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The PRECISE trial – Pain REief Combination Intervention StratEgies

Submission date
11/03/2024

Recruitment status
Recruiting

Registration date
02/04/2024

Overall study status
Ongoing

Last Edited
25/06/2024

Condition category
Musculoskeletal 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
Chronic pain affects 20-30% of Canadians, costs >$650 billion/year in North America and is recognized as a disease in its own right. Current therapies have limited efficacy and tolerability. Rational, carefully supervised, combination therapy with different treatments may provide improvements in pain relief and quality of life and potentially fewer anti-inflammatory drug-related and opioid-related mortalities. Over half of pain sufferers receive 2 or more analgesic drugs, but evidence for combination therapy is limited and more research is needed. Previous Canadian Institutes of Health Research (CIHR)-funded studies have shown improved patient outcomes with combination therapy and provided a framework for evaluating novel combination strategies to target pain and sleep impairment. This study aims to compare a pregabalin (PGB) + melatonin (MLT) combination therapy versus the monotherapies for chronic pain (fibromyalgia). The anticonvulsant, PGB, has been shown to reduce pain and improve sleep maintenance in multiple studies. The pineal gland hormone, MLT, regulates the body's daily (circadian) clock and has shown evidence of pain reduction in both laboratory and clinical settings. Multiple clinical trials have demonstrated efficacy for primary insomnia and delayed sleep phase syndrome. This study hypothesizes that a PGB+MLT combination therapy has superior effects versus monotherapy for chronic pain, because of: 1) favourable interactions between these agents; 2) evidence of superior efficacy of other PGB-containing, and MLT-containing combinations; and 3) compounded benefits of concurrently reducing both pain and sleep disturbance. The study will evaluate pain, sleep, function, mood, and adverse effects in patients taking these agents. Expected results will guide improvements in therapy by advancing knowledge about rational combination therapy for chronic pain.

Who can participate?
Patients ≥18 years old with fibromyalgia and daily moderate pain

What does the study involve?
Participants progress through three different 6-week treatment periods during which they take the following medications on an outpatient basis: melatonin alone, pregabalin alone, and a combination of melatonin and pregabalin. These three treatments will be given in a random order and the doses of each treatment will be gradually increased to a maximally tolerated level. Participants will rate their pain, side effects and other outcome measures throughout the study.

What are the possible benefits and risks of participating?
Given the known effects of pregabalin in patients with fibromyalgia, there is a possibility that participants will enjoy meaningful pain relief whenever they are receiving pregabalin during this study. There is, however, less evidence regarding the use of melatonin for fibromyalgia, which is one of the reasons for doing this study. Participants may gain no benefit from participating in the study. However, new knowledge gained from this study may help improve the quality of pain management for other patients.

Pregabalin side effects and participant safety:
Relatively common (>10%) adverse effects associated with pregabalin include dizziness, somnolence, weight gain, peripheral edema and visual symptoms such as double vision. These side effects are reversible upon stopping medication and most of these side effects gradually improve after continuing a given dose of pregabalin for several days. Although relatively uncommon, pregabalin abuse/addiction has been reported – particularly in individuals with other substance abuse issues such as opioid addiction.

Melatonin side effects and participant safety:
Current evidence suggests that oral administration of melatonin is generally safe. A recent review of 37 different studies of melatonin reported side effects of daytime sleepiness (in only 1.7% of participants), headache (in only 0.7%) and dizziness (0.7%).

Some side effects may occur more frequently during combination treatment as compared to either drug alone.

Where is the study run from?
Kingston General Hospital

When is the study starting and how long is it expected to run for?
January 2024 to August 2028

Who is funding the study?
Canadian Institutes of Health Research (CIHR)

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

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
Clinical trial of a melatonin-pregabalin combination for fibromyalgia

Acronym
PRECISE

Study objectives
The combination of melatonin and pregabalin has superior analgesic efficacy versus either single agent for fibromyalgia.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 22/05/2024, Queen's University Health Services & Affiliated Teaching Hospitals Research Ethics Board (HSREB) (355 King Street West, 2nd floor, Kingston, K7L2X3, Canada; +1-613-533-2000; HSREB@queensu.ca), ref: 6040998

Study design
Single-centre double-blind randomized double-dummy 3-period crossover design

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Home, Hospital

Study type(s)
Treatment, Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Fibromyalgia

Interventions
This study has a single-centre, double-blind, randomized, double-dummy, 3-period, crossover design (18 weeks/participant) to compare a melatonin-pregabalin combination to each monotherapy in participants with fibromyalgia. Participants will be randomly allocated to melatonin, pregabalin, and a melatonin-pregabalin combination.

Study participants will be randomized, in a double-blind fashion, to one of six possible sequences (e.g. sequence 1: combination>melatonin>pregabalin) such that each participant progresses through each of three 6-week treatment periods. Treatment periods will conclude with a 7-day dose taper and a 4-day complete washout. During each period, participants will receive two sets of capsules: 1) “melatonin” capsules - which may contain melatonin 3 mg or inert matching placebo and 2) “pregabalin” capsules - which may contain pregabalin 75 mg or inert matching placebo. During the “melatonin-pregabalin combination” period, set 1 will contain melatonin (3 mg capsules) and set 2 will contain pregabalin (75 mg capsules). During the “melatonin alone” period, set 1 will contain melatonin (3 mg capsules) and set 2 will contain an inert matching placebo. During the “pregabalin alone” period, set 1 will contain an inert placebo and set 2 will contain pregabalin (75 mg capsules). Melatonin (and melatonin placebo) study drug administration will occur only in the evenings, whereas pregabalin (and pregabalin placebo) study drug administration will occur according to twice daily dosing (morning and evening).

Outcome measures will be assessed as follows:
The primary outcome will be the mean of daily “average” pain intensity ratings from the last 7 days at MTD, of each treatment period. Pain intensity is self-rated each morning as “average pain over the last 24 hours” using a 0-10 Likert numerical rating scale with the anchors: 0 = “no pain”; 10 = “worst pain imaginable”. Following informed consent, participants receive study teaching on how to consistently rate their pain intensity, twice daily, as per the daily pain diary. The process of regular monitoring and encouragement of complete daily diary completion during weekly follow-up calls to participants has ensured excellent compliance and data completeness in our 7 previous and recent trials.

Secondary outcomes include change from treatment period baseline to MTD week, Fibromyalgia Impact Questionnaire, MOS-Sleep Scale, global pain relief, Brief Pain Inventory, Beck Depression Inventory-II, Beck Anxiety Inventory, the short-form McGill Pain Questionnaire, the SF-36 Quality of Life Survey, MTDs of melatonin and pregabalin, frequency/severity of other treatment-emergent AEs, blinding questionnaires, acetaminophen consumption, and study drug pill counts. Participant safety will be monitored through vigilant and judicious drug titration. Any occurrences of major adverse events will be tracked as secondary outcomes and also reported to the Queen’s University Research Ethics Board, and Health Canada.

Intervention Type
Drug

Pharmaceutical study type(s)
Comparative efficacy trial

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Melatonin, pregabalin, melatonin-pregabalin combination

Primary outcome measure
Mean of “average” pain intensity self-ratings at the maximally tolerated dose of each treatment period measured using a Likert numerical rating scale twice daily over the last 7 days

Secondary outcome measures
1. Review of adverse events and concurrent analgesic treatments measured by monitoring of study records throughout screening (pre-trial), baseline (pre-trial), during each treatment period (titration period, maximal tolerated dose and taper/washout), and 2 weeks and 3 months after the end of the trial
2. Pain intensity measured using pain diaries at baseline (pre-trial), during each treatment period (titration period, maximal tolerated dose and taper/washout), and 2 weeks after the end of the trial
3. Study medication dose levels and patient global impression of change during each treatment period (titration period, maximal tolerated dose and taper/washout)
4. Drug dispensing; Medical Outcomes Study (MOS); Brief Pain Inventory (BPI); Beck Anxiety Inventory (BAI); the MOS 36--item short-form health survey (SF-36) and the Fibromyalgia Impact Questionnaire (FIQ) at baseline (pre-trial) and the maximal tolerated dose during each treatment period
5. Vital signs, height, weight and Beck Depression Inventory - 2 (BDI-2) at screening (pre-trial) and the maximal tolerated dose during each treatment period
6. Pain (average and worst) measured using the Present Pain Intensity (PPI) (0-10 numerical scale), demographics, medical history and clinical laboratory assessments at screening (pre-trial)
7. Blinding questionnaire, drug compliance at the maximal tolerated dose during each treatment period

Overall study start date
31/01/2024

Completion date
31/08/2028

Eligibility

Key inclusion criteria
1. Participants ≥18 years old and over meeting the 2016 American College of Rheumatology diagnostic criteria for fibromyalgia
2. Daily moderate pain (≥ 3/10) for at least 3 months
3. Liver function test, ALT, no greater than 20% above normal
4. Creatinine clearance >50 mL/min
5. Sufficient cognitive function and language comprehension skills – regardless of native language – for questionnaire completion and communication with trial personnel (and

translator, if necessary)
6. Women of childbearing potential will be required to receive a highly effective form of contraception

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
54

Key exclusion criteria
1. Participants with any major organ system disease, psychiatric, suicidal ideation or substance abuse disorder, which, in the opinion of the investigators, would interfere with trial participation
2. Hypersensitivity to any of the study medications
3. Other painful conditions as severe as fibromyalgia pain
4. Shift workers who work during typical sleeping hours
5. Any other abnormalities or conditions that, in the judgement of the investigators would interfere with the protocol

Date of first enrolment
01/12/2024

Date of final enrolment
30/11/2027

Locations

Countries of recruitment
Canada

Study participating centre
Research Clinic, Providence Care Hospital (Queen's University)
752 King St W
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Canada
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Sponsor information

Organisation
Canadian Institutes of Health Research

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Sponsor type
Government

Website
https://cihr-irsc.gc.ca/e/193.html

ROR
https://ror.org/01gavpb45

Funder(s)

Funder type
Government

Funder Name
Canadian Institutes of Health Research

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal and presentation at several scientific conferences

Intention to publish date
01/09/2028

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 the public sharing of individual participant data. The data will be held in a non-publically available repository at Kingston Health Sciences Centre (Canada).

IPD sharing plan summary
Stored in non-publicly available repository, Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		25/06/2024	25/06/2024	Yes	No