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Use of topical phenytoin and loperamide for the treatment of neuropathic pain

Submission date 03/03/2024	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 12/03/2024	**Overall study status** Ongoing	
Last Edited 13/05/2025	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Neuropathic pain, resulting from damage to nerves or related structures, often persists for extended periods, significantly impacting a patient's quality of life. Current treatments for neuropathic pain often yield limited success due to its complex mechanism of origin. The body perceives pain signals from damaged nerves as electric impulses traveling to the brain, where neuropathic pain arises without an apparent external stimulus. Currently, there are three known therapeutic agents for topical application directly to the painful site, targeting nerves in the skin responsible for causing neuropathic pain. This route offers the advantage of lower systemic drug absorption, reducing potential side effects. In this study, a cream containing two drugs, phenytoin (commonly used for epilepsy) and loperamide (used for chronic diarrhea), will be applied to observe changes in pain characteristics. Phenytoin reduces nerve cell activity, particularly when it is abnormally increased, as seen in neuropathic pain. Loperamide, on the other hand, inhibits pain signal activity in nerves, particularly those causing chronic pain. Both drugs, with similar mechanisms of action, are expected to work synergistically to alleviate pain. This study aims to provide valuable insights into the effectiveness and safety of a cream containing phenytoin and loperamide in managing neuropathic pain among adults meeting specific inclusion criteria.

Who can participate?
Adult patients aged 18 years old and over with peripheral neuropathic pain and receiving treatment at the Pain Management Clinic of the Department of Anesthesiology, Intensive Therapy, and Pain Management at the University Medical Centre Maribor

What does the study involve?
Under the guidance of Chief Investigator Matija Primec, MD, and with mentoring support from Assistant Professor Marko Zdravković, MD, PhD, this trial focuses on patients meeting specific inclusion criteria. To identify adults with neuropathic pain, a special questionnaire will be used with individuals scoring at least 4 points out of 10 being invited to participate in the study.

Patients will be given either a placebo or the investigated cream. Pain assessment will be conducted using a questionnaire before and 45 minutes after cream application. Assuming no unexpected local side effects occur, the cream will be given to patients for home use for 14

days. They will apply 1.2 g of cream twice a day on the painful site. Follow-up assessments via phone call after two weeks will involve questionnaire completion. Previous studies on these cream formulations for neuropathic pain have demonstrated safety and potential efficacy.

Pain intensity will also be evaluated using a numerical scale ranging from 0 (no pain) to 10 (worst possible pain), with scores of 1 to 3 representing mild pain, 4 to 7 indicating moderate pain, and 8 to 10 signifying severe pain.

What are the possible benefits and risks of participating?
The possible benefits of participating in the study include the potential for improved and more efficient treatment of peripheral neuropathic pain. Additionally, participants will receive comprehensive treatment regardless of their participation, but involvement in the study offers the added dimension of addressing neuropathic pain topically alongside systemic treatment. The only expected potential side effects are local irritation due to almost no systemic absorption of the cream.

Where is the study run from?
The University Medical Centre Maribor

When is the study starting and how long is it expected to run for?
October 2022 to May 2026

Who is funding the study?
The University Medical Centre Maribor

Who is the main contact?
Dr Matija Primec, matija.primec@gmail.com

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1009529

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 1009529

Study information

Scientific Title
Impact of 20% phenytoin and 5% loperamide cream on neuropathic pain: a prospective double-blind randomized controlled study

Study objectives
Primary Hypothesis:

Null Hypothesis (H0): There is no significant difference in pain levels before and 45 minutes, 48 hours and 14 days after the application of the cream, as assessed by the Numerical Rating Scale (NRS), between patients who received the testing cream and those who received the placebo.
Alternative Hypothesis (H1): There is a significant difference in pain levels before and 45 minutes, 48 hours and 14 days after the application of the cream, as assessed by the Numerical Rating Scale (NRS), in favor of patients who received the testing cream compared to those who received the placebo.

Secondary Hypothesis:

Null Hypothesis (H0): There is no significant improvement in neuropathic pain, as assessed by the NPSI (including global assessment and ratings on five sub-scales) and as assessed by EQ5D, after 14 days of home use of the cream.

Alternative Hypothesis (H1): There is a significant improvement in neuropathic pain, as assessed by the NPSI questionnaires (including global assessment and ratings on five sub-scales) and as assessed by EQ5D, after 14 days of home use of the cream.

Null Hypothesis (H0): There is no consistency between NPSI and EQ5 questionnaires: before the first application of the cream and 14 days after the first application.

Alternative Hypothesis (H1): There is consistency between NPSI and EQ5D questionnaires: before the first application of the cream and 14 days after the first application.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 19/09/2023, The National Medical Ethics Committee of the Republic of Slovenia (Štefanova ulica 5, Ljubljana, 1000, Slovenia; +386 1 478 60 01; gp.mz@gov.si), ref: 0120-1/2023-9

Study design
Interventional double-blind randomized controlled single-centre study

Primary study design
Interventional

Study type(s)
Treatment, Efficacy

Health condition(s) or problem(s) studied
Treatment of peripheral neuropathic pain

Interventions
The study design is interventional, employing a double-blind randomized controlled design. Patients will receive either a test cream or a placebo, randomized in the hospital's apothecary, and various aspects of neuropathic pain will be assessed at different time intervals. The study will take place at the University Hospital of Maribor, making it a single-centred study. The study was designed in accordance with the CONSORT statement.

Patients who scored at least 4 points on the DN-4 questionnaire and had pain severity of at least 4 on the numeric rating scale (NRS) at the appointment or in the last 24 hours will be enrolled on the study after receiving information about the study and providing written consent. Participants in the study will be randomly allocated to one of two groups based on a computer-generated list of random numbers by a non-investigator who also concealed the group allocation by putting the group assignments (in a 1:1 ratio) in sequentially numbered opaque envelopes. Each envelope will be later opened by the pharmacist after the patient’s consented enrolment and after placing the patient's name sticker on the envelope. After enrolment, each patient will complete two validated questionnaires: the Neuropathic Pain Symptom Inventory (NPSI) and EQ-5D Health Status Questionnaire. Then, the investigators will apply 1.2 g of either the test cream, consisting of Pentravan base cream, 25% propylene glycol, 20% phenytoin, and 5% loperamide, or a placebo cream consisting of Pentravan base cream, tablettose (sucrose for identical cream texture) and 25% propylene glycol.

Forty-five minutes after the application of the cream, patients will rate the pain severity with the NRS. If there are no side effects, patients will be provided with the same cream for home use, applying 1.2 g of cream twice a day to the painful site. Participants will be contacted after 48 hours and after 14 days of home use via telephone to ask them about their pain levels and possible side effects. In that time they will apply 1.2 g of cream twice a day to the painful site and record their average daily pain level using the NRS and pain relief using the categorized pain-relief scale in a diary. Patients who used the cream regularly will complete the EQ5D and NPSI questionnaires after 14 days of cream use.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Phenytoin, loperamide

Primary outcome(s)
Pain measured using a Numeric Rating Scale (NRS) at baseline before the first application of the cream, 45 min after the first application of the cream, 48h after the first application and 14 days after the first application

Key secondary outcome(s))
1. Health-Related Quality of Life measured using the EQ5D questionnaire total score at baseline, 14 days after treatment
2. Neuropathic Pain measured using the Neuropathic Pain Symptom Inventory (NPSI) questionnaire at baseline, 14 days after treatment
3. Placebo Effect measured using the Numeric Rating Scale (NRS) at baseline, 45 minutes after the first application, 48 hours after the first application, 14 days after the first application
4. Subgroup Analysis (for patients with post-herpetic neuralgia) measured using the Numeric Rating Scale (NRS) for pain, EQ5D questionnaire total score for health-related quality of life, Neuropathic Pain Symptom Inventory (NPSI), Categorized pain relief scale at baseline, 45 minutes after the first application, 48 hours after the first application, 14 days after the first application, Daily measurements
5. Average Pain Level measured using the Numeric Rating Scale (NRS) daily
6. Average Pain Relief measured using the Categorized pain relief scale daily

Completion date
14/05/2026

Eligibility

Key inclusion criteria
1. Patients experiencing peripheral neuropathic pain and currently under treatment at the Pain Management Clinic of the Department of Anesthesiology, Intensive Therapy, and Pain Management at the University Medical Centre Maribor
2. Adults identified with neuropathic pain using the DN-4 questionnaire, scoring at least 4 points out of 10

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Allergy to phenytoin or loperamide
2. Presence of central neuropathy (multiple sclerosis, spinal cord injury, neuropathy following a stroke)
3. Pregnancy or the possibility of pregnancy
4. Treatment of neuropathic pain with any topical preparation in the last 30 days

Date of first enrolment
13/03/2024

Date of final enrolment
30/04/2026

Locations

Countries of recruitment
Slovenia

Study participating centre
University Medical Centre Maribor
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Sponsor information

Organisation
University Clinical Centre Maribor

ROR
https://ror.org/02rjj7s91

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Univerzitetni Klinični Center Maribor

Alternative Name(s)
Университетский клинический центр Марибор, University Medical Centre Maribor, Universitätsklinikum Maribor, , UKC Maribor

Funding Body Type
Government organisation

Funding Body Subtype
Other non-profit organizations

Location
Slovenia

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be available upon request from Matija Primec at matija.primec@gmail.com. Individual participant data underlying the study results will be shared upon deidentification, including text, tables, figures, and appendices. The shared documents will encompass the Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, and Analytic Code. Access will be granted through a data access agreement, and data will remain available for five years post-publication. All study participants will provide written consent for participation, ensuring compliance with ethical standards.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file			09/05/2025	No	No