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GUEST EDITORIAL

Sleep and ADHD: A complex and bidirectional relationship

In this issue of *Sleep Medicine Reviews*, McWilliams et al. [1] present a thought-provoking scoping review on sleep as an outcome measure in ADHD randomized control trials (RCTs). The authors note that only recently, mostly from 2010 onward, sleep has been employed as a primary (40) or secondary (31) outcome measure in 71 interventional ADHD RCTs.

This new trend is most welcome and timely considering the widespread prevalence of sleep disorders, nearly 50% in the ADHD pediatric population, and the role of sleep and its deprivation in modulating prefrontal dysfunction and brain plasticity.

Novel ADHD treatments should evaluate both beneficial and adverse effects on sleep; unfortunately, this is seldom the case. In fact, of the 71 RCTs considered, 45 used one or more medications to treat ADHD symptoms, whereas only 10 prescribed drugs for the treatment of sleep disorders. Furthermore, none of the trials employed iron or vitamin D supplementation, widely recognized agents for the treatment of restless legs syndrome (RLS)/periodic limb movement disorder (PLMD) and obstructive sleep apnea (OSA) [2,3].

Adverse effects on sleep were described in 19 RCTs using stimulants for ADHD, while none were noted in the trials that directly addressed sleep and/or sleep and ADHD symptoms. This corroborates that diagnosing and treating different sleep phenotypes in ADHD [4] allows for tailored treatment and improves prognostic outcome.

The trials also varied in their use of diagnostic tools. Only 18 of the 40 RCTs measuring sleep as a primary outcome utilized full polysomnography (PSG) or actigraphic measures; this deficient and restrictive use of PSG, counting only 10 RCTs, all in North America, possibly reflects the differing disposal of economic, health and personnel resources across different regions. Nevertheless, the gold standard diagnostic tool, PSG, possibly with an adequate number of EEG channels, should always be preferred to actigraphy to confirm and examine different sleep phenotypes. Whenever an ambulatory PSG is used, multiple nights should be recorded.

Whether multi-domain, symptom or disorder-specific, validated questionnaires and sleep diaries are useful complementary diagnostic tools; indeed, they should be integrated with adjunctive means of sleep recording rather than used alone to evaluate treatment protocols.

Sleep recordings also help elucidate the physiopathology of ADHD with reference to a maturational delay of sleep rhythms' frequencies and distributions and the role of different sleep phenotypes related to ADHD.

Sleep mechanisms and dynamics are essential to explaining the pathophysiology of ADHD.

The hallmark symptoms of ADHD, impaired behavioral inhibition, inattention, and excessive motor activity, derive from the disruption of circuits regulating action and attention.

ADHD neuroimaging studies indicate volumetric differences in the prefrontal cortex (PFC), the cerebellum, and striatum, consistent with the role of these region in cognitive operations that are impaired in ADHD patients. The PFC activation response to ventral tegmental dopamine neurons is modulated via diurnal influences by orexin-hypocretin. Catecholamines may act as a chemical switch to turn on the PFC during waking, while turning it off during drowsiness or stress.

Sleep deprivation, characteristic of ADHD, may affect several aspects of performance, including attention and vigilance, decision-making abilities, and memory functions.

High-density electroencephalography (EEG) studies have demonstrated an abnormally high slow (theta) oscillatory activity, paralleled by reduced fast (alpha and beta) activity during the resting state in ADHD, corresponding to hypoactivation of the executive functions and attention networks as shown through neuroimaging, as though cortical and subcortical "islands of sleep" could occur in behaviorally awake subjects [5]. Conversely, the slow physiological oscillations generated by the PFC during sleep in normal controls, supporting declarative memory, are attenuated over frontal areas and shifted to central posterior regions in ADHD children as an expression of delayed cortical maturation [6].

From a microstructural perspective, arousability and sleep stability levels may be measured via cyclic alternating pattern (CAP) analysis [7] as spontaneous or stimulus-induced episodic oscillations in brain activity during NREM sleep. Activation components As are classified as A1, A2, and A3 with a decreasing trend of slow—wave activity (SWA), with A1 best reflecting this progression. Indeed, the extant literature on the microstructural analysis of ADHD sleep shows a lower CAP A1 rate and index during N2 in ADHD children.

Three main processes modulate sleep: the circadian process C, the homeostatic process S, which regulates sleep intensity according to previous wakefulness duration and activity, and the ultradian process, which controls the intrasleep NREM-REM alternation.

According to these regulatory processes, different sleep phenotypes of ADHD have been identified: 1) a primary ADHD hypoarousal state similar to narcolepsy, possibly linked to an alteration of the ultradian process, with a global decrease of NREM instability, and the best candidate for stimulant treatment; 2) a sleep phenotype with delayed sleep onset, linked to a circadian alteration, susceptible to melatonin treatment that may prevent later development of bipolar disorder; 3) the ADHD/sleep-disordered

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breathing (SDB) phenotype; 4) the ADHD/RLS or PLMD phenotype; 5) the ADHD/epilepsy or EEG interictal discharges phenotype. The latter three are all related to the alteration of process S due to chronic sleep loss with varying levels of arousal pathology.

Undeniably, a bidirectional relationship exists between these disorders and ADHD. Their individual diagnosis is recommended to implement specific treatment and to preclude side effects arising from incongruous pharmacological management. Timely adenotonsillectomy, orthodontic treatment, or Continuous Positive Airway Pressure (CPAP) may improve behavioral abnormalities and executive functions in affected children, whereas melatonin and methylphenidate could potentially worsen OSA.

Iron depletion, consistently present in ADHD and RLS, may be ameliorated by appropriate oral or IV supplementation in children with ferritin <50 μg/L. Reduced ferritin is also typical of other sleep-related motor disorders seen in ADHD children, such as bruxism or sleep-rhythmic movement disorder, and is prevalent in ADHD children with disorders of arousal [2]. Antiepileptic drugs with sleep stabilizing properties such as levetiracetam, gabapentin, and clonazepam may prove helpful not only in ADHD children with ictal/interictal discharges but also in other sleep phenotypes with increased sleep instability, possibly except the SDB phenotype.

Two recent high-density EEG protocols [8,9] have shed light on ADHD mechanisms and phenotypic expression, confirming static and dynamic changes in SWA with an uncommon distribution in the central posterior rather than the frontal areas. This anomaly reflects a maturational delay due to both chronic sleep deprivation and diurnal activation of the prefrontal motor circuits in relation to hyperactivity.

Furthermore, Castelnovo et al. [9] report a widespread increase during NREM sleep of theta and low alpha activity (3–10 Hz). The latter, maximal at N3, could be yet another expression of higher sleep pressure and altered sleep homeostasis with delayed cortical maturation.

With respect to sleep phenotypes, a recent study [10] explored sleep microstructure via the CAP in ADHD children versus normal controls. Despite a similar CAP rate of about 50% in ADHD and controls, children with OSA or interictal epileptic abnormalities had a higher CAP rate during N3. This increased NREM instability could lead to secondary ADHD expressed by an A1 subtype increase in N3. By contrast, the other sleep phenotypes of ADHD, namely sleep onset insomnia, RLS/PLMD, and narcolepsy-like phenotype with reduced CAP rate, A1%, and index, would represent the disorder's intrinsic phenotypes, each linked to specific features and prognostic outcome: respectively, circadian disruption with a high risk for bipolar disorder, ADHD hyperactive type, and inattentive ADHD.

These results help to refine the theory considering the role of increased or decreased arousability as central to PFC dysfunction.

Indeed, SWA in ADHD would be inappropriately displaced as local sleep over the frontal-parietal and ventral attentional networks during wakefulness and in the central posterior cingulate regions rather than the frontal ones during sleep, impairing synaptic pruning and brain plasticity.

Future diagnostic and therapeutic goals of RCTs considering sleep as an outcome measure of ADHD should include the recognition of OSA and interictal spikes as preventable and treatable sources of secondary ADHD and the appropriate use of stimulants, melatonin, and iron to improve symptoms related to ADHD sleep endophenotypes.

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