ISRCTN96702191 https://doi.org/10.1186/ISRCTN96702191

Sleep and melatonin secretion in women with severe premenstrual disorder

Submission date	Recruitment status	[_] Prospectively registered
06/12/2010	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
07/02/2011	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
29/03/2011	Urological and Genital Diseases	[_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
MOP-38064

Study information

Scientific Title
Sleep and melatonin across the menstrual cycle in women with premenstrual dysphoric disorder (PMDD)

Study objectives
1. The changes in sleep organization, sleep electroencephalographic (EEG) activity, core body temperature and plasma melatonin are significant across the menstrual cycle.
2. The changes in sleep organization, sleep EEG, core body temperature and plasma melatonin across the menstrual cycle are different in women with premenstrual dysphoric disorder (PMDD) when compared to healthy controls.
3. Exogenous melatonin can significantly improve sleep quality and EEG in women with PMDD during the premenstrual period of their menstrual cycle.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Douglas Mental Health University Institute Research Ethics Board approved on the 8th December 1998 (ref: REB 98-29)

Study design
Single centre open-label intervention study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Premenstrual dysphoric disorder (PMDD)

Interventions
PMDD participants were given a 2 mg tablet of slow-release melatonin taken orally 60 minutes prior to bedtime. Melatonin was administered each night during the luteal phase of the menstrual cycle for three consecutive menstrual cycles. The treatment began three days after the projected time of ovulation and ended on the first day of the subsequent menstrual period (menses onset). This was an open-label study comparing the effect of the treatment phase with the baseline no-intervention phase which occurred during the menstrual cycle before the three months of treatment. Total duration of treatment was for three consecutive months during which exogenous melatonin was administered selectively during the luteal phase (i.e. approximately the last two weeks of the menstrual cycle).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Melatonin

Primary outcome(s)
The experimental protocol consisted of two phases, including a baseline and intervention condition. Each phase consisted of a menstrual cycle during which data were collected. The

intervention lasted three menstrual cycles with the last menstrual cycle consisting of a repeat of the data collected during baseline. During each menstrual cycle of data collection, participants entered the laboratory every third night and had two 24-hour periods of investigation at the follicular and luteal phases of their menstrual cycle. Core body temperature was measured continuously via rectal sensor throughout all nocturnal laboratory visits throughout the menstrual cycle (~ 8 - 10 visits) at baseline and treatment phases, and also during the two separate 24-hour visits planned to occur in the follicular phase and the luteal phase of the menstrual cycle in both baseline and treatment phases. Polysomnographic sleep was recorded during each nocturnal laboratory visit throughout the menstrual cycle (~ 8 - 10 visits) at baseline and treatment phases. In addition, urine samples were collected during nocturnal visits before and after the sleep episode and 1x/3 hours throughout the 24-hour visits to measure their content in 6-sulfatoxy-melatonin. Saliva samples were also collected 2x/hour at nocturnal visits and throughout the waking episode across the 24-hour laboratory visits. Plasma melatonin was sampled via indwelling forearm catheter throughout each of the two separate 24-hour laboratory visits, planned to occur during the follicular phase and the luteal phase of the menstrual cycle in both baseline and treatment phases.

Key secondary outcome(s))
All participants filled out a post-sleep questionnaire each day throughout the experiment, which assessed subjective sleep quality via a 7-point Likert Scale, subjective sleep onset latency, subjective sleep duration, morning anxiety levels via visual analogue scale (VAS; 100-mm bipolar scale, with 0 mm being "extremely calm" and 100 mm being "extremely agitated") and a summary of dream content. All participants also filled out an 11-item VAS (100-mm bipolar scale, with 0 mm being "not at all" and 100 mm being "extreme symptoms") for mood and symptom assessments which included the measures depressed mood, tension, affective lability, irritability, decreased interest, difficulty concentrating, lack of energy, change in appetite, change in sleep patterns, feeling out of control, and physical symptoms. While in the laboratory, subjective alertness (100 mm bipolar VAS administered every 20 minutes; 0: "extremely sleepy", 100: "extremely alert"), subjective mood (100 mm bipolar VAS administered every 20 minutes; 0: "extremely happy", 100: "extremely sad"), subjective excitedness (100 mm bipolar VAS administered every 20 minutes; 0: "extremely calm", 100: "extremely excited") and cognitive performance (4-minute calculation test administered every 60 minutes) were also assessed. Distal skin temperature at the hands and feet was recorded 1x/min throughout all laboratory visits in four control participants, two PMDD participants during the baseline phase, and one PMDD participant during the treatment phase. Peripheral blood mononuclear cells were collected 1x/2 hours in one control participant across both 24-hour laboratory visits.

Completion date
31/12/2012

Eligibility

Key inclusion criteria
Patients:
1. Females aged between 18 and 45 years old
2. Meet Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) research criteria for clinical diagnosis of PMDD. This was determined by meeting with a trained psychiatrist during the asymptomatic follicular phase and the symptomatic late luteal phase.
3. Required to fill out an 11-item visual analogue scale (VAS) for at least two consecutive menstrual cycles. The 11-item VAS (10-mm bipolar scale, with 0 mm being "not at all" and 100 mm being "extreme symptoms") was based on the DSM-IV criteria for PMDD diagnoses and

included the measures depressed mood, tension, affective lability, irritability, decreased interest, difficulty concentrating, lack of energy, change in appetite, change in sleep patterns, feeling out of control, and physical symptoms. An individual mean score for each of the four core PMDD symptoms (depressed mood, tension, affective lability and irritability) was calculated for days 6 - 10 after menstruation and also for the last 5 days of the menstrual cycle (late luteal phase). Eligibility criteria required an increase of at least 200% on one, or at least 100% on two or more of the core symptoms for the mean late luteal phase score compared to the follicular phase.

Age-matched controls:
4. Completed the VAS during screening and who showed no evidence of PMDD or any other psychiatric disorder

Both groups:
5. All participants had a history of regular menstrual cycles (range: 25-34 +/- 3 days)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Key exclusion criteria
1. Diagnosed with seasonal affective disorder (SAD) or any other Axis I or II disorder
2. Drug use
3. Oral contraceptives
4. History of gynecological pathology
5. History of night-shift work or transmeridian travel within three months prior to study

Date of first enrolment
20/01/2001

Date of final enrolment
31/12/2012

Locations

Countries of recruitment
Canada

Study participating centre
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Sponsor information

Organisation
Douglas Mental Health University Institute (Canada)

ROR
https://ror.org/05dk2r620

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (CIHR) (Canada) - http://www.cihr-irsc.gc.ca (ref: MOP-38064)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration