Is obstructive sleep apnea associated with ADHD?

Nagy A. Youssef, MD
Margaret Ege, MD
Sohair S. Angly, MD
Jennifer L. Strauss, PhD
Christine E. Marx, MD, MA

BACKGROUND: It has been suggested that obstructive sleep apnea (OSA) may result in symptoms similar to those experienced in attention-deficit/hyperactivity disorder (ADHD). Because this may have important public health implications, we reviewed the literature regarding this association, with a focus on interventional studies examining the effect of OSA treatment on change in ADHD symptoms.

METHODS: We performed a systematic literature search of PubMed, along with other major databases, for interventional studies published between January 1966 and June 2010 that examined the effect of OSA treatment on ADHD, which resulted in 6 studies. The literature on the prevalence of ADHD symptoms in OSA and vice versa was also reviewed.

RESULTS: Attentional deficits have been reported in up to 95% of OSA patients. In full syndromal ADHD, a high incidence (20% to 30%) of OSA has been shown. All 6 interventional studies reported improvements in behavior, inattention, and overall ADHD after treatment of OSA.

CONCLUSIONS: OSA may contribute to ADHD symptomatology in a subset of patients diagnosed with ADHD (DSM-IV criteria). Treatment of OSA appears to have favorable effects on ADHD symptoms. Controlled trials and epidemiologic investigations will be required to better understand these relationships, as well as their diagnostic and prognostic implications.

KEYWORDS: ADHD, attention, sleep apnea, sleep disorders, obstructive sleep apnea, sleep-disordered breathing
INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood disorder. Most prevalence estimates range between 3% to 7%,\(^1,2\) although at least 1 report suggests that prevalence may be as high as 16% among children and adolescents.\(^3\) Stimulants are the first line of treatment for ADHD.\(^4\) Prior reports suggest that sleep dysfunction,\(^5\) including periodic limb movement disorder (PLMD) and restless legs syndrome, can present with symptoms of ADHD.\(^6,7\)

Obstructive sleep apnea (OSA) and sleep-disordered breathing (SDB) also are common and serious health problems in children and adults. SDB refers to periodic impairment of respiration during sleep.\(^8,9\) If these obstructive types of events are associated with other symptoms, such as intermittent snoring and daytime somnolence, the clinical diagnosis of OSA can be made. The prevalence of OSA has been estimated to be at least 3% in the general population\(^10\) and up to 2.9% in children who are 6 months to 6 years of age.\(^11\) Physical findings associated with OSA in children and adults include obesity, narrow oropharynx, swollen nasal turbinates, and enlarged tonsils and adenoids (mainly in children). The potential complications of untreated OSA are limited not only to neurocognitive and behavioral complications, but include other possible deleterious effects such as pulmonary and systemic hypertension, cor pulmonale, heart failure, arrhythmias, and sudden death.\(^12\) A number of treatment interventions may effectively decrease the incidence of serious complications and improve psychosocial functioning with this disorder.\(^12-14\) Treatment approaches for OSA include weight reduction, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or surgery. Adenotonsillectomy is the most common type of surgery for OSA, particularly among children, as the most common cause of OSA in children is enlarged tonsils and adenoids. In these children and adolescents, there is some evidence that adenotonsillectomies may have favorable effects on ADHD and cognitive symptoms.\(^15\)

Preliminary evidence suggests that OSA also may produce symptoms that simulate or contribute to ADHD symptoms in a subset of patients, even when full DSM-IV criteria for ADHD are used.\(^16\) Although it seems obvious to some that sleep disorders should be ruled out (along with other medical conditions) before diagnosing ADHD, in clinical practice this does not occur routinely. This may be attributed to the preliminary nature of published evidence and/or a lack of awareness of this emerging area of research in clinical practice. Interestingly, the DSM-IV does not have exclusion criteria for ruling out sleep disorders or other medical etiologies for ADHD, unlike many other psychiatric disorders. Because the public health implications of undiagnosed OSA may be severe, and the association of OSA with ADHD is still evolving, a review of the current literature on this topic seems warranted to potentially help catalyze research in this area. Our objective in this article is to review the literature regarding this association, focusing on the interventional studies that examine the effect of OSA treatment on changes in ADHD symptoms.

METHODS

We performed a search on PubMed, the ISI Web of Knowledge, EBSCO (including PsycINFO), SCOPUS, and CINAHL databases for reports in English between January 1966 and June 2010 using the words sleep apnea, obstructive (Majr) and attention deficit disorder with hyperactivity (Majr). We also used the keywords obstructive sleep apnea and ADHD, obstructive sleep apnea and attention deficit disorder with hyperactivity, and OSA and attention deficit disorder with hyperactivity. This search resulted in 5 interventional studies relevant to the effect of OSA treatment on ADHD symptoms in patients with both disorders.\(^15-19\) The database search was supplemented by bibliographic cross-referencing, which located 1 additional interventional study\(^20\) on the effect OSA treatment on ADHD symptoms. The literature on the prevalence of ADHD symptoms in OSA and vice versa also was reviewed.

Definitions

We would like to mention a few definitions that are less commonly used in the psychiatric literature that are relevant to this publication. However, a detailed nosology of sleep disorders is beyond the scope of this review. It should be noted that these definitions, classifications, and measurements have evolved over time, and some terms, although used in some studies, are no longer in use by the International Classification of Sleep Disorders, 2nd edition (ICSD-2). The ICSD-2, the current classification system of the American Academy of Sleep Medicine (AASM), was published in 2005.\(^21\)
Measurements. The Apnea/Hypopnea Index (AHI) is the most commonly used measure to diagnose OSA. AHI is defined as the number of both apnea and hypopnea events per hour of sleep. Apnea is the cessation of breathing for 10 seconds or more, and hypopnea is partial blockage of airflow. Hypopnea has several definitions, depending on the degree of partial blockage, associated arousal, and possible drop in oxygen level. It should be noted that the ICSD-2 AHI cutoff for diagnosing OSA in adults is 5 events/hour of sleep, whereas in children the cutoff is 1 event/hour of sleep.

The Respiratory Disturbance Index (RDI) may include apneas, hypopneas, respiratory effort–related arousals (RERAs), or snore arousals (the RDI is usually greater than the AHI). RERAs are repetitive episodes of progressively negative intrathoracic pressure culminating in microarousals and sleep fragmentation without evidence of apneas, hypopneas, or gas exchange abnormalities. Consequently, RERAs are not detected on standard polysomnography (PSG). Identification of RERAs can be achieved using esophageal manometry or a nasal transducer rather than a thermistor. The term RDI is sometimes used synonymously with AHI, in some studies reflecting apneas and hypopneas only.

Sleep-disordered breathing. SDB encompasses a group of sleep disorders characterized by abnormalities in the pattern of respiration (pauses in breathing during sleep) or in the quantity of ventilation during sleep.

Since the AASM Task Force recommendations for syndrome definition and classification were published in 1999, the more specific term sleep-related breathing disorder (SRBD) has been used rather than SDB. The newly revised ICSD-2 published in 2005 classifies SRBDs into the following: central sleep apnea syndromes, obstructive sleep apnea syndromes (OSAS), sleep-related hypoventilation syndromes, sleep-related hypoventilation/hypoxemia owing to medical conditions, and other SRBDs.

OSA, sometimes called obstructive sleep apnea (OSA), is the most common of these disorders. OSA is characterized by episodes of repetitive partial (hypopnea) or complete collapse (apnea) of the upper airways during sleep, accompanied by arousals to resume ventilation. It also should be noted that obstructive breathing lies on a spectrum of severity. For instance, disruptive snoring can cause RERAs. Recurrent RERAs constitute upper airway resistance syndrome (UARS), a form of SDB. UARS was first described by the pioneering work of Guilleminault using an esophageal balloon to demonstrate increasing negative intrathoracic pressure leading to microarousals without evidence of apneas, hypopneas, or gas exchange abnormalities. Although UARS can cause many of the sequelae of OSA, RERAs are not captured on PSG and can be overlooked. Thus, SDB can be missed as benign “snoring” when PSG is performed without esophageal manometry or a nasal transducer.

RESULTS

Over the last several years, researchers have taken a number of approaches to determine possible associations between ADHD symptoms and underlying sleep disturbances. Based on our review of the literature, the following issues can be discerned.

1. Significant attentional impairments are common in patients with OSA

Several studies report that snoring and OSA (or SDB) are associated with neurocognitive symptoms and ADHD in children and adults. In a study in which extensive series of attentional tests were conducted (to examine vigilance, as well as selective, sustained, and divided attention), 95% of patients with OSA had some vigilance and/or attentional impairments. This prospective controlled study was conducted in 20 consecutively selected OSA patients (mean age, 51) and 40 control subjects (mean age, 48.4). An OSA diagnosis was given following PSG (the gold standard for OSA diagnosis). Of the 20 patients with OSA, 19 males and 1 female were consecutively selected to participate in the study. The control subjects included 28 males and 12 females. The mean AHI was 45/hour for the OSA group. Attentional tests included the Oxford Sleep Resistance Test, Continuous Performance Test, and the Driving Simulator Test. These attentional tests were performed at 3 different times of the day (9:00 AM, 11:00 AM, and 1:30 PM). Subjective sleepiness was tested by the Epworth Sleepiness Scale. The Beck Depression Inventory was used to rule out depressed mood as a possible confounding factor. In this study, 75% of OSA patients failed the Oxford Sleep Resistance Test (which assesses maintenance of wakefulness), indicating that these patients exhibited vigilance alteration characterized by shortened sleep latency and a higher number of omissions during the test throughout the day compared with the control group (P < .05). Also, 65% demonstrated impaired sustained and selective attention on the Continuous Performance Task.
II. Do patients with ADHD have a high incidence of obstructive sleep apnea or other sleep disorders?
Several studies have found that patients with full syndromal ADHD have a high incidence of OSA, snoring, and other sleep disturbances, and even high somnolence by objective measures. It was proposed that the sleep disruption associated with some sleeping disorders may contribute “to the inattention and hyperactivity seen in a subgroup of ADHD-diagnosed children.” On the other hand, OSA-induced hypoxia altering the dopaminergic, adrenergic, and/or glutamatergic transmission in the prefrontal cortex could contribute to neurocognitive deficits. Also, a common underlying dopaminergic abnormality of both ADHD and PLMD has been hypothesized, possibly via a mechanism other than hypoxia.

Only one study was not consistent with findings reporting that patients with ADHD may have a higher incidence of OSA and PLMD. In this study of 40 children with ADHD, the researchers found that all 40 had essentially normal PSGs. The study, however, excluded patients who had ADHD and “primary sleep disorders or other disorders commonly associated with secondary alterations in normal sleep patterns,” including patients with observable apneas and daytime sleepiness. Hence, potential associations between ADHD symptoms and OSA cannot be examined in the aforementioned report because patients with sleep disorders were excluded from the study population from the outset. Exclusion of patients with ADHD and daytime sleepiness also could have affected the results of the study, as sleepiness is common in patients with OSA. In addition, this study did not include a control group.

Additional studies investigating whether patients with ADHD have a high incidence of OSA and other sleep disorders include the following. A study, supported by the National Institutes of Health, found an increased frequency of obstructive sleep apnea in children (age 5 to 7) with mild ADHD. Children were classified as having mild ADHD if they scored between 1 and 2 standard deviations above the mean (ie, 61 to 69) on the ADHD index of the Conners’ Parent Rating Scale, and were classified as having severe ADHD for a score more than 2 standard deviations above the mean (ie, ≥70). Although in this study the prevalence of OSA in severe ADHD cases was not higher than that of controls, an unusually high frequency of OSA (26%) was observed among patients with mild ADHD. Another study investigated whether 143 children with symptoms of inattention and hyperactivity were more likely to have symptoms of SDB and PLMD. The authors suggested that 81% of habitually snoring children with ADHD could potentially have their ADHD “eliminated” if snoring and associated SDB were treated. They found that the group of children with ADHD with snoring and associated SDB represented approximately 25% of children with ADHD in their cohort. The authors thus argued that this association suggests that SDBs “and perhaps other sleep disorders could be a cause of inattention and hyperactivity in some children.”

In a recent retrospective study of 33 children with ADHD, 21 patients (64%) had SDB. The 64% of patients with SDB in this study were specifically diagnosed as follows: 8 (24%) had OSA, 8 (24%) had UARS, and 5 (15%) had obstructive hypoventilation. An additional 10 (30%) had PLMD. These patients with ADHD showed decreased oxygen saturation and increased snoring compared with the control group. This research group concluded that “sleep disordered breathing and periodic limb movements of sleep appear to be common among children with ADHD who have symptoms of disturbed sleep.”

Data appear to be more limited in adults. However, a small report by Surman et al examined 6 adults with sleep complaints who were “rigorously” diagnosed with ADHD using DSM-IV criteria (2 with inattentive and 4 with combined subtype). All participants with ADHD were found to have evidence of SDB after undergoing PSG.

Based on this literature review, it appears that some populations of children and adults with ADHD symptoms have a higher incidence of SDB than the general population. Other sleep disorders in ADHD patients also have been shown to be higher than that of the general population.
population. These data suggest that additional research in larger cohorts is needed in this area, and that clinicians should potentially consider the possibility of underlying SDB in the assessment of ADHD symptoms.

III. Effect of surgical and nonsurgical treatments for OSA on attention and ADHD

Tonsillectomy, adenoidectomy, or both are the most common surgical treatments for children with OSA. Children who do not respond to surgical intervention or for whom surgical intervention is not indicated can be managed successfully with nasal CPAP or BiPAP.66 Nonsurgical interventions such as weight loss, CPAP, or BiPAP are more commonly used in adults with OSA than are surgical interventions to correct anatomic airway compromise.

Several studies assessing general functioning and performance (but not ADHD directly), found improvement in academic performance after tonsillectomy and adenoidectomy for children with SDB, as reflected by an overall increase in grades52 and decrease in behavioral problems.53,60

However, the systematic review of the literature on interventional studies of OSA treatment effect on ADHD generated 5 surgical interventional studies (adenotonsillectomy) in children and 1 interventional case series in adults using CPAP and conservative measures. Some studies examined the effect of treating OSA on inattention symptoms, while others examined the effect on 1 or more subtype of ADHD (inattentive, hyperactive, and combined types). These studies are discussed in the following 2 sections (see also the TABLE).

Assessment in children. In a study designed to assess “attention deficit disorder (ADD)” in children with OSAS, Aivor et al15 used a prospective interventional comparative approach. Nineteen patients presenting to a pediatric otolaryngology clinic in Tel Aviv, Israel, with a 3-month history of OSA participated. They were excluded from the study if they had “a prior diagnosis or suspicion of ADHD.” However, during the study, children between age 5 to 14 were diagnosed as having “ADD” based on the investigators’ assessment using the Test of Variables of Attention (TOVA) rather than DSM-IV criteria. It is also noteworthy that ADD is not a formal DSM-IV diagnosis. Adenotonsillectomy was performed on these patients, with preoperative and 2-month postoperative measures obtained via the OSA-18, TOVA, and Achenbach Child Behavior Checklist questionnaires/4-8 attention problems syndrome scales (CBCL/4-8). The OSA-18 questionnaire consists of 18 quality-of-life survey items that aid identification of pediatric OSAS. This scale has been correlated with RDI and has shown to have a high level of reliability and validity.60 The TOVA is an objective measure to assist in ADHD diagnosis,61 with proven test-retest reliability.53,62 It is a 23-minute, computerized, visual continuous performance test for the evaluation of attention, impulse control, and response time that is not influenced by culture and has minimal language requirements. CBCL/4-8 is a standardized parent questionnaire that assesses behavioral and attentional problems in children.63 In this study, clinical evaluation and physical examination were conducted by a pediatric otolaryngologist. There was significant improvement in attention on the TOVA and CBCL/4-8 scores post-adenotonsillectomy in all children except one. Sleep-related quality of life also improved, as indicated by a significant reduction in OSA-18 scores. Limitations of this study (in addition to the diagnostic limitations mentioned above) were that there was no control group. In addition, OSAS was not diagnosed using PSG, but rather was diagnosed with OSA-18, assessing history of occasional cessation of breathing or respiratory effort during sleep as observed by the parents, and physical examination.

Using an AHI threshold of 1 for OSA diagnosis and an upper limit of 5 (corresponding to the AASM definition of mild OSA in the pediatric population) on PSG, Huang et al18 compared 66 children with a DSM-IV diagnosis of ADHD with 20 healthy controls. This study was designed as a prospective, nonrandomized, open trial to “determine the best treatment for children who have ADHD with mild OSA.”18 They specifically aimed to investigate whether “treating OSA has similar results as methylphenidate (MPH)” treatment in children with ADHD. Also, the study “may in addition shed some light on the relationship between mild OSA and ADHD.” Children were assessed before treatment and at a 6-month follow-up posttreatment. The children were age 6 to 12. Of 125 children referred to a university-based child psychiatry clinic in Taiwan for suspected ADHD, 66 children (55.2%) “with ADHD complaint had AHI >1 event/h and met the other ADHD entry criteria.” In this cohort, ADHD diagnoses were mild to moderate in severity, based on the ADHD Rating Scale. As noted above, the study also enrolled 20 healthy controls. PSG data were scored by an individual who was blind to whether the child was in the treatment or the control groups. The 66 children with ADHD and OSA were divided into 3 groups: the first
## TABLE

Improvement in ADHD or inattention in interventional studies of obstructive sleep apnea

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N</th>
<th>Age (y)</th>
<th>Design/method</th>
<th>ADHD assessment</th>
<th>OSA assessment</th>
<th>Intervention</th>
<th>Change in ADHD symptoms</th>
<th>RDI before (B) and after (A) intervention</th>
</tr>
</thead>
</table>
| Huang et al., 2007<sup>12</sup> | 86 | 6 to 12 | Prospective, controlled open trial  
-66 patients with ADHD and 20 healthy controls  
-Of the ADHD patients with AHI > 1 < 5 events/h: 27 were treated with MPH, 25 with AT, 14 had no treatment  
-Follow-up was performed 6 months after treatment, or diagnosis (if no treatment)  
-Pre- and post-intervention clinical interviews: pediatric, neurologic, psychiatric, and neurocognitive evaluation  
-Standard K-SADS-E  
-ADHD-RS–Parent  
-TOVA  
-TOVA-V  
-WISC-III  
-CBCL (by parents and teacher)  
-PSG (after diagnosis of ADHD) showed mild OSA  
-ENT examination | -Clinical (using DSM-IV) by 2 psychiatrists  
-Pre- and post-intervention clinical interviews: pediatric, neurologic, psychiatric, and neurocognitive evaluation  
-Standard K-SADS-E  
-ADHD-RS–Parent  
-TOVA  
-TOVA-V  
-WISC-III  
-CBCL (by parents and teacher)  
-PSG (after diagnosis of ADHD) showed mild OSA  
-ENT examination | -Surgical and MPH groups were significantly different (P = .007)  
-ADHD-RS Total Score (SD):  
-MPH  
B: 31.52 (7.01)     A: 21.16 (7.13)  
(P = .0001)  
-Control  
B: 30.17 (6.98)     A: 27.08 (6.61)  
(P = .001) | NOT REPORTED<sup>5</sup> |
| Chervin et al., 2006<sup>16</sup> | 105 | 5 to 12.9 | Prospective controlled trial  
-78 scheduled for clinically indicated AT, 27 for unrelated surgical care  
-1-year follow-up in 100 children | -Clinical (using DSM-IV) by 2 psychiatrists  
-Pre- and post-intervention clinical interviews: pediatric, neurologic, psychiatric, and neurocognitive evaluation  
-Standard K-SADS-E  
-ADHD-RS–Parent  
-TOVA  
-TOVA-V  
-WISC-III  
-CBCL (by parents and teacher)  
-PSG (after diagnosis of ADHD) showed mild OSA  
-ENT examination | -Surgical and MPH groups were significantly different (P = .001)  
-TOVA ADHD score (SD):  
-MPH  
B: –2.08 (2.14)     A: –0.01 (2.06)  
(P < .01)  
-No treatment  
B: –2.59 (2.20)     A: –2.10 (1.71)  
(P = .01) | NOT REPORTED<sup>5</sup> |
| Weber, 2006<sup>27</sup> | 30  | 4 to 13 (divided into groups: 4 to 7; 8 to 10; and over 11) | Prospective open trial  
-Evaluation before surgery and 6-month follow-up after surgery (22 patients)  
-Before and after surgery, the patient’s guardian completed a screening questionnaire of “hyperactivity disorders, attention deficit and impulsiveness, adapted from the DSM-IV”  
-H&P (of frequent snoring, constant oral breathing, restless sleep) and nasofibroscopy with obstruction of at least 80% by adenoids  
-AT  | -Clinical (using DSM-IV) by 2 psychiatrists  
-Pre- and post-intervention clinical interviews: pediatric, neurologic, psychiatric, and neurocognitive evaluation  
-Standard K-SADS-E  
-ADHD-RS–Parent  
-TOVA  
-TOVA-V  
-WISC-III  
-CBCL (by parents and teacher)  
-PSG (after diagnosis of ADHD) showed mild OSA  
-ENT examination | -AT  
B: 7.6 (±11.3)  
A: 1.1 (±6.9) | NOT REPORTED<sup>5</sup> |
### TABLE

**Improvement in ADHD or inattention in interventional studies of obstructive sleep apnea (continued)**

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N</th>
<th>Age (y)</th>
<th>Design/method</th>
<th>ADHD assessment</th>
<th>OSA assessment</th>
<th>Intervention</th>
<th>Change in ADHD symptoms</th>
<th>RDI before (B) and after (A) intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avior et al, 2004&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>19</td>
<td>5 to 14</td>
<td>-Prospective open trial -Children with OSA, with indicated AT, were evaluated for ADD preoperatively and at 2 months postoperatively and if AT resulted in improvement of ADD symptoms -Patients with a prior diagnosis or suspicion of ADHD were excluded</td>
<td>-TONA, CBCL/4-8</td>
<td>-H&amp;P, OSA-18&lt;sup&gt;P&lt;/sup&gt;</td>
<td>-AT</td>
<td>-TONA: B: –2.9 (±3.1) A: –0.4 (±2.8) (P &lt; .0001) -OSA-18: B: 6.1 (±4.7) (P &lt; .018) A: 3.8 (±2.1)</td>
<td>-No RDI reported -OSA-18: A: 30.4 (±10.1) (P &lt; .0001)</td>
</tr>
<tr>
<td>Naseem et al, 2001&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3</td>
<td>Case 1: 19, case 2: 23, and case 3: 44</td>
<td>-Case series</td>
<td>-Clinical interview and history of diagnosis and treatment for ADHD by stimulants leading to improvement</td>
<td>-H&amp;P -PSG</td>
<td>-Cases 1 and 2: CPAP -Case 3: patient elected conservative treatment (weight loss and medical treatment for nasal congestion)</td>
<td>-It was reported only in the 2 cases treated with CPAP that there were significant subjective improvement in attention and they were weaned off stimulant treatment</td>
<td>-Case 1: B: 25.6 A: Not reported -Case 2: B: 48.5 (25% sleep time at 90% O&lt;sub&gt;2&lt;/sub&gt; saturation) A: Overnight pulse oximetry showed complete resolution of nocturnal hypoxemia -Case 3: B: 7 (lowest O&lt;sub&gt;2&lt;/sub&gt; saturation was 89%) A: Not reported</td>
</tr>
<tr>
<td>All 1996&lt;sup&gt;4&lt;/sup&gt;</td>
<td>33</td>
<td>6 to 12</td>
<td>-Prospective controlled open trial -Evaluated before and 3 to 6 months after surgery by 2 investigators -AT waiting list patients were evaluated, identified 12 with a moderate SBD. 11 with similar history of snoring and sleep disturbance but without sleep or breathing difficulty (minor group). 10 referred for an unrelated surgical procedure (control group)</td>
<td>-Conners Behavior Rating Scale (Parent and Teacher) -WISC-R UK -OPT -Matching Familiar Figures Test</td>
<td>-Parents completed child sleep questionnaire -Children monitored overnight with video and oximetry -SBD group had significantly more (&gt;4%) dips in O&lt;sub&gt;2&lt;/sub&gt; saturation compared with the other 2 groups</td>
<td>AT</td>
<td>All tests were done before and after surgery except the WISC</td>
<td>-Case 1: B: –2.9 (±3.1) A: –0.4 (±2.8) (P &lt; .0001) -Case 2: B: 30.4 (±10.1) A: 30.4 (±10.1)</td>
</tr>
</tbody>
</table>

<sup>1</sup>The OSA-18 is an 18-item quality of life survey of child OSA that correlates with the RDI on nap PSG and has high reliability and validity.

<sup>2</sup>1h/hour in Cheirvin et al pre-intervention = 7.3 (±12.5) and post-intervention = 1.1 (±1.1). In Huang et al, 1h/hour pre-treatment surgical group = 3.32 (±1.11); post-treatment surgical group = 0.89 (±0.63); pre-MPH treatment group = 2.14 (±1.44); post-MPH treatment group = 2.60 (±2.95); control group: pre = 2.56 (±1.46) and post = 2.31 (±2.39); control group: pre = 0.41 (±0.40) and post = 0.37 (±0.40).

<sup>3</sup>WISC-R UK, similarities and vocabulary from the Verbal Scale and Block Design and object assembly from the Performance Scale were used.

<sup>4</sup>Absence of symptoms if AT resulted in improvement in ADHD or inattention in interventional studies of obstructive sleep apnea

<sup>5</sup>The Conners scale was shortened by including 3 subscales (instead of 5) of aggression, inattention, and hyperactivity.

<sup>6</sup>From the WISC-R UK, similarities and vocabulary from the Verbal Scale and Block Design and object assembly from the Performance Scale were used.

<sup>7</sup>ADD: attention deficit disorder; ADHD: attention deficit/hyperactivity disorder; ADHS-RD: ADHD Rating Scale; AHI: Apnea/Hypopnea Index; AT: adenotonsillectomy; B/A: before/after intervention; BHR: Behavioral Hyperactivity Index; CBCL: Child Behavior Check List; CBCL/4-8: Achenbach Child Behavior Check List; 4-8 Attention problems scales; CMS: Children’s Memory Scale; CPAP: Continuous Positive Airway Pressure therapy; CPRS: Conners’ Parent Rating Scales-Revised; CPT: Continuous Performance Test; CS-4-P: Child Symptom Inventory-4-Parent Checklist; EENT: ear, nose, and throat; H&P: clinical history and physical examination; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version (Chinese version); MPH: methylphenidate; MSIT: Multiple Sleep Latency Test; OSA: obstructive sleep disorder; OSA-18: Obstructive Sleep Disorder–18; PSG: polysomnography; RDI: Respiratory Disturbance Index; TONA: Test of Variables of Attention; TONA-V: TOVA–Visual test; WISC: Wechsler Intelligence Scale for Children.

<sup>8</sup>The Conners Behavior Rating Scale (Parent and Teacher) was used. The Conners scale was shortened by including 3 subscales (instead of 5) of aggression, inattention, and hyperactivity.

<sup>9</sup>From the WISC-R UK, similarities and vocabulary from the Verbal Scale and Block Design and object assembly from the Performance Scale were used.

<sup>10</sup>ADD: attention deficit disorder; ADHD: attention deficit/hyperactivity disorder; ADHS-RD: ADHD Rating Scale; AHI: Apnea/Hypopnea Index; AT: adenotonsillectomy; B/A: before/after intervention; BHR: Behavioral Hyperactivity Index; CBCL: Child Behavior Check List; CBCL/4-8: Achenbach Child Behavior Check List; 4-8 Attention problems scales; CMS: Children’s Memory Scale; CPAP: Continuous Positive Airway Pressure therapy; CPRS: Conners’ Parent Rating Scales-Revised; CPT: Continuous Performance Test; CS-4-P: Child Symptom Inventory-4-Parent Checklist; EENT: ear, nose, and throat; H&P: clinical history and physical examination; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version (Chinese version); MPH: methylphenidate; MSIT: Multiple Sleep Latency Test; OSA: obstructive sleep disorder; OSA-18: Obstructive Sleep Disorder–18; PSG: polysomnography; RDI: Respiratory Disturbance Index; TONA: Test of Variables of Attention; TONA-V: TOVA–Visual test; WISC: Wechsler Intelligence Scale for Children.
group (n = 27) was treated with an effective dose of MPH determined and adjusted by the patient’s own private psychiatrist, the second group (n = 25) was treated by adenotonsillectomy, and the third (n = 14) received no treatment. There were no significant demographic differences in age, sex, body mass index, subtype of ADHD, ADHD Rating Scale, or AHI between the 3 groups with ADHD and OSA. ADHD was diagnosed by “two experienced psychiatrists” using DSM-IV criteria and the standard structured interview with the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (K-SADS-E). All children were medication free during the assessments. The ADHD Rating Scale—Parent version was also performed. The ADHD Rating Scale—Parent is a structured interview based on information from the parent and the child. Each of the 18 items assessed correspond to diagnostic criteria outlined in the DSM-IV. The scale has established psychometric properties in children and has been well validated. Participants were also evaluated with the following tests: TOVA, Child Behavior Checklist (by parents and teacher), OSA-18, teachers’ questionnaires (see more details about these tests earlier in this section). Physical, neurologic, and ear, nose, and throat evaluations were performed at the same time. At 6-month follow-up, the same variables assessed at entry were obtained. There were no significant differences between groups in weight pre- or 6-month post-intervention. ADHD symptoms improved in both the MPH and adenotonsillectomy groups to a significantly greater degree, as compared with the no-treatment group. This emphasizes the nonspecific positive neurocognitive effects of stimulants, irrespective of diagnosis. However, when comparing the MPH to the post adenotonsillectomy group, both the PSG and inattention tests showed significant improvement in the surgical group vs the MPH group. There were significant improvements in the total score of the ADHD rating scale (P = .0001), inattention (P = .0001), and hyperactivity subscales (P = .0001) at 6 months post-operatively compared with preoperatively. Postsurgery, the children no longer met DSM-IV ADHD criteria.

In another study conducted in Oxford, UK, children age 6 to 12 on the adenotonsillectomy waiting list were assessed to identify 3 groups. A group of 12 children with a moderate sleep and breathing disorder were compared with a “snorer” group of 11 children (children with a similar history of snoring and sleep disturbance but without an obvious breathing problem) and a control group of 10 children. The investigator stated that the snorer group was included not “as true controls but as an intermediate group.” The 3 groups were matched for age and sex. All children were assessed before and 3 to 6 months after adenotonsillectomy with several psychological tests (TABLE) to assess inattention, hyperactivity, and impulsivity. These tests include the Conners’ Behavior Rating Scale (Parent and Teacher, using the 3 subscales of aggression, inattention, and hyperactivity), a widely used test to assess the constructs of inattention and hyperactivity. In addition, the Matching Familiar Figures Test was administered to assess impulsivity, and the Continuous Performance Test was administered to assess sustained and selective attention. Sleep and breathing disorder was assessed by overnight video recording and oximetry. Oximetry was used to measure the number of dips in oxygen saturation >4%. PSG was not conducted in this study. Preoperatively, the sleep and breathing disorder and snorer groups were significantly more restless during sleep than the control group. The sleep and breathing disorder group was differentiated from the snorer group by having more dips in oxygen saturation (>4%; median of 2.9/h with a 5% to 95% range of 1.6 to 11.3) than the snorer group (median of 1.0/h with a 5% to 95% range of 0.5 to 3.4) during sleep. However, after adenotonsillectomy, children with SBD showed a significant reduction in aggression, inattention, and hyperactivity. Also in the snorer group, hyperactive behavior and vigilance improved. Postoperatively, there were no significant differences between all 3 groups, and results were maintained 3 to 6 months after surgery.

To further understand the long-term effects of adenotonsillectomy on ADHD, Chervin and colleagues performed a well-designed prospective, controlled study to assess inattention, hyperactivity (and ADHD), and their long-term prognosis after adenotonsillectomy. The study assessed 105 children between age 5 and 12.9, of whom 78 children (recruited from 8 otolaryngology practices in Michigan) had previously undergone clinically indicated adenotonsillectomy, mostly for mild to moderate SDB as diagnosed by PSG. These children were compared with 27 control children scheduled for unrelated surgical care. Preoperatively, children who had an adenotonsillectomy were more hyperactive compared with the control group. The diagnosis of ADHD was determined by a board-certified child psychiatrist who was blind to the study results (except for the surgical status). The well-validated Diagnostic Interview Schedule for Children—Parent Interview, Present-State version was administered by the psychiatrist. The psychiatrist
also independently interviewed the parent and child to confirm the diagnosis. Other instruments (as mentioned in the TABLE) were also administered, including the well-validated Conners’ Parent Rating Scales–Revised: Long Version (CPRS-R:R)32 and the Child Symptom Inventory-4 (CSI-4): Parent Checklist.73 The CPRS-R:R is a comprehensive, 80-item instrument that is often used to assist in ADHD diagnosis when DSM-IV-consistent data are required. The CSI-4 is a 108-item rating instrument that screens for several DSM-IV-based childhood psychiatric disorders. These 2 instruments generated T scores (for inattention and hyperactivity) that were used to construct the behavioral hyperactivity index—the primary outcome for this study. The Integrated Visual and Auditory Continuous Performance Test, a well-validated, computerized test, was also administered to assess sustained attention, or vigilance.74,75 At 1-year follow-up, the adenotonsillectomy group had improved significantly on all measures, including the behavioral hyperactivity index (P < .001) and AHI (P < .001), whereas the control group did not show improvement on any measure. Twenty-eight percent of the adenotonsillectomy group had ADHD at baseline, and half of this ADHD-diagnosed group no longer qualified for the diagnosis at 1 year postsurgery.

In an open-label study to investigate ADHD symptoms in children with obstructive ventilatory disorders (OVDs) for any improvement in inattention, hyperactivity, and impulsivity after adenotonsillectomy,17 Weber and colleagues enrolled 30 children between age 4 and 13 from a university-based sleep disorders division of an otolaryngology department in São Paulo, Brazil. OVD was defined by the authors as “air flow alterations due to total or partial collapse of the upper airways. It may manifest as snoring, oral breathing, apneas, or hypopneas.” Nasofibroscopy with obstruction of at least 80% by adenoids also was used to assist in the diagnosis. The authors reported that “Some children were unable to complete the full night polysomnography, and that is why we did not use the diagnosis of OSAS but that of OVD.” There were no reported findings of PSG, and there was no control group in this study. Children were stratified into 3 groups according to age (4 to 7; 8 to 10; and >11). There was a higher percentage of boys (60.6%) than girls in the study. Attention deficits, hyperactivity, and impulsivity were assessed before surgery and at 6-month follow-up using 30 questions based on DSM-IV criteria. The study found that children age 8 to 10 manifested the highest trend of improvement in attentional deficit, hyperactivity, and impulsivity postsurgery. However, results were not statistically significant, likely due to small sample size in each group, as noted by the authors. Moreover, the diagnosis of sleep disorder was mainly given by history and physical examination rather than standard PSG. This may have affected the results by possibly selecting false-positive cases. It should also be noted that ADHD was diagnosed based on the above-mentioned questionnaire completed by the child’s guardian, but without a formal psychiatric interview.

Assessment in adults. The literature on the effect of OSA treatment on ADHD is very limited in the adult population. This effect has only been examined in a small case series of 3 patients using nonsurgical interventions.19 The patients were age 19, 22, and 44 with a long history of ADHD, and all of them were on stimulant medications. PSG with physical examination was used to assess OSA. Nasal CPAP therapy was initiated in 2 cases, and 1 case elected to pursue conservative treatment, including weight loss and a nasal decongestant. All 3 patients achieved subjective improvements on symptoms of snoring, daytime sleepiness, and inattention, as well as psycho-social functioning. The 2 patients who were treated with CPAP had significant improvement in attention and no longer required treatment with ADHD medications. These preliminary findings warrant replication in larger, well-designed studies in adults.

In summary, although these investigations are small in number, the initial studies summarized above demonstrate that successful treatment of OSA can result in resolution of previously diagnosed ADHD. With the exception of 1 study showing only a trend for improvements, changes reported in these prospective studies were statistically significant and merit additional investigational efforts. As noted previously, the DSM-IV neither requires the exclusion of OSA for diagnosis of ADHD, nor does it contain criteria for ADHD secondary to a general medical condition (OSA), yet preliminary evidence from the above studies suggests that the addition of an exclusionary criterion may be warranted.

DISCUSSION

This review of the literature suggests consistent reports of associations between OSA and ADHD symptoms. Although a definitive etiologic contribution of OSA to
ADHD symptomatology in a subset of patients with ADHD remains to be fully elucidated, initial data pointing to this association are suggestive and merit further investigation.

Several sleep disorders may lead to a clinical presentation of ADHD or subsyndromal inattention. In some of the studies examining patients with coexisting ADHD and OSA, improvements were shown not only in attention, but also in the hyperactive and impulsive domains of ADHD. Improvements in ADHD symptoms after treatment of OSA, whether by surgical or nonsurgical interventions, suggest a possible causal relationship in a subgroup of patients with ADHD. For this reason, OSA should be ruled out before diagnosing ADHD, especially in patients with sleep complaints and snoring. We advocate for the addition of an exclusion criterion in the future DSM to rule out disorders that could contribute to secondary ADHD symptoms. This could have substantive utilitarian value by communicating that ADHD symptoms may, in a subset of patients, manifest secondary to OSA and thus can be expected to resolve after treatment of OSA.

On the other hand, should underlying OSA be missed in the initial evaluation, future diagnosis of OSA may be particularly challenging, because treatment with stimulants for a presumed ADHD diagnosis will provide nonspecific improvement of neurocognitive deficits and ADHD symptoms. Improvements due to stimulant medications could mask neurocognitive symptoms of OSA, as well as fatigue and daytime sleepiness. The clinical importance of proper diagnosis of OSA cannot be underestimated. Treatment of OSA could prevent not only ADHD symptoms but also other serious complications associated with OSA, such as cardiac, systemic and pulmonary hypertension, and failure to thrive.

A more conclusive investigation of potential causative effects of OSA on behavioral problems and ADHD would require a double-blind, placebo-controlled, randomized trial to study the effect of OSA treatment with adenotonsillectomy or CPAP on improvement of ADHD symptoms. However, the design of surgical controlled trials is extremely difficult, if not impossible, due to the fact that patients, families, and clinicians could not be blinded to adenectomy/tonsillectomy and that sham surgery as a placebo would not be ethical. On the other hand, a randomized controlled trial of CPAP in patients diagnosed with both ADHD and OSA would likely be feasible. This, along with further large prospective studies and epidemiologic investigations, could greatly add to our knowledge in this area. Nonetheless, in the interim, large, prospective, well-designed studies such as the ones by Chervin et al and Huang et al [TABLE] have significantly enhanced our knowledge of this association and serve to inform clinical care until more definitive data are available.

CONCLUSIONS

OSA is common among patients with ADHD, and symptoms of inattention affect up to 95% of patients with OSA. OSA may potentially contribute to the diagnosis of ADHD in a subgroup of patients.

In this systematic review of the literature, all interventional studies in ADHD patients who were also simultaneously diagnosed with OSA resulted in the improvement or disappearance of ADHD symptoms after treatment of OSA. Initial evidence indicates that a considerable proportion of ADHD patients in this subgroup did not require stimulant medications post-OSA treatment. It also is important to note that stimulant use for ADHD could potentially mask an underlying sleep disorder. It may be reasonable to consider ADHD secondary to a medical condition such as OSA before a diagnosis of primary ADHD. Randomized controlled trials, large prospective studies, and epidemiologic investigations will be required to better understand the precise nature of the relationship between OSA and ADHD symptoms. Specifically, it is not currently known if this relationship is unidirectional, bidirectional, or potentially even causal. Also relevant to this area is the need to better understand the possible contribution of subthreshold OSA to ADHD symptoms.

ACKNOWLEDGEMENTS: Preparation of this manuscript was supported by the VA Mid-Atlantic MIRECC (PI John Fairbank, PhD); VA MIRECC Advanced Fellowship (N.A.Y.); VA Advanced Research Career Development Award (C.E.M.); VA Career Development Transition Award (C.E.M.); VA HSR&D Career Development Award-2 (J.L.S.).

DISCLOSURES: Dr. Youssef has received honoraria for presentations and was on the speakers bureau of AstraZeneca, Bristol-Myers Squibb, Pfizer Inc, and Abbott Pharmaceuticals, and has received research support from Avanir Pharmaceuticals. Drs. Ege, Angly, Strauss, and Marx report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.
REFERENCES

41. Forbes GB. Clinical utility of the Test of Variables of Attention (TOVA) in the diagnosis of attention-deficit/