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Melatonin in patients with sleep disturbance due to chronic pain

Submission date	Recruitment status	[X] Prospectively registered
10/12/2018	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
21/01/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
15/02/2024	Signs and Symptoms	

Plain English summary of protocol

Background and study aims
Chronic pain is a burden to both patients and the NHS. Many patients live with severe pain which is resistant to pain relief medication. Over 40% of patients attending a pain management clinic in Northeast Scotland rated their pain at levels of 7 or more out of 10, indicating severe pain. Higher pain scores are linked to more disturbed sleep and poorer sleep quality. Melatonin is produced in the body mainly by the pineal gland, which sits just below the brain, and controls sleeping patterns. Melatonin can also be manufactured chemically in the laboratory and given as a medication and is very safe. In people with sleeping problems melatonin has been shown to be effective at improving sleep. Melatonin has been shown to be safely given to patients with various other conditions for months at a time with no ill effects. It has been shown that as well as regulating sleep, melatonin may also act like a pain-killer (analgesic) in some pain conditions. The aim of this study is to find out whether giving melatonin to patients with severe chronic pain improves both their sleep and their pain.

Who can participate?
Patients aged 18 years or over attending the pain management clinic at Aberdeen Health Village who have a pain score of 7 or more

What does the study involve?
Participants are randomly allocated to take either melatonin tablets or a placebo (dummy drug) just before bedtime, every night for 6 weeks, followed by 4 weeks taking nothing, then 6 weeks taking melatonin if they got placebo first, or vice versa. The study assesses whether melatonin improves their sleep and has any effect on pain scores. Blood levels of melatonin and endorphins are measured at intervals and a computer-based task is ised to assess if melatonin is causing sleepiness during the day. Participants also wear an activity watch and input real-time pain and fatigue scores into it. At the end of the study participants are asked to complete a short survey to gather feedback about the trial, to contribute to improvements in future trial design and conduct as seen from participants' viewpoints.

What are the possible benefits and risks of participating?
Participants will receive melatonin for 6 weeks and this may improve sleep and may also help with pain. Melatonin is a naturally occurring substance but can be made chemically. The

melatonin we are using is called Circadin, manufactured by Flynn Pharma and is licensed for treating insomnia. Drowsiness is expected after taking melatonin. In clinical trials a total of almost 2,000 people took Circadin and the percentage of people who reported side effects other than drowsiness was similar in those receiving Circadin to those who took a placebo. There were no 'very common' (affecting up to 1 in 10 people) or 'common' (affecting less than 1 in 100 people) other side effects associated with Circadin use. 'Uncommon' (affecting between 1 in 100 and 1 in 1000 people) side effects included insomnia, bad dreams and headaches. People have taken 2 mg of Circadin daily for 12 months without increases in side effects and in a recent trial no subjects receiving 6 mg of Circadin daily reported side effects. Administration of very large daily doses of melatonin with no side effects have been reported. However, if an overdose does occur, drowsiness is to be expected but this should resolve quickly as the melatonin would normally be cleared from the body within 12 hours of taking it. No special treatment is required. Circadin tablets contain lactose so anyone who is allergic to lactose should not take it. Having blood samples taken may cause discomfort and some bruising but this is likely to be very transient. Completing questionnaires may be inconvenient.

Where is the study run from?
NHS Grampian (UK)

When is the study starting and how long is it expected to run for?
November 2018 to June 2022

Who is funding the study?
It is funded by the charitable arm of the British Journal of Anaesthesia (UK)

Who is the main contact?
Prof. Helen Galley
h.f.galley@abdn.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Helen Galley

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Additional identifiers

EudraCT/CTIS number
2018-004048-50

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
3-062-18

Study information

Scientific Title
Double blind randomised controlled trial of exogenous administration of melatonin in chronic pain

Acronym
DREAM - CP

Study objectives
Chronic pain affects ~20% of adults. Pain and sleep are inextricably linked: individuals with persistent pain experience poor sleep quality which worsens as pain intensity increases. Improvements in sleep can also improve pain. Endogenous pineal melatonin is regulated by light and regulates sleep. Exogenous melatonin also has analgesic and anxiolytic effects, however the effect of melatonin on sleep/chronic pain is unclear. Melatonin may provide an inexpensive and safe therapy for chronic pain related sleep problems and pain.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/02/2019, NHS Health and Social Care Research Ethics Committee A (Office for Research Ethics Committees Northern Ireland, Customer Care & Performance Directorate, Lissue Industrial Estate West, 5 Rathdown Walk, Moira Road, Lisburn, BT28 2RF; +44 (0)28 95361407; RECA@hscni.net), ref: 19/NI/0007

Study design
Randomized placebo-controlled double-blinded cross-over trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in a web format. Please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Severe chronic pain

Interventions
Patients will be randomised to receive either 2mg melatonin (as Circadin) tablets nightly for 6 weeks, followed by a 4 week wash out period then 2mg of an identical placebo for 6 weeks, or vice versa (i.e placebo then melatonin). Randomisation will be undertaken using a previously prepared randomised code list held in the pharmacy.

The trialists will assess whether melatonin improves their sleep and has any effect on pain scores. They will also measure blood levels of melatonin at intervals and use a computer-based task to assess if melatonin is causing sleepiness during the day. Participants will also wear an activity watch and will input real-time pain and fatigue scores into it. At the end of the trial participants complete a short survey to provide feedback about the trial.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Circadin (slow release melatonin)

Primary outcome measure
Sleep disturbance measured using actigraphy after 6 weeks melatonin/placebo treatment

Secondary outcome measures
All outcomes will be measured at 3-week intervals, final endpoint is end of each 6-week treatment arm:
1. Subjective sleep quality measured using three different sleep scales (Verran Snyder-Halpern; Pittsburgh Sleep Quality Index; Pain and Sleep 3-item index)
2. Psychomotor vigilance measured using a PC-based reaction time test
3. Pain intensity measured using the Brief Pain Inventory
4. Melatonin levels measured using enzyme immunoassay
5. Participants views on taking part assessed using a short survey at the end of the trial

Overall study start date
01/11/2018

Completion date
30/06/2022

Eligibility

Key inclusion criteria

1. Non-malignant pain of more than 3 months duration
2. Average pain score of 7 or more on the British Pain Inventory scale
3. Aged 18 years or over
4. Male or female
5. Stable, with no expected change in medication during the trial
6. Normal liver function.
7. Not taking excluded drugs (see exclusion criteria)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60

Total final enrolment
66

Key exclusion criteria
1. Malignant pain
2. Pain score below 7
3. Aged under 18 years
4. Measures of liver function above normal range
5. Concomitant treatment with nifedipine or fluvoxamine, benzodiazepines or non-benzodiazepine hypnotics (zaleplon, zolpidem and zopiclone)
6. History of drug/alcohol abuse, post-traumatic stress disorder or use of psychotropic medications
7. Insufficient English to understand trial information
8. History of lactose allergy
9. Pregnant, breastfeeding or planning to get pregnant

Date of first enrolment
01/06/2019

Date of final enrolment
14/03/2022

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
NHS Grampian
Aberdeen Royal Infirmary
Aberdeen
United Kingdom
AB25 2ZB

Sponsor information

Organisation
University of Aberdeen and NHS Grampian

Sponsor details
Research Governance
University of Aberdeen
Aberdeen
Scotland
United Kingdom
AB25 2ZB

Sponsor type
University/education

ROR
https://ror.org/00ma0mg56

Funder(s)

Funder type
University/education

Funder Name
British Journal of Anaesthesia and the Royal College of Anaesthetists

Results and Publications

Publication and dissemination plan

The study will be written up as a research article and will be submitted to a reputable peer reviewed journal for publication as soon as feasible after study end. The trialists will also display a lay summary in the chronic pain clinic.

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Professor Helen Galley (h.f.galley@abdn.ac.uk). The data will be available after data analysis is complete (March 2021). Further ethical approvals may be required. All data will be anonymised.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	16/03/2020	11/03/2020	Yes	No
HRA research summary			28/06/2023	No	No
Basic results	version 3	11/09/2023	11/09/2023	No	No
Results article		14/02/2024	15/02/2024	Yes	No