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# Sleep Problems as Predictors in Attention-Deficit Hyperactivity Disorder: Causal Mechanisms, Consequences and Treatment

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Attention-deficit hyperactivity disorder (ADHD) is notorious for its debilitating consequences and early age of onset. The need for early diagnosis and intervention has frequently been underscored. Previous studies have attempted to clarify the bidirectional relationship between ADHD and sleep problems, proposing a potential role for sleep problems as early predictors of ADHD. Sleep deprivation, sleep-disordered breathing, and circadian rhythm disturbances have been extensively studied, yielding evidence with regard to their induction of ADHD-like symptoms. Genetic-phenotypic differences across individuals regarding the aforementioned sleep problems have been elucidated along with the possible use of these characteristics for early prediction of ADHD. The long-term consequences of sleep problems in individuals with ADHD include obesity, poor academic performance, and disrupted parent-child interactions. Early intervention has been proposed as an approach to preventing these debilitating outcomes of ADHD, with novel treatment approaches ranging from melatonin and light therapy to myofunctional therapy and adjustments of the time point at which school starts.

KEY WORDS: Attention-deficit hyperactivity disorder; Sleep; Predictors; Treatment.

## INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children with prevalence rates of up to 10% among those aged 6 to 17 years old.[1-3] The core symptoms of ADHD are comprised of inattention, hyperactivity and impulsivity. However, the full spectrum of ADHD symptoms ranges from disruptive behaviors to emotional dysregulation, all of which can result in dire psychological, educational and psychiatric consequences. Previous studies have attempted to understand the disease in terms of either psychological models pertaining to cognitive processes[4] or biopsychosocial considerations that address potential biological, environmental risk factors.[2] Given the early age of onset of ADHD patients, and the fact that its symptoms exert a major influence on patients' lives during adolescence and adulthood, recent studies have focused on the need to identify endophenotypes and risk factors that can assist in the early detection and prevention of ADHD.[5,6] One of the most extensively researched areas in this domain concerns the sleep problems associated with ADHD. Complexities of the relationship between ADHD and sleep have been well delineated in the previous literatures, and numerous excellent reviews have been published, including papers elucidating sleep disorders in ADHD, pharmacological strategies, potential underlying neurobiological mechanisms of ADHD and sleep.[7-9] However, much more evidence is needed to validate propositions that sleep problems may be a potential causative factor of ADHD. Moreover, relatively few review papers have been published on the functional consequences of sleep problems in patients with ADHD, despite the clinical importance. Finally, there is relative paucity of data on treatment modalities other than conventional psychotropics for patients with concurrent ADHD and sleep problems.

The present article reviews studies supporting the role of sleep problems, especially sleep deprivation, sleep-disordered breathing (SDB), and circadian rhythm disturbance, as causative factors of ADHD. Additionally, previous reports regarding the consequences of sleep problems in ADHD as well as several recent studies on novel treatment approaches are discussed.

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## SLEEP PROBLEMS AS PREDICTORS OF ADHD

Numerous previous studies have demonstrated the effects of sleep problems on inattention, hyperactivity and impulsivity, which are core symptoms of ADHD.[10-12] Indeed, the aforementioned studies have implicated sleep problems as potential causative factors of ADHD. Extant research has focused primarily on the impact of three sleep problems on ADHD symptoms, examining their potential role as predictive factors: sleep deprivation, SDB, and circadian rhythm disturbances.

### Sleep Deprivation

At the cellular level, sleep deprivation impairs synaptic plasticity[13] increases hippocampal oxidative stress[14] and facilitates neuronal loss,[15] all of which can detrimentally affect neurocognitive function. Five-choice performance tests conducted with both humans and mice have found that sleep deprivation results in an especially marked impairment in the attentional domain.[16] Altered patterns of sustained attention were noted in auditory and visual performance tasks in sleep-deprived subjects[17] and deficits in vigilant attention due to sleep deprivation induced errors of commission.[18] Furthermore, sleep deprivation led to slowed responses to neurocognitive tasks,[19] suggesting possible delays in the appropriate allocation of attentional resources. Such attentional difficulties were presumed to stem from impairment in the top-down executive control of the brain,[20] and evidence has demonstrated disruption of default mode network of the brain[21,22] and changes in topographic electroencephalogram[23] during this process. Even one hour of sleep restriction resulted in significant event-related potential changes in children across attentional tasks.[24]

In terms of studies regarding behavioral problems, one extensive meta-analysis of the relationship between sleep deprivation and cognition in school-aged children found a significant increase in behavioral problems in children with shorter sleep duration.[25] Additionally, sleep deprivation resulted in a significant increment in alertness and emotional reactivity in children, which led to delinquency, long-term emotional and behavioral difficulties.[26-28] Consistent with such findings, sleep deprived subjects were more alert to negative stimuli,[29] and more susceptible to exaggerated aggressive impulses.[30] Emotional lability and impulsivity were all strongly correlated with sleep deprivation,[31] with the severity of emotional dysregulation worsening as a function of the degree of sleep restriction.[32]

Along with the aforementioned results on the deleterious effects of sleep deprivation and their induction of ADHD-like symptoms, previous research has demonstrated the possibility of a genetic or phenotypic disparity in vulnerability to the effects of sleep deprivation.[33,34] More research is needed to examine the suggestion that sleep-deprived children may have an intrinsic susceptibility to ADHD and that sleep deprivation may serve as a potential predictor of ADHD.

### Sleep-disordered Breathing

SDB induces an intermittent hypoxemic state during the night and patients with this condition suffer from sleep fragmentation.[35,36] Hypoxemia and sleep fragmentation reportedly induce systemic inflammation and oxidative damage that lead to endothelial dysfunction, which later can later result in vascular morbidity.[36] This inflammatory process subsequently leads to disruption of the blood brain barrier through alterations in microvessel permeability, which is one likely mechanism of the cognitive impairment associated with obstructive sleep apnea (OSA). Children with SDB were more vulnerable to oxidative stress than were those without SDB, and such susceptibility may help elucidate the mechanisms underlying the cognitive and attentional deficits in children with SDB.[37,38] In line with the aforementioned findings, hypoxemia has been found to contribute more than sleepiness to the poor continuous performance test results among patients with OSA.[39] Detrimental effects of hypoxemia evoked by SDB on attention/vigilance have also been implicated in a meta-review.[40]

SDB has been demonstrated to be highly associated with symptoms of inattention and hyperactivity in previous studies[41-44] and evidences of amelioration of behavioral, psychological problems after treatment interventions like adenotonsillectomy have been frequently reported,[45] suggesting a close link between SDB and ADHD symptoms. Pediatric patients with OSA reported lower scores on a divided attention steering simulation test,[46] and an event-related potential study revealed compensatory activation of central and temporal areas to make up for the reduced cognitive reserve in OSA children.[47] OSA had a major impact in all P300 measures, and possible disruptions in sustained attention and learning capacity have also been delineated.[48] Recent functional magnetic resonance imaging studies have revealed aberrant cerebral perfusion[49] reduced gray matter,[50] and altered patterns of intrinsic regional brain activity in patients with OSA,[51] which all might contribute to the attention, behavioral

problems children with OSA.

Possible genetic-phenotypic interactions have been purported to be responsible for the pathogenesis of SDB, and several candidate genes like tumor necrosis factor-alpha, C-reactive protein, interleukin-6 (IL-6) genes, with their major impact on inflammatory process, have been researched.[52-54] Individuals with the aforementioned genetic susceptibility might be more likely to be afflicted with not only the SDB disease process but also with ADHD-like symptoms in the long run.

### Circadian Rhythm Disturbances

Circadian rhythm is pivotal for the maintenance of human cognition, behavior, and emotion.[55] Circadian rhythm disruptions and their association with neuropsychiatric disorders have been demonstrated in the extant literatures.[56] The frequent manifestation of circadian rhythm disturbances in patients with ADHD has led to attempts to explicate a link between ADHD symptoms and circadian rhythm.

Several studies have hypothesized that various underlying mechanisms are involved in the interaction between circadian rhythm and attention. Circadian rhythm may influence human attention through the modulation of tonic alertness,[57] while one study elucidated the more pervasive role of circadian rhythm on cognition, advocating the possibility of the widespread distribution of local pacemakers in the brain.[58] Circadian rhythm affects not only one's ability to inhibit response to stimuli,[59,60] but also one's performance on tasks involving sustained attention.[61]

Deleterious effects of circadian rhythm disturbances on social behaviors in children have been reported,[62] along with effects of endogenous melatonin levels on behavioral problems in preschool-aged children.[63] Adolescents with eveningness chronotype were more subject to behavioral problems,[64] and of the ADHD symptoms, inattention was significantly associated with eveningness chronotype in patients with ADHD, advocating the eveningness chronotype as a possible endophenotype of ADHD.[65]

Several approaches to the early detection of circadian rhythm disturbances may be feasible. Salivary melatonin level differences between ADHD children and normal controls have been suggested,[66] and possibility of early diagnosis of ADHD by measuring salivary dim light onset melatonin has also been studied.[67] Moreover, genetic variability of circadian rhythm across individuals have been well documented in previous reports,[68] and morningness-eveningness preferences have been explained at a genetic level in one study.[69] Possible epigenetic mechanisms with the modulation of sirtuin 1 gene involved in human circadian rhythm have also been reported.[70] Given its possible relationship to the subsequent development of ADHD symptoms, the elucidation of genetic susceptibility to circadian rhythm disturbances may assist clinicians in the early detection of circadian rhythm problems and the prevention of ADHD symptoms.

## CONSEQUENCES OF SLEEP PROBLEMS IN ADHD PATIENTS

Considering a large portion of ADHD patients are in their childhood and adolescence, problems regarding school performances, obesity, psychiatric comorbidities, and parent-children interactions warrant more clinical attention. The aforementioned issues are frequently reported consequences of sleep problems in such patients, and they significantly affect the long-term prognosis of individuals with this order.

### Obesity

Negative impacts of sleep deprivation, circadian rhythm disturbances, and SDB have been studied, with possible mechanisms linking the aforementioned sleep disturbances and obesity. Abundant studies repetitively reported that short sleep duration in children and adolescents is significantly associated with obesity.[71-75] Additionally, high incidence of hypercholesterolemia, insulin resistance, insulin sensitivity, higher glucose levels, and hypertension was reported in this population, increasing the risk of diabetes mellitus, metabolic syndrome, and cardiovascular problems in the future.[76-80] Potential underlying mechanism of short sleep duration inducing obesity is partially explained by increased ghrelin and cortisol levels in sleep deprived subjects.[81-84] Sleep loss inevitably affects physiological control of human body and with the interaction of the aforementioned hormonal changes, increasing appetite and reducing energy expenditure, ultimately resulting in obesity.[85,86]

The close relationship between SDB and obesity has been reiterated, and obesity has been identified as a major risk factor of SDB.[87] Mechanisms involved in SDB causing obesity are controversial. Diversity of intestinal flora was disrupted due to intermittent hypoxia in mouse models of sleep apnea,[88] and an increase in lipid synthesis, subsequent hyperlipidemia were noted in both lean and obese mice which were exposed to intermittent hypoxia.[89,90] Intermittent hypoxia also increases glucose metabolism and inflammatory reactions,[91] which can contribute to the

development of obesity.

The crucial role of circadian rhythm in hormonal regulation is well established. Carbohydrate and lipid metabolism are all under regulatory control of circadian rhythm.[92] Circadian rhythm disturbances can cause disruptions in the regulatory control of clock genes on adipocytes, detrimentally affecting adipocyte metabolism, thereby inducing obesity.[93] Moreover, peripheral clocks in liver and intestine are also affected, and dyssynchrony between central and peripheral clocks results in alterations in homeostasis and metabolism.[94]

### Poor Academic Performance

The negative impact of sleep problems on academic performance of children and adolescents can have additive effect on patients with ADHD, who already have difficulty in schools due to ADHD symptoms. A meta-analytic review comprehensively delineated that poor sleep quality, short sleep duration, excessive sleepiness were correlated with poor academic performance.[95] One Swedish study reported that students with short sleep duration were more liable to academic failure.[96] Late bedtimes, but not total sleep duration was associated with school failure in another study.[97] Norwegian adolescents with short sleep duration showed poorer academic achievements and more frequent habits that have detrimentally influence on health.[98] To back up further, Finnish, Chinese and Korean studies all concordantly demonstrated positive association between sleep difficulties and poor academic performances.[99-101]

Deleterious effects of SDB on academic performance in children have been demonstrated in numerous previous studies.[102-106] Problems in school tasks likely stem from attention deficits and decreased learning capacity frequently shown in children with SDB, as reviewed earlier in this article. As in children with SDB, improvements in obstructive apnea-hypopnea index resulted in increase of academic measures.[107] Regardless of the disease severity, SDB was significantly associated with low academic achievements.[108] As with other possible correlates of SDB, one study suggested low socioeconomic status as an independent predictor of poor academic performance in children with SDB.[109]

Meanwhile, the dependence of academic performance on individual variability with regard to chronotype has been repeatedly reported. One meta-analysis revealed a negative correlation between the eveningness chronotype and academic achievements.[110] Morningness chronotypes were associated with higher levels of attention and better school grades.[111] Significant differences in cognitive tasks such as visual search tasks were revealed between morningness and eveningness chronotypes, and diurnal variations in brain activation to sustain alertness were suggested.[112]

### Disrupted Parent-Child Interactions

Despite the indispensable role of parents with children affected by ADHD and sleep problems, few reviews have demonstrated the impact of such sleep problems on parent-child interactions. General indices regarding mental health of mothers have been associated with their children's sleep, and less well-organized sleep patterns have been noted in children from poorly functioning families.[113] Mothers of children with sleep disturbances exhibited much higher psychological stress than did controls, obtaining increased scores on all factors of the General Health Questionnaire (GHQ).[114] Children's sleep quality significantly predicted that of their mothers, with maternal sleep quality associated with stress and fatigue.[115] Moreover, infants of mothers with low levels of depression and anxiety were more likely to recover from sleep problems than those with high levels of depression and anxiety after controlling for the influence of attachment patterns.[116] Sleep disturbances in early childhood were positively related to negative maternal perceptions of their child,[117] potentially interfering with the development of beneficial parent-child interactions. Disciplinary styles were also influential, with permissive, inconsistent parenting behaviors significantly correlated with sleep disturbances in children.[118]

Sleep problems in ADHD patients should not be confined to the problems of patients themselves, but should be considered in a broader context involving the parents of the child.[119] Thus, comprehensive reviews of the parents' psychiatric history, parenting styles, attachment patterns and stress levels of parents are required.

## FUTURE TREATMENT CONSIDERATIONS FOR SLEEP PROBLEMS IN ADHD

In addition to the pharmacological and behavioral interventions suggested by previous reviews, many promising treatment approaches have been tested for the future treatments in ADHD patients with sleep problems.

### Melatonin

Melatonin is well known for its central regulatory role in circadian rhythm and its concordant effect on energy

expenditure and metabolism.[120] For this reason, efficacy of melatonin on sleep-wake cycle disturbances has been delineated. Also, recent research has revealed the antioxidant profiles of melatonin[121] and its atheroprotective effects.[122] In animal models, reduction of cognitive impairment in sleep-deprived rats has been demonstrated, advocating protective effect of melatonin from oxidative stress.[123] Sleep-promoting effects of melatonin has been demonstrated in zebrafish models,[124] along with anxiolytic effects evident in both human and animal models.[125]

Melatonin significantly improves sleep onset insomnia in ADHD patients, but there have been no conclusive evidences to support association between problematic behaviors and cognition.[126] Melatonin is generally well tolerated by pediatric patients with concurrent ADHD and chronic sleep onset insomnia,[127] and one long-term follow up study with mean follow up period of 3.7 years conducted in ADHD children with chronic sleep onset insomnia revealed the efficacy of melatonin without notable adverse effects.[128] Relatively few large scale studies have been conducted to evaluate optimal dosage, safety and long term effects of melatonin. More research is needed to confirm the scientific evidence in the routine prescription of melatonin in clinical settings.

### Light Therapy

The pivotal role of light in the regulation of circadian rhythm has been well-established, with mealonopsin-containing retinal ganglion cells and suprachiasmatic nucleus involved in the process.[129] One epidemiological study in the United States reported a lower prevalence of ADHD in geographic regions with high solar intensity, suggesting that improvement in circadian rhythm disturbances are attributed to exposure to sunlight.[130] Few studies have been conducted to test the efficacy of the bright light treatment in ADHD patients with sleep problems. One open trial in adult ADHD patients reported the amelioration of core symptoms of ADHD as well as mood symptoms after the implementation of morning light therapy in the ADHD symptoms with eveningness chronotype.[131] Adolescents with ADHD underwent 4 weeks of light therapy, and the study suggested potential effectiveness of light therapy as add-on therapy, with salivary melatonin levels as indicators of improvement.[132] However, the aforementioned studies did not include results regarding the therapeutic effect of light therapy on the 'sleep problems' in ADHD patients. More large-scale structured studies are needed to test the clinical effectiveness of light therapy in ameliorating sleep problems in ADHD patients.

Accumulated evidence supports the frequent manifestation of the evennineness chronotype in patients with ADHD, suggesting the possibility of circadian rhythm disturbances as underlying mechanisms, underscoring the need for more research on the optimal schedule for light therapy and its efficacy in the treatment of ADHD patients with sleep problems.

### Myofunctional Therapy

Mounting evidence indicates the improvement of polysomnography results after adenotonsillectomy, and early surgical intervention of mild SDB in ADHD children has been suggested to stop unnecessary long-term usage of methylphenidate.[133] However, with evidences supporting the recurrence of OSA after adenotonsillectomy due to orofacial growth, the importance of myofunctional therapy in pediatric patients with OSA has been comprehensively delineated in one study.[134] Myofunctional therapy is an exercise involving the muscles of face and mouth, ultimately promoting nasal-breathing in children.[135] Not only is myofunctional reeducation an effective post-operative intervention,[136] but its potential as a treatment for OSA in children has also been suggested by evidences that the pathogenesis of OSA involves disruptions in orofacial growth of children.[137] Detailed assessments of orofacial anatomical structures using systemized protocols are needed, and myofunctional therapy is a convenient yet efficient intervention to treat OSA and prevent recurrence of OSA in post-surgical pediatric patients. Still, due to the limited accumulation of evidences in applying myofunctional therapy in clinical settings, more research is needed to confirm the effectiveness of myofunctional therapy in pediatric populations.

### Neurofeedback

Underarousal and deficient involvement of necessary cortical networks during performance tasks have been implicated as a theoretical background of ADHD in neuroimaging and electroencephalographic studies.[138] Neurofeedback is based on classical/operant conditioning involving sensory motor rhythm (SMR) training, which helps the brain to regulate its functioning.[138] Many previous literatures have reported the efficacy of neurofeedback in ameliorating core symptoms of ADHD,[139] but studies regarding associations between sleep problems in patients with ADHD and neurofeedback are relatively scarce.

The number of sleep spindles is frequently reduced in sleep deprived subjects, and seonsorimotor rhythm train-

ing significantly increases the number of sleep spindles and total sleep time, indicating its possible efficacy for patients with insomnia.[140,141] The treatment effect of neurofeedback through vigilance stabilization which is often disrupted by circadian phase delay in ADHD patients was outlined in one review,[142] which underscored the need for more extensive research on neurofeedback.

### Adjustment of School Start Times

Many literatures to date have demonstrated the beneficial effects of delaying school start times. Indeed, several stunning results have been published, reporting that even 25 minutes of school start time delay was associated with significant improvements in sleep duration,[143] and 50 minutes of delay with increased academic achievements.[144] One hour of delay in school start time was significantly associated with enhancement of attention as well as improvements in cognitive performances in students.[145] Students attending morning classes suffered more from sleep restriction than did those attending afternoon classes,[146] and a Brazilian study demonstrated the influence of school start time on the sleeping habits of students.[147] Moreover, in another study, delaying the school start time not only improved the quality of sleep, but also ameliorated mood and behavioral symptoms in adolescents.[148]

The American Academy of Pediatrics recently published a policy statement strongly recommending delaying school start times to ameliorate chronic sleep deprivation among students and consequent diversity of problems including obesity and depression.[149] A recent recommendation by the National Sleep Foundation suggests that the optimal sleep duration for school-aged children is 7 to 12 hours and that for adolescents is 7 to 11 hours.[150] Considering all the deleterious consequences of insufficient sleep in children and adolescents as mentioned earlier in this article, implementing policies advocating delay of the school start times warrants special attention, and clinicians should recognize the potential impact of school start time on their patients' sleep patterns and circadian rhythm disturbances.

## CONCLUSION

Intricacies of the relationship between ADHD and sleep remain elusive. However, many promising reports regarding the 'sleep phenotypes' of ADHD such as sleep deprivation, SDB and circadian rhythms disturbances suggest the possibility of identifying predictors of ADHD. Knowledge of such predictors would allow the early detection and treatment of disorder. Clinicians should be aware of the potential impact of sleep problems on pediatric and adolescent patients with ADHD, including obesity, poor academic performance and disrupted parent-child interactions, since they may debilitate the patients and influence the long term prognosis of the patients. Novel treatment interventions could be used for ADHD patients with sleep problems, including melatonin, light therapy, neurofeedback, myofunctional therapy and adjustments of school start times to alleviate the aforementioned long-term debilitating consequences.

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