Recent evidence has been accumulating that the sleep of individuals with attention deficit hyperactivity disorder (ADHD) is not only disrupted in a nonspecific way but that ADHD has an increased association with simple sleep related movement disorders such as restless legs syndrome/periodic limb movements in sleep (RLS/PLMS), rhythmic movement disorder (body rocking and head banging), and parasomnias, such as disorders of partial arousal (sleep walking, sleep terrors, and confusional arousals). In addition increased associations have been reported between ADHD and hypersomnias such as narcolepsy and sleep apnea as well as circadian rhythm disorders, such as delayed sleep phase syndrome. These relationships are reviewed and the implications for such associations are explored. Patients with sleep disorders should be queried about the symptoms of ADHD and vice versa.

Keywords: Restless legs syndrome, periodic limb movements in sleep, rhythmic movement disorder, sleep walking, confusional arousals, night terrors, narcolepsy, sleep apnea, delayed sleep phase syndrome

Citation: Walters AS; Silvestri R; Zucconi M; Chandrashekariah R; Konofal E. Review of the Possible Relationship and Hypothetical Links Between Attention Deficit Hyperactivity Disorder (ADHD) and the Simple Sleep Related Movement Disorders, Parasomnias, Hypersomnias, and Circadian Rhythm Disorders. J Clin Sleep Med 2008;4(6):591-600.

NARCOLEPSY

Narcolepsy is characterized by excessive daytime drowsiness with or without sudden loss of body tone under conditions of strong emotion (cataplexy). Hypnagogic hallucinations and sleep paralysis are frequently associated features.

ADHD Symptoms in Narcolepsy

Inattention in Narcolepsy

The prevalence of ADHD symptoms in patients with narcolepsy approaches 18.9% in one study. It is obvious that patients with narcolepsy can have decreased attention because they are drowsy during the day. This is captured in abnormalities of tests of arousal/alertness. Arousals can be divided into phasic (tasks that require immediate attention) and tonic (tasks that re-
Patients with narcolepsy do poorly on tests of sustained attention as well as on tests of task-switching. Patients with narcolepsy also do poorly on tests of selective attention. Selective attention is divided into focused attention (continuous focus on a single task), flexible attention (one must switch from one task to another) and divided attention (one must do 2 tasks at once). Examples would be poor performance on the Stroop and the Wisconsin Card Sorting test, which are measures of the ability to attend to a single task. However, in many instances the length of the task and the complexity of the task may also be the ones that are shorter. In addition, complex tasks are more demanding and interesting, and therefore could be more alerting. Thus, the level of attention may be confounded with the level of alertness. Others have pointed out that narcoleptics may have cognitive difficulties as well, particularly in the area of executive functioning, which is the ability to organize, plan, prioritize, and execute various activities in an appropriate sequence. Deficits in executive functioning may be a result of the drowsiness narcoleptics experience. Because of drowsiness, narcoleptics have to spend so much of their mental energy focusing on even simple tasks that they do not have mental residual to focus on the greater complexities of task integration. \[1\] Hood and Bruck examined narcoleptics in both high and low states of arousal and found that complex cognitive tasks are the most sensitive to arousal fluctuation.\[2\]

Abnormalities in narcolepsy have also been found in the Sustained Attention to Response Task (SART) and in the automobile driving simulation task “Steer Clear.” Both of these tests are measures of the ability to maintain focus on a single task. Neurophysiological tests such as the measurement of the P300 and mismatch negativity have also been used to explore the attentional matrix in narcolepsy.\[3\]

Nauman and Daum have summarized the research on cognition and narcolepsy nicely up to 2003. In summary, narcoleptics have trouble with memory (additional examples include response latency, word recall, estimation of frequency), attention (additional examples include Wilkinson auditory vigilance task, 10-minute choice reaction time test) and executive function (an additional example is Sternberg’s STM Scanning task). However, it is important to remember that these kinds of deficits are not found in all studies.\[4\]

**Hyperactivity in Narcolepsy**

One of the glaring deficits in this area of research is that there has been no attempt to see if narcoleptic patients are also hyperactive. It is theoretically possible that narcoleptics move more in order to stay alert, but this has not been formally tested.

**Narcolepsy Symptoms in ADHD**

More than a third of adults with ADHD are drowsy, as determined by a score >12 on the Epworth Sleepiness Scale according to one study. In ADHD patients, inattention scores correlated with the excessive daytime sleepiness scores. Of course, daytime drowsiness may be caused by disorders (such as sleep apnea) other than narcolepsy. In another study, 34 children with ADHD (average age 12.4 y) were objectively more drowsy than controls on a modified multiple sleep latency test, in which naps were not terminated at 20 minutes (21.9 min vs 27.9 min), p < 0.05, but half of the ADHD group had symptoms of obstructive sleep apnea as opposed to only 22% of the control group. In addition, the authors did not state whether or not they looked for 2 sleep onset REM periods, which is the hallmark of narcolepsy on MSLT. In another study by Lecendreux et al on an unselected population of 30 boys with ADHD, aged 5-10 years, results were similar with shorter sleep latencies for ADHD patients than controls in naps 1, 2, and 3. Number and duration of sleep onsets measured by the MSLT correlated significantly with hyperactivity-impulsivity and inattentive-passivity indices, as measured by the Conners Parent and Teacher rating scales. None of these differences could be attributed to any differences in nocturnal sleep. Again, the authors did not state whether they looked for 2 sleep onset REM periods on the MSLT. In a later study by the same group, in which corrections were made for the presence of anxiety and depression in 45 obese children aged 10-16 years (not selected for ADHD), drowsiness still remained associated with ADHD symptoms in those children from the group that had ADHD symptoms. To our knowledge, there is no study that systematically evaluates individuals with ADHD for the presence of either the MSLT findings of narcolepsy or secondary features of narcolepsy (sleep paralysis, hypnagogic/hypnopompic hallucinations, cataplexy).

**Summary:** To summarize, symptoms of inattention are common in narcolepsy, but symptoms of hyperactivity in narcolepsy need to be further explored. Drowsiness is common in ADHD, but the prevalence of narcolepsy in ADHD remains to be determined.

**Rhythmic Movement Disorder**

Rhythmic Movement Disorder (RMD) primarily occurs in young children and is characterized by head banging or body rocking prior to sleep onset and sometimes during sleep itself. Most children outgrow the disorder. It is not truly considered a disorder unless sleep-related injury is present (which is uncommon), or daytime consequences related to reduced sleep quality are present (ICSD-2). The disorder often disappears as children age.
ADHD Symptoms in Rhythmic Movement Disorder

Dyken et al were the first to note the association between ADHD and RMD. They reported that 3 of 7 children, aged 1-12 years, with video-polysomnographically documented RMD had attention deficit disorder (ADD) by past medical history. No attempt was made to confirm the ADD diagnosis, and the observation went without further comment. Stepanova et al confirmed these results: ADHD was present in 6 of 10 children with RMD who were formally assessed for the presence of ADHD symptoms. The authors found the inattentive subtype in 4 of the 6 children with ADHD and the combined inattentive and hyperactive type in 2 of the 6 children with ADHD. The authors suggest that immaturity of premotor and striatal circuits may be involved in both RMD and ADHD, or that RMD may be yet another sleep disorder potentially causing symptoms of ADHD. The subjects in this study were beyond the age range at which RMD usually disappears (average age in this study 14.7 years) and one of the subjects was an adult, aged 24 years.

Rhythmic Movement Disorder in ADHD

Taken from the opposite perspective, 150 children and adolescents with various psychiatric problems were compared to a normal control group of 309 subjects from the general population. Fourteen of the psychiatric patients had ADD, and 6 of these 14 had head banging, compared to none in the control group. This result will obviously have to be verified in a larger study.

Summary: ADHD seems to be more common in RMD and, in turn, RMD seems to be more common in ADHD. The sample sizes tested are small, and results need to be confirmed in larger series. Whether sleep disruption from RMD leads to symptoms of ADHD, or whether a program for increased motor activity has a common diathesis in both RMD and ADHD bears further investigation.

CIRCADIAN RHYTHM DISORDERS—DELAYED SLEEP PHASE SYNDROME

Delayed sleep phase syndrome occurs primarily in adolescence and is characterized by sleep onset insomnia if the individual tries to go to sleep early. However, if the individual is allowed to go to bed later and sleep later, the insomnia and subsequent daytime drowsiness disappear. In delayed sleep phase syndrome, the individuals with a propensity to sleep at a later time than normal is thought to be mediated through the biological clock located in the suprachiasmatic nucleus of the hypothalamus.

ADHD Symptoms in Delayed Sleep Phase Syndrome

A preliminary study did not find ADHD to be present in 5 adults with delayed sleep phase syndrome. This relationship remains to be further explored.

Delayed Sleep Phase Syndrome in ADHD

In 1991 Dahl et al described a 10-year-old girl with ADD and a 5-year history of delayed sleep phase insomnia. A trial of chronotherapy in the morning along with a behavioral modification program resulted in significant improvement in ADD symptomatology. Gruber et al in 2000 pointed out that 28 children with ADHD who were monitored with actigraphs and sleep diaries for 5 consecutive nights often had evidence of sleep onset insomnia. Van der Heijden et al in 2005 specifically characterized this sleep onset insomnia as a component of delayed sleep phase syndrome (DSPS). They compared 87 children with ADHD and sleep onset insomnia to 33 children with ADHD and no sleep onset insomnia. Salivary melatonin is a marker of circadian phase and is secreted only in the dark. The onset of secretion of melatonin under conditions of reduced illumination can be measured as the DLMO (dim light melatonin onset). The DLMO in the ADHD insomnia patients occurred at a much later time in the evening than in the ADHD patients without insomnia. This strongly implies that the sleep onset insomnia in ADHD is due to delayed sleep phase syndrome. Wake up time was also later in the ADHD insomnia group, again suggesting delayed sleep phase syndrome. The quality of sleep was comparable in both groups, thus suggesting that sleep quality was not a confounding issue. In 2006 Rybak et al performed an open trial of bright light therapy in the morning in 29 adults with ADHD. There was a significant phase advance in bedtime preference with comparable improvements in ADHD symptomatology.

Summary: ADHD seems to be characterized, in some cases, by a sleep onset insomnia characteristic of delayed sleep phase syndrome. On the other hand, the reverse relationship does not seem to hold, as a preliminary study suggests that ADHD symptoms are not common in delayed sleep phase syndrome. It may be that hyperactivity at night in ADHD causes a delayed sleep onset characteristic of Delayed Sleep Phase Syndrome, but that the sleep disruption from a delayed sleep onset is not enough to cause daytime inattentiveness and hyperactivity characteristic of ADHD.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS IN SLEEP (RLS/PLMS)

Restless legs syndrome (RLS) is a common sensorimotor disorder characterized by an irresistible urge to move the legs, which is often accompanied by uncomfortable sensations in the legs or, less frequently, other body parts. These sensations are worse at rest, relieved by movement, and worse in the evening or night and at rest. In RLS, patients frequently experience insomnia from the leg discomfort and the need to move around. The diagnosis of RLS is based on the revised RLS criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG). Although RLS is traditionally considered a disorder of middle to older age, several case series show that it may occur in childhood. In addition, one large survey of 10,523 families in Britain and the United States showed that clinically significant RLS occurs in 0.5% of children and 1% of adolescents. However, children may report RLS symptoms differently than adults, in part because of their limited ability to describe RLS sensations. Moreover, the clinical presentation of RLS may differ in children. Considering these particularities, the IRLSSG has proposed a set of criteria specific for childhood.
Patients with RLS also frequently have a related sleep disorder called periodic limb movements in sleep (PLMS). PLMS are defined as movements that last 0.5-10 seconds and recur every 5 to 90 seconds in a series of ≥ 4.26 They more commonly affect the legs, although the arms may be involved as well. Typical movements consist of simultaneous flexions of the hips, knees, and ankles. Eighty percent of adult patients with RLS have PLMS.23 PLMS have been reported in children with RLS although their prevalence in children has not been adequately studied.21 In RLS, the role of PLMS in the production of insomnia or daytime symptoms of fatigue is controversial. However, periodic leg movements sometimes occur in wakefulness (PLMW) in RLS and may contribute to the insomnia.21

In last decade, there has been growing research in sleep disruption associated with ADHD.6 It has been correctly pointed out that sleep disturbances may (1) mimic ADHD symptoms in the evening or (2) be associated with ADHD symptoms.27,28 In both cases, the appropriate treatment of sleep disturbances may significantly improve diurnal ADHD symptoms.

Given the relationship between RLS and sleep fragmentation, some clinicians started to look for a potential association between ADHD and RLS symptoms. Since then, interest in the link between ADHD and RLS has progressively grown. In a survey of the literature completed in 2005, Cortese et al29 reviewed available evidence on the relationship between RLS and ADHD.29,35 In addition, new studies have emerged since then.36-38

In light of these considerations, the aims of this section are (1) to critically review evidence on the relationship between ADHD and RLS; (2) to examine the potential mechanisms underlying this relationship; and (3) to present some future directions for the research in this area.

RESTLESS LEGS SYNDROME

ADHD in RLS

In a recent study in children by Kotagal and Silber, 8 (25%) of 32 patients with childhood RLS demonstrated inattentiveness.36 In a large community-based cross-sectional survey of 866 children, symptoms of ADHD, by objective indices, were almost twice as likely to occur with symptoms of RLS than would be expected by chance alone.33 There was a high hyperactivity index in 18% of children with RLS and 11% of children without RLS. The odds ratio between a high hyperactivity index and other parameters was 1.6 for PLMS, 1.9 for RLS, and 1.9 for growing pains. Results were similar for inattention. It has been noted in other studies that “growing pains” may be a misdiagnosis for childhood RLS. In another study by Wagner et al, up to 26% of adult subjects with RLS (average age 60.8 y [age range 47.7-73.9 years]) were found to have ADHD or ADHD symptoms, compared with 6% of patients with insomnia and 5% of normal controls (p < 0.01).33 A recent large epidemiological study by Gamaldo et al. showed no increased prevalence of ADHD in adults with RLS.38 However, the conclusions of this survey should be taken cautiously since the diagnosis of ADHD was based on one item only (“Attention or hyperactivity problems as a child”) from a retrospective telephone interview of adults. This is in contrast to the study by Wagner et al, in which all adult RLS patients were examined and interviewed personally, administered all 18 questions of the DSM-IV criteria for ADHD, and given a full battery of psychometric studies.35 Moreover, as acknowledged by the Gamaldo et al, public awareness of ADHD has changed considerably in the last 40 years. As the mean age of their subjects was 47, the ADHD diagnosis may have been largely unrecognized in most of them during their childhood.38 In addition, as opposed to the study by Gamaldo et al, the study by Wagner et al took note of symptoms of ADHD that began in adulthood as well as in childhood.35,38 Of the 20 RLS patients with a Brown ADHD adult rating scale >40, one-fourth had onset of ADHD symptoms in adulthood.35 It may therefore be that those ADHD symptoms that began in adulthood are truly secondary to RLS. Further epidemiological studies using more rigorous criteria are welcome to better assess the relationship between ADHD and RLS.

RLS in ADHD

After reviewing the literature, Cortese et al concluded that up to 44% of children with ADHD have RLS or RLS symptoms.29 One study in adults showed that 20 % of adults with ADHD have RLS as opposed to only 7.2% of controls (p < 0.01).37 The average age of the patients was 43.5 years (range 19-65 years).

However, the data on ADHD in RLS and RLS in ADHD should be considered with caution given some limitations of the reviewed studies. Firstly, with the exception of some of the studies, e.g., that of Picchietti et al, where ADHD was very prominent in RLS children in the U.S. population, these studies were performed in clinical samples.25 Therefore, possible selection bias cannot be ruled out.

Second, not all studies used full standard criteria for the diagnosis of ADHD or RLS, particularly in children. Therefore, in some studies it is not clear whether the association between ADHD and RLS symptoms is the expression of a real comorbidity between 2 disorders (diagnosed according to formal criteria) or, alternatively, whether RLS mimics some symptoms of ADHD and vice versa. However, as correctly pointed out by Wagner et al, where standard diagnostic criteria were used, it is unlikely that the association between ADHD symptoms and RLS is simply an artifact of overlapping hyperactivity.35 In their study, the authors reported that RLS was associated with symptoms of inattention as well as of hyperactivity. Moreover, the leg discomfort characteristic of RLS has not been reported in classic idiopathic ADHD.

PERIODIC LIMB MOVEMENTS IN SLEEP

A number of studies have examined the relationship of ADHD to PLMS.31,33,34,39-44 A recent meta-analysis summarizing several such studies showed an intimate link between ADHD and PLMS.45

ADHD in PLMS

Children with PLMS on polysomnography have more ADHD. Approximately 44% of children with PLMS have been found to have symptoms of ADHD.42 In a second polysomnographic study, the prevalence of ADHD in children with PLMS
>5/h was even higher, with 117 of 129 meeting objective criteria for ADHD.\textsuperscript{42} However, there is some degree of selection bias in this second study, as the center also studies ADHD patients polysomnographically in addition to patients with other sleep disorders.

**PLMS in ADHD**

In two different series, between 26\% and 64\% of children with ADHD had PLMS greater than 5/h of sleep.\textsuperscript{31,39} In the first, in which 69 ADHD patients were studied, 8 (44\%) of 18 children with ADHD and PLMS >5/h of sleep had both a personal and parental history of RLS.\textsuperscript{31} In the second, 8 (32\%) of 25 parents of the children with ADHD had symptoms of RLS as opposed to none of the control parents.\textsuperscript{39} In that same study, 6 (67\%) of 9 children who had both ADHD and PLMS >5/h of sleep had a parent with RLS.\textsuperscript{39} These data suggest a possible genetic link between RLS-PLMS and ADHD. Martinez and Guilleminault showed that 7 of 11 prepubertal children with ADHD had PLMS.\textsuperscript{40} Golan and colleagues showed that 5 (15\%) of 34 ADHD patients but none of 32 controls had PLMS.\textsuperscript{41} The previously mentioned studies are largely polysomnographic and objective, but a survey of possible PLMS in 283 school children aged 7-14 years by Gaultney et al also found an association between PLMS and ADHD. There was an additional association between SDB and ADHD, but the link between PLMS and ADHD was stronger.\textsuperscript{44}

**THEORETICAL LINKS BETWEEN RLS/PLMS AND ADHD**

**Several Hypotheses may explain the Relationship Between RLS and ADHD.**

The first hypothesis takes into consideration the sleep disruption associated with RLS. Patients with RLS often have severe insomnia because of leg discomfort and periodic limb movements while trying to fall asleep (PLMW). Moreover, associated PLMS may possibly, but less frequently, disrupt sleep because of associated multiple arousals. Although in adults, sleep disruption from any cause results in excessive daytime sleepiness, such disruption in normal children can lead to symptoms of inattention, impulsivity, and motor hyperactivity. According to the hypourorous theory of ADHD, children with ADHD are actually sleepier than controls and therefore use motor hyperactivity as a strategy to stay awake and alert, in order to counteract the tendency to fall asleep.\textsuperscript{46} Lecendreux et al. were the first to lend possible evidence to this hypothesis with objective measures of daytime sleepiness (i.e., using the MSLT) in a sample of children with ADHD.\textsuperscript{12} The findings of two other research groups are in line with these results.\textsuperscript{11,47} Therefore, RLS might lead, in some patients, to symptoms of ADHD through sleep disruption. Thus, a circular relationship could exist between RLS and ADHD with RLS exacerbating or leading to ADHD through the mechanism of sleep disruption. The attendant daytime drowsiness or fatigue from sleep disruption could, in turn, exacerbate the motor restlessness of RLS.

Another hypothesis is that diurnal manifestations of RLS may lead to ADHD symptoms. Although RLS occurs primarily at night, it may occur during the day when patients are sitting or lying down. According to Picchietti et al., some children who are seriously affected with RLS cannot sit in school during the day for extended periods because they get up and walk around to relieve their leg discomfort.\textsuperscript{31} This hyperactivity might thus lead to inattention through the mechanism of leg discomfort in a subgroup of patients.

Alternatively, both RLS and ADHD might be manifestations of a common central nervous system disease. Children with RLS and a subset of children with ADHD might share a common dopaminergic deficit. Several lines of evidence have shown a dopaminergic dysfunction in the midbrain, frontal, and prefrontal regions of the brain in patients with ADHD.\textsuperscript{48} It has also been demonstrated that dopamine deficiency is involved in the pathophysiology of RLS.\textsuperscript{49} Iron deficiency might also contribute to the pathophysiology underlying the association between RLS and ADHD. The group of Konofal et al first reported significantly lower serum ferritin levels in children with ADHD than in controls without ADHD.\textsuperscript{50} MRI, CSF, and autopsy studies have also shown that iron deficiency is involved in the pathophysiology of idiopathic RLS.\textsuperscript{51-52} The hypothesis of iron deficiency is compatible with the hypothesis of dopaminergic dysfunction, since iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Moreover, iron deficiency has been described to alter dopamine D1 and D2 receptor density and activity in animals. Improvement of RLS/PLMS with dopaminergic agents and iron lend support to the idea that RLS and PLMS may be characterized by dopamine and iron deficiency states.\textsuperscript{53-57} In addition, treatment of RLS/PLMS with dopaminergic agents not only improves the RLS/PLMS but also improves ADHD symptoms.\textsuperscript{53} This suggests that RLS/PLMS and ADHD may share a common dopaminergic deficit or that the sleep disruption from RLS/PLMS may lead to symptoms of ADHD. Moreover, we and other groups of researchers, have seen a familial aggregation for ADHD and a familial aggregation for RLS. One possibility to be further explored is whether RLS and ADHD are genetically linked, explaining their more common co-occurrence.

**Summary:** Clinical experience suggests that RLS/PLMS and ADHD symptoms may co-occur, in both children and in adults. Clinical and basic research on the exciting but usually overlooked relationship between RLS/PLMS and ADHD is still limited.

Large cross-sectional and longitudinal studies using rigorous standard diagnostic criteria for RLS and ADHD are necessary to better understand the relationship between these disorders.

Research on potential mechanisms underlying the association between RLS/PLMS and ADHD are needed. In particular, genetic studies to gain insight into potential common genetic underpinnings are welcome. Such research should help us understand if ADHD and RLS coexist as comorbid disorders with distinct etiopathogenesis, if they share common underlying pathophysiological alterations, or if one of the disorders leads to symptoms of the other one.

All this body of research should lead to a better understanding of the relationship between ADHD and RLS, allowing a better and more specific clinical management of patients who present with both of these disorders. We suggest that clinicians systematically look for RLS in patients with ADHD, and, inversely, to look for ADHD symptoms in patients with RLS.
OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is characterized by relaxation of throat muscles during sleep and temporary obstruction of the airway for ≥ 10 sec. An apnea/hypopnea index >30/h is considered severe and, over time, patients with OSA are possibly more subject to hypertension, heart disease, and stroke.\(^{32,58-60}\) A number of studies have examined the relationship between sleep disordered breathing and ADHD.\(^{45,47,58-71}\)

ADHD in Obstructive Sleep Apnea

Li et al measured the impact of adenotonsillectomy on sleep related adverse events and behavioral problems in children with sleep disordered breathing.\(^{64}\) After surgery, all the measures (AHI, Tests of Variable Attention (TOVA) scores, and Child Behavior Checklist scores) improved, but with no correlation between AHI and TOVA score.\(^{64}\) The indication of the existence of SDB-related ADHD or an exacerbation of idiopathic ADHD by SDB came from this paper, with a further recommendation to explore ENT surgery for ADHD children with OSA.

Obstructive Sleep Apnea in ADHD

Starting from subjective measures, there are some clear indications that parents of ADHD children more frequently report sleep related problems in their children than parents of controls.\(^{32,58-60}\) However, when we take in to account studies that objectively measure sleep disorders, this conclusion is not so clear, and a definite association between OSA and ADHD is far from ascertained. Different factors confound the results of the research and prevent a clear conclusion in the field: the difference in the definition of ADHD and, consequently, different patient populations enrolled in the studies; the age range and gender of children included; different sources of recruitment of ADHD children; and, finally, differences in the methodological approach for PSG studies. In a recent meta-analysis of PSG studies in ADHD children, Sadeh et al found that one of the sources of variations in the relationship between OSA and ADHD was the definition and the measurement of apnea and hypopnea in children.\(^{35}\) The authors were hopeful that some differences between ADHD and controls would emerge with standardization of definitions for abnormal respiratory events in children, including upper airway resistance syndrome. On the other hand, another meta-analysis found that children with ADHD have a mean AHI that is 1 per hour greater than controls.\(^{37}\) Although this data is of statistical significance, the implication for clinical practice is not clear.

Goodwin et al., evaluating 1494 children with an age range from 4 to 11 years by questionnaire, found that learning problems were associated with snoring, witnessed apnea, and excessive daytime sleepiness, and were more frequent in Hispanic than in Caucasian children.\(^{66}\) A more recent case-control study using polysomnography showed more SDB in ADHD children (50%, mean RDI 9.9 ± 6.9) than in controls (22%, mean RDI 0.8 ± 1.0).\(^{31}\) In a larger sample of consecutive Taiwanese children with ADHD, observed in a specialized University Center and diagnosed according to the DSM-IV criteria, Huang and colleagues found that nearly 57% of the ADHD children had an elevated apnea-hypopnea index (AHI > 1), and 20% had an AHI > 5. A control group exhibited an AHI > 1 in only 4% of the cases.\(^{67}\) The study also showed that individuals with both ADHD and OSA have poorer attention, slower response, and higher hyperactive subscale scores on the CBCL, compared to ADHD children without SDB (OSA worsens ADHD symptoms?). This is an important study, although it has some limitations, as the high prevalence of ADHD in Taiwan (5% to 10%), the craniofacial predisposition to OSA (shorter cranial base), and the high incidences of respiratory allergies, mean that the results cannot be currently generalized to all patients with ADHD. The same authors studied a group of 66 children with ADHD who also had mild OSA (AHI > 1 < 5). These children had a compromise in daytime symptoms (including attention span) and in subscales for impulse control and response time that was reversed by surgical treatment of OSA (adenotonsillectomy). These results were favorable in comparison to two other non-surgical ADHD/OSA groups who were treated with methylphenidate or not treated at all.\(^{68}\) O’Brien et al evaluated children with the Conners Parent Rating Scale and polysomnography. Forty-four children with significant symptoms of ADHD, 27 with mild symptoms of ADHD, and 39 with no symptoms of ADHD were analyzed. Polysomnography in these children showed an AHI >5 in 26% of those children with mild ADHD symptoms, compared to 5% of those with significant ADHD and 5% of controls.\(^{69}\) This has lead to the suggestion that sleep disordered breathing leads to a mild mimic of true ADHD rather than true ADHD itself.

An opposite position is that of Sangal et al who recently performed a PSG study in a group of 40 prospectively recruited 6- to 14-year-old DSM-IV diagnosed ADHD children. After exclusion of those with an RDI <5, the authors found no OSA in the ADHD group and concluded that OSA is not a common finding or an etiological factor in ADHD.\(^{70}\) However, with less narrow PSG criteria for the diagnosis of apnea, 57% of the sample had an AHI >1, with results similar to the other studies. Also Cooper et al, in two small groups of ADHD children (n = 18, mean age 10.5 years) and controls (n = 20, mean age 10.0 years) did not find a difference in AHI between the two groups.\(^{70}\)

Theoretical Links Between OSA and ADHD

The possible mechanisms for the link between OSA and ADHD are sleep fragmentation and episodic hypoxia. Sleep disruption leads to nonrestorative sleep that, together with intermittent hypoxia or hypercarbia and the consequent disruption of cellular or chemical homeostasis, may induce alterations in the neurochemical substrate of the prefrontal cortex. This in turn may result in executive dysfunction with adverse daytime effects such as poor planning, disorganization, rigid thinking, difficulty in maintaining attention and motivation, emotional lability, and overactivity/impulsivity.\(^{61}\) Another point in favor of this hypothesis are the improvements in behavior, neuropsychological functioning, and sleepiness after treatment of SDB.\(^{59,62-65}\)

The results to date suggest that it is generally the milder forms of SDB rather than the more severe ones that tend to be more common in ADHD children than in controls. This may be due both to the more frequent occurrence of milder as opposed to more severe OSA in the pediatric community, and to somnolence during the day in the severe cases, masking hyperactivity.\(^{71}\) Intermittent hypoxia and sleep fragmentation, if pres-
ent, may change the behavioral phenotype from mild SDB with ADHD symptoms to severe SDB with somnolence. This may explain the lack of correlation between objective measures of SDB and ADHD symptoms. It is also the milder forms of ADHD that tend to be more common in SDB. Thus the etiology of ADHD may vary: There is a “primary” ADHD with no OSA or other sleep disorders characterized by a reduced sleep fragmentation at night (hypoarousal) and increased levels of daytime sleepiness on MSLT, and a “secondary” ADHD, i.e., due to sleep disorders (OSA, PLMS), that, when treated result in improvement of the ADHD symptoms. As mentioned, studies looking at the association of SDB and ADHD suggest that sleep disordered breathing may cause a mild mimic of true ADHD rather than true ADHD itself. Also, as summarized earlier, the results of recent studies do indeed indicate that ADHD may improve with treatment of OSA.

To our knowledge, no studies in obese children with ADHD have considered the effect of weight reduction on the symptoms of ADHD in parallel with the improvement of sleep disordered breathing. Although the literature suggests that ADHD symptoms improve with the treatment of sleep apnea, no studies have tried to find out whether treatment of ADHD affects the severity of OSA. For example, there is no mention of a parallel treatment effect on OSA for the nonstimulants used to treat ADHD, e.g. atomoxetine, bupropion, the α-2 adrenergic agents guanfacine and clonidine, tricyclic antidepressants, or modafinil.

**Summary:** It is possible that OSA can cause mild inattention or hyperactivity, but it is still questionable whether children with a diagnosis of moderate to severe ADHD suffer from inattention or hyperactivity as a result of OSA. SDB may contribute to some mild ADHD-like symptoms that can be readily misperceived and may be the theoretical basis of overlap between the 2 diagnoses. This indicates the impact of a low level of SDB not only on sleep parameters but also on cognitive tasks, and consequently on behavioral and neurocognitive functions of children with ADHD. Therefore, the search for a respiratory disorder by PSG and the treatment, when present, are measures to take into account before starting long-term drug treatment for ADHD. Longitudinal and prospective studies evaluating the treatment effect of both the disorders may eventually clarify the relationship between OSA and ADHD.

### DISORDERS OF PARTIAL AROUSAL

Disorders of Partial Arousal (DOA) consist of complex behaviors arising out of stage N3 that are outside the conscious awareness of the individual. Patients with DOA are difficult to arouse and have little recollection of the events the next day. Subjects with DOA may walk (sleep walking- SW), talk in a confused way (Confusional arousals- CA) or run in a confused terror while screaming (Sleep Terrors- ST or Night Terrors- NT). Children usually outgrow DOA but DOA may recur in adulthood under conditions of emotional or physical stress.

### ADHD in Disorders of Partial Arousal

To our knowledge, there are no studies looking at the prevalence of ADHD symptoms in patients with disorders of partial arousal.

### Disorders of Partial Arousal in ADHD

Disorders of Partial Arousal share several common mechanisms with ADHD including familial predisposition, increased numbers of arousals, sleep fragmentation and discontinuity, increased slow wave sleep, increased prevalence of sleep disordered breathing and an increased prevalence of rolandic foci. Nonetheless, very few reports so far, in addition to that of Silvestri et al, have investigated the prevalence of disorders of partial arousal in ADHD. In one of these studies (Ishii et al.), there was a low incidence of night terrors (NT) and sleepwalking (SW) in ADHD (2.9%) in 68 patients (mean age 9.7 y). In that paper, the authors explored via clinical interview a vast range of comorbidities in ADHD from mood to conduct disorders, sleep disorders, and epilepsy. The authors found an overall lower prevalence of comorbidities in their ADHD subjects than those conventionally reported in North America. They attribute this disparity to a possible bias towards milder cases, since their children were all outpatients from a clinic without inpatient facilities. On the other hand, Gau et al. surveyed 2284 first-year college students and found an odds ratio between sleep terrors and inattention of 2.4 (95% CI 1.3 to 4.5) among subjects with definite ADHD compared to non-ADHD subjects, and 1.8 (95% CI 1.4 to 2.3) among subjects with probable ADHD compared to non-ADHD subjects. Between sleep terrors and hyperactivity she found an odds ratio of 2.4 (95% CI 1.5 to 4.1) for subjects with definite ADHD and 2.0 (95% CI 1.3 to 3.1) for subjects with probable ADHD compared to non-ADHD subjects (all results at least p < 0.01). Results for sleepwalking were similar, but the relationship was not as strong.

Miano et al found indirect evidence of sleep pattern immaturity in ADHD children recorded by PSG overnight compared to normal controls. In particular the authors report a lower cyclic alternating pattern (CAP) rate and a lower number of CAP sequences, with longer duration of A1 subtypes in patients versus controls, supporting the hypothesis of a hypoarousal state in these patients. Thirty-five percent of these patients had a report of “parasomnias,” which were not further specified. Two other groups also found an increased overall prevalence of parasomnias, which included SW and NT in association with ADHD.

In a recently published paper Silvestri et al interviewed 42 newly diagnosed, untreated ADHD children and their parents. The children were then studied polysomnographically. There was a 50% prevalence of Disorders of Partial Arousal on clinical interview (28.5% CA, 47.6% SW, 38% NT). On video-PSG, CA were recorded in 45.2% of their patients, SW in 2.3%, and NT in 4.7%. One patient reported frequent SW episodes, had a CA on video-PSG and later exhibited subclinical REM sleep behavior disorder, thus meeting criteria for parasomnia overlap disorder. In two children (10.5% of DOA + ADHD patients) who displayed confusional arousals on PSG, Silvestri et al. also recorded, as separate events, nocturnal hypermotor, atypical rolandic seizures. Both children had good evidence of interictal epileptiform discharges (IEDs) on right centro-temporal and right centro-parietal-occipital regions respectively. Several other patients (53.1%) in the ADHD sample had IEDs (28.2% rolandic spikes, 12.5% frontal spikes, 9.3% temporal occipital spikes, and 2.3% generalized abnormalities), accounting for
42% of the DOA positive group. One more patient within the whole sample of 42 ADHD children had nocturnal seizures but did not report nor show any evidence of DOA on PSG.

Of course, it is well known that frontal lobe epilepsy may mimic Disorders of Partial Arousal. However, despite the large number of patients in this series who had both interictal discharges as well as complex behaviors during sleep, the authors looked carefully for ictal discharges during the behaviors and did not find them. In addition, the complex behaviors did not have the stereotypy often found with seizures. The authors, therefore, conclude that the majority of these ADHD patients had both epileptogenic interictal discharges as well as true Disorders of Partial Arousal. The possibility of misdiagnosing true ictal events as parasomnias has been raised by several authors, especially when episodes of confusion accompany frontal or temporal lobe epilepsy\(^8\) or epileptic nocturnal wandering.\(^9\) Also Disorders of Partial Arousal could express a liability to future seizure occurrence in predisposed children who later in life could develop frontal or temporal lobe epilepsy.\(^10\) Thus, it is no surprise that in the sample of Silvestri et al, sleepwalking was associated with the presence of nocturnal seizures and night terrors with frontal IEDs.

The authors gave levetiracetam 750 to 1000 mg per day to ADHD children with nocturnal seizures, or RLS (26% of the whole sample) and/or IEDs. This proved effective not only in controlling seizures and RLS symptoms but also, unexpectedly, in controlling Disorders of Partial Arousal. Levetiracetam also reduced the frequency of IEDs by over 50% during a follow-up period ranging from 12 to 24 months. There were only minimal and tolerable side effects that subsided over time.

**Summary:** Despite scanty reports on Disorders of Partial Arousal in ADHD, this type of parasomnia seems to be quite prevalent in ADHD, and probably depends on chronic sleep deprivation via sleep fragmentation due to multiple arousals. Disorders of Partial Arousal frequently coexist with IEDs, but less so with nocturnal seizures. Levetiracetam exerts a positive overall effect not only upon epilepsy but also upon IEDs and Disorders of Partial Arousal. The reverse prevalence, i.e., the prevalence of ADHD in Disorders of Partial Arousal remains to be studied.

**CONCLUSIONS**

ADHD symptoms occur frequently in the setting of several specific sleep disorders and vice versa. We would recommend that clinicians be aware of the potential connection between ADHD and the specific sleep disorders mentioned. We have two general recommendations. First, because the various sleep disorders mentioned more frequently have symptoms of ADHD than control populations, we recommend that patients with these sleep disorders be queried about the symptoms of ADHD. Second, since ADHD patients more frequently have symptoms of the various sleep disorders in question, we also recommend that patients with ADHD be queried about the sleep disorders in question. If these sleep disorders are present in patients with ADHD, they should be addressed. In addition, there remains the possibility that treatment of the associated sleep disorder may lead to adjunctive improvement of the ADHD symptoms in conjunction with stimulant therapy

In addition to strengthening already established connections, future investigations should explore whether narcolepsy is characterized by paradoxical hyperactivity, whether ADHD patients have a higher prevalence of narcolepsy, and whether patients with DOA more frequently have ADHD symptoms.

**ABBREVIATIONS**

- ADHD: attention deficit hyperactivity disorder
- iADHD: Inattentive ADHD
- hADHD: Hyperactive ADHD
- RMD: Rhythmic movement disorder
- DSPS: Delayed sleep phase syndrome
- DOA: Disorders of Partial Arousal
- RLS/PLMS: Restless legs syndrome/Periodic limb movements in sleep
- OSA: Obstructive sleep apnea
- IED: Interictal discharges
- NT: Night terrors
- SW: Sleepwalking
- CA: Confusional arousals

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<td>Naumann and Daum</td>
<td>Narcolepsy vs Controls</td>
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<td>Review of Case Control Studies</td>
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**Review of the Relationship between ADHD and Specific Sleep Disorders**

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<td>108 with suspected SDB, 72 controls</td>
<td>SDB Mean 7 ± 4 y and controls 8 ± 4 y</td>
<td>PSG, ESS, CASQ</td>
<td>Not reported</td>
<td>Children with SDB sleepier and more hyperactive than controls</td>
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<td>6-14</td>
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<td>62 RLS, 77 controls, 32 insomnia</td>
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<td>DSM-IV criteria for ADHD, Brown Adult ADHD scale</td>
<td>None</td>
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<td>973 family members of RLS probands</td>
<td>Avg Age 47 y</td>
<td>Retrospective recollection of inattentiveness as child</td>
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<td>Martinez and Guilleminault</td>
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<td>44% of those with PLMS had ADHD</td>
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<td>Kotagal and Silver</td>
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<td>PSG, ADHD by past medical history</td>
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<td>3 of 7 children with RMD by PSG had ADHD</td>
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<td>RMD (head banging) in ADHD</td>
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<td>9.7</td>
<td>Parental and pediatric interview</td>
<td>No intervention</td>
<td>2.9% DPA in ADHD</td>
<td>Psychiatry Clin Neurosci 2003</td>
</tr>
<tr>
<td>Gau et al</td>
<td>Prevalence of Historical Sleep Disorders in ADHD vs non-ADHD</td>
<td>Cross sectional survey</td>
<td>2284 first-year college students</td>
<td>18-20 y</td>
<td>Questionnaires, ADHD scale</td>
<td>None</td>
<td>Snoring, sleepwalking, ST more common in ADHD</td>
<td>Sleep 2007</td>
</tr>
<tr>
<td>Gau et al</td>
<td>Prevalence of historical sleep disorders in ADHD vs non-ADHD</td>
<td>Cross-sectional survey</td>
<td>2463 first through ninth graders</td>
<td>6-15 y</td>
<td>CPRS, CTRS, CHQ, Sleep Habits Questionnaire</td>
<td>None</td>
<td>PLMS, SDB, parasomnias more common in ADHD</td>
<td>J Sleep Res 2006</td>
</tr>
<tr>
<td>Kraenz et al</td>
<td>ADHD in Parasomnia</td>
<td>Survey of parents of children starting school</td>
<td>--------</td>
<td>5-6 y</td>
<td>Comparison of ADHD symptoms in parasomnia vs non-parasomnia Children</td>
<td>None</td>
<td>Hyperactivity increased in parasomnia</td>
<td>Prax Kinderpsychol Kinderpsychiatr 2004</td>
</tr>
<tr>
<td>Miano et al</td>
<td>ADHD vs controls</td>
<td>Case control</td>
<td>20 ADHD vs 20 controls</td>
<td>9.3</td>
<td>Clinical Interview and PSG</td>
<td>No intervention</td>
<td>35% parasomnias, lower CAP rate and CAP sequences in ADHD</td>
<td>Sleep 2006</td>
</tr>
<tr>
<td>Silvestri et al</td>
<td>ADHD vs controls</td>
<td>Case Control</td>
<td>42</td>
<td>8.9</td>
<td>Clinical interview and PSG</td>
<td>No intervention</td>
<td>50% DPA in ADHD, 26% RLS in ADHD</td>
<td>Epilepsy Res 2007</td>
</tr>
</tbody>
</table>

Legend: Polysomnography (PSG), Attention Deficit Hyperactivity Disorder Rating Scale (ADHD RS), Conners Parents Rating Scale (CPRS); Conners Teachers Rating Scale (CTRS), Double Blind Placebo Controlled (DBPLC), Test of Variable Attention (TOVA), Adenoectomy and Tonsillectomy (A&T), Sleep Disordered Breathing (SDB), Obstructive Sleep Apnea (OSA), Hypopnea Index (AHI), Epworth Sleepiness Scale (ESS), Conners Abbreviated Symptom Questionnaire (CASQ), Child Behavior Check List (CBCL), Disorders of Partial Arousal (DPA), Cyclic Alternating Pattern (CAP), Idiopathic Hypersomnia (IHS), Multiple Sleep Latency Test (MSLT), Rhythmic Movement Disorder (RMD), Delayed Sleep Phase Syndrome (DSPS), Chinese Health Questionnaire (CHQ), Sustained Attention to Response Task (SART), Mismatch Negativity (MMN), Event Related Potentials (ERPs), Critical Flicker Fusion (CFF) Test, Visual Analogue Scale (VAS), Tiredness Symptoms Scale (TSS), Pediatric Sleep Questionnaire (PSQ), Pediatric Sleep Questionnaire (PSQ)