Study Protocol

Title:
Use of Topical Phenytoin and Loperamide for the Treatment of Neuropathic Pain: A Randomised, Double-Blind, Placebo-Controlled Trial

ISRCTN Registration Number:
ISRCTN18843536

Principal Investigator:
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Study Sponsor:
University Medical Centre Maribor

Ethics Approval:
Approved by Commission of the Republic of Slovenia for Medical Ethics, Reference Number: 0120-1/2023-9

Background and Rationale:
Neuropathic pain is a chronic condition resulting from nerve damage, leading to significant morbidity. Current treatments often have limited efficacy and undesirable side effects. Preliminary studies suggest that topical formulations containing phenytoin and loperamide may offer analgesic benefits with minimal systemic absorption, potentially reducing side effects. This study aims to evaluate the efficacy and safety of a topical cream containing phenytoin and loperamide in patients with neuropathic pain.

Objectives:

- *Primary Objective:*
  To assess the efficacy of the topical phenytoin and loperamide cream in reducing neuropathic pain intensity compared to placebo.
- *Secondary Objectives:*
  - To evaluate the safety and tolerability of the topical formulation.
  - To assess the impact on quality of life and functional outcomes.

Study Design:
A randomised, double-blind, placebo-controlled trial.

Participants:

- *Inclusion Criteria:*
  - Adults aged 18 years and older.
  - Diagnosed with peripheral neuropathic pain of at least 3 months' duration.
  - Pain intensity score of ≥4 on the Numeric Rating Scale (NRS).
  - Ability to provide informed consent.
- *Exclusion Criteria:*
  - Known hypersensitivity to phenytoin, loperamide, or any component of the cream.

    - Use of other topical analgesics on the affected area within 7 days prior to study entry.
    - Participation in another clinical trial within the last 30 days.
    - Pregnant or breastfeeding women.

Intervention:
Participants will be randomised to receive either:

- *Active Treatment:* Topical cream containing phenytoin and loperamide, applied twice daily to the affected area.
- *Placebo:* Identical cream base without active ingredients, applied with the same frequency.

Outcome Measures:

- *Primary Outcome:*
    - Change in pain intensity from baseline to Week 4, measured by the NRS.
- *Secondary Outcomes:*
    - Incidence of adverse events throughout the study period.
    - Changes in quality of life assessed by the EQ 5D.
    - Change in pain intensity assesed by the Neurophatic Pain Symptom Inventory.

Target number of participants: 50

Randomisation and Blinding:
Participants will be randomised in a 1:1 ratio using a computer-generated sequence. Both participants and investigators will be blinded to treatment allocation.

Data Collection and Management:
Data will be collected at baseline, Week 2, and daily pain levels. All data will be entered into a secure electronic database with access restricted to authorised personnel. Data quality checks will be performed regularly.

Statistical Analysis:
An intention-to-treat analysis will be conducted. Continuous variables will be analysed using t-tests or ANOVA, and categorical variables using chi-square tests. A p-value of <0.05 will be considered statistically significant.

Safety Monitoring:
Any serious adverse events will be reported to the ethics committee and relevant regulatory authorities.

Timeline:

- Recruitment Start Date: 13 March 2024
- Estimated Study Completion Date: April 2026

Dissemination Plan:
Results will be submitted for publication in peer-reviewed journals and presented at relevant scientific conferences