



ADHD, sleep & health

Prof. Dr. Sandra Kooij
ADHD Congress Tel Aviv 2022

Amsterdam UMC/VUMc and PsyQ, the
Hague, the Netherlands



Everything is timed - Timing is everything

Living out of phase means: Jetlag!



Disclosure Sandra Kooij

Geen belangen

ADHD & sleep disorders

- ADHD symptoms are associated with:
 1. Extreme evening chronotype/Delayed sleep - 78%
 2. Obstructive sleep apnea syndrome (OSAS) – 30%
 3. Restless legs syndrome (RLS) & Periodic limb movement disorder (PLMD) – 30-40%
 4. Insomnia disorder (ID) with difficulties initiating sleep (DIS) and maintaining sleep (DMS) - 43%
 5. Narcolepsy – 7%
 6. Enuresis: more often in ADHD
 7. Bruxism: more often in ADHD
 8. Nightmares: 3-fold increased



Specific Treatment for every sleep disorder!

1. Delayed sleep

1. Chronotherapy

2. Insomnia (ruminating, hyperarousal)

2. CBT-i

3. Restless legs (in evening/in bed)

3. Ferritin
suppletion;
Pregabalin

4. Sleep apnea during sleep

4. Weightloss;
Mandibular
device; CPAP



ADHD & Sleep

- - **70-80%** of adults has one or more sleep problems
- - **78% sleeps too late** & cannot sleep at an earlier time
- **This is related to 1.5 hrs delayed onset of melatonin in ADHD**
- Starting in childhood, heritable pattern or *chronotype*
- Social jetlag: early awake for school or work
- Resulting in **sleep debt:**
 - Sleep duration in ADHD 5-6 hrs
 - Optimal sleep duration 7-8 hrs ...
- **Consequences of short sleep:**
 - Sleepiness
 - Less focus, lower cognitive functioning
 - Impaired memory function
 - Irritable, sad mood
 - Binge eating ...



Symptoms of sleep debt and ADHD overlap!





Circadian Rhythm Sleep-Wake disorder,
Delayed Sleep Phase Type

DSPT is characterized by:

- (Very) late chronotype:
- A chronic pattern of (very) late sleep and late rise
- Daytime sleepiness and/or difficulty falling asleep on time
- Compensated for by irregular sleep pattern
- Dysfunctioning due to increased inattentiveness and/or social problems

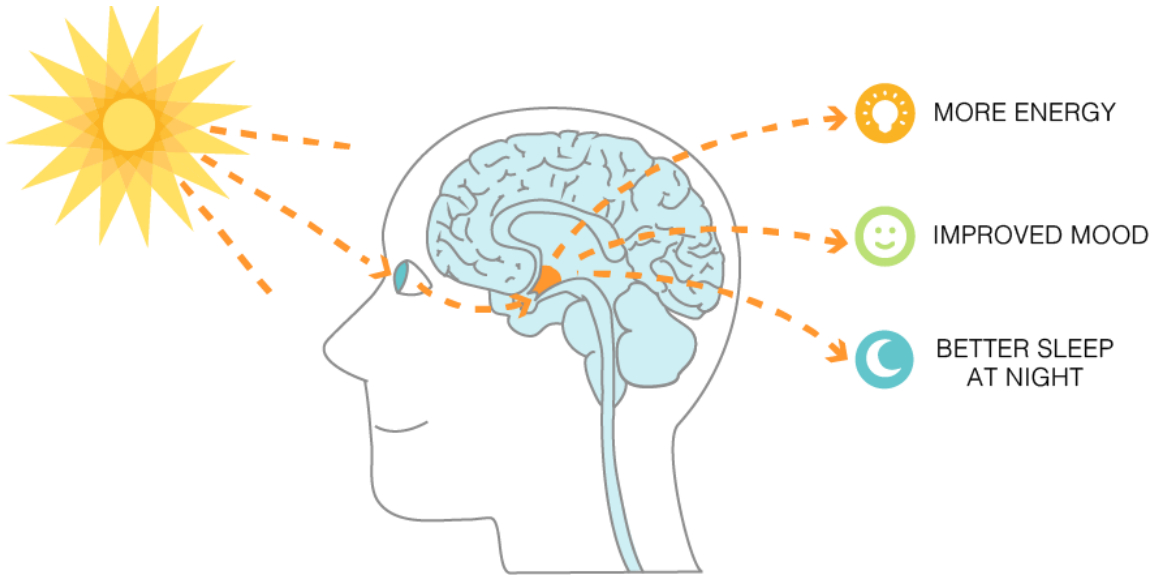
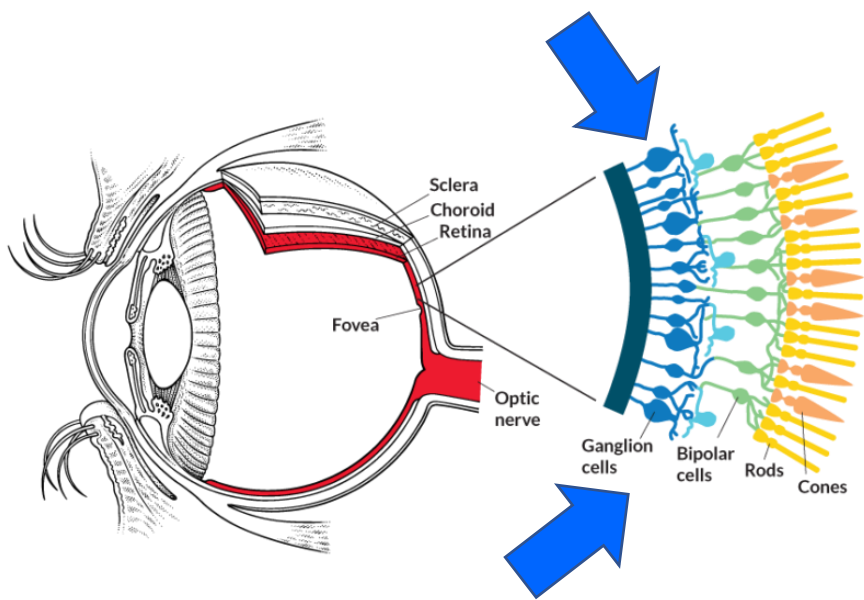
The circadian rhythm is mainly controlled by

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

And by:

- Timing of (day)light in the morning
- That stops the melatonin production via the melanopsin light sensitive cells in the retina
- Dopamine, a wake-up call for the brain!

Factors that set the circadian rhythm



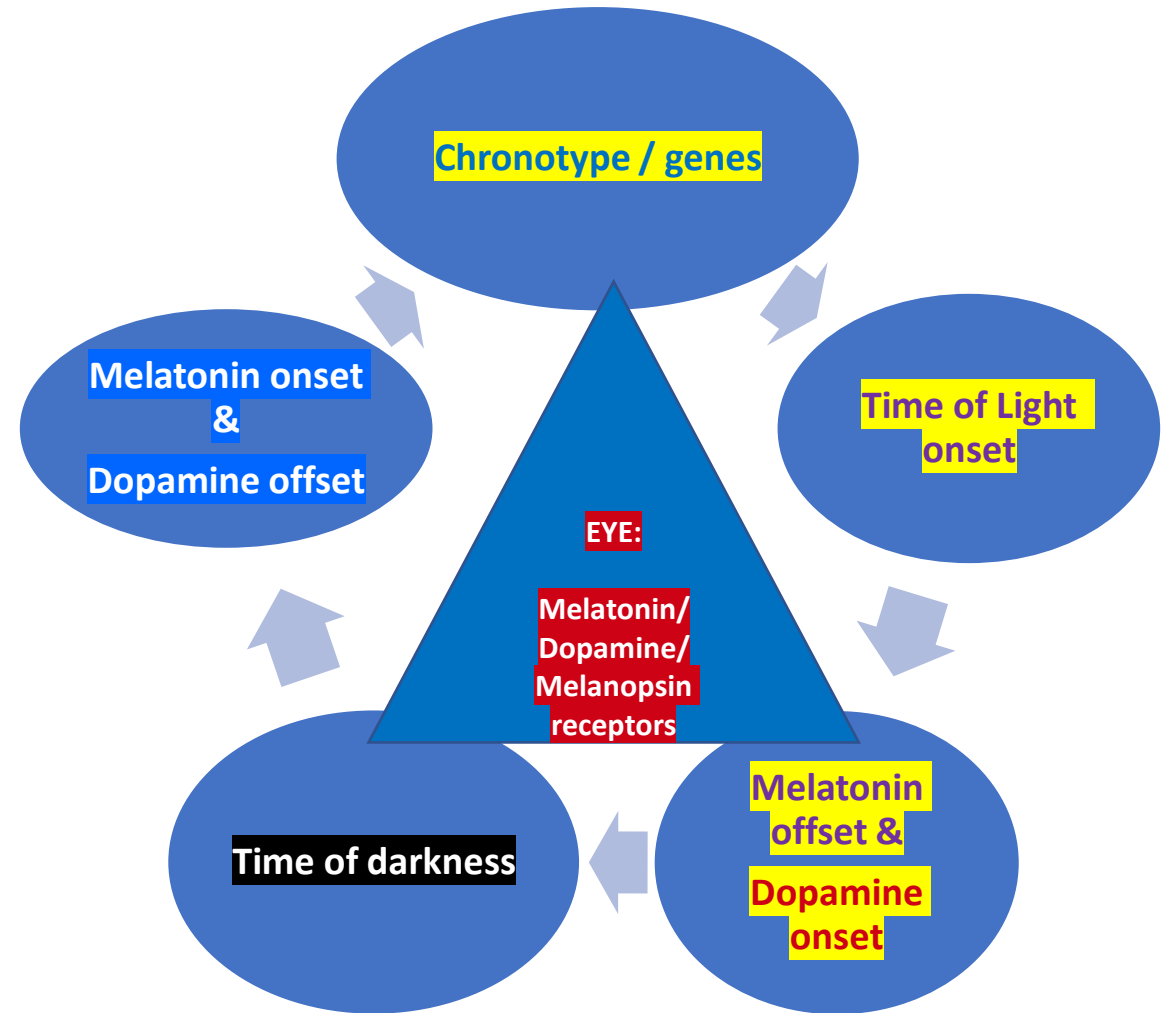
Sunlight enters through your eyes.



Acting through the hypothalamus, sunlight regulates our circadian rhythm through complex pathways that include melatonin, serotonin and body temperature.



Improving your circadian rhythm has dramatically positive effects on your body and mood.



Myranda Anya 2003; Oren 2005

› [Biol Psychiatry](#). 2010 Jun 1;67(11):1091-6. doi: 10.1016/j.biopsych.2009.12.032. Epub 2010 Feb 16.

Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia

Maaïke M Van Veen ¹, J J Sandra Kooij, A Marije Boonstra, Marijke C M Gordijn, Eus J W Van Someren

Affiliations + expand

PMID: 20163790 DOI: [10.1016/j.biopsych.2009.12.032](#)

Characteristics of 40 consecutive ADHD patients

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

C/ Late sleep separates the subtypes ...

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

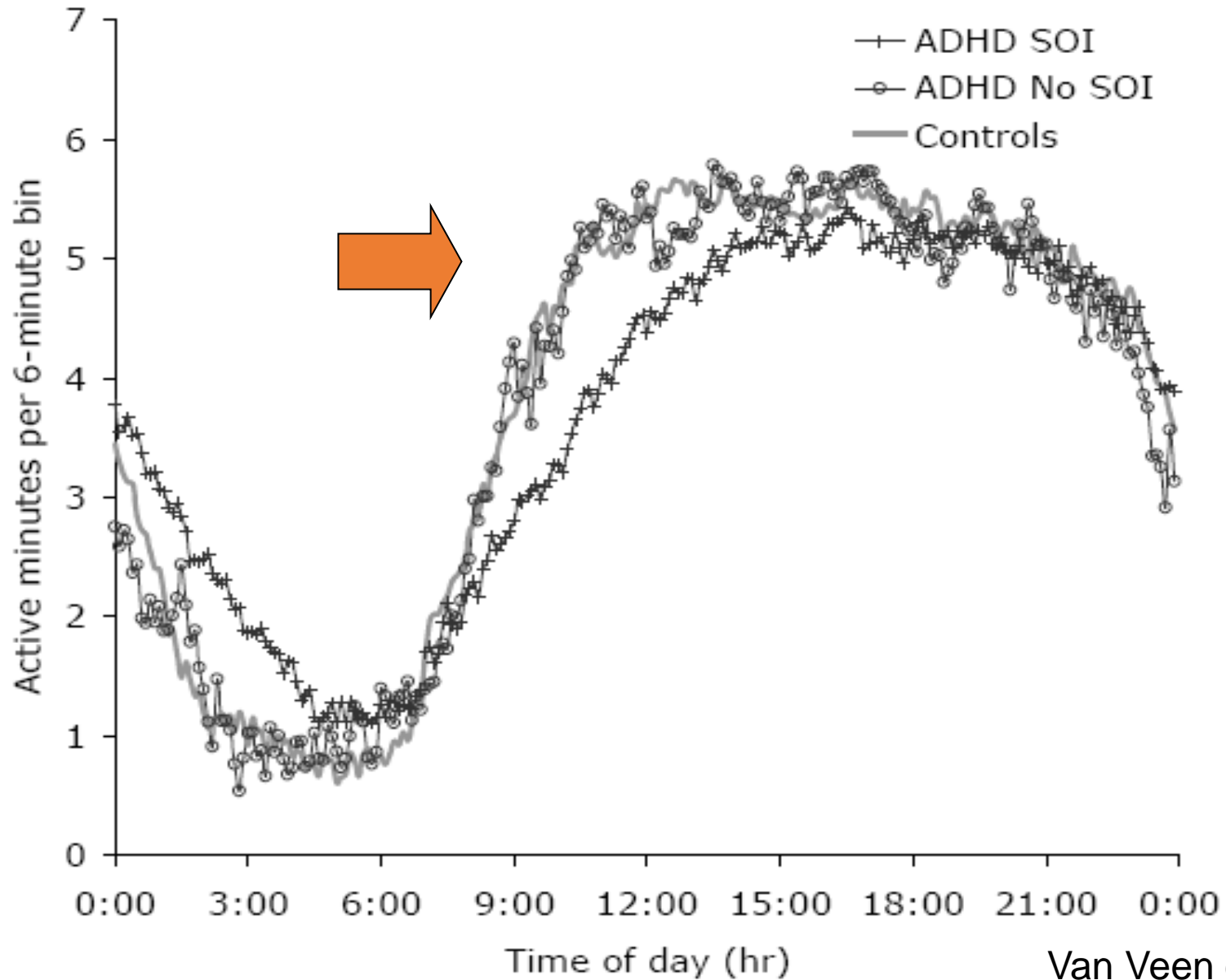
Dim Light Melatonin Onset (DLMO): delayed

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

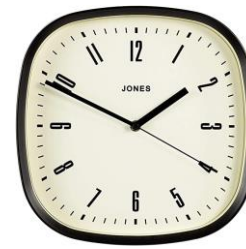
	ADHD Total	ADHD + SOI	ADHD - SOI	HC	<i>p</i> : ADHD vs HC	<i>p</i> : SOI vs HC
DLMO (hr ± sd)	22:57 ± 1:20	23:15 ± 1:19	22:00 ± 0:54	21:34 ± 0:45	0.000	0.000

- 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
- In ADHD it takes 3 hrs ...

24 hour movement patterns in ADHD + and – SOI, compared to controls (actigraphy)



ADHD is jetlagged, out of sync:



Late sleep

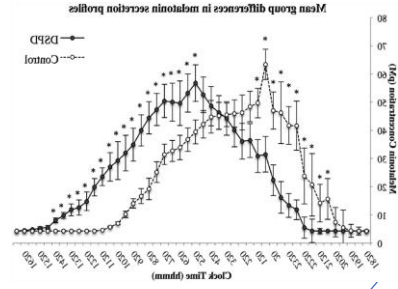


Late appetite

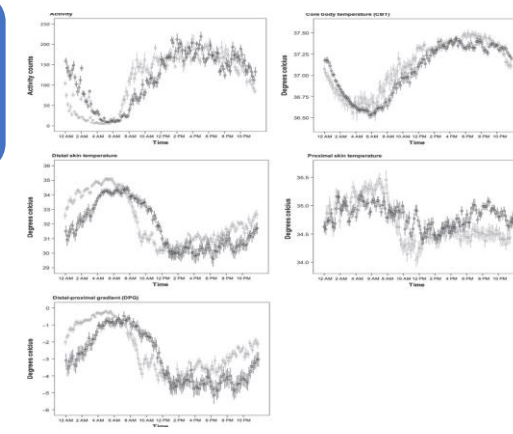
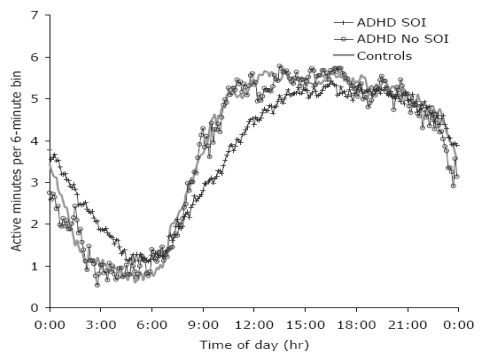
Late melatonin onset

Late movement pattern

Late temperature profile



Are ADHD symptoms diurnal, & late sleep nocturnal presentation?



Questions & Hypotheses:



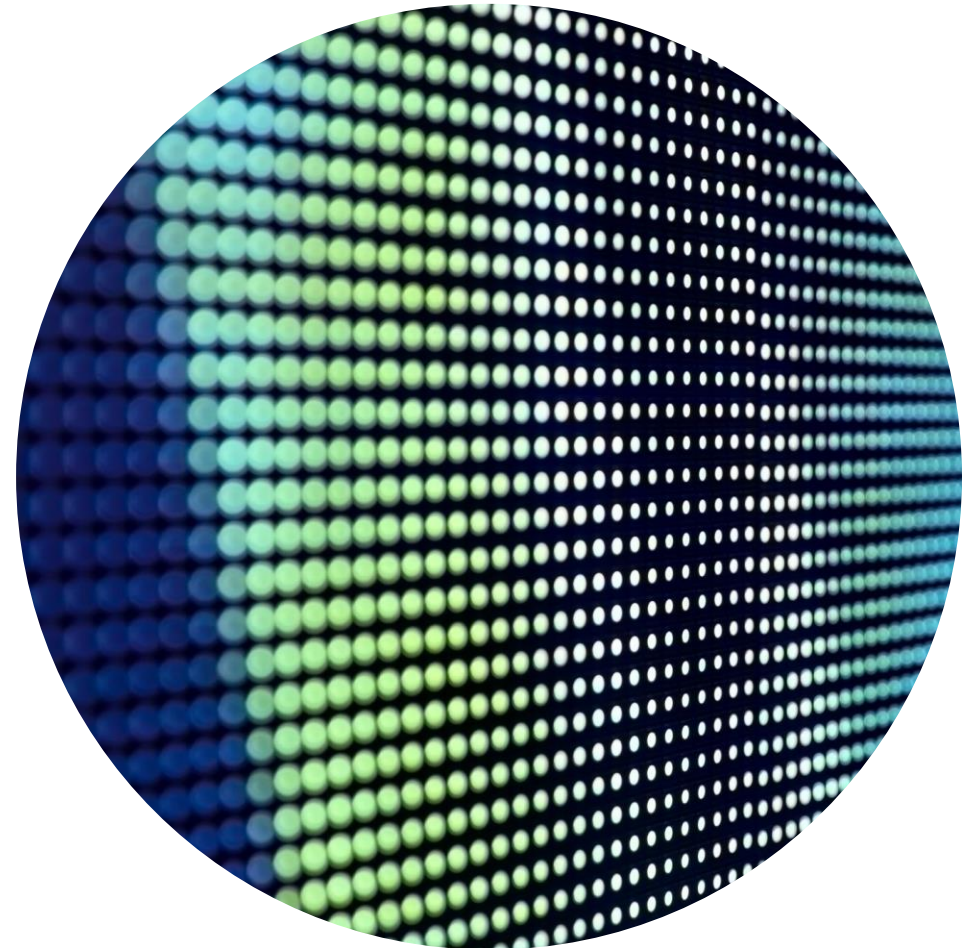
**IS ADHD IN FACT A
SLEEP DISORDER?**



**IS ADHD A DISORDER
OF THE BIOLOGICAL
CLOCK?**

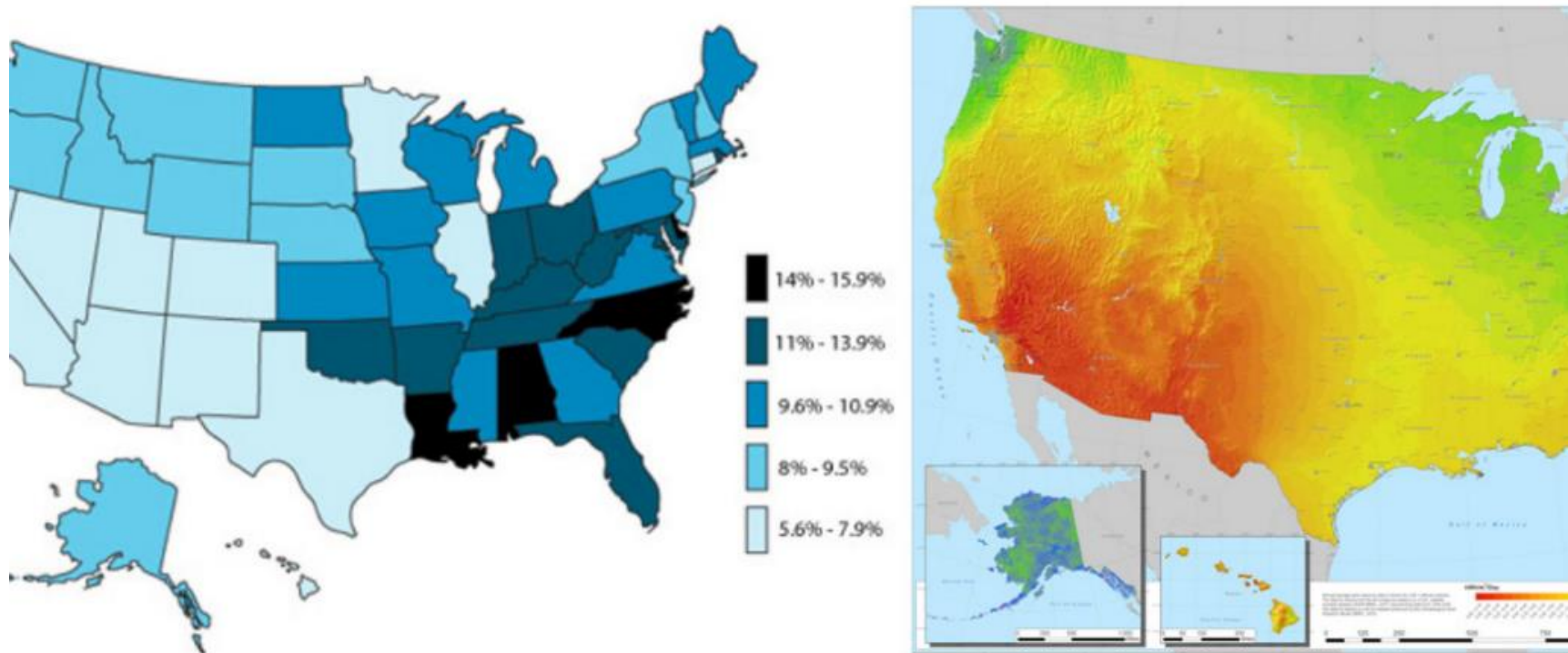


**COULD ADHD
IMPROVE BY SLEEP
TREATMENT??**



ADHD: prevalence lower in countries with intense daylight, in both US and Europe data, in both children and adults

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



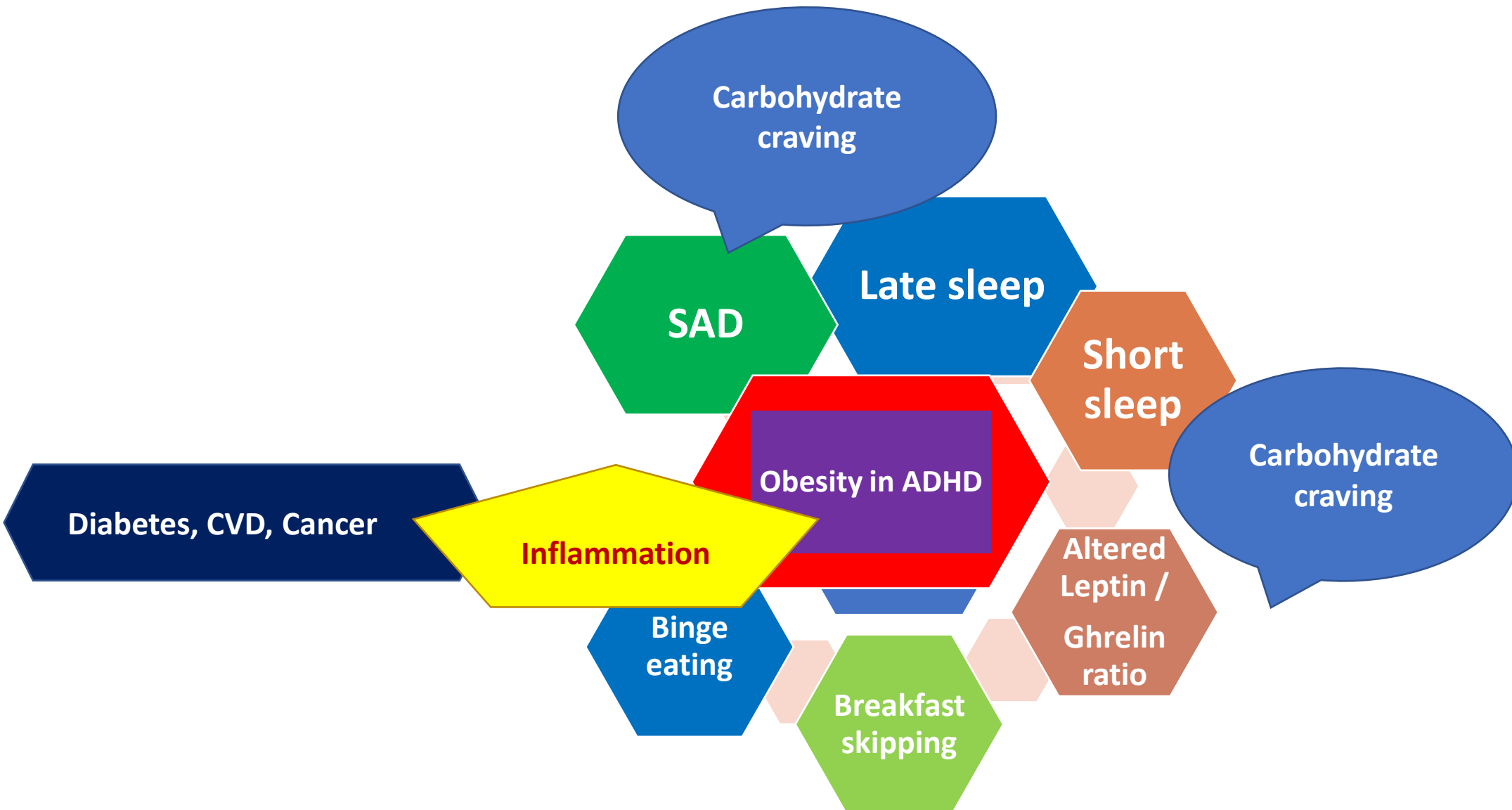
Arns ea 2013:

The preventative effect of high Solar Intensity might be related to improvement of circadian clock disturbances in ADHD

Delayed Sleep & Health in ADHD



- Delayed circadian rhythm in 75% of children and adults with ADHD (Dim Light Melatonin Onset measurements in saliva)
- Late sleep = short sleep due to school and work obligations next morning ('social jetlag')
- Short sleep induces increased appetite
- *Chronic* short sleep is associated with obesity, DM-II, CVD and cancer
- Background: genetic, environmental, behavioral & biological



Hypothesised 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

Self-reported Morbidities in ADHD versus controls

(showing only significant differences)

	% ADHD, n=202	% Controls, n=198	<i>p</i>
Depressed mood	18	6	<.001
Stress/ burnout/ fatigue	5	1	<.001
Pulmonary problems	31	16	<.001
Cardiovascular problems	43	18	<.001
Gastro-intestinal problems	33	19	.001
Metabolic problems	12	6	.042
Immune system problems	7	3	.049
Skeletal problems	50	36	.005

Somatic comorbidities associated with ADHD

N=4.7 million registry study Sweden:

Adults with ADHD: increased risk for 34 of 35 physical conditions compared with adults without ADHD;

Strongest associations:


- nervous system disorders (eg, sleep disorders, epilepsy, dementia; odds ratios [ORs] 1.50–4.62) &
- respiratory diseases (eg, asthma, chronic obstructive pulmonary disease; ORs 2.42–3.24).

Sex-stratified analyses showed similar patterns of results in men and women. Du Rietz 2021

Shift work - Short sleep & cancer risk

- Shift work may be carcinogenic in the long term (IARC 2007)
- Sleep loss by shiftwork has been associated with higher incidence of breast- and prostate cancer

How to explain?

- 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 show inhibiting effects of melatonin on cancer growth and increased survival
- In humans, many treatment studies with melatonin in cancer patients ongoing

ADHD & sleep hormone melatonin

- Later onset of melatonin (1.5 hrs)
- Melatonin is anti-oxidant, related to metabolic system & inhibits cancer growth ...
- Shorter sleep implies shorter duration of protection by melatonin ...

Reiter 2017; Hill 2015; van Veen 2010



HHS Public Access

Author manuscript

Endocr Relat Cancer. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

Endocr Relat Cancer. 2015 June ; 22(3): R183–R204. doi:10.1530/ERC-15-0030.

Melatonin: an Inhibitor of Breast Cancer

Steven M. Hill^{1,3,4,5}, Victoria P. Belancio^{1,3,4,5}, Robert T. Dauchy^{1,3,4,5}, Shulin Xiang^{1,3,4,5}, Samantha Brimer², Lulu Mao^{1,3,4,5}, Adam Hauch², Peter W. Lundberg², Whitney Summers¹, Lin Yuan^{1,3}, Tripp Frasch^{1,5}, and David E. Blask^{1,3,4,5}

¹Department of Structural and Cellular Biology, Tulane University School of Medicine New Orleans, LA 70112



Int J Mol Sci. 2017 Apr; 18(4): 843.

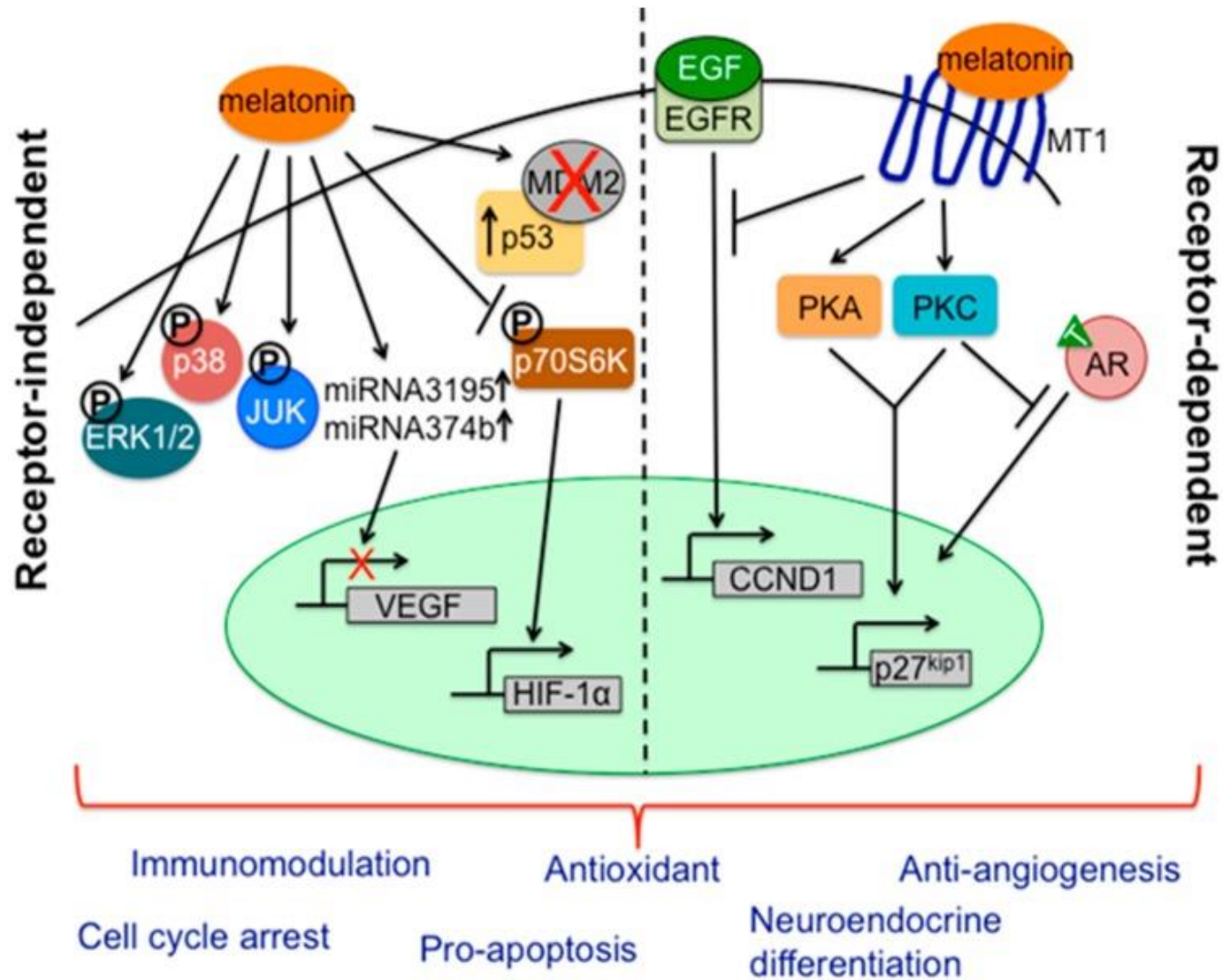
Published online 2017 Apr 17. doi: [10.3390/ijms18040843](https://doi.org/10.3390/ijms18040843)

PMCID: PMC5412427

Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis

Russel J. Reiter,^{1,*} Sergio A. Rosales-Corral,² Dun-Xian Tan,¹ Dario Acuna-Castroviejo,³ Lilan Qin,¹ Shun-Fa Yang,⁴ and Kexin Xu⁵

Anti-carcinogenic activity of melatonin



melatonin cancer treatment



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1,636 results



Melatonin for the prevention and treatment of cancer.

1 Li Y, Li S, Zhou Y, Meng X, Zhang JJ, Xu DP, Li HB.

Cite Oncotarget. 2017 Jun 13;8(24):39896-39921. doi: 10.18632/oncotarget.16379.

PMID: 28415828 [Free PMC article.](#) [Review.](#)

Share

Melatonin could also be utilized as adjuvant of **cancer** therapies, through reinforcing the therapeutic effects and reducing the side effects of chemotherapies or radiation. **Melatonin** could be an excellent candidate for the prevention and **treatment** of se ...



Melatonin and Cancer Hallmarks.

2 Talib WH.

Cite Molecules. 2018 Feb 26;23(3):518. doi: 10.3390/molecules23030518.

PMID: 29495398 [Free PMC article.](#) [Review.](#)

Share

Melatonin anticancer activity is mediated by interfering with various **cancer** hallmarks. This review summarizes the anticancer role of **melatonin** in each **cancer** hallmark. The studies discussed in this review should serve as a solid foundation for researc ...



Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis.

3

Cite Reiter RJ, Rosales-Corral SA, Tan DX, Acuna-Castroviejo D, Qin L, Yang SF, Xu K.

Int J Mol Sci. 2017 Apr 17;18(4):843. doi: 10.3390/ijms18040843.

PMID: 28420185 [Free PMC article.](#) [Review.](#)

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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**. ...Even more im ...



The potential utility of melatonin in the treatment of childhood cancer.

4

Chao YH, Wu KH, Yeh CM, Su SC, Reiter RJ, Yana SF.



Targeting cancer stem cells by melatonin: Effective therapy for cancer treatment.

5

Cite Maroufi NF, Vahedian V, Hemati S, Rashidi MR, Akbarzadeh M, Zahedi M, Pouremamali F, Isazadeh A, Taefehshokr S, Hajazimian S, Seraji N, Nouri M.

are Pathol Res Pract. 2020 May;216(5):152919. doi: 10.1016/j.prp.2020.152919. Epub 2020 Mar 9.

PMID: 32171553 [Review.](#)

In recent decades, enormous investigations showed that **melatonin** can prompt apoptosis in **cancer** cells and inhibit tumor metastasis and angiogenesis in variety of malignancies such as ovarian, melanoma, colon, and breast **cancer**; therefore, its possible therape ...



Melatonin: A new inhibitor agent for cervical cancer treatment.

6

Shafabakhsh R, Reiter RJ, Mirzaei H, Teymoordash SN, Asemi Z.

Cite J Cell Physiol. 2019 Dec;234(12):21670-21682. doi: 10.1002/jcp.28865. Epub 2019 May 27.

are PMID: 31131897 [Review.](#)

Cervical **cancer** is one of the most common **cancers** between women and is known as the third leading cause of female **cancer** related deaths annually. ...A large amount of studies indicated inhibitory effects of **melatonin** against various types of **cancers** ...



Melatonin and breast cancer: Evidences from preclinical and human studies.

7

Cite Kubatka P, Zubor P, Busselberg D, Kwon TK, Adamek M, Petrovic D, Opatrilova R, Gazdikova K, Caprnda M, Rodrigo L, Danko J, Kruzliak P.

are Crit Rev Oncol Hematol. 2018 Feb;122:133-143. doi: 10.1016/j.critrevonc.2017.12.018. Epub 2017 Dec 29.

PMID: 29458781 [Review.](#)

In breast **cancer**, **melatonin** is capable to disrupt estrogen-dependent cell signaling, resulting in a reduction of estrogen-stimulated cells, moreover, it's obvious neuro-immunomodulatory effect in organism was described. ...**Melatonin** alone or in combine ...



Melatonin is an appropriate candidate for breast cancer treatment: Based on known molecular mechanisms.

8

Cite Amin N, Shafabakhsh R, Reiter RJ, Asemi Z.

are J Cell Biochem. 2019 Aug;120(8):12208-12215. doi: 10.1002/jcb.28832. Epub 2019 Apr 30.

PMID: 31041825 [Review.](#)

Surgery, chemotherapy, radiotherapy, immunotherapy, and neoadjuvant **therapy** are the current means

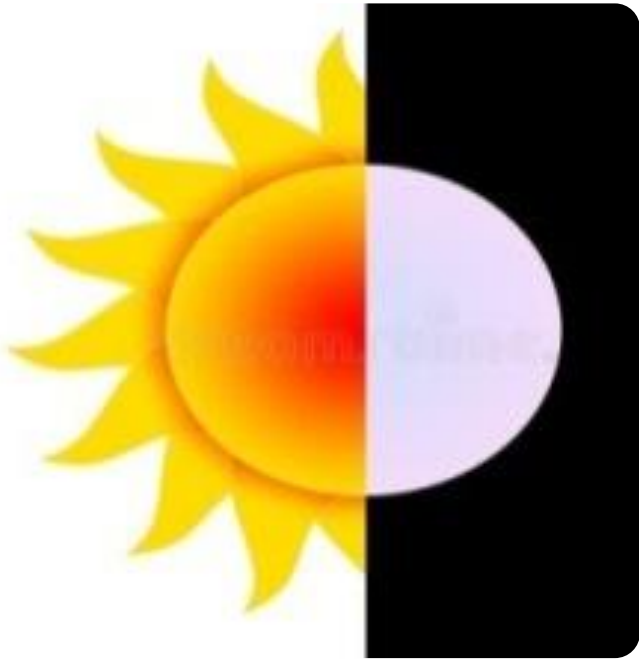
Treatment of delayed sleep phase disorder



Sleephygiene

Melatonin

Light therapy



Sleep hygiene I:

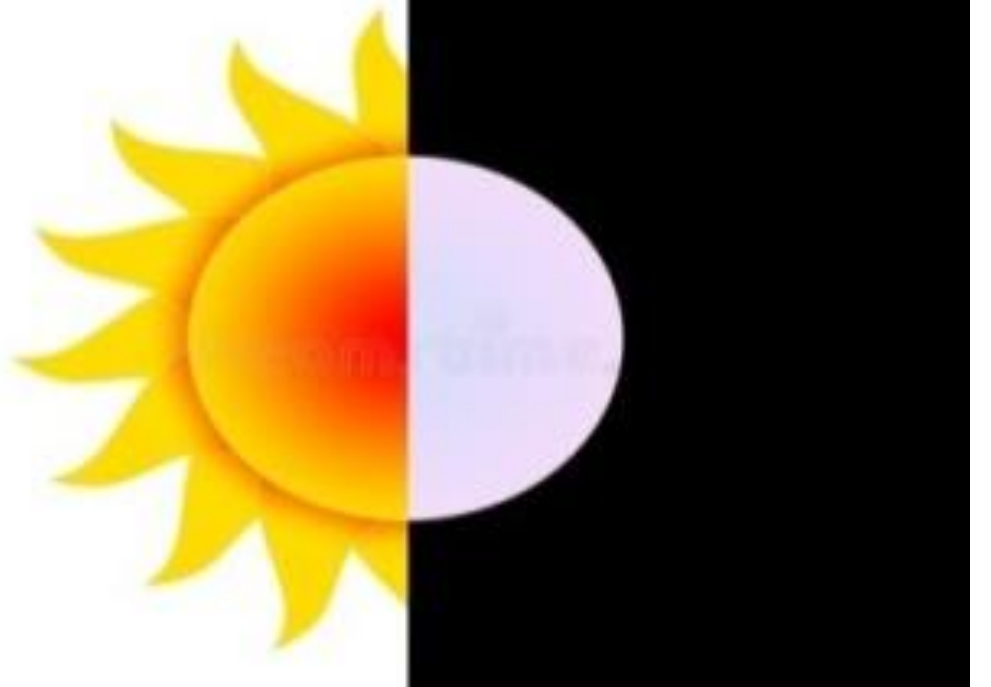
Let your day be bright, and your night as dark as possible!

- Limit drinks after 8 pm to prevent toilet visit
- When toilet: no light!
- Block all light sources: blinded curtains, (no luxaflex!), eye mask, no lights of chargers/timers/mobile phone that wake you up at night
- No screens after 9.30 pm
- Or: use orange goggles from 7 pm that inhibit blue light to enter the retina and the clock



Sleep hygiene II

- Temperature control: hot shower at night helps, warm pyjama, warm feet (higher temperature related to melatonin production)
- Wake up at same time every day, also in weekends
- Aim for sleep duration of 7-8 hrs, between 11 pm & 7 am
- No napping during daytime > 30 min
- Go outside in the morning (walk the dog)
- Advance the rhythm by light when needed
- Limit use of sunglasses during daytime
- NB: Oversensitivity to light in 70% in ADHD (!) & often use of sunglasses, thereby disturbing synchronisation with time of the day even further



Melatonin for late sleep (not for other sleep problems)

- **1-3 mg (max) at 10 pm using timer**
- **Not after 12 pm!**
- **Active during 3-4 hrs**
- **1-3 mg is already high dosis**
- **Sleepy during day when dose too high**

- **Long acting melatonin, Circadin 2 mg**
 - **may help in case of waking up at 3 am**
 - **after falling asleep using short acting melatonin, but no research**



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;
- Duration: 3 weeks for late sleep; 1-2 weeks for winterdepression. Repeat when relapse
- Dosage: 30 min every morning between 7 and 8 am



Rybak ea 2006



Light therapy 2022: Mobile light glasses!

Propeaq.com



Chronotherapy reduces ADHD symptoms

> J Psychiatr Res. 2017 Aug;91:105-110. doi: 10.1016/j.jpsychires.2017.03.004. Epub 2017 Mar 6.

Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: A pilot study

Rachel E Fargason¹, Aaron D Fobian¹, La

> Chronobiol Int. 2020 Oct 29;1-10. doi: 10.1080/07420528.2020.1835943. Online ahead of print.

Effects of chronotherapy on circadian rhythm and ADHD symptoms in adults with attention-deficit/hyperactivity disorder and delayed sleep phase syndrome: a randomized clinical trial

Emma van Andel¹, Denise Bijlenga¹, Suzan W N Vogel¹, Aartjan T F Beekman²,
J J Sandra Kooij^{1 2}

3 weeks: 0.5 mg Melatonin / vs placebo / vs Lighttherapy + 0.5 mg melatonin

Review > World J Biol Psychiatry. 2011 Sep;12 Suppl 1:40-3. doi: 10.3109/15622975.2011.598389.

Chronotherapeutics and psychiatry: setting the clock to relieve the symptoms

Andrew N Coogan¹, Johannes Thome

Background Phase study

Treatment of ADHD: coaching and stimulants

Treatment DSPS: sleep education and chronotherapy (melatonin and light therapy)

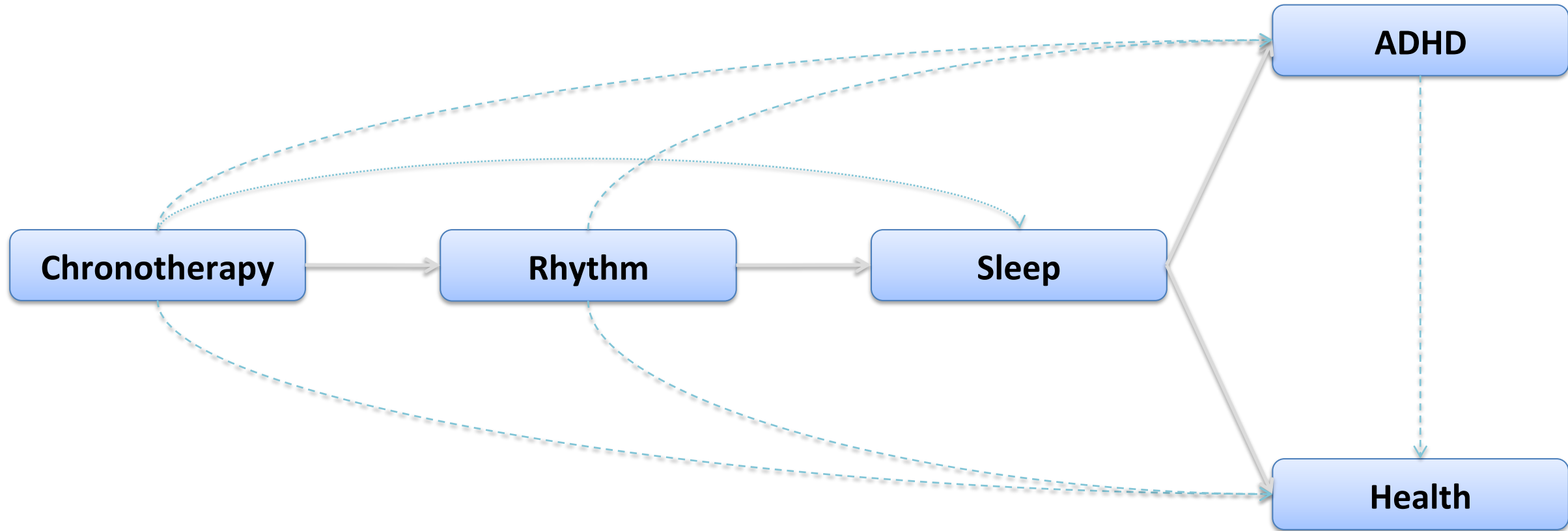
Pilotstudies: light therapy diminishes ADHD-symptoms

First RCT: Phase shift in ADHD of Sleep and Appetite (PhASE)



Emma van Andel

Questions Phase study



Phase-studie

51 adults with AD(H)D and DSPS (18-55 yrs)

Sleep education + 3 weeks treatment:

- 1) Placebo 0,5 mg
- 2) Melatonin 0,5 mg
- 3) Melatonin 0,5 mg + light therapy (BLT) 30 min 7.00-8.00 am



Phase-study

Individual scheme based on Dim-Light Melatonin Onset (DLMO) at baseline

Measures: DLMO, actigraphy, ADHD Rating Scale

- baseline
- directly after 3 wks treatment
- 2 wks after end of treatment

Conclusions

- Chronotherapy advanced the rhythm with 1.5 - 2 hrs, but not sleep
- ADHD-symptomen reduced with 14% after 0.5 mg of melatonin treatment
- Additional intensive CBT necessary to advance sleep as well
- Timing light therapy also needs to be individualised in the morning

**Melatonin is an important part of
effective ADHD treatment**

But: sleep coaching needed!

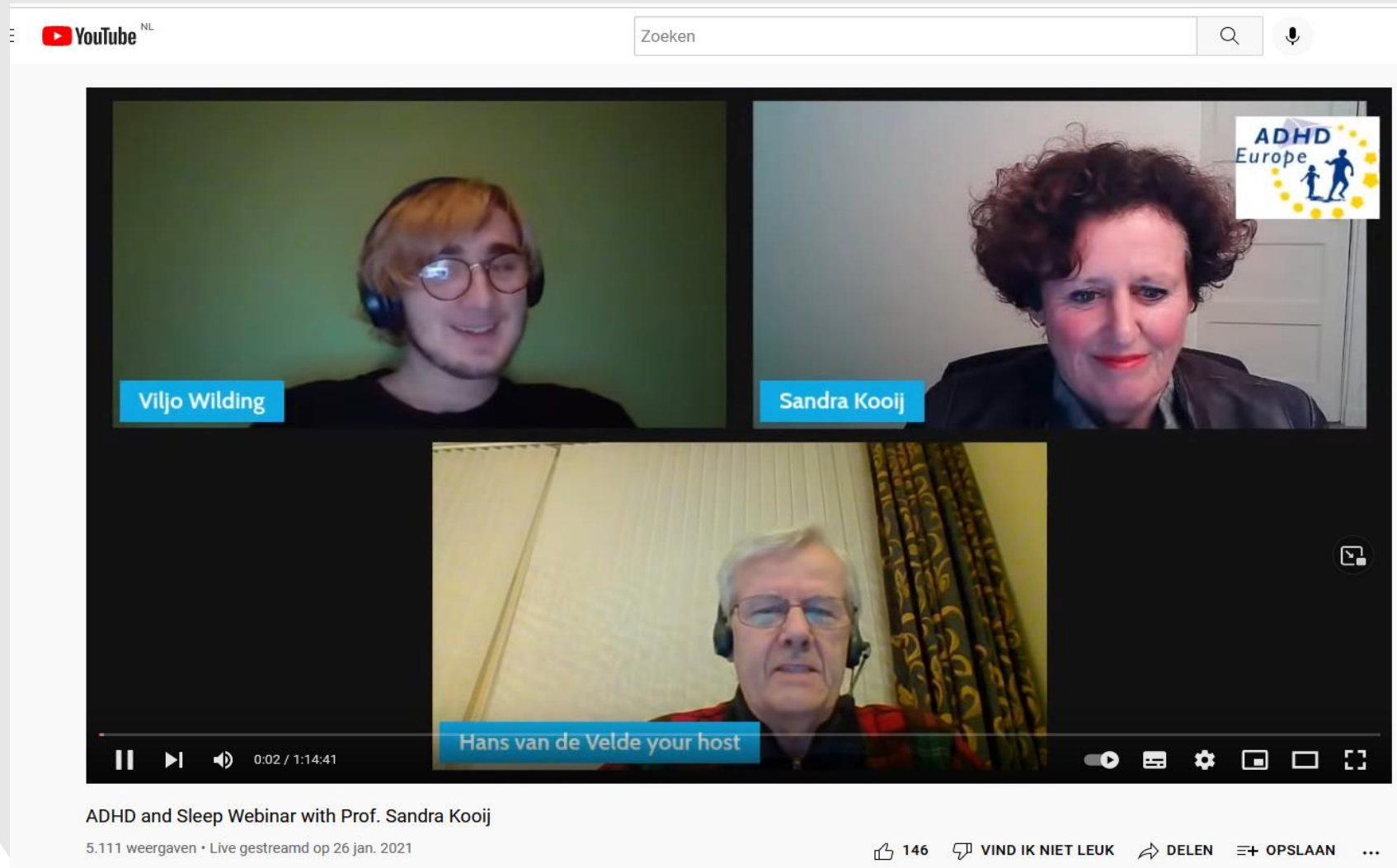
e.vanandel@psyq.nl

Thanks to:

- PsyQ Kenniscentrum ADHD
- Emma van Andel
- Dr. Denise Bijlenga
- Dr. Suzan Vogel
- Mylène Böhmer
- Farangis Dorani
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- Prof. Dr. Aartjan Beekman
- Prof. Dr. Eus van Someren
- Ziekenhuis Gelderse Vallei Ede
- Frank van de Bunt
- All participants & the ADHD-team
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- Piet Sturm
- Nederlands Herseninstituut KNAW
- Prof. Dries Kalsbeek
- LUMC Trialapotheek
- Star Medisch Diagnostisch Centrum
- Fysiologic
- VUmc Endolab

Emma van Andel

MORE INFO on ADHD, sleep and health op YouTube



The screenshot shows a YouTube live stream interface. At the top, the YouTube logo and a search bar with the text 'Zoeken' are visible. The main content area displays a video player with three participants in a grid layout. The top-left participant is a man with glasses and a headset, identified as 'Viljo Wilding'. The top-right participant is a woman with curly hair, identified as 'Sandra Kooij', with an 'ADHD Europe' logo in the top right corner of her video frame. The bottom-center participant is an older man with glasses and a headset, identified as 'Hans van de Velde your host'. The video player includes a progress bar showing '0:02 / 1:14:41' and various control icons. Below the video player, the title 'ADHD and Sleep Webinar with Prof. Sandra Kooij' is displayed, along with the text '5.111 weergaven • Live gestreamd op 26 jan. 2021'. At the bottom right, there are interaction buttons: a thumbs-up icon with '146', a thumbs-down icon with 'VIND IK NIET LEUK', a share icon with 'DELEN', and a save icon with 'OPSLAAN'.

YouTube NL Zoeken

Viljo Wilding

Sandra Kooij

ADHD Europe

Hans van de Velde your host

ADHD and Sleep Webinar with Prof. Sandra Kooij

5.111 weergaven • Live gestreamd op 26 jan. 2021

146 VIND IK NIET LEUK DELEN OPSLAAN ...