ISRCTN16215617 https://doi.org/10.1186/ISRCTN16215617

Clinical trial of melatonin for the treatment of neuropathic pain

Submission date
26/04/2022

Recruitment status
No longer recruiting

Registration date
04/05/2022

Overall study status
Completed

Last Edited
29/09/2022

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Sleep is commonly disturbed in patients with neuropathic pain; treatments that improve sleep may have an overall beneficial effect in patients with chronic pain. Given the need to identify effective, and safer, non-opioid pain treatments for chronic pain, the aim of this trial is to evaluate the effectiveness and safety of melatonin for the treatment of chronic neuropathic pain.

Who can participate?
Adults with chronic peripheral neuropathic pain

What does the study involve?
In this 10-week study, participants will receive two different sets of study treatments, each one consisting of a 4-week treatment period and a 1-week washout period (i.e. period when no pain medication is taken). During each treatment period participants will take one set of capsules. The number of capsules taken will be increased gradually over the first 3 weeks of each 5-week period. As the number of capsules increases some degree of pain relief may be experienced, as well as side effects such as drowsiness, and possibly other side effects. The goal will be to achieve the highest possible dose, yet a dose which does not cause intolerable side effects. Once that dose is reached, participants will continue to receive that dose for the entire fourth week of that treatment period. On the fifth week of each treatment period, the study medication will be stopped and participants will then continue to the next treatment period which will progress in a similar fashion.
In each of these treatment periods, the capsules will contain either filler (placebo) or melatonin. The two different treatment periods will come in random order. For example, participants may receive melatonin during the first treatment period and placebo during the second period, or, vice versa. Participants will not be told the contents of any of the contents during the study unless there is a medical emergency.

What are the possible benefits and risks of participating?
Given the known effects of melatonin in other pain conditions, there is some possibility that participants might enjoy meaningful sleep improvement and/or pain relief during parts of the study. It is also possible that participants gain no benefit from participating in the study.

However, new knowledge gained from this study may improve the quality of pain management for other patients.
Growing evidence suggests that oral administration of melatonin is generally safe. A review including 37 melatonin studies reported side effects of daytime sleepiness (1.7%), headache (0.7%), other sleep-related side effects (0.7%), dizziness (0.7%) and hypothermia (0.6%) with very few reported serious adverse effects. However, if at any point during the study participants begin to feel any side effects that may be associated with taking this study treatment, they are urged to contact the study nurse and/or study physician immediately so that the dose can be adjusted appropriately.

Where is the study run from?
Queen's University and Providence Care Hospital, Kingston, Ontario (Canada)

When is the study starting and how long is it expected to run for?
December 2020 to October 2025

Who is funding the study?
Physicians' Services Incorporated Foundation (Canada)

Who is the main contact?
Dr Ian Gilron
gilroni@queensu.ca

Contact information

Type(s)
Principal investigator

Contact name
Dr Ian Gilron

ORCID ID
https://orcid.org/0000-0002-5293-8792

Contact details
Dept Anesthesiology, Victory 2, KGH
76 Stuart Street
Kingston
Canada
K7L2V7
+1 (0)613 548 7827
gilroni@queensu.ca

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Melatonin for neuropathic pain

Acronym
MNP

Study objectives
Oral administration of melatonin improves neuropathic pain and pain-related sleep disturbance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Queen's University Research Ethics Board (Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, 74 University Avenue, 251 Richardson Hall, Kingston, ON K7L 3N6, Canada, +1 (0)613-533-6000 ext. 78223; jennifer.couture@queensu.ca), ref: 6036266

Study design
Double-blind placebo-controlled two-period crossover trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic peripheral neuropathic pain

Interventions
Oral melatonin (3 mg capsules, or matching placebo) titrated over 21 days towards the maximal tolerated dose to a maximal dosage ceiling of 12 mg/day.

Study participants will be randomized, in a double-blind fashion, to one of two possible treatment sequences (e.g. sequence 1: melatonin>placebo; sequence 2: placebo>melatonin;) such that each participant progresses through each of two 5-week treatment periods.

Treatment periods will conclude with a 7-day complete washout. During each period, participants will receive study medication capsules - “melatonin” capsules which may contain melatonin 3 mg or an inert placebo. During the melatonin period, study medication will contain melatonin (3 mg capsules) and during the placebo, study medication will contain inert placebo. Melatonin, and melatonin placebo, study drug administration will occur only in the evenings.

Intervention Type
Supplement

Primary outcome(s)

Mean daily pain measured using a 0-10 numerical rating scale with 0 = “no pain”, 10 = “worst pain imaginable”, averaged over the “MTD fixed-dose week” (days 22-28) of each period

Key secondary outcome(s))

1. Maximal tolerated doses of melatonin measured using research nurse report based on participant self-report at 1st and 3rd weeks of treatment, 4th week of treatment, washout 3 months post-trial completion
2. Frequency/severity of AEs measured using research nurse report based on participant self-report at screening, baseline, 1st and 3rd weeks of treatment, 4th week of treatment, washout 3 months post-trial completion
3. Global improvement, measured using the Patient Global Impression of Change (PGIC, a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention) at 1st and 3rd weeks of treatment, 4th week of treatment, washout 3 months post-trial completion
4. Pain dimensions, measured using the Short-form McGill Pain Questionnaire, an instrument to efficiently capture both the sensory and affective dimensions of pain, at pre-trial baseline and 4th week of treatment
5. Neuropathic pain symptoms, measured using the Neuropathic Pain Symptom Inventory, a 12-item self-questionnaire specifically designed to evaluate the different symptoms of neuropathic pain, at baseline and 4th week of treatment
6. Pain interference, measured using the Brief Pain Inventory, a survey instrument that measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, at baseline and 4th week of treatment
7. Mood, measured using the Beck Depression Inventory-II at screening, baseline and 4th week of treatment
8. Anxiety, measured using the Beck Anxiety Inventory at pre-trial baseline and 4th week of treatment
9. Quality of life, measured using the SF-36 survey at baseline and 4th week of treatment
10. Quality of blinding, measured using the Blinding questionnaires at 4th week of treatment
11. Acetaminophen consumption measured using participant self-report at 1st and 3rd weeks of treatment, 4th week of treatment, washout 3 months post-trial completion

Completion date

31/10/2025

Eligibility

Key inclusion criteria

1. Score of 4 or higher on the DN4 interview, a validated questionnaire that distinguishes between neuropathic and non-neuropathic pain.14 As indicated, investigations will be done to confirm NP diagnosis including, but not limited to, nerve conduction studies and electromyography.
2. Daily pain (≥4/10) for at least 3 months
3. AST/ALT ≤120% upper limit of normal
4. Creatinine clearance ≥60 ml/min
5. Glycosylated hemoglobin ≤9.5%
6. Necessary abilities, visual acuity, and language skills for questionnaire completion and phone communication with nurses

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Major organ system disease
2. Cardiovascular autonomic neuropathy
3. Trigeminal neuralgia, complex regional pain syndrome or central neuropathic pain
4. Moderate to severe sedation or ataxia due to other required concomitant drugs
5. Allergy/hypersensitivity to study medications or any components in the study drug formulations or their containers
6. Seizure disorder
7. Other painful condition >50% as severe as their NP
8. A major, poorly controlled, psychiatric disorder, depression or suicidal ideation, or active substance use disorder
9. History of angioedema
10. Candidates who live alone and cannot assure daily contact with a friend, family member, or caregiver
11. Women of childbearing potential who will not receive a highly effective form of contraception (total abstinence, hormonal birth control methods, intrauterine devices, confirmed successful vasectomy of partner, double-barrier methods such as condom/diaphragm, etc.) and/or a positive pregnancy test at baseline (If a study participant becomes pregnant, she must stop using study medications immediately and will be withdrawn from the study)
12. Women who are breastfeeding or who plan to breastfeed
13. Regular daily administration of opioids at a dose greater than 90 mg morphine equivalents
14. Lack of a primary care physician

Date of first enrolment
01/09/2022

Date of final enrolment
31/08/2025

Locations

Countries of recruitment
Canada

Study participating centre
Kingston Health Sciences Centre and Providence Care Hospital
Victory 2 Pavillion, KGH
76 Stuart Street

Kingston
Canada
K7L2V7

Sponsor information

Organisation
Physicians' Services Incorporated Foundation

ROR
https://ror.org/0385yzn06

Funder(s)

Funder type
Charity

Funder Name
Physicians' Services Incorporated Foundation

Alternative Name(s)
PSI Foundation, PSI

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Canada

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available as the research unit does not yet have the policies and procedures in place for public sharing of individual participant data. The data will be held in Kingston General Hospital (Canada).

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		28/09/2022	29/09/2022	Yes	No