However, the average baseline SpO2 was 97%, improved from 93% off oxygen, and the degree of desaturations improved from 57% to 72%.[16] More significant improvements were seen after the initiation of Treprostinil. At the five month follow-up, six-minute walk distance increased to 660m.[16] The echocardiogram displayed an estimated <1/2 systemic right ventricular systolic pressure, showing a significant reduction in the pulmonary pressures.[16] The polysomnography reflected a normalisation of her breathing pattern with no evidence of apnoeas.[16] The CAI was within normal limits at 0.5, baseline mean SpO2 improved to 95%, and there were significantly fewer desaturations throughout the night (ODI=0.5).[16] Raw polysomnography data was also not detailed for the patient in Joseph et al's study.[21] Desaturations ceased, but apnoeas persisted after applying supplemental oxygen.[21] A suboccipital craniectomy was performed with cervical laminectomy after the discovery of ACM1. A follow-up polysomnography showed improvement in apnoeas (AHI=2.3, CAI=0.9), with no significant desaturations.[21] Taytard et al reported that there was an increased periodic breathing cycle length compared with the recording in room air, and no decrease in central apnoea frequency after trialling supplementary oxygen therapy (AHI=17, CAI=12, ODI=9).[26]

Non-Invasive Ventilation

Nine articles investigated the impact of NIV to treat CSA in children with underlying diagnoses.[18-20,22-27] These included cerebellar dysplasia affecting the vermis (with none of the usual clinical features associated with Joubert syndrome and related disorders), ACM1, neuromyelitis optica spectrum disorder (NMOSD), Klippel-Feil syndrome, UNC80 and KCNJ11 mutations, a diffuse midline glioma, post-head trauma (epidural haematoma), and treatment-emergent CSA (TECSA). [18-20,22-27]

Intervention Characteristics

Continuous positive airway pressure, bilevel positive airway pressure (BiPAP), and adaptive-servo ventilation (ASV) were all variably implemented across the nine studies. Three studies utilised CPAP as an intervention strategy for CSA.[18,24,27] Various pressures were applied, ranging from 6-15cmH2O following titration.[18,24,27] Er et al trialled both nasal and full-face masks following a suspected nasal mask leakage, whereas Quera-Salva and Guilleminault only piloted a nasal mask.[18,24] The remaining study did not detail the mask interface.[27] A portable negative pressure ventilator (cuirass ventilator), which was specially moulded to the patient, was used both in isolation and combined with nasal CPAP in Quera-Salva and Guilleminault's study.[24] It was trialled at 14 ventilations/minute, decreasing to 12 and 10 (pressures +2 to -30cmH2O). Adherence to the CPAP intervention was only reported in one study.[18]

Adaptive servo ventilation was only implemented in a single study and participant.[18] As this device adjusts air pressure depending on the individual's breathing pattern, specific pressures were not reported.[18] Furthermore, the mask interface was not detailed.[18]

Bilevel positive airway pressure was the most implemented form of NIV, utilised in a total of eight studies and ten patients, either with or without a backup respiratory rate. Only two participants received BiPAP without a backup respiratory rate.[18,23] Spontaneous mode was employed for the patient in Morelli et al's study, whereas the mode was not reported in Er et al's study.[18,23] Er et al and Morelli et al used inspiratory positive airway pressure (IPAP) values of 14.3cmH2O and 11cmH2O, respectively, and expiratory positive airway pressure (EPAP) values of 7.8 cmH2O and 7cmH2O. [18,23] The mask interface employed for both participants were not detailed.[18,23]

A backup respiratory rate was frequently set with participants who received BiPAP (eight participants in total). The median rate, IPAP, and EPAP were 14.5 breaths/minute (12, 20), 11.5cmH2O (8, 19), and 6cmH2O (4, 10) respectively. The mask interface was not detailed in four studies.[18,22,25,26] A nasal mask was utilised for three patients and an oronasal mask for a single participant, as a mouth leak was present.[19,20,27] Spontaneous/timed mode was frequently chosen and employed in a total of five patients.[19,20,22,26,27] Hong et al utilised timed mode in one patient, as given her young age she was less likely to trigger spontaneous breaths effectively, and the mode was not detailed in two studies.[18,19,25] Huang et al reported the driver's minimum and maximum time in inspiratory positive airway pressure, set at 200 milliseconds and 1.6 seconds, respectively.[20] Furthermore, Hong et al detailed that one patient received supplemental oxygen through the circuit (one litre/minute), and another had an inspiratory time set at 0.8 seconds.[19] Only one study utilising BiPAP reported adherence data.[19]

Effectiveness of Interventions

Following the initial polysomnography, automatic titration of CPAP therapy was performed in Yosunkaya and Pekcan's study.[27] A severe number of central apnoeas were noted (CAI=83.2), even though obstructive apnoeas and hypopneas were well controlled.[27] A magnetic resonance image (MRI) of the brain demonstrated ACM1 and tetra-ventricular hydrocephalus.[27] Manual titration of BiPAP was performed, and the researchers saw excellent control of respiratory events, hypoxia, and short arousals (AHI=12.9, CAI=2, OAI=0).[27] Similar results were seen when nasal CPAP was used in isolation during Quera-Salva and Guilleminault's study.[24] Oxygen saturation values improved, even though the frequency of central apnoeas did not decrease (RDI, REM sleep=91; RDI, non-REM sleep=68).[24] A portable negative pressure ventilator was trialled, and the patient demonstrated repeated mixed and obstructive apnoeas; however, the frequency of apnoea did not decrease (RDI, REM sleep=86; RDI, non-REM sleep=72).[24] Nasal CPAP used in combination with the portable negative pressure ventilator was successful. Apnoea was controlled, sleep was unfragmented, SpO2 was maintained above 92% regardless of sleep state, and there was a disappearance of the repeated short electroencephalogram arousals (RDI, REM sleep=0; RDI, non-REM sleep=0).[24] Continuous positive airway pressure treatment was also ineffective for TECSA in Er et al's study.[18] After CPAP usage for three months with adequate adherence, body mass index continued to decrease, and the central apnoea component remained high (AHI=30, 54.9% central events).[18] Nineteen months of CPAP usage saw a progression in the patient's central apnoea component (AHI=40.9, 73.2% central events).[18] Bilevel positive airway pressure without a backup respiratory rate was trialled, where CSA was still significantly present (AHI=28.1, 90.4% central events).[18] Bilevel positive airway pressure with a backup respiratory rate for three months saw smooth breathing with no central apnoeas.[18] Normalised school performance was observed, the patient's attention-deficit/hyperactivity disorder improved, and the intermittent catheterisation program and cystostomy were withdrawn.[18] Growth failure remained. Under ASV titration, the AHI was 3.8, and growth was improving (height percentile 1.2%, weight percentile 0.32%).[18]

Following neurosurgical intervention in Martirosyan and Malhotra's study, a significant improvement in symptoms was seen, with a resolution of nocturnal gagging, drooling, and choking.[22] This was consistent with an improved pediatric daytime sleepiness scale score of 12.[22] Seven weeks after neurosurgical decompression, a repeat polysomnography was ordered, revealing severe CSA (CAI=41.6).[22] Given the severity of CSA, the patient was started on BiPAP. After commencing NIV, the CAI was 0, the highest TcCO2 was 52mmHg, the SpO2 nadir was 93%, and snoring was not attenuated.[22] Similar results were seen after posterior fossa

decompressive surgery in Strang and Katwa's study.[25] The patient reported resolution of his neurological symptoms, daytime sleepiness, and sleep quality.[25] The CAI was nine with an SpO2 nadir of 83%, four months post-surgery. Nocturnal BiPAP was continued. The patient continued to have ongoing CSA approximately 15 months after surgery (CAI=26).[25] Bilevel positive airway pressure was continued over the next four years with no changes in settings required.[25] The residual CAI was improved to 13 at 68 months after decompression surgery.[25] The final sleep study (performed 88 months post-surgery) showed near complete resolution of CSA (CAI=1.1).[25] Bilevel positive airway pressure was then discontinued.

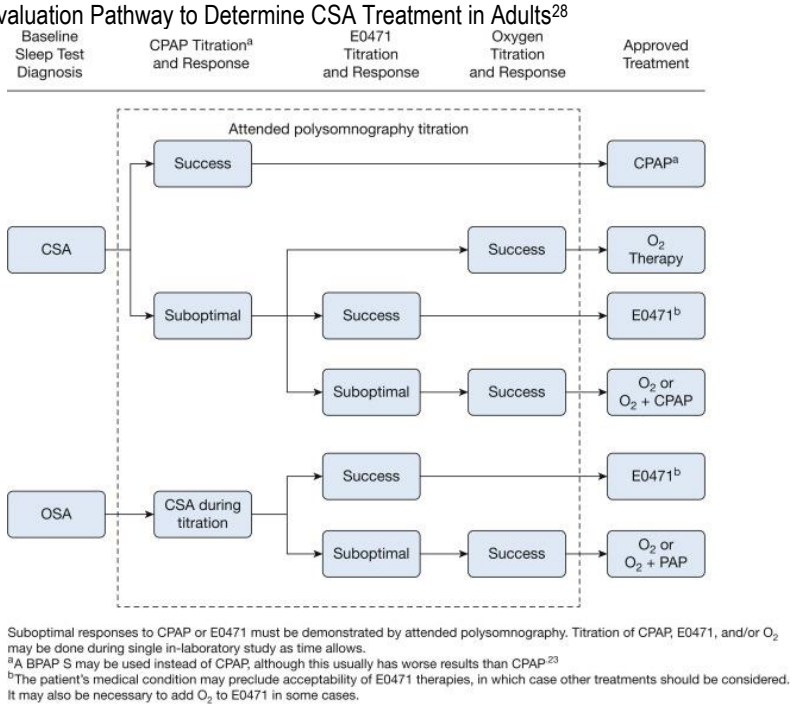
Polysomnography was repeated seven days following the initiation of BiPAP therapy in the study by Huang et al, and the patient's AHI was reduced to 13.6.[20] The CAI was reduced to 5.7, and oxygen desaturation events were reduced from 1082 to 553.[20] The tumour showed a slow progression and enlargement at the six-month follow-up, with no new neurological signs.[20] On the night of the initial polysomnography, under NIV, no apnoea was observed in the participant of Morelli et al.[23] The patient was discharged on day 36 with nocturnal NIV as home treatment, azathioprine, and prednisone.[23] Two months after the initiation of the immunosuppressive treatment, dysphagia and dysphonia were resolved.[23] The final polysomnography was performed with and without NIV at a three-year follow-up. Without NIV, the CAI was 110.[23] Nocturnal NIV was maintained. At the time, serum AQP4-IgG was negative, and the brain MRI showed a complete recovery of the previous detectable lesions.[23] Taytard et al, after an unsuccessful trial of supplementary oxygen therapy, pursued BiPAP, with dramatic efficacy on CSA (CAI=0).[26] The first patient in Hong et al's case series displayed a CAI similar to five years prior at 213.5.[19] Bilevel positive airway pressure therapy was initiated and titrated to resolve central apnoeas and desaturations.[19] Following discharge from inpatient care, serum bicarbonate values normalised by one week.[19] The family and machine usage data confirmed good adherence to the therapy.[19] The second patient tolerated BiPAP well, her respiratory status improved, and she was discharged from inpatient care.[19] A formal BiPAP titration polysomnography was ordered; however, she died at home (details unknown) before further follow-up care at the institution.[19]

DISCUSSION

Although statistical analyses were only utilised in one study, nocturnal oxygen therapy and NIV generally positively impacted polysomnography results and other pertinent outcomes. All the studies included in this review were small, observational trials, with limited external validity and subject to a high risk of biases. Eleven of the included studies were case reports/series, reflecting the highly varied paediatric CSA patient presentation and the increasing amount of emerging research on the topic.[16-20,22-27] This is corroborated by a previous scoping review conducted by the study authors and in previously published literature.[3,8]

Three studies trialled either oxygen therapy or CPAP before the efficacy of BiPAP was explored.[18,26,27] Without high-quality, rigorous studies investigating the best CSA treatments for long-term outcomes, clinicians need to individualise therapy to achieve better sleep continuity, symptomatic relief, improved blood oxygenation, and polysomnographic evidence of stabilised breathing patterns.[28] A suggested pathway for determining the ventilatory treatment of CSA in adults is detailed in Figure 2. This algorithmic approach suggests that CPAP should be initially trialled and titrated under attended polysomnography, and if therapeutic responses are suboptimal, then BiPAP and supplementary oxygen therapy should then be piloted.[28] Two studies followed this pathway, trialling CPAP before BiPAP therapy.[18,27] In the five articles that applied supplementary oxygen therapy, it was always the intervention that was initially explored, contrasting the algorithmic approach displayed in Figure 2.[9,16,17,21,26] It can be theorised that in children, the application and titration of oxygen therapy via nasal prongs is simpler to setup and implement than NIV. Although supplementary oxygen therapy displayed mixed success amongst included studies, the ease of trialling this intervention, and subsequently lower cost to purchase for the home environment if significant improvements in patient outcomes are seen on polysomnography, means it may be useful to consider piloting this intervention earlier in the algorithm. There was also no apparent relationship between the selection of an intervention and a specific patient presentation. For example, two separate studies reported patients with diagnoses of ACM1; however, two different management approaches were employed.[21,25] Again, the choice of intervention strategies is highly dependent on 'trial and error,' using polysomnography data to clinically reason the suitability of the intervention for the individual patient.

Figure 2. Suggested Evaluation Pathway to Determine CSA Treatment in Adults[28]



Suboptimal responses to CPAP or E0471 must be demonstrated by attended polysomnography. Titration of CPAP, E0471, and/or O_2 may be done during single in-laboratory study as time allows.
[a]A BPAP S may be used instead of CPAP, although this usually has worse results than CPAP.[23]
[b]The patient's medical condition may preclude acceptability of E0471 therapies, in which case other treatments should be considered. It may also be necessary to add O_2 to E0471 in some cases.

Note. E0471 is a bilevel device with a backup rate.
Abbreviations: BPAP, bilevel positive airway pressure; CSA, central sleep apnoea; O2, oxygen; PAP, positive airway pressure; S, spontaneous.

The pathophysiology of CSA falls into one of two main categories: hypoventilation or hyperventilation.[29] Hypoventilation-related CSA involves impaired ventilation due to factors such as abnormalities in chest wall mechanics, neuromuscular disorders, or central nervous system lesions. Sleep results in a general drop in ventilatory drive within this patient group, with prolonged apnoea or profound hypoventilation.[29] Phases of arousal from deep sleep terminate these periods but recommence once deeper sleep is re-established.[29] Central sleep apnoea with hyperventilation is characterised by induced hypocapnia through periods of hyperpnoea during sleep, causing apnoeas.[29] A decrease in partial pressure of carbon dioxide to a level below the central chemoreceptor threshold required for the ventilatory drive is a partial cause.[29] Apnoeic episodes lead to increased partial pressures of carbon dioxide, either leading to another phase of hyperventilation (restarting the cycle) or may restore normal ventilation.[29] Continuous positive airway pressure and BiPAP are theorised to effectively resolve apnoeas by providing a pneumatic splint effect, compensating central apnoeas, and reducing oscillations in partial pressures of carbon dioxide.[30] A backup ventilation frequency implemented in most patients who received BiPAP in the included studies may also improve ventilation.[30] Adaptive-servo ventilation normalises breathing patterns by delivering pre-set minute ventilation, mitigating hyperventilation and associated hypocapnia.[31] The effect of oxygen on ventilatory control during sleep is poorly understood. The underlying mechanisms may include increased cerebral carbon dioxide levels or reduced carbon dioxide chemoreflex sensitivity.[31] Through inhibiting peripheral chemosensitivity, hyperoxia exposure can result in reduced controller gain.[31]

Adherence to NIV was only mentioned in two studies, and no included study reported adherence/tolerance to oxygen therapy. Given that these interventions would be prescribed long-term in the home environment and obtaining benefits relies on achieving adequate adherence, this is a crucial variable to consider. Existing studies exploring compliance with positive airway pressure have seen comparable results. Marcus et al aimed to determine adherence to NIV in children with obstructive apnoea, finding a high dropout rate associated with treatment and that nightly use is suboptimal even in the adherent children.[32]

Adverse events associated with ventilatory treatment were reported in three studies.[18,26,27] An increased periodic breathing cycle length was seen after initiation of oxygen therapy in the study by Taytard et al, and nasal mask leakage during NIV use resulted in the implementation of an oronasal interface in two studies.[18,26,27] Patout et al reported the frequent side effects amongst adult NIV home users, which included: rhinorrhoea, eye redness, mouth dryness, bloating, hoarseness, noticeable leaks, pressure sores, interface related pain, perceived patient ventilator-asynchrony, and deventilation dyspnoea.[33] These adverse events affected both compliance and quality of life.[33] Nocturnal oxygen therapy can cause similar problems, leading to skin rash or nasal irritation.[34] An

elevated partial pressure of carbon dioxide has been seen in some chronic obstructive pulmonary disease patients receiving oxygen therapy, likely due to changes in carbon dioxide transport in the bloodstream and ventilation-perfusion matching in the lung.[34] Seven studies monitored TcCO2 during polysomnography and two studies measured end-tidal carbon dioxide.[9,16,17,19-21,23,25,26]

A large proportion of studies involving adult populations with diagnoses of CSA focus on patients with chronic heart failure.[31] Currently, ASV is considered best for these patients; however, new concerns about the safety of this intervention have emerged, and little research explores its applicability to paediatric presentations.[35,36] The SERVE-HF trial identified that all-cause and cardiovascular mortality were increased with this therapy and had no significant effect on patients with predominantly CSA and heart failure with a reduced ejection fraction.[35,36] A follow-up, non-randomised, multicentre study determined that although ASV had significant impacts on AHI and Epworth sleepiness scale scores, CPAP as a prerequisite for ASV needs to be better defined, and iterative cardiological assessments and night-monitoring in ASV-treated patients are required due to consecutive setting changes and high rates of cardiac comorbidities.[36] Interestingly, no patient received BiPAP in the study by Jaffuel et al, which contradicts its frequency of use in included articles in this study.[36]

Given the number of underlying pathologies for paediatric patients with CSA, relevant contraindications and precautions to oxygen therapy and NIV should be considered. Congenital facial or airway abnormalities are a contraindication to NIV use, in addition to cardiovascular instability.[37] Given the occurrence of CSA in patients with ACM1 and space-occupying lesions in the cranium, the relationship between positive pressure ventilation and intracranial pressure is important to note. Boone et al[38] found no clinically significant effect on intracranial pressure or cerebral perfusion pressure with positive end-expiratory pressure, suggesting that NIV can be applied safely in these patients. Contraindications pertinent to oxygen therapy include congenital heart disease patients with ductal-dependent lesions, as it can act as a potent pulmonary vasodilator, causing over circulation within the pulmonary system.[39]

Quera-Salva and Guilleminault were the only study to utilise a portable negative pressure ventilator (cuirass ventilator).[24] An external pump is connected to a domed plastic shell, encasing the patient's upper abdomen and chest.[40] The device generates negative and positive pressures to stimulate respiration and is designed to apply equal pressure throughout the thorax.[40] Annunziata et al, exploring negative-pressure ventilation in neuromuscular diseases in the acute setting, list sleep-disordered breathing as a contraindication to its use.[40] This is due to a lack of protection of the upper airways and possible upper-airway obstruction due to decreased pre-inspiratory upper-airway muscle activation and downfall of the tongue on the posterior pharyngeal wall.[40] There is also limited evidence for use amongst adult and paediatric patients with CSA diagnoses.

Limitations

Critical appraisal of the studies through the CCAT identified that research was generally poor quality, highlighting common weaknesses in ethical matters, results, and discussion categories. Six studies did not report raw polysomnography data, meaning it was difficult to determine the true effects of an intervention (reporting bias). Another concern was that study strengths/limitations and suggestions for future research were rarely described.

Although 11 of the included articles were case studies/series, an improvement in CAI was seen in ten studies following the initiation of NIV or nocturnal oxygen therapy. Thus, given the varying interventions and range of underlying conditions associated with paediatric CSA, it would be beneficial to undertake a controlled trial testing a modification of the algorithm mentioned above (Figure 2). Carefully selected, small samples in these study designs increase the possibility of detecting false negatives, undermine the results' external validity, and reduce their ability to detect a true effect. Finally, only studies published in the English language were eligible for inclusion.

Implications for Clinical Practice

This systematic review has identified various underlying conditions associated with paediatric CSA. The use of nocturnal oxygen therapy or NIV, in addition to managing the underlying disease, generally has positive outcomes on polysomnographic data. The wide variety of clinical presentations, reflected by a large number of small, observational studies, along with shortcomings in the studies' designs identified during the critical appraisal, makes it difficult to draw definitive conclusions surrounding the interventions' effectiveness and applicability to specific presentations. The importance for health professionals highly involved in these patients' care to remain vigilant for CSA symptomatology is vital.

To provide recommendations, future research should include larger samples through the organisation of multi-centred trials to increase the generalisability and validity of the results. Studies with broader inclusion criteria, including multiple underlying conditions with a significant diagnosis of CSA, will also assist with this. Using polysomnography values, specifically SpO2 and the

CAI, in addition to questionnaires such as the Epworth sleepiness scale, would provide consistent outcomes to utilise amongst a variety of clinical presentations to measure the severity of CSA and sleep-related symptomatology objectively. The impact of patient adherence to the intervention, given its importance to successful implementation in the home environment, is another crucial variable to consider. Machine usage data, available on a wide range of NIV systems, may be the best method to quantify this outcome.

Given the frequency that ASV is implemented in adult populations and the recent discussion surrounding its safety, future studies should also aim to explore the efficacy of this intervention amongst paediatric cohorts. Given that BiPAP with a backup respiratory rate is commonly utilised for paediatric CSA patients, comparison to ASV is another future area requiring exploration.

CONCLUSION

This systematic review aimed to determine the effectiveness of oxygen therapy and NIV for children with CSA and additional underlying comorbidities. Thirteen relevant articles were identified and interpreted, with critical appraisal of the studies establishing the quality of literature and gaps in the current evidence base. The mean total CCAT score was 69%, with total scores ranging from 43% to 80%. Large multicentred trials with broader inclusion criteria, to facilitate larger sample sizes, should be undertaken to increase the generalisability and validity of the results. Consideration of patient adherence to the prescribed ventilatory intervention should also be explored in future research.

Nocturnal oxygen therapy and NIV generally have positive impacts on sleep-related outcomes; however, applicability to specific patient presentations could not be determined. The choice of a treatment strategy was based on the impact on polysomnography outcomes, and studies did not reason why one management strategy was chosen over another. The CCAT was utilised to appraise articles based on merit, not a 'gold standard'. Articles frequently lacked specifics in the ethical matters, results, and discussion sections. It is vital that health professionals involved in the care of paediatric patients with underlying cardiovascular, neurological, genetic, autoimmune, congenital, and oncological conditions are aware of the possible occurrence of CSA and the need for early recognition and effective treatment.

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APPENDICIES

Appendix A: Search Syntax

Medline (Ovid)

1. Sleep Apnea, Central/
2. central sleep apnoea.mp.
3. central sleep apnoeas.mp.
4. central apnoea.mp.
5. central apnoeas.mp.
6. central sleep apnoea syndrome.mp.
7. exp child/ or exp infant/
8. exp Pediatrics/
9. paediatric.mp.
10. paediatrics.mp.
11. Adolescent/
12. toddler.mp.
13. exp Respiration, Artificial/
14. exp Oxygen Inhalation Therapy/
15. exp Physical Therapy Modalities/
16. exp Physical Therapists/
17. exp Physical Therapy Specialty/
18. 1 or 2 or 3 or 4 or 5 or 6
19. 7 or 8 or 9 or 10 or 11 or 12
20. 13 or 14 or 15 or 16 or 17
21. 18 and 19 and 20

CINAHL Complete (EBSCOhost)

1. (MH "Sleep Apnea, Central+")
2. (MH "Infant+") OR (MH "Child+") OR (MH "Adolescence+")
3. (MH "Respiration, Artificial+")
4. (MH "Oxygen Therapy+")
5. (MH "Ventilators, Mechanical") OR (MH "Oxygen Delivery Devices+")
6. (MH "Oxygen Therapy Care (Saba CCC)") OR (MH "Pulmonary Care (Saba CCC)+")
7. (MH "Oxygen Therapy (Iowa NIC)") OR (MH "Mechanical Ventilation (Iowa NIC)") OR (MH "Ventilation Assistance (Iowa NIC)")
8. (MH "Physical Therapy+")
9. S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. S1 AND S2 AND S9

Emcare (Ovid)

1. exp central sleep apnea syndrome/
2. central apnea.mp.
3. central apnoea.mp.
4. central apneas.mp.
5. central apnoeas.mp.
6. central sleep disordered breathing.mp.
7. exp pediatrics/
8. exp adolescent/ or exp child/
9. exp artificial ventilation/
10. exp oxygen therapy/
11. exp physiotherapy practice/ or exp physiotherapy/
12. exp assisted ventilation/
13. exp respiratory therapeutic device/
14. 1 or 2 or 3 or 4 or 5 or 6
15. 7 or 8
16. 9 or 10 or 11 or 12 or 13
17. 14 and 15 and 16

Scopus and PubMed

("child*" OR "paediatric*" OR "pediatric*" OR "infan*" OR "toddler" OR "newborn" OR "neonat*" OR "baby" OR "juvenile" OR "youth" OR "adolescent")

AND

("central sleep disordered breathing*" OR "central sleep apnoea*" OR "central sleep apnea*" OR "central apnoea*" OR "central apnea*" OR "central sleep apnoea syndrome" OR "central sleep apnea syndrome" OR "central alveolar hypoventilation*")

AND

("physiotherap*" OR "physical therap*" OR "physio" OR "artificial ventilation" OR "non-invasive ventilation" OR "continuous positive airway pressure" OR "intermittent positive pressure breathing" OR "intermittent positive pressure ventilation" OR "CPAP" OR "biPAP" OR "positive end expiratory pressure" OR "bilevel positive airway pressure" OR "positive pressure ventilation" OR "adaptive servo ventilation" OR "artificial respiration" OR "mechanical respiration" OR "mechanical ventilation" OR "intermittent mandatory ventilation" OR "pressure support ventilation" OR "controlled respiration" OR "controlled ventilation" OR "auxiliary respiration" OR "assisted respiration" OR "ventilatory assistance" OR "assisted ventilation" OR "positive pressure respiration" OR "oxygen inhalation therap*" OR "oxygen therap*" OR "nocturnal oxygen*" OR "supplemental oxygen" OR "oxygen treatment" OR "oxygen administration" OR "o2 therapy" OR "oxygen supply")

Appendix B: PRISMA Checklist[10]

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6, 18-19
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-15
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	6
Competing interests	26	Declare any competing interests of review authors.	6
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A