Is ADHD a circadian rhythm disorder?

ADHD Foundation, Liverpool, Nov 8, 2018

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The Netherlands
Conflict of interest JJS Kooij

• None to declare
ADHD and sleep: chicken or egg?

- ADHD causes sleep problems;
- Sleep problems cause ADHD symptoms;
- ADHD and sleep problems interact, with reciprocal causation;
- ADHD and sleep problems have shared underlying etiology

Hvolby, Att Def Hyp Dis, 2015
ADHD & sleep in adults

Increased prevalence of:

- Delayed Circadian rhythm: 78% (1)
- Longer sleep latency, shorter sleep (2)
- Daytime fatigue: 62% (3)
- Variability of sleep schedule (3)
- Restless Legs Syndrome: 35-44% (4,5)
- Obstructive Sleep Apnea
- Nightmares (7)

Circadian Rhythm Sleep-Wake disorders, Delayed Sleep Phase Type

**DSPT** is characterized by:

- (Very) late chronotype
- A chronic pattern of (very) late sleep and preference for late rise
- Daytime sleepiness and/or insomnia
- Compensated for by irregular sleep pattern
- Dysfunctioning due to increased inattentiveness and/or social problems
- Main complaint is sleep onset insomnia
The circadian rhythm is mainly controlled by

- Genes
- Time of melatonin onset at night, induced by darkness at night

And by:
- Timing of (day)light in the morning
- That stops the melatonin production via the melanopsin system in the eyes
- Dopamine, a wake-up call for the brain!
## Characteristics of 40 consecutive ADHD patients

<table>
<thead>
<tr>
<th></th>
<th>Sleep Onset Insomnia (SOI)</th>
<th>No SOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31 (78%)</td>
<td>9 (22%)</td>
</tr>
<tr>
<td>Male</td>
<td>17 (55%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>28.2 (7.6)</td>
<td>30 (11.9)</td>
</tr>
<tr>
<td>ADHD, combined type</td>
<td>29 (94%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>ADHD, inattentive type</td>
<td>2 (6%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Alcohol (U/wk)</td>
<td>6.76</td>
<td>5.67</td>
</tr>
<tr>
<td>Nicotine (Sig/day)</td>
<td>8.16</td>
<td>1.11</td>
</tr>
<tr>
<td>Sleep diagnosis</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

C/ Late sleep separates the subtypes …
Question: is hyperactive behaviour coping for sleepiness??

Van Veen 2010, Biological Psychiatry
Dim Light Melatonin Onset (DLMO): delayed

N= 40 adults with ADHD w/wo Sleep Onset Insomnia versus healthy controls

<table>
<thead>
<tr>
<th></th>
<th>ADHD Total</th>
<th>ADHD + SOI</th>
<th>ADHD - SOI</th>
<th>HC</th>
<th>p: ADHD vs HC</th>
<th>p: SOI vs HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLMO (hr ± sd)</td>
<td>22:57 ± 1:20</td>
<td>23:15 ± 1:19</td>
<td>22:00 ± 0:54</td>
<td>21:34 ± 0:45</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

- 78% of consecutive ADHD patients had SOI
- DLMO: 105 min later in SOI vs controls
- After DLMO, it generally takes still 2 hours to fall asleep …

Van Veen ea, 2010
Sleep phase delay in ADHD

![Graph showing Melatonin level over time for normal and evening types. Normal type has a later peak in Melatonin level compared to the evening type.](image-url)
24 hour movement patterns in ADHD + and – SOI, compared to controls (actigraphy)
24 hr Activity, Core and Skin Temperature, in ADHD versus controls

Bijlenga ea 2013
ADHD with DSPS vs controls (n=24)

- Activity, core and skin temperature, and melatonin: all equally delayed
- Longer period between DLMO and sleep onset (3 vs 2 hrs)
- Variable bed times; mean bed time 2:52 AM
- Mean of 5 hrs sleep on workdays
- Variable sleep times not caused by variability of DLMO times

Bijlenga, J Sleep Res, 2013
ADHD with DSPS, versus controls
ADHD, circadian rhythm, sleep, mood & season

- ADHD
- Overweight
- Late sleep
- Winter depression
- Bipolar II

100%
75%
30%
10%
Does light drive sleep, and sleep drive ADHD?

Solar Intensity explained 34%–57% of the variance in ADHD prevalence

Arns *et al.* 2013: the preventative effect of high Solar Intensity might be related to improvement of circadian clock disturbances in ADHD
ADHD adds risk to circadian sleep disturbance up and above depression and anxiety

• Self-reported sleep characteristics of 2090 participants in the Netherlands Study of Depression and Anxiety (NESDA)
• 3 groups: healthy controls (HC), lifetime depression and/or anxiety (LDA), and LDA+ADHD

ADHD increased odds ratio for:
• late chronotype (OR=2.6; p=.003)
• indication of DSPS (OR=2.4; p=.002)
• and short sleep duration < 6h (OR=2.7; p=.007)

Bron ea 2016
DSPS & (winter)Mood (SAD)

- Both disorders of the biological rhythm, & increased in ADHD (1, 2)
- Difficulty synchronizing to external cues, especially when they are weak (1, 3)
- Suboptimal melanopsin system functioning in the eye in SAD (3)
- Both treated by phase resetting using light (1)
- Prevalence of SAD in ADHD: 27% (vs 3% in controls) (4)

Delayed Sleep & Health in ADHD

- Delayed circadian rhythm in 75% of children and adults with ADHD (DLMO measurements saliva)
- Late sleep = short sleep due to school and work obligations next morning
- Chronic short sleep is associated with obesity, DM-II, CVD and cancer
- Etiology: genetic, environmental, behavioral & biological: delayed onset of melatonin at night (105 min in adults, 45 min in children)

Kooij & Bijlenga 2014
Late sleep = short sleep late meals

Possible impact of a delayed rhythm on weight and health:

- **Sleeping late** may lead to a short sleep duration
- **Short sleep** duration is associated with obesity
- Adults with ADHD tend to **skip breakfast**
- Breakfast skipping is associated with obesity
- ADHD patients suffer from eating problems in 80%, mostly **binge eating**
- Their **weight fluctuates** 10 - 20 kg’s
- ADHD is sign. associated with increased BMI
- Obesity is associated with diabetes, cardiovascular disease and cancer

Biological clock & organic rhythms

- High alertness: 10:00
- Highest testosterone secretion: 10:00
- Bowel movement likely: 08:30
- Melatonin secretion stops: 07:30
- Sharpest rise in blood pressure: 06:45
- Lowest body temperature: 04:30
- Deepest sleep: 02:00
- Noon: 12:00
- Best coordination: 14:30
- Fastest reaction time: 15:30
- Greatest cardiovascular efficiency and muscle strength: 17:00
- Highest blood pressure: 18:30
- Highest body temperature: 19:00
- Melatonin secretion starts: 21:00
- Bowel movements suppressed: 22:30
Sleep loss causes loss of control over appetite

Leptin (satiety hormone) and ghrelin (hunger hormone):

• 2 hours less sleep already lowers levels of leptin, the satiety ("fullness") signal
• Sleep restriction study: leptin ↓ by 18% and ghrelin ↑ by 28%, leading to increased appetite and feelings of hunger
• 13 epidemiologic studies in adults and 8 in children: sleep loss is associated with increased BMI
• Sleep loss is a novel risk factor for insulin resistance and type 2 diabetes

N=270 adults
6 yrs follow up

Relationship between short & long sleep &

- Weight
- Waist circumference
- % Body fat

Chaput ea 2008
ASESA: case-control study

- To explore the sleep/wake patterns, psychiatric and somatic comorbidity, BMI and eating patterns in adults with ADHD (n=202) compared to the general population (n=189)

Results:

- More morbidities, complaints, and unhealthy lifestyle in ADHD
- More (extreme) evening chronotype in ADHD
- More sleep problems in ADHD: shorter sleep, longer sleep-onset latency, later mid-sleep, more variable bed times
- DSPS relates to SAD and to health issues, in ADHD as well as in controls
- Shorter sleep is related to a higher BMI

Bijlenga ea, 2013
## Self-reported Morbidities

(showing only significant differences)

<table>
<thead>
<tr>
<th></th>
<th>% ADHD, n = 202</th>
<th>% Controls, n = 198</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood</td>
<td>18</td>
<td>6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Stress/ burnout/ fatigue</td>
<td>5</td>
<td>1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pulmonary problems</td>
<td>31</td>
<td>16</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cardiovascular problems</td>
<td>43</td>
<td>18</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gastro-intestinal problems</td>
<td>33</td>
<td>19</td>
<td>.001</td>
</tr>
<tr>
<td>Metabolic problems</td>
<td>12</td>
<td>6</td>
<td>.042</td>
</tr>
<tr>
<td>Immune system problems</td>
<td>7</td>
<td>3</td>
<td>.049</td>
</tr>
<tr>
<td>Skeletal problems</td>
<td>50</td>
<td>36</td>
<td>.005</td>
</tr>
</tbody>
</table>
Obesity in ADHD

Diabetes, CVD, cancer

Inflammation

SAD
Late sleep
Short sleep

Carbohydrate craving
Altered Leptin/Ghrelin ratio
Breakfast skipping

Binge eating

Cascade of events

Kooij & Bijlenga 2013; Kooij 2012, book Adult ADHD; Dubois 2009; Boere 2008; Davis 2009; Mota 2008; Copinschi 2000; Spiegel 2005; Irwin 2017
Short sleep and cancer risk

- Shift work is considered carcinogenic in the long term (IARC 2007)
- Sleep loss by shiftwork is associated with higher incidence of breast- and prostate cancer
- Short sleep short exposure to and/or low levels of melatonin
- Melatonin has anti-oxidative properties and protects against cancer growth
- Animal and in vitro research shows inhibiting effects of melatonin on cancer growth and increased survival
- In humans, first studies with melatonin in cancer patients ongoing

Cancer risk and exposure to light at night

- Use of artificial light at night stops melatonin production through the eyes, feedback to pineal gland
- The light coming from TV, PC or Ipad also suppresses melatonin production and delays natural sleep onset easily by hours
- Light is the natural antidote to melatonin and wakes us up every day …
- Timing of light may be crucial for health in general
- … women with total visual blindness have less cancer than sighted women

Schernhammer ea, 2006-2017; Flynn-Evans ea, 2009
Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis

Russel J. Reiter, Sergio A. Rosales-Corral, Dun-Xian Tan, Dario Acuna-Castroviejo, Lilan Qin, Shun-Fa Yang, and Kevin Xu

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Abstract

There is highly credible evidence that melatonin mitigates cancer at the initiation, progression and metastasis phases. In many cases, the molecular mechanisms underpinning these inhibitory actions have been proposed. What is rather perplexing, however, is the large number of processes by which melatonin reportedly restrains cancer development and growth. These diverse actions suggest that what is being observed are merely epiphenomena of an underlying more fundamental action of melatonin that remains to be disclosed. Some of the arresting actions of melatonin on cancer are clearly membrane receptor-mediated while others are membrane receptor-independent and involve direct intracellular actions of this ubiquitously-distributed molecule. While the emphasis of melatonin/cancer research has been on the role of the indoleamine in restraining breast cancer, this is changing quickly with many cancer types having been shown to be susceptible to inhibition by melatonin. There are several facets of this research which could have immediate applications at the clinical level. Many studies have shown that melatonin’s co-administration improves the sensitivity of cancers to inhibition by conventional drugs. Even more important are the findings that melatonin renders cancers previously totally resistant to treatment sensitive to these same therapies. Melatonin also inhibits molecular processes associated with metastasis by limiting the entrance of cancer cells into the vascular system and preventing them from establishing secondary growths at distant sites. This is of particular importance since cancer metastasis often significantly contributes to death of the patient. Another area that deserves additional consideration is related to the role of melatonin in the cancer stem cell phenotype. The results of several studies suggest that administration of melatonin at critical times can significantly reduce the population of cancer stem cell-like cells, thereby markedly reducing the potential for recurrence and eventually cure the disease.

Go to: ▼

Cited by other articles in PMC

Antiproliferative and pro-apoptotic activity of melatonin analogues on melanoma and breast cancer cells [Oncotarget, 2017]

Melatonin and Hippo Pathway: Is There Existing Cross-Talk? [International Journal of Molecular...]

See all...

Links

Compound

Pub Med
Influence of light on melatonin production

![Graph showing the influence of light on melatonin production with eyes covered and eyes exposed.]
Proposed treatment / prevention of obesity in ADHD

To reset the clock and increase sleep duration:

- Psycho education \textit{on the meaning of time}, the light/dark cycle for sleep, appetite, metabolic entrainment, mood and health
- Sleep hygiene (early to bed and early to rise …)
- No light@night; temperature control: shower before going to bed, bedsocks in winter
- Melatonin in evening*
- Light therapy in early morning

To reduce binge eating and weight gain:

- Treatment of comorbidity (depr/anx)
- Treatment of ADHD with stimulant
- Exercise, diet
Sleep hygiene: Let your day be bright, and your night as dark as possible …

- Limit drinks after 8 pm to prevent visits to toilet at night
- Don’t use light when visiting toilet
- Good ventilation, good matrass
- Prevent light waking you up: dark curtains, no light at night of lamps or clocks
- No screens or dim light after 9.30 pm, or after ingestion of melatonin
- If needed, use dark or red sunglasses while watching TV
- Temperature control: hot shower before bed, bed socks
- Go to bed and get up at the same time every day, also in weekends
- Strive for 7-8 hrs of sleep between 11 pm and 7 am
- No napping > 30 min during daytime
- Use light in the morning to advance the rhythm if needed
- Limit use of sunglasses to synchronise with day light
Melatonin treatment

• To fall asleep: 1-3 mg at 22:00 in order to sleep at 23:00

• To reset the clock: 0.1 mg - 0.5 mg between 16:00 and 19:00, advance in steps of 1.5 hour/wk, starting from the habitual sleep onset time to the desired bedtime. For instance: from bedtime at 3 am start – 3hrs= midnight, then advance dosing 1.5 hrs per week, until sleep onset is around 11 pm. Do not dose before 4 pm or after midnight.

• Circadin 2 mg (long acting melatonin) for those who wake up nevertheless at 03:00 am

• No light exposure of tablets of melatonin! (tablets may be photosensitive)

Lewy 2005, 2006, continued; Kooij 2012 Book Adult ADHD; Kooij & Bijlenga 2014
Light therapy in the morning: for low mood & late sleep

- Especially in winter more sleep phase delay in ADHD
- More difficult to get up on time
- Strong early artificial morning light usually works as time cue, like sunlight in summer; 3 weeks
- Melatonin is reduced through closed eyelids by light, which is our natural wake up call
- Light box of 500 W directed to ceiling, or light therapy device of 10.000 lux close to the eyes, and timer 30 min before wake up time
- Wake Up Light uses only 75 W and does not wake all patients with delayed sleep phase
- Warning: 500 W light becomes hot and contains UVA+B

Rybak ea 2006
Light therapy 2018: Light glasses!
Indications:

Winterdepression
Jet Lag
Delayed sleep phase
& ADHD??

www.propeaq.com
High prevalence of self-reported photophobia in adult ADHD

J. J. Sandra Kooij and Denise Bijlenga*

PsyO Psycho-Medical Programs, Expertise Center Adult ADHD, The Hague, Netherlands

Many adult outpatients with attention-deficit/hyperactivity disorder (ADHD) report an oversensitivity to light. We explored the link between ADHD and photophobia in an online survey ($N = 494$). Self-reported photophobia was prevalent in 89% of respondents, and in 28% of respondents without ADHD (symptoms). The ADHD (symptoms) group wore sunglasses longer during daytime in all seasons. Photophobia may be related to the functioning of the eyes, which mediate dopamine and melatonin production systems in the eye. In the brain, dopamine and melatonin are involved in both ADHD and circadian rhythm disturbances. Possibly, the regulation of the dopamine and melatonin systems in the eyes and in the brain are related. Despite the study’s limitations, the results are encouraging for further study on the pathophysiology of ADHD, eye functioning, and circadian rhythm disturbances.

Keywords: adult ADHD, photophobia, photosensitivity, chronotype, sleep, circadian rhythm

INTRODUCTION

From clinical experience, we learned that a substantial number of adult patients with attention-deficit/hyperactivity disorder (ADHD) wear sunglasses throughout the year, even on overcast days. Many of these patients report a sensitivity or even oversensitivity of their eyes to bright light. Besides this clinical observation of photophobia, there are a number of studies indicating a link between ADHD and other optical dysfunctions. In children with ADHD, 76% have reduced visual acuity, caused by more strabismus (cross-eyes) and smaller optic disks (1). Another study found a prevalence of 63% myopia or hyperopia, and in total 83% refractive errors in children with ADHD (2). In comparison, in a study among Dutch schoolchildren, the prevalence of myopia and hyperopia was 36% (3). Moreover, young adults with ADHD more often have problems with depth perception, peripheral vision, photophobia, and photophobic episodes that are related to or caused by circadian rhythm disturbances. The suppression of melatonin in the morning is initiated by light reaching the retina of the eye (10). Melatonin may be suppressed later or less by the use of sunglasses during the day (11). This may cause the production of melatonin in the evening to be delayed, which in turn further delays the sleep/wake cycle. This is important because late sleep is associated with a short-sleep duration that on a chronic basis has a negative impact on health, with short sleep being associated with increased risks of chronic diseases such as obesity, diabetes, cardiovascular diseases, and cancer (12, 13). It is therefore important to study the potential role of the retinal functioning and its effect on chronotype, sleep, and ADHD symptoms.

The combination of our clinical experience and the findings in the available literature suggest that there may be an increased prevalence of visual problems and photophobia in adults with ADHD. In order to study a possible link between photophobia and ADHD, further studies are necessary to determine the incidence of visual problems and photophobia in adults with ADHD, and to identify risk factors for the development of these problems.
Ongoing: the EYE-ADHD study

- ADHD in 70% oversensitive to light
- Suboptimal functioning melanopsin system in the eye in SAD (Roecklein 2013), also in ADHD?
- Many wear sunglasses during the day, preventing synchronisation with daylight
- And use light@night from screens that reduces melatonin levels and postpones sleep
- All lead to increased shift of sleep phase
- Retina contains both melatonin and dopamine receptors that project to the biological clock
- EYE study: Measuring the PIPR: pupillary response to light in ADHD vs controls

Kooij & Bijlenga 2014