Cover Page

Title	Long-term Opioid Therapy, Misuse and Mortality in Patients with Chronic Non-cancer Pain in Germany
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Country(-ies) of Study	Germany
Data used in study	German health claims data
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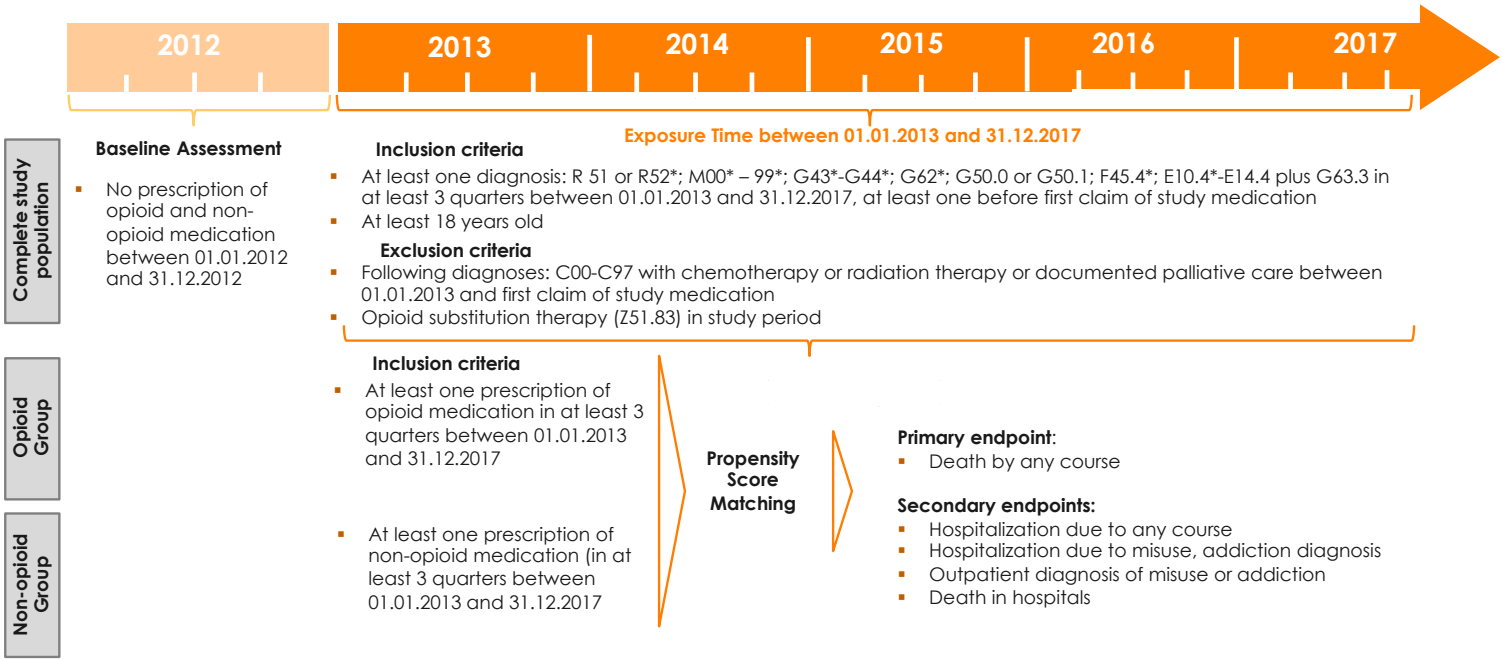
Study Design Schema

Figure 1: Study design schema



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2. List of Abbreviations

Term	Definition
ATC	Anatomical Therapeutic Chemical (ATC) classification
CCI	Charlson Comorbidity Index
GM	German Modification
HIV	Human Immunodeficiency Virus
d	Day
EBM	Einheitlicher Bewertungsmaßstab
GP	General practitioner
Mg	Milligram
Max	Maximum
Min	Minimum
N/A	Not Applicable
NSAIDs	Nonsteroidal anti-inflammatory drugs
OPS	Operationen- und Prozedurenschlüssel, an official classification of operational procedures, German version of international Classification of Procedures in
PZN	Pharmazentralnummer / Identification code for pharmacy products
PS	Propensity Score
SD	Standard Deviation
SHI	Statutory Health Insurance

3. Responsible Parties

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4. Abstract

Study Title: Long-term Opioid Therapy, Misuse and Mortality in Patients with Chronic Non-cancer Pain in Germany

Study Background and Rationale: Among patients receiving opioids for noncancer pain, recent research in North America showed a strong association between doses and opioid-related mortality, especially at dosages exceeding thresholds recommended in recent guidelines. However, the focus on over-dosage may underestimate overall opioid-related mortality and data on death associated with opioid use in a population-based cohort of chronic noncancer pain patients in Europe is scarce. Especially comparative studies studying the safety of long-term opioid therapy in a real-world setting relative to non-opioid medication for chronic noncancer pain are needed in a European context.

Research Question and Objective(s): The primary objective is to investigate the association between mortality among patients with chronic noncancer pain with long-term opioid-therapy compared to non-opioid pain medication. The secondary objectives are to determine the risk of addiction/abuse and hospital admissions among opioid users with chronic non-cancer pain compared to patients with non-opioid pain medication.

Study Design/Type: This is a cross-sectional observational cohort study between 2012 and 2017 of patients with chronic noncancer pain.

Study Population and Data Resource: The data will be retrieved from an anonymized German health claims database including 4,00,000 persons insured by 69 German statutory health insurances. The data set includes 5.0% of the population covered by statutory health insurances

from January 1, 2012, to December 31, 2017. Only anonymized and aggregated data (no directly or indirectly identifying data) will be extracted.

Summary of Patient Eligibility Criteria: From the data extraction, the cohort will be analysed according to the following criteria:

Inclusion criteria: At least one diagnosis of pain R51 (headache), R52* (pain, not elsewhere classified), M00 – M99 (Diseases of the musculoskeletal system and connective tissue), G43* (migraine), G44*(other headache syndromes), G50.0 (trigeminal neuralgia), G50.1 (atypical facial pain), F45.4* (persistent somatoform pain disorder), G62* (polyneuropathies), E10.4*-E14.4 plus G63.3 (diabetes mellitus with neurological complications) in at least 3 quarters between 01.01.2012 and their first opioid claim AND opioid medication (Cohort A) OR non-opioid medication (Cohort B) between 01.01.2012 and first pain medication claim.

*Exclusion criteria: P*atients with previous prescription of opioid medication or non-opioid medication between 01.01.2012 and index treatment will be excluded. Patients with cancer treatment, palliative care or opioid substitution after index treatment will be excluded.

Follow-up: Patients' follow-up period include 5 years after start of opioid resp. non-opioid treatment and chronic pain diagnosis between 01.01.2013 and 31.12.2017. Each patient will be censored at death (death date), switching of study group (opioid --> non-opioid or vice versa), 12 months without treatment or followed-up 5 years until last known record for the patient in the German health claims database, latest at 31.12. 2017 (end of latest data cut), whichever happens first.

Variables:

Outcome Variables include death by any course as primary endpoint and hospitalization due to any course, hospitalization with misuse, addiction diagnoses, outpatient diagnosis of misuse or addiction and treatment procedures as secondary endpoints.

Exposure Variables are pain treatments including opioid and non-opioid treatments.

Other Covariates will be collected for assessments over the course of the study: Age and gender (sex: male, female), charlson comorbidity index. Comorbidities, comedications, region will be collected for Propensity Score Matching.

Data Analysis: The main analysis will focus on each of the 2 main cohorts with chronic pain patients as defined at inclusion and:

- with opioid treatment between 01.01.2013 and 31.12.2017 (named cohort A)
- with non-opioid treatment between 01.01.2013 and 31.12.2017 (named cohort B)

To address the group comparisons adequately, a propensity score matching will be conducted. The main analyses will include a multivariate Cox proportional hazards regression. Additional stratified analyzes will be carried out as follows: Subgroup analyses for each following pain conditions will be conducted: headache (R 51*); pain, not elsewhere classified (R52*); persistent somatoform pain disorder (F45.4*); polyneuropathy in diabetes (E10.4*-E14.4 plus G63.3), kyphosis and lordosis (M40), scoliosis (M41), spinal osteochondrosis (M42), other deforming dorsopathies (M43), ankylosing spondylitis (M45), other inflammatory spondylopathies (M46), spondylosis (M47), other spondylopathies (M48), and spondylopathies in diseases classified

elsewhere (M49), Cervical disc disorders (M50), thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (M51), Other and unspecified dorsopathies, not elsewhere classified, and dorsalgia (M54).

5. Protocol amendments and Updates

Table 5-1: Protocol amendments and updates

Version	Description	Name / Author	Date
V.01	First draft	LinkCare GmbH	10 September2018
V.02	Amendments following TCs and mails with the other authors	LinkCare GmbH	31 October 2018
v.03	Ammendments following e-mail of Prof. Haeuser	LinkCare GmbH	28 November 2018

6. Milestones

Table 6-1: Milestone plan

Milestone	Planned date
Finalization of study design	*30. September 2018*
Writing of a detailed analytical protocol/ study plan	*15. November 2018*
Contracting with German health insurances	*15. November 2018*
Data obtaining, quality assurance and data analysis	*31. January 2019*
Writing of publication	*28. February 2019*
Submission and peer-review process	*31. March 2019*
Publication	*31. July 2019 (dependent on journal)*

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Chronic non-cancer pain describes back, musculoskeletal, abdominal, headache and other neurologic pain without an evidence of cancer[1].

[1] Dowell et al., 2016

Today, chronic pain is one of major health care problems in Europe. For instance, a large telephone survey in 15 European countries and Israel showed that chronic non-cancer pain of moderate to severe intensity has a prevalence of 19 % affecting the quality of patient's social and working lives[2]. Common treatment of moderate to severe chronic pain includes opioids, analgesic anticonvulsants[3] and low-dose cyclic antidepressants[4]. Analgesic anticonvulsants and low-dose cyclic antidepressants can have serious adverse effects[5]. But also the tendency of increased prescriptions of opioid analgesics leads to a discussion about potential harms of this medication[6].

7.2 Rationale

Among patients receiving opioids for treatment of noncancer pain, recent research in North America showed a strong association between doses and opioid-related mortality, especially at dosages exceeding thresholds recommended in recent guidelines[7]. However, the focus on over-dosage may underestimate overall opioid-related mortality and data on death associated with opioid use in a population-based cohort of chronic non-cancer pain patients in Europe is scarce. Especially comparative studies studying the safety of long-term opioid therapy relative to non-opioid medication for chronic noncancer pain are needed in a European context.

[2] Breivik et al., 2006
[3] Moore et al., 2011
[4] Carragee et al., 2005
[5] Ray et al., 2004
[6] Okie et al., 2010
[7] Ray et al., 2016

8. Research Question and Objectives

8.1 Primary objectives

Objective of this study is to investigate the association between mortality among patients with chronic noncancer pain with long-term opioid-therapy compared to non-opioid pain medication (nonsteroidal anti-inflammatory drugs (NSAIDs, Metamizole), anticonvulsants, antidepressants).

In order to address the primary objective, following hypotheses will be examined in the study:

- How many patients with chronic noncancer pain on long-term opioid therapy and patients with non-opioid pain medication died in time period of five years?
- Which demographic factors, comorbidities and comedication predict mortality and time to mortality among patients with chronic noncancer pain on long-term opioid therapy and of patients with non-opioid pain medication?
- Does mortality differ between patients with chronic noncancer pain on long-term opioid therapy compared to patients with non-opioid pain medication in time period of five years?

8.2 Secondary objectives

In addition, present study aims to determine the risk of addiction/ abuse and hospital admissions among opioid users with chronic non-cancer pain compared to patients with non-opioid pain medication.

The secondary objectives will be addresses with following hypotheses:

- How often do patients on long-term opioid therapy and patients with non-opioid pain medication being hospitalized and how long do they stay in hospital?
- Does the number of hospitalizations and length of stay in hospital differ between patients on long-term opioid therapy compared to patients with non-opioid pain medication in time period of five years?
- How many misuse and addiction diagnoses were coded in outpatient sector for patients on long-term opioid therapy and patients with non-opioid pain medication in time period of five years?
- Does the number of outpatient misuse and addiction diagnoses differ between patients on long-term opioid therapy compared to patients with non-opioid pain medication in time period of five years?
- How many sick leave days do patients on long-term opioid therapy and patients with non-opioid pain medication have in time period of five years?

9. Research Methods

9.1 Study Design

This is a retrospective observational cohort study based on an anonymized German health claims database. This database contains data on around 4 million insured people from 69 German statutory health insurances (SHI). This research database is a complete, longitudinal claims dataset of approx. 7 million individual patients (ca. 10% of the statutory insured population of Germany) between 2012 and 2017. The analyses for this study will be done on a 4 million patients subset that is stratified by age

and gender based on the 2013 population structure of Germany as reported by the German Federal Statistical Office DeStatis.

This study consists of two cohorts: opioid and non-opioid patients. Only patients who started their therapy between 2013 and 2017 and had no therapy in 2012 (therapy naïve patients) will be included in the study. Exposure time is defined as max. 5 years after the initial prescription for each patient, so that exposure time is max. 60 months per patient. Exposure time may end before the end of study if patient died, stopped treatment (end of follow-up after 1 year without treatment with opioids / other pain medication), changed treatment group (from opioids to other pain medication or vice versa) or was lost to follow up due to other reasons (e.g. change of insurance), whichever occurs first.

9.2 Setting and Study Population

The database contains data on around 4 million insured people from 69 German statutory health insurances (SHI). German SHI system comprises of approximately 120 independent health insurance companies. Funds paid by these SHI to any provider of health care (e.g. hospitals, physicians, pharmacies, psychotherapists and physiotherapists) represent almost the complete picture of the total health care costs of individual patients. All health insurance data can be linked to patients' demographics including age and gender. Health care data in the database include:

- *Patient demographics:*
    - age
    - gender
    - date of death

- region of residence
- insurance status
- date of insurance start and end

- *Hospital care:*
  - main diagnosis (ICD-10-GM codes) and additional diagnoses
  - procedures and surgeries
  - date of hospital admission
  - reason for admission (e.g. accident, emergency, normal)
  - date of end of hospital stay
  - reason of end of hospital stay (e.g. regular discharge from hospital, death)
  - DRG-Code
  - costs
- *Outpatient care:*
  - diagnoses (ICD-10-GM codes)
  - quarter in which the diagnosis was documented
  - procedures performed (EBM codes, e.g. laboratory tests, radiology, echocardiography) and date of procedure
  - type of specialist that documented the diagnosis and performed the procedure (e.g. cardiologist, general practitioner)
  - costs
- *Pharmaceutical claims:*

- drug dispensed (PZN code, which identifies medications at the package level) – this is mapped to ATC codes and DDDs
- quantity dispensed
- day of prescription
- day of dispensing
- type of specialist prescribing the medication (e.g. general practitioner)
- costs of drugs dispensed from the perspective of the statutory health insurance (without individual rebates between insurance and pharmaceutical companies)

- *Physical therapy and technical aids:*
  - type of therapy (e.g. massage, occupational therapy, walker, wheel chair)
  - quantity prescribed
  - type of care provider
  - start and end date
  - costs
- *Sick leave:*
  - diagnoses that cause sick leave
  - duration of sick leave
  - start date of sick leave
  - end date of sick leave

- type of specialist that filled out the sick leave form (e.g. general practitioner)
- costs of sick leave

To note, data are adjusted within the database to Germany's typical age and sex distribution in accordance with the Federal Statistical Office based on the year 2013 (https://www-genesis.destatis.de/genesis/online) to foster its overall representativeness in regards to the population in Germany. Privately insured patients in Germany are not included in this database.

All data used are explicitly approved by the involved statutory health insurances for health care research usage according to § 287 or § 75 of the German social security law (SGB V).

Source population of the study are patients covered by the German Health Claims database over 2012-2017 years.

Study population are patients from the source population meeting inclusion (eligibility) criteria (see section 9.2.2).

9.2.1 Study Period

Due to data protection regulations in Germany, only an extract of maximum 6 years of data coverage could be available for the research purposes: 1st January 2012 to 31st December 2017.

The **baseline period** is defined as the period prior to the date of first diagnosis of diagnoses or first opioid or non-opioid treatment initiation as described in inclusion criteria (Chapter 9.2.2.1). The baseline assessment period endures between January 01, 2012 and first study medication prescription.

Index treatment is definded as the date of first opioid or non-opioid treatment prescription between 1st January 2013 and 31st December 2017.

Exposure time is defined as time between index treatment and December 31, 2017. Considering data availability of a maximum of 6 years and prescription in a required time period of 60 months, exposure time endures maximum five years. Thus, patients can be censored at death (death date in the linked records), last known record for the patient in the German health claims database, switching of treatment groups (from opioid group to non-opioid group or vice versa), 12 months without opioid/non-opioid treatment or 31st December 2017 (end of latest data cut), whichever comes first.

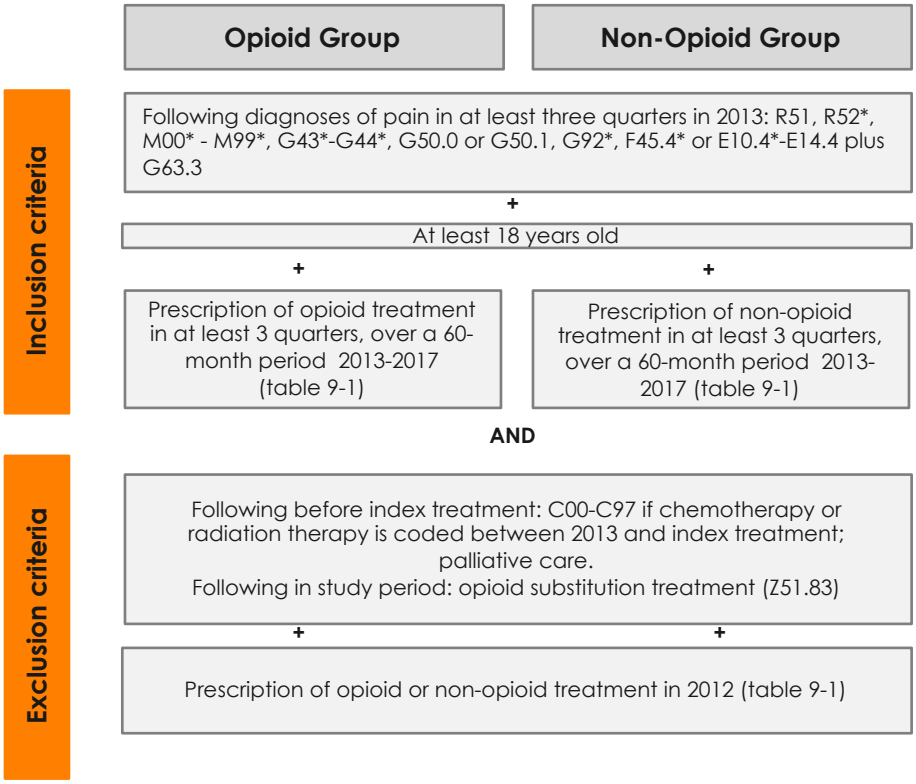
The **outcomes** will be assessed between index treatment and 31.12.2017.

9.2.2 Patient Eligibility

9.2.2.1 Inclusion Criteria

For the purposes of this study, the requested extraction of the database consists of population of patients with chronic non-cancer pain corresponding to the following criteria. Inclusion and exclusion criteria are also provided in Figure 2.

Figure 2: Inclusion and exclusion criteria



Cohort A

- Patients are included in the long-term opioid group if they started an opioid-therapy between 2013 and 2017 and received consecutive prescriptions for opioid medications over a minimum of 3 quarters, over a 60-month period between January 1, 2013, and December 31, 2017. The treatment will be assessed using the ATC codes of opioid treatment N02AA01, N02AA05, N02AB03, N02AE01, N02AX02, N02AX01, N02AX06 see also Table 9-1) reported in reimbursed medicines to patients.

- Patients are only included if they have been diagnosed in at least three quarters in the study period with one of the following diagnoses: R51, R52*, M00*-M99*, G43*-G44*, G50.0 or G50.1, F45.4*, G62*, or E10.4*-E14.4 plus G63.3. At least one diagnoses must be between 1 January 2012 and index treatment and main and secondary hospital diagnoses *(i.e. Haupt- und Nebendiagnosen*) will be used to include the patients.

Cohort B

- Patients with non-opioid pain medication are included, if they received a medication therapy with anticonvulsants (gabapentin, pregabalin, carbamazepine), antidepressants or non-opioid analgesics (NSAIDs, Metamizole) over a minimum of 3 quarters, over a 60-month period between January 1, 2013, and December 31, 2017. The non-opioid treatment will be assessed using the ATC codes (N03AX12, N03AX16, N03AF01, see also Table 9-1) of treatment reported in reimbursed medicines to patients.

- Patients are only included if they have been diagnosed in at least three quarters in 2012 with one of the following diagnoses: R51, R52*, M00*-M99*, G43*-G44*, G50.0 or G50.1, F45.4*, G62*, or E10.4*-E14.4 plus G63.3.At least one diagnoses must be between 1 January 2012 and index treatment and main and secondary hospital diagnoses *(i.e. Haupt- und Nebendiagnosen*) will be used to include the patients.

All diagnoses that lead to patient inclusion when coded between 01.01.2012 and index treatment and in at least three quarters within the study period are provided in Table 9-2 below.

Table 9-1: List of ATC codes of study opioid and non-opioids

Name	ATC Code
Study opioids	
Morphine	N02AA01
Oxycodone	N02AA05
Fentanyl	N02AB03
Buprenorphine	N02AE01
Tramadol	N02AX02
Tilidine	N02AX01
Tapentadol	N02AX06
Study non-opioids (anticonvulsive)	
Gabapentin	N03AX12
Pregabalin	N03AX16
Carbamazepine	N03AF01
Study non-opioids (antidepressants)	
Non-selective monoamine reuptake inhibitors	N06AA*
Selective serotonin reuptake inhibitors	N06AB*
Monoamine oxidase inhibitors, non-selective	N06AF*
Monoamine oxidase A inhibitors	N06AG*
Other antidepressants	N06AX*
Study non-opioids (Nonsteroidal anti-inflammatory drugs)	
Butylpyrazolidines	M01AA*
Acetic acid derivatives and related substances	M01AB*
Oxicams	M01AC*
Propionic acid derivatives	M01AE*
Fenamates	M01AG*
Coxibs	M01AH*

Other antiinflammatory and antirheumatic agents, non-steroids	M01AX*
Study non-opioids (others)	
Metamizole	N02BB02

Table 9-2: List of included ICD-10 diagnoses for both cohorts

Name	ICD-10 Code
Diseases of the musculoskeletal system and connective tissue	M00* - M99*
Headache	R51
Pain, not elsewhere classified	R52*
Migraine	G43*
Other headache syndromes	G44*
Trigeminal neuralgia	G50.0
Atypical facial pain	G50.1
Persistent somatoform pain disorder	F45.4*
Other and unspecified polyneuropathies	G62*
Diabetes mellitus with neurological complications AND Polyneuropathy in diseases classified elsewhere	E10.4-E14.4 G63.3

9.2.2.2 Exclusion Criteria

Following exclusion criteria will be used to extract the eligible study population (see also Figure 2):

Cohort A and B:

- Patients with present opioid and non-opioid pain medication prescriptions in 2012 are excluded from analysis (therapy-naïve patients only).

- Cancer patients will be excluded if the cancer diagnosis is accompanied by at least one of the following treatments in the same quarter: radiation therapy or chemotherapy all defined by the codes in Table 9-3. Diagnoses will be assessed via ICD-10 diagnoses during the inclusion period from 1 January 2012 until index treatment and main and secondary hospital diagnoses *(i.e. Haupt- und Nebendiagnosen*) will be taken into account.

- Palliative care, coded by ICD-10 code Z51.5 or OPS code 8-982*, 8-98e*, 8-98h* before index date is excluded

- Opioid substitution treatment with ICD-10 code Z51.83 in the study period is excluded.

Table 9-3: Exclusion criteria for cancer patients

Name		**ICD-10 Code**
Malignant neoplasms		C00-C97
Plus at least one the following in the same quarter		
Name	**Code**	**Type of Code**
Palliative care	Z51.5	ICD-10
Chemo therapy	Z51.1	ICD-10
Radiation therapy	Z51.0	ICD-10
Chemo therapy	8-541* 8-542* 8-543* 8-544* 8-546*	OPS Code

Radiation therapy	8-52*	OPS Code
Palliative care	8-982* 8-98e* 8-98h*	OPS Code

9.3 Risk adjustment

9.3.1 Propensity Score Matching

For the planned analyses, patients with opioid and non-opioid treatment need to be comparable. Mortality rates are expected around 100 and 200 per 10,000 persons years[8] thus limiting the number of covariates for risk-adjustment to avoid over-fitting (10:1 rule of thumb: Not more than 1 predictor/covariate for 10 events). To avoid this overfitting problem but still be able to adjust for a large number of covariates, a propensity score (PS) matching will be conducted before the acutual Cox regression.

PS-Matching will be based on logistic regression and reflect the probability of getting an opioid treatment considering the following risk factors. The choice of covariates is based on a previous retrospective cohort study about opioid dependency and mortality in the US[9] (see Apendix A, for the list of study covariates based on Ray et al.)

- region (i.e. 'Bundesland')
- comorbidities: obstructive sleep apnoea, depression and other comordidities
- comedication with other anticonvulsants than gabapentin, pregabalin or carbamazepine, comedication with neuroleptics, NSAR, tranquilizer or muscle relaxants, metamizole, comedication

[8] Numbers from Ray et al. (2016)
[9] Ray et al., 2016

with cannabinoid drugs, year of index treatment and drug dosage of the opioids/non-opioids as defined in section 9.4.

- medical procedures based on OPS-codes assessed as a number of procedures (see Appendix B, for the list of OPS codes), e.g. dialysis

PS matching will be based on a logistic regression (logit model) and reflects the likelihood that a patient will be prescribed by opioid medication if certain risk factors/comornbidities are considered. All binary predictors are included in the model as dummy variables (1 vs. 0). The influence of each variable is given as odds ratios with 95% confidence intervals.

The following equation will be employed for PS matching:

$$P_i = \frac{e^{\beta_0 + \sum_{j=1} \beta_j x_{j,i}}}{1 + e^{\beta_0 + \sum_{j=1} \beta_j x_{j,i}}}$$

The dependent variable is the treatment and will be dummy coded as 1 (opioid treatment in index year) and 0 (no opioid treatment) (P_i).

Age and gender will also be uses for risk adjustment and will be assessed using national insurance data, for age by date of birth and is calculated based on the index treatment. For age, a variance of 5 years is allowed, i. the age can vary by plus / minus 5 years when matching.

Finally, based on the propensity scores, matching will be performed using the GenMatch function of the R statistical package. The probability values p_i of the matched patients may vary by ± 0.2 * standard deviation. This range is often used in PS matching using logistic regression, provides a balance of included covariates, and thus no large number of patients are lost because they are still treated as comparable for small deviations[10].

[10] Austin et al., 2011

The frequency matching will be performed by dividing the study cohort into 1 % centiles according to the long-acting opioid propensity score distribution[11]. Within each centile, one patient that had a prescription of non-opioid treatment will be randomly selected to increase the likelihood that all matches have equal quality and permit an analysis with unmatched data.

9.3.2 Other risk adjustment

The following Cox proportional hazards time to event regression model describes the method of another risk adjustment:

$$\lambda(tX_j) = \lambda_0(t) * exp\ (\beta_1 X_{j1} + \beta_2 X_{j2} + ... + \beta_m X_{jm})$$

This expression gives the hazard rate at time t for person j

- $\lambda(tXj)$ is the hazard for outcome at time t for person j
- where *exp* is a mathematical constant, Euler's number (e = 2,71828)
- $X_1, \ldots, X_m$ are the values of exposure variables and covariates
- $\beta_1, \ldots, \beta_m$ are estimated regression coefficients that indicate the importance of exposure variables and covariates.
- $\lambda_0(t)$ is the baseline hazard indicating hazard for the outcome if all exposure variables are zero (similar meaning "intercept").

Following covariates will be used in the Cox proportional hazards time to event regression:

- **Gender** (sex – male, female) will be assessed via indicated sex in the social insurance register

[11] Ray et al., 2016

- **Age** will be assessed using national insurance data by date of birth and calculated based on the 'index treatment' (the date of first study medication claim between 1st January 2012 and 31st December 2017).
- **Charlson Comorbidity Index (CCI)** will base on the the modified CCI according to Quan (2005) and Quan (2011). Using modified CCI is preferebale because is was validated by ICD-10 while, for example, the Romano-CCI was validated using ICD-9[12]. The modified CCI predicts the one-year mortality for a patient who may have a range of comorbid conditions (e.g. AIDS, or cancer) with a total of 16 conditions[13]. Each condition is assigned a score between 0 (no risk) and 6 (high risk), depending on the risk of dying associated with conditions. Age and gender are defined as hazard ratios. The scores are summed up to provide a total score to predict mortality. CCI will be added as a covariate in the Cox regression model (Table 9-4).
- **Duration of the opioid /non-opioid treatment** will be used as a one of the predictors of opioid treatment in be added as a covariate in the Cox regression model and assessed as the difference between the last opioid or non-opioid prescription based on ATC codes and the first opioid or non-opioid prescription in months, between January 1st 2012 and December 31st 2016. The prescription will be dummy coded as 1 (prescription available) or 0 (no prescription available).
- **Quarter of index treatment:** Quarter in which index treatment was initiated, wheras Q1/2012 is quarter=1, Q2/2012 is quarter=2 and so on.
- **Propsensity Score** as calculated before

[12] Yurkovich et al 2015
[13] Quan et al 2011

Table 9-4: Charlson Comorbidity Index

Conditin	Scale	Points	ICD-10-GM Code
Myocardial infarction	No	0	
	yes	1	I21*-I22*, I25.2
Congestive Heart Failure	No	0	
	yes	1	I50*
Peripheral vascular disease	No	0	
	yes	1	I73*, I74.2, I74.3, I74.4, I71.3, I71.5, I71.4, I71.6
Cerebrovascular accidents	No	0	
	yes	1	I60*-I69*
Dementia	No	0	
	yes	1	F00*-F03*, F05.1
Chronic obstructive pulmonary disease	No	0	
	yes	1	J44*
Rheumatic disease	No	0	
	yes	1	M05*, M06*, M31.5, M32–M34, M35.3, M45*,
Peptic ulcer disease	No	0	
	yes	1	K25*, K26*, K27*, K28*
Liver disease	No	0	
	Mild	1	K70.1-K70.3, K70.9, K71-K71.0, K71.2-K71.8, K73*, K74.0, K74.2, K74.6, K74.3, K74.4, K74.5
	Severe	3	K70.4, K71.1, K72*, K76.3
Diabetes mellitus	No	0	
	Un-complicated	1	E10.9*, E11.9*, E13.9*, E14.9*, E10.1*, E11.1*, E13.1*, E14.1*
	Complicated / end organ damage	2	E10.2*, E11.2*, E13.2*, E14.2* E10.3*, E11.3*, E13.3*, E14.3* E10.4*, E11.4*, E13.4*, E14.4*, E10.5*, E11.5*, E13.5*, E14.5*
Hemiplegia	No	0	
	yes	2	G81*
Kidney diseases	No	0	
	yes	2	N17*-N19*
Cancer	No	0	
	Solid	2	C00*-C76*, C80*, C81*, C82*, C83*, C84*, C88.3, C88.7, C88.9, C96*, C90.1, C91*-C95*, C81*, C82*, C83*, C84*, C85*, C86*, C88*
	Metastatic	6	C77*, C78*, C79*, C80*
AIDS / HIV	No	0	
	yes	6	B20* - B24*
Demographics as risk factors			
	Hazard Ratio		
age (> 65 years)	4,40		
gender (male)	1,28		

The Cox proportional hazards model will use treatment dosage as time-varying covariates, re-calculating it annually during follow up. The model will also be adjusted for age, gender, CCI at the baseline. Covariates will not be treated as time varying variables.

9.4 Variables

The following variables will be collected for assessments over the course of the study.

9.4.1 Exposure Assessment

Opioid and non-opioid treatments will be assessed using ATC and PZN codes (see Table 9-1) as described below:

- **Opioid Treatment** received between January 1st 2012 and December 31st 2016 in at least 3 quarters, over a 60-month period based on ATC code N02A%.
- **Non-Opioid Treatment** (NSAIDs, anticonvulsants, antidepressants) received between January 1st 2012 and December 31st 2016 in at least 3 quarters, over a 60-month period, based on ATC code in Table 9-1.
- **Treatment Dosage** will be assessed based on DDD assessment per ATC code using DIMDI data. Dosage will thus be calculated as medication dose per day based on the average prescription per year of the year. The number of medication claums, the number of drug packages and DDD per package are used to estimate the daily dose.

- Treatment dosage of opioid treatment will be defined based on morphine equivalence. The low dosage is thus defined as less than 60mg/d morphine equivalence. The intermediate dosage will be defined as a dosage between 60mg/d and 120mg/d morphine equivalence. The high dosage will be defined as 120mg/d morphine equivalence or higher.
- Treatment dosage for non-opioid treatment is defined as follows:
  - Anticonvulsive: based on gabapentin equivalence. The low dosage is thus defined as a daily dosage of less than 600mg/d gabapentin equivalents and a high dosage of 600mg/d or more gabapentin equivalents.
  - Antidepressants: via standard psychiatric dose according to AKDÄ (2006) recommendations: daily doses below the minmum standard psychiatric dose will be defined as "low", dosages above as "high". The standard psychiatric dose per ATC can be seen in Table 9-5.

Table 9-5:: Standard psychiatric doses as threshold for low/high dosage

Active substance	ATC code	Minimum standard psychatric dose
Amitriptylin	N06AA09	100
Amitriptylinoxid	N06AA09	100
Clomipramin	N06AA04	100
Desipramin	N06AA01	100
Dibenzepin	N06AA08	240
Doxepin	N06AA12	100
Imipramin	N06AA02	100
Maprotilin	N06AA21	100
Nortriptylin	N06AA10	50

Trimipramin	N06AA06	100
Citalopram	N06AB04	20
Escitalopram	N06AB10	10
Fluoxetin	N06AB03	20
Fluvoxamin	N06AB08	100
Paroxetin	N06AB05	20
Sertralin	N06AB06	50
Moclobemid	N06AG02	300
Tranylcypromin	N06AF04	20
Venlafaxin	N06AX16	75
Duloxetin	N06AX21	60
Reboxetin	N06AX18	8
Mianserin	N06AX03	60
Mirtazapin	N06AX11	15
Trazodon	N06AX05	200

- **Duration of treatment** will be operationalized as time in months between the last and first prescription of an opioid or non-opioid treatment between between 01.01.2013 and 31.12.2017. Duration might endure at least 9 months because 3 quarters of prescription are the inclusion criterion. The duration of treatment might be 60 months as a Maximum (5 years of exposure time).

9.4.2 Outcome Assessment

The study will assess the following main outcomes during the follow-up period.

9.4.2.1 Primary endpoint

Primary endpoint is **death** by any course in the study follow-up. Death will be assessed during the follow-up period by number of patients who deceased during follow-up period (2013 – 2017) via the date of death in German claims data base. Additionally, mortality rate will be estimated as number of patients who died during the follow-up divided by person-time

of follow-up, censoring at time of death, last known record for the patient in the database, or 31st December 2017 (end of latest data cut), whichever is earlier.

9.4.2.2 Secondary endpoints

Secondary endpoints are following:

- **Hospitalization due to any course.** Hospitalization will be assessed via the number of hospitalisations (calculated by counting the number of discharge dates (KH_Fall. Entlassungsdatum) in the year of interest, hospitalization rate, and length of stay in the hospital (KH_Fall. Verweildauer). The rate of hospitalization will be estimated as the number of patients with at least one hospitalization during the follow-up period divided by person-time of follow-up, censoring at time of death, last known record for the patient in the database, or 31st December 2017 (end of latest data cut), whichever is earlier.
- **Intensive care unit** (ICU-stay) stay is defined as patient's stay based on specialty of departement in hospital (KH_OPS.Fachabteilung = 3600).
- **Hospitalization with to misuse or addiction.** The hospitalization with misuse or addiction will be analysed, if principal (main) diagnosis at discharge date between January 1st 2013 and December 31st 2017 contains at least one ICD-10 diagnosis of misuse/addiction: F10* or F11* or F13* or F19* or T40* (see also Appendix B in **Fehler! Verweisquelle konnte nicht gefunden werden.**).
- **Hospital admission diagnoses.** We report the hospital admission diagnoses based on ICD-10 codes between January 1st 2013 and December 31st 2017.
- **Coding of procedures in hospitals** that indicate number of patients that were hospitalized with severe diseases such as cardiovascular

diseases will be assessed via OPS-Codes provided in Appendix B as an excelsheet.

- **Coding of a misuse or addiction diagnosis in the outpatient sector** will be assessed via number of codings of misuse/addiction (ICD Codes = F10* or F11* or F13* or F19* or T40*) in outpatient sector by general practitioner or a specialist (e.g. psychiatrist), as ensured diagnosis (Diagnosesicherheit='G'). Additionally, the number of patients with a least one coding of ICD 10 codes of an ensured misuse/addiction in outpatient sector by general practitioner or a specialist (e.g. psychiatrist) will be assessed.
- **Sick leave** will be assessed as an absolute number and relative frequencies of patients with an attest of inability to work (patients with attest of inability to work as a percentage of all patients) in 2013-2017 and number of days being off work.
- **Hospital deaths** will be assessed via reason of discharge = death (Entlassgrund = Tod)
- **Main- and secondary discharge diagnoses** from hospital deaths will be assessed as the TOP 20 diagnoses of patients who deceased during a hospital stay

9.5 Validity and Reliability

The external validity of the used data set is checked against the national reference data from official resources: Information System of the Federal Health Monitoring for the total German population and from the German Drug Prescription Report for the German population insured within the SHI system (Anderson et al., 2016). The reliability of each outcome variable (i.e., diagnoses) will be warranted due to the use of only "ensured"

(instead of suspected diagnosis) outpatient diagnoses or inpatients diagnoses.

9.6 Data Management

9.6.1 Obtaining Data Files

The data authority of the involved statutory health insurance (SHI) will obtain the data based on this analytical protocol. There will be an approval process of the data used and the methods applied. The involved SHIs will therefore get a copy of this analytical protocol to review whether the issues addressed are for health care research only.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

The frequency of missing data will be provided for each variable in the outputput tables. Range (min and max) will be reported in order to find inplausible low or high values for each continuous variable in the analysis.

9.7 Data Analysis

All analysis will be conducted using R (version 3.3.1 or subsequent versions) amd the SAS Statistical Package 9.4 .

Main analysis will focus on each of the 2 main cohorts as defined at inclusion:

- Patients with pain diagnosis and opioid treatment between 1st January 2013 and 31st December 2017

- Patients with pain diagnosis and non-opioid treatment between 1st January 2013 and 31st December 2017

Stratified analyzes will be carried out for each of the 2 main sub-cohorts and each following pain conditions will be conducted: headache (R 51*); pain, not elsewhere classified (R52*); persistent somatoform pain disorder (F45.4*); polyneuropathy in diabetes (E10.4*-E14.4 plus G63.3).

9.7.1 Planned Analyses

To adress the main research questions, descriptive analyses, Cox proportional hazards regression and test for examining group differences (T-test and Chi^2 test) will be provided.

Descriptive analyses using mean, median, standard deviation, absolut and relative frequency, minimum and maximum will be reported.

To address the research questions about the differences between opioid and non-opioid treatment, inductive analyses using Chi^2 Tests and t-test with critical value at the 5% significance level will be employed.

9.8 Subgroup and Sensitivity Analysis

9.8.1 Subgroups for addidional descriptive analyses

The following main sub-groups of patients will be distinguished to stratify during descriptive analyses while assessing study objectives:

Subgroup analyses for each following pain conditions will be conducted:

Subgroup
Headache (R 51*)
Pain, not elsewhere classified (R52*)

Persistent somatoform pain disorder (F45.4*)
Polyneuropathy in Diabetes (E10.4*-E14.4 plus G63.3)
Back pain (M54*)
Arthrosis (M15*-M19*)

9.8.2 Sensitivity analysis

The following main sensitivity analysis will be conducted:

Sensitivity analysis
No cancer patients: Exclude all patients with at least one C00 – C96 diagnosis before index date

9.9 Quality Control

Assessment of availability and completeness of variables, including missing data and implausible ranges, as described in previous sections, will be conducted.

9.10 Limitations of the Research Methods

9.10.1 Internal Validity of Study Design

The statutory health insurances database uses billing data which are designed for invoices and not for research activities, and therefore lack detailed clinical information and lab data. About 10% of German inhabitants are members of the private health insurance companies. Because the access to a private health insurance companies in Germany has special requirements, among others income, there are differences between insured patients of statutory and private health insurance

companies in terms of their socioeconomic status and health (care) behavior. Therefore the study sample may not be completely representative of the general German population in terms of socioeconomic status.

Given the data structure of the German health care system, the exact treatmnet dosage of a medication has to be estimated and might differ from the real dosage. There is also no clinical patient information and we do not know whether the dispensed drugs were used immediately, saved for later use, diverted or not used at all. The assumption that all drugs were used at a time close to dispensation would probably lead to an overestimation of drug use.

9.10.1.1 Measurement Error(s)/Misclassification(s)

Due to administrative nature of the database, the possibility of misclassification and miscoded data exists. This study is using prescription data to assess possession, which is only a proxy for patients taking their medication. There may be missing data due to limitations of the linkage between different datasets, with fully linked data available for subsets of patients.

9.10.1.2 Information Bias

There is a potential for misreporting of information in the existing health systems from where data are retrieved (medical records and national health registries). However, due to a large sample size in present study, an error in classification of a condition would unlikely to have a significant effect on final results. The current study focuses on deaths and

hospitalisations as key outcome measures that are less likely to be missing and less likely to be subject to bias.

9.10.1.3 Selection Bias

All eligible patients who meet inclusion criteria will be considered for the analysis. The selection bias is less likely in claims data of health insurances data.

9.10.1.4 Confounding

Confounding occurs when a covariate is independently associated with the exposure and the outcome of interest. The size of the datasets should allow analysis to explore and control this bias satisfactory. Subgroup analyses of subpopulations with different chronic pain diagnoses will be considered. However, unmeasured confounding cannot be excluded.

9.10.2 External Validity of Study Design

External validity describes the degree to which findings are able to be generalizable to the total population. Due to the retrospective observation design, the present study shows benefits of interventions under real conditions and increases the external validity. Insurees contributing to the German statutory health insurances are broadly representative of the German general population, although given these were originally employer based sickness funds, it is possible there are some residual differences in the demographic profile. Also, as indicated in section 9.9.1, private insurance patients (about 10% of German population) are not covered in this database. The demographic profile of

covered patients will be compared with general population demographics as far as data allow.

9.10.3 Analysis Limitations

Some of the subgroups might be too small and thus the interpretation of results should report the sample size and possible limitations of interpretation.

There might be other unknown predictors or confounders of the outcomes that limit the interpretation of final results.

9.10.4 Limitations Due to Missing Data and/or Incomplete Data

Missing data are a frequent feature of any real-world study using secondary databases, and depending on its nature and extent, could have a significant impact on the conclusions that can be drawn from the data.

The present study includes a limited number of exposure variables in a large sample size that makes the impact of random missing data less important than in a study with a small sample size. Descriptive statistics of all variables will provide an insight into the extent of missing data. Missing data on covariates is not expected to be problematic in this study, but should we need to address missing data for an unanticipated reason, we will use the method of multiple imputations and also consider casewise deletion. Imputation will not be used for the outcome variables.

9.11 Other Aspects

Not applicable.

10. Protection of Human Subjects

The planned analysis is based solely on claims data of health insurances. All data in the database are anonymized, i.e. there are no identifiable patients in the dataset (i.e. by date of birth, name, or others). Furthermore, all data are analysed on an aggregated level, not on a patient-individual level. Cohorts of patients smaller 5 will not be reported.

All data used are explicitly approved by the involved statutory health insurances for health care research usage according to the German social security law (§ 287 SGB V or § 75 SGB X).

11. Plans for Disseminating and Communicating Study Results

The study results will be reported as a manuscript in a peer-reviewed journal. Planned submission is in QII – QIV 2019.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Grünenthal as study sponsor has no role in the design of the study, in the collection, analyses and interpretation of the data, in the writing of the manuscript, and in the decision to submit the paper for publication. The manuscript with the data analyses will be made available to the sponsor after acceptance of the manuscript.

12. Contributions to improve health care

In order to further improve the care of patients with chronic noncancer pain, a close knowledge of the current care of these patients and the therapies used is essential. The present study will help to characterize the differences between opioid and non-opioid patients with chronic noncancer pain regarding mortality, hospitalizations and misuse. The data from the SHI research database are the ideal data basis, as they represent the care of patients in Germany in a representative way.

13. Innovative strength of the project

In an increasingly complex health care environment, valid and representative data are essential to understand if and how the treatment of chronic non-cancer pain patients can be improved. Previous studies showed strong association between doses and opioid-related mortality, esp. at doses exceeding thresholds recommended in recent guidelines, but the data on death associated with opioid use is scarce. Especially comparative studies are needed in a European context. Thus, this study

will use the innovative approach of obtaining the data directly from SHI's representative database. This approach allows for accurate conclusions about the mortality of opioid and non-opioid patients with non-cancer pain in Germany.

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