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REVIEW ARTICLE

A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder

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Abstract Reports of sleep disturbances in attention deficit hyperactivity disorder (ADHD) are common in both children and adults; however, the aetiology of such disturbances is poorly understood. One potentially important mechanism which may be implicated in disrupted sleep in ADHD is the circadian clock, a known key regulator of the sleep/wake cycle. In this systematic review, we analyse the evidence for circadian rhythm changes associated with ADHD, as well as assessing evidence for therapeutic approaches involving the circadian clock in ADHD. We identify 62 relevant studies involving a total of 4462 ADHD patients. We find consistent evidence indicating that ADHD is associated with more eveningness/later chronotype and with phase delay of circadian phase markers such as dim light melatonin onset and delayed sleep onset. We find that there is evidence that melatonin treatment may be efficacious in addressing ADHD-related sleep problems, although there are few studies to date addressing other chronotherapeutic approaches in ADHD. There are only a small number of genetic association studies which report linkages between polymorphisms in circadian clock genes and ADHD symptoms. In conclusion, we find that there is consistent evidence for circadian rhythm disruption in ADHD and that such disruption may present a therapeutic target that future ADHD research might concentrate explicitly on.

Keywords ADHD · Circadian · Sleep · Melatonin · clock gene

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
BD	Bipolar disorder
CSM	Composite scale of morningness
DLMO	Dim light melatonin onset
DSPD	Delayed sleep phase disorder
IS	Interdaily stability
IV	Intradaily variability
MEQ	Morningness–eveningness questionnaire
MCTQ	Munich chronotype questionnaire
MPH	Methylphenidate
PER	PERIOD
SOI	Sleep-onset insomnia
RCT	Randomised control trial

Introduction

Attention deficit hyperactivity disorder is a common condition affecting in the region of 7% of children and adolescents and 5% of adults (Willcutt 2012). It is characterised by the core psychopathologies of attention difficulties, impulsivity and hyperactivity (American Psychiatric Association 2013). In children, the condition may be diagnosed as a primarily hyperactive/impulsive subtype, a primarily inattentive subtype, or a combined subtype (Willcut 2012). In adults, the condition is described mostly as a combined type (Bell 2011). ADHD is associated with poorer psychosocial outcomes (Loe and Feldman 2007) and shows a high frequency of comorbidity with other psychiatric and psychological disorders (Matthews et al. 2014). The aetiology of ADHD is complex and incompletely understood, although there appears to be a high level of heritability of the condition, indicating a significant genetic component (Matthews et al. 2014).

A common finding in ADHD in both adults and children is that there are significant sleep disturbances associated with the condition (Hvolby 2015). For example, chronic insomnia has been reported in 27% of adults with ADHD (Schredl et al. 2007). Intriguingly, many of the core cognitive and behavioural symptoms of ADHD can also be contributed to by poor sleep quality and/or quantity (Babkoff et al. 1991), and as such sleep disturbance may be important in the aetiology of ADHD. In terms of the regulation of sleep, the classic two-process model (Borbély et al. 2016) proposes that sleep/wake behaviour is driven by overlapping homeostatic processes (accumulating drive to sleep with increasing cumulative hours of wakefulness) and circadian drive to wakefulness (normally strong during the day, declining moving towards the later evening). The circadian component of this process is now known to be determined by an endogenous circadian timekeeping mechanism which manifests itself in a host of rhythms in behavioural, physiological and biochemical rhythmic outputs recurring with periods of approximately 24 h (Buttgereit et al. 2015). Such outputs include diurnal rhythms in cortisol resulting from strong circadian control of the hypothalamic–pituitary–adrenal axis (Spiga et al. 2014) and nocturnal secretion of the pineal hormone melatonin gated through the suprachiasmatic nucleus (Erren and Reiter 2015).

The clock itself is encoded at a genetic level by a number of clock genes, whose expression leads to the formation of a series of interlocking feedback/feedforward transcriptional loops which result in the near 24-h expression of clock gene products, but also the rhythmic expression of a large set of clock-controlled genes across the genome (Zhang et al. 2014). From an anatomical perspective, the master circadian clock resides in the suprachiasmatic nuclei of the hypothalamus, with other clock distributed widely throughout the brain and periphery (Mohawk et al. 2012). Given this widespread distribution of components of the circadian timing system, it is somewhat unsurprising that the operation of the internal clock imposes a temporal governance on a wide range of physiological and molecular processes (Buijs et al. 2016) and as such are also implicated in a wide range of diseases (Smolensky et al. 2016). Amongst these are involvements in common psychiatric conditions such as major depression, bipolar disorder and schizophrenia (Coogan 2013; Tam et al. 2015; Melo et al. 2016). Given this, it is being increasingly recognised that circadian function in these conditions may be an appropriate target for psychological, behavioural and/or pharmacological therapies (Dallaspezia and Benedetti 2015). Such therapies may take advantage of fundamental knowledge of the neurobiology of the circadian system. For example, the main photoreceptive system for the circadian clock is not the visual system, but rather a system utilising the photopigment melanopsin in a subset of light-sensitive retinal ganglion cells (Lucas et al. 2014). It is long known that light is the most profound influence on circadian function and circadian clock are normally entrained to environmental light/dark cycles (Mohawk et al. 2012). As some psychiatric conditions, such as bipolar disorder and seasonal affective disorder, have been described to be associated with alterations in circadian phase reflective of altered entrainment of the clock to the environment, the use of timed light therapy has been shown to be of promise in resynchronising rhythms and improving clinical ratings (Dallaspezia and Benedetti 2015; Lewy 2007).

Given the prevalence of sleep problems in ADHD, recent attention has begun to focus on the role that circadian dysfunction may play in such sleep problems, and more generally how circadian dysfunction might contribute to the aetiology and/or symptomatology of ADHD. We have recently reviewed the mechanisms that could link ADHD and circadian rhythm abnormalities (Coogan et al. 2016). However, to date there has been no systematic review of the relevant literature linking circadian rhythms and ADHD, and it is to this gap that the present study addresses itself.

Methods

Search strategy

A structured search of PubMed, the Cochrane Library and Clinical Trials.gov was conducted in July and September 2016 using the terms “circadian” OR “chronotype” OR “diurnal preference” OR “biological rhythm” OR “sleep” OR “melatonin” OR “light” AND “attention deficit hyperactivity disorder” OR “ADHD”. Publication date and language were not restricted. Articles that focussed solely on sleep parameters, with no measures of sleep timing or sleep/wake cycle descriptions, or circadian or diurnal rhythms description, were excluded, as the focus of this review is on circadian function in ADHD. Only primary studies were included, so reviews and meta-analyses were excluded. Studies of neurodevelopmental disorders that did not explicitly delineate ADHD populations were excluded. Animal studies were also excluded. Genetic studies were included once they included descriptions of links between ADHD and core circadian clock genes. Interventional studies assessing impact on circadian function were included. Studies assessing the impact of melatonin, whether used as a somnolent or as a chronobiotic, were also included.

Measures of circadian rhythmicity

There are a number of different measures of circadian function that are appropriate for the assessment of circadian function in clinical populations. An area that is relatively accessible for examination is inter-individual differences in sleep/wake behaviour (chronotype) and diurnal preference for sleep/wake behaviour. These parameters can be examined using psychometric instruments for the assessment of diurnal preference, such as the morning–eveningness questionnaire (MEQ) and the composite scale of morningness (CSM). These instruments may be described as being indicators of psychological preference for the timing of sleep/wake behaviour, and as such may not be fully indicative of underlying circadian phase (Levandovski et al. 2013; Adan et al. 2012). The Munich Chronotype Questionnaire (MCTQ) is another instrument which records actual timing of sleep/wake behaviour, and as such may be a truer indicator for underlying endogenous circadian phase (Roenneberg et al. 2003). The timing of mid-sleep on "free" days is taken as the key measure from the MCTQ. The MCTQ also differentiates between "free" and "work" days, and as such allows for calculation of the discrepancy between the timing of sleep on both work days, a construct referred to as social jetlag (Wittmann et al. 2006). The MEQ, CSM and MCTQ are well validated and have been deployed in numerous studies interrogating the epidemiology of circadian rhythmicity in humans. The MCTQ and MEQ measures are correlated with melatonin secretion profiles (Kantermann et al. 2015), and there is a moderate to strong correlation between the MEQ and MCTQ (Zavada et al. 2005).

Objective measures of sleep/wake behaviour and circadian rhythms in locomotor activity include the use actigraphy. This approach utilises accelerometers, usually wrist-worn, to gather data on activity patterns and from these derive measures of circadian function as well as measures of sleep timing and quality (Ancoli-Israel et al. 2003). Measures of circadian rhythms often involve nonparametric analysis of circadian rhythms, yielding measures such as relative amplitude of the rhythm (higher values indicating clearer demarcation between consolidated bouts of rest and activity), L5 and time of L5 onset (where L5 is the activity in the least active 5 h), M10 and M10 onset (amount of activity in the most active 10 h), and measures of rhythm precision (interdaily stability or 'IS') and fragmentation (intradaily variability or 'IV'; van Someren et al. 1997). Sleep parameters of interest for this review that can be derived from actigraphy include time of bedtime, time of sleep onset and time of wakening.

As many endocrine systems operate under profound circadian control, measures of daily variability salivary or serum levels of hormones such as cortisol and melatonin (or melatonin's metabolite 6-sulfatoxymelatonin in urine) are important indicators of circadian function. For melatonin, an important measure is the dim light melatonin onset (DLMO), which is taken as an important indicator of underlying circadian phase (Pandi-Perumal et al. 2006). On a molecular level, the circadian clock is known to be driven by a series of interlinked transcriptional feedback and feedforward loops involving a panel of circadian clock genes. Expression patterns of such genes can be followed in peripheral tissues such as oral epithelia or peripheral blood mononuclear cells to allow insight into the molecular clockwork. Polymorphisms in clock genes have also been implicated in various neuropsychiatric disorders (Landgraf et al. 2014), and as such genetic association studies between ADHD (and ADHD symptoms) and clock gene polymorphisms are included in this review.

Chronotherapeutic studies

There are a number of pharmacological and non-pharmacological interventions that may be utilised to alter circadian function, and such approaches are broadly termed chronotherapy. Such treatments may include melatonin [in either its application at higher doses as a somnolent, or in smaller, time-controlled doses as a chronobiotic to alter circadian phase (Lewy 2007)], drugs that specifically target the circadian system [such as the antidepressant agomelatine (San and Arranz 2008)], or environmental or behavioural manipulations, such a light therapy, which alters circadian phase and/or amplitude (Terman 2007). We included in our review any study seeking to manipulate the circadian system as a primary intervention.

Results and discussion

A total of 1719 articles were initially identified through database searches. Figure 1 shows the process for article selection. A final total of sixty-two articles were included for review, with the oldest article included being from 2000. Overall, studies involving 33,212 participants were included in this review. Of these, a total of 4462 ADHD patients were studied. Of the studies included for review, 25 studies were in adult populations whilst 37 studied children or adolescents.

Chronotype and diurnal preference in ADHD

The strongest and most consistent finding in the analysed literature is for association of later chronotype/evening preference with ADHD and ADHD symptoms. In total, 9 papers examining chronotype/diurnal preference were reviewed (Table 1). Assessment of chronotype/diurnal

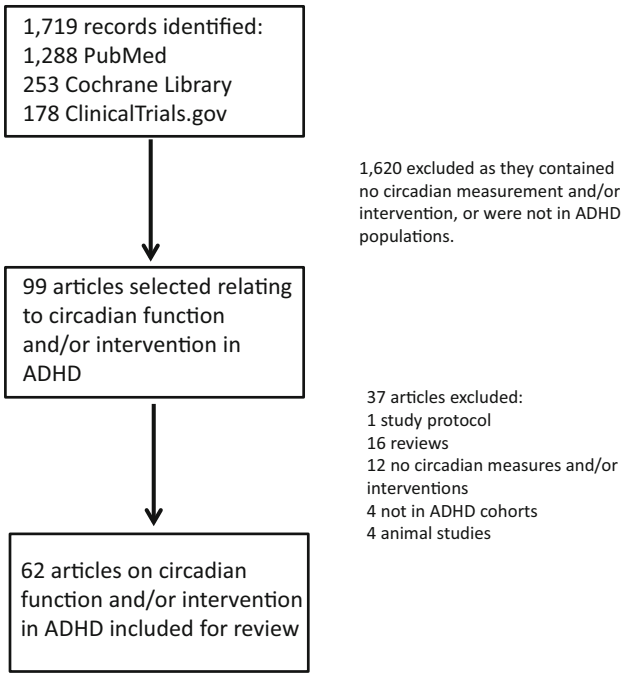

Fig. 1 Graphic representation of the study selection process

preference is made through the morningness/eveningness questionnaire (MEQ; 6 studies), the Munich Chronotype Questionnaire (MCTQ; 4 studies), the composite scale of morningness (CSM; 3 studies) and derivative questionnaires based on the MEQ and/or MCTQ (3 studies), with some studies utilising overlapping measures. In studies of ADHD adult patients, there is a remarkable agreement of findings of later chronotype/increased eveningness in ADHD groups compared to controls. Rybak et al. (2007) report increased eveningness associated with increased ADHD symptoms and poorer sustained attention on a continuous performance task in 29 adults with ADHD. A similar report of increased eveningness is reported in 13 adults with ADHD by Baird et al. (2012), whilst Bijlenga et al. (2013b) report that ADHD was associated with later mid-sleep on free days measured by the MCTQ in 202 adults with ADHD. Vogel et al. (2015) report that ADHD was associated with later chronotype and with more prevalent delayed sleep phase disorder and unstable timing of meals in 202 adults with ADHD. Kooij and Bijlenga (2014) report in a sample of 543 adults that more extreme evening typology associates with ADHD. Similarly, Gruber et al. (2012) report greater eveningness in 26 children with ADHD, and this later diurnal preference was associated with later sleep onset.

A number of studies have examined the link between diurnal preference/chronotype and ADHD symptoms too using ADHD screening instruments applied to non-clinical samples. In a cross-sectional study of 205 adults, Caci et al. (2009) report that eveningness rated on the CSM was associated with inattentive symptoms, more than impulsiveness and hyperactivity. Voinescu et al. (2012) also used the CSM in a cross-sectional study of 301 adults and report that evening preference is associated with likely-ADHD status and inattentive symptoms. McGowan et al. (2016) report, using the MCTQ in a sample of 396 adults, that social jetlag, rather than chronotype, is a predictor of ADHD symptoms and impulsivity possibly indicating that circadian desynchrony is an important factor mediating the putative relationship between chronotype/circadian typology and ADHD.

Sleep-onset insomnia and delayed sleep phase disorder in ADHD

Delayed sleep phase disorder (DSPD) is believed to be driven by circadian factors (Micic et al. 2016). Likewise, sleep-onset insomnia (SOI) may have a significant circadian component in its aetiology (Lack and Wright 2007). Sixteen studies were included in this review examining either DSPD or SOI in ADHD (Table 2). Van der Heijden et al. (2005) report that SOI in ADHD was associated with a phase delay of the dim light melatonin onset (DLMO) compared to subjects with ADHD but without SOI. In this study, 87 of 110 children with ADHD had SOI, indicating that it is prevalent in ADHD. Van der Heijden et al. (2006) report that sleep hygiene measures do not account for the differences in the ADHD + SOI group and the ADHD alone group. Hvolby et al. (2008) report that 45 children with ADHD had significantly longer sleep latencies, as assessed by actigraphy, compared to both control and children with other psychiatric diagnoses. Hoebert et al. (2009) examined the use and discontinuation of melatonin for SOI in ADHD in 94 children and report that melatonin discontinuation was associated with relapse of SOI in 92% of cases. Similar to the finding of van der Heijden et al. (2005) in children, Van Veen et al. (2010) report that of 40 adults with ADHD studied, 31 reported SOI that was associated with attenuated circadian rhythm amplitude of activity and delayed DLMO. Fargason et al. (2013) on the other hand report that in a group of 105 adults with ADHD, circadian delay was not associated with ADHD, although later dosing time with stimulants was associated with later sleep times.

The role of ADHD medication in sleep-onset problems in ADHD is indicated by the findings of Boonstra et al. (2007) who report that in a double-blind crossover trial in 31 adults with ADHD, methylphenidate treatment was associated with later bed times and greater sleep latency. Likewise, Ironside et al. (2010) report that methylphenidate treatment of 16 children with ADHD was associated with a phase delay of the sleep/wake cycle and that methylphenidate treatment was associated with an increase in motor

Table 1 Summary of studies included for review which examined chronotype/diurnal preference in ADHD

Authors and publication year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Baird et al. (2012)	Case–control study	$N = 32$ (13 ADHD, 19 control)	Adult	Actigraphy, MEQ, salivary cortisol and melatonin, oral mucosa expression of PER2 and BMAL1	N/A	ADHD was associated with loss of the molecular rhythm of PER2 and BMAL1 in the oral mucosa. ADHD was also associated with greater eveningness and a delay of the cortisol rhythm referenced to wake time
Bijlenga et al. (2013b)	Cross-sectional	$N = 391$ (202 ADHD, 189 healthy control)	Adult (19–65)	Dutch Vragenlijst Ochtend/Avondmens questionnaire, based on MEQ and MCTQ; MCTQ	N/A	ADHD was associated with increased prevalence of delayed sleep phase disorder. ADHD was associated with later mid-sleep on free days
Caci et al. (2009)	Cross-sectional	Students ($N = 205$)	Adult	CSM	N/A	Eveningness related to inattentive symptoms of ADHD more so than hyperactivity/impulsivity
Gruber et al. (2012)	Case–control study	$N = 75$ (26 ADHD, 49 healthy control)	Childhood	Child morning–evening preference scale	N/A	ADHD was associated with greater eveningness. Evening orientation was associated with subjectively and objectively rated sleep-onset delay
Kooij and Bijlenga (2014)	Cross-sectional	$N = 543$	Adult	Likert-like self-rating of chronotype, self-reported presence of photophobia	N/A	More extreme evening types associated with ADHD; higher level of self-reported photophobia associated with ADHD
McGowan et al. (2016)	Cross-sectional	$N = 396$	Adults (mean age = 24)	MCTQ	N/A	Social jetlag is a significant predictor of ADHD symptoms and impulsivity, chronotype is not when social jetlag is included in the regression model
Rybak et al. (2007)	Cross-sectional	ADHD ($N = 29$)	Adult (20–60 yrs)	MEQ	N/A	Later circadian preference associated with increased self-reported symptoms of ADHD and increased commission errors on Conner's Continuous Performance Task
Vogel et al. (2015)	Case–control study	ADHD ($N = 202$), obesity ($N = 114$), healthy controls ($N = 154$)	Adult (18–65 yrs)	Dutch Vragenlijst Ochtend/Avondmens questionnaire, based on MEQ and MCTQ	N/A	ADHD group had shorter sleep on free days, later chronotype, more delayed sleep phase disorder indicators and more unstable eating patterns than the obese group
Voinescu et al. (2012)	Cross-sectional	$N = 301$	Adult	CSM	N/A	ADHD symptoms are associated with increased eveningness

activity during the sleep latency period. Interestingly, Gruber et al. (2000) report that in an actigraphic study of 32 children with ADHD that sleep onset times are unstable, perhaps indicating a weakened circadian component of sleep/wake regulation.

Regarding DSPD in ADHD, there are case reports of the condition co-occurring in ADHD (Khurshid and Khan 2009), including a striking example of seemingly complete inversion of the sleep/wake cycle in one patient (Fargason et al. 2013). Chiang et al. (2010) report that in a cross-sectional study of 325 children with ADHD, the combined subtype of ADHD was associated with circadian rhythm sleep disorders. Sivertsen et al. (2015) report that in a retrospective cohort of 9338 adolescents there was a moderate association of DSPD with inattentive and hyperactive symptoms, whilst Hysing et al. (2016) report in a cohort of 9816 adolescents that likely-ADHD status is associated with DSPD and later bedtimes. Bron et al.

Table 2 Summary of studies included for review which examined sleep-onset insomnia and delayed sleep phase disorder in ADHD

Authors and publication year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Boonstra et al. (2007)	Baseline group comparison and double-blind, placebo-controlled, crossover trial	ADHD ($N = 33$) and healthy controls ($N = 39$) for baseline comparisons. ADHD ($N = 31$) included in medication trial	Adult	Actigraphy derived sleep onset time and nonparametric circadian rhythm analysis	Daily dose of Methylphenidate titrated over a 3-week treatment period ramping up from 0.5 to 1 mg/kg/d or placebo	Methylphenidate treatment led to significantly later bedtime and sleep-onset latency. Methylphenidate treatment associated with later phase and increase in rhythm fragmentation
Bron et al. (2016)	Retrospective cohort	$N = 2090$	Adults (18–65) at risk for anxiety/ depression	MCTQ	N/A	Increased odds ratio (2.4–2.7) of late chronotype, delayed sleep phase and sleep shorter than 6 h for those scoring high on ADHD symptoms via screener
Chiang et al. (2010)	Cross-sectional	ADHD ($N = 325$) and healthy controls ($N = 257$)	Childhood/ adolescent (10–17 years)	Sleep disturbance questionnaire		ADHD associated with earlier bedtime and later rise time on weekdays
Fargason et al. (2013)	Case report	$N = 1$	Adult (31)	Actigraphy	N/A	Case report of an adult with ADHD exhibiting a complete phase reversal of the sleep wake cycle
Fargason et al. (2013)	Case–control study	$N = 105$ (ADHD + stimulants = 39, ADHD + non-stimulants = 15, ADHD no medication = 26, healthy control = 26)	Adult (19–65)	Mid-sleep calculated from pittsburgh sleep quality index	N/A	No delay in mid-sleep time associated with ADHD; later time of stimulant dosing was associated with later mid-sleep
Gruber et al. (2000)	Case–control study	ADHD ($N = 38$) and healthy controls ($N = 64$)	Childhood (7.5–11.5 years), boys	Sleep-onset time determined by actigraphy and daily sleep logs	N/A	More variable sleep-onset time in ADHD compared to healthy controls
Hoebert et al. (2009)	Long-term follow-up study	ADHD + chronic SOI ($N = 94$)	Childhood	Parental questionnaire focusing on melatonin use or discontinuation of use and consequences for sleep and behaviour	N/A	Long-term melatonin treatment effective against sleep-onset problems. Relapse of SOI occurs when treatment temporarily discontinued in 92% of children
Hvolby et al. (2008)	Case–control study	Total $N = 206$ (45 ADHD, 64 psychiatric control, 97 healthy controls)	Childhood (5-11 yrs)	Actigraphy derived sleep recordings and parent-estimated sleep diaries	N/A	Children with ADHD had significantly longer sleep-onset latency than both the psychiatric control group and healthy control group
Hysing et al. (2016)	Retrospective Cohort	$N = 9816$	Adolescent (16–19)	Presence of delayed sleep phase, sleep timing	N/A	Significantly higher prevalence of delayed sleep phase disorder in participants scoring higher on the ASRS screener than those with Low ASRS scores, significantly later betimes in higher ASRS than lower ASRS
Ironside et al. (2010)	Blinded, placebo-controlled, medication trial	ADHD ($N = 16$) stimulant medication naïve	Childhood (6–12 years)	Actigraphy derived sleep and circadian activity data	Methylphenidate three times daily over a 3-week period. Dose range 5- to 15-mg dependant on child's bodyweight or placebo	Patients treated with Methylphenidate showed a significant reduction in relative circadian amplitude and showed a significant phase delay in the timing of daily activity rhythms

Table 2 continued

Authors and publication year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Khurshid and Khan (2009)	Patient case study	Single case of ADHD with suspected comorbid delayed sleep phase disorder (DSPD)	Adult/ adolescent (18-year-old male)	Daily sleep logs detailing habitual bedtime and rise time		Self-reported and clinical history indicating extremely late bedtime and rise time consistent with DSPD
Sivertsen et al. (2015)	Retrospective cohort	9338	Adolescent (16–19 years)	Prevalence of delayed sleep phase disorder and comorbidity with ADHD symptoms	N/A	DPSD showed a moderate association with inattentive and hyperactive symptoms
Van der Heijden et al. (2005)	Case–control study	ADHD + SOI ($N = 87$) and ADHD controls without SOI ($N = 33$) all medication naïve	Childhood (6–12 years)	Sleep-onset time and wake-up time determined by actigraphy, DLMO	N/A	Sleep-onset time and wake-up time were significantly delayed in ADHD + SOI compared to ADHD without SOI. DLMO significantly more delayed in ADHD + SOI compared to ADHD without SOI
Van der Heijden et al. (2006)	Case–control study	ADHD + SOI ($N = 74$) and ADHD controls without SOI ($N = 23$) all non-medicated	Childhood (6–12 years)	Actigraphy evaluated sleep onset and sleep latency		Significantly later sleep onset and significantly long sleep latency in ADHD + SOI compared to ADHD without SOI
Van Veen et al. (2010)	Case–control study	ADHD ($N = 40$, including 31 reporting SOI) and healthy controls ($N = 24$)	Adult (18−55 years)	Sleep logs, actigraphy derived sleep measures and circadian activity variables, DLMO		Compared to healthy controls ADHD patients showed significantly longer sleep-onset latency. ADHD adults with SOI showed a significantly delayed start and end of sleep and a delayed DLMO. Rest-activity pattern showed an attenuated 24-h amplitude in ADHD + SOI
Wynchank et al. (2016)	Retrospective cohort	2239 (175 ADHD symptoms, 2064 no ADHD symptoms)	Adults (18–65) at risk for anxiety/ depression	MCTQ	N/A	Those screening for presence of clinically significant ADHD symptoms showed later sleep onset, shorter sleep and increased risk of seasonal affective disorder

(2016) report in another retrospective cohort of adults at risk for anxiety or depression there is an increased risk of late chronotype and delayed sleep phase in those scoring highly on the ADHD screener. An increased risk for delayed sleep was also noted in a cohort study by Wynchank et al. (2016).

Functional assessment of circadian rhythms in ADHD

Twenty-two studies included in this review examined functional circadian rhythms in ADHD (Table 3). These rhythms include actigraphy recorded activity/rest cycles, diurnal sampling of the hormones melatonin and cortisol, assessment of DLMO as a circadian phase marker, patterns of clock gene expression in accessible tissues, cognitive assessments and physiological measures such as heart rate variability. In a case–control study of 42 children with ADHD, Dane et al. (2000) report that actigraphy indicates greater afternoon, but not morning, activity in ADHD and that there is no subtype difference between inattentive and combined types. As noted earlier, Van der Heijden et al. (2005, 2006) indicate that ADHD is associated with a significant delay of DLMO. Van Veen et al. (2010) report that in 40 adults with ADHD that there was a delay of the diurnal cycle of activity/wake and a delayed DLMO. Baird et al. (2012) report that in 13 adults with ADHD there was loss of rhythmic expression of the clock genes *PERIOD 2 (PER2)* and *BMAL1* in oral mucosa, and the period of the actigraphic rest/activity rhythm differed significantly from 24 h. Gamble et al. report (2013) in 24 adults with ADHD that the rest/activity cycle was delayed and that this delay was correlated positively to the severity of the ADHD symptoms. A case–control study of 12 adults with ADHD reported that ADHD was associated with phase delays in DLMO, sleep onset and core and skin temperature to similar extents (Bijlenga et al. 2013a). Faedda et al. (2016) report that actigraphy can reveal differences in circadian parameters diurnal skew, L5 and relative circadian amplitude that can be used to discriminate ADHD from bipolar disorder and control in children, indicating that changes in rest/activity patterns associated in ADHD may be different from those associated with other psychiatric populations.

In studies which examined the daily profile in melatonin and/or cortisol, there are more mixed findings. Daily rhythms in salivary cortisol in 28 adults with ADHD were examined in a case–control study, and no difference was reported in ADHD compared to control (although there was not a complete diurnal sampling procedure utilised in this study, with cortisol assessment taking place at awakening, 30 min after awakening, between 17:00 and 18:00 and at 23:00; Hirvikoski et al. 2009). Personen et al. (2011) also do not report ADHD-symptom-related changes in salivary cortisol profiles assessed across the day in a cross-sectional study of 322 children with ADHD. Imeraj et al. (2012a, b) showed no differences in morning cortisol levels in 33 children with ADHD, but did note a steeper afternoon decline of cortisol in children with ADHD and oppositional defiant disorder. Baird et al. (2012) report a significant delay of the cortisol diurnal rhythm relative to wakening time in a sample of 13 adults with ADHD with 6 samples taken across 24 h. Isaksson et al. (2015) report that in a case–control study of 81 children with ADHD, wakening levels of cortisol were lower in the ADHD than the control group, and the area under the curve was also lower in the ADHD group for the daily profile compared to controls.

With regards to melatonin, as noted above a number of studies have reported delayed DLMO in adults and children with ADHD (van der Heijden et al. 2005, 2006; Van Veen et al. 2010; Bijlenga et al. 2013a). Paclt et al. (2011) report that ADHD score correlation with melatonin levels was dependent on symptoms of conduct disorder. In a case–control study of 34 children with ADHD, (Nováková et al. 2011) note that ADHD is not associated with alterations of the 24 h melatonin profile in the overall sample, although older children with ADHD showed narrower melatonin secretion profiles than controls. In their study, Baird et al. (2012) noted a blunted melatonin rhythm in adults with ADHD, but also noted more nocturnal light exposure in the ADHD group which may have contributed to acute suppression of melatonin secretion. A higher level of serum melatonin in children with hyperactive-impulsive ADHD with comorbid conduct disorder compared to inattentive ADHD was noted by (Cubero-Millán et al. 2014) in a study of 148 children. These authors also report that methylphenidate treatment was associated with a lower level of the melatonin metabolite 6-sulfatoxymelatonin. Molina-Carballo et al. (2013) report that in 226 children with ADHD treatment with methylphenidate ablates morning/evening differences in melatonin levels, possibly through raising morning levels of melatonin. An increase in urinary 6-sulfatoxymelatonin was noted in another study of 27 children and adolescents with ADHD (Büber et al. 2016). A potential involvement of pineal function and anatomy in mediating ADHD-related changes in melatonin is suggested by the study of Bumb et al. (2016) which reports that ADHD was associated with lower pineal volume in a sample of 74 adults. Further, in a case report Cunniffe et al. (2010) report that sleep/wake alterations in an adolescent with a pineal tumour had been masked clinically by the presence of an ADHD diagnosis, thus highlighting the overlap of sleep/wake symptoms resulting from ADHD or pineal dysfunction.

There are three studies included in this review which have examined rhythms in physiological and cognitive parameters. Imeraj et al. (2011) report that children with

Table 3 Summary of studies included for review which involved functional assessment of circadian rhythms in ADHD

Authors and publication Year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Baird et al. (2012)	Case–control study	$N = 32$ (13 ADHD, 19 control)	Adult	Actigraphy, MEQ, salivary cortisol and melatonin, oral mucosa expression of PER2 and BMAL1	N/A	ADHD was associated with loss of the molecular rhythm of PER2 and BMAL1 in the oral mucosa. ADHD was also associated with greater eveningness and a delay of the cortisol rhythm referenced to wake time
Bijlenga et al. (2013a)	Case–control study	$N = 24$ (12 ADHD, 12 healthy control)	Adult (18–55)	MCTQ, actigraphy, DLMO, core body and skin temperature	N/A	ADHD was associated with delays in DLMO, sleep onset and body temperature. ADHD was also associated with shorter sleep
Büber et al. (2016)	Case–control study	ADHD ($N = 27$, non-medicated) and healthy controls ($N = 28$)	Childhood and Adolescent (6–16 yrs)	Urinary 6-sulfatoxymelatonin	N/A	Significantly increased daytime, night-time and 24-h 6-sulfatoxymelatonin in the ADHD group
Buchhorn et al. (2012)	Case–control study	$N = 50$ (12 ADHD, 19 ADHD + Methylphenidate, 19 healthy controls)	Childhood	Diurnal rhythms of heart rate variability	N/A	Heart rate sharply increases in ADHD group in the afternoon, less heart rate variability in ADHD with no treatment, methylphenidate treatment increase heart rate variability towards control levels
Bumb et al. (2016)	Case–control	74 ADHD, 86 healthy controls	Adults (18–55)	MEQ, MRI of Pineal volume	N/A	Greater eveningness and lower pineal volume associated with ADHD
Cubero-Millán et al. (2014)	Prospective open quasi-experimental study	ADHD $N = 148$	Childhood (5–14)	Blood melatonin and urinary 6-sulfatoxymelatonin	N/A	Melatonin is higher in hyperactive-impulsive/conduct disordered ADHD-subtype than inattentive ADHD subtype; methylphenidate lowers 6-sulfatoxymelatonin levels
Cunniffe et al. (2010)	Case study	Single case of ADHD with co-occurring pineal gland tumour	Adolescent (17-year-old male)	Clinical record		Case report highlights how sleep disturbances and behavioural symptoms associated with organic brain disease may be masked by ADHD diagnosis
Dane et al. (2000)	Case–control study	ADHD-I ($N = 20$), ADHD-C ($N = 22$), and healthy controls ($N = 22$)	Childhood (7–12 years)	Motor activity assessed by wrist-worn actigraph	N/A	ADHD patients presented with greater motor activity in the afternoon compared to controls. No differences were noted during morning test session. No differences detected between ADHD-I and ADHD-C subtypes
Faedda et al. (2016)	Case–control study	ADHD ($N = 44$), ADHD + depressive disorder ($N = 21$), Bipolar Disorder ($N = 44$) or healthy control ($N = 42$), all non-medicated	Childhood and Adolescent (5–18 years)	Belt-worn actigraphy	N/A	Diurnal skew, L5 and relative circadian amplitude can discriminate between ADHD, BD and controls

Table 3 continued

Authors and publication Year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Gamble et al. (2013)	Case–control study	$N = 38$ (24 ADHD, 14 healthy control)	Adult (19–65)	Actigraphy	N/A	ADHD was associated with delay of the sleep/wake cycle. Severity of ADHD was correlated with magnitude of delay of sleep onset
Hirvikoski et al. (2009)	Case–control study	ADHD ($N = 28$) and healthy controls ($N = 28$)	Adult (19-54 yrs)	Diurnal rhythm and levels of salivary cortisol	N/A	No differences in diurnal rhythm or levels of cortisol secretion between ADHD and control groups
Hunt et al. (2012)	Randomized experiment	$N = 55$	Adults (mean age = 20.7)	Test of variables of attention (TOVA) in the morning and afternoon, MEQ	N/A	No time-of-day effect in ADHD patients on TOVA performance; evening types made less errors on TOVa, but had higher self-reported inattention
Imeraj et al. (2011)	Case–control study	$N = 60$ (30 ADHD, 30 healthy controls)	Childhood (6–11)	Diurnal heart rate, actigraphy	N/A	ADHD was associated with higher heart rate, especially during afternoon and night. ADHD was not associated with increase nocturnal motor activity
Imeraj et al. (2012)	Case–control study	$N = 66$ (22 ADHD + oppositional defiant disorder, 11 ADHD, 33 healthy control)	Childhood (6–12)	Diurnal salivary cortisol	N/A	No difference in morning cortisol between groups, ADHD + oppositional/defiant disorder showed steeper daytime decline of cortisol
Isaksson et al. (2015)	Case–control study	ADHD ($N = 81$) and Healthy Control ($N = 88$)	Childhood	Diurnal salivary cortisol	N/A	ADHD was associated with lower wakening cortisol
Molina-Carballo et al. (2013)	Prospective open quasi-experimental study	$N = 226$	Childhood (5–14)	Serum melatonin, urinary 6-sulfatoxymelatonin	Prolonged release methylphenidate treatment	Methylphenidate treatment ablates the morning/evening difference in melatonin in the ADHD group
Nováková et al. (2011)	Case–control study	$N = 77$ (34 ADHD and 43 healthy controls)	Childhood (6–12)	Diurnal salivary melatonin rhythms	N/A	Nocturnal melatonin did not differ between ADHD and controls; older ADHD children showed altered melatonin rhythm profile than controls
Paclt et al. (2011)	Case–control	$N = 88$ (34 ADHD, 11 anxiety, 43 healthy controls)	Childhood (6-12)	Diurnal patterns of salivary melatonin	N/A	Comorbid conduct disorder with ADHD was associated with alterations in melatonin profiles
Pesonen et al. (2011)	Cross-sectional	321	Childhood (mean age = 8)	Diurnal salivary cortisol	N/A	ADHD symptoms were not associated with changes in the diurnal cortisol profile
Van der Heijden et al. (2005)	Case–control study	ADHD + SOI ($N = 87$) and ADHD controls without SOI ($N = 33$), all medication naïve	Childhood (6-12 years)	Sleep-onset time and wake-up time determined by actigraphy. dim light melatonin onset (DLMO)	N/A	Sleep-onset time and wake-up time were significantly delayed in ADHD + SOI compared to ADHD without SOI. DLMO significantly more delayed in ADHD + SOI compared to ADHD without SOI

Table 3 continued

Authors and publication Year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Van der Heijden et al. (2006)	Case–control study	ADHD + SOI ($N = 74$) and ADHD controls without SOI ($N = 23$) all non-medicated	Childhood (6-12 years)	Actigraphy evaluated sleep onset and sleep latency		Significantly later sleep onset and significantly long sleep latency in ADHD + SOI compared to ADHD without SOI
Van Veen et al. (2010)	Case–control study	ADHD ($N = 40$, including 31 reporting SOI) and healthy controls ($N = 24$)	Adult (18–55 years)	Sleep logs, actigraphy derived sleep measures and circadian activity variables, and salivary melatonin to determine DLMO		Compared to healthy controls ADHD patients showed significantly longer sleep-onset latency. ADHD adults with SOI showed a significantly delayed start and end of sleep and a delayed DLMO. Rest-activity pattern showed an attenuated 24-h amplitude in ADHD + SOI

ADHD ($N = 30$) showed elevated heart rate, most pronounced in the afternoon and the night. Buchhorn et al. (2012) also examined diurnal changes in heart rate, and heart rate variability, in a case–control study of 31 children with ADHD, and report that ADHD was associated with a marked increase in heart rate in the afternoon and less pronounced diurnal variation in heart rate variability. Both of these studies indicate that altered circadian function may manifest in alterations of autonomic function relevant for ADHD (Buijs et al. 2016; Rash et al. 2012). Impaired sustained attention is a key cognitive dysfunction in ADHD, one that can be assessed using objective tests of attention and vigilance. Hunt and colleagues (2012) report that for one such cohort, the test of variables of attention, applied to 55 young adults with ADHD in the morning and the late afternoon, indicates that there is no time-of-day effect on performance on this test.

Intervention studies

Nine studies included in this review have examined the impact of various interventions that target the circadian system in ADHD (Table 4). The largest group of these studies examine the impact of melatonin administration on ADHD symptoms and other associated outcomes. Tjon Pian Gi et al. (2003) examined the efficacy of melatonin administration prior to bedtime in 24 children with ADHD and insomnia in a prospective open quasi-experimental study and report that such treatment lead to a rapid onset decrease in sleep latency, which was significantly sustained at three-month follow-up. Weiss et al. (2006) report that in a randomised, double-blind crossover trial in 27 children and adolescents with ADHD, melatonin reduced insomnia; the largest reduction in insomnia resulted from co-administration of melatonin and a sleep hygiene intervention. Van der Heijden et al. (2007) report results from a randomised double-blind placebo-controlled trial of evening melatonin for 105 children with ADHD, which indicate that melatonin treatment resulted in advanced sleep-onset time and DLMO, indicating an effect of melatonin on underlying delayed circadian phase. Mohammadi et al. (2012) conducted a randomised control trial (RCT) in 60 children with ADHD which examined the co-administration of methylphenidate with melatonin over a period of 8 weeks and report that melatonin treatment was associated with shorter sleep latency, but not with ADHD ratings. Similar decrease in sleep latency was described in a study by Mostafavi et al. (2012) using melatonin co-administered with methylphenidate, which also noted an increase in height and weight following melatonin treatment, with no effect reported on food intake or appetite. A long-term follow-up study by Hoebert et al. (2009) in 94 children with ADHD and sleep-onset insomnia indicated that melatonin discontinuation was

Table 4 Summary of studies included for review which examined chronotherapeutic interventions in ADHD

Authors and publication year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Furster and Hallerbäck (2015)	Register study	N/A	Childhood and adolescent	Exogenous melatonin usage in the Swedish Prescribed Drug Register	N/A	>50% of children and adolescents in Sweden using melatonin were also using ADHD medication. Melatonin use is more prevalent in boys than girls
Gruber et al. (2007)	Case report	$N = 1$	Child (11)	Actigraphy	Morning bright light therapy	Improvement in sustained attention and teacher rated ADHD score, amelioration of delayed phase sleep disorder following light therapy
Hoebert et al. (2009)	Long-term follow-up study	ADHD + chronic SOI ($N = 94$)	Childhood	Parental questionnaire focusing on melatonin use or discontinuation of use and consequences for sleep and behaviour	N/A	Long-term melatonin treatment effective against sleep onset problems. Relapse of SOI occurs when treatment temporarily discontinued in 92% of children
Mohammadi et al. (2012)	Randomized control trial	$N = 60$	Childhood (7–12)	Subjective sleep scoring, ADHD ratings	Melatonin co-administered with methylphenidate, 8-week trial	Melatonin treatment was associated with shorter sleep latencies; no changes in ADHD ratings with melatonin treatment
Mostafavi et al. (2012)	Double-blind RCT	$N = 50$	Childhood (7–12)	Subjective sleep latency, calorific intake, subjective appetite ratings, height, weight	Melatonin co-administered with methylphenidate	Melatonin decreased sleep latency and was associated with increased height and weight after 8-week melatonin treatment. No effects on food intake or appetite were found
Niederhofer (2012)	Placebo-controlled trial	$N = 10$ ADHD	Adolescent (17–19)	Wender-Utah Questionnaire for ADHD	Agomelatine treatment (4 weeks)	Agomelatine treatment was associated with decreased ADHD scores across a range of Wender-Utah subscales compared to placebo
Tjon Pian Gi et al. (2003)	Prospective open quasi-experimental study	ADHD with insomnia ($N = 24$)	Childhood	Sleep onset time	Melatonin before bed in conjunction with normal methylphenidate treatment	Subjects fell asleep significantly faster than pre-treatment baseline. Immediate effect noticed in week 1 of study and was present after long-term follow-up in month 3

Table 4 continued

Authors and publication year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Rybak et al. 2006	Prospective open quasi-experimental study	ADHD (N = 29)	Adult (18–60 years)	Morningness–eveningness questionnaire (MEQ) and daily self-report sleep/wake diary	3-week standard light therapy during autumn and winter months	Increased morningness scores among patients after completing LT. Reduction in ADHD symptom severity indicated by Brown Adult ADD scale and CAARS associated with greater MEQ scores
Van der Heijden et al. (2007)	Randomized, double-blind, placebo-controlled trial	ADHD (N = 105, medication free)	Childhood (6–12 years)	Actigraphy-derived sleep onset and DLMO	Oral administration of 3 or 6 mg melatonin (depending on body weight) or placebo delivered in the evening for 4 weeks	Sleep onset time advanced with melatonin treatment and delayed with placebo. DLMO showed significant advances in treated group compared to placebo group which was significantly delayed. No effects noted on behaviour or cognition
Weiss et al. (2006)	Randomized, double-blind, placebo-controlled, crossover trial	ADHD (N = 27, stimulant treated)	Childhood and adolescent (6–14 years)	Reduction in initial insomnia (sleep onset insomnia >60 min)	Sleep hygiene protocol. Non-responders treated with 5 mg melatonin	Significant reduction in initial insomnia (<60 min) in 5 cases receiving sleep hygiene therapy alone. Melatonin-treated cases showed a significant reduction in initial insomnia relative to placebo. Largest effect size noted for combined sleep hygiene therapy and melatonin treatment

associated with relapse of sleep-onset insomnia in 92% of cases. A register study in Sweden indicates that 50% of children prescribed melatonin were also using ADHD medications and that melatonin usage was higher in boys than girls (Furster and Hallerbäck 2015).

There is little comprehensive evidence for other chronotherapeutic approaches in ADHD. Gruber et al. (2007) report a single case for the use of morning bright light therapy in a child with ADHD with resulting improvements in ADHD ratings and amelioration of delayed phase sleep disorder. Niederhofer (2012) report results of a small randomised placebo-controlled trial of the use of the chronobiotic antidepressant agomelatine in 10 adolescents with ADHD which indicate that agomelatine treatment was associated with decreased ADHD symptoms. Rybak et al (2006) report that morning light therapy in adults with ADHD results in alleviation of core ADHD symptoms, improvement of mood symptoms and advances of circadian preference.

Genetic and environmental association studies

Five studies are included in this review that examined association of polymorphisms in circadian clock genes with ADHD (Table 5). Kissling et al. (2008) reported that the T3111C single-nucleotide polymorphism (SNP) in *CLOCK* is associated with ADHD symptoms in a forensic, adult male population of 143, with the T allele conferring risk. Xu et al. (2010) report similar results from adult ADHD, with the T allele of the T3111C SNP in *CLOCK* associated with ADHD. Jeong et al. (2014) report that the T3111C SNP in *CLOCK* is also associated with ADHD symptoms in males. Cao et al. (2012) also find that the T3111C SNP in *CLOCK* is associated with ADHD in

Table 5 Summary of studies included for review which examined circadian-related genetic and environmental associations with ADHD

Authors and publication year	Study design	Participants	Paediatric, adolescent or adults	Circadian rhythms measures	Intervention	Summary of main results
Arns et al. (2013)	Analysis of cross-sectional studies	N/A	Childhood, adolescent and adult	Solar intensity	N/A	An association between solar intensity and ADHD prevalence was described, with higher solar intensity associated with lower prevalence. Solar intensity predicts 34–57% of variance n ADHD prevalence
Arns et al. (2015)	Analysis of cross-sectional studies	N/A	Childhood, adolescent and adult	Solar intensity	N/A	The previously described relationship between altitude and ADHD prevalence (Huber et al. 2015) may be mediated via solar intensity
Brookes et al. (2006)	Genome-wide association study	$N = 1442$ (674 ADHD, 808 control)	Childhood	Genetic association	N/A	Speculative association of SNP in PER2 with ADHD (not study-wide or genome-wide significant)
Cao et al. (2012)	Genetic association study	$N = 316$ (166 ADHD, 150 healthy control)	Childhood	Genetic association of T3111C SNP in *CLOCK* gene with ADHD	N/A	C allele of 3111 SNP in *CLOCK* was associated with the ADHD group (odds ratio 1.7)
Chaste et al. (2011)	Genetic association study	321 (101 ADHD, 220 healthy control)	Adults	Presence of coding variants in the melatonin biosynthesis pathway	N/A	Non-coding mutations in melatonin synthesis pathway were found in ADHD, but these were not significantly enriched compared to controls
Jeong et al. (2014)	Genetic Association Study	$N = 1289$	Adult	*CLOCK* genotype, composite scale of morningness (CSM)	N/A	3111T/C SNP in *CLOCK* is associated with retrospective ADHD ratings via WURS-25; significant correlation between CSM and WURS-25 scores
Kissling et al. (2008)	Candidate gene association study	$N = 143$ adult males	Adult	*CLOCK* genotype	N/A	T-mutation of the *CLOCK* 3111 T/C SNP associated with self-reported symptoms of ADHD and diagnostic interview
Langevin and Ramdé (2012)	Case–control study	$N = 15$ (10 ADHD, 5 control)	Childhood (7–9)	Actigraphy	Natural changes in photoperiod	Shortened photoperiod is associated with more nocturnal agitation in ADHD
Xu et al. (2010)	Candidate gene association study	ADHD probands from the UK ($N = 180$) and Taiwan ($N = 212$)	Childhood/ adolescent (5–15 years)	*CLOCK* genotype		Transmission bias of T allele of *CLOCK* 3111 T/C SNP associated with ADHD

children, although contrary to previous finings the authors found in their study that the C allele confers risk. Brookes et al. (2006) in a genome-wide study provide speculative evidence that polymorphisms in *PER 2* may be associated with ADHD in children, but the association was not significant at the study-wide or genome-wide level, and so this evidence should be treated with caution. Chaste et al. (2011) report the presence of coding mutations in the melatonin biosynthesis pathway found in a sample of 101 adults with ADHD, but these mutations were not significantly enriched compared to the control population.

Three studies examining the association of circadian-relevant environmental factors with ADHD are included in this review (Table 5). Arns et al. (2013) report that in an analysis of records from ten countries that solar intensity is associated with ADHD prevalence and postulate that this may be in part due to enhanced early morning bright light which might advance and correct otherwise delayed circadian phase, which may be associated with ADHD symptoms. Arns et al. (2015) also suggest that an association noted by Huber et al. (2015) between altitude and ADHD prevalence may be mediated through solar intensity. Finally, in a

naturalistic study in northern latitudes, Langevin and Ramdé (2012) find that the shortening of photoperiod in the winter is associated with more nocturnal agitation in ten children with ADHD studied with actigraphy.

Conclusions

This review of the literature highlights a number of striking findings with regards to circadian function and ADHD. First is the remarkable consensus in findings for delayed circadian phase and later chronotype/evening preference associated with ADHD. This level of consistency is in contrast with the mixed picture reported for phase alterations associated with different psychiatric conditions, where a mixture of phase delays, phase advances and no changes are reported (e.g. bipolar disorder; Melo et al. 2016). This circadian phase delay may of course be linked to the observed link between ADHD and sleep-onset insomnia and delayed sleep phase disorder. There appears to be little evidence for other circadian changes in ADHD, such as alterations in rhythm amplitude. This again is in contrast with circadian changes associated with other conditions such as dementia, where dampened circadian amplitude may be the major change that occurs (Coogan et al. 2013a, b). It is not clear why circadian rhythms show such delays in ADHD, although the observation by Kooij and Bijlenga (2014) of higher than expected levels of photophobia associated with ADHD may indicate that there is a change in the melanopsin photoreceptive system, as this is associated with both circadian entrainment and other non-visual responses to light including photophobia (La Morgia et al. 2011). Future studies might address themselves to the role of melanopsin function and circadian entrainment explicitly in ADHD.

The presence of consistent findings of delayed circadian rhythms in ADHD raise the possibility of chronotherapeutic approaches to "correct" underlying phase alterations with a view to increasing sleep quality/quantity and ultimately leading to a decrease in ADHD symptoms. Such an approach has been shown in other conditions to be of considerable promise (e.g. Lewy et al. 2006). However, the current evidence base for such approaches in ADHD is disappointingly weak, with only one small trial of agomelatine and one case report for light therapy assessed in the course of this review. Thus, there would appear to be considerable scope to develop this avenue of investigation in future work. There is stronger evidence of the use of melatonin in ADHD, with studies included in this review indicating beneficial effects on sleep but not on ADHD symptoms. It should be noted that most of the studies examined utilised melatonin as a somnolent, and not explicitly as a chronobiotic whose main effect would be to advance circadian phase. Such use of melatonin requires lower doses, but timing of dosing is vital and should be tailored to the underlying circadian phase misalignment (Lewy 2007). Further, the use of the chronobiotic antidepressant agomelatine, which is a melatoninergic agonist, should be further explored in ADHD. There is clearly a need here for well-designed, sufficiently powered RCTs for such interventions in ADHD, and it should be noted that recent results of chronotherapy from RCTs are providing promising results (e.g. light therapy in major depression; Lam et al. 2016).

From an aetiological perspective, as there is a lack of prospective and longitudinal studies of circadian function in ADHD, inferences about causality of circadian dysfunction and ADHD cannot be made. Further, whilst there are some indications that polymorphisms in clock genes may be associated with ADHD, evidence is not strong although there are four separate studies implicating the *CLOCK* gene. Another potentially important issue on which there appears to be too little information to make firm conclusions is the role ADHD medication plays in observed circadian changes in ADHD. Animal studies indicate that stimulant and non-stimulant medications can impact on circadian processes (e.g. Antle et al. 2012; Baird et al. 2013; O'Keeffe et al. 2012). There are also indications that ADHD medications can impact on sleep (e.g. Cortese et al. 2013). However, there are little explicit analyses of ADHD medication on circadian function, and future studies might address medicated and non-medicated ADHD populations for circadian function in either case–control or crossover studies.

Overall, results from this systematic review highlights a striking commonality of findings of circadian phase delays associated with ADHD, but also highlights the weakness of the literature surrounding chronotherapeutic interventions in ADHD and delineation of the aetiological significance of circadian dysfunction in ADHD.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by the authors.

References

Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C (2012) Circadian typology: a comprehensive review. Chronobiol Int 29(9):1153–1175

Antle MC, van Diepen HC, Deboer T, Pedram P, Pereira RR, Meijer JH (2012) Methylphenidate modifies the motion of the circadian clock. Neuropsychopharmacol 37(11):2446–2455

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5. D.C: American Psychiatric Association, Washington

Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP (2003) The role of actigraphy in the study of sleep and circadian rhythms. Sleep 26(3):342–392

Arns M, van der Heijden KB, Arnold LE, Kenemans JL (2013) Geographic variation in the prevalence of attention-deficit/hyperactivity disorder: the sunny perspective. Biol Psychiatry 74(8):585–590

Arns M, Swanson JM, Arnold LE (2015) ADHD Prevalence: altitude or sunlight? Better understanding the interrelations of dopamine and the circadian system. J Atten Disord. doi:10.1177/1087054715599574

Babkoff H, Caspy T, Mikulincer M (1991) Subjective sleepiness ratings: the effects of sleep deprivation, circadian rhythmicity and cognitive performance. Sleep 14(6):534–539

Baird AL, Coogan AN, Siddiqui A, Donev RM, Thome J (2012) Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. Mol Psychiatry 17(10):988–995

Baird AL, Coogan AN, Kaufling J, Barrot M, Thome J (2013) Daily methylphenidate and atomoxetine treatment impacts on clock gene protein expression in the mouse brain. Brain Res 1513:61–71

Bell AS (2011) A critical review of ADHD diagnostic criteria: what to address in the DSM-V. J Atten Disord 15(1):3–10

Bijlenga D, van der Heijden KB, Breuk M, van Someren EJ, Lie ME, Boonstra AM, Swaab HJ, Kooij JJ (2013a) Associations between sleep characteristics, seasonal depressive symptoms, lifestyle, and ADHD symptoms in adults. J Atten Disord 17(3):261–275

Bijlenga D, Van Someren EJ, Gruber R, Bron TI, Kruithof IF, Spanbroek EC, Kooij JJ (2013b) Body temperature, activity and melatonin profiles in adults with attention-deficit/hyperactivity disorder and delayed sleep: a case-control study. J Sleep Res 22(6):607–616

Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJ (2007) Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 30(4):433–442

Borbély AA, Daan S, Wirz-Justice A, Deboer T (2016) The two-process model of sleep regulation: a reappraisal. J Sleep Res 25(2):131–143

Bron TI, Bijlenga D, Kooij JJ, Vogel SW, Wynchank D, Beekman AT, Penninx BW (2016) Attention-deficit hyperactivity disorder symptoms add risk to circadian rhythm sleep problems in depression and anxiety. J Affect Disord 200:74–81

Brookes K, Xu X, Chen W, Zhou K, Neale B, Lowe N, Anney R, Franke B, Gill M, Ebstein R, Buitelaar J, Sham P, Campbell D, Knight J, Andreou P, Altink M, Arnold R, Boer F, Buschgens C, Butler L, Christiansen H, Feldman L, Fleischman K, Fliers E, Howe-Forbes R, Goldfarb A, Heise A, Gabriëls I, Korn-Lubetzki I, Johansson L, Marco R, Medad S, Minderaa R, Mulas F, Müller U, Mulligan A, Rabin K, Rommelse N, Sethna V, Sorohan J, Uebel H, Psychogiou L, Weeks A, Barrett R, Craig I, Banaschewski T, Sonuga-Barke E, Eisenberg J, Kuntsi J, Manor I, McGuffin P, Miranda A, Oades RD, Plomin R, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Taylor E, Thompson M, Faraone SV, Asherson P (2006) The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Mol Psychiatry 11(10):934–953

Büber A, Çakaloz B, Işıldar Y, Ünlü G, Bostancı HE, Aybek H, Herken H (2016) Increased urinary 6-hydroxymelatoninsulfate levels in attention deficit hyperactivity disorder diagnosed children and adolescent. Neurosci Lett 617:195–200

Buchhorn R, Conzelmann A, Willaschek C, Störk D, Taurines R, Renner TJ (2012) Heart rate variability and methylphenidate in children with ADHD. Atten Defic Hyperact Disord 4(2):85–91. doi:10.1007/s12402-012-0072-8 **(Epub 2012 Feb 11 PubMed PMID: 22328340)**

Buijs FN, León-Mercado L, Guzmán-Ruiz M, Guerrero-Vargas NN, Romo-Nava F, Buijs RM (2016) The circadian system: a regulatory feedback network of periphery and brain. Physiol (Bethesda) 31(3):170–181

Bumb JM, Mier D, Noelte I, Schredl M, Kirsch P, Hennig O, Liebrich L, Fenske S, Alm B, Sauer C, Leweke FM, Sobanski E (2016) Associations of pineal volume, chronotype and symptom severity in adults with attention deficit hyperactivity disorder and healthy controls. Eur Neuropsychopharmacol 26(7):1119–1126

Buttgereit F, Smolen JS, Coogan AN, Cajochen C (2016) Clocking in: chronobiology in rheumatoid arthritis. Nat Rev Rheumatol 11(6):349–356

Caci H, Bouchez J, Baylé FJ (2009) Inattentive symptoms of ADHD are related to evening orientation. J Atten Disord 13(1):36–41

Cao YL, Cui QT, Tang CH, Chang X (2012) Association of CLOCK gene T3111C polymorphism with attention deficit hyperactivity disorder and related sleep disturbances in children. Zhongguo Dang Dai Er Ke Za Zhi 14(4):285–288

Chaste P, Clement N, Botros HG, Guillaume JL, Konyukh M, Pagan C, Scheid I, Nygren G, Anckarsäter H, Rastam M, Ståhlberg O, Gillberg IC, Melke J, Delorme R, Leblond C, Toro R, Huguet G, Fauchereau F, Durand C, Boudarene L, Serrano E, Lemière N, Launay JM, Leboyer M, Jockers R, Gillberg C, Bourgeron T (2011) Genetic variations of the melatonin pathway in patients with attention-deficit and hyperactivity disorders. J Pineal Res 51(4):394–399

Chiang HL, Gau SS, Ni HC, Chiu YN, Shang CY, Wu YY, Lin LY, Tai YM, Soong WT (2010) Association between symptoms and subtypes of attention-deficit hyperactivity disorder and sleep problems/disorders. J Sleep Res 19(4):535–545

Coogan AN (2013) Chronobiology and chronotherapy of affective disorders. J Cognit Behav Psychother 13:1–13

Coogan AN, Baird AL, Popa-Wagner A, Thome J (2013a) Circadian rhythms and attention deficit hyperactivity disorder: the what, the when and the why. Prog Neuropsychopharmacol Biol Psychiatry 67:74–81

Coogan AN, Schutová B, Husung S, Furczyk K, Baune BT, Kropp P, Häßler F, Thome J (2013b) The circadian system in Alzheimer's disease: disturbances, mechanisms, and opportunities. Biol Psychiatry 74(5):333–339

Coogan AN, Baird AL, Popa-Wagner A, Thome J (2016) Circadian rhythms and attention deficit hyperactivity disorder: the what, the when and the why. Prog Neuropsychopharmacol Biol Psychiatry 67:74–81

Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Graham J, Taylor E, Sergeant J; European ADHD Guidelines Group (2013) Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry 54(3):227–246

Cubero-Millán I, Molina-Carballo A, Machado-Casas I, Fernández-López L, Martínez-Serrano S, Tortosa-Pinto P, Ruiz-López A, Luna-del-Castillo JD, Uberos J, Muñoz-Hoyos A (2014) Methylphenidate ameliorates depressive comorbidity in ADHD children without any modification on differences in serum melatonin concentration between ADHD subtypes. Int J Mol Sci 15(9):17115–17129

Cunniffe G, Murthy R, Beigi B (2010) Attention deficit hyperactivity disorder: diagnosis and treatment masking the ophthalmic clinical presentation of a pineal gland tumour in a teenager. Int Ophthalmol 30(6):727–730

Dallaspezia S, Benedetti F (2015) Chronobiology of bipolar disorder: therapeutic implication. Curr Psychiatry Rep 17(8):606

Dane AV, Schachar RJ, Tannock R (2000) Does actigraphy differentiate ADHD subtypes in a clinical research setting? J Am Acad Child Adolesc Psychiatry 39(6):752–760

Erren TC, Reiter RJ (2015) Melatonin: a universal time messenger. Neuro Endocrinol Lett. 36(3):187–192

Faedda GL, Ohashi K, Hernandez M, McGreenery CE, Grant MC, Baroni A, Polcari A, Teicher MH (2016) Actigraph measures discriminate pediatric bipolar disorder from attention-deficit/hyperactivity disorder and typically developing controls. J Child Psychol Psychiatry 57(6):706–716

Fargason RE, White BA, Gamble KL (2013) Complete sleep-wake cycle reversal related to ADHD detected by actigraphy. Ann Clin Psychiatry 25(4):307–308

Furster C, Hallerbäck MU (2015) The use of melatonin in Swedish children and adolescents—a register-based study according to age, gender, and medication of ADHD. Eur J Clin Pharmacol 77(7):877–881

Gamble KL, May RS, Besing RC, Tankersly AP, Fargason RE (2013) Delayed sleep timing and symptoms in adults with attention-deficit/hyperactivity disorder: a controlled actigraphy study. Chronobiol Int 30(4):598–606

Gruber R, Sadeh A, Raviv A (2000) Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 39(4):495–501

Gruber R, Grizenko N, Joober R (2007) Delayed sleep phase syndrome, ADHD, and bright light therapy. J Clin Psychiatry 68(2):337–338

Gruber R, Fontil L, Bergmame L, Wiebe ST, Amsel R, Frenette S, Carrier J (2012) Contributions of circadian tendencies and behavioral problems to sleep onset problems of children with ADHD. BMC Psychiatry 12:212

Hirvikoski T, Lindholm T, Nordenström A, Nordström AL, Lajic S (2009) High self-perceived stress and many stressors, but normal diurnal cortisol rhythm, in adults with ADHD (attention-deficit/hyperactivity disorder). Horm Behav 55(3):418–424

Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res 47(1):1–7

Huber RS, Kim TS, Kim N, Kuykendall MD, Sherwood SN, Renshaw PF, Kondo DG (2015) Association between altitude and regional variation of ADHD in youth. J Atten Disord pii:1087054715577137

Hunt MG, Bienstock SW, Qiang JK (2012) Effects of diurnal variation on the test of variables of attention performance in young adults with attention-deficit/hyperactivity disorder. Psychol Assess 24(1):166–172

Hvolby A (2015) Associations of sleep disturbance with ADHD: implications for treatment. Atten Defic Hyperact Disord 7(1):1–18

Hvolby A, Jørgensen J, Bilenberg N (2008) Actigraphic and parental reports of sleep difficulties in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 162(4):323–329

Hysing M, Lundervold AJ, Posserud MB, Sivertsen B (2016) Association between sleep problems and symptoms of attention deficit hyperactivity disorder in adolescence: results from a large population-based study. Behav Sleep Med 14(5):550–564

Imeraj L, Antrop I, Roeyers H, Deschepper E, Bal S, Deboutte D (2011) Diurnal variations in arousal: a naturalistic heart rate study in children with ADHD. Eur Child Adolesc Psychiatry 20(8):381–392

Imeraj L, Antrop I, Roeyers H, Swanson J, Deschepper E, Bal S, Deboutte D (2012a) Time-of-day effects in arousal: disrupted diurnal cortisol profiles in children with ADHD. J Child Psychol Psychiatry 53(7):782–789

Imeraj L, Sonuga-Barke E, Antrop I, Roeyers H, Wiersema R, Bal S, Deboutte D (2012b) Altered circadian profiles in attention-deficit/hyperactivity disorder: an integrative review and theoretical framework for future studies. Neurosci Biobehav Rev 36(8):1897–1919

Ironside S, Davidson F, Corkum P (2010) Circadian motor activity affected by stimulant medication in children with attention-deficit/hyperactivity disorder. J Sleep Res 19(4):546–551

Isaksson J, Allen M, Nilsson KW, Lindblad F (2015) Polymorphisms in the FK506 binding protein 5 gene are associated with attention deficit hyperactivity disorder and diurnal cortisol levels. Acta Paediatr 104(9):910–915

Jeong SH, Yu JC, Lee CH, Choi KS, Choi JE, Kim SH, Joo EJ (2014) Human CLOCK gene-associated attention deficit hyperactivity disorder-related features in healthy adults: quantitative association study using Wender Utah Rating Scale. Eur Arch Psychiatry Clin Neurosci 264(1):71–81

Kantermann T, Sung H, Burgess HJ (2015) Comparing the morningness-eveningness questionnaire and munich chronotype questionnaire to the dim light melatonin onset. J Biol Rhythms 30(5):449–453

Khurshid KA, Khan AA (2009) Delayed sleep phase disorder and attention deficit and hyperactivity symptoms in a teenager. Atten Defic Hyperact Disord 1(2):211–213

Kissling C, Retz W, Wiemann S, Coogan AN, Clement RM, Hünnerkopf R, Conner AC, Freitag CM, Rösler M, Thome J (2008) A polymorphism at the 3′-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147(3):333–338

Kooij JJ, Bijlenga D (2014) High prevalence of self-reported photophobia in adult ADHD. Front Neurol 5:256

La Morgia C, Ross-Cisneros FN, Hannibal J, Montagna P, Sadun AA, Carelli V (2011) Melanopsin-expressing retinal ganglion cells: implications for human diseases. Vis Res 51(2):296–302

Lack LC, Wright HR (2007) Treating chronobiological components of chronic insomnia. Sleep Med 8(6):637–644

Lam RW, Levitt AJ, Levitan RD, Michalak EE, Cheung AH, Morehouse R, Ramasubbu R, Yatham LN, Tam EM (2016) Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. JAMA Psychiatry 73(1):56–63

Landgraf D, McCarthy MJ, Welsh DK (2014) The role of the circadian clock in animal models of mood disorders. Behav Neurosci 128(3):344–359

Langevin R, Ramdé J (2012) Attention deficit hyperactivity disorder (ADHD) in children, seasonal photoperiods, nocturnal movements and diurnal agitation. J Can Acad Child Adolesc Psychiatry 21(1):53–58

Levandovski R, Sasso E, Hidalgo MP (2013) Chronotype: a review of the advances, limits and applicability of the main instruments used in the literature to assess human phenotype. Trends Psychiatry Psychother 35(1):3–11

Lewy AJ (2007) Melatonin and human chronobiology. Cold Spring Harb Symp Quant Biol 72:623–636

Lewy AJ, Lefler BJ, Emens JS, Bauer VK (2006) The circadian basis of winter depression. Proc Natl Acad Sci USA 103(19):7414–7419

Loe IM, Feldman HM (2007) Academic and educational outcomes of children with ADHD. J Pediatr Psychol 32(6):643–654

Lucas RJ, Peirson SN, Berson DM, Brown TM, Cooper HM, Czeisler CA, Figueiro MG, Gamlin PD, Lockley SW, O'Hagan JB, Price LL, Provencio I, Skene DJ, Brainard GC (2014) Measuring and using light in the melanopsin age. Trends Neurosci 37(1):1–9

Matthews M, Nigg JT, Fair DA (2014) Attention deficit hyperactivity disorder. Curr Top Behav Neurosci 16:235–266

McGowan NM, Voinescu BI, Coogan AN (2016) Sleep quality, chronotype and social jetlag differentially associate with symptoms of attention deficit hyperactivity disorder in adults. Chronobiol Int 33(10):1433–1443

Melo MC, Abreu RL, Linhares Neto VB, de Bruin PF, de Bruin VM (2016) Chronotype and circadian rhythm in bipolar disorder: a systematic review. Sleep Med Rev S1087–0792(16): 30059–30064

Micic G, Lovato N, Gradisar M, Ferguson SA, Burgess HJ, Lack LC (2016) The etiology of delayed sleep phase disorder. Sleep Med Rev 27:29–38

Mohammadi MR, Mostafavi SA, Keshavarz SA, Eshraghian MR, Hosseinzadeh P, Hosseinzadeh-Attar MJ, Kooshesh SM, Chamari M, Akhondzadeh S (2012) Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. Iran J Psychiatry 7(2):87–92

Mohawk JA, Green CB, Takahashi JS (2012) Central and peripheral circadian clocks in mammals. Annu Rev Neurosci 35:445–462

Molina-Carballo A, Naranjo-Gómez A, Uberos J, Justicia-Martínez F, Ruiz-Ramos MJ, Cubero-Millán I, Contreras-Chova F, Augustin-Morales MD, Khaldy-Belkadi H, Muñoz-Hoyos A (2013) Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD. J Psychiatr Res 47(3):377–383

Mostafavi SA, Mohammadi MR, Hosseinzadeh P, Eshraghian MR, Akhondzadeh S, Hosseinzadeh-Attar MJ, Ranjbar E, Kooshesh SM, Keshavarz SA (2012) Dietary intake, growth and development of children with ADHD in a randomized clinical trial of Ritalin and Melatonin co-administration: through circadian cycle modification or appetite enhancement? Iran J Psychiatry. 7(3):114–119

Niederhofer H (2012) Treating ADHD with agomelatine. J Atten Disord 16(4):346–348

Nováková M, Paclt I, Ptáček R, Kuželová H, Hájek I, Sumová A (2011) Salivary melatonin rhythm as a marker of the circadian system in healthy children and those with attention-deficit/hyperactivity disorder. Chronobiol Int 28(7):630–637

O'Keeffe SM, Thome J, Coogan AN (2012) The noradrenaline reuptake inhibitor atomoxetine phase-shifts the circadian clock in mice. Neuroscience 201:219–230

Paclt I, Ptácek R, Kuzelová H, Cermáková N, Trefilová A, Kollárová P, Cálková T, Csemy L, Cíhal L (2011) Circadian rhythms of saliva melatonin in ADHD, anxious and normal children. Neuro Endocrinol Lett 32(6):790–798

Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, Kayumov L (2006) Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog Neuropsychopharmacol Biol Psychiatry 31(1):1–11

Pesonen AK, Kajantie E, Jones A, Pyhälä R, Lahti J, Heinonen K, Eriksson JG, Strandberg TE, Räikkönen K (2011) Symptoms of attention deficit hyperactivity disorder in children are associated with cortisol responses to psychosocial stress but not with daily cortisol levels. J Psychiatr Res 45(11):1471–1476

Rash JA, Aguirre-Camacho A (2012) Attention-deficit hyperactivity disorder and cardiac vagal control: a systematic review. Atten Defic Hyperact Disord 4(4):167–177

Roenneberg T, Wirz-Justice A, Merrow M (2003) Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 18(1):80–90

Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD (2006) An open trial of light therapy in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry 67(10):1527–1535

Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD (2007) Seasonality and circadian preference in adult attention-deficit/hyperactivity disorder: clinical and neuropsychological correlates. Compr Psychiatry 48(6):562–571

San L, Arranz B (2008) Agomelatine: a novel mechanism of antidepressant action involving the melatonergic and the serotonergic system. Eur Psychiatry 23(6):396–402

Schredl M, Alm B, Sobanski E (2007) Sleep quality in adult patients with attention deficit hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 257(3):164–168

Sivertsen B, Harvey AG, Pallesen S, Hysing M (2015) Mental health problems in adolescents with delayed sleep phase: results from a large population-based study in Norway. J Sleep Res 24(1):11–18 (**Cited in PMCRelated citations**)

Smolensky MH, Hermida RC, Reinberg A, Sackett-Lundeen L, Portaluppi F (2016) Circadian disruption: new clinical perspective of disease pathology and basis for chronotherapeutic intervention. Chronobiol Int 33(8):1101–1119

Spiga F, Walker JJ, Terry JR, Lightman SL (2014) HPA axis-rhythms. Compr Physiol 4(3):1273–1298

Tam SK, Pritchett D, Brown LA, Foster RG, Bannerman DM, Peirson SN (2015) Sleep and circadian rhythm disruption and recognition memory in schizophrenia. Methods Enzymol 552:325–349

Terman M (2007) Evolving applications of light therapy. Sleep Med Rev 11(6):497–507

Tjon Pian Gi CV, Broeren JP, Starreveld JS, Versteegh FG (2003) Melatonin for treatment of sleeping disorders in children with attention deficit/hyperactivity disorder: a preliminary open label study. Eur J Pediatr 162(7–8):554–555

Van der Heijden KB, Smits MG, Van Someren EJ, Gunning WB (2005) Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. Chronobiol Int 22(3):559–570

van der Heijden KB, Smits MG, Gunning WB (2006) Sleep hygiene and actigraphically evaluated sleep characteristics in children with ADHD and chronic sleep onset insomnia. J Sleep Res 5(1):55–62

Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry 46(2):233–241

Van Someren EJ, Kessler A, Mirmiran M, Swaab DF (1997) Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. Biol Psychiatry 41(9):955–963

Van Veen MM, Kooij JJ, Boonstra AM, Gordijn MC, Van Someren EJ (2010) Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry 67(11):1091–1096

Vogel SW, Bijlenga D, Tanke M, Bron TI, van der Heijden KB, Swaab H, Beekman AT, Kooij JJ (2015) Circadian rhythm disruption as a link between attention-deficit/hyperactivity disorder and obesity? J Psychosom Res 79(5):443–450

Voinescu BI, Szentagotai A, David D (2012) Sleep disturbance, circadian preference and symptoms of adult attention deficit hyperactivity disorder (ADHD). J Neural Transm (Vienna) 119(10):1195–1204

Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. J Am Acad Child Adolesc Psychiatry 45(5):512–519

Willcutt EG (2012) The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 9(3):490–499

Wittmann M, Dinich J, Merrow M, Roenneberg T (2006) Social jetlag: misalignment of biological and social time. Chronobiol Int 23(1–2):497–509

Wynchank DS, Bijlenga D, Lamers F, Bron TI, Winthorst WH, Vogel SW, Penninx BW, Beekman AT, Kooij JS (2016) ADHD, circadian rhythms and seasonality. J Psychiatr Res 81:87–94

Xu X, Breen G, Chen CK, Huang YS, Wu YY, Asherson P (2010) Association study between a polymorphism at the 3′-untranslated region of CLOCK gene and attention deficit hyperactivity disorder. Behav Brain Funct 6:48

Zavada A, Gordijn MC, Beersma DG, Daan S, Roenneberg T (2005) Comparison of the munich chronotype questionnaire with the Horne-Ostberg's morningness-eveningness score. Chronobiol Int 22(2):267–278

Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB (2014) A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci USA 111(45):16219–16224