Is ADHD a Circadian Rhythm Sleep Disorder?

& relationship with health

ADANA, Barcelona, May10, 2019

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- Associate Professor of Psychiatry, VUMc Amsterdam, The Netherlands
- Head Expertise Center Adult ADHD, PsyQ, the Hague, The Netherlands
Conflict of interest JJS Kooij

None
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)
- Nightmares (6)
- Sleep apnea

Circadian Rhythm Sleep-Wake disorders, Delayed Sleep Phase Type

**DSPT** is characterized by:

- A chronic pattern of (very) late sleep and preference for late rise
- Daytime sleepiness and/or sleep onset insomnia
- Compensated for by irregular sleep pattern
- Dysfunctioning due to increased inattentiveness and/or social problems

DSM-5
Nobelprijs gaat naar de biologische klok

De Nobelprijs voor medicijnen gaat naar de ontrafelings van moleculaire mechanismen van het dag-nachtritme bij dieren door drie Amerikaanse genetici. Zij vestigden het vakgebied van de 'circadiane biologie'.

Sander Voormolen 2 oktober 2017

Jeffrey C. Hall
Michael Rosbash
Michael W. Young

De Nobelprijs voor Geneeskunde en Fysiologie is maandag toegekend aan drie Amerikanen: Jeffrey Hall, Michael Rosbash en Michael Young voor hun ontdekkingen rond het moleculaire mechanisme dat biologische klok van mens en dier controleert. Dankzij hun werk hebben we nu een beter begrip van hoe ons lichaam reageert op zon en maan.
ADHD and circadian rhythm

Genetic basis

• Circadian rhythm is regulated by genes: PER1, PER2, PER3, CRY1, CRY2, CLOCK, BMAL1, CK1e (1-3)

• Polymorphism in CLOCK gene: associated with delayed/short sleep, ADHD, Bipolar-II, depression (4, 5)

• BMAL1 and PER2 genes: less solid circadian rhythm in ADHD vs controls (6)

The circadian rhythm is controlled by:

- Dark & light regulate melatonin production
- So in ADHD: dysregulation of both melatonin & dopamine ...

Bijlenga 2019
ADHD prevalence lower in countries with intense daylight, in both US and European data, in both children and adults

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

Arns ea 2013: The preventative effect of high Solar Intensity might be related to improvement of circadian clock disturbances in ADHD
ADHD and circadian rhythm

Prevalence of ADHD in adults: Netherlands: 5%; Spain: 1.2%

Fayyad ea 2017

Adult ADHD often comes with **circadian based disorders**:

75% has other disorders (mean 3 disorders):

- **Depression (60% SAD)** 25-50%
- **Anxiety** 25%
- **Substance Use Disorders** 20-45%
- **Personality Disorders** 6-25%
- **Eating Disorders (Bulimia)** 9%
- **Binge eating** 86%
- **Obesity** 30%
- **Sleep problems, DSPS pattern** 78%

## 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>

C/ Late sleep separates the subtypes …

Question: is hyperactive behaviour adaptive in order to stay awake?

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 Sleep Onset Insomnia (SOI)
- DLMO: 105 min later in SOI vs controls
- After DLMO, it generally takes still 2 hours to fall asleep
- In ADHD it takes 3 hrs …

Van Veen ea, 2010; Bijlenga ea, 2013
24 hour movement patterns in ADHD + and – SOI, compared to controls (actigraphy)
ADHD with late sleep versus 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, circadian rhythm, sleep, mood & season

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

100%
75%
30%
10%
Delayed Sleep & Health in ADHD

- Late sleep: 75% of children & adults with ADHD
- Late sleep = short sleep due to school / work

Kooij & Bijlenga 2014; van der Heijden ea 2005, 2006
Biological clock & organic rhythms

- Highest testosterone secretion: 09:00
- 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
- Midnight: 00:00
- 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
- Light-Dark cycle
Hypothesised cascade of events:

- **Carbohydrate craving**
- **Late sleep**
- **Short sleep**
- **Altered Leptin / Ghrelin ratio**
- **Breakfast skipping**
- **Binge eating**
- **Inflammation**
- **SAD**
- **Diabetes, CVD, Cancer**

Kooij & Bijlenga 2013; Kooij 2012, book Adult ADHD; Dubois 2009; Boere 2008; Davis 2009; Mota 2008; Copinschi 2000; Spiegel 2005; Irwin 2017
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
Influence of light on melatonin production
Sleep hygiene: Let your day be bright, and your night as dark as possible ...

- Limit drinks after 8 pm to prevent visits to toilet @night
- Don’t use light when visiting toilet
- Good ventilation, good matrass
- Prevent light waking you up: dark curtains, no light in bedroom 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: an Inhibitor of Breast Cancer

Steven M. Hill, Victoria P. Belancio, Robert T. Dauchy, Shulin Xiang, Samantha Brimer, Lulu Mao, Adam Hauch, Peter W. Lundberg, Whitney Summers, Lin Yuan, Tripp Frasch, and David E. Blask

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Abstract

This review discusses recent work on melatonin-mediated circadian regulation and metabolic and molecular signaling mechanisms involved in human breast cancer growth and associated consequences of circadian disruption by exposure to light at night (LEN). The anti-cancer actions of the circadian melatonin signal in human breast cancer cell lines and xenografts heavily involve MT1 receptor-mediated mechanisms. In estrogen receptor alpha (ERα)-positive human breast cancer, melatonin, via the MT1 receptor, suppresses ERα mRNA expression and ERα transcriptional activity. As well, melatonin regulates the transactivation of other members of the
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 Kexin Xu

Andrzej Slominski, Academic Editor

Author information ▶ Article notes ▶ Copyright and License information ▶

This article has been cited by other articles in PMC.

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-
Melatonin treatment

• **To fall asleep**: 1-3 mg at 22:00 in order to sleep at 23:00
• No light after intake of melatonin!

• Long acting melatonin (Circadin ®) for those who wake up at 3 am after taking short acting melatonin at bedtime

• 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
- Melatonin is reduced through closed eyelids by light, which is our natural wake up call
- Light therapy device of 10,000 lux at 20 cm to the eyes, and timer 30 min before (fixed) wake up time
- Duration: 1-2 weeks for winterdepression, 3 weeks for DSPS. Repeat when relapse.
- Wake Up Light uses only 75 W and does not wake all patients with delayed sleep phase

Rybak ea 2006
Light therapy 2019: Light glasses!

**THE GLASSES**

- Light- and chronotherapy embedded
- Patented
- High quality materials
- App and Bluetooth control
- Rechargeable

- Indicator Light
- On/Off Switch
- Integrated LED Lights
- Bluetooth connection
- SoftGrip
- Micro USB
- Rechargeable battery
- Interchangeable lenses
Indications:

Winterdepression
Jet Lag
Delayed sleep phase
& ADHD??

www.propeaq.com
Correcting Delayed Circadian Phase with Bright Light Therapy Predicts Improvement in ADHD Symptoms: A Pilot Study

Rachel E. Fargason, MD, Aaron D. Fobian, PhD, Lauren M. Habilitz, PhD, Jodi R. Paul, PhD, Brittney A. White, MS, Karen L. Cropsey, PsyD, and Karen L. Gamble, PhD

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Discussion
Hormonal Mood Changes in Women with ADHD

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Psychiatre, PsyQ Den Haag
Associate professor psychiatrie, VUMc

50e ADHD Netwerk Meeting
14 mrt 2019
Women & mood

- Women have twice the risk for depression compared to men
- Women have a fivefold increased risk for seasonal depression

Goldstein ea 2019; Wirtz-Justice 2018
Mood disorders in ADHD

• In 55% lifetime diagnosis of depression (n=115)

• In 27% seasonal depression: 72.9% of females and 52.2% of males

Amons ea 2006
The prevalence of ADHD in Mood Disorders is:

- 15-20% in bipolar disorder
- 8% in depression
- 22% in dysthymia

Fayyad ea 2017

Prevalence of Adult ADHD:
One in 5 mood disorder patients
ADHD prevalence increases with severity and chronicity of Depression

NELDA study: N=2053, 3 groups: Healthy Controls /Depression /Depression + Anxiety:

ADHD prevalence:
• 0.4% in healthy controls
• 5.7% in remitted depression
• 22.1% in current depression

ADHD symptoms were significantly increased among:
• Severe depression (OR=6.8),
• Chronic depression (OR=3.8),
• Earlier age of onset of depressive symptoms (OR=1.5),
• Comorbid anxiety disorders (OR=3.4).

Conclusion:
ADHD symptom rates increased across clinical stages of depression, up to **22.5% in chronic depression**
Clinical experience:

Premenstrual mood problems in women with ADHD

Women with ADHD report severe premenstrual mood instability & increased severity of ADHD:

- Inattention, inability to focus
- Impulsivity
- Irritability and anger outbursts
- Depressed mood
- Increased sleep disturbance
- Anxiety, panic attacks
- Suicidal thoughts
- Symptoms recur next premenstrual period
- Efficacy of ADHD medication seems reduced

= DANGER WEEK !!
Besides premenstrual, also postnatal & perimenopausal mood changes

- From clinical experience, postnatal depression and perimenopausal depression also seem more severe and more frequent than normal.
- But no data so far.
- Research question:

  *Are hormonal mood problems indeed more severe and more frequent in women with ADHD compared to women without?*

  - PMS in 20-30% of women in general
  - PMDD in 3-8%

Hylan 1999; Halbreich 2003
1st Pilot study 2016

- Dutch ADHDWoman conference 2016
- N=200 participants

Self report questionnaire on mood changes to the level of clinical depression during:

- the menstrual cycle: premenstrual dysphoric disorder (PMDD) (=more severe than PMS)
- the postnatal period: postpartum depression (PPD)
- the perimenopausal period
Questionnaire consisted of validated scales, adapted for selfreport.

- Neuropsychiatric Interview Plus version 5.0 (M.I.N.I. Plus) for Premenstrual Dysphoric Disorder (PMDD)
- Edinburgh Postnatal Depression Scale (EPDS) for life-time Post Partum Depression (PPD)
- Greene Climacteric Scale (GCS) for Perimenopausal Mood Symptoms
- Munich Chronotype Questionnaire (MCTQ) for sleep characteristics
Women with ADHD were asked to vote for their most urgent question to science:

Highest votes for hormonal mood changes during the lifecycle
### Phases of the Ovarian Cycle

<table>
<thead>
<tr>
<th>Gonadotrophic hormone levels</th>
<th>Follicular Phase</th>
<th>Luteal Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>LH</td>
<td></td>
</tr>
</tbody>
</table>

**Ovarian cycle**
- Primary follicle
- Theca
- Antrum
- Ovulation
- Corpus luteum formation
- Mature corpus luteum
- Corpus albicans

**Ovarian hormone levels**
- Estrogen
- Inhibin
- Progesterone

**Uterine cycle**

**Phases of the Uterine Cycle**
- MENSES
- PROLIFERATIVE PHASE
- SECRETORY PHASE

**Basal body temperature (°C)**
- Days 28/0: 36.7
- 7: 36.4
- 14: 36.4
- 21: 36.4
- 28/0: 36.4

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**Danger!**
Results

Premenstrual Dysphoric Disorder

• N=200 women
• No clinical diagnoses but ‘indication for PMDD’
• Comparing prevalences of possible PMDD between women with and without ADHD

Results:
• 62% of ADHD woman had an indication for PMDD, versus 3-8% in controls

Halbreich, 2003
Results
Postpartum Depression

• 67% of ADHD women had an indication for PPD, versus 13-19% in controls

O’Hara & McCabe 2013
Results
(Peri)menopausal women with ADHD had a 2 fold increased severity of mood and somatic symptoms compared to controls

Barentsen 2001; Bromberger & Kravitz 2011
Replication study

Women diagnosed with ADHD at PsyQ

- Outpatient Clinic for Adult ADHD at PsyQ, the Hague, the Netherlands
- N=209 women with diagnosed ADHD
- Age 18-71 years
- Same questionnaires
- Expectation: lower prevalences compared to 1st pilot study in participants ADHDWomen conference
Results PMDD in 2nd study

- Comparison with women from the general population
- **Indication of PMDD** in women with ADHD: 46% versus 3-8%
- Also severity increased: in 70% ≥ 6 symptoms of PMDD (range 0-13)
- Higher use of contraceptives in PMDD group

Dorani, in preparation; Halbreich 2003
Results PPD in 2nd study

• Of 85 women with children, **58%** reported lifetime postnatal depressive symptoms, versus **13-19%** in the general population

Dorani, in preparation; O’Hara & McCabe 2013; Gavin 2005
Results
Perimenopausal Depression 2nd study

• N=37 perimenopausal women with ADHD reported a **3-fold increased** number of symptoms of anxiety, depression and somatic complaints vs women from the general population.

Dorani, in preparation; Barentsen 2001; Bromberger & Kravitz 2011
Summary

• Confirmation of increased PMDD, PPD and perimenopausal mood symptoms in ADHD women in a clinical sample
• Three periods of hormonal changes
• Why are these episodes more severe in ADHD?
• How can we treat them better?

<table>
<thead>
<tr>
<th></th>
<th>ADHD Women Conference</th>
<th>Women diagnosed with ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMDD</td>
<td>62%</td>
<td>46%</td>
<td>3-8%</td>
</tr>
<tr>
<td>PPD</td>
<td>67%</td>
<td>58%</td>
<td>13-19%</td>
</tr>
<tr>
<td>Menopausal Depressive symptoms</td>
<td>2x increased</td>
<td>3x increased</td>
<td></td>
</tr>
</tbody>
</table>

Dorani, in preparation
Little research on hormonal influences on the brain in women

Cycle often exclusion criterion due to changing hormonal levels, more research in males

No studies in women with ADHD
- ADHD = low dopamine levels brain
- Estrogen & progesteron influence serotonin and dopamine
- Sex hormones play a role in brain cell development
- Ovarian hormones directly affect the brain regarding cognition, memory, learning, and emotion
- Estrogen influences blood flow and uptake of glucose, and this changes during the cycle

Haimov-Kochman 2014; Volkow 2009; Barth 2015; Diekhof 2015; Soares & Zitek 2008; Fanselov & Dong 2010; Hines 2010; Reiman 1996; Sacher 2014; Frey 2014; Song 2019
Estrogen effect on a Women’s Body

**Heart**
- Protects from cholesterol

**Liver**
- Reduces cholesterol in blood

**Ovary**
- Produced from growing eggs

**Uterus**
- Monthly preparation for pregnancy or menstrual cycle

**Vagina**
- Makes it moist
- Protects from infection

**Brain**
- Helps adjust body temperature
- Increases memory
- Adjusts libido

**Breast**
- Grows and shapes breast
- Prepare breast for feeding

**Skin**
- Makes skin young

**Bone**
- Strengthens bone and
  - Increase its density
Estrogen & Progesteron x Dopamine

Estrogen:
• **increases dopamine** synthesis and decreases its degradation, reuptake, and recapture
• **upregulates** dopaminergic receptors
• effect of estrogen esp. in the PFC, a region with high amounts of estrogen
• It impacts working memory function by affecting dopamine levels.
• effects on limbic regions (such as the nucleus accumbens), estrogen influences emotional and motivational behaviors

Progesteron:
• effect of progesterone on dopaminergic systems depends primarily on the previous priming by estrogen

Giannini 2018
Hypothesis in ADHD women

- Low prefrontal dopamine in ADHD x low estrogen in the luteal phase = 2x low levels of neurotransmitters (enhancement): you’re stuck
- Explaining increased mood instability and increased ADHD severity ...

Jacobs & d’Esposito 2011; Song 2019
Sex hormones & ADHD Symptoms Across the Menstrual Cycle

• Study in 32 normal women, 18-22 yrs, regular cycle

• ADHD symptoms x Estrogen (E) - Progesteron (P) - Testosteron (T)

When estrogen is low:

higher impulsivity and inattention

• NB  Stimulant response may also differ across the cycle

• Roberts 2018
Treatment options in PMDD, PPD & Climacteric depression

So far these treatments have been shown effective for hormone related mood disorders in women in general:

- Hormones (contraceptives, continuously without stopweek; suppletion in menopause)
- Anti-depressants (SSRIs) (for mood)

Not yet proven effective: Light therapy

Probably in ADHD women also:

- PMDD: increased dosage of ADHD meds in week before period (but no data!)

Ryu 2015
Next step: MoodCycles study in ADHD women

**MoodCycles:**
Measuring mood and ADHD symptoms during the cycle, cognitive performance, hormone levels, sleep, emotional lability, in ADHD women versus controls.

Twice in one cycle:
- Qb test
- Hormone levels
- Questionnaires on mood, sleep, & ADHD
MoodCycles study will start in June

Because ADHD women need it

Because we got support from PsyQ & ADHD Netwerk!

Medical Ethical approval pending
DISCUSSION