Article

Sleep and Circadian Rhythmicity in Adult ADHD and the Effect of Stimulants: A Review of the Current Literature

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Abstract

Objective: This review updates information on sleep and circadian rhythmicity in adult ADHD, especially circadian rhythmicity and the influence of stimulants. **Method:** Investigations into sleep, chronotype, and circadian rhythm in adult ADHD were searched in the Cochrane Library, Embase, Medline, and PsycInfo databases. **Results:** ADHD in adults is associated with longer objective sleep latency, irrespective of insomnia complaints. Sleep maintenance is disturbed and waking up time is delayed. Adult ADHD is associated with increased eveningness, delayed dim light melatonin onset (DLMO), and later waking up time. Stimulant treatment induces delay of nonparametric circadian parameters, whereas light therapy (LT) induces shifts toward morningness, which is associated with a reduction of ADHD symptoms. **Conclusion:** Adult ADHD is associated with delayed circadian rhythmicity and analogous sleep characteristics, which are typical of a delayed sleep phase disorder. Stimulants induce delay of circadian rhythmicity. *(J. of Att. Dis. 2017; 21(1) 14-26)*

Keywords

ADHD, sleep, circadian rhythm, psychostimulants

Introduction

ADHD is a common psychiatric disorder characterized by persistent symptoms of inattention, hyperactivity, and impulsive behavior, starting in early childhood. In 46% to 66% of patients, ADHD persists into adulthood (Barkley, Fischer, Smallish, & Fletcher, 2002), resulting in a prevalence of 4.4% in adults in the United States (Kessler et al., 2006) and 3.4% in a group of 11,422 people in the general population in 10 countries in the Americas, Europe, and the Middle East (Fayyad et al., 2007).

ADHD frequently co-occurs with primary sleep disorders such as restless legs syndrome, sleep apnea, and insomnia (Walters, Silvestri, Zucconi, Chandrashekariah, & Konofal, 2008). In addition to these primary sleep disorders, increased nocturnal motor activity appears to be the only objective secondary sleep disturbance in adult ADHD (Philipsen, Hornyak, & Riemann, 2006; Roth & Zinsenheim, 2009), but impaired subjective sleep quality is also related to ADHD in adults (Boonstra et al., 2007; Philipsen et al., 2005; Schredl, Alm, & Sobanski, 2007). Roth and Zinsenheim (2009) reviewed the literature on the effect of stimulants on sleep in adult ADHD. They concluded that in general, stimulant treatment does not worsen sleep parameters, but rather improves them.

In children with ADHD, sleep onset insomnia (SOI) has been described as a component of circadian rhythm problems (Walters et al., 2008). For example, salivary dim light melatonin onset (DLMO), a crucial marker of circadian phase, occurred at significantly later times in the evening in children with ADHD and SOI than in ADHD patients without insomnia (van der Heijden, Smits, van Someren, & Gunning, 2005).

Research on sleep in adult ADHD is increasingly focusing on the role of circadian rhythm and circadian preference (chronotype), as disturbances in circadian rhythm often result in sleep disturbances such as delayed sleep phase disorder (DSPD; Arendt, 2000).

Hypothetically, primary insomnia (sleep onset or sleep maintenance), secondary insomnia due to ADHD symptoms, and chronobiological disturbances resulting in

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sleep onset problems may cause daytime sleepiness complaints in adult ADHD patients (Schredl et al., 2007; Surman et al., 2009), which are associated with higher number of symptoms of inattention (Mahajan, Hong, Wigal, & Gehricke, 2010).

Psychostimulant medication in adult ADHD reduces daytime dysfunction, such as trouble staying awake or lack of motivation (Adler, Goodman, Weisler, Hamdani, & Roth, 2009). It is most likely that the therapeutic effects of psychostimulants relate to the enhancing effect on central nervous system activity, particularly in cerebral regions important for higher order cognitive functions such as the prefrontal cortex. However, it is also possible that a positive effect of stimulants on sleep maintenance or a shift in circadian preference might be the underlying mechanism of the therapeutic effect.

In recent years, several studies on adult ADHD, sleep, and circadian rhythm have been published. Together with recent findings—such as that psychostimulants influence the circadian pacemaker activity (Bergheim, Yang, Burau, & Dafny, 2012)—they put previous findings in a new light. Therefore, we reviewed the literature to improve understanding of the influence of the circadian rhythm on sleep parameters in adult ADHD and the effect of stimulants.

The aim of this review is to answer the following questions:

1. Is adult ADHD associated with subjective increased sleep latency, disrupted sleep maintenance, difficulty waking up, and shorter total sleep time? Our hypothesis is that adult ADHD is associated with increased latency, difficulty waking up, disrupted sleep maintenance, and shorter total sleep time as a result.
2. Is adult ADHD associated with disturbed objective (polysomnographic and actigraphic) sleep parameters, that is, increased sleep latency, disrupted sleep maintenance, shorter total sleep time, and later waking up times? Our hypothesis is that adult ADHD is associated with disrupted objective sleep—increased latency, disrupted sleep maintenance, shorter total sleep time, and waking up later.
3. Does stimulant treatment increase sleep onset latency, decrease disrupted sleep maintenance, and help patients to wake up easier? Our hypothesis is that stimulant treatment increases sleep onset latency, decreases disrupted sleep maintenance, and helps patients to wake up easier.
4. Do adults with ADHD show differences in chronotype and circadian rhythm compared with control populations? Our hypothesis is that adults with ADHD have an evening circadian preference.
5. Does ADHD treatment shift the circadian preference to greater morningness? Our hypothesis is that ADHD treatment shifts the circadian preference to greater morningness.
6. Can the therapeutic effect of stimulant treatment be partly explained by its effects on sleep and circadian rhythm? Our hypothesis is that better sleep quality and more morningness as a result of stimulant treatment leads to a reduction of ADHD symptoms.

Method

We performed an Ovid search (Cochrane Library, Embase, Medline, PsycInfo) with the following keywords: ADHD, attention deficit disorder, attention deficit hyperactivity disorder, adult, sleep, chronotype, and circadian rhythm, for the years 1990 to 2011. This search produced 429 publications, which were screened for information on sleep in adult ADHD and/or chronotype/circadian rhythm in adult ADHD. Articles on the relationship between ADHD and primary sleep disorders only (except DSPD) were excluded because earlier reviews have already described that relationship (Philipsen et al., 2006; Walters et al., 2008). Studies primarily based on children were also excluded.

Results

We found 19 publications that met our criteria. We also checked the references of the articles for useful articles and relevant presentations from scientific conferences for the years 1990 to 2010. This yielded three additional articles. Two articles were excluded (Gau et al., 2007; Kass, Wallace, & Vodanovich, 2003) because no formal clinical diagnosis of ADHD had been made. Another study was excluded (Oosterloo, Lammers, Overeem, de Noord, & Kooij, 2006) because it only reported on daytime functioning, without data on sleep and circadian rhythm.

The 19 articles were divided into three groups (see Tables 1 to 3): (a) ADHD and sleep (Table 1), (b) ADHD/sleep and the effect of treatment (Table 2), and (c) ADHD and circadian rhythm, and the effect of treatment (Table 3).

ADHD and Sleep: Subjective and Objective Parameters

Design, Inclusion Criteria, and Endpoints of the Studies

Ten articles were found on ADHD and subjective sleep parameters, of which five (Baird, Coogan, Siddiqui, Donev, & Thome, 2011; Boonstra et al., 2007; Philipsen et al., 2005; Sobanski, Schredl, Kettler, & Alm, 2008; Van Veen, Kooij, Boonstra, Gordijn, & van Someren, 2010) also studied objective sleep parameters (Table 1). Six articles had not been reviewed before (Baird et al., 2011; Bijlenga et al.,

Table 1. ADHD and Sleep: Subjective and Objective Parameters.

Authors	Design	Female (%)	Age, *M* range (*SD*)	Diagnosis (number)	ADHD instrument	Exclusion disorders	Number	ADHD medication	Subjective sleep	Objective sleep	Duration of study
Subjective sleep parameters											
Dodson (1999) (abstract)[a]	Cross-sectional	—	>18 years	ADHD (217)	Lifelong *DSM-IV* criteria	—	217	Situation before stimulant treatment	Sleep log		
Schredl, Alm, and Sobanski (2007)	Case-control	Pat: 56 C: 85	Pat: 35.3 (10.8) C: 23.5 (5.7)	ADHD-C (46) ADHD-I (14) ADHD-H/I (1)	*DSM-IV* criteria BADDS (*M* = 76.6, *SD* = 24.5)	PC Med SD/U	Pat: 61 C: 444	None	SF-B LISST		
Surman et al. (2009)[a]	Case-control	Pat: 48 C: 53	Pat: 36.3 (10.8) C: 29.4 (8.6)	Full ADHD (107) late-onset ADHD (75)	SCID	ND (Major sensorimotor handicaps) PC (Psychosis, IQ < 80)	Pat:182 C: 117	Stimulants (57) Nonstimulants (4)	CSBS		
Mahajan, Hong, Wigal, and Gehricke (2010)[a]	Cross-sectional	18	29 (8.2)	ADHD-C (9) ADHD-I (10) ADHD-H/I (3)	Questionnaire (semistructured interview based on *DSM-IV*)	SD/U Pregnancy Med	22	None	PSQI		
Bijlenga et al. (2011)[a]	Case-control	Pat: 47 C: 65	Pat: 34.9 (10.6) C: 33 (13.6)	ADHD-C (168) ADHD-I (33) ADHD-H/I (1)	DIVA (child ≥6/9; adult ≥4/9) ADHD-RS	None	Pat: 202 C: 189	Pat: 36 C: 2	MCTQ		
Subjective and objective sleep parameters											
Philipsen et al. (2005)	Single-blind Comparative	Pat: 45 C: 45	Pat: 33.5 (8.9) C: 33.3 (8.8)	ADHD-C (20)	ICD-10 *DSM-IV* (≥12 symptoms for ADHD-C) WURS	PC (major depression, Axis II disorder) SD/U OSAS (apnea index > 5)	Pat: 20 C: 20	None	SF-A PSQI	PSG	2 nights
Boonstra et al. (2007)	Comparative	Pat: 52 C: 54	Pat: 37.9 (10.3) C: 37.8 (9.5)	ADHD-C (32) ADHD-H/I (1)	Semistructured interview based on *DSM-IV* for ADHD and comorbidity	Lab ND PC (unstable) Med (psychotropic)	Pat: 33 C: 39	None	Sleep log	Actigraphy	1 week
Sobanski, Schredl, Kettler, and Alm (2008)	Comparative	Pat: 38 C: gender-matched	Pat: 36.1 (9.3) C: age-matched	ADHD-C (28) ADHD-I (6)	Lifelong *DSM-IV* criteria Structured interview WURS (≥30 points) BADDS (≥50 points)	PC (Axis I: which required being treated with priority or could explain assessed symptoms) Working in night shift OSAS (apnea index > 5, obstructive snoring) Contr. ind. sti.	Pat: 34 C: 34	None for the last 28 days	SF-A SF-B	PSG	2 nights
Van Veen, Kooij, Boonstra, Gordijn, & Van Someren (2010)[a]	Comparative	Pat: 48 C: 50	SOI: 28.2 (7.6) No-SOI: 30.0(11.9) C: 29.1 (7.9)	ADHD-C (34) ADHD-I (6)	*DSM-IV* (child ≥ 6/9; adult ≥ 5/9) Semistructured interview for ADHD and comorbidity.	Med (sleep) Traveling within more than one time zone/shift work PC (severe) SD/U (alcohol/drugs)	Pat: 40 C: 24	None (≥30 days washout)	Sleep log	Actigraphy	1 week
Baird, Coogan, Siddiqui, Donev, and Thome (2011)[a]	Comparative	Pat: 39 C: 37	Pat: 31.3 (11.7) C: 32.3 (13.3)	ADHD	Structured clinical interview based on *DSM-IV* CAARS Adult ADHD Self-Report Scale WURS	PC (severe) shift work	Pat: 13 C: 19	Stimulants (3) Atomoxetine (1)	Sleep log	Actigraphy	1week

Note. ADHD = not specified; — = data not available; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994); pat = patients; C = controls; ADHD-C = ADHD–combined subtype; ADHD-I = ADHD–inattentive subtype; ADHD-H/I = ADHD–hyperactive/impulsive subtype; BADDS = Brown Attention Deficit Disorder Scale; PC = psychiatric comorbidity; med = medication use; SD/U = substance dependence or misuse (drugs and/or alcohol); SF-B = Schlaffragebogen B; LISST = Landecker Inventar zur Erfassung von Schlafstörungen; SCID = *Structured Clinical Interview for DSM* Disorders; ND = neurological disorders (tic disorder, and/or mental retardation, and/or organic brain disorder, and/or major sensorimotor handicaps); CSBS = Children's Sleep Behavior Scale; PSQI = Pittsburgh Sleep Quality Index; DIVA = Semistructured interview for ADHD in adults, based on *DSM-IV*; ADHD-RS = ADHD Rating Scale; MCTQ = Munich Chronotype Questionnaire; ICD-10 = International Classification of Diseases; WURS = Wender Utah Rating Scale; OSAS = obstructive sleep apnea syndrome (or symptoms); SF-A = Schlaffragebogen A; PSG = polysomnography; lab = laboratory blood investigation abnormalities; contr. ind. sti. = contraindications to the use of stimulant medication (seizures, cardiac problems, ECG abnormalities, hypertension, pregnancy, lactation); SOI = patients with sleep onset insomnia; no-SOI = patients without sleep onset insomnia; CAARS = Conners Adult ADHD Rating Scale.
[a]First reviewed.

Table 2. ADHD and Sleep: Subjective and Objective Parameters and Stimulant Treatment.

Authors	Design	Female (%)	Age, *M* range (*SD*)	Diagnosis (number)	ADHD instrument	Exclusion disorders	Number	ADHD medication	Subjective sleep	Objective sleep	Intervention	Duration of intervention	Duration of study
Subjective sleep parameters													
Dodson (1999) (abstract)[a]	Cross-sectional	—	>18 years	ADHD (217)	Lifelong *DSM-IV* criteria	—	217	Stimulants (Adderall, Dexedrine Spansule, Ritalin)	Sleep log		Stimulants (Adderall, Dexedrine Spansule, Ritalin)	≥6 months	
Adler, Goodman, Weisler, Hamdani, and Roth (2009)[a]	Double-blind, placebo-controlled, randomized, parallel-group	Pat: 44-49 Placebo: —	Placebo: 35.2 (10.9) LDX group: 34.2 (10.0)-35.8 (10.5)	ADHD (402)	Adult ADHD Clinical Diagnostic Scale ADHD-RS	PC SD/U Med (psychotropic)	Pat: 402 Placebo: 62	None	PSQI		LDX (30, 50 or 70 mg)	30 days	7 weeks
Surman and Roth (2011)[a]	Double-blind, placebo-controlled, randomized trial	Placebo: 48 LDX 30: 44 LDX 50: 44 LDX 70: 48 Total LDX: 45	Placebo: 35.2 (10.9) LDX 30: 35.3 (10.1) LDX 50: 34.2 (10.0) LDX 70: 35.8 (10.5)	Moderate to severe ADHD	*DSM-IV* criteria (≥6/9) Comprehensive psychiatric interview Adult ADHD Clinical Diagnostic Scale ADHD Rating Scale ≥ 28	PC (with significant symptoms) Contr. ind. sti. Med (affecting CNS of BP) Lab SD/U (positive urine drug results)	Pat: 420 Placebo: 62	7-28 days washout	PSQI		LDX (30, 50, or 70 mg) forced dose titration	4 weeks	4 weeks
Surman and Roth (2011)[a]	Double-blind, placebo-controlled, randomized trial	43	Placebo: 35.6 (9.8) Triple-bead MAS: 37.7 (9.7)	Moderate to severe ADHD	*DSM-IV* criteria (6/9) Psychiatric evaluation Adult ADHD Clinical Diagnostic Scale 1.2 ADHD Rating Scale ≥ 24	PC (with significant symptoms) Contr. ind. sti. Lab SD/U (positive urine drug results) ND BMI < 18.5 kg/m^2 Morbid obesity	Pat: 411 Placebo: 62	>28 days washout	PSQI		MAS (25, 50, 75 mg) forced dose titration	6 weeks	6 weeks
Subjective and objective sleep parameters													
Kooij, Middelkoop, van Gils, and Buitelaar (2001)	Open-label case-control study	Pat: 38 C: 50	Pat: 29.4 (8.2) C: 33.1 (7.2)	ADHD-C (7) ADHD-I (1)	Lifelong *DSM-IV* criteria Semistructured interview for ADHD and comorbidity Family report	None	Pat:8 C: 8	None for at least 8 weeks	Sleep log	Actigraphy	MF mean (range) 51 mg (15-90 mg), DA 30 mg	6 nights	3 weeks
Boonstra et al. (2007)	Double-blind, placebo-controlled, cross-over trial	Pat: 52 C: 54	Pat: 37.9 (10.3) C: 37.8 (9.5)	ADHD (31)	Semistructured interview for ADHD and comorbidity	Lab ND PC (unstable) Med (psychotropic)	Pat: 31 C: 39	None	Sleep log	Actigraphy	MF (Week 1: 0.5; Week 2: 0.75; Week 3: 1.0 mg/kg/day) mean 3rd week: 72.9 mg	3 weeks	7 weeks
Sobanski, Schredl, Kettler, and Alm (2008)	Open-label therapy study	0	35.0 (8.7)	ADHD-C (6) ADHD-I (4)	Lifelong *DSM-IV* criteria Structured interview WURS (≥30) BADDS (≥50)	PC (Axis I: which required being treated with priority or could explain assessed symptoms) Working in night shift OSAS (apnea index >5, or obstructive snoring) Contr. ind. sti.	10	None for the last 28 days	SF-A SF-B	PSG	MF mean (range): 36.7 mg (20-60)	At least 26 days	2 nights

Note. ADHD = not specified; — = data not available; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994); pat = patients; LDX = lisdexamfetamine dimesylate; ADHD-RS = ADHD Rating scale; PC = psychiatric comorbidity; SD/U = substance dependence or misuse (drugs and/or alcohol); med = medication use; PSQI = Pittsburgh Sleep Quality Index; contr. ind. sti. = contraindications to the use of stimulant medication (seizures, cardiac problems, ECG abnormalities, hypertension, pregnancy, lactation); lab = laboratory blood investigation abnormalities; MAS = triple-bead mixed amphetamine salts (Adderall); C = controls; ND = neurological disorders (tic disorder, and/or mental retardation, and/or organic brain disorder, and/or major sensorimotor handicaps); MF = methylphenidate; DA = dextroamphetamine; ADHD-C = ADHD–combined subtype; ADHD-I = ADHD–inattentive subtype; WURS = Wender Utah Rating Scale; BADDS= Brown Attention Deficit Disorder Scale; OSAS = obstructive sleep apnea syndrome (or symptoms); SF-A = Schlaffragebogen A; SF-B = Schlaffragebogen B; PSG = polysomnography; CAARS = Conners Adult ADHD Rating Scale.

[a]First reviewed.

Table 3. ADHD, Chronotype and Circadian Rhythm, Subjective and Objective Parameters, With and Without Treatment.

Authors	Design	Female (%)	Age, *M* range (*SD*)	Diagnosis (number)	ADHD instrument	Exclusion disorders	Number	ADHD medication	Subjective circadian variable	Objective circadian variable	Intervention	Duration of intervention	Duration of study
Subjective chronotype and circadian rhythm parameters													
Caci, Robert, and Boyer, (2004)[a]	Cross-sectional	0	22.8 (3.5)	ADHD-like temperament and character traits	TCI	None	129	—	CSM				
Rybak, McNeely, Mackenzie, Jain, and Levitan (2007)	Cross-sectional	48	40.4 (10.2)	ADHD-C (11) ADHD-I (14) ADHD-H/I (2)	WURS (>36) Lifelong symptoms with impairment CAARS ≥6/9 *DSM-IV* criteria or ≥3-5/9 (patients taking stimulants)	ND PC (suicidal ideation) SD/U Med (lithium/ phenothiazines)	29	Some	MEQ				
Caci, Bouchez, and Bayle, (2009)[a]	Cross-sectional	78	Students from a university: 27.3 (8.81); parents of children referred to a consultation for ADHD: 42.2 (11.5)	ADHD symptoms	ASRS	None	205 (students from a university: 167; parents of children referred to a consultation for ADHD: 38)	—	CSM				
Gruber, Oiveri, and Tong (2009)[a]	Cross-sectional	0	39.8 (—)	ADHD symptoms	CAARS	—	53	—	MEQ				
Bae et al. (2010)[a]	Cross-sectional	61	43.5 (14.2)	Potential ADHD ADHD symptoms	ASRS	PC (Axis I, SCID-IV)	344	—	MEQ				
Bijlenga et al. (2011)[a]	Case-control	Pat: 47 C: 65	Pat: 34.9 (10.6) C: 33 (13.6)	ADHD-C (168) ADHD-I (33) ADHD-H/I (1)	DIVA ADHD-RS	None	Pat: 202 C: 189	Pat: 36 C: 2	VOA MCTQ				
Objective circadian rhythm parameters													
Boonstra et al. (2007)[a]	Comparative	Pat: 52 C: 54	Pat: 37.9 (10.3) C: 37.8 (9.5)	ADHD-C (32) ADHD-H/I (1)	Semistructured interview for ADHD and comorbidity	Lab ND PC (unstable) Med (psychotropic)	Pat: 33 C: 39	None		Actigraphy			1 week

(continued)

Table 3. (continued)

Authors	Design	Female (%)	Age, *M* range (*SD*)	Diagnosis (number)	ADHD instrument	Exclusion disorders	Number	ADHD medication	Subjective circadian variable	Objective circadian variable	Intervention	Duration of intervention	Duration of study
Van Veen, Kooij, Boonstra, Gordijn, & Van Someren (2010)[a]	Comparative	Pat: 48 C actigraphy: 50 C DLMO: 47	18-55 SOI: 28.2 (7.6) No-SOI: 30.0 (11.9) C actigraphy: 29.1 (7.9) C DLMO: 28.9 (9.9)	ADHD-C (34) ADHD-I (6)	*DSM-IV* criteria (child ≥ 6/9; adult ≥5/9) Semistructured interview for ADHD and comorbidity	Med (sleep) Traveling within more than one time zone/shift work PC (severe) SD/U (alcohol/drugs)	Pat: 40 C actigraphy: 24 C DLMO: 38	None (≥30 days washout)		Actigraphy DLMO			1 week
Baird, Coogan, Siddiqui, Donev, and Thome (2011)[a]	Comparative	Pat: 39 C: 37	Pat: 31.3 (11.7) C: 32.3 (13.3)	ADHD	Structured clinical interview based on *DSM-IV* CAARS Adult ADHD Self-Report Scale WURS	PC (severe) Shift work	Pat: 13 C: 19	Stimulants (3) Atomoxetine (1)	MEQ	Actigraphy			1 week
Subjective and objective chronotype and circadian rhythm parameters and treatment													
Rybak, McNeely, Mackenzie, Jain, and Levitan, (2006)[a]	Open trial	48	40.4 (10.2)	ADHD-C (11) ADHD-I (14) ADHD-H/I (2)	WURS (>36) Lifelong symptoms with impairment CAARS ≥6/9 *DSM-IV* criteria or ≥3-5/9 (patients taking stimulants)	ND PC (suicidal ideation) SD/U Med (lithium/phenothiazines)	29	Some	MEQ		LT	3 weeks	3 weeks
Boonstra et al. (2007)[a]	Double-blind, placebo-controlled, cross-over trial	Pat: 52 C: 54	Pat: 37.9 (10.3) C: 37.8 (9.5)	ADHD (31)	Semistructured interview for ADHD and comorbidity	Lab ND PC (unstable) Med (psychotropic)	Pat: 31 C: 39	None		Actigraphy	MF (Week 1: 0.5; Week 2: 0.75; Week 3: 1.0 mg/kg/d) mean 3rd week: 72.9 mg	3 weeks	7 weeks

Note. ADHD = not specified; TCI = Temperament and Character Inventory; — = data not available; CSM = Composite Scale of Morningness; ADHD-C = ADHD–combined subtype; ADHD-I = ADHD–inattentive subtype; ADHD-H/I = ADHD–hyperactive/impulsive subtype; WURS = Wender Utah Rating Scale; CAARS = Conners Adult ADHD Rating Scale; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994); ND = neurological disorders (tic disorder, and/or mental retardation, and/or organic brain disorder, and/or major sensorimotor handicaps); PC = psychiatric comorbidity; SD/U = substance dependence or misuse (drugs and/or alcohol); med = medication use; MEQ = Horne-Ostberg Morningness–Eveningness Questionnaire; ASRS = Adult Self-Report Scale v1.1; pat = patients; C = controls; DIVA = semistructured interview for ADHD in adults, based on *DSM-IV*; SCID = *Structured Clinical Interview for DSM* Disorders; ADHD-RS = ADHD Rating scale; VOA = Vragenlijst ochend/avondmens: Dutch questionnaire based on MEQ; MCTQ = Munich Chronotype Questionnaire; lab = laboratory blood investigation abnormalities; SOI = patients with sleep onset insomnia; no-SOI = patients without sleep onset insomnia; DLMO = dim light melatonin onset; LT = light therapy; MF = methylphenidate; BADDS = Brown Attention Deficit Disorder Scale; contr. Ind. Sti.: contraindications to the use of stimulant medication (seizures, cardiac problems, ECG abnormalities, hypertension, pregnancy, lactation).
[a]First reviewed.

2011; Dodson, 1999; Mahajan et al., 2010; Surman et al., 2009; Van Veen et al., 2010).

Of the five studies that only reported on subjective sleep parameters, two (Dodson, 1999; Mahajan et al., 2010) had a cross-sectional design and three had a case-control design (Bijlenga et al., 2011; Schredl et al., 2007; Surman et al., 2009). In all the studies, ADHD was diagnosed based on *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association [APA], 1994) criteria. Only Mahajan et al. (2010), Schredl et al. (2007), and Surman et al. (2009) excluded severe psychiatric comorbidity but not sleep disorders. Bijlenga et al. (2011) and Surman et al. (2009) included participants using ADHD medication. In each of these studies, 17,8% and 34%of the participants, respectively, uses some form of ADHD medication. In each of these studies, 34% and 17.8% of the participants, respectively, used some form of ADHD medication. In Bijlenga et al. (2011), 15.3% also used antidepressants. Both ADHD medication and antidepressant use were significantly different compared with the controls. The five studies (Baird et al., 2011; Boonstra et al., 2007; Philipsen et al., 2005; Sobanski et al., 2008; Van Veen et al., 2010) reporting on objective sleep parameters were comparative studies. One was single blind (Philipsen et al., 2005). ADHD was diagnosed based on the *DSM-IV* criteria, on the basis of various structured and semistructured interviews. Participants with severe psychiatric comorbidity were excluded. With the exception of Baird et al. (2011), in which some patients used ADHD medication, stimulants were washed out for at least 28 days.

Sleep Onset Latency

Subjective. ADHD patients more often have difficulty going to bed on time willingly than healthy controls (Surman et al., 2009). In all, 87% have trouble going to bed on time (Boonstra et al., 2007) leading to later bedtimes (Surman et al., 2009). About 72% of ADHD patients report SOI following difficulties ending the day and going to bed (Dodson, 1999). In comparison with nonpatients, they complain more about difficulty falling asleep (Boonstra et al., 2007; Schredl et al., 2007) and psychosomatic symptoms during sleep onset (Philipsen et al., 2005). For 53% of ADHD patients, it habitually takes longer than 1 hr to fall asleep (Baird et al., 2011), and a significantly larger proportion reported being in bed for more than 1 hr before falling asleep, compared with controls (Surman et al., 2009).

Patients reporting sleep onset latency retrospectively revealed no difference compared with controls (Schredl et al., 2007; Sobanski et al., 2008), whereas Bijlenga et al. (2011) found longer latencies.

Contrasting results were also found when latency was measured prospectively. Philipsen et al. (2005) and Sobanski et al. (2008) both used the same questionnaire over two nights. Sobanski et al. found longer sleep latency in ADHD patients, whereas Philipsen et al. found no difference. Boonstra et al. (2007) found longer sleep latency in ADHD patients after recording a sleep log over 1 week.

Objective. Longer sleep onset latency was found in adult ADHD patients compared with controls in three actigraphic studies (Baird et al., 2011; Boonstra et al., 2007; Van Veen et al., 2010), which recorded data over 1 week. Polysomnographic measuring over two nights did not show any differences (Philipsen et al., 2005; Sobanski et al., 2008). No difference in sleep onset latency was found between ADHD patients with and without SOI (Van Veen et al., 2010). SOI was defined based on retrospective subjective parameters as difficulty getting to sleep at a desired bedtime and/or sleep onset latency of longer than 30 min at least four nights a week, over a period of at least 6 months, leading to impairment.

Sleep Maintenance

Subjective. Besides complaints about poor sleep quality and SOI, 83% of ADHD patients reported disrupted sleep maintenance (Dodson, 1999). Compared with controls, they are more likely to report restless sleeping (Surman et al., 2009) and more frequent nocturnal awakenings (Bijlenga et al., 2011; Sobanski et al., 2008). Boonstra et al. (2007) found no difference in nocturnal awakenings. The time spent awake during the night was the same in ADHD patients and controls (Philipsen et al., 2005; Surman et al., 2009).

Objective. Patients with ADHD showed more nocturnal awakenings (Sobanski et al., 2008) and shorter average sleep bout durations uninterrupted by wakefulness (Boonstra et al., 2007). Despite frequent awakenings, the percentage wakefulness did not differ from controls (Boonstra et al., 2007).

Total Sleep Time

Subjective. Total sleep time differed depending on the setting in which it was measured. At home, ADHD patients reported shorter total sleep time compared with controls (Bijlenga et al., 2011). However, there were no differences when ADHD patients' sleep time was measured in a laboratory over two nights (Philipsen et al., 2005).

Objective. Compared with controls, only ADHD patients without SOI showed longer total sleep time (Van Veen et al., 2010). No difference was found between patients with and without SOI. In studies in which ADHD patients were not divided based on whether they had SOI, total sleep time

did not differ from controls (Boonstra et al., 2007; Philipsen et al., 2005).

Waking Up

Subjective. After sleeping, about 70% of ADHD patients have difficulty waking up in the morning and getting out of bed (Boonstra et al., 2007; Dodson, 1999). Furthermore, compared with controls, they were significantly more likely to report difficulty waking up in the morning (Surman et al., 2009).

ADHD patients rated their feeling of being refreshed in the morning significant lower than healthy controls (Boonstra et al., 2007; Philipsen et al., 2005; Schredl et al., 2007), although Sobanski et al. (2008) found no differences. The severity of ADHD symptoms was closely related to the feeling of being refreshed in the morning (Schredl et al., 2007).

Objective. ADHD patients wake up significantly later than controls (46 min), without differing with respect to the time at which they went to sleep (Van Veen et al., 2010). Within this group, ADHD patients with SOI wake up later than patients without SOI, whose waking up time did not differ from controls (Van Veen et al., 2010). Baird et al. (2011) also found that ADHD patients woke up later (39 min) than controls, although this was not found to be significant.

ADHD and Sleep: Subjective and Objective Parameters and Stimulant Treatment

Design, Inclusion Criteria, and Endpoints of the Studies

Seven studies were found on the effect of stimulant treatment on subjective sleep parameters, of which three (Boonstra et al., 2007; Kooij, Middelkoop, van Gils, & Buitelaar, 2001; Sobanski et al., 2008) also studied the effect on objective sleep parameters (Table 2).

Three of the studies only reporting on subjective sleep parameters (Adler et al., 2009; Surman & Roth, 2011) were double-blind, placebo-controlled trials, which had not been reviewed before. In all three studies, ADHD was diagnosed based on *DSM-IV* criteria, using various scales and interviews, and psychiatric comorbidity, substance abuse, and psychotropic medication were excluded. Surman and Roth (2011) described the results of two trials, one with lisdexamfetamine dimesylate (LDX) and one with triple-bead mixed amphetamine salts (MAS). Adler et al. (2009) made a distinction between the different dosages of LDX. The time at which patients took the medication and so at what time had worked out is not clear from either study.

Three studies also reported on objective parameters: two open-label studies (Kooij et al., 2001; Sobanski et al., 2008) and one double-blind, placebo-controlled cross-over trial (Boonstra et al., 2007).

In all three studies, ADHD was diagnosed based on *DSM-IV* criteria, using various scales and interviews. Kooij et al. (2001) did not use any exclusion criteria. In all three studies, one patient used dextroamphetamine (DA), and all the others took methylphenidate (MF). Although most patients used MF, various doses and schedules were used in the different studies. Kooij et al. used a schedule where doses were administered three times a day (8:00 a.m., 12:00 noon, 4:00 p.m.), resulting in a mean daily dose of 51 mg. In Boonstra et al. (2007), doses were administered four to five times a day, depending on rebound effects, but the last dose was always given at 8:00 p.m., resulting in a mean daily dose of 72.9 mg. Sobanski et al. (2008) started twice daily, but did not describe the time at which the last dose was taken. The mean daily dose was 36.7 mg.

Sleep Onset Latency

Subjective. Stimulants reduced the average time taken to fall asleep to 26 min poststimulant treatment from 106 min pretreatment (Dodson, 1999). The other studies (Adler et al., 2009; Boonstra et al., 2007) found no significant differences in subjective sleep latency between patients receiving stimulants and those receiving a placebo.

Different results were found in the studies looking at subjective SOI. For retrospective measurements of sleeping at home, Dodson (1999) reported reduced insomnia symptoms after stimulant treatment, whereas Sobanski et al. (2008) found no difference compared with a placebo, in line with Boonstra et al. (2007).

Objective. Two actigraphic studies (Boonstra et al., 2007; Kooij et al., 2001) and one polysomnographic study (Sobanski et al., 2008) investigated the effect of MF on sleep onset latency in adult ADHD patients. Boonstra et al. (2007) found that MF (last dose 8:00 p.m.) was associated with increased sleep onset latency in ADHD compared with controls. Kooij et al. (2001; last dose 4:00 p.m.) found no difference. When the situation before and after treatment was compared, MF (time of last dose not clear) was associated with decreased sleep onset latency (Sobanski et al., 2008).

Sleep Maintenance

Subjective. A reduced nocturnal awakening rating was found in ADHD patients receiving stimulants compared with controls (Boonstra et al., 2007). Over 2 nights in a sleep laboratory, Sobanski et al. (2008) found a nonsignificant trend of fewer nocturnal awakenings after stimulant treatment.

Objective. MF treatment was associated with a reduced number of nocturnal awakenings, an increased average duration of uninterrupted sleep bouts, and a lower percentage time of wakefulness (Boonstra et al., 2007). Kooij et al. (2001) and Sobanski et al. (2008) found no difference in the number of nocturnal awakenings when they compared stimulant-treated ADHD patients with controls and the situation before treatment.

Total Sleep Time

Subjective. Only Adler et al. (2009) studied the subjective total sleep time. There were no differences between any dose of LDX and placebo.

Objective. MF treatment was associated with a reduced total sleep time in ADHD patients compared with controls (Boonstra et al., 2007).

Waking Up

Subjective. The positive effect on the restorative value of sleep was highly significant over the two nights in the sleep laboratory after stimulant treatment (Sobanski et al., 2008). However, Boonstra et al. (2007) found no difference in the subjective feeling of being well rested between the MF group and placebo.

ADHD, Chronotype and Circadian Rhythm, Subjective and Objective Parameters, With and Without Treatment

Design, Inclusion Criteria, and Endpoints of the Studies

Ten studies were found on ADHD and chronotype or circadian rhythm (Table 3). With the exception of Rybak, McNeely, Mackenzie, Jain, and Levitan (2007), none have been reviewed before. Although the sleep parameters in Boonstra et al. (2007) have been reviewed before (Roth & Zinsenheim, 2009), the circadian parameters have not yet been reviewed.

Of the six studies measuring subjective chronotype parameters (Bae et al., 2010; Bijlenga et al., 2011; Caci, Bouchez, & Bayle, 2009; Caci, Robert, & Boyer, 2004; Gruber, Oiveri, & Tong, 2009; Rybak et al., 2007), only one had a case-control design (Bijlenga et al., 2011). All others had a cross-sectional design. Four studies (Bae et al., 2010; Caci et al., 2004; Caci et al., 2009; Gruber et al., 2009) looked at ADHD symptoms in the general population. In Rybak et al. (2007) and Bijlenga et al. (2011), ADHD was diagnosed based on *DSM-IV* criteria using semistructured interviews and rating scales. Caci et al. (2004) and Gruber et al. (2009) only included male participants.

Three comparative studies (Baird et al., 2011; Boonstra et al., 2007; Van Veen et al., 2010) measured circadian rhythm objectively with actigraphy in securely diagnosed ADHD patients without severe psychiatric comorbidity. Van Veen et al. (2010) also used the DLMO as the circadian parameter. While none of the ADHD patients included in Van Veen et al. (2010) and Boonstra et al. (2007) used stimulants, 4 of the 13 patients included in Baird et al. (2011) used ADHD medication.

One double-blind, placebo-controlled, cross-over trial (Boonstra et al., 2007) and one open trial (Rybak, McNeely, Mackenzie, Jain, & Levitan, 2006) were found on the effect of treatment (MF and light therapy [LT], respectively) on circadian rhythm. In both studies, ADHD was diagnosed securely, and comorbid neurological and psychiatric disorders were excluded. Rybak et al. (2006) did not exclude the use of ADHD medication.

ADHD-Like Symptoms and Chronotype/Circadian Rhythm

Subjective. Various studies demonstrated that ADHD-like symptoms in the general population are related to circadian preference and vice versa. In males, eveningness was associated with inattention, impulsivity-hyperactivity, and higher total ADHD symptom scores (Bae et al., 2010). Gruber et al. (2009) reported corresponding results confirming the association between circadian preference and daytime attention, memory, and social functioning in males. The participants with morning preference reported significantly better memory functioning, better social relationships, higher self-esteem, and more self-confidence, compared with the participants with evening preference. In another study, morningness in males was negatively correlated with novelty seeking (Caci et al., 2004).

In female participants, eveningness was associated with inattention and higher total ADHD scores, but not with impulsivity-hyperactivity (Bae et al., 2010). In a group where 77.6% of the participants were female, inattention was more strongly related to eveningness than impulsivity-hyperactivity (Caci et al., 2009).

Between two groups of male participants, one of which had high ADHD symptom scores and another with low scores, lower morningness and higher eveningness was found in the potential ADHD group (Bae et al., 2010). Caci et al. (2004) found corresponding results in males where impulsivity, extravagance, and disorderliness were associated with the tendency to plan activities in the late hours. There were no differences in circadian preference between two female groups (non-ADHD and potential ADHD; Bae et al., 2010).

ADHD and Chronotype/Circadian Rhythm

Subjective. Three studies (Baird et al., 2011; Bijlenga et al., 2011; Rybak et al., 2007) investigated circadian preference using the Morningness–Eveningness Questionnaire (Horne-Ostberg MEQ), or an MEQ-based questionnaire in adult ADHD patients, and reported similar results. ADHD patients scored significantly higher on the MEQ compared with controls, indicating a shift to eveningness (Baird et al., 2011). They are more often and more extreme evening chronotypes and reported later midsleep on free days, corrected for sleep debt on workdays (MSFsc), a standardized measure for chronotype classification (Bijlenga et al., 2011; Roenneberg et al., 2004). In all, 40.7% of them were designated as evening type (Rybak et al., 2007).

ADHD patients met the proposed criteria for DSPD (sleep onset latency ≥ 30 min with bedtime of ≥ 00:30 a.m. on workdays, or an extreme evening type score on the vragenlijst ochend/avondmens [VOA]; Dutch questionnaire based on the MEQ) significantly more often than controls (25.8% vs. 2.1%; Bijlenga et al., 2011). Within the control group, the participants with an indication of DSPD were more likely to have a high score on the ADHD Rating Scale (ADHD-RS; 50% vs. 7.1%).

Objective. Three studies (Baird et al., 2011; Boonstra et al., 2007; Van Veen et al., 2010) looked at circadian rhythm measured in objective actigraphic parameters in ADHD. Almost all parameters in the studies showed inconsistent results.

DLMO was only used in Van Veen et al. (2010) to measure circadian rhythm. Van Veen et al. found a significant difference in DLMO between ADHD-SOI patients and healthy controls. The DLMO was 83 min later in the ADHD-SOI group. There was no difference between the controls and the group of ADHD patients without SOI. In the ADHD-SOI group, the DLMO was 75 min later than that in ADHD participants without SOI.

The Effect of Stimulant Treatment and LT on Circadian Rhythm in ADHD

Stimulant treatment of ADHD patients delayed the onset of the 5 least active hours (L5) onset by 18 min, compared with a placebo (Boonstra et al., 2007). Treating ADHD patients with LT resulted in an increase in morningness, which was correlated with a reduction in ADHD symptoms, which was in turn more closely related to a phase advance in circadian preference than to an amelioration of depression (Rybak et al., 2006).

Discussion

Almost all of the studies on subjective sleep parameters in adult ADHD that we reviewed reported disrupted sleep maintenance (Bijlenga et al., 2011; Dodson, 1999; Schredl et al., 2007; Sobanski et al., 2008; Surman et al., 2009) and difficulty waking up in the morning (Boonstra et al., 2007; Dodson, 1999; Surman et al., 2009). However, the studies showed inconsistent results for subjectively measured sleep onset latency and total sleep time.

Adult ADHD is associated with longer objectively measured sleep onset latency (Baird et al., 2011; Boonstra et al., 2007; Van Veen et al., 2010), disrupted sleep maintenance (Boonstra et al., 2007; Kooij et al., 2001; Philipsen et al., 2005; Sobanski et al., 2008), later waking up times, and no change in total sleep time.

Studies on the effect of stimulants on subjective and objective sleep parameters showed inconsistent results. We found no answer to our third research question in the current literature.

All studies on subjective circadian preference in ADHD (Baird et al., 2011; Bijlenga et al., 2011; Rybak et al., 2007) reported that ADHD patients were more often evening chronotypes and also more extreme evening chronotypes. Actigraphical circadian parameters showed no corresponding results. A delayed DLMO was found for ADHD patients with SOI (Van Veen et al., 2010). Treatment with stimulants led to more eveningness in one study (Boonstra et al., 2007). Treatment with LT increased morningness (Rybak et al., 2006).

Eveningness is positively correlated with ADHD symptoms (Bae et al., 2010; Bijlenga et al., 2011; Caci et al., 2004; Caci et al., 2009; Gruber et al., 2009; Rybak et al., 2007), and an increase in morningness is negatively correlated with ADHD symptoms (Rybak et al., 2006). Stimulant treatment led to a delay in the L5 (Boonstra et al., 2007). Therefore, the therapeutic effect of stimulants cannot be explained by the effect on the circadian rhythm. Furthermore, the effect of stimulants on sleep showed no consistent results, and so it is not clear whether the therapeutic effect of stimulants can be explained by positive effects on sleep.

SOI is a common complaint among adult ADHD patients (Boonstra et al., 2007; Dodson, 1999; Philipsen et al., 2005; Schredl et al., 2007). The same objective delayed sleep latencies and total sleep times were found for ADHD patients who were retrospectively and subjectively defined as having SOI (difficulty getting to sleep at a desired bedtime and/or sleep onset latency of 30 min or more at least four nights a week, persisting over at least 6 months, and leading to impairment in several areas) and ADHD patients without SOI (Van Veen et al., 2010). Studies on subjective sleep onset latency and total sleep time showed no corresponding results. Comparing these results, it seems that ADHD patients underreport increased sleep onset latency in retrospective studies and have difficulty estimating total sleep time, which may be caused by the deficit in time awareness in ADHD patients.

Sleep maintenance is disrupted in adult ADHD due to subjective movement disorder symptoms (Schredl et al., 2007) and objective measured (actigraphy and polysomnography [PSG]) increased nocturnal motor activity (Kooij et al., 2001; Philipsen et al., 2005), leading to more frequent objective and subjective measured nocturnal awakenings (Bijlenga et al., 2011; Sobanski et al., 2008), but not to longer time spent awake during the night (Boonstra et al., 2007; Philipsen et al., 2005; Surman et al., 2009). Apparently, in ADHD patients, sleeping is restless with more awakenings from which they quickly fall back asleep.

ADHD patients treated with LT, who shifted to greater morningness as a result, reported decreased ADHD symptoms (Rybak et al., 2006). On other hand, regular treatment with MF, which has proven to be effective in the management of ADHD symptoms, shows delayed onset of the L5 (Boonstra et al., 2007), suggesting a shift to greater eveningness. This is in accordance with the results of the actigraphic study by Ironside, Davidson, and Corkum (2010). This study found a circadian phase-delay in children with ADHD treated with stimulants, when compared with controls. These results suggest that the therapeutic effect of MF is not due to the effect on the circadian rhythm shift as greater eveningness is associated with higher ADHD symptom scores. This may be one of the reasons why some ADHD patients do not respond to stimulants. Hypothetically, it may be the case that the shift to greater eveningness due to MF negates the positive effect of the medication. A recent study by O'Keeffe, Thome, and Coogan (2012) reported that atomoxetin, a noradrenalin reuptake inhibitor, licensed for the treatment of ADHD, can alter circadian rhythmicity in mice. They suggested that part of the therapeutic profile of atomoxetine may be through circadian rhythm modulation. In the general population, eveningness was associated not only with ADHD-like core symptoms but also with secondary problems that are often seen in adult ADHD such as low self-esteem and self-confidence, and problems with social relationships (Bae et al., 2010; Caci et al., 2004; Caci et al., 2009; Gruber et al., 2009). Because LT in adult ADHD led to greater morningness and a decrease in ADHD symptoms, hypothetically, it may have positive effects on self-esteem, self-confidence, and social functioning.

Although the studies on sleep and circadian rhythm parameters show different results on various parameters, it is striking that the sleep parameters that show consistent results, insomnia, and difficulty waking up in the morning/getting out of bed, are often seen in delayed circadian preference, which corresponds to the eveningness preference and delayed DLMO in adult ADHD with SOI. ADHD patients, subjectively defined as having SOI, have the same sleep onset latency (which is longer than controls) but later waking up times and later DLMOs (Van Veen et al., 2010) as patients without SOI. The combination of increased sleep onset latency and later waking up time is highly indicative of DSPD, which was found significantly more often in ADHD patients compared with controls (Bijlenga et al., 2011). Because increased sleep onset latency is common in ADHD, independent of subjective SOI and later DLMO, waking up time seems to be a better discriminating parameter for suspected DSPD than later sleep onset (Van Veen et al., 2010).

Our study has several limitations. Only three of the studies we found had a double-blind, placebo-controlled design. Also, the number of participants studied was relatively small. Because of the heterogeneity of the studies, it was not possible to perform a meta-analysis. Results found using various methodologies such as retrospective and prospective objective and subjective measures, and in different settings (at home or at the sleep laboratory), had to be compared. In the various studies looking at the effect of stimulants, various forms of stimulants were used. None of the studies mentioned the time at which the stimulants stopped working, so the rebound effects on sleep are not clear. In future studies, it is important to use strict medication schedules and pay attention to rebound effect.

Nevertheless, it can be concluded that adult ADHD is associated with delayed circadian rhythmicity and late sleep–wake rhythm, which are characteristics of DSPD. Clinicians should be aware of circadian rhythm sleep disorders in their ADHD patients and ask their patients not only about SOI but also about the waking up time when not using an alarm clock, because, independently of an existing DSPD, adult ADHD patients often complain about SOI. Delayed waking up time seems to be the discriminating factor in the anamnesis. In addition to the anamnesis, DSPD can now be easily diagnosed by measuring DLMO in saliva, as delayed DLMO is one of its crucial characteristics (Pandi-Perumal et al., 2007).

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