Phase shift in adult ADHD of sleep and apetite.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46908

Source
ToetsingOnline

Brief title
FASE

Condition

- Other condition
- Sleep disorders and disturbances

Synonym
Delayed sleep phase syndrome; chronic delayed sleep/wake pattern

Health condition

ADHD

Research involving
Human

Sponsors and support

Primary sponsor: Parnassia Bavo Groep (Den Haag)
Source(s) of monetary or material Support: Fonds NutsOhra;PsyQ Onderzoeksfonds;eigen gelden

Intervention

Keyword: ADHD, Delayed Sleep Phase Syndrome, Light therapy, Melatonin

Outcome measures

Primary outcome

The phase advance time of the DLMO (the moment that the natural melatonin production reaches the 3 pg/mL threshold in saliva) at Followup 1.

Secondary outcome

- Improvement of the apetite profiles of hormones leptin and ghrelin
- Improvement of insulin resistence
- Improvement of biomarker profiles
- Improvement of heart rate variability
- Improvement of blood pressure and possibly weight
- Prolongiation of the sleep duration, shortening of the sleep onset delay and the advancement of the wake-up time (as measured by Actigraphy)
- Decrease of daytime sleepiness
- Improvement of quality of life
- Decrease of ADHD symptoms
- Decrease of intake of carbonhydrate-rich food
- Treatment satisfaction

Study description

Background summary

In 80% of adults with ADHD there are chronic sleep-onset problems of which most have commenced in childhood (van Veen et al, 2010).The sleep problems consist of a chronic pattern of late sleep time and late rise time. People with this sleep pattern are often referred to as 'nightowls', and their sleep pattern a 'delayed sleep phase'. The diagnosis of this condition is called the Delayed Sleep Phase Syndrome (DSPS). Patients with DSPS cannot sleep at an earlier preferred time, but often only around 2 or 3 AM. The consequence is a chronic short sleep because they need to get up on time for their daily obligations.

There are clues that the delayed sleep phase in ADHD has a genetic foundation. Our research has shown that this sleep pattern correlates with a late endogeneous melatonin production in the evening (van Veen et al, 2010). Melatonin is the sleep hormone that in healthy people rises around 9:30 PM (the moment it reaches a threshold is termed Dim Light Melatonin Onset, or DLMO)so that they can sleep around two hours later, around 11:30 PM. In adults with ADHD the DLMO has a mean of 11:15 PM (van Veen et al, 2010). In adults with ADHD and DSPS this is at 0:08 AM (Bijlenga et al, 2011b). The simple advice to go to bed at an earlier time is not effective, because the sleep is only supported by melatonin only late at night. Going to bed earlier results in an even longer sleep onset duration or even insomnia.

A chronic short sleep has negative consequences for physical health. In healthy people one night of short sleep has already shown to increase the blood glucose and to decrease insulin resistence, which result in blood values that are similar to the prestadium of diabetes (Spiegel et al., 2005). A onetime short sleep also lead to direct increase of the apetite the next day, a preference for more calory and carbon rich food, probably to compensate for the loss of energy (Spiegel et al., 2004). On the long term a chronic short sleep is associated with increase in weight, obesity, diabetes, hypertension, metabolic syndrome, cardiovascular disease and even cancer (Maury, Ramsey & Bass, 2010; Knutson, 2010). These alarming figures indicate that betekenen adults with ADHD may have increased risk of these serious chronic conditions.

Possible interventions
The delayed sleep phase in ADHD can be advanced with treatment with melatonin in the evening and/or with light therapy in the morning. Both are termed 'zeitgebers' because they influence the biological clock and the timing of the sleep. By advancing the sleep phase the potential sleep duration increases. Our hypothesis is that resetting the biological clock will also influence other *timed* processes such as apetite, hormone production, and temperature.

Study objective

In this study the best treatment of DSPS will be investigated by comparison of existing treatments. We will investigate is patients with ADHD and DSPS have less favorable blood values for biomarkers of chronic diseases in comparison with norm values and a less favourable cardiovasculair profile, in treatment with Melatonin has effect on sleep length, sleep phase, ADHD-symptoms, appetite hormones and other biomarkers, and if light therapy in the morning in addition to Melatonin treatment has an additive effect on the treatment. We will also investigate the relationship between the delayed sleep phase and appetite in adults with ADHD and DSPS. In addition, DNA samples will be collected for a *Genome-wide association study*.

Study design

The study has a double-blind placebo controlled randomized design with three intervention groups of 17 adults with ADHD and DSPS each; total N=51.

The effect of treament of DSPS will be evaluated by randomisation of patients for:
1) Sleep education plus 0,5 mg dd Melatonin following individual medication scheme during 3 weeks (MEL)
2) Sleep education plus 0,5 mg dd placebo following individual medication scheme during 3 weeks (PLAC)
3) Sleep education plus 0,5 mg dd Melatonin following individual medication scheme plus 30 minutes light therapy in the morning between 7 and 8 AM during 3 weeks (MEL+LT)

The individual medication scheme consists of administration of the study medication 3, 4 and 5 hours before the individual's time of DLMO in the first, second, and third intervention week, respectively.

Intervention

Baseline (week 1)
All patients fill out questionnaires about demographic characteristics, sleep characteristics (MCTQ), ADHD symptoms (ADHD-RS), life style, daytime sleepiness, any illness or colds within the last week (to correct the inflammation markers), food type preference, apetite, and quality of life (AAQOL). A DNA sample will be collected. All patients will wear a holter and an ambulant blood pressure monitor during 1 day and a wrist Actometer during 3 days and record their sleep in a sleep log; during 1 night the salivary melatonin will be assessed between 8 PM and 3 AM on the hour, during 1 morning salivary cortisol will be assessed (directly after wake-up, 15 minutes, and 30 minutes after wake-up), blood will be drawn sober at 8AM for the assessment of leptin, ghrelin, insulin/glucose ratio, insulin resistentance (with OGTT),

IGF-1, CRP, vitamin B12, vitamin D, magnesium, iPTH, leukocyte count, and ferritin; and the assessment of blood pressure, length and weight.

Randomisation and intervention (weeks 2-4); patients will be randomised for one of the following interventions:
1) Sleep education plus 0,5 mg dd Melatonin 3 hours before DLMO during 3 weeks (MEL)
2) Sleep education plus 0,5 mg dd placebo 3 hours before DLMO during 3 weeks (PLAC)
3) Sleep education plus 0,5 mg dd Melatonin 3 hours before DLMO plus 30 minutes light therapy in the morning between 7 and 8 AM during 3 weeks (MEL+LT)

Followup 1 (week 5): directly after intervention
All patients fill out the same questionnaires about sleep characteristics (MCTQ), ADHD symptoms (ADHD-RS), life style, daytime sleepiness, any illness or colds within the last week (to correct the inflammation markers), food type preference, apetite, quality of life (AAQOL), and also treatment satisfaction. All patients will again wear a holter and an amulant blood pressure monitor during 1 day and a wrist Actometer during 3 days and record their sleep in a sleep log; during 1 night the salivary melatonin will be assessed between 8 PM and 3 AM on the hour, during 1 morning salivary cortisol will be assessed (directly after wake-up, 15 minutes, and 30 minutes after wake-up), blood will be drawn sober at 8 AM for the assessment of leptin, ghrelin, insulin/glucose ratio, insulin resistentance (with OGTT), IGF-1, CRP, vitamin B12, vitamin D, magnesium, iPTH, and leukocyte count; and the assessment of blood pressure and weight.

Followup 2 (week 7): delayed effect
All patients fill out the same questionnaires about sleep characteristics (MCTQ), ADHD symptoms (ADHD-RS), life style, daytime sleepiness, any illness or colds within the last week (to correct the inflammation markers), food intake, apetite, quality of life (AAQOL), and also treatment satisfaction. All patients will again wear a wrist Actometer during 3 days and record their sleep in a sleep log; during 1 night the salivary melatonin will be assessed between 8 PM and 3 AM on the hour, during 1 morning salivary cortisol will be assessed (directly after wake-up, 15 minutes, and 30 minutes after wake-up), blood will be drawn at 8 AM for the assessment of leptin, ghrelin, insulin/glucose ratio, insulin resistentance, IGF-1, CRP, vitamin B12, vitamin D, magnesium, iPTH, and leukocyte count; and the assessment of blood pressure and weight.

Study burden and risks

The burden of participation will be held to a minimum. Participants are asked to visit our clinic 9 times in 7 weeks. Travel expenses are covered and they will receive ¤100 for study participation. Filling out the questionnaires is not burdening. The keeping of the sleep logs is minimally burdening and will take 5 minutes per dag durig 3 weeks. To wear the wrist Actometer during 3 days

per measurement is also not burdening.

The assessment of Melatonine in saliva can be somewhat burdening because they may experience loss of some night rest . The patient is asked to chew on the cotton swabs under dim light and is asked not to take certain foods and drinks (caffeine, alcohol, and banana). In total, 8 cotton swabs need to be chewed in one night. If one cotton swab takes 1 minute then the time investment for this part of the study is about 8 swabs x 3 measurements = 24 minutes.

To draw blood three times can be somewhat burdening. For each draw the patient needs to be sober and at the clinic at 8:00 AM . At Baseline and at Followup 1 a venflon will be inserted to draw blood, or we will collect blood by venipuncture or from finger pricks if it is not possible to insert a venflon.After first blood draw an OGTT will be performed using standard protocol. The patient needs to stat at the clinic for the OGTT for 2 hours but can work on a computer or laptop or can sit quietly and read. For the OGTT the patients need to drink a glucose containing solution after which every 30 minutes blood is drawn. After the OGTT the patient will receive a breakfast. At Followup 2 there is no OGTT but the blood will be drawn without a venflon.

To wear a holter and an ambulant blood pressure monitor for 24 hours is not very burdening. The collection of a DNA sample is also regarded as not very burdening.

The risics of complications because of study participation are deemed minimal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age between 18-55 years old
- Diagnosis ADHD
- Diagnosis DSPS

Exclusion criteria

- Psychotic illness;
- Untreated mood disorder;
- Untreated anxiety disorder;
- Alcohol intake > 2 U/day, or for women >15 U/week, for men >;21 U/week;
- Use of cannabis;
- Use of harddrugs;
- Suspected dementia, anamnestic disorder of other cognitive disorder (DSM-IV);
- Mental retardation;
- Use of the following medication within 1 month prior to study participation: psychostimulants, melatonin, mirtazapin, sleep medication, antipsychotics, clonidin, benzodiazepins, bèta-blockers;
- Insufficient fluency of the Dutch language;
- Evening or night shift work;
- Travel over > 2 time zones within 2 weeks prior to study participation (because of possible jet lag);
- Pregnancy or breast feeding;
- Having joung children who may disturb night rest;

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-05-2013
Enrollment:	51
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Melatonin
Generic name:	Melatonin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-09-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-11-2012

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	12-01-2018

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22013
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-000320-18-NL
CCMO	NL39579.058.12
OMON	NL-OMON22013