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CLINICAL REVIEW

Sleep in attention-deficit/hyperactivity disorder in children and adults: Past, present, and future

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SUMMARY

The understanding that sleep can give rise to, or exacerbate symptoms of attention-deficit/hyperactivity disorder (ADHD), and that good sleep hygiene improves attention and concentration tasks has sparked interest in the investigation of possible etiological relationships between sleep disorders and ADHD.

Studies indicate that 30% of children and 60–80% of adults with ADHD have symptoms of sleep disorders such as daytime sleepiness, insomnia, delayed sleep phase syndrome, fractured sleep, restless legs syndrome, and sleep disordered breathing. The range and diversity of findings by different researchers have posed challenges in establishing whether sleep disturbances are intrinsic to ADHD or whether disturbances occur due to co-morbid sleep disorders. As a result, understanding of the nature of the relationship between sleep disturbances/disorders and ADHD remains unclear.

In this review, we present a comprehensive and critical account of the research that has been carried out to investigate the association between sleep and ADHD, as well as discuss mechanisms that have been proposed to account for the elusive relationship between sleep disturbances, sleep disorders, and ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention and/or impulsivity/hyperactivity.[1] Accounts of ADHD date back to the early 1900's, when the disorder was not yet defined and conditions such as ADHD, conduct disorders (CD), and oppositional defiant disorder (ODD) were clumped together as "moral imbecility", in which individuals were described as having an "…inability to display moral restraint and lawful behavior (while) … being, in many cases, of normal or even superior intelligence…".[2]

Since then, considerable research has been carried out with regards to ADHD. In the last fifteen years, evidence points to ADHD as a pervasive condition that continues with some robustness into adulthood in up to 60% of patients.[3] With the advent of technologies such as fMRI, PET scanners, and advances in certain facets of psychopharmacology, it is now understood that areas of the brain involved with catecholamine signaling are affected in ADHD.[4,5] Additionally, more recent studies report that serotonergic and cholinergic pathways are affected in ADHD, suggesting that there is an intricate interplay of signaling pathways in the pathology of ADHD.[6,7]

ADHD is categorized as three subtypes: ADHD of the primarily inattentive subtype (ADHD-I), ADHD of the primarily hyperactive/impulsive subtype (ADHD-HI), and ADHD of the combined subtype (ADHD-C). ADHD is also associated with a slew of co-morbidities, including depression, anxiety, behavioral disorders such as CD and ODD, substance abuse disorders, and sleep disorders.[3,8–12]

Sleep disorders are interesting in the context of ADHD. Twenty five to fifty percent of children and more than half of adults with ADHD reportedly suffer from sleep problems.[13–15] Sleep plays a pivotal role in cognitive function, learning, and memory consolidation.[16,17] Sleep deprivation or disturbances can result in symptoms varying in severity, from unconscious deficits in cognitive performance to disabling sleepiness and fatigue that noticeably affect cognitive, emotional, and physical function, putatively giving rise to, or exacerbating ADHD symptoms.[18,19]

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Abbreviations

ACTH	adrenocorticotropic hormone
ADHD	attention-deficit/hyperactivity disorder
ADHD-C	ADHD of the combined subtype
ADHD-HI	ADHD of the hyperactive/impulsive subtype
ADHD-I	ADHD of the primarily inattentive subtype
AHI	apnea hypo-apnea index
CAP	cyclic alternating pattern
CD	conduct disorder
DLMO	dim light melatonin onset
EDS	excessive daytime sleepiness
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
GH	growth hormone
HPA	hypothalamic-pituitary-adrenal
IQ	intelligence quotient
LC	locus coeruleus
ODD	oppositional defiant disorder
OSA	obstructive sleep apnea
PET	positron emission tomography
PFC	prefrontal cortex
PLMS	periodic limb movement in sleep
PS	primary snoring
PSG	polysomnography
RDI	respiratory disturbance index
RLS	restless legs syndrome
SDB	sleep disordered breathing

Relatively extensive research has been carried out to investigate the nature of sleep disturbances in ADHD. Nevertheless, the topic remains obscure, and while researchers and clinicians sense that there is a sleep problem in subjects with ADHD, the exact nature of this association is not well understood. From an etiological perspective, the distinction between sleep disorders and sleep disturbances in ADHD is blurred, because it is currently not clear whether sleep disturbances are intrinsic to ADHD; whether sleep disturbances result due to co-morbid sleep disorder; or whether sleep disorders cause ADHD-like symptoms and thus, result in a misdiagnosis.

The aim of this review is to present a comprehensive and critical account of the research that has been conducted on the relationship between sleep disorders and ADHD. The literature review has been organized into sections that address i) studies demonstrating that ADHD-like symptoms can manifest in patients with sleep disorders, and ii) studies demonstrating that sleep disturbances can manifest in patients with ADHD. An attempt at integrating these two lines of evidence is then discussed, along with some putative involved mechanisms.

ADHD-like symptoms in sleep disorders

Primary sleep disorders are associated with ADHD-like symptoms. Although whether the nature of such association is causative is not known, sleep fragmentation may give rise to ADHD-like symptoms. Indirectly, sleep deprivation due to sleep fragmentation may lead to excessive daytime sleepiness, which may in turn interfere with sustained attention. Alternatively, direct changes in sleep architecture due to sleep fragmentation may affect daytime processes associated with mood, memory, and learning – all of which are affected in ADHD. Studies in which ADHD-like symptoms were investigated are discussed in the following sections.

Hypersomnia

Oosterloo and colleagues[20] carried out a study comparing adults with ADHD to adults with excessive daytime sleepiness (EDS) and found that approximately 18% of EDS patients met DSM-IV criteria for ADHD; while approximately 37% of ADHD patients met criteria for EDS.[20]

Restless legs syndrome/periodic limb movement in sleep

ADHD-like symptoms have been documented in restless legs syndrome (RLS) and Periodic Limb Movement in Sleep (PLMS). In a retrospective clinical study, 93% of children with RLS met DSM-IV criteria for ADHD.[21] Although the high percentage is likely to be the result of recruitment bias, as the clinic at which the study was conducted specializes in ADHD and RLS, other groups have reported associations between ADHD symptoms and RLS in both children and adults.[22–24]

Sleep disordered breathing

Sleep disordered breathing (SDB) is associated with inattentive and hyperactive behavior in children.[23,25] Children with primary snoring (PS) suffer from more sleepiness, inattention, and hyperactivity than healthy controls.[26–29] Also, children with obstructive sleep apnea (OSA) have problems with sustained attention and verbal skills, while adults with OSA have attention problems.[30,31] While these studies support an association between SDB and ADHD symptoms, O'Brien and colleagues[32] observed that while children with SDB had lower attention and executive function, no differences in ADHD-associated behavior were found between children with SDB and healthy controls. Moreover, Chervin and Archbold[33] reported that while there are no associations between hyperactivity and SDB, there was an association between PLMS scores and hyperactive behavior when children had SDB, suggesting an inter-relationship between SDB, PLMS, and hyperactive behavior.

Sleep disorders in ADHD

In this section, studies designed to investigate the manifestation of sleep disturbances/disorders in patients with ADHD are discussed.

Sleep quality and sleep architecture

With the exception of three studies[39,41,78] studies using subjective methods reported sleep problems such as early and middle insomnia, nocturnal awakenings, snoring, breathing problems, restless sleep, parasomnias, nightmares, short sleep time, daytime sleepiness, and anxiety around bedtime in children with ADHD (Table 1).[27–37,40,42–47]

The use of objective methods such as actigraphy and polysomnography (PSG) for the assessment of sleep in children with ADHD resulted in variable findings (Table 2). Of note, increases in sleep onset latency,[14,64] daytime sleepiness,[50,57] and REM sleep latency[49,50,54,55,69] were reported. There are, however, controversies as to whether there are increases or decreases in REM sleep percentage,[54–57,60,67,69] or total sleep time[60,63,67–69] in children with ADHD.

In contrast, some studies found no abnormalities in sleep by actigraphy[51,62] or PSG[53,61] in children with ADHD. Interestingly,

Table 1
Studies of sleep disturbances in children with ADHD with subjective methods.

Authors, year of publication	Classification (sample size)	Mean age and/or Age range	Medication status	Co-morbidity	Major findings	Strengths (S) and/or weaknesses (W)
Ball et al., 1997[34]	Medicated ADHD (28) vs. non-medicated ADHD (74) vs. controls (78)	9 (±2.7)	As noted	Not specified, but included LD or other emotional and/or behavioural problems	Medicated children reported more sleep problems and night awakenings than controls. There were no significant differences between medicated and non-medicated children with respect to reports of sleep problems.	S: Medication status was accounted for W: No specifications as to whether children had any potentially confounding co-morbidities, or types and doses of medications used by the medicated ADHD group.
Chervin et al., 1997[35]	ADHD (27) vs. psychiatric controls (43) vs. healthy controls	9 (±4.7) 2–18	44% of children with ADHD were taking stimulants	Not specified	Subjects with ADHD had more habitual snoring than other groups.	S: Since patients were consecutively recruited, there was no recruitment bias W: Medication status or comorbidities were not controlled
Marcotte et al., 1998[36]	Clinical group consisting of children with ADHD and/or LD (77) vs. controls (71)	8.8 (±1.7)	Not medicated	LD and other psychiatric or neurologic conditions, although children with psychiatric/neurologic conditions were not included in the final clinical group	The clinical group scored higher on the sleep and breathing problems scale and the sleepiness scale.	W: Effect of LD cannot be ascertained in this study as a result of grouping of children with ADHD, children with ADHD with LD, and children with LD into the clinical group.
Ring et al., 1998[37]	ADHD (13) vs. healthy siblings (16)	8.8 (±2.7) 5–13	All children had been taking a fixed dose of MPH for at least 4 weeks	All children with Axis I disorder were excluded	Although the mean duration of sleep in ADHD children and their siblings did not differ significantly, those with ADHD had higher rates of initial and middle insomnia, as well as nocturnal enuresis, and sleepwalking	S: Use of siblings of children with ADHD as controls to minimize confounding errors. W: The fact that mean duration of sleep does not differ between groups, while the rates of sleep disturbances is higher in children with ADHD reflects inaccuracies in parent reports of either sleep duration, or sleep complaints. Authors fail to discuss this issue.
Corkum et al., 1999[38]	Non clinical comparison group (36) vs. unmedicated ADHD (79) vs. medicated ADHD (22) vs. clinical comparison group (35)	9.1 6–12	As noted	Children with low IQ, PTSD, anxiety, or autism were excluded. Children included in the study had comorbidities with ODD, CD, GAD, SAD, and DEP	Regression analysis revealed that dyssomnias and involuntary movements during sleep in children had a stronger association with medication status, comorbidity with ODD, and separation anxiety than with ADHD diagnosis.	S: Medicated and non-medicated children were compared in different groups. Proper control of confounding factors such as medication status and comorbidities.
Mick et al., 2000[39]	ADHD (122) vs. controls (105)	15 (±3)	Approximately half of the ADHD group was on stimulant medication	Mood disorders, anxiety, CD/ODD	Although sleep difficulties were associated with ADHD, regression analysis revealed that such difficulties were associated with the use of stimulant medication and comorbidity with anxiety disorder.	S: Statistical analyses taking medication status and co-morbidities into account.
Owens et al., 2000[40]	ADHD (46) vs. controls (46)	5–10	Not medicated	ODD, CD, LD	Children with ADHD had increased rates of bedtime resistance, sleep onset delays, night awakenings, parasomnias, and daytime sleepiness; and decreased sleep duration.	W: Small sample size led to inability to assess whether co-morbid disorders in some of the children with ADHD played a role in the development of sleep problems.

(*continued on next page*)

Table 1 (*continued*)

Authors, year of publication	Classification (sample size)	Mean age and/or Age range	Medication status	Co-morbidity	Major findings	Strengths (S) and/or weaknesses (W)
Stein et al., 2002[41]	Medicated ADHD (17) vs. unmedicated ADHD (18) vs. control (46) children	13–16	As noted	Children with Axis I disorders were excluded from the study. However, children with CD, ODD, and mild anxiety or depression may have been inadvertently included in the study.	Medicated adolescents with ADHD had increased rates of moderate to severe sleep disturbances compared to non-medicated adolescents with ADHD and controls. However, sleep disturbances in medicated adolescents were associated with depression, rather than with ADHD diagnosis, while in the non-medicated group, sleep disturbances were associated with anxiety.	S: Medication status and confounding effects of anxiety and depression taken into account W: Relatively small sample size
LeBourgeoi s et al., 2004[42]	ADHD-I (21) vs. ADHD-HI (24) vs. ADHD-C (16) vs. controls (29)	6–16	Some children were taking stimulant or hypnotic medications	Children with learning disabilities were excluded from the study. Comorbidities included depression, OCD, ODD, and BD	A higher percentage of children with ADHD suffered from daytime sleepiness, poor sleep quality, initial insomnia, and trouble waking up in the morning compared to controls. Among subtypes, ADHD-HI children snored more and had a tendency towards more trouble going to bed than their ADHD-C counterparts. No other differences were reported between ADHD subtypes.	S: Comparison of ADHD subtypes W: Presence and influence of comorbidities and/or medication status were not taken into account in the data analysis
Gau et al., 2006[43]	Children with T-score > 60 (414) vs. $T \leq 60$ (2047) according to the CPRS-R:S and $T > 60$ (318) vs. $T \leq 60$ (2145) according to the CTRS-R:S	11.6 ($\pm$2.6) 6–16	Not specified	Not specified	According to parental reports using the CPRS-R:S, children with T-score ≤ 60 had more differences in bedtime in weekdays and weekends, and more sleep problems such as dyssomnia, parasomnia, SDB, and inadvertent daytime naps than children with T-score > 60. According to teacher reports using the CTRS-R:S, children with T-score > 60 had later rise times on weekdays, shorter sleep time on weekends, and more sleep problems such as dyssomnia, SDB, and inadvertent daytime naps than children with T-score ≤ 60.	W: No information on medication status or co-morbidities
Lim et al., 2008[44]	ADHD (101) vs. controls (60)	5–13	Not clearly specified. 41/114 ADHD children had been prescribed medications, but only the data for 101 children were included in the statistical analyses	Other than aggression problems, externalizing problems, and delinquent behaviours in some of the subjects in either group, not specified	Subjects in the ADHD group were reported to sleep less than subjects in the control group	W: No information as to comorbidities in subjects. Also, although it is claimed by authors that interviewed subjects did not appear to have significant sleep complaints as a result of medication, medication status in the studied groups not clearly specified.
Sung et al., 2008[45]	ADHD (239)	11.7 ($\pm$3.2) 5–18	About 86% of the study subjects were taking medications (ADHD meds, clonidine, and other)	LD, ODD, CD, depression and/or anxiety, Asperger disorder, other	About 30% of children with ADHD had mild sleep problems and about 45% had moderate to severe sleep problems such as trouble falling asleep, bedtime resistance, difficulty getting up, night awakenings, restless sleep, breathing difficulty during sleep, and tiredness on waking.	W: Effects of medication status and co-morbidities not taken into account in statistical analyses

Hvolby et al., 2009[46]	ADHD (45) vs. clinical control (64) vs. healthy control (212)	5–11	No	ODD, CD, emotional disorders, other	No significant differences were found between clinical controls and healthy controls. On the other hand, ADHD children were found to have more sleep problems such as bedtime resistance, difficulty falling asleep, restless sleep, sleep talking, teeth grinding, nightmares, and difficulty waking in the morning. Moreover, sleep onset latency was higher in the ADHD group in comparison to clinical and healthy controls.	W: No comparisons made between ADHD and clinical control, only between clinical control and healthy control. Thus, not a proper control for psychiatric co-morbidities in ADHD group.
Li et al., 2009[47]	ADHD (853) vs. controls (19299)	9 (±1.6) 5–11	MPH	Children with anxiety, depression, or LD excluded from study	A multiple regression model controlled for age, gender, and medication status revealed that history of ADHD correlated significantly with sleep problems such as bedtime resistance, sleep onset delay, sleep anxiety, night awakenings, parasomnia, SDB, and daytime sleepiness.	S: Medication status was controlled for, and given exclusion of children with co-morbid anxiety/depression/LD, comorbidities were somewhat controlled for.
Mayes et al., 2009[48]	ADHD-C (271) vs. ADHD-I (144) vs. ADHD-C with ODD (102) vs. ADHD-C with anxiety or depression (79) vs. ADHD-C with ODD and anxiety or depression (43) vs. ADHD-I with anxiety or depression (42) vs. controls (135)	9 (SD2) 6–16	212 children treated with medication	ODD, Anxiety disorder, and depression	While ADHD-I children did not differ from controls, ADHD-C children had more sleep problems than ADHD-I (trouble falling asleep, restless sleep, night awakenings) and control children (trouble falling asleep, sleeping less than normal). Also, ADHD-I children had more reports of daytime sleepiness. In both the ADHD-I and ADHD-C groups, comorbidity with anxiety or depression was associated with greater sleep problems (trouble falling asleep, restless sleep, night awakenings, sleep walking/talking, early rise, and reduced sleep time). Although medicated children had higher T-scores on sleep problems, medicated children also had more severe ADHD. Moreover, in all the children in the study, ADHD symptom severity correlated with sleep problem scores. With ADHD severity as a covariate in statistical analyses, other than greater difficulty falling asleep, medication status was not found to be associated with more sleep problems.	S: Stratification of ADHD children into ADHD subtypes and ADHD subtypes with co-morbidities, as well as medication status. W: In determining correlations between ADHD severity and T-scores of sleep problems, authors did not stratify data into subtypes. Considering that ADHD severity is determined by the addition of scores on inattentive and hyperactive/impulsive symptomatology, it would have been interesting to see whether the correlation between ADHD severity and sleep problems holds when groups are stratified into ADHD subtypes.

ADHD = Attention-deficit/hyperactivity disorder, ADHD-C = ADHD of the combined subtype, ADHD-H/I = ADHD of the hyperactive/impulsive subtype, ADHD-I = ADHD of the inattentive subtype, BD = bipolar disorder, CD = conduct disorder, DEP = major depressive episode, C(P/T)RS-R:S = Conner's (parent/teacher) rating scale-revised: short forms, GAD = generalized anxiety disorder, IQ = intelligence quotient, LD = learning disability, MPH = methylphenidate, OCD = obsessive compulsive disorder, ODD = oppositional defiant disorder, PTSD = post-traumatic stress disorder, SAD = separation anxiety disorder, SD = standard deviation.

Table 2
Studies of sleep disturbances in children with ADHD with objective methods.

Authors, year of publication	Classification (sample size)	Mean age and/or Age range	Medication status	Co-morbidity	Major findings	Strengths (S) and/or weaknesses (W)
Busby et al., 1981[49]	Hyperkinetic children (11) vs. controls (11)	8–12	Not medicated	Children with major psychosis, overanxiety, or unsocialized aggressive behaviour were excluded from the study.	PSG, five nights: Increased REM sleep latency in hyperkinetic group.	S: Multiple nights of PSG W: Classification of hyperkinesis is likely to be somewhat different from what ADHD is defined as at present.
Palm et al., 1992[50]	Children with deficits in attention, motor control, and perception (DAMP) (9) vs. controls (16)	9.3 6.3–12.3	Not medicated	Children with severe neurotic or psychotic disorders were excluded from the study	PSG, two nights: On the second night of recordings, DAMP children had small increases in TSP, REM percentage, SOL, and REM sleep latency; and a small decrease in S1 sleep percentage. In three of the DAMP children, SOL was decreased in MSLT, suggesting daytime sleepiness.	S: Two nights of PSG W: Small sample size
Gruber et al., 2000[13]	ADHD (38) vs. control children (64)	9 (±2) 6–14	Not Medicated	Children with behavioural problems and LD were excluded from the study	Actigraphy, five nights: While there were no significant differences on SOT, sleep duration, or true sleep between ADHD and control groups, the standard deviations of these parameters were significantly different between groups, suggesting increased night to night variability in ADHD.	S: Interesting take, looking at night-to-night variation rather than averaged outcomes for the analysis of sleep parameters in the studied groups W: Study consisted of boys only
Corkum et al., 2001[51]	ADHD (25) vs. controls (25)	9 (±1.3) 7–11	Not medicated	ODD, CD, GAD, SAD, MD	Actigraphy, seven nights: Although parents reported increases in sleep duration, SOL, restless sleep, bedtime resistance, and difficulties arising in the morning in ADHD, actigraphy revealed no significant differences between groups.	S: Eliminated possible confounding effect of collapsing all the week data by stratifying data into weekday and weekend variables W: Co-morbidities were not controlled for, which may have masked possible differences between ADHD and controls
Konofal et al., 2001[52]	ADHD (30) vs. controls (30)	5–10	Not medicated	Children with psychotic disorders were excluded from the study	PSG and video recording, one night: No significant differences between ADHD children and controls, although video recordings revealed more limb movements in ADHD children.	W: Only one night of PSG. S: Additional information gained from the video recording, without which the conclusion would have been that ADHD children and controls do not differ in variables of sleep.
Crabtree et al., 2003[53]	ADHD (97)	8.3 (±3) 3–18	Stimulants, other psychotropic agents, and sleep promoting agents	Non-specified co-morbidities	PSG, one night in 69 children: 7% had SDB, 36% had PLMI>5, and 6% had sleep fragmentation. No other abnormalities found in the averaged means of sleep variables. Actigraphy, 14 days in 16 children: Significant night to night variability.	W: This study was a chart review, thus, medication status or comorbidities were not properly controlled for. Also, only the data for one night of PSG recordings were available for each child.
O'Brien et al., 2003[54]	Children with significant ADHD symptoms (44) vs. children with mild ADHD symptoms (27) vs. controls (39)	5–7	Not specified, but likely medication free	Children with psychiatric diagnoses were excluded from the study	Subjective data: Children with significant and mild ADHD symptoms had more enuresis and snoring compared to controls. Children with significant ADHD symptoms had more restlessness, awakenings, talking, teeth grinding, difficulties initiating sleep, daytime sleepiness, and unwillingness to go to sleep. PSG, one night: Children with significant ADHD symptoms had increased REM sleep latency and decreased REM sleep percentage compared to controls.	W: Only one night of PSG. Also,although it is likely that children were medication free, authors did not specify whether the study subjects were taking medications or whether they suffered from mild comorbidities such as, among others,depression or anxiety.

O'Brien et al., 2003[55]	Clinical sample of children with ADHD (ADHDcl) (47) vs. community sample of children with ADHD (ADHDcom) (53) vs. controls (49)	Clinical ADHD sample 8 (±1.6) Commu nity ADHD sample 6.6 (±0.4) Controls 6.7 (0.4)	72% and 51% were medicated in the clinical and community ADHD sample, respectively	Children with psychiatric diagnoses were excluded from the study	Subjective data: More difficulties initiating sleep, restless sleep, nightmares, and EDS in ADHDcl and ADHDcom; and increased sleep walking, enuresis, and stops in breathing in ADHDcl. PSG, one night: ADHDcl and ADHDcom had increased REM sleep latency and decreased REM sleep percentage. ADHDcl had increased SWS and PLMI, and decreased spontaneous arousal index.	S: Comparison of clinical and community ADHD samples to account for referral bias. W: Only one night of PSG. Also, no control of medication status
O'Brien et al., 2003[56]	Medicated ADHD (ADHDmed) (53) vs. unmedicated ADHD (ADHDnon) (34) vs. controls (53)	3–11	As indicated. 60% of ADHDmed were taking MPH and 40% were taking DEX	Not specified	Subjective Data: ADHD children had nightmares and nocturnal enuresis. A higher percentage of medicated children had restless sleep. PSG, one night: Children with ADHD had decreased REM sleep percentage in comparison to controls. Also, ADHDmed children had reduced TST	W: No specification of comorbidities and only one night of PSG
Golan et al., 2004[57]	ADHD (34) vs. controls (32)	12 (±3.6)	Stimulant medication free for 3 days prior to study	Not specified	PSG, one night: The ADHD group had increases in REM sleep percentage, arousal index, RDI, number of children with SDB, and number of children with PLMD compared to controls. MSLT revealed that children with ADHD are sleepier than controls.	W: No specification of comorbidities and only one night of PSG, which may not be representative of habitual sleep patterns in either the ADHD or control groups.
Gruber and Sadeh, 2004[58]	ADHD (24) vs. controls (25)	7–11	Not medicated	No comorbidities	Actigraphy, five days: Higher night to night variability in variables such as sleep onset time, TST, and true sleep time in the ADHD group.	W: Boys only
Huang et al., 2004[59]	ADHD (88) vs. controls (27)	9	Not specified, but most likely not medicated	Exclusion of children with a history of BD, psychosis, anxiety, seizure disorder, substance abuse, or mental retardation	PSG, one night: Children had increased S3 sleep percentage and AHI, and decreased mean saturated oxygen (SaO2).Closer inspection of AHI values revealed a higher percentage of ADHD children with AHI>1, suggesting a higher prevalence of SDB in these children. Also, a higher percentage of children with ADHD had PLMI>5 than controls.	W: Only one night of PSG. S: Though not described in detail in this table, stratification of data into ADHD children with OSA and ADHD children without ADHD revealed differences in sleep variables REM and Stage 4 sleep percentage, as well as in the incidence of PLMI>5, thus shedding some light into the characteristics of sleep variables in the two groups.
Kirov et al., 2004[60]	ADHD (17) vs. controls (17)	11 (±2) 8–14	Not medicated	Dyslexia, CD, panic disorder, nocturnal enuresis	PSG, two nights: In comparison to controls, children with ADHD had increases in time in bed, TST, REM sleep time, number of sleep cycles, and short movement-related epochs.	S: Two nights of PSG. W: Relatively small sample sizes and no control of co-morbidities.
Sangal et al., 2005[61]	ADHD (40)	6–14	Not medicated	Children with primary sleep disorders or psychiatric diagnosis were excluded from the study	PSG, one night: Values were found to be within the normal range in sleep variables	W: Only one night of PSG
Wiggs et al., 2005[62]	ADHD-I (8) vs. ADHDH/I (19) vs. ADHD-C (23) vs. controls (21)	3–15	Not medicated	Antisocial behaviour, emotional symptoms, peer problems, CD, autism	Actigraphy, five nights: Other than some discrepancies between subjective reports of parents and objective data obtained from actigraphies on SOT (parents of ADHD-I children reported earlier SOT than what was revealed by actigraphy), there were no significant differences between ADHD subtypes. SDB, sleeplessness as a result of poor sleep hygiene, and RLS appeared to be common in ADHD.	S: Stratification of ADHD into subtypes, even though no differences were found between subtypes. W: Small sample sizes

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Table 2 (*continued*)

Authors, year of publication	Classification (sample size)	Mean age and/or Age range	Medication status	Co-morbidity	Major findings	Strengths (S) and/or weaknesses (W)
Miano et al., 2006[63]	ADHD (20) vs. controls (20)	6–13	Not medicated	LD, language disorders, and mild neurologic signs	PSG, two nights: In comparison to controls, the ADHD group had decreases in time spent in bed, sleep period time, TST; and an increase in stage shifts. Also, decreases in CAP rate were found in stage 2 of NREM sleep.	S: Using micro-architecture variables of sleep may be a new window for the investigation of the sleep disturbances in ADHD, which may explain contradictions between subjective and objective data in reports of sleep problems in subjects with ADHD. W: For the time being, however, the use of micro-architecture variables of sleep is not well established for investigating sleep disturbances
Van der Heijden et al., 2006[64]	ADHD with sleep onset insomnia (SOI) vs. ADHD without SOI (33)	6–12	Not medicated	Disruptive behavioural disorder, anxiety disorder, and affective disorder	Actigraphy, five days: Significant delays in the SOI group with regards to DLMO time, sleep latency, sleep onset, wake up-, and get up times.	S: Control for ADHD subtype and co-morbidities in statistical analyses. W: Although authors state that 87 ADHD-SOI children were compared to 33 ADHD-noSOI children, DLMO data were only available for 78 out of 87 ADHD-SOI children and 33 out of 33 ADHD-noSOI children. Demographics for these new groups may have been different from those published in the paper, which may have introduced confounding errors to the study. Also, the sleep onset time used to define sleep onset delay has been deemed too early by other groups.
Silvestri et al., 2007[65]	ADHD (42)	8.9 ($\pm$2.8)	Not medicated	ODD, dyslexia, language disorder, tic disorder, eating disorder, dyspraxia	PSG, one night: Increased prevalence of sleep disorders such as ictal and interictal epileptiform discharges, RLS, sleep related movement disorders, arousals, and SDB.	S: Use of Spearman correlation coefficients to assess association between, among others, comorbidities and variables of sleep such as EEG and sleep efficiency. W: Only one night of PSG.
Hvolvy et al., 2008[14]	ADHD (45) vs. psychiatric controls (64) vs. healthy controls (97)	6–11	Not medicated	ODD, CD, emotional disorders, other	Actigraphy, seven nights: Although parents of children with ADHD overestimated SOL, actigraphy revealed that these children had the highest SOL in comparison to psychiatric and healthy controls. Stratification into ADHD children with and without ODD revealed that ODD is not associated with increases in SOL in ADHD.	S: Control for co-morbidities such as ODD and anxiety.
Goraya et al., 2009[66]	ADHD (33)	3–6	48% of children were on stimulant medication	Not specified	PSG, one night: Increases in arousal index, wake after sleep onset, and daytime sleepiness; and decrease in sleep efficiency were observed in children with ADHD in comparison to reference values. Also, with a threshold value set at AHI $>$ 1/hour, 64% of children with ADHD met criteria for SDB.	S: Stratification of group into ADHD children with and without SDB revealed that ADHD children with SDB had increases in SOL, REM latency, wake after sleep onset, arousal index, and AHI; and decreases in REM percentage, SE, and O2 saturation W: One night of PSG. Also, neither co-morbidities nor medication status were controlled for.
Gruber et al., 2009[67]	ADHD (15) vs. controls (23)	7–11	Not medicated	Children with any psychiatric diagnosis excluded from study	PSG, one night: Decreases in the ADHD group with respect to TST and REM percentage. According to parental reports, children with ADHD had more sleep onset delays and anxiety compared to controls.	W: Relatively small sample size, and only one night of PSG

Owens et al, 2009[68]	ADHD (107) vs. controls (46)	6–14	Not medicated	While patients with ODD were included; patients with BD, affective or anxiety disorder, or a history of primary sleep disorders were excluded from the study.	Parent Reports: ADHD children had more difficulties getting up, transitioning in the evening, getting ready for bed and falling asleep. Child Diary Reports: ADHD children had more difficulties getting up in the morning, poorer sleep quality, and more daytime sleepiness. Actigraphy, five days: Although ADHD and controls did not differ in TST, ADHD children had decreased real sleep time, likely due to more interruptions during sleep.	S: In addition to comparisons of ADHD with healthy controls, sleep variables were compared in children with Mild/Moderate and Severe forms of ADHD; as well as in inattentive and combined subtypes of ADHD. However, no significant differences were found between the comparison groups. Child diary reports were included in the study thus avoiding complete reliance on parental reports.
Silvestri et al., 2009[69]	ADHD (55) vs. controls (20)	8.9 (±2.7)	Not specified	ODD, dyslexia, language disorder, tic disorder, eating disorder, and dyspraxia	PSG, one night: Compared to controls, ADHD children had decreases in TST, SE, and REM sleep; and increases in stage 3 NREM sleep, arousal index, and REM latency. When data were stratified into ADHD-I and ADHD-HI/C children, PLMS index was found to be higher in ADHD-HI/C children.	W: Although at least one night of video PSG was recorded in the study, it is not clear exactly how many nights each child was recorded for and, thus, whether the "first night effect" was taken into consideration when analyzing data. Also, medication status in the study sample was not specified, suggesting that the confounding effects of mixed medication status may have been an issue in data analysis. Lastly, although a percentage of the study sample suffered from various co-morbidities, they were not controlled for in data analysis.

AHI = Apnea hypopnea index, BD = bipolar disorder, CD = conduct disorder, DEX = dextro-amphetamine, DLMO = dim light melatonin onset, GAD = generalized anxiety disorder, LD = learning disability, MD = major depression, MPH = methylphenidate, MSLT = multiple sleep latency test, ODD = oppositional defiant disorder, PLMI = periodic limb movement index, RDI = respiratory disturbance index, REM = rapid eye movement, S1 = stage 1 sleep, SAD = separation anxiety disorder, SDB = sleep disordered breathing, SE = sleep efficiency, SOL = sleep onset latency, SOT = sleep onset time,TSP = total sleep period.

however, two studies reported increased variability in the standard deviations of sleep variables such as total sleep time and sleep onset time in children with ADHD, suggesting that sleep in these children is characterized by marked night-to-night instability.[13,58]

Although sleep studies in adult ADHD patients are scarce, it has been reported that adults with ADHD report subjective sleep problems such as non-restorative, poor sleep quality,[72] initial/middle insomnia,[71,73] restless sleep[72,73] and daytime sleepiness[20,70] (Table 3).

As with childhood ADHD, objective methodologies have yielded inconsistent findings in adult ADHD, and while one group reported no difference between ADHD subjects and controls,[76] other studies reported increased movement index[75]; and decreases in sleep onset latency,[77] sleep efficiency,[77,78] and REM sleep percentage (Table 4).[78]

PLMS

A number of studies have provided evidence that suggests an association between RLS/PLMS and ADHD in children. While two studies reported no differences in the frequency of periodic limb movement in ADHD compared to controls,[35,61] five studies reported more frequent RLS, PLMS, or limb movement during sleep in ADHD.[52,57,79–81,92,93] In the adult population, there is only one published study of an increased frequency of RLS in ADHD*.[82]

SDB

Children with ADHD have more habitual snoring,[35] and increased apnea hypo-apnea index (AHI)[59] and respiratory disturbance index (RDI)[57] values compared to healthy controls. Although snoring has been reported in young adults with ADHD,[71] SDB has not been objectively assessed in adult ADHD*.

Circadian sleep disorders

The observation that sleep onset delays are common in subjects with ADHD led to the observation by Van der Heijden and colleagues[64] that dim light melatonin onset (DLMO), a reliable marker of circadian function,[83] is delayed in children with ADHD. Moreover Rybak and colleagues showed that in adults, the severity of ADHD related deficits strongly correlates with later circadian preference (evening types)[84]; and that morning bright light, which has phase advancing effects and improves seasonal mood symptoms, improves neuropsychological symptoms of ADHD and depression.[85] These studies provide a preliminary indicator that there may be a circadian sleep disorder in ADHD that is associated with a phase delay.

Differences between ADHD subtypes

Differences in sleep disturbances have been found between ADHD subtypes. LeBourgeois and colleagues compared subjective measures of sleep in healthy pediatric controls and children of the ADHD-I, ADHD-HI, and ADHD-C subtypes, and found that children with ADHD were sleepier than children without ADHD. Although no significant differences were found between subtypes, children of the inattentive subtype had a tendency to be sleepier than ADHD-HI and ADHD-C subtypes.[42] In another study, Mayes and colleagues found that ADHD-I children had increases in daytime sleepiness and sleep duration compared to ADHD-C children, who in turn had more sleep problems such as initial insomnia, restlessness and waking during sleep, and nightmares.[48] It should be noted that the study by LeBourgeois, compared to the study by Mayes, had a smaller sample size, which may account for the lack of

Table 3
Studies of sleep disturbances in adults with ADHD with subjective methods.

Authors, year of publication	Classification (sample size)	Mean age and/or Age range	Medication status	Co-morbidity	Major findings	Strengths (S) and/or weaknesses (W)
Sangal and Sangal, 2004[70]	ADHD (18) vs. subjects with complaints of snoring and sleepiness (38)	48.7 (±15.5) for sleep disorder patients 31.9 (±12.2) for ADHD	Not specified	Not specified	ADHD subjects had a significantly lower ESS score than sleep disordered subjects. With a mean score of 8.3, ADHD subjects did not meet criteria for EDS. ESS score was not found to correlate with inattention or hyperactivity/impulsiveness scores in ADHD subjects.	W: Relatively small sample size
Oosterloo et al., 2006[20]	ADHD (61) vs. narcolepsy (67) vs. Idiopathic Hypersomnia (IH) (7)	48.45 (±16.21) for IH patients 34.98 (±10.28) for ADHD patients	Not medicated at the beginning of the study	Not specified	Approximately 38% of ADHD patients met criteria for excessive daytime sleepiness (EDS), compared to 96% in HI patients.	W: Co-morbidities and medication status were not clearly specified or controlled for
Gau et al., 2007[71]	ADHD-I, subdivided into ADHD (53) vs. probable ADHD (486) vs. non- ADHD (1745); and ADHD-HI, subdivided into ADHD (16) vs. probable ADHD (130) vs. non- ADHD (2138)	19.3 (±2.7)	Not specified	Not specified	ADHD-I group: Differences reported in sleep need and number of sleep problems between ADHD, probable- ADHD and non-ADHD subgroups, with ADHD subgroup having the highest number of needed sleep hours and sleep problems, both current and lifetime. Significant sleep problems in ADHD and probable-ADHD subgroups included early and middle insomnia, sleep talking, nightmares, and snoring. ADHD-HI group: Differences reported in the number of sleep problems between ADHD, probable-ADHD, and non- ADHD subgroups, with ADHD subgroup having the highest number of sleep problems, both current and lifetime. Significant sleep problems in ADHD and probable-ADHD subgroups included early insomnia, sleep terrors, and snoring.	W: Though compelling due to the large sample size, the analysis of data could have yielded interesting results, had it been stratified so as to compare ADHD subtypes. Also, neither medication status nor co-morbidities were specified or controlled for in statistical analyses.
Schredl et al., 2007[72]	ADHD (120, out of whom 61 were medication or co-morbidity free) vs. controls (444)	34.78 (±10) for medicate d ADHD 35.3 (±10.8) for nonmedicate d ADHD 23.5 (±5.7) for controls	As noted. Medications included MPH, reboxitine, serotonin reuptake inhibitors, venlafaxine, tricyclic antidepressants and fenetyllin	As noted, including depression or dysthymia, anxiety, tic disorder, OCD, and current substance abuse	In comparison to controls, ADHD subjects had lower sleep quality, un-refreshing sleep, insomnia, increased SOL and nocturnal awakenings, problems with sleep quality and sleep/wake patterns, nocturnal breathing disorders, parasomnias, movement disorders, and felt more tired during the day. Of note, movement disorders, insomnia, problems with sleep quality and sleep/wake disorders, parasomnnias, and tiredness during the day were found to be associated with depression scales, rather than with ADHD scales; while comorbidity with depression appeared to be associated with insomnia, poor sleep quality, and feeling un-refreshed in the morning. Medication status did not appear to affect the presence or severity of sleep problems.	S: Multiple statistical analyses taking into consideration comorbidities, severity of comorbidities, and medication status.
Surman et al., 2008[73]	ADHD (182) vs. controls (117)	18–55	Not specified	MDD, mania, separation anxiety, agoraphobia, panic disorder, OCD, GAD, specific phobias, PTSD, social phobia, and substance use	Compared to controls, ADHD subjects had more difficulties going to sleep, waking up in the morning, restless sleep, sleep talking, nightmares, and repetitive actions in sleep; and increases in sleep latency, nocturnal awakenings, and daytime sleepiness. Controlling for medication status and co-morbidities, it was found that the associations between ADHD and sleep disturbances still hold.	S: Co-morbidities and medication status were taken into consideration in statistical analyses
Caci et al., 2009[74]	ADHD (204)	Adults 42.18 (±11.46) Students 27.33 (±8.81)	Not specified	Not specified	A negative association was found between scores for the CSM and inattention in the ASRS, suggesting that there may be ADHD subtype differences with respect to circadian preference, with the inattentive subtype being more of an evening type.	W: No specification of medication status or co-morbidities

ADHD = attention-deficit/hyperactivity disorder, ADHD-C = ADHD of the combined subtype, ADHD-H/I = ADHD of the hyperactive/impulsive subtype, ADHD-I = ADHD of the inattentive subtype, ASRS = adult self report scale, CSM = composite scale of morningness, EDS = excessive daytime sleepiness, ESS - Epworth sleepiness scale, IH = idiopathic hypersomnia, GAD = generalized anxiety disorder, MDD = major depressive disorder, MPH = methylphenidate, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder.

Table 4
Studies of sleep disturbances in adults with ADHD with objective methods.

Authors, year of publication	Classification (sample size)	Mean age and/or Age range	Medication status	Co-morbidity	Major findings	Strengths (S) and/or weaknesses (W)
Kooij et al., 2001[75]	ADHD (8) vs. controls (8)	21–44	All subjects started medication free. Then, 7 patients were treated with MPH, and one patient was treated with DEX	Dependent personality disorder, dysthymia, eating disorder, borderline personality disorder, MDD	Actigraphy, six nights: At baseline, ADHD subjects had poorer sleep quality and increased activity level and movement index in comparison to controls. After three weeks of medication, sleep quality improved, and movement index decreased in ADHD subjects.	W: Given the small sample size of this study, it is difficult to ascertain what the role of co-morbidities is in the sleep disturbances. Also, the fact that the mean activity level increased in the control group after 3 weeks somewhat undermines the significant differences found between baseline and week 3 in the ADHD group. It should be noted, however, that to account for the small sample size of this study, authors set the level of statistical significance at 0.10.
Phillipsen et al., 2005[76]	ADHD (20) vs. controls (20)	33.45 (±8.94) 22–55	Not medicated	Lifetime, but not current, history of drug abuse, BRD, MDD, agoraphobia, bulimia nervosa	PSG, two nights: No differences between ADHD and control subjects. Subjectively, adults with ADHD reported poorer sleep quality, lower restorative value of sleep, worse mood in the evening, and more fatigue and psychosomatic symptoms during sleep onset.	S: The data for two nights of PSG were used in statistical analysis to assess night (adaptation and baseline) and group (ADHD and controls) interactions. W: Relatively small sample size.
Boonstra et al., 2007[77]	ADHD (33) vs. controls (39)	37 (±10)	MPH for drug trial	Depression and anxiety	Actigraphy, seven nights: ADHD subjects had lower SE and increased SOL compared to controls. Effects of MPH treatment included decreases in nocturnal awakenings, time in bed, actual sleep; increased sleep onset latency; and delayed sleep bedtime. Correlation tests revealed no associations between comorbidities and sleep variables.	
Sobanski et al., 2008[78]	ADHD (34) vs. controls (34)	35 (±9)	10 ADHD patients were treated with MPH as part of the study	Combined motor and tic disorder, social phobia, and dysthymia, all mild forms	PSG, two nights: In comparison to controls, all ADHD subjects had decreased SE and REM sleep; and increased nocturnal awakenings and stage 1 sleep percentage. ADHD subjects free of comorbidities exhibited lowered SE, duration of first REM sleep period, and REM sleep percentage; and higher nocturnal awakenings and percentage of sleep in the wake state were reported. After a four week treatment with MPH, ADHD subjects showed improvements in SE and decreased SOL.	S: The effects of medications and co-morbidities on sleep disturbances and complaints in ADHD were well controlled for.

DEX = dextro-amphetamine, BRD = brief recurrent depression, MDD = major depressive disorder, MPH = methylphenidate, PSG = polysomnography, REM = rapid eye movement, SE = sleep efficiency, SOL = sleep onset latency.

significant differences between subtypes in LeBourgeois' study. Finally, in a PSG study in ADHD children and controls by Silvestri and colleagues, stratification of data into ADHD-I and ADHD-HI/C revealed that the latter have more periodic limb movements per hour.[69]

There are no available data on sleep differences between adult ADHD-I and ADHD-C subtypes. However, it has been reported that sleepiness is associated with inattentiveness in young adults,[71] and that adult ADHD-I subtypes tend to have a later circadian preference. These findings suggest a circadian phase delay in adults of the inattentive subtypes.[74]

Discussion

The studies discussed in the previous sections provide evidence that patients with sleep disorders can display ADHD-like symptoms and, alternatively, that patients with ADHD can suffer from sleep disturbances characteristic of sleep disorders. However, despite the relative abundance of research in this area, there remain many unanswered questions regarding sleep disturbances in ADHD. Some issues include: i) whether there are objectively verifiable sleep disturbances in ADHD; ii) whether sleep disturbances are intrinsic to ADHD; and iii) if ADHD is co-morbid with a sleep disorder, what biological/physiological mechanisms account for such co-morbidity.

Are there sleep disturbances in ADHD?

As discussed in "Sleep disorders in ADHD", there have been two prominent issues with regards to sleep disturbances in ADHD: i) subjective reports of sleep disturbances have not been consistently verifiable by objective methods, and ii) there has been variability in reports of objectively measured sleep variables.

Discrepancies between subjective and objective data

In children, the discrepancy has been suggested to be caused by a possible tendency of parents/guardians of children with ADHD to over-report problems, perhaps as a result of increased sensitivity to behavioral problems in these children[44,51,62]; while in adults, it has been proposed that subjects with ADHD may attribute daytime sleepiness to poor sleep quality, which may not necessarily be the case.[76]

While the discussion above suggests that subjective methods may not be reliable tools for the detection of sleep problems, to discard subjective data altogether would be to disregard the experience of the patient. Objective methods are not without flaws either. Changes in sleep architecture cannot be detected with actigraphs, and PSGs can produce similar findings in normal sleepers and in those who suffer from insomnia, whose complaints of non-restorative and poor quality sleep are believed to be the result of sleep fragmentation.[86] By regular standards, sleep fragmentation is assessed by the presence of arousals. Parrino et al. argued that the inability to detect differences between normal sleepers and insomnia patients may stem from using only the quantification of arousals as a rendition of fragmented sleep.[87] While arousals are identified by a rapid shift towards more rapid EEG frequencies; K-complexes, K-alpha complexes, and delta bursts, are slow phasic activities that do not qualify as arousals, and thus, are not reported by conventional PSG analyses.[88] This is important because the distribution of these activities, represented by the cyclic alternating pattern (CAP) rates, is crucial to the maintenance of sleep. In fact, it has been shown that while the number of arousals is comparable in normal sleepers and in patients with insomnia, CAP rates correlate with subjective estimates of sleep in those complaining of insomnia.[87] Thus, Parrino et al. argue that micro-structure sleep variables of PSG such as CAP rates may have higher validity than measurement of sleep macro-structure variables (number of awakenings/arousals). In line with this, it has been reported that while no differences are found in sleep architecture by macro-structure standards between ADHD and control groups, CAP rates are lower in the ADHD group, suggesting a condition of hypo-arousal in ADHD.[110]

Another issue associated with PSG is the "first night effect". The use of numerous electrodes and wires in PSG studies produces an unfamiliar sleep environment for the study subjects, which has a distorting effect on sleep on the first night of recordings. This is called the "first night effect".[89] To mitigate for this, many sleep laboratories resort to using two or three nights of PSG recordings, discarding the data from the first night, as subjects acclimatized to their new surroundings would produce PSG recordings that are more representative of their habitual sleep on the second and third nights of recording.[90] This emphasizes the importance of carrying out at least two nights of PSG in research studies when sleep quality is evaluated. However, only nine out of fourteen studies collected PSG data from two or more nights of recordings,[53–55,57,61,65–67,69] making it difficult to interpret the findings (Tables 2 and 4).

Discrepancies between objective studies of sleep in ADHD

In both childhood and adult studies, the fact that different groups have reported different sleep disturbances has made the understanding of the relationship between sleep disorders and ADHD more difficult. In studies of childhood ADHD, the discordance is partly due to flaws in research methodology. Factors related to statistical power, differences in inclusion/exclusion criteria, differences in subjective (different questionnaires) and objective (actigraphy vs. PSG) methods used, or the number of nights of recordings, and unsatisfactory control of confounding variables such as age, co-morbidity, and medication status have made it difficult to make comparisons between studies so as to draw conclusions about the relationship between sleep disorders and ADHD[39,68,91–93] (see Table 1, 2, 3, and 4 for detailed descriptions of study designs).

Specific to the adult population, the scarcity of published data has been a central issue. While insomnia, changes in sleep architecture, EDS, PLMS, SDB, and delayed sleep phase syndrome (DSPS) have been reported in children with ADHD, it is currently not known whether there are similar sleep problems in adults. If the reports of childhood ADHD are any indication, however, adult ADHD is expected to be associated with as much diversity in the reports of sleep disturbances/disorders as childhood ADHD.

The diversity of reports, however, also reflects the complexity of ADHD. That ADHD is associated with multiple sleep disturbances, multiple co-morbidities, and multiple symptoms, suggests that ADHD may in fact encompass a number of disorders. Just as ADHD, CD, and ODD were once clumped together under the rubric of "moral imbecility", perhaps ADHD as we know it today is the composite of a number of disorders. As such, the disparity of reports of sleep disturbances in ADHD may reflect the fact that a patient who presents with, for example, ADHD and RLS has a form of ADHD that is etiologically different from a patient that presents with ADHD and decreased REM sleep. The idea that ADHD is a common denominator for a number of related disorders may be manifest in the fact that ADHD is sub-classified as ADHD-I, ADHD-HI, and ADHD-C. The subtypes are known to differ, not only in the presentation of symptoms, but also in the presentation of co-morbidities. As such, it has been reported that individuals with ADHD-C are more prone to develop co-morbidities such as anxiety, depression, and drug addiction.[78,94,95,97] Differences in cognitive performance have also been documented, as children with ADHD-I are associated with slower cognitive tempo, under-arousal, and under-activity.[96] As such, it has been proposed that ADHD-I may be

associated with neurophysiologic under-arousal, while the ADHD-HI/C may be associated with overactive neurophysiologic processes.[42,48]

The observation that the ADHD-I subtype is associated with under-arousal, and the ADHD-HI/C subtype is associated with higher levels of energy is interesting in the context of sleep disorders, because arousal levels may directly relate to sleep disorders.[34] As such, it has been proposed that a problem of under-arousal in ADHD-I may be accountable for the excessive daytime sleepiness and hypersomnia seen in children with ADHD-I, whereas a problem of over-arousal in ADHD-HI/C may be accountable for difficulties initiating/maintaining sleep, and RLS seen in children with ADHD-HI/C.[42,48,69]

Are sleep disturbances intrinsic to ADHD?

Some investigators have argued that sleep disturbances are not intrinsic to ADHD, and that they only occur in the presence of co-morbidities such as ODD, depression or anxiety, as a result of an underlying primary sleep disorder, or as a result of stimulant medication use.

While reports that stimulant medications affect sleep latency, sleep quality, and total sleep time[38,39,41,98–101] can undermine the results of some of the studies described above,[20,35,42–45,53,54,66,69–71,74] it should be noted that well-controlled studies have demonstrated that sleep problems exist in medication-free ADHD patients,[13,14,34,40,47,48,58,60,63,64,68,72,73,75,78] which suggests that sleep disorders are not exclusively associated with the use of stimulant medication. Moreover, there have been reports of improvements in sleep quality in medicated ADHD patients.[75,78]

The issue of co-morbidities is controversial as it has been proposed that sleep disturbances in ADHD are attributed to co-morbid mood disorders such as ODD, anxiety, and depression.[38,39,41,48] The link between mood disorders and sleep disturbances has had a long standing history of research. Total REM sleep, for instance, has been reported to be increased in depressed patients[102]; and either total or REM sleep deprivation have been reported to result in acute antidepressant effects.[103] Circadian cycles are also reported to be affected in depressed patients, for whom elevated nocturnal body temperature, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and lower blood levels of melatonin have been reported.[104,105]

While the link between mood disorders and sleep disturbances is undisputed, mood disorders are also well known to be common co-morbidities of ADHD.[8,9,39] Studies have shown that 20–37% of subjects with ADHD suffer from co-morbid depression, and 32% suffer from co-morbid anxiety disorders.[106] The extent to which mood disorders can be separated from ADHD, however, is not clear. For instance, serotonergic pathways are altered in ADHD,[7] which may account for the high incidence of depression in ADHD. From an etiological viewpoint, it is difficult to determine whether symptoms of depression and anxiety are part of the ADHD symptomatology, or whether mood disorders are co-morbidities of ADHD. If mood disorders are part of the ADHD symptomatology, the sleep disturbances associated with mood disorders could be argued to be intrinsic to ADHD as well.

As mentioned earlier, arguments have also been put forward that sleep disturbances are not intrinsic to ADHD, but the result of an underlying sleep disorder. If there is an underlying sleep disorder in ADHD that accounts for the sleep disturbances, the possibility exists that such sleep disorder may also account for some ADHD-like symptoms. The array of studies discussed in "ADHD-like symptoms in sleep disorders", documenting the manifestation of ADHD-like symptoms in patients with primary sleep disorders, suggests that in a proportion of patients diagnosed with ADHD, misdiagnosis may be an issue. The similarity in the presentation of symptoms between ADHD and sleep disorders can make it difficult to discriminate one condition from the other. That misdiagnosis can occur is best illustrated by the studies of Walters et al.[107] and Huang et al.[108] Walters et al.[107] reported that out of 7 children with ADHD and co-morbid RLS, 3 no longer met criteria for ADHD after RLS was treated; while Huang et al. reported that in ADHD children with mild OSA ($1 > AHI > 5$), tonsillectomy led to more improvements in attention span and impulse control than treatment with methylphenidate.[108] Also, studies have shown that adenoidectomy and tonsillectomy in children with obstructive breathing problems in sleep result in significant improvements on measures of attention and behavioral problems such as aggression and hyperactivity[109,110], and a case study on misdiagnosis of OSA for ADHD in adults has been published.[111]

While the overlap of symptoms in sleep disorders and ADHD may give rise to problems with misdiagnosis, it also highlights the importance of sleep in ADHD. As mentioned earlier, sleep plays a pivotal role in cognitive function. For instance, the process of long-term memory consolidation is compromised in the absence of sleep, and higher order executive functions that require impulse control have been reported to be profoundly affected by sleep deprivation. Given that ADHD is characterized by deficits in cognitive functions such as attention and impulse control, there is a possibility that sleep disorders may exacerbate the symptoms of ADHD. However, given the lack of studies comparing tasks of cognitive function in ADHD patients with sleep disorders and ADHD patients without sleep disorders, it is difficult to determine the extent to which sleep disturbances can affect ADHD symptoms. There are some data, however, that suggest that the cognitive deficits seen in ADHD may occur independent of sleep problems. For instance, in the study by Gruber and Sadeh,[58] ADHD patients and healthy controls were assessed on variables of sleep such as quantity, quality, and variability with actigraphy; and on neurobehavioral function on simple and complicated tasks. While neurobehavioral function was lower in the ADHD group, a canonical correlation analysis revealed that the deficit was not associated with sleep. On the other hand, in the control group, neurobehavioral function for complicated tasks was directly associated with sleep variables, suggesting that the relation between sleep fragmentation and cognitive function is different in ADHD patients and healthy controls.[58] Moreover, as discussed in "Hypersomnia" in the section "ADHD-like symptoms in sleep disorders", Oosterloo and colleagues compared daytime sleepiness and ADHD symptoms in patients with ADHD and in patients with EDS and found that patients with ADHD met criteria for EDS, while patients with EDS met criteria for ADHD.[20] Interestingly, an association was found between inattention scores and ESS measures in patients with EDS, but no such correlation was found in patients with ADHD, suggesting that although the two patient groups share common characteristics such as sleepiness and inattention, the mechanisms underlying the manifestations of such symptoms may differ between the two groups.[20]

While the studies described above suggest that the cognitive deficits in ADHD occur independent of sleep problems, given the paucity of studies specifically investigating cognitive performance as a function of sleep in ADHD, it should not be concluded that sleep deficits have no effect on ADHD symptomatology.

If ADHD is co-morbid with a sleep disorder, is there a mechanism accountable for such co-morbidity?

ADHD and sleep disorders are two conditions for which differential diagnosis is complex when patients with ADHD also display symptoms of a sleep disorder. The overlap of symptoms in sleep disorders and ADHD highlights the possibility that common

mechanisms may exist that give rise to both sleep disorders and ADHD. From a structural point of view, some areas of the brain that are affected in ADHD are the very same structures that are involved in the regulation of sleep. Activation of areas of the cortex by the midbrain and locus coeruleus (LC) is required for sustained attention, alertness, and discrimination of salient features.[4,6,112] Attention and alertness, in turn are properties that define the wake state. Cycling through the wake state and sleep state is an autonomically governed process that reflects changes in brain arousal.[113] In ADHD, subjects appear to have problems with arousal; and deficits in cortical functioning have been reported.[114] Thus, in ADHD, it has been proposed that problems with attention and alertness, and problems with sleep such as insomnia or hypersomnia, may be the results of abnormal cortex arousal function.[34,114] In this respect, it could be argued that sleep disturbances are part of the ADHD symptomatology.

Proposals have also been put forward, attempting to explain the co-morbidity of ADHD with primary sleep disorders such as SDB and RLS/PLMS. In SDB, it has been proposed that in addition to sleep fragmentation, alveolar hypoventilation and intermittent hypoxia affect catecholamine and glutamate signaling pathways in the prefrontal cortex (PFC).[115–117] Some of these respiratory disorders may cause irreversible changes that affect cognition even after the respiratory disorder has resolved, and may contribute to ADHD pathology. The permanent deleterious effects of intermittent hypoxia on measures of development such as intelligence quotient (IQ) and vocabulary have been excellently reviewed elsewhere.[118]

With respect to PLMS in RLS, initial interest in the RLS co-morbidity with ADHD developed because the two disorders are characterized by iron deficiency in some individuals. The nature of the deficit, however, differs between the two disorders. In RLS, dopaminergic deficiency is caused by inadequate dopamine synthesis, evidenced by the effectiveness of dopamine precursor L-Dopa and dopamine receptor agonists in ameliorating the disorder.[119] In ADHD, dopaminergic deficiency is thought to be caused by increased clearance of the neurotransmitter and abnormal signaling of the dopamine receptor. This is supported by the observed effectiveness of drugs such as methylphenidate and dextro-amphetamine, both of which act by inhibiting the reuptake of dopamine, thus prolonging the time that dopamine remains at the synapse.[120]

Recently, some groups have focused on iron, as it affects both dopamine synthesis and dopaminergic signaling. Both RLS/PLMS and ADHD have been reported to be associated with lower ferritin levels.[81] Ferritin is a protein that carries iron inside the cell, and thus, is a measure of intracellular iron levels. Low iron levels may result in reduced dopamine synthesis and abnormal dopaminergic signaling, thus resulting in RLS/PLMS and ADHD comorbidity.[81] In line with this hypothesis, it has been reported that ADHD children with low serum ferritin levels ($<$45 μg/l) present with more severe ADHD symptoms and problems with sleep-wake transitions.[121] Moreover, iron supplementation reportedly results in significant improvement in ADHD symptoms.[122]

Although circadian sleep disorders have not been investigated extensively in ADHD (see "Circadian sleep disorders" in the section "Sleep disorders in ADHD"), there is evidence to suggest that subjects with ADHD may have a sleep phase delay. This is relevant in ADHD because proper alignment of the circadian cycle is crucial for proper executive function. For instance, being awake during the biological night is believed to have deleterious effects on alertness, mood, and performance. Moreover, sleep inertia, described as impaired cognitive performance immediately upon awaking, is 3.6 times larger during the biological night[123]. Interestingly, diurnal cortisol secretion has been reported to be abnormal in over half of the participants in a study investigating HPA axis function in children with ADHD.[124] Given the importance of diurnal cortisol secretion in maintaining wakefulness and alertness, and the studies described in "Circadian sleep disorders" in the section "Sleep disorders in ADHD"; the issue of circadian sleep disorders in ADHD merits further research.

Sleep disorders and ADHD – clinical implications

Given the poor understanding of the relationship between sleep and ADHD, it is difficult to determine the extent to which sleep disturbances are accountable for the core symptoms of ADHD, namely, the cognitive deficits exclusively associated with ADHD. ADHD, however, is a condition that is closely associated with problems in lifestyle management, in which sleep plays a central role because a bulk of the associated symptoms of ADHD such as procrastination, and problems with mood, motivation, and energy may be traced back to sleep problems. For instance, sleep affects mood, which may in turn affect attention and motivation. Sleep can also affect energy, which may in turn affect, not only motivation, but also performance at school or in the workplace. Moreover, sleep problems are in many cases the result of procrastination, where the ADHD patient's poor time management problems lead to the extension of work hours into the sleep hours, thus perpetuating the chronic symptoms of mood and sleep history.

The management of sleep problems in the ADHD patient is thus desirable and it should begin with the patient's commitment to change a life of bad habits. Good sleep hygiene practices such as turning off stimuli like TVs or computers at least an hour prior to bedtime, and the adoption of a regular bedtime routine that allows the patient to "wind down" should be encouraged. These practices may be complemented with sleep diaries to keep track of bedtimes and rising times, as well as logs of activities done prior to bedtime.

When sleep problems persist in the face of good sleep hygiene practices, it is recommended that the patient be referred to do a PSG, and if the patient is afflicted by ADHD-sleep disorder co-morbidity, that open communication be maintained with a sleep specialist to tailor a treatment plan appropriate for the patient. Given the possibility that sleep disorders may give rise to- or exacerbate ADHD symptoms, it may be beneficial to first attempt to treat the sleep disorder and assess whether such route of action leads to any improvements in daytime function. This will not only minimize the chance of misdiagnosis, but may also aid in the dose-optimization of ADHD medications.

As a final note, it is important to remind the readers that, although not extensively discussed in this review, the possibility exists that ADHD medications may exacerbate some of the sleep problems in ADHD. For such cases, options for long-acting medications exist, with different time release profiles - the physician may need to explore these options, as well as conduct a thorough assessment of the patient's timetables and lifestyle, and construct a treatment plan accordingly.

The future of research in sleep disorders and ADHD

Sleep disorders have clinical implications in ADHD because the two disorders may be misdiagnosed, may exacerbate the symptom characteristics of the other condition, and/or may have common underlying neurological mechanisms. Currently, the research of sleep disorders in ADHD is not advanced, and amid research of variable quality, more research needs to be done. The following are some suggestions as to what direction should be taken in future research.

A "holistic" approach to the study of sleep in ADHD

The field of sleep research is relatively new, and our understanding of sleep – its role, architecture, physiological changes,

neurochemical pathways involved – is only partially known. Thus, the understanding necessary to objectively discriminate important from unimportant sleep variables is poor and the validity of using only one objective tool can be questionable given the complexity of sleep. Although PSGs are reportedly the gold standard in assessing sleep architecture, they are not without flaws see "Discrepancies between subjective and objective data". Most importantly, processes occur during sleep, which are not detected by PSG or actigraphy. Such processes include, among others, changes in levels of hormones such as growth hormone (GH), cortisol, and ACTH, changes in core body temperature and temperature regulation, and the activation of different brain structures[125]. As a result, when sleep is investigated, a more "holistic" approach - collection of information on sleep measures related to changes in body temperature, and sleep-wake cycle hormone levels and their relation to circadian cycles may be key in better understanding sleep disturbances associated with ADHD.

Stardardized inclusion/exclusion criteria across all new research studies

The diversity of published results suggests that studies need to be carried out with well-controlled, well defined groups of comparison. Factors such as medication status, co-morbidities, ADHD subtype, and circadian preference need to be taken into account. Moreover, it is important to determine the role that these confounding factors play on the development of sleep disturbances in ADHD. For instance, in light of the growing body of evidence on differences between ADHD subtypes, it seems necessary to conduct studies investigating sleep differences between ADHD subtype by objective methodologies in both children and adults. Also, investigating the role of co-morbidities such as anxiety and mood disorders in the development of sleep disturbances is important. This may be achieved by means of studies designed to better characterize symptoms exclusively associated with ADHD, symptoms exclusively associated with anxiety or mood disorders, and symptoms exclusively associated with co-morbid ADHD and anxiety or mood disorders. In conducting such studies, collaborations between groups specializing in different aspects of disease – that is, clinical, behavioural, and molecular – may be beneficial in the interpretation of results.

An approach to better characterize and differentiate ADHD from co-morbidities

Since the problem of misdiagnosis stems from an overlap of symptoms in sleep disorders and ADHD, research studies designed to investigate the differences between sleep disturbances in ADHD and sleep disorders is necessary. Studies should be designed to compare ADHD, sleep disorders, and sleep disturbances in ADHD, so that the exclusiveness of symptoms to each condition may be elucidated. In a study adopting such approach, Huang et al.[59] compared children with ADHD to children with ADHD and OSA co-morbidity and reported differences such as decreased REM sleep and increased stage 4 sleep in ADHD children with OSA co-morbidity. This kind of approach is helpful not only in characterizing each condition: ADHD, sleep disorders, and sleep disturbances in ADHD; but also in investigating the ways in which sleep disturbances affect cognitive functioning in ADHD patients. Although it has been reported that there is an association between ADHD severity and severity of sleep disturbances,[22,28] it is not clear whether sleep disturbances negatively affect ADHD symptoms, or whether sleep disturbances only appear in more severe cases of ADHD. As such, studies designed to investigate the contribution of sleep disturbances to the cognitive deficits seen in ADHD will be beneficial in assessing possible etiological factors contributing to the severity and symptomatology of ADHD.

Conclusion

The ADHD population appears to be a heterogeneous mixture of patients with: i) sleep disturbances, ii) patients without sleep disturbances, and iii) patients who have been misdiagnosed as having ADHD when the primary problem is a sleep disorder. Our understanding of sleep disturbances/disorders in ADHD is far from comprehensive. In this review, we have discussed some issues regarding the complexities of ADHD and sleep disorders. Most importantly, problems still remain as to how to differentiate sleep disorders from sleep disturbances in ADHD, and before the research of sleep disturbances/disorders in ADHD can progress, the nature of sleep disturbances needs to be characterized and well defined. Research methodologies that are based on careful inspection of symptoms exclusively associated with each condition will enable us to discriminate sleep disorders from ADHD. Only then, can possible neurological mechanisms underlying sleep disturbances in ADHD be explored.

Practice points

1) Subjects who suffer from sleep disorders such as excessive daytime sleepiness, restless legs syndrome, periodic limb movement in sleep, sleep disordered breathing, and obstructive sleep apnea have been reported to exhibit symptoms of attention-deficit/hyperactivity disorder.
2) Alternatively, studies have shown that both children and adults with ADHD exhibit symptoms of periodic limb movements in sleep, and sleep disordered breathing. Also, children and adults with ADHD have been reported to suffer from initial and middle insomnia, fractured and/or shortened sleep, and altered sleep architecture.
3) Although most studies have revealed sleep problems exist in ADHD, different studies have yielded different findings. As a result, determining the nature of the sleep disturbances in ADHD – and the relationship between sleep disorders and ADHD – has been difficult.
4) The similarity of symptoms in sleep disorders and ADHD suggests that: i) Misdiagnosis may be common, ii) different forms of ADHD may exist.
   i) Misdiagnosis: Given that sleep disorders and ADHD can give rise to similar symptoms, it is possible that patients with sleep disorders may be misdiagnosed with ADHD and vice-versa. This possibility raises questions about the effectiveness of diagnostic tools for differentiating sleep disorders from ADHD and vice versa.
   ii) Different forms of ADHD: Although misdiagnosis may be an issue, the similarity of symptoms between sleep disorders and ADHD is suggestive of underlying mechanisms that may link sleep to ADHD. As such, mechanisms have been proposed to account for co-morbid ADHD and restless legs syndrome, ADHD and sleep disordered breathing, and ADHD and delayed sleep onset. The possibility that such mechanisms may exist is indicative of the complexity of the etiology of ADHD, as a number of factors may contribute to the manifestation of different forms of ADHD. As such, the classification – and treatment – of ADHD, may be dependent on the kind of sleep disorder it is associated with.

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