ADHD & the circadian rhythm in adults with ADHD

Implications for sleep, mood and health

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Financial Disclosures 2012-2013

• Dr. Sandra Kooij has disclosed she has received royalties from Springer Science and Business Media from her book: Adult ADHD: Diagnostic Assessment and Treatment
Learning Objectives

Upon completion of this educational activity, participants should be able to:

• Recognize the delayed sleep phase in adults with ADHD.
• Explain the consequences for health in general of late and short sleep on the long term and how to treat the delayed sleep phase.
Adult ADHD is highly comorbid with circadian based disorders

75% has comorbidity (mean 3 disorders):

- Depression (60% SAD) 25-50%
- Anxiety 25%
- Substance Use Disorders 20-45%
- Personality Disorders 6-25%
- Eating Disorders (BN) 9%
- Binge eating 86%
- Obesity 30%
- Sleep problems, DSPS pattern 75%

ADHD and sleep problems in children

Subjective measures:
- Sleep onset latency / bedtime resistance
- Difficulty waking up
- Fragmented sleep
- Decreased sleep efficiency
- Excessive daytime sleepiness

Objective measures (MSLT, actigraphy, PSG, DLMO):
- Excessive Daytime Sleepiness (EDS)
- Periodic limb movement disorder (PLMD) / Restless Leg Syndrome (RLS)
- Reduced % REM sleep
- Obstructive Sleep Apnea Syndrome (OSAS)
- Delayed Sleep Phase Syndrome (DSPS): DLMO 45 min delayed
Sleep questionnaire in 120 adults with ADHD

Difficulty …

• going to bed on time: 78%
• falling asleep: 70%
• sleeping through: 50%
• getting up in the morning: 70%
• daytime sleepiness: 62%

This pattern lifetime in 60%, suggestive of Eveningness or Delayed Sleep Phase Syndrome

Kooij, Society of Light Treatment and Biological Rhythms 2007
Chronotypes: being a lark or an owl

- Morningtype: gets up early, active in morning (20-25%)
- Eveningtype: late to bed, active in evening (20-25%)
- In between: 50%
- Normal variation may differ +/- 2 hrs
- More variation disallows normal participation in society
- Clockgenes define chronotype and biological rhythm
- Zeitgebers: light through the eyes in the morning, and melatonin production in the brain at night synchronise us with the light/dark cycle of the world
- Artificial light may delay melatonin production at night (computer!)
Are most adults with ADHD evening types?

- Evening types are more active at night, prefer to go to bed late
- They get up late as well
- Evening types may be late due to a delayed onset of melatonin
- If sleeping longer is not possible due to work or school obligations, a chronic sleep debt can result
- Working in evening- or nightshifts may be adaptive
- Question: do adults with ADHD work more often in nightshifts?
- And if so, is that a problem?
- Morningness is associated with low impulsiveness / sensation seeking.
- Eveningness the other way round…

Kooij 2012, book Adult ADHD
Delayed Sleep Phase Syndrome

DSPS is characterized by:

- (Very) late chronotype
- A chronic pattern of (very) late sleep and preference for late rise
- May result in daytime sleepiness and/or insomnia
- May be compensated for by an irregular sleep pattern
- Leads to dysfunctioning due to increased inattentiveness and/or social problems
- Main complaint is sleep onset insomnia
Sleep phase delay in ADHD

![Graph showing Melatonin level vs Time for normal type and evening type. Red line for normal type and green line for evening type. Arrows indicating phase delay.]
## 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><strong>N</strong></td>
<td>31 (78%)</td>
<td>9 (22%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>17 (55%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>28.2 (7.6)</td>
<td>30 (11.9)</td>
</tr>
<tr>
<td><strong>ADHD, combined type</strong></td>
<td>29 (94%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td><strong>ADHD, inattentive type</strong></td>
<td>2 (6%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td><strong>Alcohol (U/wk)</strong></td>
<td>6.76</td>
<td>5.67</td>
</tr>
<tr>
<td><strong>Nicotine (Sig/day)</strong></td>
<td>8.16</td>
<td>1.11</td>
</tr>
<tr>
<td><strong>Sleep diagnosis</strong></td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

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>SOI</th>
<th>no-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 HC
- After DLMO, it generally takes 2 hours to fall asleep

Van Veen ea, 2010
24 hour movement patterns ADHD + SOI compared to controls (actigraphy)

Van Veen et al. 2010
New study: core and skin temperature, DLMO and activity patterns

- N = 12 ADHD + DSPS (medication naïve) and 12 controls
- 5 consecutive days and nights

Results:
- More variable bedtimes in ADHD, but melatonin onset is the same every day in both groups
- DLMO 1.5 hours later in ADHD
- Sleep duration 1 hr shorter on days before workdays in ADHD
- Second delay, between DLMO and sleep onset was ≥ 1 hr longer in ADHD
- Melatonin, activity and temperature were all delayed to a similar degree in ADHD
- Overall temperatures were lower in ADHD
- Colder hands in ADHD, related to sleep onset difficulties

Bijlenga, J Sleep Res, 2013 Aug 16
24 hr Activity, Core and Skin Temperature, in ADHD versus controls

Bijlenga, J Sleep Res 2013, Aug 16
ADHD patients lack any sense of time

Clinical experience: adults with ADHD seem to lack any sense of time, as well as any rhythm in day/night.

Their habitually being late has been regarded as part of their inattentiveness, a planning problem, but may in fact reflect a fundamental problem of the biological clock.
Nucleus supra chiasmaticus (NSC): the biological clock
ADHD, circadian rhythm, sleep, mood and season

Bijlenga 2013, J Att Disord; 17(3):261-75
Bijlenga 2013, J Sleep Res. Aug 16 epub
ADHD and disturbed rhythms

ADHD may not only be associated with circadian, but also with cyclical and seasonal disturbances, leading to problems with impulsiveness, eating, sleeping and mood:

- Impulsivity/novelty seeking has been associated with eveningness
- Lack of sleep rhythm may lead to lack of rhythm in eating and activity patterns as well
- Evening types, or those with a delayed sleep phase may prefer irregular work or work in night-shifts, thereby increasing the sleep phase delay, as well as obesity
- ADHD has a higher percentage of Seasonal Affective Disorder (SAD) or winter depression, and possibly also of Premenstrual Dysphoric Disorder than normal

Amons 2006, J Affect Disord;91(2-3):251-5
Levitan 2004, Biol Psychiatry;56(9):665-9
ADHD & seasonal mood changes

- Adult ADHD co-occurs with lifetime depressive disorder in 55%
- Most of them (60%) have Seasonal Affective Disorder (SAD) or winter depression
- Open trial of Light therapy effective for SAD and ADHD, as well as for Delayed Sleep Phase
- SAD has a circadian phase delay in 70%
- Are SAD and ADHD related via circadian disturbances?
- Clockgenes associated with ADHD

Circadian disturbance, ADHD and health

- ADHD is associated with chronic DSPS
- ADHD patients often work in night shifts or are active at night
- May be gene-environment interaction: circadian preference based on (clock)genes and dopaminergic pathways

- But: chronic work (>30 yrs) in night shifts is associated with higher risk of (breast) cancer
- Melatonin acts as a **circadian anti-cancer signal** at night
- Among others (light at night), chronic low melatonin levels may protect less well against development of cancer

**is ADHD a high risk group for cancer?**

Relative risk of breast cancer

First degree relatives
Flight attendants
Hormone Replacement Therapy

Shiftwork
Alcohol > 45 g/day
BMI > 30
First birth > 35
Current use of contraceptives
Nulliparous

Increased risk

Physical activity
1 full time pregnancy
First birth < 20
Breastfeeding

Decreased risk

>7 children
1 full time pregnancy
First birth <20
Breastfeeding

Does cancer risk cluster in ADHD?

Several lifestyle risk factors may cluster in ADHD individuals:

- Night shift work
- High BMI
- Alcohol/drug abuse
- Smoking
- Low melatonin levels?
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 research shows inhibiting effects of melatonin on cancer growth and increased survival
- In humans, first studies with melatonin in cancer patients ongoing

Schernhammer 2004, 2006; Parent ea 2012; Sigurdardottir ea 2012; Anisimov ea 2012
Cancer risk and exposure to light@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

Flynn-Evans ea, 2009
ASESA 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)

Bijlenga ea, 2013
### General characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHD, n = 202</th>
<th>Controls, n = 198</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>47 %</td>
<td>65 %</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age: mean</td>
<td>34.9</td>
<td>33.0</td>
<td>.121</td>
</tr>
<tr>
<td>BMI: mean</td>
<td>24.8</td>
<td>23.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI ≥ 30 (obese)</td>
<td>17 %</td>
<td>4 %</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unemployed</td>
<td>27 %</td>
<td>6 %</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smokes</td>
<td>52 %</td>
<td>18 %</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;14 U alcohol p/wk</td>
<td>17 %</td>
<td>7 %</td>
<td>.016</td>
</tr>
</tbody>
</table>
# 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>
### Sleep characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age ≤ 30 yrs</th>
<th></th>
<th>Age &gt; 30 yrs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADHD n = 83</td>
<td>Controls n = 106</td>
<td>p</td>
<td>ADHD n = 119</td>
</tr>
<tr>
<td>Bed time work days: mean</td>
<td>23:45</td>
<td>23:10</td>
<td>.002</td>
<td>23:33</td>
</tr>
<tr>
<td>Bed time free days: mean</td>
<td>01:02</td>
<td>0:13</td>
<td>&lt;.001</td>
<td>0:20</td>
</tr>
<tr>
<td>Sleep length work days: mean</td>
<td>7:25</td>
<td>7:55</td>
<td>.029</td>
<td>7:01</td>
</tr>
<tr>
<td>Sleep-onset latency work days: mean</td>
<td>0:39</td>
<td>0:22</td>
<td>.002</td>
<td>0:34</td>
</tr>
</tbody>
</table>

Indication of DSPS: 26% in ADHD vs. 2% in controls (p<.001)
Summary

• 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
• This is also apparent within the control group
• Shorter sleep is related to a higher BMI
Next step: biomarkers in ADHD and DSPS

PHASE study: Phase shift in ADHD of sleep and appetite:

- 50 adults with ADHD and DSPS
- 3 wk treatment: Mel, Plac, Mel + LT
- Measurement at baseline, after 3 wks Tx and after 3 wks washout: DLMO, cortisol, leptin/ghrelin, glucose, insuline markers, inflammation markers, HRV

Vogel ea, in preparation
Hypothesized relations

Delayed rhythm
Shorter sleep duration
Lower melatonin levels
Less protected against cancer

Skipping breakfast
Binge eating
No rhythm in meals
Higher glucose levels

Obesity, DM, Hypertension, Cardiovascular disease, Cancer

ADHD index predicts weight and binge eating

Davis 2009, J Psychiatr Res;43(7):687-96
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 associated with increased BMI
- Obesity is associated with diabetes, cardiovascular disease and cancer

Kooij 2012, book Adult ADHD;
Boere 2008, NTG;152(6):324-30;
Davis 2009, J Psychiatr Res;43(7):687-96;
Mota 2008, Ann.Hum.Biology;35(1)1-10;
Copinschi 2000, Novartis Found Symp;227:143-57
Sleep loss causes loss of control over appetite

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

- Reducing sleep duration by 2 hours already lowers levels of leptin, the satiety ("fullness") signal
- Sleep restriction study (n = 12): 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

Sleep duration USA

As sleep time fell in USA, average weights rose
Whether and how sleep time and weight are connected is still unclear

Kripke 2002; Keith 2006; Lauderdale 2006
Treatment of ADHD in obese patients

- N = 242 patients with severe therapy resistant obesity, ADHD in 32%!
- Comorbidity: depression, sleep apnea, binge eating
- 75% of the ADHD group got stimulant treatment
- Stimulants: effective for ADHD, and inhibit appetite
- Weight loss: 15 kg in stimulant treated group, while others increased 3 kg during treatment for obesity
- After follow up at 1.5 yrs, in which medication was continued, the results remained
- Patients: less restlessness, anxiety and tiredness, & needed less food to compensate for these feelings. Binge eating disappeared, better contact with feeling of hunger and satiety.
- Better able to plan and comply to the treatment for obesity.

Pagoto ea 2010; Albayrak ea 2011; Levy ea 2009
Proposed treatment / prevention of obesity in ADHD

To reset the clock and increase sleep duration:

- Psycho education 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, shower before going to bed, bedsocks
- Melatonin in evening*
- Light in morning

To reduce binge eating and weight gain:

- Treatment of comorbidity (depr/anx)
- Treatment of ADHD with stimulant
- Exercise, diet

*Melatonin has not been reviewed or approved by the FDA for the treatment of sleep disorders. Kooij, book Adult ADHD 2012
Melatonin treatment

• To fall sleep: 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, *in steps of 1.5 hour/wk from the normal sleep time to the desired bedtime*
• Circadin 2 mg for those who wake up nevertheless at 03:00 am
• No light exposure of tablets of melatonin!

Lewy 2005, 2006, continued; Kooij 2012 Book Adult ADHD
Gewenste inslaaptijd – 8 uur = uiteindelijke tijdstip inname 0.5 mg melatonine

<table>
<thead>
<tr>
<th>Gewenste inslaaptijd</th>
<th>Tijdstip inname Mel</th>
</tr>
</thead>
<tbody>
<tr>
<td>01:00</td>
<td>17:00</td>
</tr>
<tr>
<td>00:30</td>
<td>16:30</td>
</tr>
<tr>
<td>23:00-24:00</td>
<td>16:00</td>
</tr>
</tbody>
</table>

Niet innemen voor 16:00 en na 24:00!!
Light therapy in the morning

• Especially in winter more sleep phase delay
• More difficult to get up on time
• Inducing strong early morning light artificially, usually does work as sunlight in summer
• Melatonin is reduced through closed eyelids by light, which is our natural wake up call
• Light box of 500 W, or Light therapy device 10.000 lux 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
New: is the eye implicated as well in ADHD?

• Webbased questionnaire in n = 495, 47% with ADHD (symptoms)
• ADHD had in 68% photophobia vs 28% of controls
• ADHD wore sign. more hours/day sunglasses in every season, because of photophobia
• By wearing sunglasses, less entrainment by light during the day, possibly delaying sleep phase further
• No relationship with chronotype or season of birth

Kooij & Bijlenga, submitted
Next: looking into the eye of ADHD

- Children with ADHD have in 70-80% visual acuity difficulties, that may respond to stimulant treatment
- Adults with ADHD have difficulties with depth and blue-spectrum colour perception, visual search and processing, and peripheral vision
- Photophobia may point to deficiencies in the pupillary response to light

Mezer 2012; Gronlund 2007; Kim 2013; Martin 2008
Adult ADHD
Diagnostic Assessment and Treatment

Including DIVA 2.0
JJS Kooij, 3rd edition
2012

www.springer.com
Search for ‘Adult ADHD’
Thanks to the circadian rhythm study group:

- Denise Bijlenga
- Reut Gruber
- Eus van Someren
- Marijke Gordijn
- Maaike van Veen
- Annet Bron