Assessing the Risk of Falls and Fractures in Older Adults with Diabetic Polyneuropathy Initiated on Gabapentinoids, SNRIs, or TCAs: An Observational Study (SAFER-PDPN)

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000419

Study ID

1000000419

DARWIN EU® study

No

Study countries

Denmark

Switzerland

Study description

Painful diabetic polyneuropathy (PDPN) affects up to a quarter of patients with diabetes and requires effective pain management. However, first-line treatments, including gabapentinoids, serotonin-noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), all carry risks, particularly in older adults. Importantly, all three drug classes increase the risk of falls, which is worrying because falls are a major cause of morbidity and mortality. To date, there is no evidence comparing the risk of falls and fall-related injuries in older people receiving first-line therapies for PDPN. Therefore, this study aims to assess and compare the risk for falls and fractures in patients with painful diabetic neuropathy after initiation of gabapentinoids versus SNRIs or TCAs. This study will emulate a clinical trial of gabapentinoids, SNRIs and TCAs in older people with PDPN using the Danish nationwide registers. Patients are eligible if they are 65 years or older, have PDPN and are starting one of the drugs being studied. Patients are excluded if they have an alternative indication or a contraindication for one of the initiated drugs. Follow-up will be 6 months. We will mimic randomisation using propensity score weighting.

Study status

Ongoing

Research institutions and networks

Institutions

Department of Drug Design and Pharmacology, University of Copenhagen

Inselspital

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Institution

Contact details

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Study timelines

Date when funding contract was signed

Planned: 07/01/2025

Actual: 07/01/2025

Study start date

Planned: 05/05/2025

Actual: 21/05/2025

Data analysis start date
Planned: 12/05/2025

Date of final study report
Planned: 31/08/2025

Sources of funding

- Other public funding (e.g. hospital or university)

More details on funding

AG received a "UniBE Short Travel Grants for (Post)Docs" from the University of Bern financing the short research stay to conduct this study. The University of Bern was not involved in designing the study.

Study protocol

PDPN_Protocol_v6.pdf (716.85 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study topic:

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

We will emulate a clinical trial of gabapentinoids versus SNRIs or TCAs in PDPN using the Danish nationwide registers. Randomisation will be mimicked using a set of pre-specified propensity score weights.

Main study objective:

1°: To estimate the risk for falls and fractures in patients with painful diabetic neuropathy after initiation of gabapentinoids versus SNRIs or TCAs.
2°: To estimate the risk for falls and fractures in patients with painful diabetic polyneuropathy after initiation of gabapentin versus pregabalin, duloxetine, venlafaxine, amitriptyline or nortriptyline.

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

GABAPENTIN

PREGABALIN

AMITRIPTYLINE

VENLAFAXINE

DULOXETINE

Anatomical Therapeutic Chemical (ATC) code

(N02BF01) gabapentin

gabapentin

(N02BF02) pregabalin

pregabalin

(N06AA09) amitriptyline

amitriptyline

(N06AA10) nortriptyline

nortriptyline

(N06AX16) venlafaxine

venlafaxine

(N06AX21) duloxetine

duloxetine

Medical condition to be studied

Fall

Fracture

Additional medical condition(s)

Painful diabetic polyneuropathy (PDPN)

Population studied

Short description of the study population

Persons aged 65 with diabetes initiating any of the studied drugs (proxy for painful diabetic polyneuropathy), with no treatment with any of the studied drugs in the last year and without diagnoses for depression, restless-legs syndrome, migraine, epilepsy, cardiac arrhythmia, heart block, congestive heart failure, urinary incontinence, falls or fractures in the last five years and no myocardial infarction in the last year.

Age groups

- Elderly (≥ 65 years)

Study design details

Setting

Danish national registries in the timeperiod from 01.01.2004 to 31.12.2024.

Interventions

Initiation of gabapentinoids (pregabalin or gabapentin), selective noradrenalin reuptake inhibitors (duloxetin or venlafaxine) or tricyclic antidepressants (amitriptyline or nortriptyline).

Comparators

Only active comparators.

Outcomes

1°: Crude and propensity score weighting adjusted Hazard ratios (HRs) for falls and fall-related injuries for gabapentinoids versus SNRI or TCA initiators.
2°: Crude and propensity score weighting adjusted Hazard ratios (HRs) for falls and fall-related injuries for initiators of gabapentin versus initiators of pregabalin, an SNRI or a TCA.

Data analysis plan

First, we will determine, whether pregabalin and gabapentin are a suitable reference group (i.e. whether they are homogenous enough). We will do this by assessing the covariate overlap, crude and adjusted HRs. We will calculate propensity scores with logistic regression, where the exposure to either gabapentin or pregabalin will be the dependent variable and the predefined covariates the independent variables. We will use standardised mortality ratio weights (SMRWs) to estimate the average effect on the treated, with gabapentin as the reference. Should there be no clinically relevant difference, we will proceed with a drug class based comparison described below.

We will calculate propensity scores with logistic regression, where the exposure to any of the studied drugs will be the dependent variable (gabapentinoids are the reference and the respective other drug groups the comparator). Predefined covariates will be the independent variables. We will perform the analysis with propensity score weighting using SMRWs. For this, we will set the weights to 1 for gabapentinoid initiators and to calculated weights for TCA and SNRI initiators. As SMRWs can be susceptible to extreme weights, we will follow Stürmer, et al.'s approach to trim the weights at the 2.5th and the 97.5th percentile. Therefore, our estimand is the average effect on the treated (i.e., what would have been the fall and fracture risk had gabapentinoid initiators, instead initiated TCAs or SNRIs). We will analyse the effect of study drug initiation using a multivariate Cox regression model, estimating crude and propensity score weighted hazard ratios (HRs). We will use a sandwich (robust covariance matrix) estimator for the confidence intervals (CIs), to take into account the multiple inclusion of patients.

The analysis of for the secondary outcomes will follow the same procedure.

Documents

Study, other information

PDPN_Supplementary materials.pdf (934.44 KB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Danish Health Data Registries

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after creation of study variables