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# Treatment alternatives for sleep-disordered breathing in the pediatric population

**Ann C. Halbower**[a], **Brian M. McGinley**[b], and **Philip L. Smith**[c]

[a]Department of Pediatrics, Pulmonary Section, The Children's Hospital and University of Colorado Denver School of Medicine, Aurora, Colorado

[b]Department of Pediatrics, Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University

[c]Department of Medicine, Division of Pulmonary and Critical Care, Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland, USA

## Abstract

**Purpose for review—**Childhood sleep-disordered breathing (SDB) is associated with a myriad of health problems that underscore the need for early diagnosis and treatment. Children with SDB present with behavior problems, deficits of general intelligence, learning and memory deficits, evidence of brain neuronal injury, increased cardiovascular risk, and poor quality of life. Children are in a rapid state of cognitive development, therefore, alterations of health and brain function associated with SDB could permanently alter a child's social and economic potential; especially if the disorder is not recognized early in life or is treated inadequately.

**Recent findings—**There is evidence that the majority of the problems associated with SDB improve with treatment. Treatment strategies are now being aimed at mechanisms underlying the disorder. There are multiple treatment options available to children; some are novel, with pending treatments on the horizon that may replace age-old therapies such as adenotonsillectomy or nasal positive pressure.

**Summary—**It is imperative that healthcare workers actively seek out signs and symptoms of SDB in patients to improve early detection and treatment for prevention of long-term morbidity.

### Keywords

adenotonsillectomy; continuous positive airway pressure; nasal cannula; obesity; obstructive sleep apnea; pediatric; sleep-disordered breathing; transnasal insufflation; treatment

## Introduction

Childhood sleep-disordered breathing (SDB) is associated with a myriad of health problems that underscore the need for early diagnosis and treatment. Children with SDB present with behavior problems [1,2••], deficits of general intelligence [3,4], learning and memory deficits [5], evidence of brain neuronal injury [6], increased cardiovascular risk profiles [7••], and poor quality of life (QOL) [8••]. Children are in a rapid state of cognitive development, therefore,

Correspondence to Ann C. Halbower, MD, Department of Pediatrics, Pulmonary Section, The Children's Hospital and University of Colorado Denver School of Medicine, 13123 E 16th Ave, B-395, Aurora, CO 80045, USA Tel: +1 720 777 4950; fax: +1 720 777 7284; Halbower.ann@tchden.org.

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alterations of health and brain function associated with SDB could permanently alter a child's social and economic potential; especially if the disorder is not recognized early in life or treated inadequately. It is imperative that healthcare workers actively seek out symptoms of SDB in patients and educate parents and teachers about the signs and symptoms of SDB to improve early detection and treatment prevention of long-term morbidity.

## The reason to treat

Although the results of large randomized trials are still pending, treatment of childhood sleep apnea in smaller case studies demonstrates improvement in several domains. From a neuropsychological perspective, treatment of pediatric SDB has improved behavior [9,10] and even reversed diagnoses of Attention Deficit Hyperactivity Disorder (ADHD), a common overlap symptom of SDB [2••].

Cardiovascular risk profiles, such as inflammatory markers in children [11,12], abnormal lipid metabolism in obese children [7••], and markers related to the development of hypertension in adults [13] reversed after treatment of SDB. QOL after treatment also improves in children with SDB, as does school performance [8••,14,15]. Evidence of brain neuronal injury associated with childhood sleep apnea has been reported by our laboratory [6] and studies are underway to determine whether these neuronal findings are reversible with treatment, or whether they may have predated and perhaps caused the finding of sleep apnea. Adult studies of brain imaging in patients with obstructive sleep apnea (OSA) do not conclusively show reversibility of brain injury [16], but long-standing OSA in adults with other comorbidities such as hypertension and cardiovascular risk factors may not be comparable. Evidence suggests that treatment improves function and outcome in many domains, suggesting that early diagnosis and treatment should be the standard of care in order to protect children from brain or cardiovascular injury, until proven otherwise.

## Mechanisms underlying sleep-disordered breathing: direction for treatment strategies

Treatment strategies for SDB may improve with better understanding of underlying mechanisms. Evidence suggests that a combination of factors is associated with the occurrence of SDB [17•]. Craniofacial and pharyngeal structural narrowing certainly plays a role. Early reports of childhood sleep apnea focused on the presence of large tonsils and adenoids, which have an increased relative hypertrophy in children less than 6 years old [18]. More recently, attention has been focused on other craniofacial structures that contribute to SDB, including nasal obstruction from septal deviation or large turbinates [19••]; lingual tonsils that are associated with lower pharyngeal narrowing [20•]; and maxillary narrowing or mandibular retro-position that can narrow the oropharynx [19••].

Of equal, if not greater importance, is the role of neural tone in the pathophysiology of SDB [21]. Neuromuscular control allows for pharyngeal patency during sleep and increases during higher mechanical loads such as obesity and adenotonsillar hypertrophy. Neuromuscular responses to obstruction have been found to be blunted in adults [17•] and children [22,23] with sleep apnea compared with normal controls. More studies are required to determine mechanisms for this finding. Speculations include reversible mechanical damage to the airway secondary to chronic apnea [23], habituation to abnormal blood gas values, and findings of neuronal injury [24].

Obesity, a global pandemic, has been found to associate with SDB, but not just due to mechanical changes in the oropharynx. Interestingly, SDB appears to play an independent role in that it exacerbates obesity-related morbidities, such as glucose intolerance [25,26] and

metabolic syndrome. Metabolic syndrome is a constellation of systemic abnormalities including fasting hyperglycemia, hypertension, visceral obesity, and increased triglycerides with lipid metabolism abnormalities [27]. Metabolic syndrome has been found to be significantly increased in adolescents with SDB compared with those without SDB [28] Gozal *et al*. [7••] discovered a finding unique to children with SDB. OSA does not appear to induce insulin resistance in nonobese pediatric patients but seems to play a significant role in obese patients. There were significant improvements in lipid profiles, C-reactive protein, and apolipoprotein B after adenotonsillectomy in both obese and nonobese children suggesting a pathogenic role for SDB in lipid homeostasis and systemic inflammation independent of the degree of adiposity. Additionally, there is a link between disordered ventilatory control and obesity, which was found to involve leptin, a hormone that signals satiety secreted by adipocytes, cells which make up adipose tissue. Humans with sleep apnea and obesity have demonstrated elevated levels of leptin, indicating leptin insensitivity [29]. Leptin has a secondary function, with a role in the regulation of respiration. Impairment of leptin signaling has been shown to reduce the ventilatory response to hypercapnia in animal studies [30,31]. Regulation of ventilation by leptin at the level of the hypothalamus, or downstream peptides [31], may contribute to the neural pathways necessary for maintaining proper degrees of pharyngeal tone in normal individuals. Disruptions of those pathways may be involved in the observed alterations of critical closing pressure in patients with sleep apnea [17•].

## Treatment strategies addressing mechanisms underlying sleep-disordered breathing: pharyngeal structural narrowing

As the underlying disorder in SDB involves one or more processes causing structural narrowing of the upper airway, treatment strategies have focused on surgeries or appliances that enlarge the oropharynx or inhibit closing pressures. Adenotonsillectomy has long been the mainstay of surgical therapy for children with SDB. Reports of cure rates vary depending on the diagnostic criteria used to label a patient with SDB, comorbidities such as obesity, respiratory parameters used, and especially, the definition of cure that varies severely between adults and children, and within the literature on childhood SDB. Early reports of surgical interventions in childhood sleep apnea suggested an 85–95% cure with adenotonsillectomy [32-34]. However, recent articles reporting wide-ranging clinical presentations of sleep apnea including obese children and children with craniofacial diagnoses suggest that the cure rate is far less promising [19••,35]. A study by Guilleminault *et al.* [19••] estimates less than 50% cure rate with adenotonsillectomy in children. In their prospective survey, including questionnaires, clinical examination, polysomnography, and esophageal pressure monitoring (a tool which increases diagnostic sensitivity for SDB), 94 out of 199 children still had abnormal sleep recordings on repeat evaluation after adenotonsillectomy. Factors associated with failure of adenotonsillectomy treatment for SDB included a Mallampati score of 3–4, retro-position of mandible, enlargement of nasal inferior turbinates, and deviated septum. It should be noted that there may have been a referral bias to that clinic, with a predilection for children with craniofacial disorders because of the availability of specialists in craniofacial surgery. However, in a recent long-term follow-up of 615 preschool children, only half of the children who underwent surgery for SDB showed complete symptomatic improvement by follow-up [36]. In a group of 79 healthy children with a mean age of 6 years, QOL and apnea/hypopnea index improved dramatically, but using the new criteria for defining pediatric SDB, only 71% had normal polysomnogram parameters after adenotonsillectomy [37]. Postoperative polysomnography may be indicated for children with craniofacial abnormalities and also for children who are obese, because obesity has been shown to increase the risk of persisting SDB [35,38,39].

The procedure for adenotonsillectomy varies and actual surgical results, which include resolution of sleep apnea, postoperative pain, and recovery time, differ by procedure. Two

reviews of the history of adenotonsillectomy [40,41] and discussions of various forms of the procedure allow nonsurgical specialists an educated view of the issues surrounding outcomes that may guide surgical choice. Regardless of the procedure, it should be noted that pediatric patients with a history of SDB, obesity, or very young age are at increased risk of postoperative side effects [42], and those with alterations of ventilatory drive due to recurrent hypoxemia are at severe risk of postoperative blood gas abnormalities and respiratory depression with the use of opiates [43,44].

Children with high-arched palates, or with craniofacial abnormalities resulting in maxillary narrowing, might benefit from rapid maxillary distraction. In some cases, the procedure is curative [45]. This procedure has been used with good results in children [46•]. Rapid maxillary distraction is performed without surgical intervention, whereas several facial and invasive nasal surgeries are often delayed to allow permanent bone growth. The procedure involves the placement of a device between the left and right molars, with the turn of a screw every few days until expansion is complete. Children can tolerate a rapid expansion, which enlarges the nasal cavity and the lateral diameter of the palate and oropharynx, leading to improvement in SDB.

Mandibular advancement surgery, or mandibular distraction osteogenesis for treatment of retro-positioned mandibles such as seen in Pierre Robin Sequence or in mandibular hypoplasia, has demonstrated significant and permanent improvement in flow limitation for children with SDB [47]. Repeat polysomnography may be recommended as the results in some cases still demonstrate levels of SDB that require further treatment [48].

Airflow limitation in SDB is located in a collapsible part of the pharynx between the nasopharynx and hypopharynx. The data on the role of nasal obstruction as a contributing factor in SDB in adults is mixed [49]. The nose is responsible for up to two out of three airway resistance [50], and increasing nasal resistance studied during sleep causes both apnea and increased drive to dilator muscles in adults [51]. Neuromuscular tone contributes to relief of a substantial amount of airway resistance, and by measuring genioglossus electromyographic activity, Basner *et al.* [52] demonstrated increased tone in awake individuals with nasal breathing, which decreased with oral breathing, and with application of local anesthetic, indicating that nasal flow is important to neuronal signaling for maintenance of tone. Mouth breathing during sleep increases resistance further [53]. Children with severely enlarged adenoidal tissue may present with a total lack of airflow from the nose and mouth breathing that is continuous day and night. Long-term nasal obstruction is associated with stunted maxillary and mandibular development that partially improves after relief of the obstruction [54,55]. Nasal surgery for septal deviation, enlarged turbinates, and polyps may not only improve nasal airflow but also improve comfort with nasal interfaces for positive pressure devices in children.

Oral appliances have shown promise for treatment of adult sleep apnea, especially in nonobese adults with mild-to-moderate OSA. The oropharynx of children under 16 years of age is still developing, and orthodontists are reluctant to use oral devices made to advance the mandible. Research in this area of pediatrics is virtually nonexistent. Compliance with positive airway devices is poor, and alternatives such as oral appliances that do not affect dentition or structural development of the facial bones, in children who are old enough to understand, deserves further research.

Positive pressure devices such as continuous positive airway pressure (CPAP) are first-line therapy for the diagnosis of OSA in adults. CPAP provides a distending pressure to the nasal or oropharynx (depending on the device used) [56], which decreases the likelihood that closing pressure will cause airway obstruction during both inspiration and during phasic muscle

relaxation in exhalation. Adherence of CPAP is poor and studies in adults consider the use of 4 h per night sufficient for treatment [57]. CPAP in children has been studied for safety and efficacy and has been shown to relieve SDB [58]. CPAP is useful when surgery is not deemed an option, or when surgery does not alleviate SDB. Children require many more hours of sleep than adults and, therefore, CPAP use for only 4–5 h per night would provide treatment for less than half the total sleep time. Many pediatric sleep laboratories have adopted the use of behavioral psychologists to desensitize children from the fear or discomfort of CPAP and, thus, improve the acceptance of the device. Unlike CPAP introduction in adults, CPAP use in children includes the training of the parents, whose complete support of the therapy is essential in order for the child to accept the use of the device. CPAP introductions in clinic that include positive reinforcement, slow education, and distraction with interesting activities improve initial acceptance. Strategies to help the child avoid escape behaviors while reinforcing the need to use the device are helpful skills that parents learn with the help of behavioral psychologists [59•]. Our laboratory uses the interaction of other experienced pediatric CPAP users for live demonstrations as well as videos of children applying and wearing the nasal interface.

Known complications of CPAP in all users include gastric distension with air, dry eyes, or nasal congestion. Heated humidifiers have been quite helpful in reducing nasal dryness or congestion. Masks adjusted for leaks improve eye irritation. Anecdotal complications of nasal interfaces in children include the unfortunate development of maxillary compression with continued adherent use. Maxillary compression will eventually cause dental problems and a misaligned bite. In our population, this occurred more commonly in children with neuromuscular disorders in whom muscle tone in the face was lax. Nasal interfaces where positive pressure is used directly into both nostrils, or devices that pull away from the face with the help of a second flap adherent to the skin (the positive flow of air pushes the mask off the face and pushes the flap onto the skin) may decrease this problem. Oral devices for air delivery in the oropharynx alone have not been studied in children; furthermore, they do not come in small sizes. Full face masks are often used in both children and adults, but the evidence for their effectiveness treating OSA is controversial. Although full face masks have been used with success in certain diseases causing hypoxia from ventilation/perfusion mismatch in the lung, under conditions when the upper airway is obstructed, pressure applied simultaneously to the nose and mouth is problematic. These full face interfaces over the nasal and oral cavities cause equal pressures being applied to both the tongue (oral) and the soft palate (nasal) without creating a positive transmural pressure which is essential to open the airway [60••]. Additionally, pressure from the mask is applied in a posterior direction to the mandible, which may contribute to narrowing of the oropharynx. A final word of caution regarding full face masks in children: very young children, children with neuromuscular weakness, those with significant gastroesophageal reflux or children with mental delays are at risk of aspiration of stomach contents with the use of a full face mask, and the risk increases if they are unable to pull the mask off in an emergency. The use of these interfaces in children should be discouraged except in rare circumstances in which the benefits outweigh the risks.

Home use of nasal interfaces for SDB in very young children (under age 7 years) and infants has not been approved by the Federal Drug Administration (FDA) in the United States, and healthcare workers are left in a serious bind when attempting to treat young children in whom the final surgical option is a tracheotomy. Although ventilators are available for home use in infants, nasal interfaces for noninvasive use are not. Pediatric practitioners have taken to creating `jerry-rigged' or homemade devices [61,62]. Additionally, nasal masks made for older children or adults have been used as full face masks in infants and children with neuromuscular disorders because of their availability, with the complication of risks mentioned above. Although CPAP has been studied and used in children [58,63], and is a safe and effective noninvasive alternative to tracheotomy [62], and is commercially available for young children

and infants in most developed countries throughout the world (manufactured by companies from the United States), the smallest pediatric devices are not available in the United States due to lack of profitability [64,65]. Evidence suggests that the use of nasal CPAP and noninvasive ventilation will increase dramatically with the increased recognition of pediatric SDB, and the increase in obesity in developed countries [63], and especially with the availability of pediatric nasal interfaces. The Pediatric Medical Device Safety and Improvement Act of 2007 (Title 111 for the FDA Amendments Act of 2007) was passed to address this pressing medical need. A plan for expanding and funding pediatric medical device research and development is in progress. In the mean time, healthcare workers should put significant pressure on device manufacturers to initiate the availability of these interfaces in the United States.

On the horizon may be new therapies that will improve treatment adherence compared with traditional CPAP. A recent investigation by McGinley *et al.* [66••] at Johns Hopkins University demonstrated the effectiveness of a high flow, low pressure, humidified nasal cannula for the treatment of OSA in adults. This device delivered humidified air through a specialized heated circuit at 20 LPM via open nasal cannula and improved the apnea/hypopnea index in most adults with mild–moderate sleep apnea to less than 10 events per hour in the majority of research participants. The device also reduced arousals during sleep. The mechanism for the improvement is not yet completely understood. An increase in pharyngeal pressures was slight (an average of 2 $cmH_2O$) and suggests that the marked reduction in apnea/hypopnea indices may involve additional mechanisms of action such as neural activation of dilator muscles, increased lung volumes, or decreased dead space ventilation. Studies assessing the effect of this research device on SDB are underway in children.

## Treatment strategies for obstructive sleep apnea with obesity

Pharyngeal structural narrowing is just one component resulting in SDB in children. Obesity in combination with SDB appears to exacerbate and expedite the notable risks associated with both disorders, with evidence that the combination increases the risk of early mortality [67, 68]. Treatment strategies aimed at weight reduction have indicated improvements in the overall apnea/hypopnea index, even in obese people with a moderate weight loss [69]. Weight reduction attempts often lead to failure or eventual relapse, but more research is required on the effect of exercise itself in obese individuals, the ‘fit fat’ population. Preliminary evidence from questionnaire data from the Sleep Heart Health Study suggests that that exercise alone may have beneficial effects on symptoms of SDB and perhaps conferred some protection against SDB [70]. Snoring itself has been shown to improve after a trial of vigorous exercise, as has visceral adiposity associated with sleep apnea risks [71,72]. Whether there is a reduction of ventilation abnormalities or cardiovascular inflammatory markers is less understood but is an area of active research. Bariatric surgery for morbidly obese adults is a therapy with demonstrable results including sustained weight loss, decreased levels of inflammation and an improved apnea/hypopnea index. Gastric band surgery aimed at the adolescent population is now being performed in a few specialized centers with good results [73].

## Medical therapy of sleep-disordered breathing

Medications aimed at improving respiratory drive, such as caffeine, and therapy with protriptyline have not shown benefit in the resolution of SDB respiratory parameters. However, Mirtazepine, a mixed 5HT2/5-HT3 antagonist that promotes serotonin release in the brain improved the apnea/hypopnea index of patients with SDB. However, the study also demonstrated that the drug was associated with weight gain and sedation, therefore, was not recommended for therapy [74]. The study highlights the need for more research into the effects of medical therapies for improving neuronal control of pharyngeal dilators. Promising results

in children have been noted with the treatment of one of the underlying causes of SDB, structural narrowing from tissue inflammation in the nasopharynx. Goldbart *et al.* [75,76] showed an improvement of mild apnea and snoring with leukotriene antagonists, after demonstrating an increase in leukotriene receptors in the lymphatic tissues of patients with sleep apnea compared with those without SDB. The downside to this therapy is the unknown long-term duration of response or the length of medical therapy required. However, a combination therapy aimed at nasopharyngeal treatments such as nasal irrigations combined with nasal steroids and leukotriene antagonists is helpful both for relieving mild SDB and also for reducing the swelling and inflammation noted with CPAP therapies at high flow.

Several attempts have been aimed at attacking the daytime sleepiness associated with SDB in adults not improved with standard CPAP therapy. Modafinil, which increases the release of monoamines and elevates hypothalamic histamine, has been used for this purpose [77]. The treatment of sleepiness with underlying SDB in adults is controversial. The question is whether the patient is sleepy because of inadequate treatment, or nonadherence to treatment, in which case, the stimulant is acting merely to hide the symptoms rather than treat the cause. If that is the case, ongoing inflammation and oxidant injury could be occurring from SDB despite improvements in overall sleepiness and cognition. There is a suggestion that adults tend to use CPAP only on average four or so hours per night, which may not be adequate to prevent the occurrence of sleepiness and cardiovascular inflammation. On the contrary, a recent study demonstrates the persistence of brain neuronal injury in adults with SDB and continued sleepiness while on CPAP therapy, compared with those who were treated and not sleepy, indicating that in some people the mechanism for sleepiness is not treatment failure but brain injury [16]. In that case, Modafinil might be a reasonable addition to the ongoing treatment of the airway with sleepiness and SDB.

## Treatment of blood gas abnormalities in sleep-disordered breathing

Hypoxemia is suggested to play a key role not only in the development of cardiovascular disorders [13] associated with SDB but also in the neuropsychological and neuronal injury associated with SDB [6]. A study comparing oxygen therapy with CPAP or placebo in 38 sleep apnea patients demonstrated significant reductions in general psychological symptoms with oxygen therapy or CPAP but not placebo; however, depression improved with oxygen and not CPAP or placebo, indicating that hypoxemia plays an important role in some symptoms occurring with SDB [78•]. A study examining sleepiness as an outcome showed no long-term improvement with oxygen [79]. Infants have demonstrated improved total sleep time, decreased periodic breathing, and decreased apnea with supplemental oxygen [80]. In children with a mean age of 4 and significant OSA, supplemental oxygen significantly reduced hypopnea density, obstructive apnea index, and paradoxical breathing, but was considered a temporary treatment while patients were awaiting long-term therapy [81]. It is unknown if cardiovascular risk factors, long-term mortality risk, or stress hormones such as catecholamines associated with hypertension in SDB decrease with the use of supplemental oxygen, therefore, more research in this area is needed.

## Treatment of underlying medical problems

Medical problems often exacerbate SDB, and most commonly, are the associations of SDB with asthma, allergies, thyroid disorders, and gastroesphageal reflux. Allergies often present with symptoms similar to SDB, including snoring and mouth breathing [82], as well as concurrent symptoms of asthma which can cause nighttime breathing abnormalities. Treatment of allergies may reduce SDB [75]. Thyroid disorders can cause SDB and treatment of hypothyroidism has been shown to reverse the signs of SDB [83]. Gastroesophageal reflux has been linked to sleep apnea and occurs frequently in obese individuals. Treatment of reflux

improved the apnea index in patients with SDB [84]. A complete history for the signs and symptoms of comorbid medical disorders is warranted, as is the treatment of these disorders so as to improve the results of treatment for SDB.

## Conclusion

There is evidence that the majority of the health problems associated with SDB improve with treatment. There are multiple treatment options available to children; some are novel, with pending treatments on the horizon that may replace age-old therapies. It is imperative that healthcare workers actively seek out signs and symptoms of SDB in patients to improve early detection and treatment for prevention of long-term morbidity.

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