Socio-economic Consequences of Pain-Intensive Diseases in Denmark

Jan Christensen · Lone Bilde · Anders Gustavsson

PUBLICATION DECEMBER 2011

Danish Institute for
Health Services Research
Dampfærgevej 27-29
Postbox 2595
DK-2100 Copenhagen Ø
Phone +45 35 29 84 00
Fax +45 35 29 84 99
www.dsi.dk · dsi@dsi.dk

DSI
Dansk Sundhedsinstitut

Danish Institute for Health Services Research/
Dansk Sundhedsinstitut
Dampfærgevej 27-29
Postboks 2595
DK-2100 København Ø
Denmark
Tlf. +45 35 29 84 00
Fax +45 35 29 84 99
www.dsi.dk · dsi@dsi.dk

ISBN 978-87-7488-684-6 (elektronic version)
DSI project No. 3112

Design: DSI

Preface

This report outlines the results of a study on the patterns of health care consumption, health care costs, and socioeconomic factors for 1.9 million patients in Denmark who suffer - or have suffered - from one or more pain-intensive diseases. The study is based on a comprehensive set of data for a period of 11 years (1998-2008) from a number of Danish registries.

The study has been undertaken by Jan Christensen and Lone Bilde from the Danish Institute for Health Services Research.

Researchers Anders Gustavsson, Christina Ljungkrantz and Brenda Gannon from i3Innovus have undertaken an equivalent study on the pain population in Västra Götaland in Sweden and drafted a first version of the protocol for the Danish study. Anders Gustavsson has reviewed and commented on this Danish analysis and study report.

Professor Dorte Gyrd-Hansen ACERH, University of Queensland & Health Economics Research Unit, University of Southern Denmark & The Danish Institute for Health Services Research has undertaken the internal review of the report at DSI.

The authors wish to thank the following advisors who have provided useful comments and have discussed a first draft of the report with us: Dr. Christian Kronborg and Dr. Christian F. Christiansen, University of Southern Denmark, and Specialist in General Practice, Dr. Med. Villy Meinicke Schmidt, Multidisciplinary Pain Team.

Also we thank the involved employees of Statistics Denmark, the Social Appeals Board, the Data Protection Agency, The Danish Medicines Agency, the National Board of Health, and the Ministry of Health for smooth and timely handling of data extraction logistics for this study. The study has received funding from Grünenthal Denmark Aps.

Jes Søgaard
Professor, Executive Director
Danish Institute for Health Services Research

Contents

List of Figures

Summary

Cross-country and country-specific studies of the epidemiology and cost of pain suggest that chronic pain is associated with increased health care costs, increased mortality, increased premature retirement from work, and days off work. Also, medical treatment of chronic pain is substantial, yet often insufficient or not optimal. A number of studies undertaken in Denmark support these findings. These studies have mainly been based on self-reported and/or patient record data and are based on relatively small study populations.

This is the first retrospective, longitudinal cohort study in Denmark on the epidemiology, health care resource use and societal costs of patients with pain-intensive diseases. A process of linking a clinical classification system algorithm to ICD-10 diagnoses in a German study resulted in the identification of a number of specific diagnoses relating to severe and chronic pain. Among many ICD-10 diagnoses, these diagnoses were found to be most likely at some point during the course of the disease to result in treatment with slow-release strong opioids. Slow-release strong opioids are indicated for the treatment of severe pain, when other treatment possibilities are exhausted, hence the attribute, "pain-intensive".

The diagnoses include many cancer diagnoses, arthritis and other musculoskeletal diagnoses, neuropathies, and post-traumatic fracture diagnoses, and non-specific chronic pain diagnoses.

The study is based on a comprehensive set of data from the National Patient Registry, the DRG and DAGS grouped National Patient Registry, the Health Care Reimbursement Scheme Registry, the Causes of Death Registry, the Register of Medicinal Product Statistics, the Coherent Social Statistics Database, the Income Registry, and the Social Appeals Board. Data from these registries on each of the included pain-intensive patients have been linked together for a follow-up time of eleven years.

The study aims to:

1) describe the included patients in terms of demographical and epidemiological parameters,
2) identify important drivers of costs in nine different pain-intensive patient groups,
3) estimate the societal cost related to the treatment of patients with pain-intensive diseases in Denmark and,
4) describe patterns of pharmacological treatment of pain.

Patients included in the study were admitted to a Danish hospital and registered in the National Patient Registry with at least one diagnosis requiring intensive pain treatment, between 1 January 1998 and 31 December 2007.

The inclusion criteria counted 66 pain-intensive diagnoses, which were stratified into nine main pain-intensive diagnosis groups for subsequent analysis. These groups were cancer, specific back conditions, inter-vertebral back disorders, arthritis, post-traumatic fractures, multi-morbidities, headaches, neuropathies, and other conditions associated with chronic pain.

The main results of the study are summarised here:

Epidemiology

More than 1.9 million patients were admitted to hospital with a pain-intensive diagnosis between 1998 and 2007. Of these 53.3% were women and 46.7% men. 14.4% of the included patients died during the study period. At the beginning of 2007, our study population constituted almost one third of the Danish population.

As to health care facility of inclusion, 52% of the patients were included in the study when visiting a hospital day care ambulatory. The vast majority of patients with specific back conditions (75%), intervertebral disc disorders (79%), arthritis (82%) and neuropathies (75.4%) were included in the study when visiting the hospital as day care ambulatory for diagnostics and/or treatment. Only post-traumatic fracture patients and cancer patients were mainly included as in-patients.

The average age of the study population at the time of inclusion was 46.4 years. The age distribution of the study population is different to that of the general Danish population with a relatively larger proportion of elderly. However, the study population also includes patients in work active ages as well as adolescents and children.

The standardised ratios of mortality (SMR) for patients in the nine pain-intensive diagnosis groups relative to that of the general population without the diagnosis show a substantially higher mortality in our study population. With the exception of patients diagnosed with intervertebral disorders (SMR = 1) and arthritis (SMR = 1.06), all members of the study population had a higher mortality in 2007 which was the last year of mortality data available. Cancer patients died 7.86 times as often as the general background population in 2007. Most patients did not have a second pain-intensive diagnosis belonging to another pain-intensive group than the one they were included with, during the rest of the study period. Of those who did have a second diagnosis, this was most often a non-specific pain diagnosis, and most rarely a headache diagnosis.

Healthcare costs

Publicly financed healthcare costs relating to in-patient and day care hospital admissions, out-patient visits and reimbursed, prescribed pain therapy including patient co-payments for the included patients were calculated from one year before the inclusion to two years after, and adjusted for mortality.

The patients with a cancer diagnosis had the highest healthcare costs during the year following the inclusion, DKK 208,830 on average per patient year, followed by the multi-morbid pain patients with DKK 94,085 per patient year. The patients with headache and non-specific pain diagnoses accounted for DKK 34,784 and 38,284 respectively, which were the lowest average costs per patient year among the nine diagnosis groups.

Hospital costs, including in-hospital medical treatment of pain, account for 89-97% of the average cost per patient year, and prescribed pain medication purchased at a pharmacy only for 1-3%, depending on diagnosis. Generally, healthcare costs are lowest before the inclusion, then peak tremendously during the month of inclusion, drop somewhat during the subsequent months, but remain higher than before the inclusion during the following 24 months. Posttraumatic fracture pain diagnoses are an exception to this, as their average costs reach the same level as before the inclusion after a couple of months.

In the table below, we estimated the total, average healthcare cost, which can be attributed to a patient, during the three years of follow-up for costs. "Baseline costs" corresponds to the level of costs 24-12 months before the inclusion in the study. Expectedly, a cancer patient has the highest healthcare costs, followed by a patient with multi-morbidity and a patient with specific back conditions.

Diagnosis group	Baseline costs	Year before inclusion	Year after inclusion	Year 2 after inclusion	Total costs, DKK
1 Cancer	22,992	18,495	185,531	57,722	261.748
2 Specific back conditions	23,933	6,974	33,436	9,445	49,855
3 Intervertebral disc disorders	14,633	3,305	34,285	9,203	46,793
4 Arthritis	13,733	2,183	28,267	7,326	37,776
5 Posttraumatic fractures	14,262	1,961	27,455	3,893	33,309
6 Multi-morbidities	35,458	16,519	58,061	9,602	84,182
7 Headaches	16,466	1,863	19,895	1,025	22,783
8 Neuropathies	22,628	8,751	33,978	5,310	48,039
9 Non-specific chronic pain	15,401	6,109	24,749	2,963	33,821

Looking at different calendar years, we find that the total health care costs per patient year after inclusion have increased during the four years 2003, 2004, 2005 and 2006 measured in 2010 prices, by approximately 8-12% for intervertebral disc disorders, posttraumatic fractures, headaches, arthritis, neuropathies, and other non-specific chronic pain conditions. Cancer, specific back conditions, and multi-morbidities remain almost at the same level as in 2003.

The increase for specific diagnoses groups comes from an increase in hospital costs only, and generally we see a shift in the cost distribution from in-patient to ambulatory day care costs. However, this finding does not take into account any shift in incident types of diagnoses, e.g. implying different resource use, and should therefore be interpreted with caution.

Medical treatment and prescription

During the study period, there has been a shift in the types of prescribed pain medication for our study persons, with large increases in prescriptions for oxycodone, fentanyl, and a decrease in prescribed morphine. Also, prescriptions for tramadol, paracetamol, and gabapentine increased.

At the same time, we find a decrease in the total number of prescription per thousand study persons in the year they were included, from 4,019 prescriptions in 1998 to 3,679 in 2001, and an increase again between 2002 and 2007 to approximately 4,000 prescriptions per thousand again.

The vast majority of the study population, 82%, released at least one pain therapy prescription at some point of time during the study period. Depending on the diagnosis group, 12-46% of the study persons released at least one slow-release strong opioid prescription, whereas 6-21% released at least one neuropathic pain prescription.

Patterns of prescribed slow-release strong opioid treatment and neuropathic pain treatment with regard to treatment duration, shift and add-on of treatment, discontinuation etc. have been analysed in the report.

Productivity losses

The prevalence and incidences of early retirement and long-term absence from work due to sickness are significantly higher in our study population than in the Danish background population. Approximately 60% of our 15-64 year old study population members experience at least one period of long-term absence from work due to sickness during the study period. The average number of weeks for study persons on sick leave allowance increases from approximately 5 weeks the year before to approximately 13 weeks in the year after inclusion in the study.

In 2007, 60% of the total Danish population who had at least one period of long-term sick leave were members of our study population. No data were available for short-term absence from work.

As to premature retirement from work, approximately 11% of our study population of work-active ages have been granted early retirement benefit due to a reduced ability to work, at some point during the study period.

This result confirms previous findings that pain and pain-intensive diseases imply long term absence from work due to sickness.

Annual disease-attributable costs of pain-intensive diseases

The total socio-economic of the pain-intensive diseases was estimated as the sum in Danish Kroner per calendar year of different types of costs which can be attributed to the pain intensive disease. This is the net cost of hospital services, primary care (out-patient) services, prescribed medicines, and net cost of productivity losses relating to absence from work due to sickness and premature retirement.

The table below shows the annual, disease-attributable costs in million DKK of the pain-intensive diagnoses. The patients with non-specific chronic pain incur most costs (DKK 8 billion), followed by arthritis (DKK 4.57 billion), and cancer (DKK 3.76 billion).

Total disease attributable costs in 2006 in mil. DKK 2010-prices	Healthcare	Long-term sick leave	Premature retirement	Total 2006
1 Cancer	2,924	791	46	3,761
2 Specific back conditions	1475	260	6	1,740
3 Intervertebral disc disorders	904	1,130	42	2,076
4 Arthritis	3,331	1,228	14	4,573
5 Posttraumatic fractures	1,346	455	0	1,801
6 Multi-morbidities	967	24	0	991
7 Headaches	404	158	3	565
8 Neuropathies	1,309	509	17	1,835
9 Non-specific chronic pain	5,440	2,582	31	8,053

A number of relevant cost items could not be included in the study; the most important in monetary terms being the cost borne by the municipalities, relating to home nursing, home help, medical aids, restructuring of homes etc. for the pain patients with a reduced ability to perform daily activities. The patients' own costs relating to treatment, e.g. physiotherapy and transport to treatment were not included either.

As approximately 70% of our patients have more than one of the pain-intensive diagnoses, and thus occur in more than one group, aggregating the numbers is not directly possible. However, assuming that 30% of the costs are double counted, we reach a total annual cost of DKK 17.8 billion. Healthcare accounts for DKK 12.8 billion, total productivity loss cost relating to long-term sick leave for 5 billion per year and total cost of the productivity loss relating to premature retirement of DKK 111 million.

As to healthcare costs, even in this careful and conservative estimate, they still account for 18-23% of the counties' net operational expenses for healthcare in 2006.

Comparison with similar studies

The inclusion criteria comprise 66 diagnoses which according to a German study were the most likely diagnoses to require treatment with slow-release strong opioids. The strong opioids are indicated as the last resort in the pharmacological treatment of severe pain after other pharmacological pain treatment has proved insufficient. 12-46% of the study population released at least one prescription for a slow-release strong opioid at a pharmacy at some point during the study period, and this figure does not include the opioids used during the patients' admission to hospital. Therefore, we cannot directly compare our findings with the German study. However, overall 82% of our study population used prescribed pain medication before or after hospital admission, and although the 66 diagnoses are very different from each other in terms of aetiology, epidemiology, course and cause of disease, acute pain versus chronic pain, they all involve treatment of (severe) pain at some point during the course of disease.

Despite methodological differences which make studies difficult to compare, overall, the study confirms previous findings on the epidemiology, patterns of health care, cost and socio-economic influence of diagnoses involving (chronic) pain. Other studies have found that health care costs are highest during the year of diagnosis and remain higher than before the inclusion, and this study supports this conclusion.

The challenges of measuring societal cost of pain-intensive diagnoses

The societal cost of pain-intensive diseases includes all types of resource consumption incurred as a consequence of the diseases, as well as potential productivity losses due to reduced ability to work.

Although the availability of Danish data on the individual patient is outstanding seen in an international perspective, there are still some important challenges of using the data as an indicator of the societal cost of pain-intensive diseases.

One important challenge relates to the trade-off between the sensitivity and specificity of the inclusion criteria. The precision of the cost estimate requires inclusion of all patients who at some point suffered from one or more of the pain-intensive diseases defined for the study.

The inclusion criteria applied in this study does not count patients who have never been admitted to a hospital, and although the long follow-up time of 11 years increases the likelihood that the chronic pain patient will have visited a hospital at some point, the omission of these patients is still a limitation in the study.

Also, and perhaps more importantly, the precision of the cost estimate requires exclusion of patients who have died or who may have been cured from the pain-intensive diseases, and exclusion of costs which are not related to the pain-intensive disease.

In order to address these issues, we adjusted our estimates for mortality. We used the patients' own historical levels of costs as a control for costs that would have been without the diagnosis. Also, we narrowed the follow-up time to three years, although pain-intensive diseases may persist with severe and disabling pain symptoms beyond the two years and perhaps even during a lifetime. Whether these follow-up times appropriately capture the costs associated with the pain-intensive diagnoses that triggered hospital admission and thereby inclusion in our study, will depend on the specific diagnosis and on the duration of the given illness. Finally, we used the friction cost method to value the production loss relating to premature retirement, which has resulted in a substantially lower cost estimate than the commonly used human capital method for assessment of production loss would have done.

These were all methodological choices to ensure that costs were not overestimated. We then ended up with a conservative, yet presumably robust estimate, of the cost relating to pain-intensive diseases in Denmark.

1. Introduction

Highlights introduction:

Cross-country and country-specific studies of the epidemiology and cost of pain suggest that chronic pain is associated with increased health care costs, increased mortality, increased premature retirement from work, and days off work. Also, medical treatment of chronic pain is substantial, yet often insufficient or not optimal. A number of studies undertaken in Denmark support these findings. These studies have mainly been based on self-reported and/or patient record data and are based on relatively small study populations.

In a cohort study design based on longitudinal data extracted from a number of national databases, this study aimed to estimate the societal cost and identify important cost drivers for patients with pain-intensive diseases in Denmark, and to describe patterns of health care resource use, income and productivity losses before and after the first admission to hospital with the pain-intensive diagnosis.

1.1 Background and Rationale

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (1). It is subjective in its nature and therefore ultimately defined by the person experiencing it. Pain can be classified into chronic and acute pain, differing mainly in the length of persistence (2). Chronic pain can be defined as pain that persists longer than the temporal course of natural healing, associated with a particular type of injury or disease process, typically 12 weeks, whereas acute pain may be defined as pain persisting less than 12 weeks (3).

Chronic pain is considered to be the third most common healthcare problem after heart disease and cancer with a substantial impact on quality of life and societal costs worldwide (4;5).

According to a large-scale survey on pain symptoms and self-reported diagnoses, impact on daily life and treatment of non-malignant chronic pain, chronic pain of moderate to severe intensity occurs in 19% of adult Europeans. This seriously affects the quality of their social and working lives and the ability to perform daily activities. The analysis is based upon respondents from 15 European countries and Israel. The prevalence in Denmark was estimated at 16%, and 61% of the chronic pain sufferers reported that their pain was inadequately managed. The study also found that 29% of the Danish respondents who experienced chronic pain lost their job due to their chronic pain, and this proportion was larger than what was observed in most of the other countries (6).

Eriksen et al performed two studies on the epidemiology and health care utilisation of patients with chronic non-malignant pain in Denmark. In the observational study (N=2,649) (7) and the national surveys of self-reported health (N=6,000 in 1994 and 16,684 in 2000) (8) the estimated prevalence of chronic non-cancer pain was 19% and 20% respectively, with an incidence of 1.8% per year. According to these studies, risk factors for having chronic pain and for developing chronic pain are female gender, low educational status and poor self-rated health and age.

Also, individuals reporting long-lasting pain visit primary care providers almost twice as often as respondents not reporting long-lasting pain, i.e. 12.8 annual visits to primary care providers compared

with 7.8 for controls. The annual number of working days in Denmark lost due to chronic pain is estimated at about 1,000,000 (8).

A study of the long-term socio-economic consequences of chronic non-malignant pain based on patient-reported data and national registry data from 204 patients on the waiting list for treatment at the multi-disciplinary pain clinic in the past County of Funen found that health care costs are particularly high during the first year after pain onset and remain high compared with health care costs before the onset of pain (9).

As the prevalence increases with age, the societal costs are expected to increase in parallel to the increasing proportion of elderly. These include both health care costs and to a much greater extent indirect costs from lost productivity due to sick leave and early retirement from work (5).

Chronic pain is often insufficiently treated due to side-effects causing patients to discontinue effective treatment. Better treatment options may lower the societal costs from chronic pain and increase the quality of life of sufferers. Evidence is needed on treatment patterns, side-effects, costs of care and quality of life of different patients in clinical practice suffering from chronic pain. This would help to understand how improvements can be made in relation to the treatment of pain, e.g. by identifying priority areas and links between treatment patterns and costs as well as quality of life.

For cancer pain, the three-step WHO Analgesic Ladder is generally accepted as guidance on the medical treatment of pain relief (9). The ladder suggests that the strength of the analgesic should be linked to the severity of the pain. That is, mild pain should be treated with paracetamol or a non-steroidal anti-inflammatory drug (NSAID), while opioids (e.g. Morphine, Oxycodone and Fentanyl) should only be used in managing severe pain (4;7;10).

Patients on treatment with analgesics are commonly burdened by side effects such as respiratory depression, sedation, drowsiness, dry mouth, myosis, pruritus, constipation, nausea, vomiting and urinary retention (11). This implies a problem with adherence and compliance as some patients prefer the pain to burdensome side effects.

Also, there are some studies about opioid pain management of chronic pain. Thomsen et al did a study on opioid rotation, in which the aim was to improve the analgesic effect, get a better pain control and reduce side effects. The study described two different types of opioid rotation in chronic non-malignant pain patients: 1) rotation from short-acting opioids (SAO) to long-acting opioids (LAO) to establish stable analgesia in order to minimise withdrawal symptoms, risk of tolerance and addiction and 2) rotation between different LAO to improve alleviation of pain and reduce side effects. Insufficient analgesic effect was the most important reason for rotation. Opioid rotations between different LAO resulted in better pain control and fewer side effects at dose levels predicted to be equi-analgesic (equivalent alleviation of pain). The majority of patients who rotated from SAO to LAO obtained improved analgesic effect through the uptitration, but the cost was a near doubling (1;10) since the opioid dose had to be adjusted upwards to achieve a higher and more adequate efficacy and hence better pain control.

Hamunen et al (1;11) used national registry data to examine the consumption of opioids in the Nordic countries from 2002 to 2006. They estimated the consumption of the most common weak and strong opioids at 21 (17 weak and 4 strong) daily defined doses per 1,000 inhabitants per day. Denmark was the greatest consumer of strong opioids (about 10 DDD/1000 inhabitants/day), while Finland had the lowest of the Nordic countries (1.7-2.6 DDD/1000 inhabitants/day). Danish patients consumed the least weak opioids (9.4-12.1 DDD/1000 inhabitants/day), while Sweden demonstrated the greatest level of consumption (21.7-17.3 DDD/1000 inhabitants/day).

Furthermore, this study also showed that the use of Oxycodone (strong opioids) increased by 300% in Denmark during the years 2002-2006. The overall consumption of opioid analgesics in Denmark was relatively stable with an increase of 4% during the five year period (11).

In an international context, the Danish comprehensive administrative registries provide an ideal opportunity for studying patient populations and health care consumption patterns based on registry data with a high internal validity (12;13). Due to the existence of a personal identification code, every entry in the Danish registries has a reference to a specific person. Thereby, in principle, the use of health care and social services for each individual person, as well as for the entire population, can be traced through the registries.

In our initial literature search, we identified a number of studies on the epidemiology, resource use and socio-economic cost of pain based on relatively small sample sizes. This is the first attempt to study patients with pain-intensive diagnoses based on large-scale retrospective data analysis of the epidemiology, resource use and socio-economic cost of pain-related diseases in Denmark, including the consumption of prescribed pain medication.

Although it would be desirable to document the societal burden of chronic pain, it is difficult to isolate the chronic pain component from other disease symptoms in a study using common cost-of-illness design methods such as diagnosis specific cost calculation, cohort analysis or a case-control approaches. Therefore, there is a need to develop a valid design concept and method specifically in order to assess the socio-economic consequences of pain.

This study is a first step towards this concept development, and aims to describe treatment patterns, health care costs and productivity consequences for patients with diseases during which there may be several episodes of severe, often chronic and disabling pain.

1.2 Study objectives

The aims of this study are to:

- describe the included patients in terms of demographical and epidemiological parameters,
- identify important drivers of costs in nine different pain-intensive patient groups,
- estimate the societal cost related to the treatment of patients with pain-intensive diseases in Denmark and,
- describe patterns of pharmacological treatment of pain.

1.3 Study questions

The following questions will be addressed in the report:

Epidemiology and demographics

- What is the number, age and gender distribution of patients included in the study?
- What is the prevalence and annual incidence of pain-intensive diagnoses?
- What is the mortality of the included patients – and standardised mortality ratio vis à vis the mortality rate of the background population not included in the study?
- How is the distribution of included patients in the nine diagnosis groups?
- At which hospital facility was the patient included in the study (hospital day care ambulatory or inpatient departments?)

Resource use and costs

- What is the net socio-economic cost in Danish Kroner (2010 prices) of treating patients with a pain-intensive diagnosis when comparing periods before and after inclusion (9 main diagnosis groups)?
- How are these costs distributed across different health care resources and does the distribution change over time?
- How do the costs for the individual patient develop over time, before and after inclusion?
- What are the incidences of long-term absence from work due to sickness and premature retirement of patients with a pain-intensive disease, and what is the associated socio-economic cost in Danish Kroner (2010 prices) of the resulting loss of work productivity?
- How do the costs develop over time, before and after the first pain prescription and depending on treatment continuation?

Treatment patterns

The following will be described for slow-release strong opioid and neuropathic drug consumption respectively:

- What is the distribution across different compounds of the patients' first/second/third prescription?
- What are the proportions of patients continuing on their first/second/third prescription over time?
- To what compound are patients switching?
- What are the strengths (mg/ml) of the compounds prescribed over time?
- What other pain medications are prescribed before and after the first (slow-release strong opioid/neuropathic pain prescription?
- How do the treatment patterns differ between patients with/without a diagnosis of cancer/neuropathic pain?
- Who is the prescriber? (General practitioner, hospital specialist, out-patient specialist, dentist)

1.4 Report outline

The report follows the structure of a scientific paper: After a report summary, chapter one contains the introduction outlining the rationale and aims of the analysis. Chapter two describes sources and extraction of data, analytical methods used, and patient inclusion criteria. Chapter three outlines the epidemiological and demographic results, chapter four the analysis of pain medication treatment patterns. Chapter five looks at health care costs, and chapter six at productivity losses relating to pain-intensive diseases and their consequent costs. Finally, chapter seven contains an overview of the total annual socio-economic costs and chapter eight a discussion of the study methods and results. The appendices contain a list of the pain-intensive diagnoses (appendix 1), ATC codes (appendix 2) and definitions of treatment patterns of the drugs included (appendix 3), slow-release strong opioid and neuropathic pain medication prescription patterns (appendix 4), and costs over time by main diagnosis groups (appendix 5), cost over time for slow-release strong opioid users (appendix 6), and neuropathic pain medication users (appendix 7).

2. Data and Methods

Highlights data and methods:

This study was designed as a retrospective cohort study of treatment patterns and health care costs, mortality, productivity, and income development of patients admitted to a Danish hospital and registered in the National Patient Registry with a pain-intensive diagnosis during 1998-2007. The pain-intensive diagnoses used as inclusion criteria were defined in a German study using a clinical classification system algorithm linking usage of strong analgesia to ICD 10 diagnoses. Data were extracted from the National Patient Registry, the DRG and DAGS grouped National Patient Registry, the Health Care Reimbursement Scheme Registry, the Causes of Death Registry, the Register of Medicinal Products Statistics, the Coherent Social Database, and the Early Retirement Registry from the National Board of Social Appeals.

Disease-attributable healthcare costs and productivity losses in Danish Kroner were assessed using historical controls, and prevalence-based, annual societal costs were derived for the incident patient cases included within a time window of three years.

2.1 Study design

This study is designed as a retrospective cohort study of treatment patterns and health care costs, mortality, productivity, and income development of patients admitted to a Danish hospital with a pain-intensive diagnosis during 1998-2007. This period is referred to as "inclusion period". The pain-intensive diagnoses used as inclusion criteria have been defined using a clinical classification system algorithm linking usage of strong analgesia to ICD 10 diagnoses (14).

Data sources

The study is based on data from the registries described below. Availability of data from the different registers differs with respect to the years covered within the period from 1998 to 2008, which however is referred to as "the study period".

The National Patient Registry contains information about hospital admissions and discharges, including in-patient and day case, ambulatory care, length of stay and a recording of SKS procedural codes[1] to describe the patient pathway in the hospital. In addition, the registry has a recording of diagnoses based on the ICD 10 classification. Data from this registry will be available for the entire study period and will be used in identifying and selecting the patients with the defined inclusion diagnoses.

The DRG and DAGS grouped National Patient Registry groups the patients in different diagnosis-related groups (DRG), defined as resource-homogeneous. DRG-groups for in-patients, and DAGS[2] groups for hospital day cases. For each DRG/DAGS group, a DRG/DAGS tariff has been attached. This tariff represents the average treatment costs from all individual patients in the same group, based on cost accounting information from the hospitals two years before. Data from this registry will be availa-

[1] SKS = Sygehusklassifikationssystem
[2] Dansk Ambulant Grupperings System (DAGS)

ble from 2002-2008 and will provide the hospital cost relating to each admission, in-patient or day care admission.

The Health Care Reimbursement Scheme Registry contains information on the individual use of primary health care services, contact to general practitioners and other primary care specialists, reimbursement information and fees. This register does not contain information on diagnoses. Activity data from this registry are included 1998-2008, and cost data from the registry from 2002-2008.

The Causes of Death Registry has a recording of all deaths in Denmark and the underlying causes of death. Data on actual death dates (not causes) for study persons between 1998 and 2007 (inclusion period) has been included from this registry.

Data on use of prescription drugs has been collected from the **Register of Medicinal Product Statistics** held by the Danish Medicines Agency. This registry contains information on individual sales of medicinal products in Denmark since 1994 and covers 5.4 million registered Danes and has 300 million registered recipes. Data from this registry on the prescription of pain therapy for the study population, the prescriber, the strengths and pharmacy sales price, based on ATC codes are included in the study period, 1998-2008. The sales prices will be used for the period 2002-2008 only to match the available cost data from the other registries. Over the counter sales and non-pain therapy prescribed medicine are not included in the study. The cost of drugs prescribed and used during hospital stays are with a few exceptions included in the DRG/DAGS cost. However, it is not possible to separate the hospital drug cost from the data available in the registry.

The Coherent Social Statistics Database contains information on pensions and transfer incomes to the Danish population. Data from this database provides the incidences and periods of long-term sick-leave allowances. Data are available for the entire study period, 1998-2008.

The Early Retirement Registry from the Social Appeals Board contains information on allowances for early retirement and data are available from 1998-2008 and will be used as an indicator of incidences of early retirement in the study population.

Data extraction

The analysis is based on retrospective data from an 11 year period extracted from a number of Danish national registries and linked together using the personal identification code. This enables us to get a full picture of the patterns of care and resource use of the individual patient. Patients were included during 1998-2007 and data for costs and health care resources are available for the years 2002 to 2008. Data for pain medication prescription patterns were available from 1998-2008.

The data extraction was organised as a research project at the Statistics Denmark and includes data from the National Patient Registry, the DRGs and DAGs grouped Patient Registry, The National Health Insurance Registry, The Register of Medicinal Products, the Cause of Death Registry, the Coherent Social Statistics database, the Income and Education Registries, and data from the Social Appeals Board on early retirements. 2007 was the latest year of the National Patients Registry data available for research projects at Statistics Denmark at the time of data extraction. This means that patients meeting the inclusion criteria between 1998 and 2007 both inclusive have been included, whereas patients eligible for the study after 2007 are not included.

Inclusion criteria and censoring of data

Pain algorithm

The inclusion criteria and the methods to select and stratify patients into cohorts of patients with pain-intensive diagnoses are developed from a study on German data (1;14) whose rationale originates from the lack of possibility to identify pain patients in the current ICD 10 diagnosis classification system. From a sickness fund registry,"Deutschen Angestellten Krankenkasse", all patients who had received at least two opioid prescriptions in 2006 were compared with a randomly selected control group of patients of the same number, gender and age composition as the case group, but who had neither received prescriptions for opioids nor for any other analgetica. Using univariate regression analyses, the three digit ICD 10 diagnoses in the two groups were then compared, and diagnoses in the case group with an odds ratio of 2 or more were selected for further analysis. This process resulted in 661 ICD 10 diagnoses which were at least twice as frequent in the case (opioid) group as in the control group. Second, these diagnoses were grouped into 166 CCS diagnoses using the Clinical Classification Software which allocates combinations of ICD10 diagnoses to primary diagnoses of origin. Third, the CCS diagnosis with the largest proportion of patients on opioid therapy was identified and used to split the sample in two (with and without the diagnosis).

In each of the two new subsamples another CCS diagnosis (again the one with the largest proportion of patients on pain therapy) was identified and used to create new subsamples. This process was reiterated until no more CCS diagnosis with an increased proportion of patients on pain therapy could be identified. This analysis resulted in 28 identified CCS diagnoses which were clustered into 9 CCS diagnosis groups, or "pain types" to which 77.1% of all patients with at least two opioid prescriptions in the German sickness fund could be allocated.

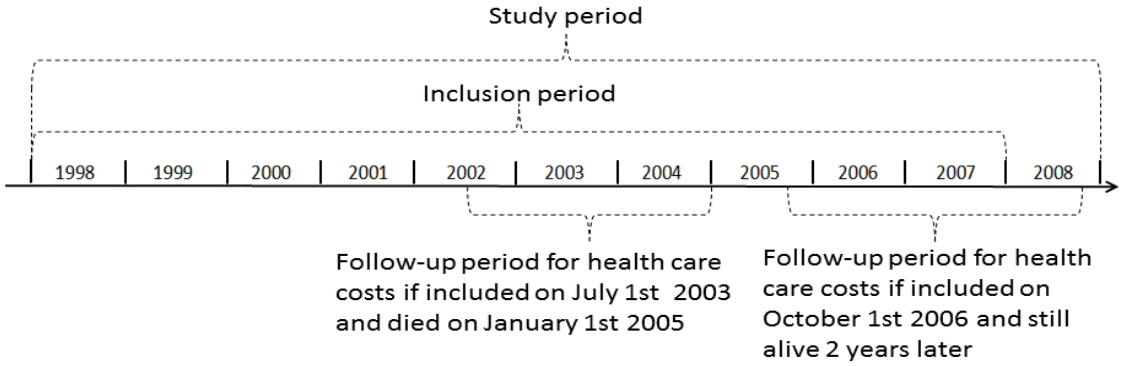
Inclusion criteria and censoring

The algorithm was used to select the pain-intensive ICD10 diagnoses and stratify them in nine groups. For the German subgroup system to better fit into the Danish setting, a Danish enriched version including some missing diagnoses was developed based on local clinical expert guidance.

The ICD 10 diagnoses included are listed in appendix 1. Patients who were admitted to hospital with at least one of these diagnoses – be that as primary or secondary diagnosis – at some point of time during 1998-2007 - were included in the pain intensive study population. These patients were then studied until the end of the study period or death within the study period.

The follow-up time for including health resource use and costs for each individual included patients is one year before the date of inclusion to two years after inclusion. Due to limitations of data availability, time window for costs can go no longer back than 1 January 2002 and no longer forward than 31 December 2008. If the patient dies within that time frame, the follow-up time ends at the time of death. The follow-up period is shown in the figure below with 2 patient examples. Follow-up on healthcare costs for the patient who is included in 2003 and dies on 1st January 2005 will be medio 2002 to 31 December 2004, and for the patient who is included in October 2006 and still alive when the study period ends, costs will be followed up from October 2006 to October 2008.

Figure 2-1: Inclusion of patients and censoring – examples of follow-up period for 2 patients



Sample size and statistical analysis

The study is based on a total count of patients in Denmark meeting the inclusion criteria, and therefore, *per definition* no statistical analysis addressing the representativity of the Danish population is required. Also, since all analyses are provided with a descriptive aim, no statistical analyses, e.g. testing for trends, will be included.

2.2 Analysis

Standardised mortality ratios

Standardised mortality rates (SMR) (19) show the difference in mortality in the study population and the background population.

Generally, SMRs are calculated as:

$$\text{SMR} = \text{O/E} = \frac{\text{Observed number of deaths in the diagnosis group}}{\text{Expected deaths in the diagnosis group}}$$

The **observed number** of deaths O for a given year is calculated as the number of persons who are

1. included in the study population in that particular year or earlier, and
2. died in that particular year.

The **expected number of deaths** is calculated as: E = (death rate in the rest of the population)* (the number of persons in the study population at risk).

The number of persons at risk is calculated for each year as the sum of persons who:

1. are included in the study population in previous years and have survived until and including the preceding year, or
2. are included in the study population in the year in question, counted with a weight reflecting the proportion of the year in which they were included (for example, a person included on April 1st is only counted for 9 months of the year and therefore weighing .75 or 75%).

The mortality rate in the background population is calculated using statistics for each year on the population and deaths of the total population in Denmark and subtracting the study population: (deaths in the total population – deaths in the study population)/(number of persons in the total population-number of persons at risk).

The study population has a different age and gender composition than the background population. Therefore, calculations of the observed and expected number of deaths are performed across different gender and age strata.

Regarding newborns, unfortunately no statistics are available on the number of deaths within the year of birth. With the data available, it is not possible to calculate the expected number of deaths for newborns. Therefore, they are excluded from the calculation of the SMR's. In the overall picture, they account for a small proportion of the study population, implying that excluding them from the calculations does not significantly affect the results.

Calculating the Costs of Care

Societal costs included in this study are represented by public health care costs relating to somatic hospital treatment, visit to out-patient providers (GPs, specialists, physiotherapists, chiropodists, psychologists etc.), public reimbursement of pain therapy drugs and the patient co-payment. Also productivity losses, representing the alternative cost to society of not being able to work due to premature retirement or long-term sickness, are included.

Healthcare unit costs

Monthly and annual health care costs are usually calculated by multiplying the number of resources used in each period by the corresponding unit costs. However, as valid and patient specific cost estimates are already available from the registries, the actual unit costs have been extracted directly from the registries for this analysis.

For in-patient care and hospital day cases, the DRG and DAGS tariffs represent the cost of hospital treatment, including the medical treatment at the hospital. They are calculated as the average of patient-related treatment costs and hospital indirect costs based on data from all hospitals. This means that sometimes they overestimate the specific treatment costs and sometimes underestimate. However, they are calculated so that when aggregated for all hospital activity, they correspond to the total cost of producing the service (zero-sum game) and are therefore considered valid as unit costs in the large patient population anticipated.

For out-patient visits, the actual (gross) fees paid to out-patient providers such as general practitioners, out-patient specialists and physiotherapists have been used to cost the resource use.

For prescribed pain medication outside the hospital, the pharmacy retail price will constitute the societal cost. This price includes the patient co-payment.

Health care costs are adjusted to 2010 prices using an index based on the average wage of nurses, approximating development of health care costs. The index is calculated using wages from Statistics Denmark – table LON36.

It should be noted that the analysis does not contain data on the cost of treatment in a mental hospital/mental care hospital department, or cost of prescribed medicines which is not pain-related.

Indirect costs

Generally, two methods for assessing indirect costs are applied in cost-of-illness studies: the "human capital approach" (15), and the "friction cost method" (16). In the human capital approach, productivity loss to society due to a disease is represented by the present value of future losses of income because of cease or absence from work. However, this method assumes that the production loss persists for the duration of a person's life expectancy or until the disease is cured. The friction cost method (16), takes into account that in a situation with a certain level of unemployment, it may be reasonable

to assume that after a certain period, "the friction period", of absence from work, the sick, retired or dead person can be fully substituted by another person, and therefore the productivity loss ceases to exist. In this study, to be conservative, we therefore apply the friction cost method and assume a friction period of three months from the day of early retirement. For long-term disease absence from work we assume that the entire period implies a production loss.

Friction costs will be calculated using the disease attributable incidences (see section below) of early retirement and long-term disease absence multiplied by the average personal income for men and women in 2006 of DKK 296,961 (17). This will provide an estimate of the productivity loss to employers and society due to long term sickness of our incident pain-intensive patient population.

Generally, the overall incidences of long term sick-leave allowances and early retirement from work one year before the inclusion will be followed and described through 2008-2009 or to death, whereas their costs will only be included from one year before to two years after the inclusion – the approach used for health care costs as well. Although the indirect cost of premature death due to a pain-intensive disease may also be relevant, it has been omitted as the cause-relationship between the pain elements of the pain-intensive diseases and death is impossible to establish for this type of study and very heterogeneous patient population.

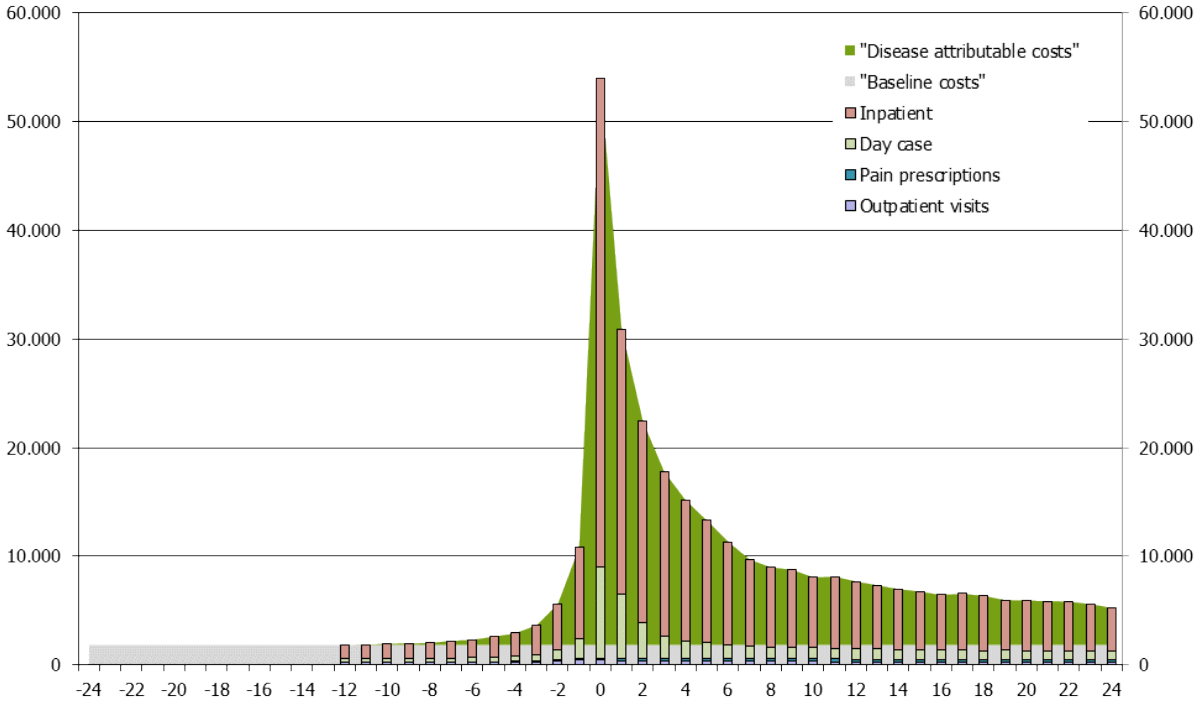
Incidence-based disease-attributable costs

In the absence of the possibility to select a proper control group from the background population, the patients' own historical level of costs, denoted "baseline costs", is used in the analysis to represent the level of costs which would have been, had the patient not had the pain-intensive diagnosis. The difference between the total costs incurred by the patients and the baseline costs is defined as the "disease-attributable costs".

The total societal, disease-attributable cost of the pain-intensive diseases is then the sum in Danish Kroner per calendar year - and per patient year respectively - of different types of costs which can be attributed to the pain-intensive disease, that is the net cost of hospital services, primary care (out-patient) services, prescribed medicines, and net cost of productivity losses relating to absence from work due to sickness and premature retirement.

The figure below illustrates the method with monthly healthcare costs for cancer patients as an example (see appendix 4). The baseline level is approximated by the level of costs experienced at month 12 before the patient's admission to ambulatory or inpatient hospital care which is our inclusion criteria. To arrive at annual baseline costs, we multiply the level of health care costs at months – 12 by 12. The month of the hospital visit by which the patient is included in the study corresponds to month 0 in the figure. Illustrated by the grey area in the figure, baseline costs are assumed to remain constant during the period considered relevant for the cost assessment. Health care costs (in green) above the baseline are assumed to be implied by the pain-intensive diagnosis.

Figure 2-2: Baseline costs and disease-attributable costs, DKK per month, cancer patients



The model illustrates that for the cancer diagnoses, health care costs start to increase already 6-8 months before the patient visits the hospital. Therefore it seems reasonable to assume that for the cancer diagnoses, costs relating to a certain period before the hospital visit are also "disease-attributable", and that as far as the entire patient population is concerned, the relevance of including costs before the hospital visit will be highly dependent on the diagnosis. For the arthritis group, which includes chronic diseases, it may be reasonable to include costs for a long period before the hospital visit, whereas for post-traumatic fracture patients, the period should be very short, as the patient is generally admitted to hospital right after the incidence. For simplicity, the "baseline" level for all patients was assumed to be month – 12 before the inclusion.

After the hospital admission in month 0, the analysis is restricted to a limited time horizon of 2 years. Around the time of inclusion, where the disease has led to a hospital visit it seems reasonable to attribute costs above the baseline to the disease. A certain proportion of the patients can be expected to be either cured from the pain-intensive disease e.g. after surgery, or they may die, whereas other patients are not cured and the condition remains. However, it is not possible, given the heterogeneous nature of the patient population of the study, to build in reasonable assumptions in the study about the duration of the disease for the different diagnoses. Therefore, to minimize the risk of including costs of patients who have been cured after a certain period of treatment, the assumption in the study is then that pain-intensive diseases last only three years – one year before the hospital admission and two years after, and the analysis of costs relating to the individual patient has been restricted to this period. This will give us a conservative estimate of costs.

From incidence-based to prevalence-based socio-economic costs

In order to estimate the annual socio-economic costs in Danish Kroner in a calendar year of the pain-intensive patient population, we aggregate the disease-attributable costs described above for patients who were included in the study (first hospital visit) 24-12 months before the calendar year or in the

calendar year itself. To illustrate this method, a cross sectional view of 2006 of healthcare costs for cancer patients is provided. The following costs (see section above) are aggregated in the calculations:

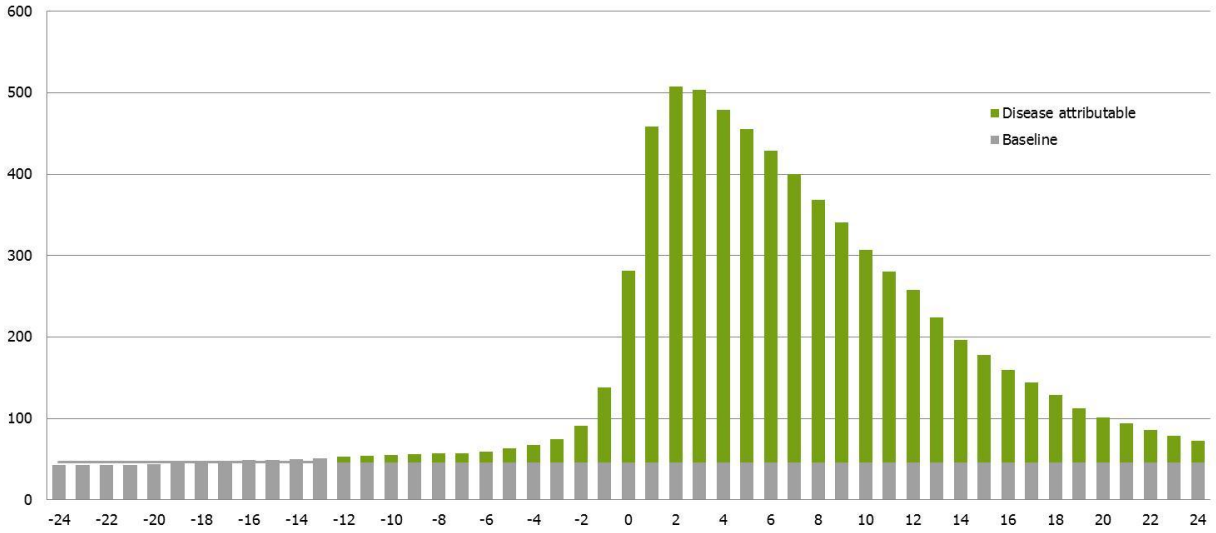
- Net disease-attributable costs for patients included in 2006 reflect the cost level before the inclusion and part of the level after.
- Net disease-attributable costs for patients included in 2005, reflect the cost level in the year following the inclusion.
- Net disease-attributable costs for patients included in 2004 reflect the subsequent cost level in year 2 after the inclusion.

Table 2-1: From incidence-based to prevalence-based costs in 2006, cancer patients, mil. DKK

Total disease-attributable costs in 2006 in mil. DKK 2010-prices	Cross section characteristic of the 2006 population at the beginning of 2006			Total for the diagnosis group
	Costs for patients included in 2006	Costs for patients included in 2005	Costs for patients included in 2004	
1 Cancer	1.368	1.064	492	2.924

For long-term sick-leave and premature retirement, the disease-attributable incidences are estimated first, as exemplified in the figure for long-term sick-leave below.

Figure 2-3: Long-term sick-leave cancer patients – months per 1,000 at risk. Baseline and disease attributable sick leave



To arrive at the prevalence-based months on long-term sick-leave in one calendar year, we then aggregate the following figures:

- Total net disease-attributable long-term sick-leave in months for patients included in 2006 to reflect the level before the inclusion (month 0 in figure) and part of the level after
- Total net disease-attributable long-term sick-leave in months for patients included in 2005, to reflect the level of sick-leave in the year following the inclusion.

- Total net disease-attributable long-term sick-leave in months for patients included in 2004 to reflect the subsequent post-diagnosis sick leave, in year 2 after the inclusion.

Censored data

In the study, we include data for patients from the date of inclusion after 1 January 1998 to the end of 2008. Some of the patients die before 2008, and naturally the time period for data coverage is shorter. Health care costs will therefore be calculated as average costs per patient year.

Stratification

The included patients will be stratified according to nine diagnosis groups representing nine potential causes of chronic pain using an algorithm developed and validated in Germany and adapted to the Danish situation (14). Resource use data are available from 1998 and onwards and (hospital) cost data from 2002 to 2008. For patients included 1 January 1999 and after, resource use is included one year back from the inclusion. Stratification of costs and cross tabulation by diagnosis group will be made on the time (year of) inclusion.

Further stratification will be conducted according to specific pain prescriptions of drugs, according the WHO ladder step 3 as defined in the appendix.

Drug therapy treatment patterns

The report includes an analysis of the patterns of pain therapy prescribed to our study persons before and after the inclusion in the study at a hospital site. Specifically, as strong opioids are indicated (WHO and the Institute for Rational Pharmacotherapy in Denmark) for the treatment of severe pain when treatment with other, and weaker analgesia are exhausted and/or insufficient, these prescription patterns are relevant for the identification of severe pain episodes with our study population. Also there will be a separate analysis of treatment patterns with medicines for treatment of neuropathic pain.

3. Epidemiology and Demographics

Highlights epidemiology and demographics:

More than 1.9 million patients were admitted to hospital with a pain-intensive diagnosis between 1998 and 2007.

By far, most of the patients were included when visiting a hospital ambulatory for diagnostics or treatment, as day care patients.

The average age of the study population at the time of inclusion was 46.4 years. The age distribution of the study population is different to that of the general Danish population with a relatively larger proportion of elderly.

Measured at the beginning of 2007, the study population constituted 31% of the total Danish population.

With the exception of patients diagnosed with intervertebral disc disorders and arthritis, all members of the study population had a substantially higher mortality than the background population without the pain-intensive diseases. E.g. cancer patients died 7.86 times as often as the general background population in 2007.

Most patients (70%) did not have a second pain-intensive diagnosis belonging to another pain-intensive group than the one they were included with. Of those who did have a second diagnosis, this was most often a non-specific pain diagnosis, and most rarely a headache diagnosis.

3.1 Descriptive Statistics

Description of the data Set

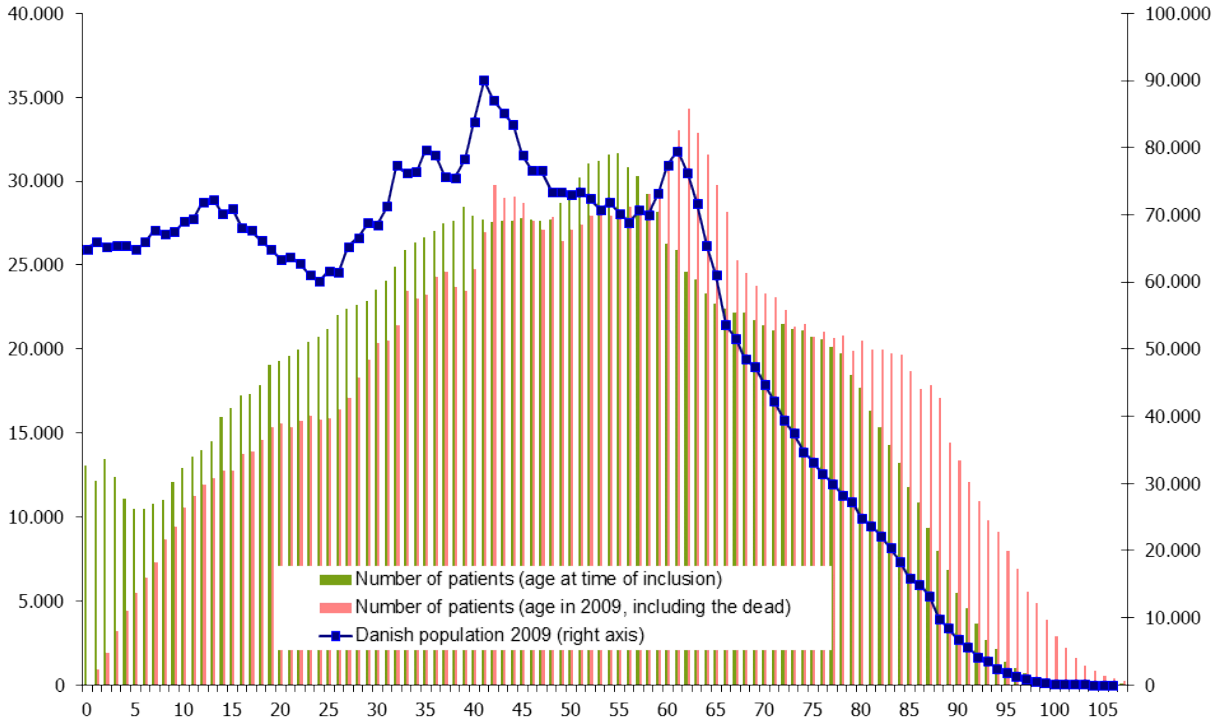
A total of 1,918,823 individuals were admitted to hospital in Denmark with one or more of the pain-intensive diagnoses at some point of time between 1998 and 2007, and were included in the study. Of these, 53.3% were women, and 46.7% men. Of the study population 14.4%, or 277,129 persons, died during the study period. At the beginning of 2007, the study population amounted to 1,667,463 patients, or 31% of the total Danish population.

1,572,943 persons or 82% of the study population released a prescription for pain medication during the follow-up period. Health care costs of the study population were included from 2002 to 2008.

Demographics

Figure 3-1 below compares the actual age of the study population individuals when they were included (numbers in left axis) with the age distribution of the total Danish population in 2009 (numbers in right axis). Although the scales are different, as the general population is almost four times larger than the study population, the age distributions can be compared. The figure shows that the study population is relatively older than the general population.

Figure 3-1: Age distribution of included patients compared with general population



The mean age at the time of inclusion was 46.4 years.

105,045 patients, or 5.4% of the study population, were under 9 years of age at the time of inclusion. An analysis of the inclusion diagnoses shows that more than three quarters of children were included in the study with post-fracture pain or with other, non-specific pain diagnoses.

Table 3-1: Number of patients included, death and net study population per year

Year	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
No. included	261,094	226,564	205,736	190,781	186,952	176,551	174,991	170,932	163,386	161,836	1,918,823
No. of deaths	14,204	20,048	23,619	26,352	28,704	30,262	31,278	32,431	34,462	35,769	277,129
Study population	261,094	473,454	659,142	826,304	986,904	1,134,751	1,279,480	1,419,134	1,550,089	1,677,463	

In table 3-1 above, the study population in 2007 and the total number of deaths do not add up to the total number of included patients. The difference amounts to 35,769 patients and is due to the fact that patients dying in 2007 are part of the study population in 2007, but are also included in the total number of deaths.

Figure 3-2 below shows the number of patients according to their inclusion diagnosis. By far the largest group is the non-specific pain group counting almost 1.1 million patients. The second largest group contains 547,000 patients who were included with arthritis. The cancer group counts 201,000 patients.

Figure 3-2: Number of patients per diagnosis group

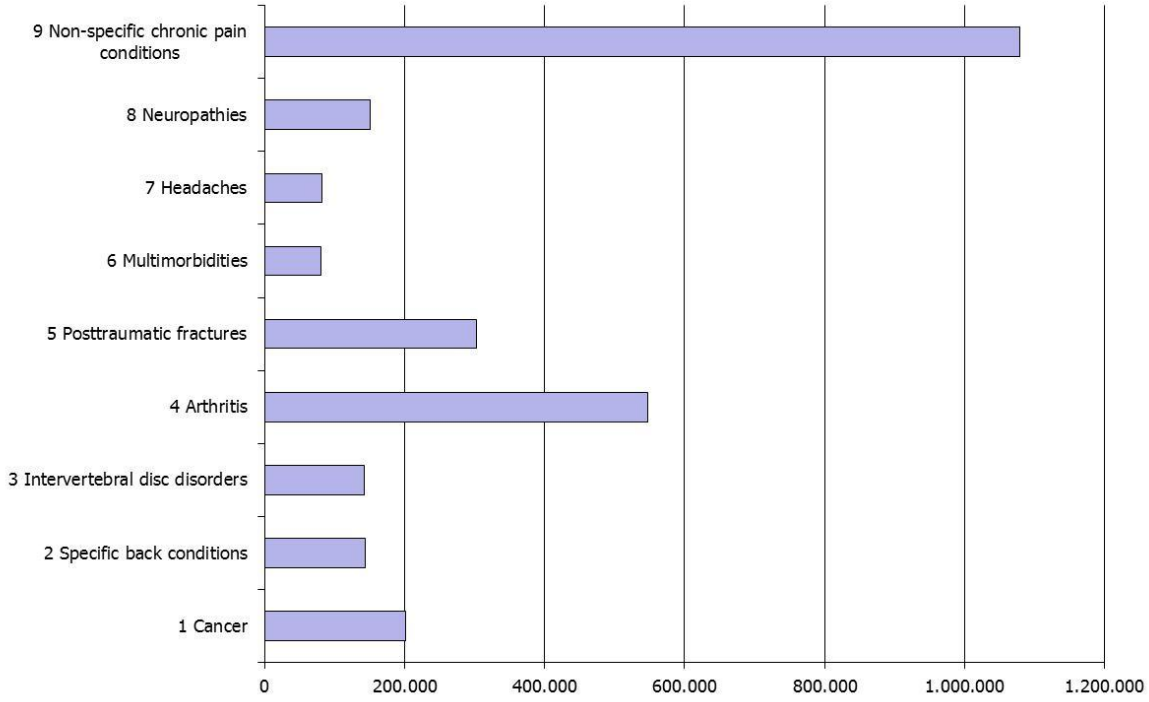


Table 3-2 below shows the number of patients by diagnosis group, the number and proportion of men, and deaths within the study period. The proportions of deaths were particularly high in the cancer group and in the multi-morbidity group.

The majority of patients (51.7%) were included in hospital ambulatory day care as their first point of hospital contact. The ambulatory day care departments in Denmark undertake a wide range of diagnostic, surgical and control procedures and medical treatment for e.g. arthritis patients. Especially patients with back conditions (75.2%), intervertebral disc disorders (79.1%), arthritis (81.9%) and neuropathies (75.4%) are included as ambulatory day care patients, whereas, as can be expected, patients with cancer and fractures are mainly included as in-patients.

Table 3-2: Number and proportions of included patients by diagnosis group, in ambulatory day care, men, and deaths within study period

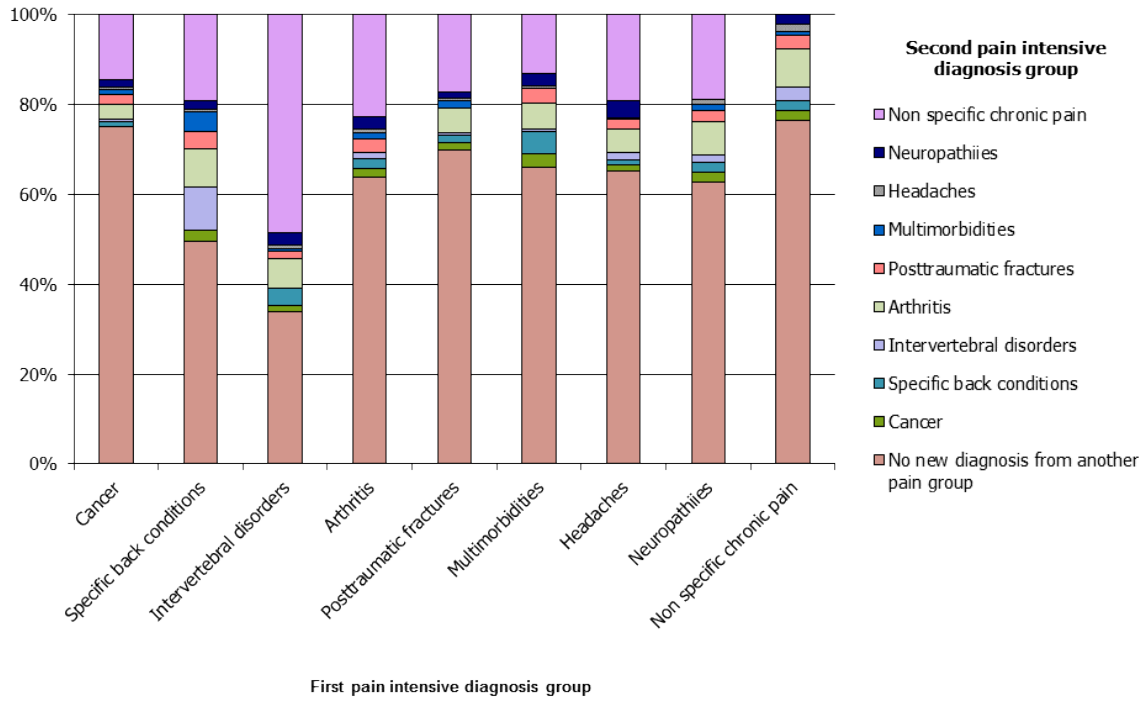
Disease group	Total	No. included in ambulatory day care	%	No. men	%	No. Deaths	%
0 Full sample	1,918,823	992,572	51.7%	896,865	46.7%	277,129	14.4%
1 Cancer	201,941	71,572	35.4%	105,520	52.3%	128,593	63.7%
2 Specific back conditions	143,921	108,287	75.2%	41,119	28.6%	24,969	17.3%
3 Intervertebral disc disorders	143,173	113,226	79.1%	71,443	49.9%	8,986	6.3%
4 Arthritis	547,107	448,210	81.9%	254,162	46.5%	53,956	9.9%
5 Posttraumatic fractures	302,233	36,126	12.0%	155,067	51.3%	46,943	15.5%
6 Multi-morbidities	80,608	48,376	60.0%	29,523	36.6%	32,356	40.1%
7 Headaches	82,745	34,189	41.3%	31,170	37.7%	3,715	4.5%
8 Neuropathies	150,468	113,437	75.4%	63,569	42.2%	17,847	11.9%
9 Non-specific chronic pain conditions	1,079,175	517,082	47.9%	493,602	45.7%	105,940	9.8%

Diagnoses from other pain-intensive diagnosis groups after the inclusion diagnosis

Figure 3-3 below shows the proportion of patients in each of the diagnosis groups, who received an additional (second) diagnosis during the inclusion period.

The majority of patients only occurred in one of the nine diagnosis groups (rose column) during the inclusion period. In the cancer group 75% of the patients, in the non-specific chronic pain group 77% of the patients and in the posttraumatic fracture group 70% of the patients did not occur in another pain diagnosis group during the inclusion period. Patients with intervertebral disc disorders were the ones who most often got admitted to hospital again with a diagnosis belonging to another pain-intensive diagnosis group and this was most likely to be a diagnosis in the non-specific chronic pain group. The non-specific pain diagnosis was the most frequent second diagnosis. Cancer was a relatively seldom second diagnosis occurring in less than 5% of the cases.

Figure 3-3: Proportion of patients occurring in another pain-intensive diagnosis group after the inclusion diagnosis group



Standardised mortality ratio

In table 3 below, we compared the observed mortality rates of the study population with expected mortality rates in the general population with similar age and gender distribution as the study population. Results are reported as standardised mortality ratios per year. Patients are stratified according to inclusion diagnosis, but some of them of them have more than one of the pain-intensive diagnoses, as indicated in figure 3-3.

Table 3-3: Standardised mortality ratios (SMR)

Diagnosis group	smr1998	smr1999	smr2000	smr2001	smr2002	smr2003	smr2004	smr2005	smr2006	smr2007
1 Cancer	19.71	13.13	11.51	10.28	9.45	9.01	8.80	8.41	8.18	7.86
2 Specific back conditions	2.69	2.12	1.89	1.76	1.62	1.57	1.48	1.44	1.39	1.38
3 Intervertebral disorders	1.02	1.14	1.17	1.08	1.00	1.01	0.99	1.03	0.96	1.00
4 Arthritis	1.38	1.16	1.17	1.15	1.12	1.08	1.07	1.06	1.06	1.06
5 Posttraumatic fractures	3.18	2.23	2.04	1.93	1.91	1.87	1.82	1.78	1.79	1.80
6 Multi-morbidities	4.64	3.49	3.18	3.00	2.86	2.70	2.72	2.54	2.53	2.38
7 Headaches	2.01	1.46	1.36	1.46	1.22	1.27	1.35	1.21	1.18	1.17
8 Neuropathies	2.46	1.88	1.93	1.78	1.67	1.72	1.73	1.77	1.70	1.67
9 Non-specific chronic pain	3.18	2.34	2.19	2.00	1.90	1.87	1.88	1.84	1.88	1.72

The table shows that if the inclusion diagnosis was cancer, the patients died 19.71 times as often as the general population in 1998 and 7.86 times as often as the general population in 2007. For 1998, all persons included are diagnosed at a hospital in 1998, with a very high excess mortality relative to the rest of the population.

In the following years, persons included are either survivors from previous years or newly diagnosed. Whereas the mortality for newly diagnosed cancer patients is very high, the excess mortality for persons having survived cancer is considerably smaller. This heterogeneity in the population at risk causes the SMR's to decrease over the years, as the population of cancer patients converges towards a somewhat stable mixture of newly diagnosed and survivors.

If the inclusion diagnosis was headache, the ratio for dying to that of the general population was 2.01 in 1998 and 1.17 in 2007. The SMR may – ceteris paribus – increase over time as the number of persons at risk of dying as well as comorbidity and disease severity of the individual patient in the study group increase over time, while at the same time, the number of persons at risk in the background population is reduced.

4. Pain Medication Prescription Patterns

Highlights pain medication prescription patterns:

The majority of the study population, 82 %, released at least one pain medication prescription at a Danish pharmacy at some point during the study period. The main prescribers were general practitioners followed by hospital specialists.

During the study period, there has been a decrease in the total number of prescription per 1,000 study persons in the year they were included, from 4,019 prescriptions in 1998 to 3,679 in 2001, followed by an increase between 2002 and 2007 to approximately 4,000 prescriptions.

Most patients did not continue their slow-release strong opioid treatment beyond 18 months, and most of the patients who released a prescription for a slow-release strong opioid did not have a cancer diagnosis.

Most patients on neuropathic pain medication treatment were not admitted to hospital with a neuropathic diagnosis and did not continue their treatment beyond 18 months.

The main other pain medications prescribed to the patients before and after the first prescription of slow-release strong opioid was NSAID, paracetamol, and tramadol.

4.1 Overview of prescribed pain medication

To provide a comparable picture of the number of prescriptions over the study period, we have looked at the pain prescriptions during the year in which study person was included in the study. Table 4-1 below shows the number of prescriptions per 1,000 in the study population in the year they are included. As can be seen, the total number of prescriptions per thousand fell from 4,019 in 1998 to approximately 3,700 in 2001, and increased again up to approximately 4,000 pain prescriptions per 1,000 in 2004.

The distribution between the different prescribed pain medicines has changed, e.g. for strong opioids, the prescription of morphine has more than halved, whereas prescriptions for Oxycodone have increased by almost 400% since 2002.

This resembles the results by Hamunen et al (11) which saw an increase in the consumption of Oxycodone of 300 % between 2002 and 2006. Also, prescriptions for Fentanyl doubled during the study period, and prescriptions for paracetamol and tramadol increased slightly.

Table 4-1: No. of prescriptions by ATC pain group per 1,000 study persons included in the particular year

ATC Pain Group	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
01 Morphine	335	261	242	232	208	203	191	184	172	154
02 Hydromorphone	1	1	1	1	0	0	0	0	1	3
03 Oxycodone	12	24	41	61	97	144	200	272	330	377
06 Codeine comb. excl. psychotropics	124	135	147	151	143	137	127	127	119	111
11 Pethidine	62	49	39	31	23	26	26	18	22	16
12 Fentanyl	55	51	68	77	91	90	90	94	99	100
13 Buprenorphine	57	48	42	38	33	32	44	56	64	72
14 Tramadol	583	563	569	598	623	660	684	684	695	688
17 Ketobemidon (Ketogan Novum)	53	39	38	32	7	1	1			
18 Metadon (tablet)	111	98	90	65	66	57	63	53	53	59
20 Acetylslicylic acid (ASA)	7	4	3	2	3	2	2	2	1	1
21 Paracetamol	708	646	620	622	630	677	732	774	826	838
23 NSAID	1089	1033	1067	1181	1213	1192	1365	1264	1169	1098
24 Tricyclic antidepressants (TCA)	132	122	118	114	110	117	118	117	111	116
25 Gabapentin	6	15	23	41	68	69	74	72	73	75
26 Codeine	263	231	215	211	201	191	186	169	165	158
27 Dextropropoxyphene	56	46	36	29	22	19	14	13	10	9
31 Ketogan	365	286	243	195	186	169	154	129	114	103
Total number of prescriptions	**4019**	**3653**	**3600**	**3679**	**3725**	**3785**	**4074**	**4029**	**4027**	**3980**

According to table 4-2 below, the mean ages at the time of inclusion differ between diagnosis groups. The cancer and multi-morbid patients are the oldest with mean ages of 64.2 years and 66.9 years and the headache and posttraumatic fracture groups the youngest with mean ages of 38.9 and 42.6 years.

At some point during the follow-up; that is one year before the inclusion to the end of 2008 or death; 12-46% of the patients, depending on diagnosis group, released at least one slow-release strong opioid (SRSO) prescription at a pharmacy. They were relatively older and more often females than the ones who did not release a prescription. 6-21 % of the patients included in each of the groups and relative more older and female patients than young and male released a neuropathic pain prescription.

Table 4-2: Mean age at time of inclusion and % with slow-release strong opioid (SRSO) and neuropathic pain prescription (NPP)

Diagnosis groups	Number	Mean age	% men	With SRSO	% total	Mean age SRSO	% men SRSO	With NPP	% total	Mean age NPP	% Men NPP
1 Cancer	201,941	64.2	52.3	93,563	46%	66.4	51.5	26,416	13%	63.0	47.6
2 Specific back conditions	143,921	61.7	28.6	45,921	32%	68.2	28.8	23,997	17%	63.2	29.3
3 Intervertebral disc disorders	143,173	49.9	49.9	38,736	27%	54.8	45.6	30,701	21%	51.6	41.1
4 Arthritis	547,107	50.7	46.5	97,651	18%	63.4	39.0	47,266	9%	57.5	33.6
5 Posttraumatic fractures	302,233	42.6	51.3	48,029	16%	66.4	37.9	18,685	6%	59.5	38.6
6 Multi-morbidities	80,608	66.9	36.6	31,448	39%	73.9	31.0	12,342	15%	68.3	35.2
7 Headaches	82,745	38.9	37.7	10,265	12%	52.7	35.8	13,997	17%	46.7	31.1
8 Neuropathies	150,468	51.2	42.2	28,624	19%	62.0	42.0	27,590	18%	56.5	39.9
9 Non-specific chronic pain conditions	1,079,175	44.0	45.7	165,032	15%	60.0	42.0	106,860	10%	53.3	36.7

Note: Patients may belong to more than one diagnosis groups, and can therefore be counted twice.

4.2 Slow-release strong opioid treatment pattern

In the following sections, an analysis of slow-release strong opioid (SRSO) treatment patterns is provided. SRSO's are indicated for the treatment of severe pain where other treatments are insufficient or exhausted, and is thus indicative of severe pain in the patient population.

Slow-release strong opioid prescription sequence

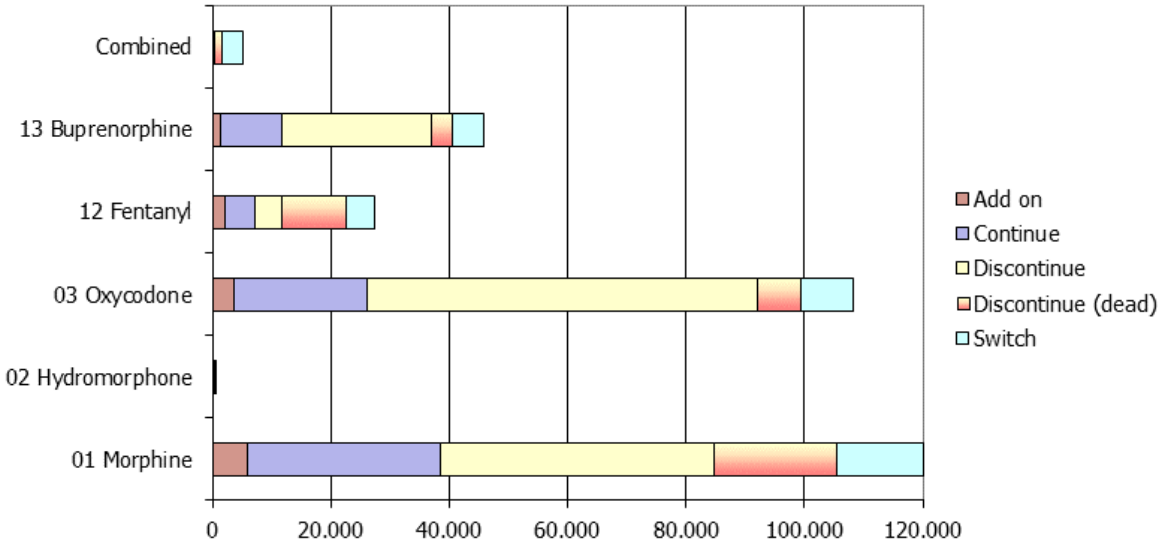
During their time of follow-up a total of 306,349 patients in the study population released a prescription for a slow-release strong opioid.

Morphine as a first line treatment was prescribed to 119,882 or 39% of the patients, followed by oxycodone, which was prescribed to 108,225 or 35% of the patients, buprenorphine prescribed to 45,578 or 15% of the patients and Fentanyl prescribed to 27,316 patients or 9%, while hydromorphone was prescribed in less than 1% of the cases.

In the figure 4-1 below, the patients are grouped according to their first line prescription and subsequent treatment pattern. The definitions are described in Appendix 3. "Co_med" refers to the situation where a patient releases a prescription for two or more SRSOs on the same date.

When morphine was the first line treatment, it was discontinued in 38.6% of the cases including the 17.3% who died. 27.1% continued and 12.1% switched to another treatment within 3-6 months after prescription. The picture for Oxycodone was that 60.8% discontinued within the 3-6 months window (6.8% because they died), and 20.8% continued.

Figure 4-1: Number of patients on each 1st line long-term pain prescription and the proportions with another dispatch between 3 to months after prescription



Appendix 4 provides figures of the analysis for 2nd and 3rd line users for the 1st line users of the five SRSO's. Among the first line morphine users who switched to oxycodone as a 2nd line treatment, the majority, 375, switched back to morphine as a 3rd line treatment or as an add-on to oxycodone, and 197 switched to, or added, fentanyl to their 2nd line treatment.

The same pattern (switch back to morphine) is seen for 2nd line fentanyl users.

Most of the 1st line oxycodone users, who switched, had fentanyl as their 2nd line treatment, and the majority of the switching patients were terminal. Most of the 1st line surviving oxycodone users, who switched to morphine, switched back to oxycodone as their 3rd line medication. The same pattern is seen for 2nd line fentanyl users. Buprenorphine was the least used of the four drugs.

Slow-release strong opioid treatment continuation

In appendix 4, patients who had a first slow-release strong opioid prescription were followed for 18 months. Most patients did not continue treatment. However, for morphine, about 40% continue their treatment beyond 6 months, and 18% or 19,618 patients continue for 18 months or more. For oxycodone only 33% continue treatment, and 14.5 %, or 11,581 patients continue for 18 months or more.

Strength of slow-release strong opioid prescriptions

As can be seen from the figures in appendix 4, the proportions of patients on different strengths of their SRSO prescriptions on higher doses/strengths of the medication expectedly increases the longer they stay on treatment.

Other pain medication prescribed to slow-release strong opioid users

A total of 238,353 patients or 77% of the patients with a 1st line slow-release strong opioid prescription had a dispatch of another pain prescription during the three months before the slow-release strong opioid prescription. 145,247 patients or 47% had another pain prescription during the 3-6 months following the first slow-release strong opioid prescription. In figures 7 and 8, it can be seen that the predominant, prescribed treatments are paracetamol, NSAID and tramadol, both before and after the first prescription for a slow-release strong opioid.

Figure 4-2: Number of patients on each pain prescription during 3 month before their first slow-release strong opioid prescription

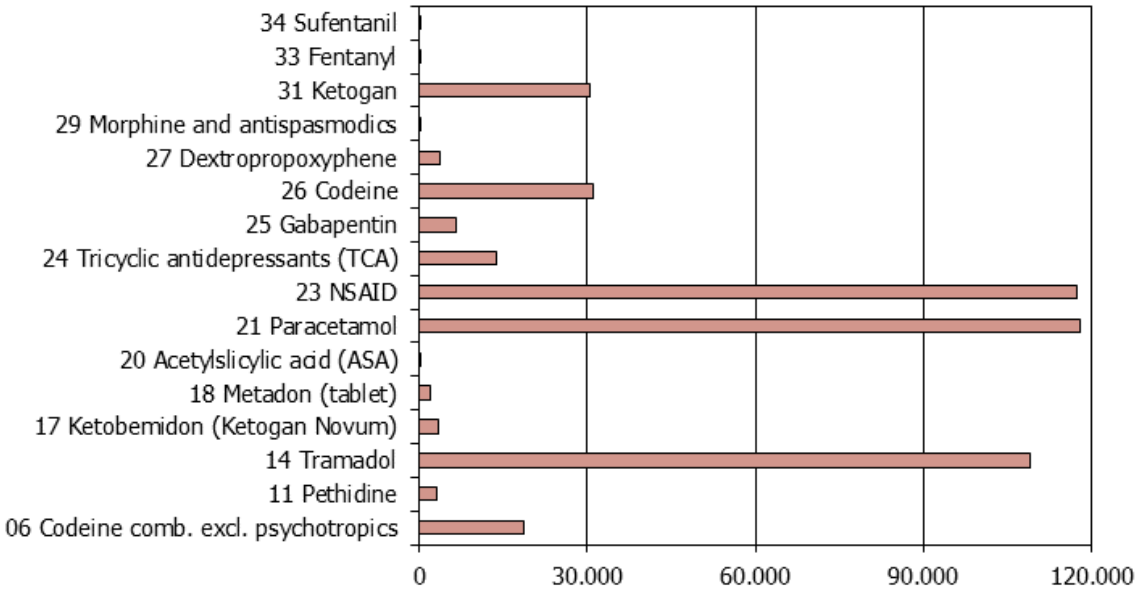
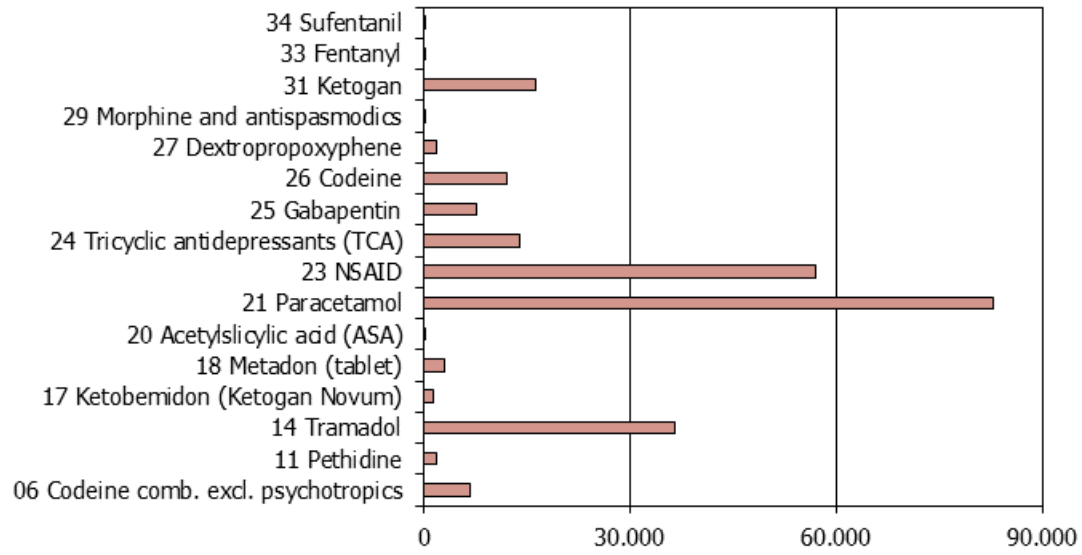
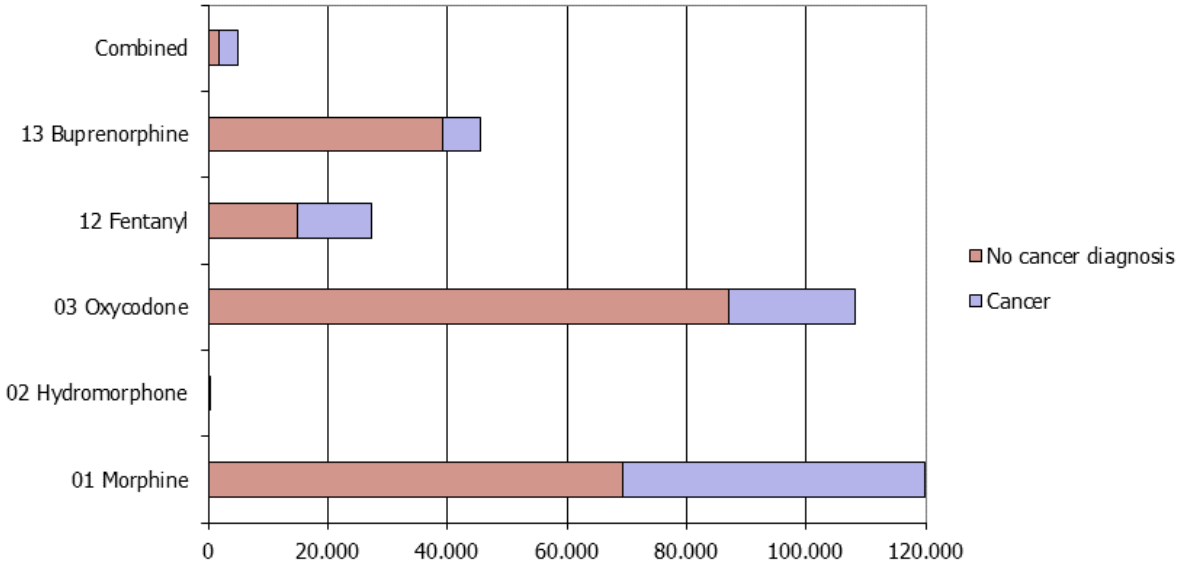


Figure 4-3: Number of patients on each pain prescription between 3 and 6 months after their first slow-release strong opioid prescription, by strong opioid continuation



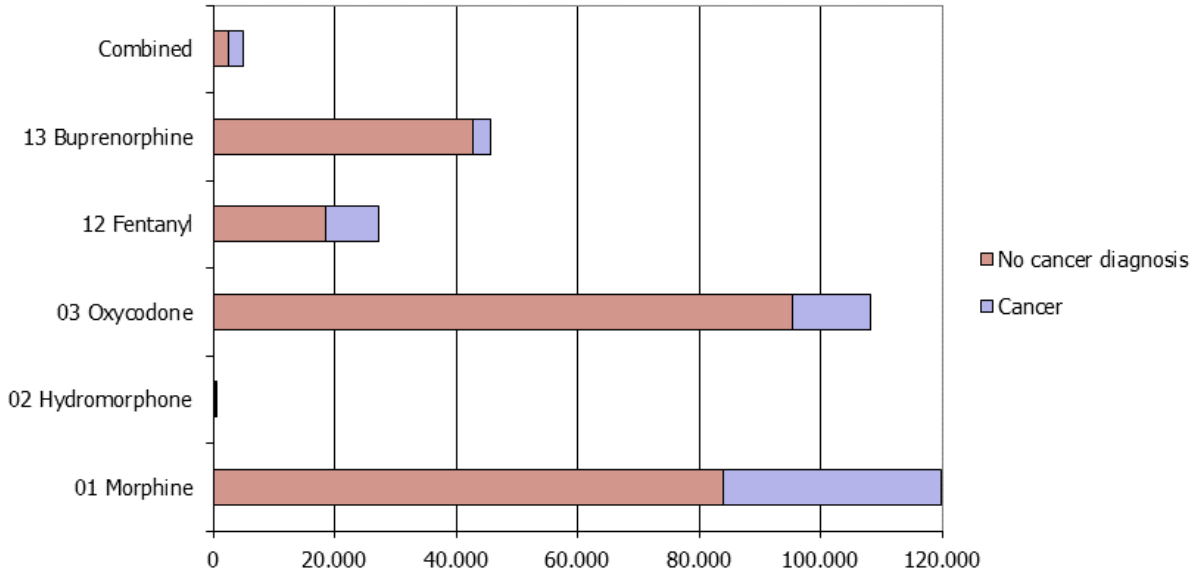
Slow-release strong opioid prescription by cancer diagnosis

Figure 4-4: Number of patients on any 1st line slow-release strong opioid prescription and whether they have a cancer diagnosis



In figure 4-4, patients with a first line slow-release strong opioid prescription and whether or not they had a cancer diagnosis are shown. Figure 4-5 stratifies the data according to whether or not patients had their first cancer diagnosis 6 months before to 12 months after the prescription. Cancer patients are more often prescribed morphine and oxycodone as their first line treatments, than other strong opioids.

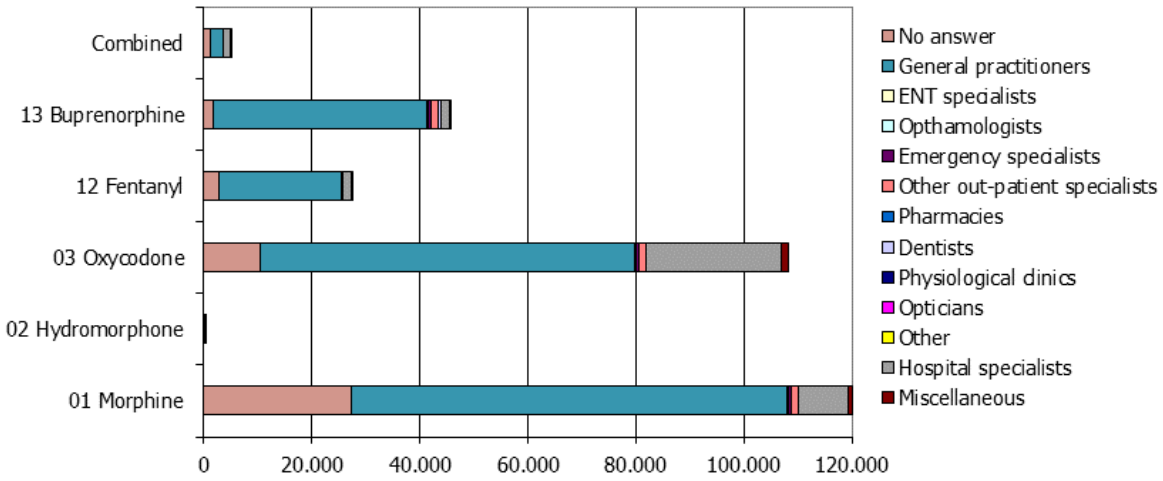
Figure 4-5: Number of patient on any 1st line slow-release opioid prescription and first cancer diagnosis (-6 to +12 months after 1st prescription)



Slow-release strong opioid prescribers

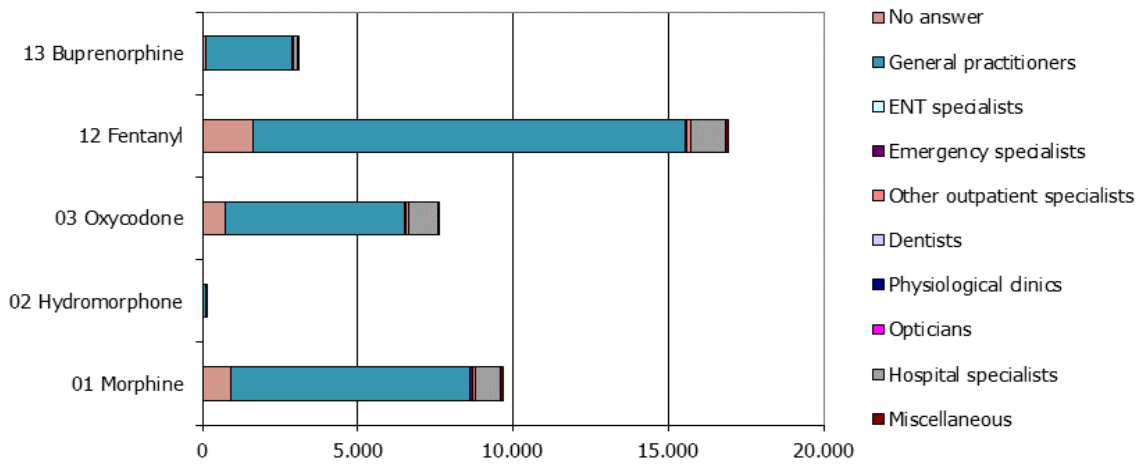
In the two figures below, the patients on first and second line slow-release strong opioid are divided according to the prescriber. The vast majority of prescribers of slow-release strong opioids are general practitioners, followed by hospital specialists for oxycodone and morphine in particular. Drugs used as hospital treatment are paid by the hospital, but the hospital specialist may prescribe a drug, when discharging the patient from hospital. There are also a large proportion of prescriptions without an indication of the prescriber. These "no answers" may be hospital prescribers as well, an assumption which was confirmed by the Danish Medicines Agency[3].

Figure 4-6: Number of patients on each 1st line slow-release strong opioid prescription and prescriber



[3] Personal communication, Danish Medicines Agency

Figure 4-7: Number of patients on each 2nd line slow-release strong opioid prescription and prescriber



4.3 Neuropathic Pain Treatment Pattern

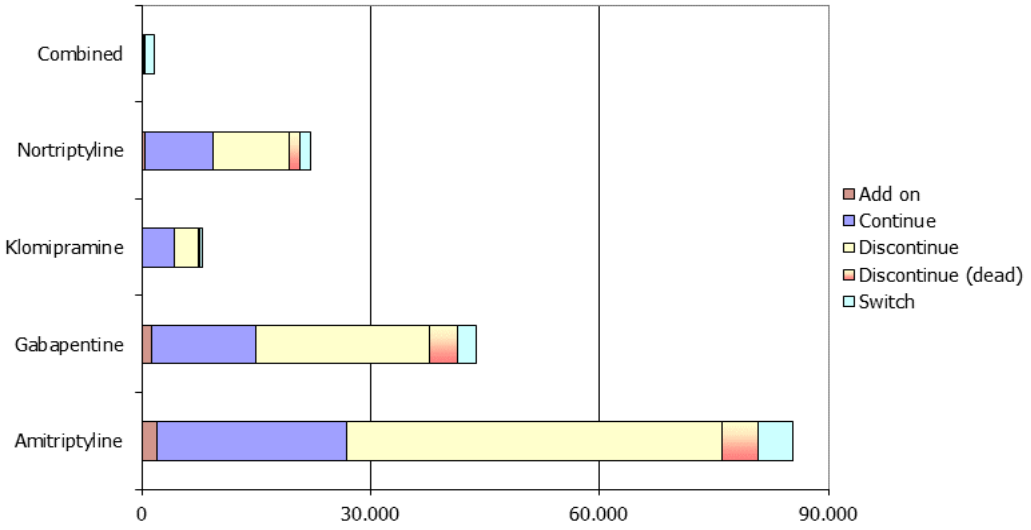
Neuropathic pain medication prescription sequence

A total of 160,445 patients had their first neuropathic pain prescription during the study period.

Amitriptyline was the most common first line prescription (53%) followed by gabapentine (27%) and nortriptyline (14%). Patients on amitriptyline discontinued treatment in 58% of the cases (5.8% died), patients on gabapentine discontinued in 52% of the cases (8.5% died), whereas only 42% on klomipramine and 46% on nortriptyline discontinued.

8.3% of the total number of 1st line patients, or 13,255 persons, switched to or added another neuropathic pain drug.

Figure 4-8: Number of patients on 1st line neuropathic pain prescriptions and the proportion with another dispatch between 3 to 6 months after prescription



In Appendix 4, 3rd line prescriptions for 1st line amitriptyline and 2nd line gabapentine who switched are shown. The general pattern is that patients switch back to their 1st line drug, amitriptyline. For 1st line gabapentine users who switched, most of them switched to amitriptyline as a 2nd line treatment (4-29). 3rd line treatment were mostly gabapentine again.

Most of the nortriptyline users who switched to another treatment, switched to gabapentine and most of the klomipramine users who switched, switched to amitriptyline.

Neuropathic pain medication treatment continuation

Most patients did not continue their amitriptyline and gabapentine treatment (58-59%), but for both drugs approximately 20% continue treatment for 18 months or more. For the 7,514 first line users of klomipramine, only 40% discontinued treatment.

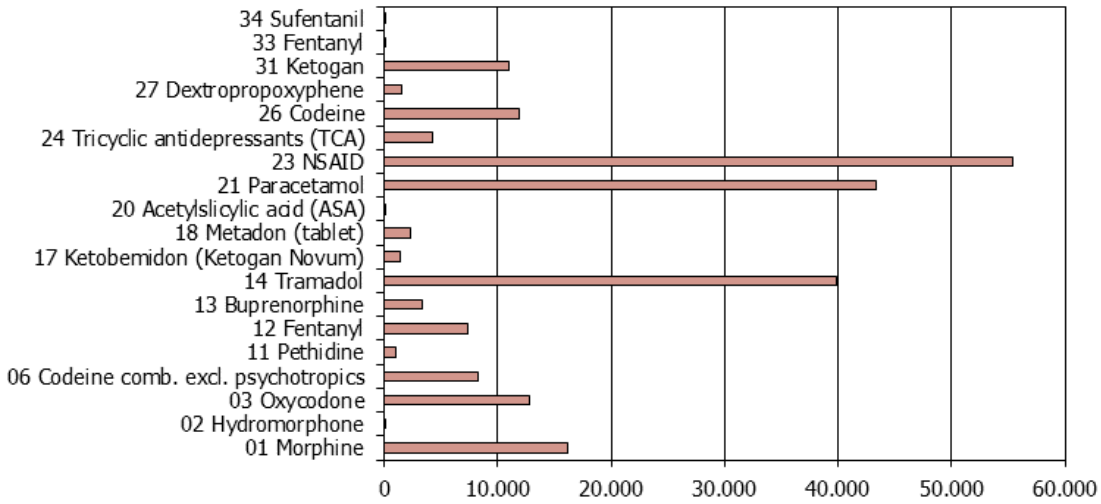
Strength of Prescriptions

In appendix 4, the proportions of patients on different strengths of their prescriptions are displayed[4]. As was the case with SRSO, the proportion of patients on higher doses/strengths of the neuropathic pain medication expectedly increased the longer they stayed on treatment, although the picture is not as evident as for SRSO's.

Other pain treatments for patients with neuropathic pain medication prescriptions

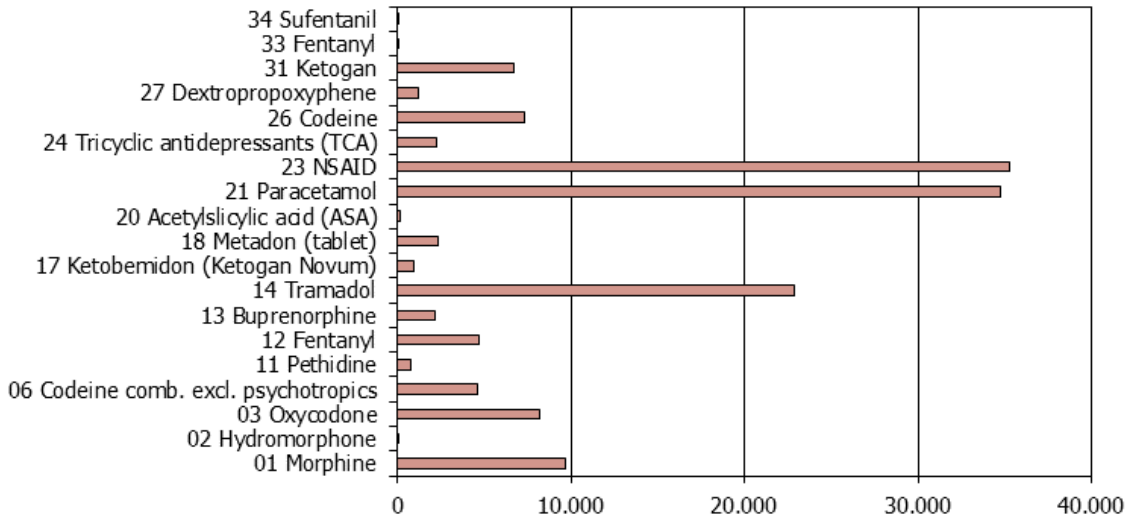
A total of 105,268 or 66% of patients who had their first neuropathic pain prescription, had another pain prescription during the 3 months before the first neuropathic pain prescription and 49% or 80,082 patients had another prescription during the 3-6 months after the neuropathic pain prescription. As can be seen in figures below, NSAID and paracetamol are the most frequently prescribed types of treatment, followed by tramadol, morphine and oxycodone, ketogan and codeine.

Figure 4-9: Number of patients on each pain prescription during the 3 months before their first neuropathic pain prescription by types of prescriptions



[4] As to morphine and oxycodone, the calculation is limited to prescription with the strength unit, mg. This means that prescriptions with the strength unit MGM (mg/ml) are not included, as the quantity is not available. The same goes for Fentanyl, which is displayed in mg/hour.

Figure 4-10: Number of patients on each pain description during the 3-6 months <u>after</u> their first neuropathic pain prescription by types of prescriptions



Prescriptions by neuropathic pain diagnosis

As can be seen in the figures below, the vast majority of patients on neuropathic pain prescription have not been admitted to a hospital with one of the neuropathic pain diagnosis during the study period.

Figure 4-11: Number of patients on any 1st line neuropathic pain prescription and whether they have neuropathic pain diagnosis at any point of time during study period

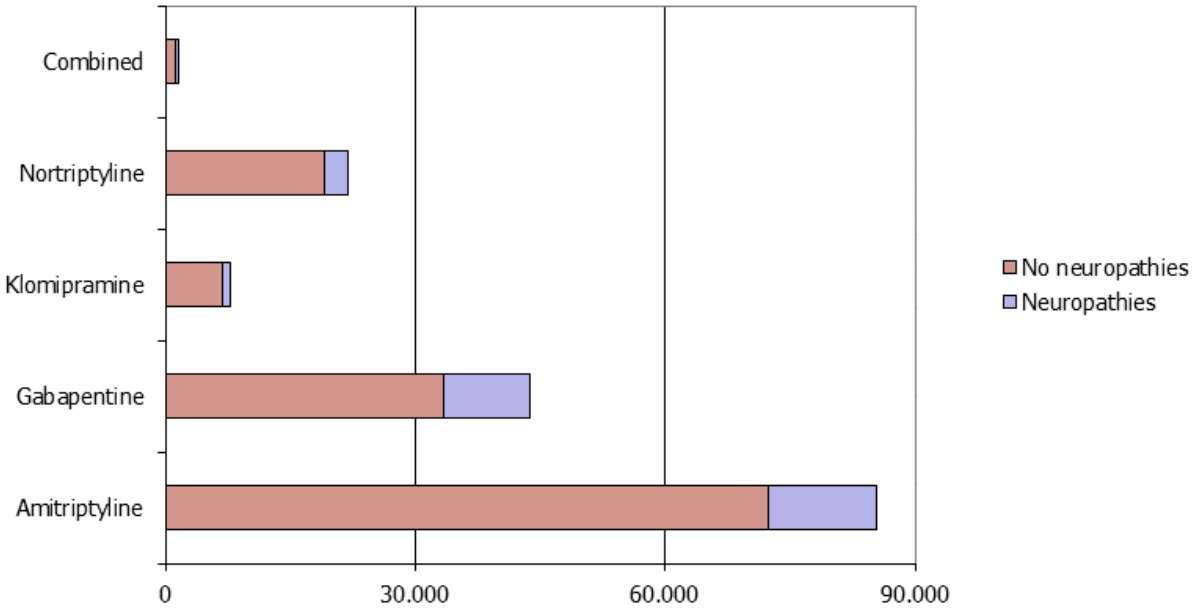
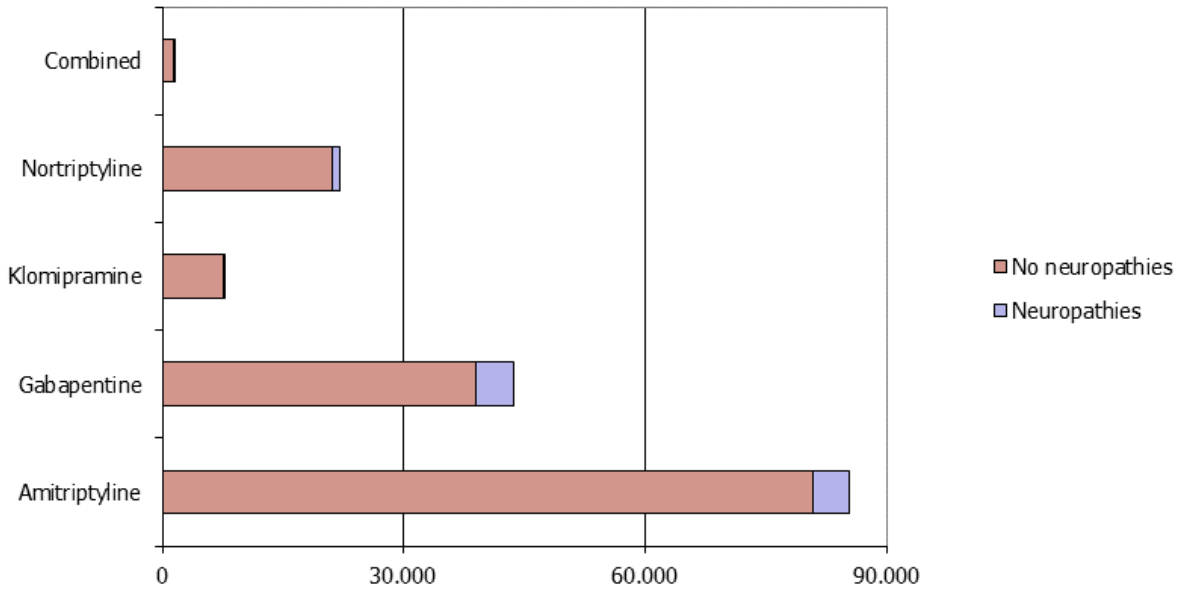


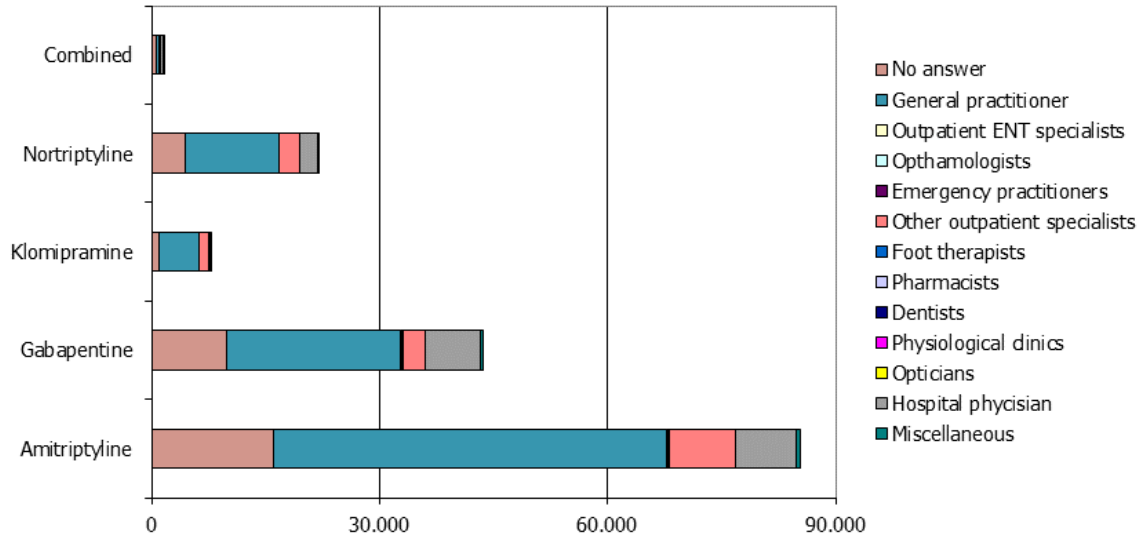
Figure 4-12: Number of patients on any 1st line neuropathic pain prescription and whether they have neuropathic pain diagnosis from 6 months before to 12 months after inclusion



Neuropathic pain medication treatment prescribers

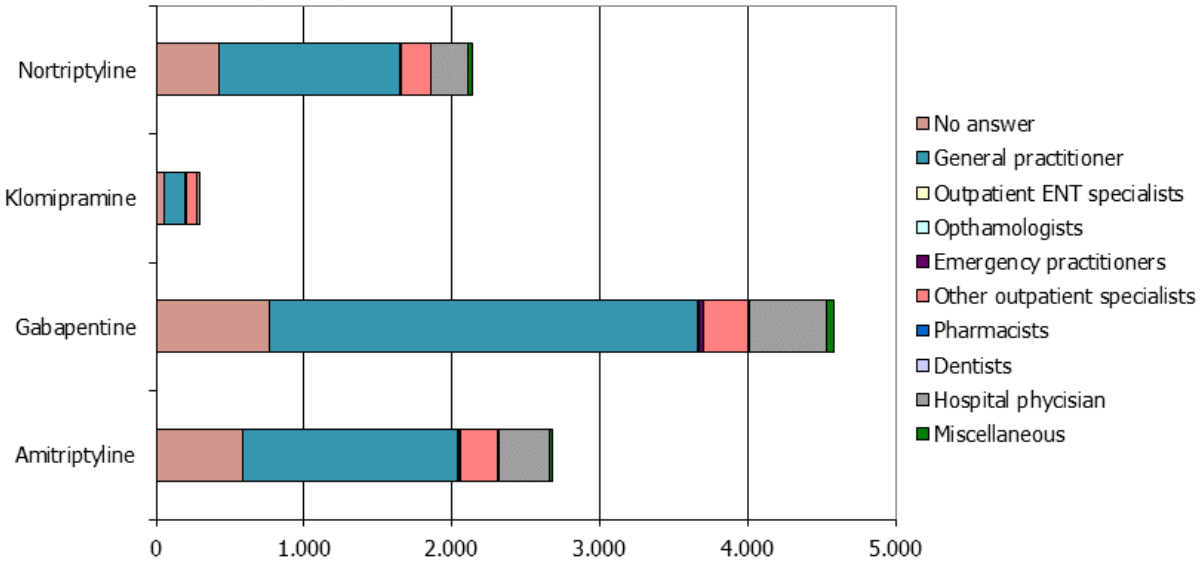
The main prescriber both for first and second-line neuropathic pain prescriptions is the general practitioner, followed by hospital specialists and other out-patient-specialists. The large proportion of "no answer" may be hospital prescribers as well. [5]

Figure 4-13: Number of patients on 1st line neuropathic pain prescriptions and prescriber



[5] Personal communication Danish Medicines Agency

Figure 4-14: Number of patients on each 2nd line neuropathic pain prescription and prescriber



5. Healthcare Costs

Highlights health care costs:

The patients with a cancer diagnosis had the highest healthcare costs during the year after the inclusion in the study, DKK 208,830 on average per patient year, followed by the multi-morbid pain patients with DKK 94,085 per patient year. The patients with headache and non-specific pain diagnoses accounted for DKK 34,784 and DKK 38,284 respectively which were the lowest average costs per patient year among the nine diagnosis groups.

Hospital costs, including medical treatment of pain at the hospital, account for 89-97% of the average cost per patient year, and prescribed pain medication purchased at a pharmacy only for 1-3%.

Generally, healthcare costs are lowest before the inclusion, then peak tremendously during the month of inclusion, drop somewhat during the subsequent months, but remain higher than before the inclusion during the following 24 months. Posttraumatic fracture patients are an exception to this.

For the entire three years of follow-up, disease-attributable healthcare costs amount to e.g. DKK 261,000 for cancer and DKK 84,000 for multi-morbidity.

5.1 Healthcare costs in the first year after inclusion

In the table below, we calculated the average healthcare costs in the year following the inclusion in the study. As can be seen, the cancer group has the highest cost, DKK 208,830 per patient year followed by the multi-morbid pain patients with DKK 94,085.

The lowest costs per patient year after inclusion are in the headache group (DKK 34,784), and non-specific pain groups (of DKK 38,284).

The main part of the costs during the first year are hospital costs with inpatient costs constituting 71%-83%, and day care hospital costs accounting for 11%-25% of the average costs per patient year. Out-patient costs relating to visits to GPs and other out-patient specialists constitute 2%-10% of the costs, and pain prescriptions constitute 1%-3% of the total costs per patient year. However, it should be noted that this proportion of pain therapy in the total cost is not the full picture. Some of the pain therapy is provided during hospital stay and is included the in-patient (DRG) and day care hospital (DAGS) costs[6].

[6] The hospital drug costs occur both in general hospital and in departmental budgets and cannot be directly separated from e.g. the bed day cost in the DRG/DAGS database

Table 5-1: Healthcare costs per patient in the first year after inclusion, 2010 Danish Kr., and % of total [7]

Diagnosis groups	In-patient hospital	% of total	Day care hospital	% of total	Out-patient	% of total	Pain prescrip-tions	% of total	Total DKK
1 Cancer	172,392	83%	29,271	14%	4,097	2%	3,071	1%	208,830
2 Specific back conditions	42,971	74%	9,234	16%	3,981	7%	1,654	3%	57,840
3 Intervertebral disc disorders	33,869	72%	8,174	17%	3,405	7%	1,296	3%	46,745
4 Arthritis	26,709	66%	9,907	25%	2,868	7%	781	2%	40,264
5 Posttraumatic fractures	30,390	76%	6,173	15%	2,608	7%	753	2%	39,924
6 Multi-morbidities	76,461	81%	10,557	11%	4,646	5%	2,420	3%	94,085
7 Headache	24,181	70%	6,545	19%	3,549	10%	509	1%	34,784
8 Neuropathies	39,133	71%	11,416	21%	3,821	7%	1,001	2%	55,371
9 Non-specific chronic pain conditions	27,348	71%	7,89	19%	2,914	8%	733	2%	38,284

5.2 Development in healthcare costs over a time period

To compare the development of the distribution of healthcare costs over time, we calculated the total health care costs per patient year, for patients who were included in 2003, 2004, 2005 and 2006 respectively (table 5-2).

As can be seen, the total health care costs per patient year after inclusion have increased between 2003 and 2006, by approximately 8-12% for intervertebral disc disorders, posttraumatic fractures, headaches, arthritis, neuropathies, and other chronic pain conditions. Cancer, specific back conditions and multi-morbidities remain almost at the same level as in 2003.

Table 5-2: Total healthcare costs per patient year, first year after inclusion in 2003, 2004, 2005, and 2006 respectively

Diagnosis Group	2003	2004	2005	2006
1 Cancer	204,552	215,647	202,779	208,523
2 Specific back conditions	57,885	59,584	57,059	57,370
3 Intervertebral disc disorders	45,744	46,551	46,037	48,917
4 Arthritis	37,741	41,153	41,117	42,000
5 Posttraumatic fractures	38,122	39,996	39,958	41,717
6 Multi-morbidities	94,812	96,796	91,874	93,518
7 Headaches	33,014	34,077	35,520	36,361
8 Neuropathies	50,752	56,735	56,175	56,607
9 Other chronic pain conditions	36,033	38,462	38,623	40,150

In table 5-3 and 5-4, the total cost per patient year in 2003 and 2006 respectively, has been broken down into categories of costs.

The figures show that, when comparing the two years, the increase in total per patient costs seems to come from an increase in hospital costs, whereas e.g. pain prescription costs per incident patient case seem to have decreased slightly (although the figures have not been tested for statistical significance). For cancer patients in particular, a significant proportion of costs have shifted from in-patient stay to day-care treatment.

[7] The table is based on data from 2002-2008 depending on the time of inclusion. Therefore, the figures are not directly comparable with subsequent tables based on 2006 data only.

When comparing 2003 (table 5-3) with 2006 (table 5-4), we see that costs shifted from being 85% in-patient costs and 12% ambulatory day-care costs to 80% and 17% respectively. However, the results do not show whether there has been a shift in the distribution of diagnoses under the group headings, leading to a shift in resource use. The results should therefore be interpreted with caution.

Table 5-3: Healthcare costs per patient year, first year after inclusion. Patients included in 2003, 2010 Danish Kr., and % of total.

Diagnosis groups	In-patient hospital	% of total	Day care hospital	% of total	Out-patient	% of total	Pain prescrip-tions	% of total	Total DKK
1 Cancer	173,539	85%	23,889	12%	4,041	2%	3,082	2%	204,552
2 Specific back conditions	43,532	75%	8,692	15%	3,893	7%	1,769	3%	57,885
3 Intervertebral disc disorders	33,985	74%	7,055	15%	3,309	7%	1,395	3%	45,744
4 Arthritis	25,351	67%	8,782	23%	2,765	7%	842	2%	37,741
5 Posttraumatic fractures	29,190	77%	5,652	15%	2,521	7%	758	2%	38,122
6 Multi-morbidities	77,905	82%	9,720	10%	4,699	5%	2,487	3%	94,812
7 Headache	23,247	70%	5,798	18%	3,443	10%	526	2%	33,014
8 Neuropathies	35,976	71%	9,957	20%	3,724	7%	1,094	2%	50,752
9 Other chronic pain conditions	25,984	72%	6,439	18%	2,851	8%	759	2%	36,033

Table 5-4: Healthcare costs per patient year, first year after inclusion. Patients included in 2006, 2010 Danish Kr., and % of total.

Diagnosis groups	In-patient hospital	% of total	Day care hospital	% of total	Out-patient	% of total	Pain prescrip-tions	% of total	Total DKK
1 Cancer pain	166,859	80%	34,640	17%	4,077	2%	2,948	1%	208,523
2 Specific back conditions	42,251	74%	9,531	17%	4,019	7%	1,568	3%	57,370
3 Intervertebral disc disorders	35,233	72%	8,937	18%	3,481	7%	1,267	3%	48,917
4 Arthritis	27,608	66%	10,684	25%	2,972	7%	737	2%	42,000
5 Posttraumatic fractures	32,144	77%	6,150	15%	2,670	6%	754	2%	41,717
6 Multi-morbidities	75,459	81%	11,219	12%	4,607	5%	2,233	2%	93,518
7 Headache	25,461	70%	6,766	19%	3,654	10%	480	1%	36,361
8 Neuropathies	39,976	71%	11,768	21%	3,900	7%	963	2%	56,607
9 Other chronic pain conditions	28,737	72%	7,748	19%	2,966	7%	698	2%	40,150

5.3 Cost over time by main diagnosis groups

Appendix 5 shows the development in healthcare costs from 12 months before the inclusion (month 0) to 24 months after for each of the nine main diagnosis groups. For cancer, the average cost per patient is above DKK 50,000 in the inclusion month. Costs drop to a little more than DKK 30,000 in the second month, and even more in the following months, but never down to the level before the diagnosis.

The same picture is seen for specific back conditions although the costs in months zero are much less than for the cancer group (DKK 17,000 on average). Again the costs drop the following months, and approach the level before the inclusion.

The treatment of intervertebral disc disorders costs approximately DKK 14,200 on average during the inclusion month. Costs then drop down to approximately DKK 5,000 the following month, to DKK 4,000 in month three and keeps dropping, but never down to the level before the diagnosis.

Arthritis patients cost approximately DKK 10,200 on average during the inclusion month, then their drop to approximately DKK 4,300, in month 9 they reach a level of about DKK 2,000 per month, and remains higher than before the inclusion in the following months.

For posttraumatic fracture patients, the costs are highest in month 0 (DKK 17,000 on average), and drops to DKK 4,200 the following month. After 5-6 months the average monthly health care costs are the same as before the inclusion in the study.

Patients with multi-morbidities have higher costs than patients included in the other eight diagnosis groups in the year before the inclusion, with costs ranging from DKK 2,000 to 9,000 during the months before the inclusion month, where costs raise to approximately DKK 33,000. In the following months costs drop, but remain higher than for those of the other diagnoses, except cancer.

Patients with headache incur approximately DKK 15,000 in healthcare costs the month of diagnosis at a hospital. In the subsequent months costs drop, but remain slightly higher than before the inclusion.

For neuropathic patients costs increase before the diagnosis, peak to more than DKK 20,000 on average during month 0 and drop again down to previous levels after a couple of months.

For non-specified chronic pain patients, costs also peak at month 0 up to nearly DKK 13,500 per patient, drops again after about 8 months to a level which is slightly higher than before the diagnosis.

5.4 Disease-attributable healthcare costs per patient year

To arrive at the disease-attributable healthcare costs per patient year, we compared costs after the inclusion with baseline costs, as here exemplified by cancer costs. In Appendix 5 the costs in each of the nine main diagnoses groups 12 months before and 24 months after are visualized in a column diagrams.

Table 5-5: Disease-attributable costs for cancer patients 2006, DKK (2010 prices)

Cancer	Average costs per patient year	Average annual baseline health care costs	Average disease-attributable costs per patient year
Year before inclusion	41,488	22,992	18,495
Year 1 after inclusion	208,523	22,992	185,531
Year 2 after inclusion	80,714	22,992	57,722

5.5 Disease-attributable healthcare costs per 3 year follow-up

In the table below, we calculated the total disease-attributable costs for the three-period of follow-up for costs.

Table 5-6 Baseline and disease-attributable healthcare costs, 3 year follow-up, Danish Kr., 2010 prices

Diagnosis group	Annual baseline costs	Year before inclusion	Year after inclusion	Year 2 after inclusion	Total costs
1 Cancer	22,992	18,495	185,531	57,722	261,748
2 Specific back conditions	23,933	6,974	33,436	9,445	49,855
3 Intervertebral disc disorders	14,633	3,305	34,285	9,203	46,793
4 Arthritis	13,733	2,183	28,267	7,326	37,776
5 Posttraumatic fractures	14,262	1,961	27,455	3,893	33,309
6 Multi-morbidities	35,458	16,519	58,061	9,602	84,182
7 Headaches	16,466	1,863	19,895	1,025	22,783
8 Neuropathies	22,628	8,751	33,978	5,310	48,039
9 Non-specific chronic pain	15,401	6,109	24,749	2,963	33,821

As can be seen in the table, and from the diagrams in Appendix 5, there is a run-in period in the year before the inclusion where costs starts to supersede the baseline level already the year before inclusion. During the year of inclusion, costs peak, and then drop again in year 2 after the inclusion, although they are still higher than baseline for all diagnosis groups.

When aggregating the disease-attributable costs for the three years of follow-up, we get an estimate of the cost per patient of treating the pain-intensive disease. Here we see that e.g. the disease-attributable cost of treating cancer is DKK 261,748 and for multi-morbidity DKK 84,182.

5.6 Prevalence-based healthcare costs in 2006

Using the disease-attributable costs described in chapter 2, "data and methods" for patients included in 2004, 2005 and 2006, a cross-section view of 2006 is now taken in table 5-7.

Table 5-7: Total disease attributable healthcare costs in 2006, mil. DKK (2010 prices)

Total disease attributable costs in 2006 in mil. DKK 2010-prices	Cross section characteristic of the 2006 population at the beginning of 2006			Total for the diagnosis group, Mil. DKK
	Patients included in 2006	Patients included in 2005	Patients included in 2004	
1 Cancer	1,368	1,064	492	2,924
2 Specific back conditions	417	626	431	1,475
3 Intervertebral disc disorders	265	351	288	904
4 Arthritis	1,005	1,306	1,021	3,331
5 Posttraumatic fractures	389	516	441	1,346
6 Multi-morbidities	319	381	268	967
7 Headaches	98	166	139	404
8 Neuropathies	420	543	346	1,309
9 Non-specific chronic pain	1,540	2,113	1,788	5,440

Patients included in more than one group of the pain-intensive diagnoses, may incur costs in more than one group and therefore totals for the patient population cannot be directly counted in a meaningful way.

Healthcare costs seem to remain well above the baseline level beyond the 24 month post-inclusion period (for details for each of the diagnosis groups, see appendix 5). As argued previously, the more distant from the time of inclusion, the less meaningful it is to attribute those costs to the disease.

However, in addition to the numbers in table 5-7, as a sensitivity analyses, healthcare costs for 2006 for patients having had the inclusion for at least 24 months, but no longer than 36 months (patients included in 2003) are calculated. These costs for the different diagnosis groups are lower than for patients included in 2004 – corresponding to 70.0-92.1%, of the costs for patients included in 2004. No firm conclusions can be drawn as to attributing these costs to the disease.

5.7 Cost over time by slow-release strong opioid continuation

Appendix 6 shows the average monthly costs for patients who had a first line slow-release strong opioid prescription, 12 months before and 24 months after the month of the prescription (month 0). As a general tendency, healthcare costs are lower before the prescription, peak during the month of the prescription, then drop the following months, but never reaches the same level as before the prescription.

Costs are higher among continuers of the slow-release strong opioid treatment than discontinuers.

For the patients who die within 3-6-months from the prescription health care costs remain high – above DKK 25,000, during the terminal months.

Healthcare costs for slow-release strong opioid first line users with unspecified chronic pain

The same calculation was done in for patients who had a first line slow-release strong opioid prescription and the ICD 10 diagnosis R52, "pain, not elsewhere classified" (see Appendix 6). The picture is the same as before, within peaking costs during the month of prescription and costs which decrease again, but remain higher than before the prescription.

5.8 Cost over time by neuropathic treatment continuation

In the Appendix 7, we calculated the average monthly costs for patients who had a first line neuropathic pain prescription, 12 months before to 24 months after the month of the prescription (month 0). As a general tendency, healthcare costs are lower before the prescription, peak the month before of the prescription, then drop from month 3, but never reaches the same level as before the prescription. They are lower on average than for patients on first line slow release opioids, e.g. at a maximum DKK 11,000 per month.

For the patients who die costs remain high: DKK 25,000-32,000 per month during the last 6 months before death.

6. Productivity Losses

Highlights health care costs:

The prevalence and incidences of early retirement and long-term absence from work due to sickness are significantly higher in our study population than in the Danish background population.

Approximately 60% of our 15-64 year old study population members experience at least one period of long-term absence from work due to sickness, during the study period. The average number of weeks for study persons on sick leave allowance increases from approximately 5 weeks the year before to approximately 13 weeks in the year after the inclusion in the study. No data were available for short-term absence from work.

Approximately 11% of our study population of work-active ages have been granted early retirement benefit due to a reduced ability to work, at some point during the study period.

The total number of months on long-term sick-leave per year for the incident study population alone represents 16-23% of the total number of months on long-term sick-leave in Denmark in 2006.

These results confirm previous findings that pain and pain-intensive diseases imply long term absence from work.

6.1 Early retirement and long-term sickness

In table 6-1 below, we identified the number of persons from the study population who had at least one long-term sickness allowance during the study period. The Danish municipalities partly reimburse the employers for absence due to sickness, beyond a period of 14-21 days[8]. Figures for short-term absence from work due to sickness are not available.

We also identified the number of persons who had been granted early retirement benefits due to disease and functional disability. Both figures are counted in table 6-1 from one year before to one year after the pain-intensive inclusion diagnosis and at any point during the study period.

Table 6-1 shows that at some point during the study period, 728,204 persons or 38% of the study population, and 58-61% of study population persons in work-active ages (15-64 years), experience at least one long-term absence from work due to sickness[9]. Sometime between one year before and one year after the inclusion, 489,700 patients or 26% of the study population, and 38-41% of persons aged 15-64, experience long-term absence from work due to sickness.

At any point during the study period[10], 138,929 study persons, 7% of the study population and 11-12 % of the subset of persons in work-active ages have been granted early retirement due to reduced ability to work. In 2007, Denmark counted approximately 240,000 persons on premature retirement, and the figure for our study population is well above country prevalence.

[8] Before 2007, the criteria for municipal co-financing of absence from work due to sickness was 14 days of continued absence in 2007 this was increased to 15 days and on 1st June 2008 to 21 days (Source: http://www.ams.dk/Ams/Vejviser-for-borgere/Sygedagpenge.aspx)

[9] At the time of inclusion 1,263,649, and in 2009 1,189,508 patients of the study population were between 15 and 64 years of age

[10] "At any point" can be both before and after the inclusion within the 1998-2008 time period

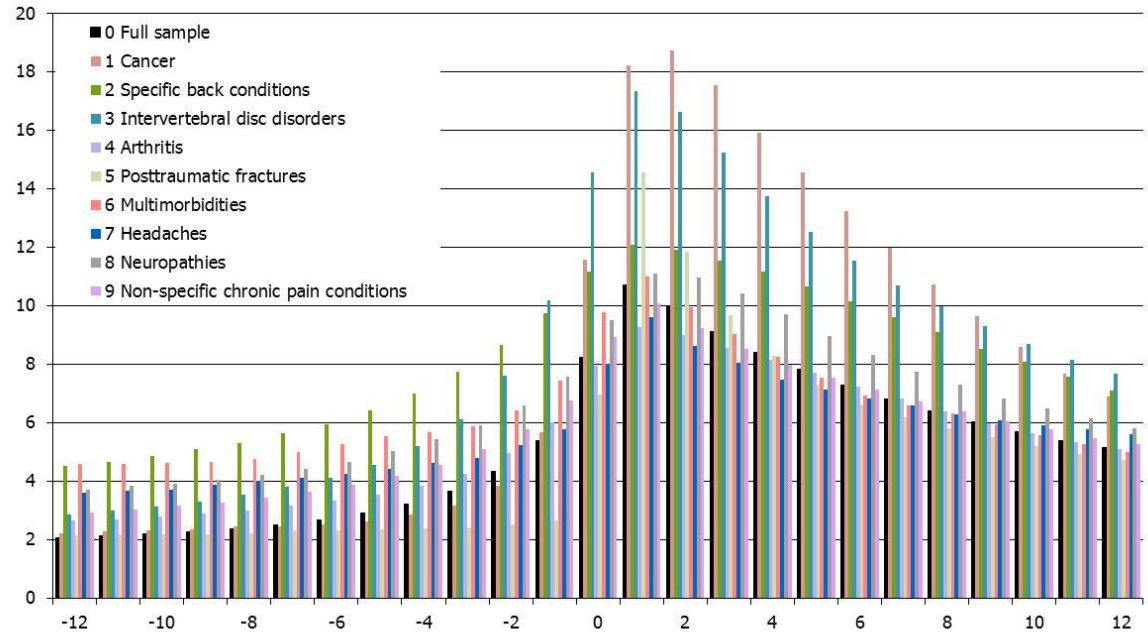
Table 6-1: Number of persons on long-term sickness allowance and early retirement

Diagnosis group	Total population	Long-term sickness allowance		Early retirement	
		1 yr before and after inclusion	At any point	1 yr before and after	At any point
0 Full sample	1.918.823	489.700	728.204	51.619	138.929
1 Cancer	201.941	39.357	52.432	9.936	23.841
2 Specific back conditions	143.921	23.909	40.831	4.796	19.399
3 Intervertebral disc disorders	143.173	63.926	83.529	6.791	25.800
4 Arthritis	547.107	135.373	222.336	10.102	48.199
5 Posttraumatic fractures	302.233	56.875	87.723	4.293	21.669
6 Multi-morbidities	80.608	7.718	13.763	1.836	8.428
7 Headaches	82.745	21.667	37.926	2.320	10.311
8 Neuropathies	150.468	44.222	66.247	5.564	21.584
9 Non-specific pain/Other chronic pain conditions	1.079.175	278.747	467.726	23.877	105.998

The figure 6-1 shows the average number of days of long-term absence from work paid by a sickness allowance from the municipality for the patients aged 15-64 years.

The average number of days per month on long-term sickness allowance is highest among patients with cancer, followed by patients with intervertebral pain diagnoses, and neuropathic pain. The average number of days on long-term allowance due to sickness leave starts to increase 1-2 months before the hospital admission, and remain high the 12 months following the inclusion.

Figure 6-1: Average number of days on municipal allowances for long-term absence from work due to sickness, for persons aged 15-64, by diagnosis group

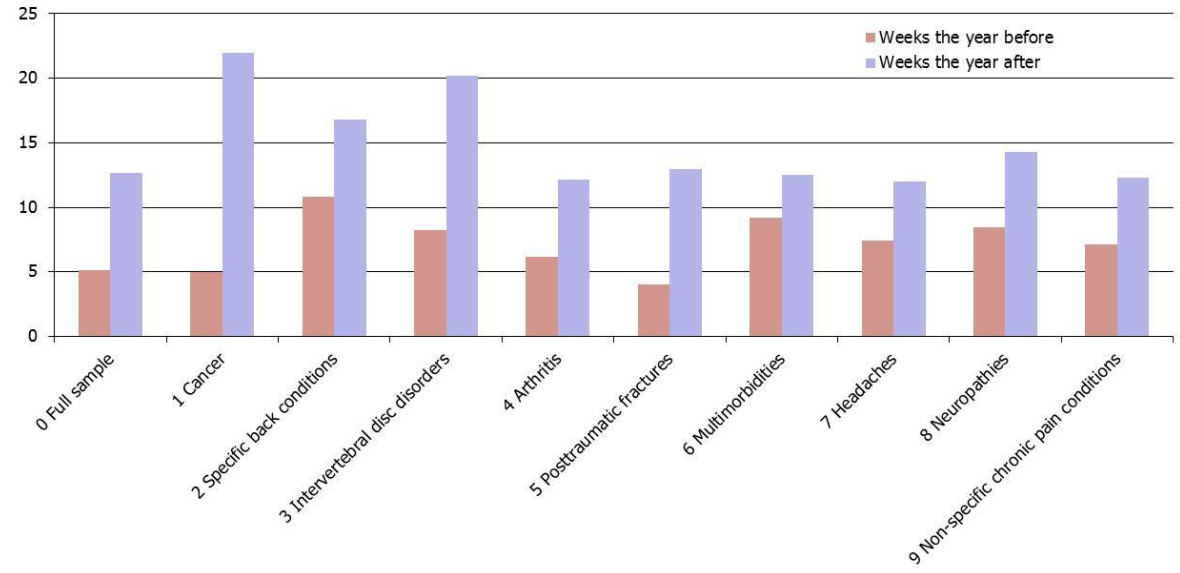


In figure 6-2 below, we calculated the average number of weeks on long-term sickness allowance for the patients with at least one long-term sickness period the year before and the year after the inclu-

sion[11]. As can be expected, the average number of weeks is lower (5.1 weeks for the full sample) before the inclusion than after (12.68 days for the full sample). The pattern of long-term sickness varies according to diagnosis.

Although not directly comparable as our figures do not show calendar year, in comparison, the average number of weeks for the persons on long term sick leave in 2007 was approximately 10 weeks[12]. Our study population members constitute approximately 60% of the total Danish population on sick leave allowance.

Figure 6-2: Average number of weeks on long-term absence allowance due to sickness, by diagnosis group



Incidence based disease attributable sick leave

Table 6-2 below reflects the numbers illustrated in figure 6-3 and is calculated in 1,000 patient years alive. Using the baseline level as a control, 275 months of long-term sick leave are attributable to the cancer disease, the year before the inclusion, 4,261 months, the year after the inclusion, indicating that each patient alive throughout the year on average has 4.26 months of disease-attributable sick leave. The level drops again, and so forth with year 2 after the inclusion, where the level of long-term sick leave is still relatively high.

Table 6-2: Disease-attributable long-term sick leave for cancer patients 2006, per 1,000 patient years

Cancer	Average months on sick leave	Average baseline sick leave months	Average disease attributable sick leave months
Year before inclusion	824.8	549.6	275.2
Year after inclusion	4,810.7	549.6	4,261.1
Year 2 after inclusion	1,758.1	549.6	1,208.5

[11] Based on the number of patients we had data for one year back and one year forward between 1999 and 2006 (362,746)
[12] Source: Nyt fra Danmarks Statistik, 2008

Prevalence based disease-attributable sick leave and costs

Table 6-3 illustrates the total disease-attributable sick-leave in months in 2006 and the productivity loss in DKK, calculated as described in chapter 2.

As indicated in figure 6-1, months on sick leave seem to remain well above the baseline level during the 24 months period after the inclusion.

Table 6-3: Total disease-attributable sick leave, and productivity loss, mil. DKK, 2006

Total disease-attributable sick leave in months	Cross section characteristic of the 2006 population at the beginning of 2006			Total for the diagnosis group	Productivity loss, Long-term sick leave, Mil. DKK
	Patients included in 2006	Patients included in 2005	Patients included in 2004		
1 Cancer pain	12,742	10,590	1,655	24,987	790,6
2 Specific back conditions	5,623	2,589	0	8,212	259,8
3 Intervertebral disc disorders	19,041	14,029	2,647	35,718	1130,1
4 Arthritis	20,873	15,386	2,563	38,822	1228,3
5 Posttraumatic fractures	8,323	5,871	184	14,378	454,9
6 Multi-morbidity	762	0	0	762	24,1
7 Headache	2,846	1,980	162	4,988	157,8
8 Neuropathies	10,639	5,451	0	16,090	509,1
9 Non-specific chronic pain	43,159	31,435	7,022	81,617	2582,4

When summing up the total number of weeks we arrive at 255,574 months of long-term sick-leave for our incident patient population in 2006. Although this figure does not include our entire study population included from 1998, but only those included in 2004-2006, this is still a significant proportion of the total long-term sick leave in 2006, which was 957,000 months (4,149 mil. weeks) (18).

This incident number of months on long-term sick-leave corresponds to 16-23% of the total number of months on long-term sick-leave in Denmark in 2006, depending on the proportion of study persons assumed to be double-counted as they occur in more than one of the nine diagnosis groups. Naturally, reservations have to be made about this estimation of the proportion.

As can be seen, non-specific chronic pain represents the highest productivity loss of DKK 2.58 billion, followed by arthritis of DKK 1.23 billion and intervertebral disc disorders of DKK 1.13 billion. The productivity loss of multi-morbid patients is relatively low, probably because this is a group with relatively many elderly and, thus, retired persons.

Incidence based early retirement

The same approach was used to estimate the disease-attributable incidences for early retirement in our study population. Here illustrated again with cancer as an example. The total cancer disease-attributable incidence for early retirement was 134.5 per thousand patient years.

Table 6-4: Disease-attributable incidences of early retirement allowances per 1,000 patient years, cancer 2006

Cancer	Early retirement allowances in 2006 per 1,000 patient years	Baseline level	Disease attributable retirement incidences per 1,000 patient years
Year before	63,8	22,0	41,9
Year after	91,2	22,0	69,2
Year 2 after	45,4	22,0	23,5
Total	200,5	65,9	134,5

Prevalence based early retirement and productivity loss, 2006

Table 6-5 below shows the disease-attributable incidences of early retirement in 2006 for patients included between 1st Jan 2004 and 31 December 2006.

Table 6-5: Disease-attributable incidences of early retirement and productivity loss in 2006, mil. DKK

Total disease attributable early retirements	Disease attributable incidences of early retirement in 2006			Total for the diagnosis group	Productivity loss early retirement, 3 months friction period, Mil. DKK
	Patients included 2006	Patients included 2005	Patients included 2004		
1 Cancer	127,5	285,8	75,8	489,1	46,4
2 Specific back conditions	0	58,1	0	58,1	5,5
3 Intervertebral disc disorders	29,4	218,4	192,6	440,5	41,8
4 Arthritis	0	107	36,8	143,8	13,6
5 Posttraumatic fractures	0	0	0	0	0
6 Multi-morbid patients	0	0	0	0	0
7 Headache	0	21,6	12,1	33,7	3,2
8 Neuropathies	44,4	106	24,2	174,6	16,6
9 Non-specific chronic pain	0	221,8	102,5	324,3	30,8

The zeros indicate situations where the baseline levels are higher than the periods after, hence persons may already enter early retirement before the inclusion, or alternatively, they may enter into early retirement due to the pain-intensive diagnosis after the three year follow-up period and are therefore not captured here.

Due to our choice of cost calculation method ("friction cost" see Chapter 2), early retirement does not result in as much productivity loss as sickness absence. The range of costs between groups is DKK 0-46.4 mil., and highest for the cancer group. If we assume the friction period to be six months instead of three, the productivity loss of course doubles.

7. The Socio-economic Cost of Pain intensive Diseases

In this study, the annual socio-economic cost of pain-intensive diseases includes publicly financed healthcare costs for hospital admission, treatment at private out-patient providers, including general practitioners, physiotherapists and other specialists, public reimbursement and patient co-payment of pain medication, and production losses related to long-term diseases and early retirement.

When taking into account that some 30% of our study population occurs in more than one of the nine main diagnosis groups, the annual socio-economic cost of pain-intensive diseases can be estimated at DKK 17.8 billion, consisting of DKK 12.67 billion in healthcare costs, DKK 4.99 billion in productivity loss relating to long-term sickness absence, and DKK 0.11 billion in productivity loss relating to premature retirement. For healthcare, the majority (70-83%) of costs relates to hospital care.

For cancer patients the annual cost is estimated at DKK 3.7 billion, for patients with specific back conditions DKK 1.7 billion, for patients with intervertebral disc disorders DKK 2.1 billion, for arthritis DKK 4.6 billion, for fracture patients DKK 1.8 billion, for patients with multi-morbidities DKK 1 billion, headache DKK 0.6 billion, and neuropathies DKK 1.8 billion. The non-specific chronic pain group amounts to DKK 8.1 billion per year. Although cancer patients are more costly per patient year, the non-specific chronic pain group counts most patients and is the most costly group of patients in total.

The table below shows the annual, prevalence based, disease-attributable costs in million DKK of the pain-intensive diagnoses based on the data from chapter 5 and 6 and shown in 2010 prices.

The patients with non-specific chronic pain incur most costs (DKK 8 billion), followed by arthritis (DKK 4.6 billion), and cancer (DKK 3.7 billion).

Table 7-1: Total disease attributable costs in 2006 in mil. DKK (2010 Prices)

Total disease attributable costs in 2006 in mil. DKK 2010-prices	Healthcare	Long-term sick leave	Premature retirement	Total 2006
1 Cancer	2,924	791	46	3,761
2 Specific back conditions	1,475	260	6	1,740
3 Intervertebral disc disorders	904	1,130	42	2,076
4 Arthritis	3,331	1,228	14	4,573
5 Posttraumatic fractures	1,346	455	0	1,801
6 Multi-morbidities	967	24	0	991
7 Headaches	404	158	3	565
8 Neuropathies	1,309	509	17	1,835
9 Non-specific chronic pain	5,440	2,582	31	8,053

As approximately 70% of our patients have more than one of the pain-intensive diagnoses, and thus occur in more than one group, aggregating the numbers is not directly possible. However, assuming that 30% of the costs are double counted, we reach a total annual cost of DKK 17.8 billion.

These costs consist of DKK 12.8 billion for healthcare costs, total productivity loss cost relating to long-term sick leave of DKK 5 billion per year and total cost of the productivity loss relating to premature retirement of DKK 111 million.

As to healthcare costs, even in this very careful and conservative estimate, they still account for 16-20% of the counties' net operational expenses[13] for healthcare in 2006.

[13] "Health care" is in this sense defined as hospital care, primary and specialist care with different private out-patient providers, and publicly reimbursed, prescribed medicines. The figure for 2006 is based on an approximation of the figures for the Regions in 2007 (net operational expenses approximately DKK 78 billion).

8. Discussion

The strength of this study is that it links data from different national registries with high internal data validity together and provides a total count of the 1.92 million (1.68 million still alive in 2007) patients with one or more of the pain-intensive diagnoses. The study design, and the consequent large study population in particular, is ideal for forming hypotheses that may be used for prospective study design within a pain population or concept development.

A number of relevant cost items for pain-intensive patients could not be included the study and this is a limitation.

Although pain – be it chronic or acute - is likely to be a common element of the patients included, we faced two challenges in the assessment of the patient-specific costs: 1) how to control the analysis for healthcare and productivity costs which are not likely to be related to the pain-intensive disease and 2) how to identify an appropriate follow-up time for costs for such a heterogeneous disease population.

To address these challenges, we chose to follow-up on costs from one year before the patient was included in the study to two years after, assuming that the pain-intensive disease was cured. Historical levels of costs were used as controls. This resulted in a disease-attributable cost per patient. Despite a very conservative approach to assessing costs, we still end up with a substantial societal cost per year relating to patients with pain-intensive diseases.

The study results highly demonstrate the challenge and importance of addressing sensitivity and specificity, as well as alternative costs in cost-of illness studies.

8.1 Study strengths and limitations

The strength of this study is that it links data from different national registries with high internal data validity together and provides a total count of the 1.92 million (1.68 million still alive in 2007) patients with one or more of the pain-intensive diagnoses. The study design, and the consequent large study population in particular, is ideal for forming hypotheses that may be used for prospective study design within a pain population or concept development.

By following patients with diseases involving severe, and most often chronic, pain over a long period of time, rather than following the diseases alone, we were able to include both costs relating to the diseases as primary diagnoses and direct and indirect costs of relevant comorbidities to the pain-intensive diseases and thereby get a more realistic picture of the socio-economic consequences of this patient population.

This study included the most important primary and secondary healthcare costs and consequences of absence from work due to sickness, but certain relevant cost items were not included, mainly because they were not available in the registries. This is a limitation in our study.

Such cost items include the cost to the municipalities of long-term care, including home nursing and home help and orthopaedic aids and devices to support the disabled citizen with a pain-intensive diagnosis. They include patient co-payments of e.g. physiotherapists and chiropodists, household work carried out by an informal caregiver (e.g. family member), reduced work capacity while at work and intangible costs associated with e.g. reduction in quality of life due to the pain. Also, we omitted the cost of premature death due to the pain-intensive disease or its complications.

As to the inclusion of the cost of pain therapy medication, we had no data on pain co-medication, OTC drugs and limited data on hospital drug utilization. The costs of pain treatment drugs prescribed during hospital stays were included in the DRG/DAGS cost estimates. Also, prescription data only show what drugs have been sold to the patient and not whether the drug has actually been consumed by the patient. As to pain co-medication – a similar cohort study on the cost of pain-intensive diseases of some 840,000 patients in the Swedish county of Västra Götaland found that the cost of non-pain prescriptions were 4-10 times higher than the cost of pain prescription, depending on diagnosis groups (1).

The last relevant cost item which could not be included in our estimates relates to short-term absence from work due to sickness. Data for this absence is not available in national registries as the employers are responsible for sick leaves up until the 14th-21st day of sickness absence (depending on the year).

8.2 Sensitivity and specificity challenges, inclusion criteria, and cost assessment method

An important aim of this study was to estimate the socio-economic costs per full patient year of pain-intensive diseases based on retrospective data on health care consumption, patterns of early retirement and long-term absence from work due to sickness.

In the ideal world, to do this, all relevant resource use and the associated costs of treating, palliating, and nursing the patients with pain-intensive diseases, and all productivity costs from the patients' being absent from work due to the disease/pain, should be included.

These costs should be measured from the first symptoms to the potential cure of the pain-intensive disease, or to the patients' death, in order to optimize the sensitivity of the study. Also, irrelevant patients and costs should be excluded i.e. specificity should be addressed (19). These issues can be resolved through the design of the study depending on the research question and the nature and course of the disease - and in real-life - on the nature, availability, and censoring of data.

Although the study does count a large proportion of Danish patients on strong opioid treatment, and therefore with one or several episodes of severe, and often chronic, pain, it still involves a wide range of diseases with different aetiologies, epidemiology, symptoms, degrees of acuteness, curability and course of disease.

Therefore, although pain – be it chronic or acute - is likely to be a common element of the patients included, we faced two challenges in the assessment of the patient-specific costs: 1) how to control the analysis for healthcare and productivity costs which are not likely to be related to the pain-intensive disease and 2) how to identify an appropriate follow-up time for costs for such a heterogeneous disease population, i.e. when is the onset of the disease and when does it – if ever – end?

As to the control for costs not related to the disease, an obvious choice would be a case-control design (19), with a selection of controls from the same background population to represent the costs without the disease. As the study is a total count of Danes meeting the inclusion criteria, selection of sufficient numbers of appropriate controls for all age groups has not been possible. Also, the criteria for selecting e.g. matched controls, e.g. confounding factors, are expected not to be the same across all diagnoses and therefore such a strategy was not feasible for this project.

In the absence of a real possibility to select a control group from the general population, we used the patients' own historical level of costs, 24-12 months before the inclusion "baseline", as a control. A comparison of the baseline levels with the subsequent cost levels for the next three years resulted in

disease-attributable health care costs and productivity losses per patient year and per calendar year for the incident patient cases.

A retrospective cohort study undertaken in the county of Västra Götaland in Sweden (1) with a similar design found lower direct healthcare costs per patient year than our study. This may be due to country-specific differences, to the adjustment for mortality differences in the Danish study, and to the fact that patients in the Swedish study were included already at out-patient visits at primary care providers. Also, when extrapolating the findings from Västra Götaland to the total Swedish population, the Swedish study finds total annual societal costs of EU 32 billion or DKK 238 billion per year. This is a considerably higher societal cost than the equivalent found in our study on the Danish population. The reason for this is the choice of method for assessment of indirect costs, e.g. the approach of estimating disease-attributable costs was not used in the Swedish study.

In principle, for our study purposes, patients with the pain-intensive diseases should be followed from the symptom start until the disease is cured or the patient dies. Although relevant, it is not possible with the current registry data available to include patients from the onset of symptoms, as there is no recording of diagnoses in general practice or out-patient specialist practice. However, general practitioners, rheumatologists, physiotherapists, private out-patient pain specialists etc. do see many of the pain patients in Denmark, some of whom may never visit a hospital with that particular pain-intensive disease.

A prevalence based study of the socio-economic cost relating to back conditions and back pain in Denmark (20) from 2011 based on self-reported symptoms and diagnoses compared direct treatment costs and indirect costs relating to absence from work or early retirement for respondents reporting back pain versus back disease or both. The total annual costs for these patients, when extrapolated to the general population, were DKK 9.8 billion for back diseases, DKK 12.1 billion for back pain and DKK 13.0 billion for respondents reporting both pain symptoms and disease. Although the study was only based on a sample of 14,566 persons and the methods for assessing and controlling costs were different from ours, the study still gives us an indication that although the patients do not (yet) have a pain-intensive diagnosis – in this case a back condition – they may still incur relevant costs.

However, although there is a risk that we have not included all relevant patients, using a long follow-up time increases the probability that patients with enduring symptoms do visit hospitals at some point e.g. for diagnostics, e.g. x-rays or scans, in ambulatory hospital day care, which is the point of inclusion for the majority of our patients.

In relation to study specificity, one issue was the "risk" that during the time of follow-up the patient would be cured from the pain-intensive disease, and he/she would no longer belong to the study population. E.g. if the osteoarthritis patient has a total replacement of the affected joint, the cancer patient is cured, or the post-traumatic fracture heals correctly. As the study consists of a number of very different diagnoses with regard to onset and course of disease, aetiology and epidemiology, treatment patterns etc. it has not been possible to define exclusion criteria for "cures". We tried to minimize the risk of including patients who may be cured, in the prevalence-based annual cost estimate, by only looking at costs for patients included in a three-year period, one year before and two years after the first visit to a hospital (inclusion).

Although there are differences between the nine diagnosis groups, generally there is a certain "run-in period" where costs start to increase a couple of months before the patient visits the hospital. The average costs increase manifold in the year following the inclusion, and then drop again during the second year, although not always to the level before the inclusion. This may indicate that for some pain-intensive diagnoses, relevant costs may persist beyond the period under study and that our assessment is underestimated for some diseases. Also, we analysed data for the same observation peri-

od before and after inclusion, for all nine diagnosis groups, so that for simplicity, the follow-up time for health care costs remain the same across all groups. However, it should be noted that the relevance of including resource use of the patients before the inclusion (hospital visit) depends on the nature of the diagnosis. It is highly relevant for chronic diseases, such as arthritis, since the disease may have been symptomatic and treated in the primary care sector long before the patient gets admitted to hospital. It is less relevant for trauma patients whose traumatic incidence directly leads to hospital admission.

The issues mentioned above all relate to the challenges of assessing the socio-economic cost of pain-intensive diseases. Also, pain is not (always) a disease, but a symptom which cannot easily be identified in a registry based study using a set of inclusion criteria for patients and costs. We based our inclusion criteria on ICD-10 diagnosis codes which may be potentially pain-intensive, but which do not sufficiently describe the degree of pain-intensity of the diseases. The same code can be used for the same condition regardless of the degree of pain.

8.3 Concluding remarks: A conservative estimate of the societal cost of pain-intensive diseases

Generally, the study confirms the previous findings from other studies in Denmark on the epidemiology and healthcare resource use of chronic pain patients. In Kronborg et al (9) healthcare costs were particularly high during the year of the inclusion and remained higher than before the inclusion, and this result is confirmed here, and seems to be the case across almost all of the nine diagnosis groups, except the post-fracture pain group.

We chose a conservative approach to estimating costs: controlled our costs, narrowed the follow-up time for costs to two years, and omitted many, yet relevant cost items relating to the pain-intensive patient group due to in-availability of data. Still, the socio-economic cost of pain-intensive diseases to the Danish society per year is considerable. Over the nine diagnosis group it ranges from DKK 565 million (headache) and DKK 8 billion (non-specific chronic pain) per year.

The incident disease-attributable costs cannot be aggregated across diagnosis groups as one patient can occur in more than one group, which is the case in approximately 30% of the patients. However, to provide a rough estimate for healthcare costs alone: if we assume that 30% of the costs are double counted, we end up with DKK 12.7 billion. This figure corresponds to 16-20% of the total annual regional and municipal primary and secondary healthcare costs per year.

Also, our pain-intensive population accounts for a considerable part of the total long-term sickness in Denmark. This is not only a burden to the patients themselves, but also to the employers who suffer a productivity loss, and to the municipalities who co-finance long-term sickness. We chose a conservative approach to assessing the cost of premature retirement and assumed a friction period of three months after which the retired person can/will be replaced by another person. Using the human capital approach to calculate the present value of future productivity losses would have resulted in higher costs. So, in all, despite a conservative and careful estimation approach, the socio-economic consequences and cost of pain-intensive diseases in Denmark can still be said to be substantial.

Although the availability of data on the individual pain patient in Denmark for this study is outstanding seen in an international perspective, there are still some important challenges of using the data as an indicator of the societal cost of pain-intensive diseases. The study results highly demonstrate the challenge and importance of addressing sensitivity and specificity, as well as alternative costs in cost-of illness studies.

References

(1) Gustavsson A, Björkman J, Llungcrantz C, Rhodin A, Rivano-Fischer M, Sjölund KF, Mannheimer C. Socio-economic burden of patients with a diagnosis relating to chronic pain – Register data of 840,000 Swedish patients, Eur Jour Pain 2011, in press; 2010.

(2) Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2. ed. Seattle: IASP Press; 1994.

(3) What is the definition of chronic pain? The British Pain Society 2011. Available from URL: http://www.britishpainsociety.org/index.htm

(4) [Multi-media website with pain assessment tools]. National Pain Education Council 2011. Available from URL: http://www.npecweb.org

(5) Thomsen AB, Sørensen J, Sjøgren P, Eriksen J. Chronic non-malignant pain patients and health economic consequences. Eur J Pain 2002;6:341-52.

(6) Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10(4):287-333.

(7) Eriksen J, Sjøgren P. Epidemiologiske forhold vedrørende langvarige/kroniske noncancersmertetilstande i Danmark. Ugeskrift for Læger 2010;168(20):1947-50.

(8) Eriksen J, Sjogren P, Ekholm O, Rasmussen NK. Health care utilisation among individuals reporting long-term pain: an epidemiological study based on Danish National Health Surveys. Eur J Pain 2004;8(6):517-23.

(9) Kronborg C, Handberg G, Axelsen F. Health care costs, work productivity and activity impairment in non-malignant chronic pain patients. Eur J Health Econ 2009;10(1):5-13.

(10) Thomsen AB, Becker N, Eriksen J. Opioid rotation in chronic non-malignant pain patients. A retrospective study. Acta Anaesthesiol Scand 1999;43(9):918-23.

(11) Hamunen K, Paakkari P, Kalso E. Trends in opioid consumption in the Nordic countries 2002-2006. Eur J Pain 2009 Oct;13(9):954-62.

(12) Bilde L, Rud SA, Dollerup J, Baekke BH, Lange P. The cost of treating patients with COPD in Denmark--a population study of COPD patients compared with non-COPD controls. Respir Med 2007;101(3):539-46.

(13) Hallas J. Conducting pharmacoepidemiologic research in Denmark. Pharmacoepidemiol Drug Saf 2001;10(7):619-23.

(14) Freytag A, Schiffhorst G, Thoma R, Strick K, Gries C, Becker A, et al. Identifikation und Gruppierung von Schmerzpatienten anhand von Routinedaten einer Krankenkasse. Der Schmerz 2010;24(1):12-22.

(15) Rice DP, Cooper BS. The economic value of human life. Am J Public Health Nations Health 1967;57(11):1954-66.

(16) Koopmanschap MA, Rutten FF, van Ineveld BM, van RL. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14(2):171-89.

(17) Personindkomster efter indkomsttype, socio-økonomisk status, enhed, køn og tid. Table INDKP4. Statistics Denmark 2011 [cited 2011 Aug 5]; Available from URL: http://www.statistikbanken.dk/statbank5a/SelectVarVal/Define.asp?MainTable=INDKP4&PLanguage=0&PXSId=0

(18) [Statistics Denmark]. Nyt fra Danmarks Statistik 2007;166(20. april).

(19) Hennekens CH, Buring JE. Epidemiology in Medicine. Philadelphia PA: Lippincott,Williams & Wilkins; 1987.

(20) Koch MB, Davidsen M, Juel K. De samfundsmæssige omkostninger ved rygsygdomme og ryg-smerter i Danmark. København: Statens Institut for Folkesundhed; 2011.

Appendix 1: Diagnosis groups (ICD-10 classification)

Cancer diagnoses (1)

Z51	Other medical treatment
C80	Malignant neoplasm with no specification of the location
C78	Secondary malignant neoplasm of the respiratory and digestive organs
C79	Secondary malignant neoplasm in other locations
C34	Malignant bronchial and pulmonary neoplasm
C77	Secondary and non-specified malignant neoplasm of the lymph nodes
C20	Malignant rectal neoplasm
C85	Other and non-specified types of non-Hodgkin lymphoma
D47	Other neoplasms of uncertain or unknown behaviour of the lymphatic, haemopoietic and related tissues
C64	Malignant renal neoplasm, except renal pelvis
C90	Plasmocytoma and malignant plasma cell neoplasms
D38	Neoplasm of uncertain or unknown behaviour of the middle ear, respiratory and intrathoracic organs
C83	Diffuse non-Hodgkin lymphoma
C32	Malignant laryngeal neoplasm
C25	Malignant pancreatic neoplasm
D46	Myelodysplastic syndromes
C49	Malignant neoplasms of other connective and soft tissues
C10	Malignant oropharyngeal neoplasm
D43	Cerebral and central nervous neoplasm of uncertain or unknown behaviour
C55	Malignant uterine neoplasm, part not specified
C21	Malignant neoplasm of the anus and anal canal
C71	Malignant cerebral neoplasm
C81	Hodgkin's disease [lymphogranulomatosis]
C04	Malignant neoplasm of the floor of the mouth
C15	Malignant oesophageal neoplasm
C02	Malignant neoplasm of other non-specified parts of the tongue
C92	Myeloid leukaemia
C82	Follicular [nodular] non-Hodgkin lymphoma
C13	Malignant hypopharyngeal neoplasm
C09	Malignant tonsillar neoplasm
C76	Malignant neoplasm of other or imprecisely specified locations
C48	Malignant retroperitoneal and peritoneal neoplasm
C41	Malignant neoplasm of the bone and joint cartilage of other and non-specified locations
C01	Malignant neoplasm of the base of the tongue
D01	Carcinoma in situ of other non-specified digestive organs
D90	Immunocompromisation after radiation, chemotherapy and other immunsuppressant treatment
C22	Malignant neoplasm of the liver and intrahepatic biliary ducts
C06	Malignant neoplasm of other non-specified parts of the mouth
C17	Malignant neoplasm of the small intestine

C05 Malignant gingival neoplasm
C88 Malignant immunoproliferative diseases
C75 Malignant neoplasm of other endocrine glands and related structures
C65 Malignant neoplasm of the renal pelvis
C38 Malignant cardiac, mediastinal and pleural neoplasm
C40 Malignant neoplasm of the bones and joint cartilage of the extremities
C14 Malignant neoplasm of other imprecisely specified locations of the lips, buccal cavity and pharynx
C07 Malignant parotid neoplasm
C24 Malignant neoplasm of other non-specified parts of the biliary tract
C31 Malignant nasal sinus neoplasm
D02 Carcinoma in situ of the middle ear and respiratory system
C66 Malignant neoplasm of the ureter
C11 Malignant nasopharyngeal neoplasm
C00 Malignant labial neoplasm
D00 Carcinoma in situ of the buccal cavity, oesophagus and stomach
C08 Malignant neoplasm of other non-specified large salivary glands
C03 Malignant neoplasm of the gums
C72 Malignant neoplasm of the spinal cord, cerebral nerves and other parts of the central nervous system
C45 Mesothelioma
C74 Malignant adrenal neoplasm
C52 Malignant vaginal neoplasm
C46 Kaposi's sarcoma [sarcoma idiopathicum multiplex haemorrhagicum]
C37 Malignant thymus neoplasm
D42 Meningeal neoplasm of uncertain or unknown behaviour
C70 Malignant meningeal neoplasm
C39 Malignant neoplasm of other or imprecisely specified locations ofthe respiratory system and other intrathoracic organs
C30 Malignant neoplasm of the nasal sinuses and middle ear
C47 Malignant neoplasm of the peripheral nerves and autonomic nervous system

Specific pain-intensive back diagnoses (2)

M48 Other spondylopathies
M81 Osteoporosis with no pathological fracture
M46 Other inflammatory spondylopathies
M45 Ankylosing spondylitis
M43 Other deformities of the spine and back
M82 Osteoporosis in diseases classified elsewhere
M49 Spondylopathies in diseases classified elsewhere

Intervertebral disc pain (3)

M51 Other intervertebral disc damage
M50 Cervical intervertebral disc damage

Arthritic pain (4)

M17	Osteoarthritis of the knee
M16	Osteoarthritis of the hip
M19	Other forms of arthritis
M15	Rheumatoid arthritis
M18	Osteoarthritis of the base of the thumb
M25	Other joint diseases not classified elsewhere
M06	Other forms of rheumatoid arthritis
M13	Other forms of arthritis
M05	Seropositive rheumatoid arthritis
M24	Other specified joint damage
R26	Gait and mobility disorders
M07	Psoriatic arthritis and arthritis in primary gastrointestinal diseases
M12	Other specified joint diseases
M14	Joint diseases in other diseases classified elsewhere
M08	Juvenile arthritis
M36	Systemic connective tissue diseases in diseases classified elsewhere
M10	Gout
M11	Other crystal arthropathies
M23	Internal derangement of knee
M77	Other enthesopathies
M77.0	Medial epicondylitis
M77.1	Lateral epicondylitis

Posttraumatic fracture pain (5)

S32	Fracture of the lumbar spine and pelvis
S22	Fracture of the rib(s), sternum and thoracic spine
T08	Fracture of the spine, level not specified
S42	Fracture of the shoulder and upper arm
S12	Cervical fracture
T02	Fractures involving several regions of the body
T91	Sequelae of injuries of the neck and body
S43	Dislocation, sprain and strain of joints and ligaments of shoulder girdle
S53	Dislocation, sprain and strain of joints and ligaments of elbow

Multi-morbid patients (6)

L89	Bed sores
L97	Leg ulcers, not classified elsewhere
L98	Other dermal and subcutaneous diseases, not classified elsewhere
M80	Osteoporosis with pathological fracture

Headache (7)

G43.9	Migraine, not specified
R51	Headache

G44.2 Tension headache
G43.0 Migraine without aura [common migraine]
G43.1 Migraine with aura [classical migraine]
G44.8 Other specified headache syndromes
G43.8 Other types of migraine
G44.1 Vasomotor headache, not classified elsewhere
G44.0 Cluster headache
G43.3 Complicated migraine
G44.4 Drug-induced headache, not classified elsewhere
G44.3 Chronic posttraumatic headache
G43.2 Migrainous condition

Neuropathic pain (8)

G62 Other polyneuropathies
G56 Mononeuropathies of the upper extremity
G63 Polyneuropathy in diseases classified elsewhere
G58 Other mononeuropathies
G50 Trigeminal neuropathies
M79.2 Other soft-tissue diseases, not classified elsewhere
M89.0 Other osteopathies
G57 Mononeuropathies of the lower extremity
G54 Nerve root and plexus diseases
G53 Cerebral neuropathies in diseases classified elsewhere
G55 Nerve root and plexus compression in diseases not classified elsewhere
G60 Hereditary and idiopathic neuropathy
G61 Polyneuritis
G52 Diseases of other cerebral nerves
G59 Mononeuropathy in diseases not classified elsewhere
G64 Other diseases of the peripheral nervous system
G62 Other polyneuropathies
G82 Paraplegia and tetraplegia
G97 Postprocedural disorders of nervous system, not elsewhere classified
R29 Other symptoms and signs involving the nervous and musculoskeletal systems

Non-specific pain/other pain conditions (9)

M54 Back pain
M53 Other diseases of the spine and back, not classified elsewhere
M47 Spondylosis
F45 Somatoform disorder
G96 Other disorders of central nervous system
M70 Soft tissue disorders related to use, overuse and pressure
M75 Shoulder lesions
M75.2 Bicipital tendinitis
M75.0 Adhesive capsulitis of shoulder

M75.4	Impingement syndrome of shoulder
M75.8	Other shoulder lesions
M75.1	Rotator cuff syndrome
M77.9	Enthesopathy, unspecified
M79	Other soft tissue disorders, not elsewhere classified
M79.1	Myalgia
M79.7	Fibromyalgia
M99	Biomechanical lesions, not elsewhere classified
R07	Pain in throat and chest
R07.4	Chest pain, unspecified
R10	Abdominal and pelvic pain
R10.1	Pain localized to upper abdomen
R10.2	Pelvic and perineal pain
R52	Pain, not elsewhere classified
R52.9	Pain, unspecified
S13	Dislocation, sprain and strain of joints and ligaments at neck level
S13.4	Sprain and strain of cervical spine (Whiplash injury)
T85	Complications of other internal prosthetic devices, implants and grafts
T88	Other complications of surgical and medical care, not elsewhere classified
T92	Sequelae of injuries of upper limb
T93	Sequelae of injuries of lower limb
T94	Sequelae of injuries involving multiple and unspecified body regions

Appendix 2: Moderate and severe pain treatment groups

Group ATC Title

1	N02AA01	Morphine
2	N02AA03	Hydromorphone
3	N02AA05	Oxycodone
4	N02AA08	Dihydrocodeine
5	N02AA55	Oxycodone combined with naloxone
6	N02AA59	Codeine comb. excl. psychotropics
7	N02AA64	Codeine combined with propyphenazone
8	N02AA65	Codeine combined with diclofenac
9	N02AA66	Codeine combined with acetylsalicylic acid
10	N02AA69	Codeine combined with paracetamol
11	N02AB02	Pethidine
12	N02AB03	Fentanyl
13	N02AE01	Buprenorphine
14	N02AX02	Tramadol
15	N02AX52	Tramadol combinations
16	N02AX52	Tilidate combinations
17	N02AB01	Ketobemidon (Ketogan Novum)
18	N02AG02	Ketogan
19	N07BC02	Metadon (tablet)

Group ATC Title WHO ladder step

1	N02AA01	Morphine	3
2	N02AA03	Hydromorphone	3
3	N02AA05	Oxycodone	3
4	N02AA08	Dihydrocodeine	2
5	N02AA55	Oxycodone combined with naloxone	3
6	N02AA59	Codeine comb. excl. psychotropics	2
7	N02AA64	Codeine combined with propyphenazone	2
8	N02AA65	Codeine combined with diclofenac	2
9	N02AA66	Codeine combined with acetylsalicylic acid	2
10	N02AA69	Codeine combined with paracetamol	2
11	N02AB02	Pethidine	3
12	N02AB03	Fentanyl	3
13	N02AE01	Buprenorphine	3
14	N02AX02	Tramadol	2
15	N02AX52	Tramadol combinations	2
16	N02AX52	Tilidate combinations	2
17	N02AB01	Ketobemidon (Ketogan Novum)	3
18	N07BC02	Metadon (tablet)	na
19	N02AC04	Dextropropoxyphene	3

20	N02BA01	Acetylslicylic acid (ASA)	1
21	N02BE01	Paracetamol	1
22	N02BE51	Paracetamol combination (Citodon)	na
23	M01A	NSAID	1
24	N06AA	Tricyclic antidepressants (TCA)	na
25	N03AX12	Gabapentin	na
26	R05DA04	Codeine	2
27	N02AC04	Dextropropoxyphene	2
28	N02AC54	Dextropropoxyphene, comb. excl. Psycholeptics	2
29	N02AG01	Morphine and antispasmodics	3
30	N02AB	Phenylpiperidine derivatives	3
31	N02AG02	Ketogan	3
32	N02AC	Diphenylpropylamine derivatives	3
33	N01AH01	Fentanyl	3
34	N01AH03	Sufentanil	3
35	N02AG04	Hydromorphone and antispasmodics	3
36	N01AH02	Alfentanil	3
37	N02AF02	Nalbuphine	3

Appendix 3: Definitions for Analysis of Pain Medication Prescription Patterns

From 1st pain prescription until 6 months (0= first prescription = first line treatment)

CONTINUERS (a new prescription 3-6 months after the first)

MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
DRUG									
Morphine	x			x				(x)	
Fentanyl									

2nd line treatment (or SWITCH) (no first line prescription 3-6 months after 1st prescription)

MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
DRUG									
Morphine	x								
Fentanyl			x						

ADD-ON (must be a subset of "continuers as well"?)

MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
DRUG									
Morphine	x			x				(x)	
Fentanyl		x							

DISCONTINUERS

MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
DRUG									
Morphine	x								
Fentanyl									

Late switchers (with a repeated 1st line prescription)

A 2nd line drug WITH a repeated first line prescription

MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
DRUG									
Morphine	x				x				
Fentanyl								x	

From 2nd line pain prescription and 6 months (0= first prescription of second line treatment for morphine)

	CONTINUERS 2nd line (a new prescription 3-6 months after the 2nd line prescription following Morphine)								
First line	MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	DRUG									
Morphine	Fentanyl	x			x				(x)	
	Oxycodone									

	3rd line treatment (or SWITCH) (no renewed second-line prescription 3-6 months after 1st prescription								
First line	MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	DRUG									
Morphine	Fentanyl	x								
	Oxycodone			x						

	ADD-ON (must be a subset of "continuers as well"?)								
First line	MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	DRUG									
Morphine	Fentanyl	x			x				(x)	
	Oxycodone		x							

	2nd line DISCONTINUERS								
First line	MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	DRUG									
Morphine	Fentanyl	x								
	Oxycodone									

Late switchers (with a repeated 2nd line prescription)

A 2nd line drug WITH a repeated first line prescription

First line	MONTHS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	DRUG									
Morphine	Fentanyl	x				x				
	Oxycodone								x	

Appendix 4: Pain Medication Prescription Patterns

Slow-Release Strong Opioid Prescription Patterns

Slow-Release Strong Opioid 2nd and 3rd line users

Below, the 2nd and 3rd line slow-release strong opioid treatments of each of the 1st line users are shown. The 2nd line treatment for the 14,505 first line morphine users who switched is shown below. Most of them switched to Fentanyl.

Figure B 1: 2nd line prescriptions for 1st line morphine users who switched

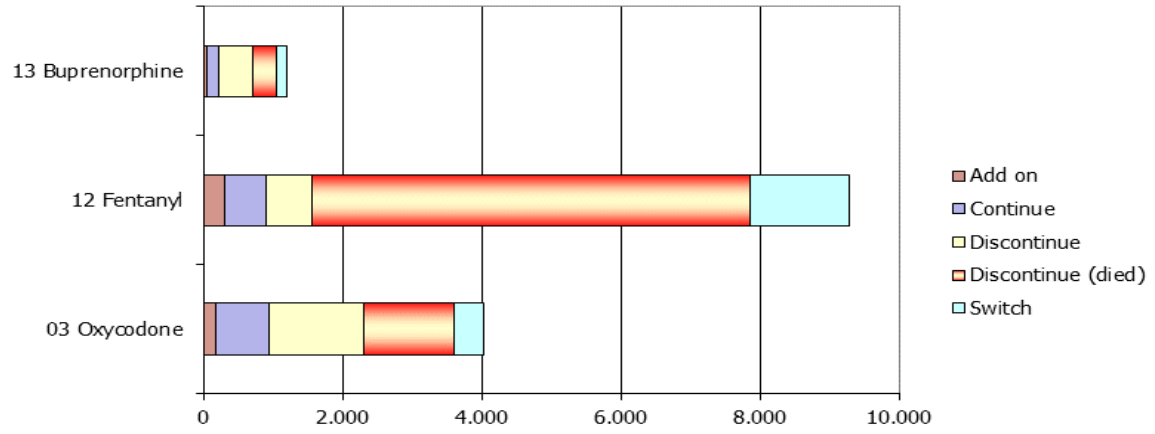
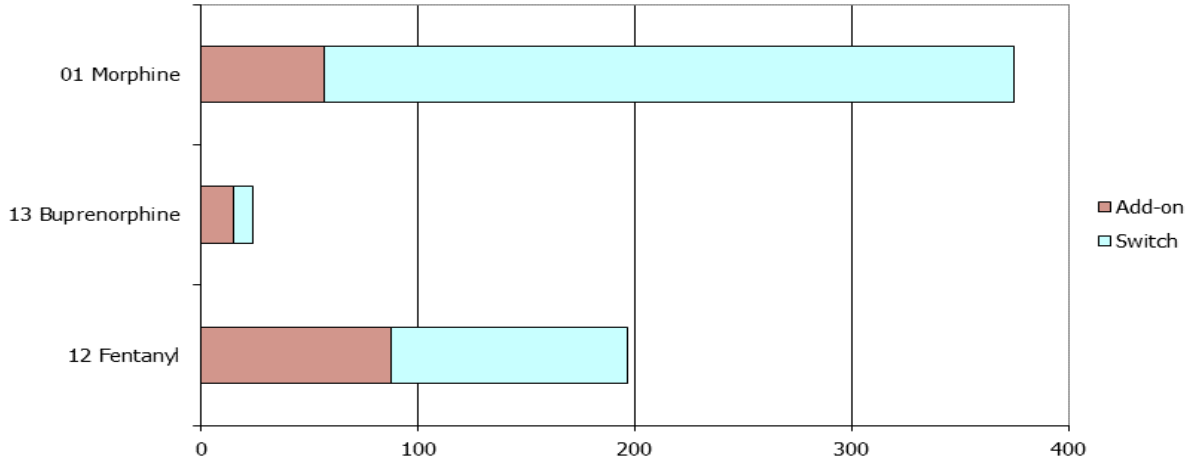
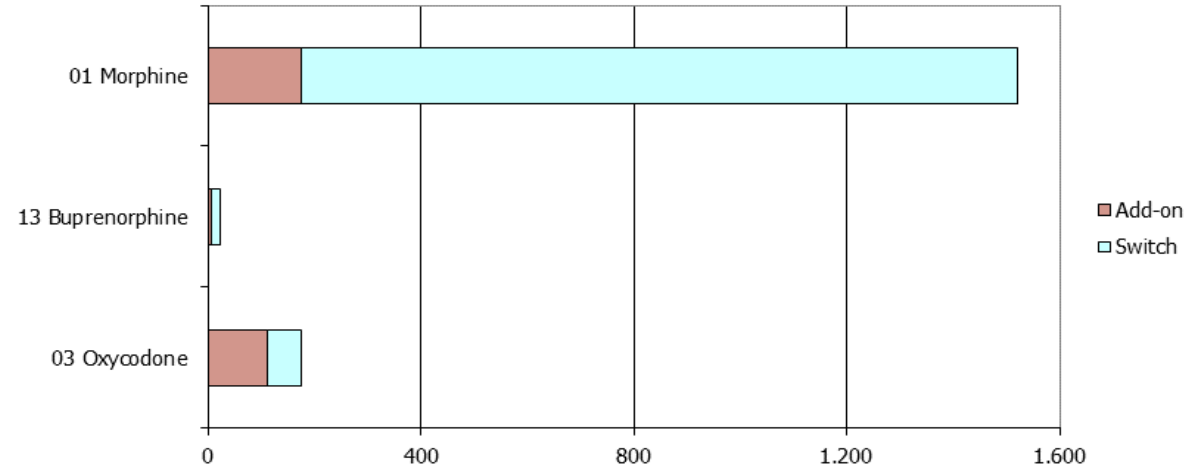


Figure B 2: 3rd line prescriptions for 1st line morphine and 2nd line oxycodone users who switched



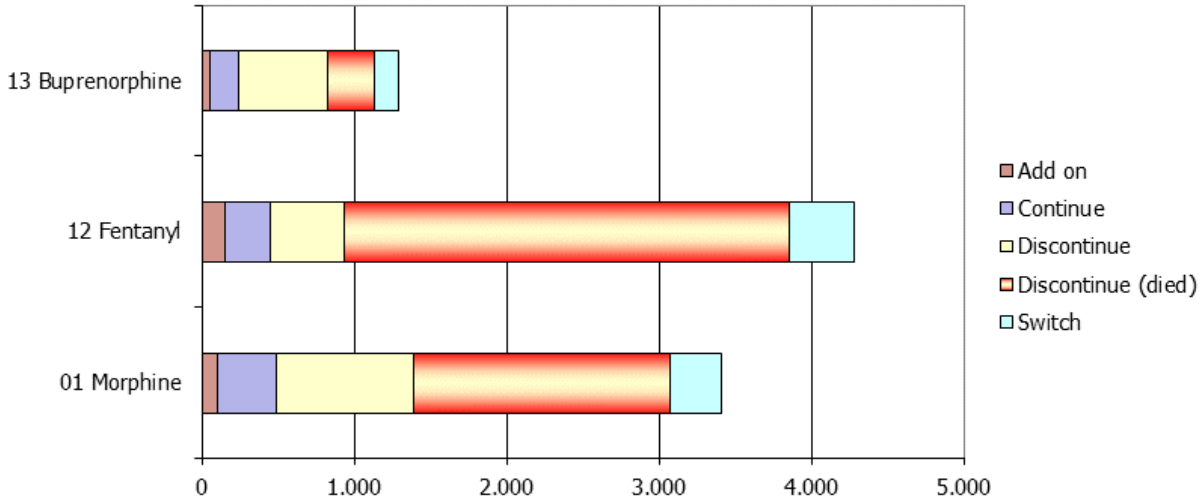
Among the first line morphine users who switched to oxycodone as a 2nd line treatment, the majority, 375, switched back to morphine as a 3rd line treatment or as an add-on to oxycodone, and 197 switched to, or added, Fentanyl to their 2nd line treatment.

Figure B 3: 3rd line treatment for 1st line morphine and 2nd line fentanyl users who switched



The same pattern (switch back to morphine) is seen for 2nd line fentanyl users.

Figure B 4: 2nd line prescriptions for 1st line oxycodone users who switched



Most of the 1st line oxycodone users who switched, had fentanyl as their 2nd line treatment, and the majority of these patients were terminal.

Figure 0-5 shows the 3rd line prescriptions for 1st line oxycodone users who switched to morphine. Most of them switched back to oxycodone. The same pattern is seen for 2nd line fentanyl users (figure 0-6).

Figure B 5: 3rd line prescriptions for 1st line oxycodone and 2nd line morphine users who switched

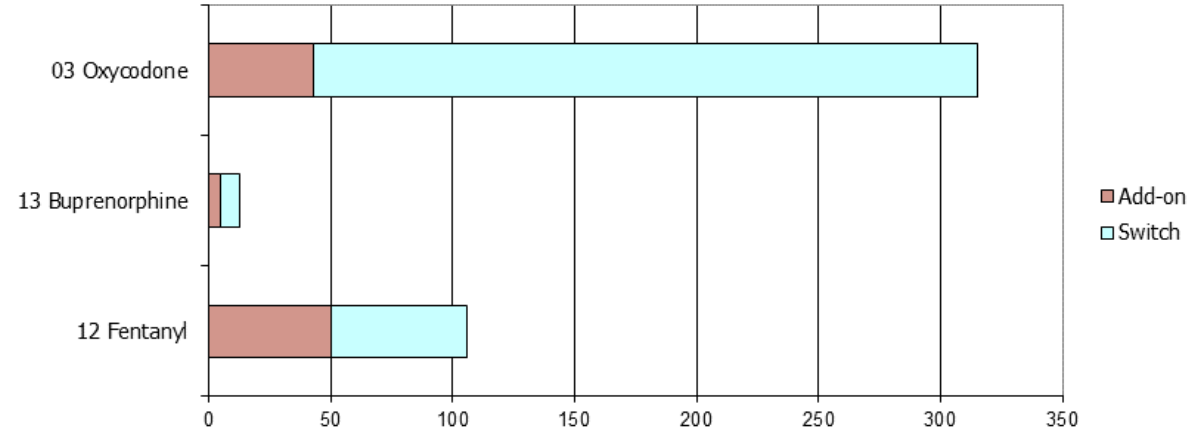
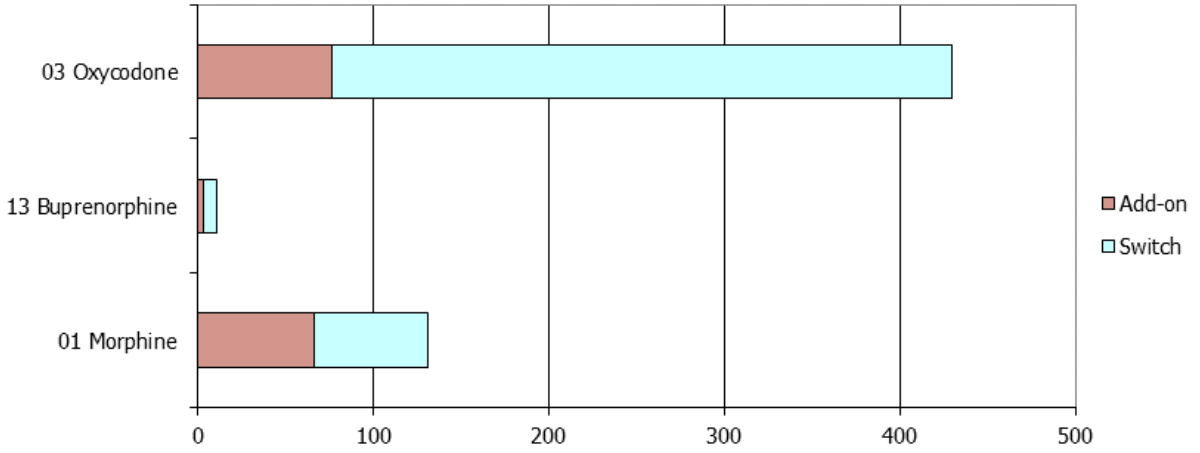


Figure B 6: 3rd line prescriptions for 1st line oxycodone and 2nd line fentanyl users who switched



For 1st line fentanyl users who switched most of them had morphine as a 2nd line treatment (figure 0-7), and most of them were terminal patients.

Figure B 7: 2nd line prescriptions for 1st line fentanyl users who switched

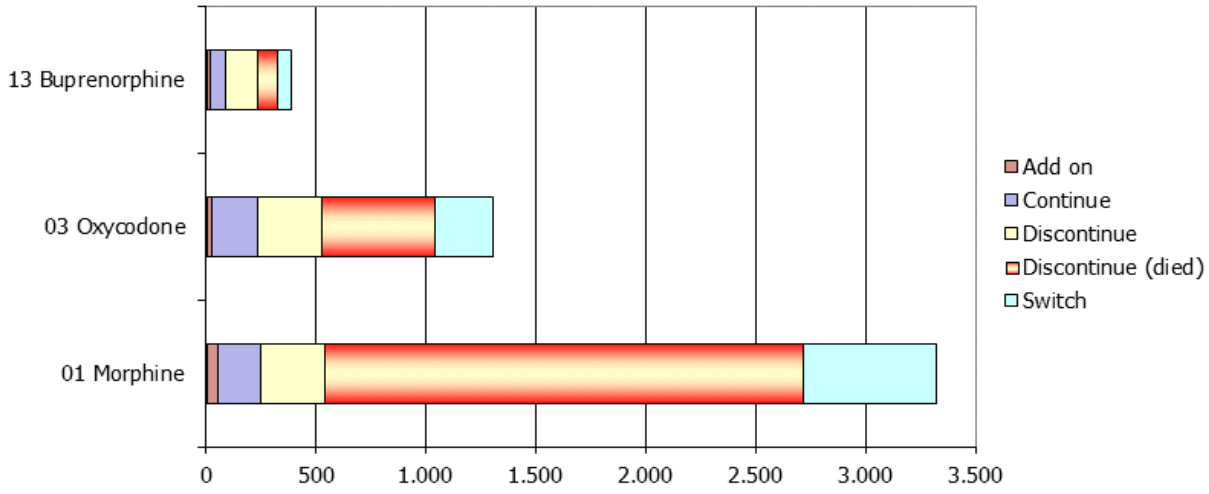


Figure B 8: 3rd line treatment for 1st line fentanyl and 2nd line morphine who switched

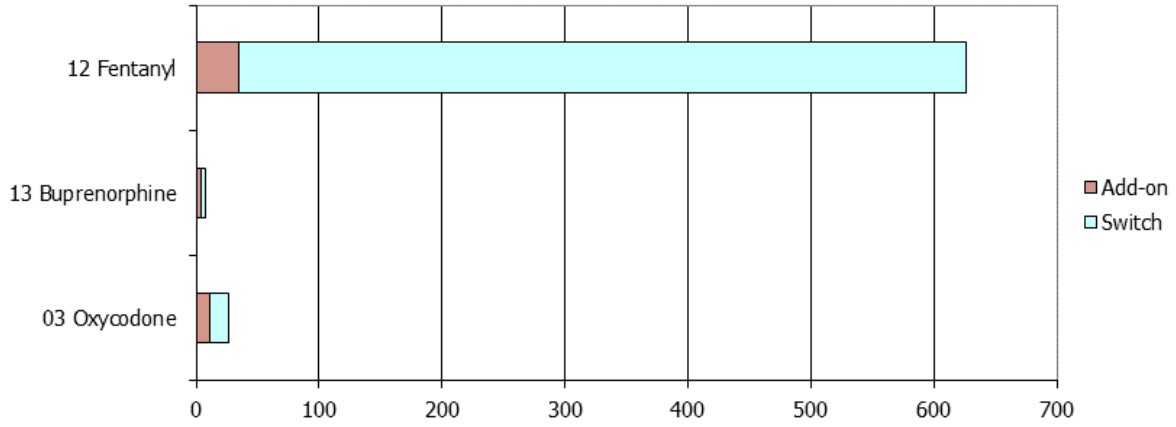
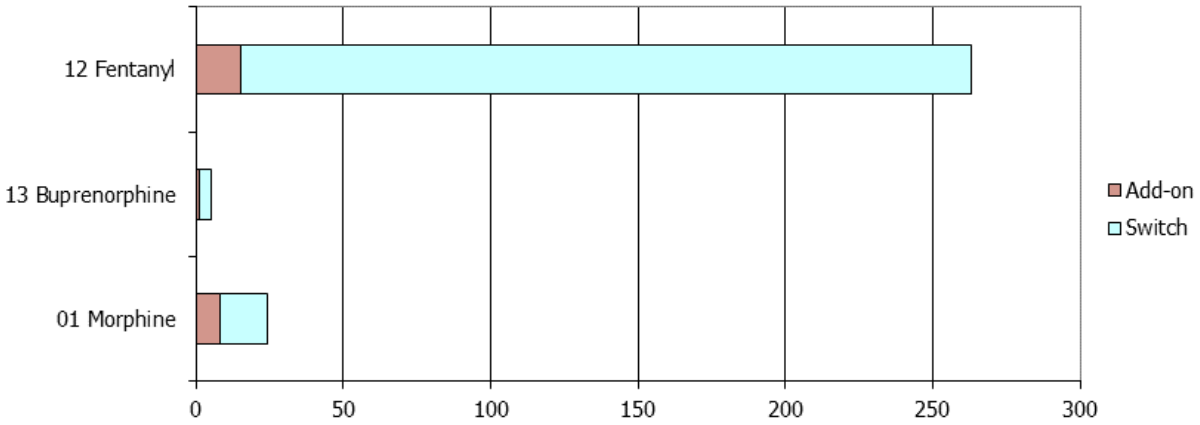


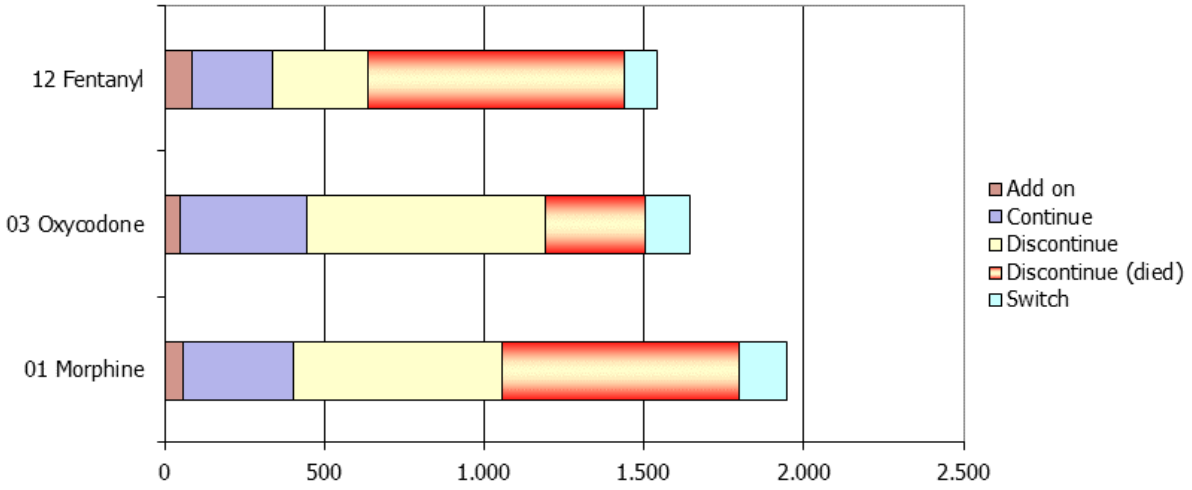
Figure B 9: 3rd line treatment for 1st line fentanyl and 2nd line oxycodone users who switched



For the 1st line fentanyl users who switched to either morphine (figure 0-8) or oxycodone (figure 0-9) most of them switched back to fentanyl.

Buprenorphine was the least used of the four drugs. 2nd line drugs for burprenorphine users who switched were both fentanyl, oxycodone, and morphine (figure 0-10).

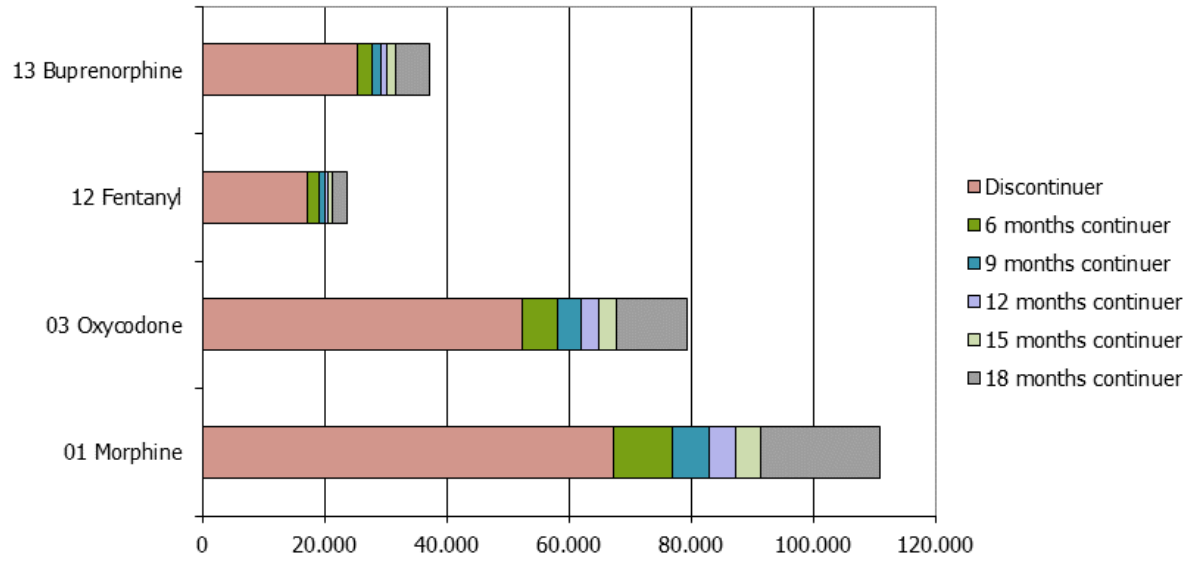
Figure B 10: 2nd line prescriptions for 1st line buprenorphine users who switched



Slow-Release Strong Opioid Medication Treatment Survival

Figure 0-11 below follows the patients who had a first slow-release strong opioid prescription for 18 months. As data are only available until the end of 2008, the figure only includes patients who had their first prescription before the middle of 2007[14]. Most patients do not continue treatment. However, for morphine, about 40% continue their treatment beyond 6 months, and 18% or 19,618 patients continue for 18 months or more. For oxycodone only 33% continue treatment, and 14.5 %, or 11,581 patients continue for 18 months or more.

Figure B 11: Number of patients on each 1st long-term slow-release strong opioid prescription and the proportion with another dispatch over the following 18 months



[14] Therefore not including some 8,000 morphine users from 2007-08.

Slow-Release Strong Opioid Medication - Strength of Prescriptions

In the following three tables, the proportions of patients on different strengths of their SRSO prescriptions are displayed[15]. The proportion of patients on higher doses/strengths of the medication expectedly increases the longer they stay on treatment.

Figure B 12: Strength of prescription (mg), morphine

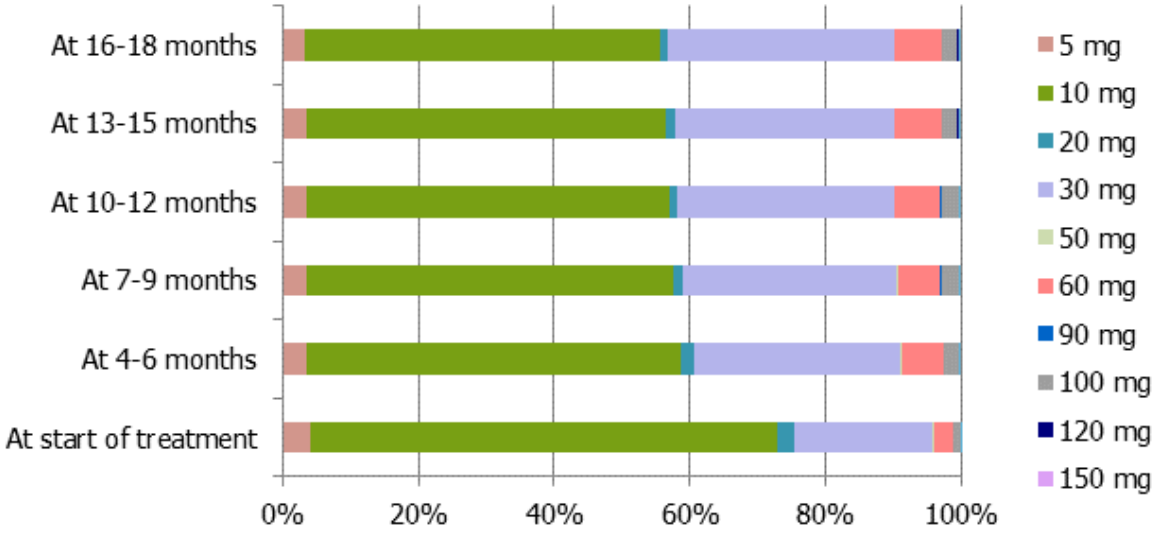
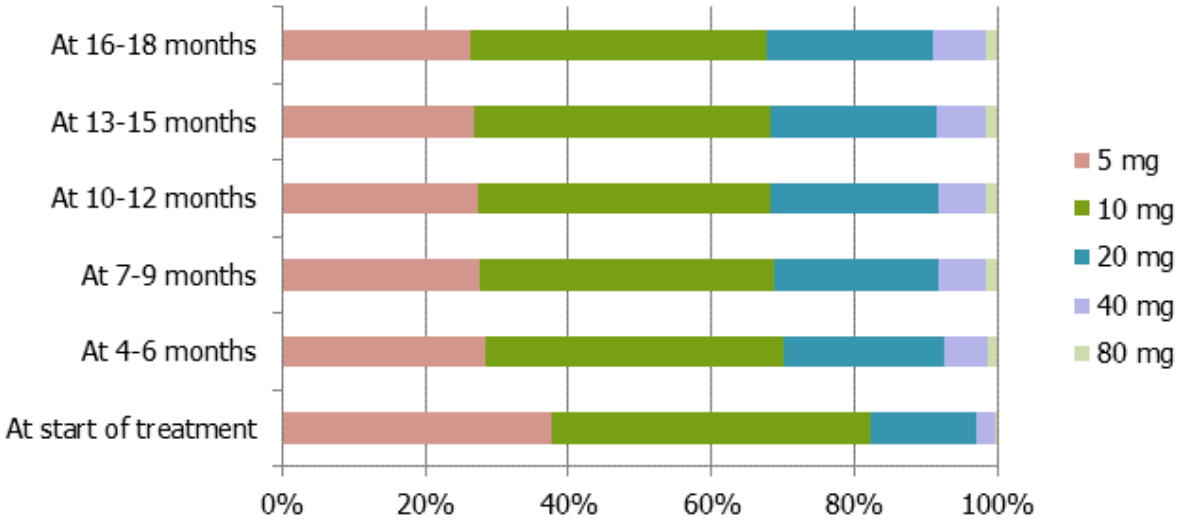
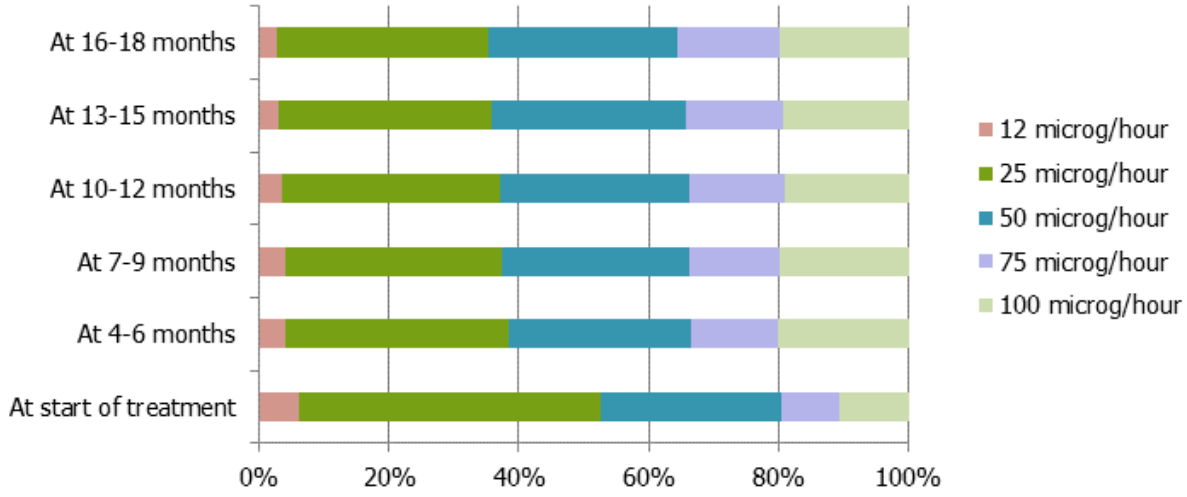


Figure B 13: Strength of prescription (mg) oxycodone



[15] As to morphine and oxycodone, the calculation is limited to prescription with the strength unit, mg. This means that prescriptions with the strength unit MGM (mg/ml) are not included, as the quantity is not available. The same goes for Fentanyl, which is displayed in mg/hour.

Figure B 14: Strength of prescription (mg/hour), fentanyl



Slow-Release Strong Opioid Late Switches

"Late switches" were defined as a switch in slow-release strong opioid treatment after a continuation of the first line treatment for at least 3-6 months. Late switches were only observed in a small proportion of patients (1,799 patients). Most frequent late switches are oxycodone and fentanyl.

Figure B 15: **Number of patients with a late switch after continued 1st line slow-release strong opioid prescription**

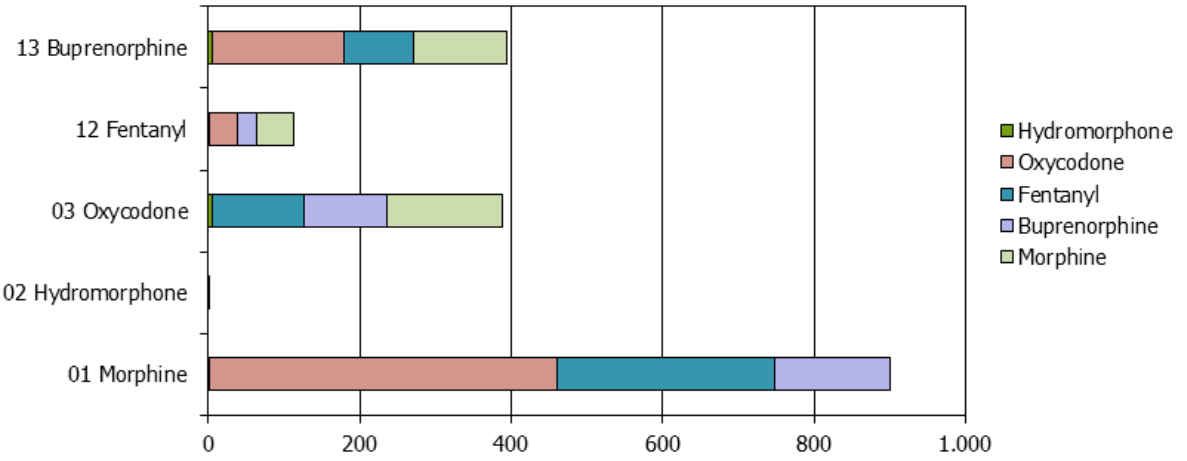
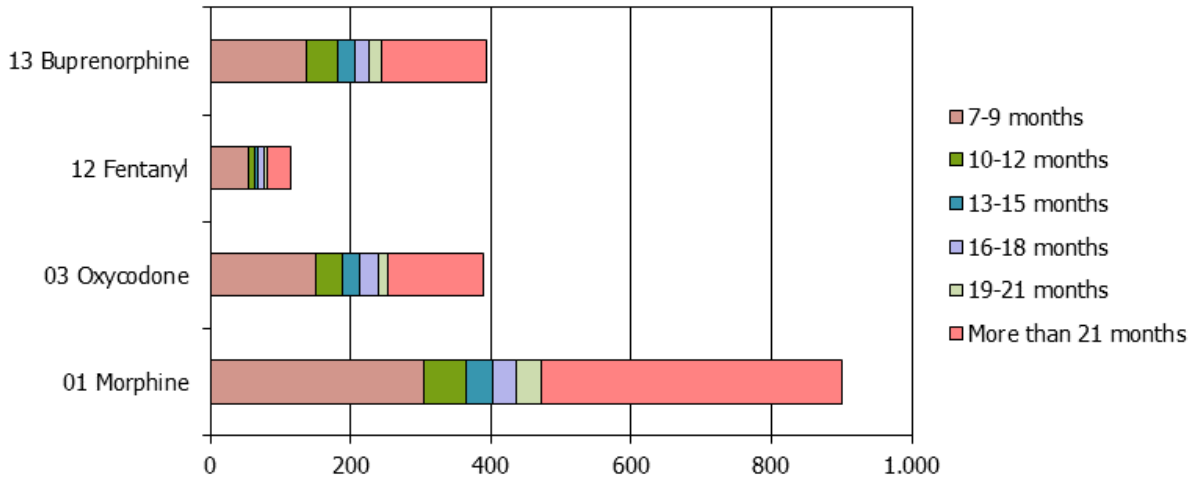


Figure B 16: Number of patients with a late switch from one slow-release strong opioid prescription to another and time of switch



Other pain treatments for patients discontinuing the first line SRSO treatment (4-9 months)

A large proportion of patients on SRSO 1st line treatment discontinue the treatment, without switching to other SRSO's. These patients are denoted discontinuers.

The switch patterns analysed so far include the 4-6 month period following the first SRSO-prescription. The tables below show what other pain prescriptions the SRSO discontinuers have had in the 4-9 months following the first SRSO prescription. Even though these patients per definition are denoted "discontinuers", they might actually get another prescription of the first line SRSO in the 7-9 months period after the first SRSO-prescription. For example, morphine users having no new morphine prescriptions in the following 4-6 month period are denoted discontinuers, even though they might have a morphine prescription in the 7-9 months period.

Table 0-1 presents results for the most frequent (more than 1,000 patients) pain prescription groups. It should be noted, that each SRSO discontinuer belongs to one particular column according to first line SRSO, but can appear in more than one row in that particular column.

For all possible 1st line SRSO discontinuers, NSAID, paracetamol and tramadol are the three most frequent other pain treatments prescribed in the 4-9 months period.

Furthermore, these subsequent pain treatments prescribed to the SRSO discontinuers are analysed according to combinations thereof. Table 0-1 gives a total picture of all SRSO discontinuers with respect to possible other pain treatments.

Frequencies for combinations of pain treatments involving one or more of NSAID, paracetamol and tramadol are presented. For example, for "Tramadol" for the morphine discontinuers the frequency of 2.545 covers all combinations involving tramadol but neither paracetamol nor NSAID (but possibly some of the less frequent pain treatments).

The number of patients having pain treatments not including any of the three most frequent is also provided in the table, along with the number of patients not having new pain treatments, allowing summing to the total number of SRSO discontinuers.

Table B-1: Pain prescriptions for 1st line SRSO discontinuers in the 4-9 months period following the first line SRSO. Patients can appear in more than one row for the respective column.

First line SRSO treatment		Morphine	Hydro-morphone	Oxycodone	Fentanyl	Bupren-orphine	Total
Total number of discontinuers		46,295	128	65,778	4,646	25,190	142,037
Prescribed pain treatment pur-chased in the period 4-9 months after the first SRSO for discontinuers	Morphine	2,743	0	324	84	201	3,352
	Oxycodone	499	2	2,600	99	219	3,419
	Codeine combinations excl. psychotr	1,744	6	2,004	232	1,115	5,101
	Buprenorphine	170	0	228	41	962	1,401
	Tramadol	9,655	44	10,615	1,387	5,435	27,136
	Methadone tablets_	539	6	252	85	335	1,217
	Paracetamol	14,295	46	15,784	2,299	7,280	39,704
	NSAID	13,069	36	18,646	1,331	7,928	41,010
	Tricyclic antidepressants	2,129	9	2,114	262	1,178	5,692
	Gabapentin	1,025	5	1,291	151	486	2,958
	Codeine	3,699	6	2,896	390	2,086	9,077
	Dextropropoxyphene	514	2	275	80	288	1,159
	Ketogan	3,476	11	1,629	514	1,075	6,705

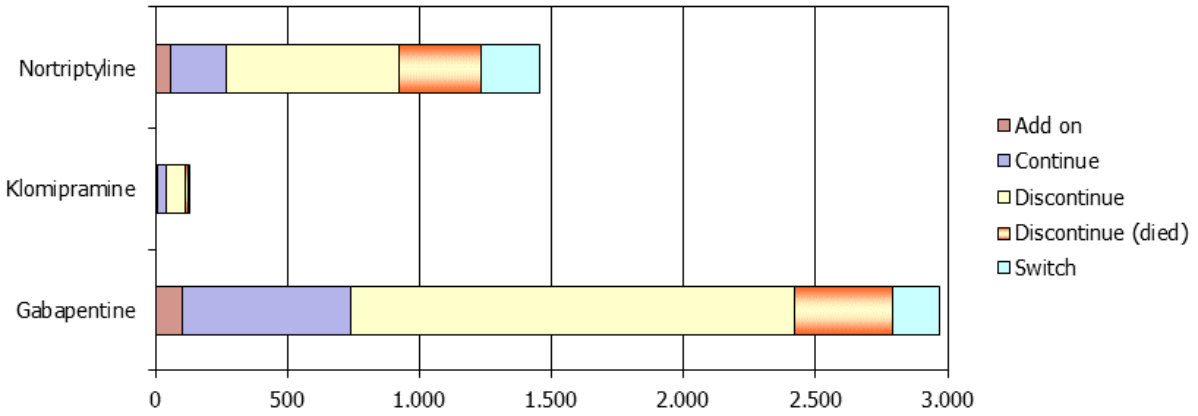
Table B-2: Pain prescriptions for 1st line SRSO discontinuers in the 4-9 months period following the first line SRSO. Tramadol, paracetamol and NSAID are presented, being the most frequent other pain prescriptions of these discontinuers. Patients appear only once in this table.

Combination of other pain treatments	Morphine	Hydro-morphone	Oxycodone	Fentanyl	Bupre-norphine	Total no. of other pain treatments
No other pain prescription	17,997	40	31,806	1,178	9,763	60,784
Tramadol	2,545	17	3,085	315	1,508	7,470
Tramadol and paracetamol	3,180	14	2,856	582	1,518	8,150
Tramadol, paracetamol and NSAID	2,135	6	2,454	350	1,274	6,219
Tramadol and NSAID	1,795	7	2,220	140	1,135	5,297
Paracetamol	5,752	12	6,205	898	2,612	15,479
Paracetamol and NSAID	3,228	14	4,269	469	1,876	9,856
NSAID	5,911	9	9,703	372	3,643	19,638
Combinations neither involving tramadol, paracetamol nor NSAID	3,752	9	3,180	342	1,861	9,144
Total number of discontinuers	46,295	128	65,778	4,646	25,190	142,037

Neuropathic pain prescription patterns

2nd line and 3rd line Neuropathic pain prescription patterns

Figure B 17: Number of 1st line amitriptyline users (who switched), on each 2nd line neuropatic pain prescription and the proportions with another dispatch after prescription



In figures 0-18 – 0-30 below, 3rd line prescriptions for 1st line amitriptyline and 2nd line gabapentine who switched are shown. The general pattern is that patients switch back to their 1st line drug, amitriptyline.

Figure B 18: 3rd line users for 1st line amitriptyline and second line gabapentine who switched

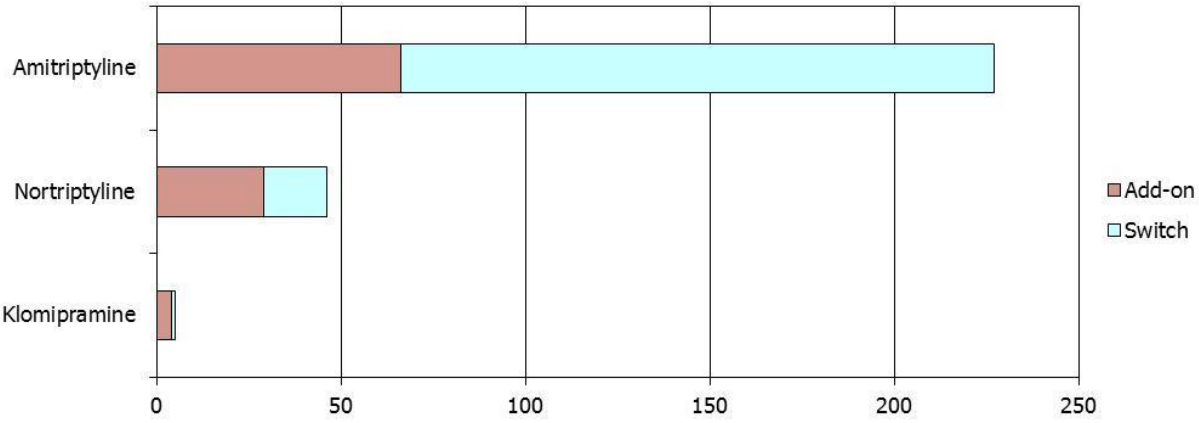


Figure B 19: Number of 3rd line users for 1st line amitriptyline and 2nd line klomipramine who switched

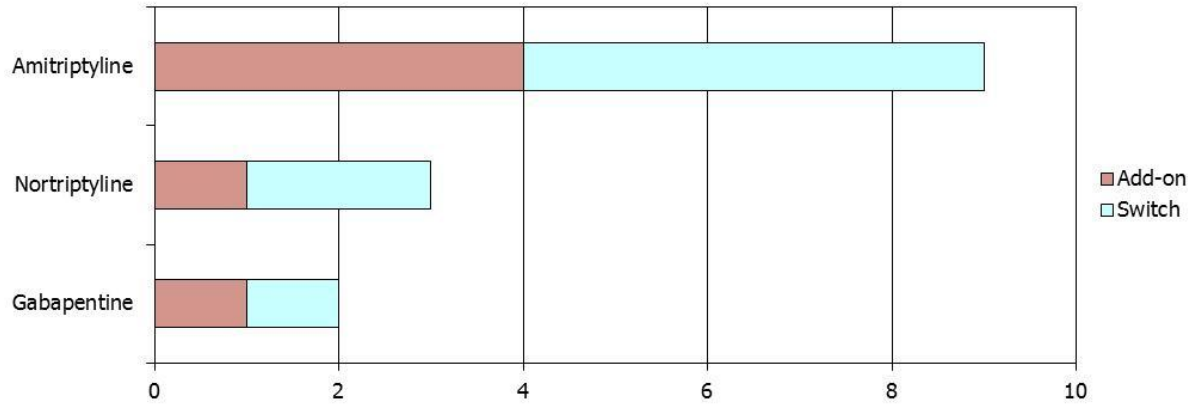
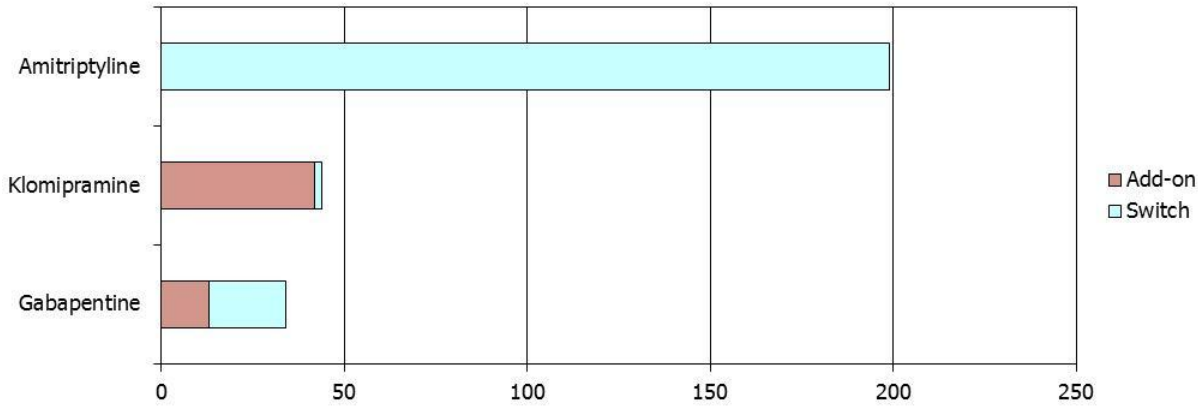


Figure B 20: Number of 3rd line users for 1st line amitriptyline and 2nd line nortriptyline who switched



For 1st line gabapentine users who switched, most of them switched to amitriptyline as a 2nd line treatment (0-21). 3rd line treatment were mostly gabapentine again (0-22 – 0-24)

Figure B 21: Number of 1st line gabapentine users who switched on each 2nd line neuropathic pain prescription and the proportions with another dispatch after prescription

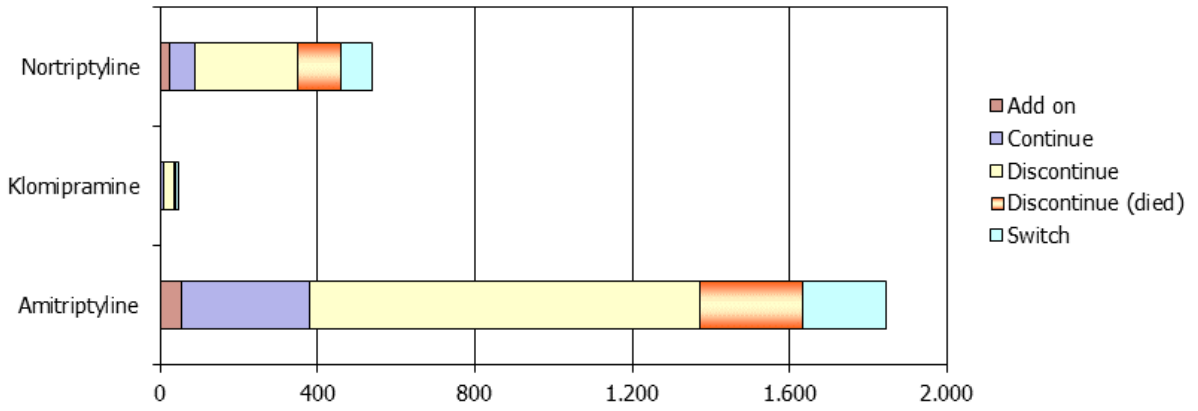


Figure B 22: 3rd line users for 1st line gabapentine and second line amitriptyline who switched

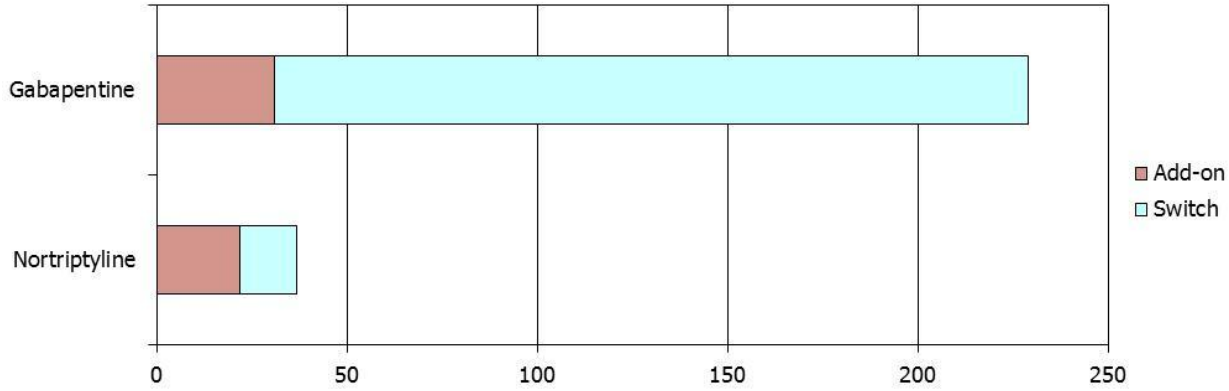


Figure B 23: 3rd line users for 1st line gabapentine and 2nd line nortriptyline who switched

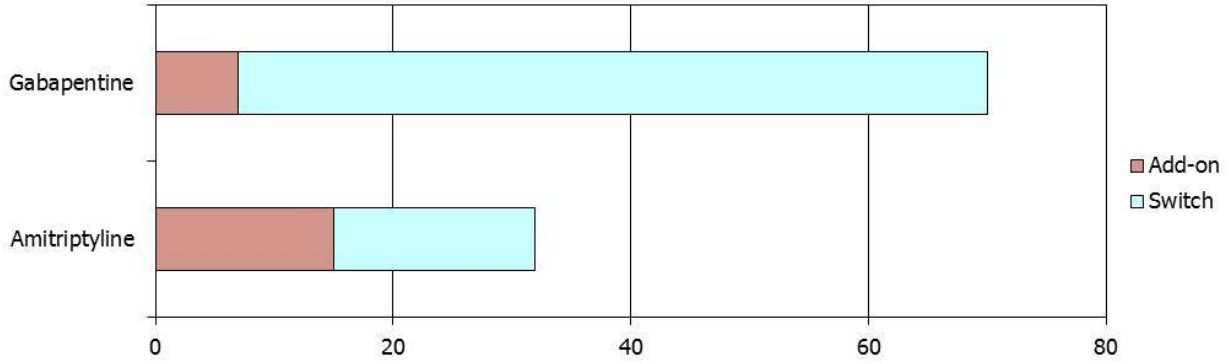


Figure B 24: 3rd line users for 1st line gabapentine and 2nd line klomipramine who switched

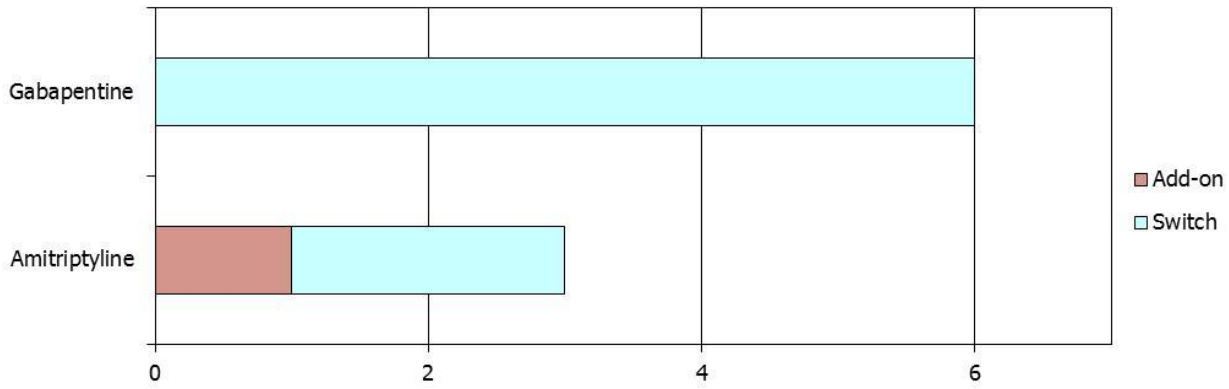
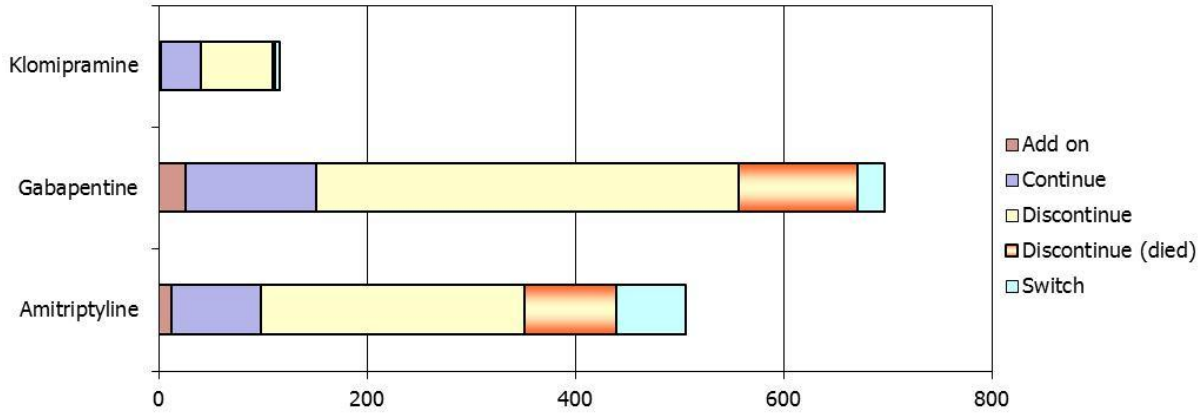
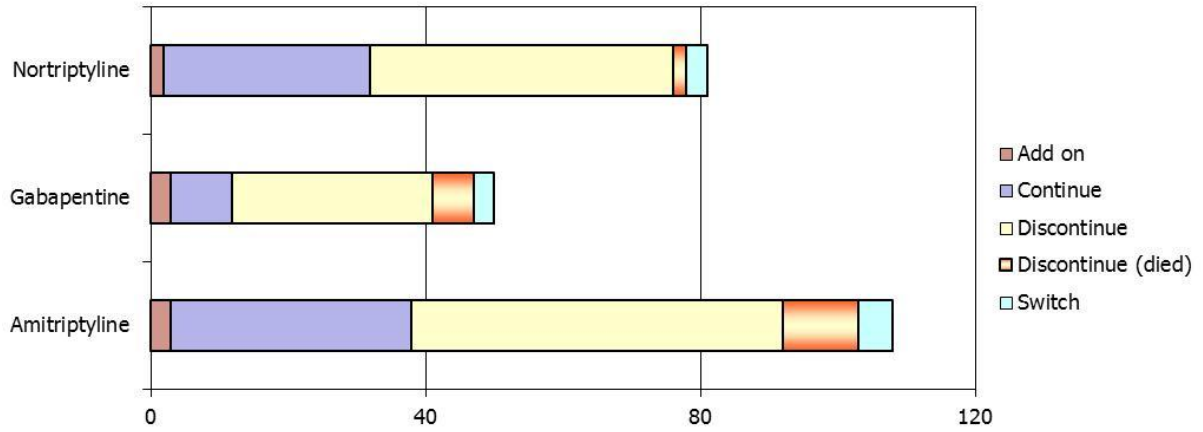


Figure B 25: Number of 1st line nortriptyline users who switched on each 2nd line neuropatic pain prescription and the proportions with another dispatch after prescription



Most of the nortriptyline users who switched to another treatment, switched to gabapentine (0-25), and most of the klomipramine users who switched, switched to amitriptyline (0-26).

Figure B 26: Number of 1st line klomipramine users who switched on each 2nd line neuropatic pain prescription and the proportions with another dispatch after prescription

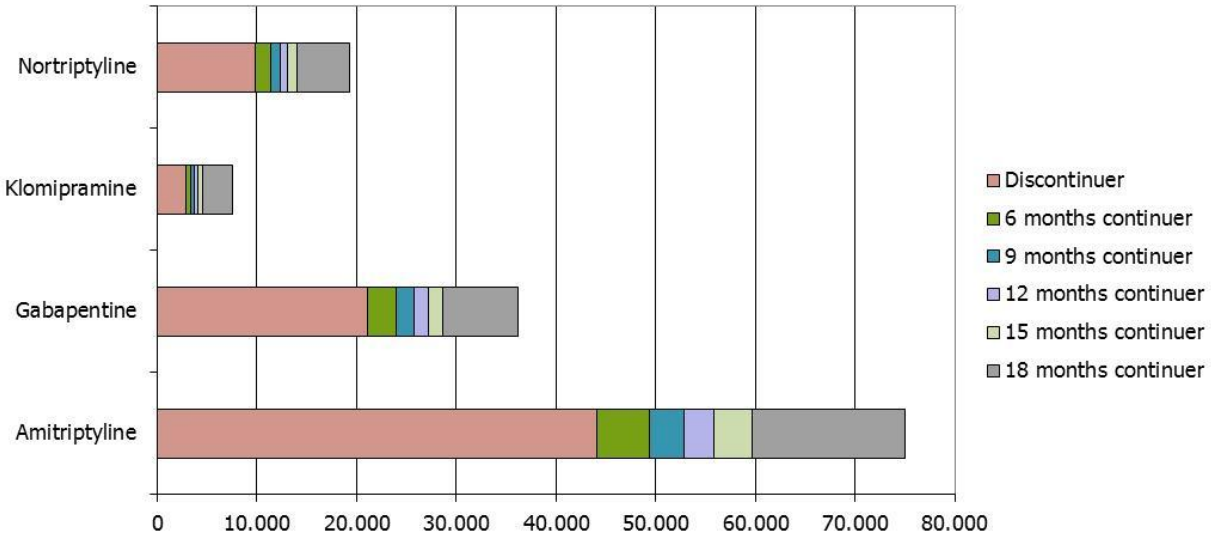


Neuropathic Pain Medication Treatment Survival

The figure below follows the patients who had a first line neuropathic pain prescription before in the middle of 2007[16]. Most patients do not continue their amitriptyline and gabapentine treatment (58-59%), but for both drugs approximately 20% continue treatment for 18 months or more. For the 7,514 first line users of klomipramine, only 40% discontinue treatment.

[16] Therefore not including some neuropathic pain therapy users from 2007-08.

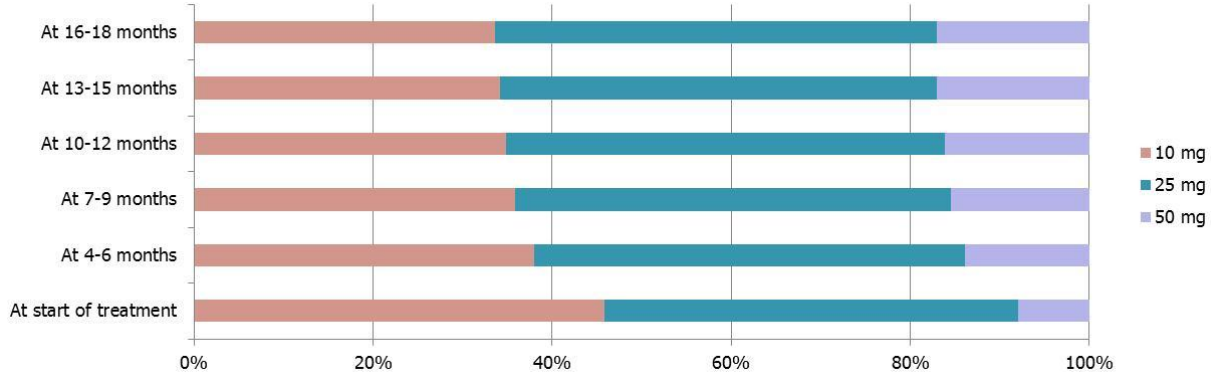
Figure B 27: Number of patients on each 1st line neuropathic pain prescription and the proportions with another dispatch over the following 18 months



Neuropathic pain medication: Strength of Prescriptions

In the following tables, the proportions of patients on different strengths of their prescriptions are displayed[17]. As was the case with SRSO, the proportion of patients on higher doses/strengths of the neuropathic pain medication expectedly increases the longer they stay on treatment, although the picture is not as evident as for SRSO's.

Figure B 28: Strengths of prescription (mg), amitriptyline



[17] As to morphine and oxycodone, the calculation is limited to prescription with the strength unit, mg. This means that prescriptions with the strength unit MGM (mg/ml) are not included, as the quantity is not available. The same goes for Fentanyl, which is displayed in mg/hour.

Figure B 29: Strengths of prescription (mg) gabapentine

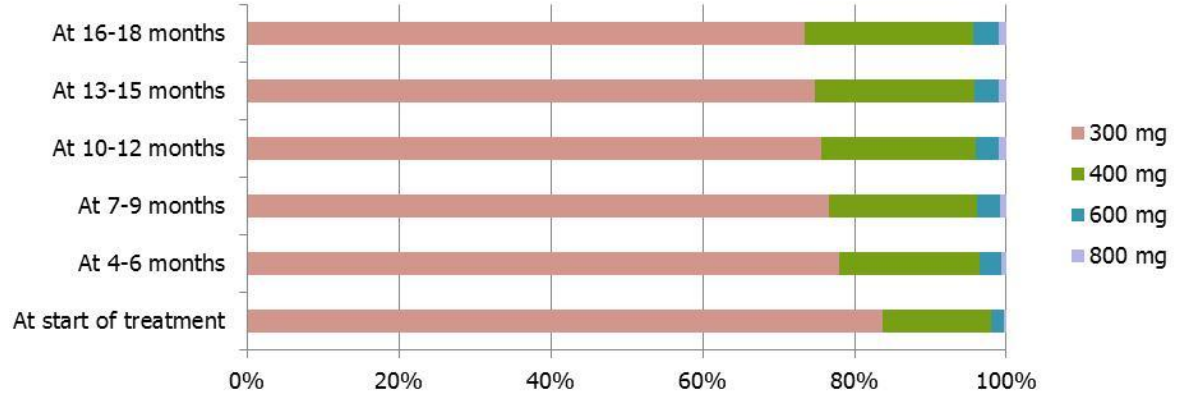


Figure B 30: Strength of prescription (mg) klomipramine

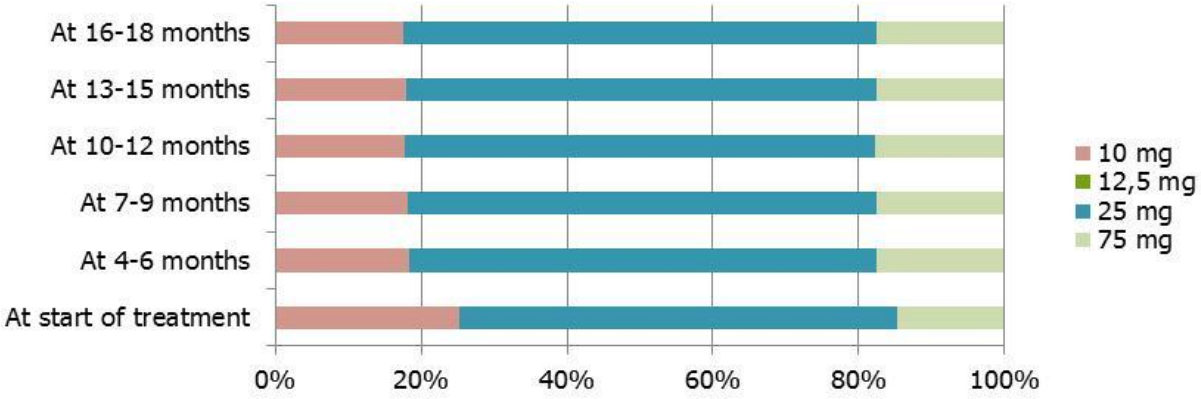
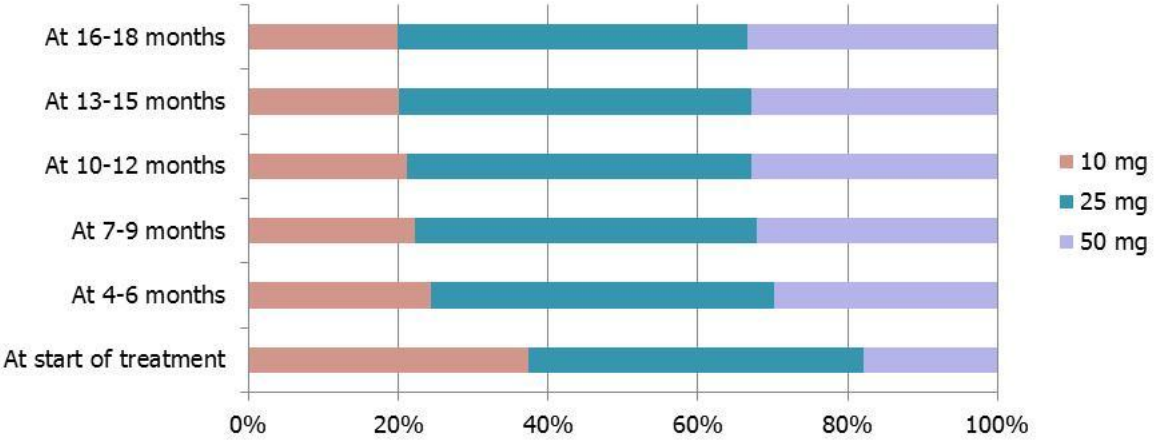


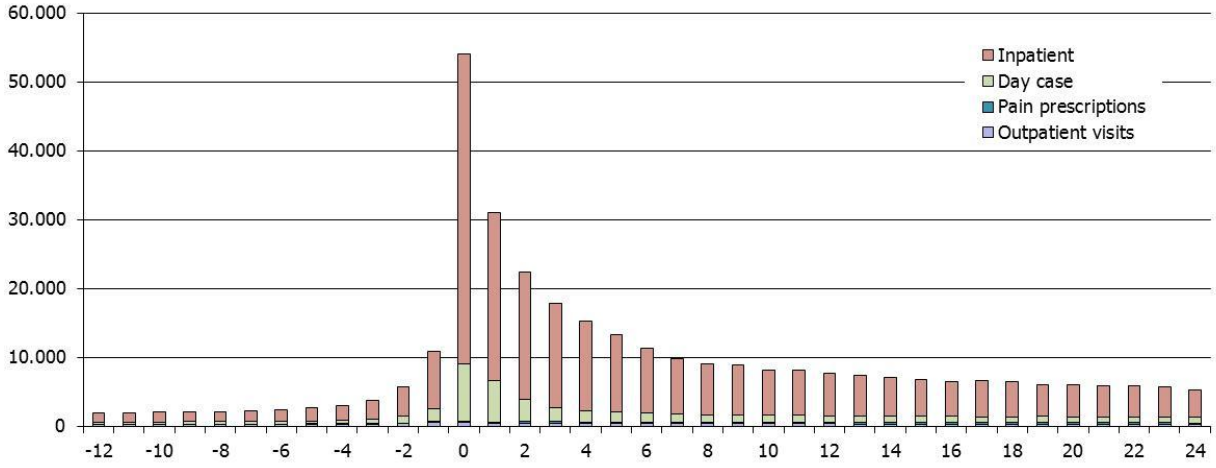
Figure B 31: Strength of prescription (mg) nortriptyline



Appendix 5: Healthcare Cost over time by Diagnosis Groups

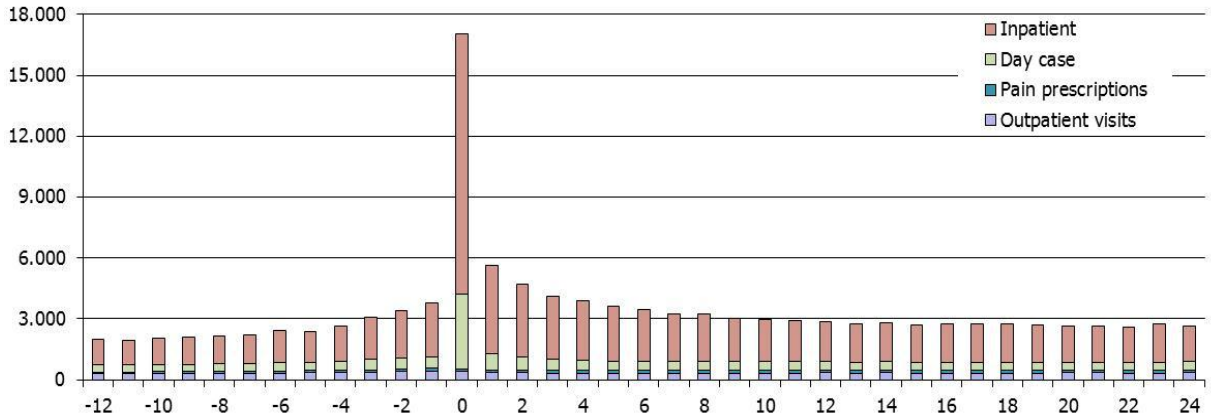
In the following nine figures below, we calculated healthcare costs from 12 months before the inclusion (month 0) to 24 months after. Patients only count in months where they are alive. With cancer in below, the average cost per patient is above DKK 50,000 in the inclusion month. Costs drop to a little more than DKK 30,000 in the second month, and even more in the following months but never down to the level before the inclusion.

Figure B 32: Monthly costs (2010 DKK) from inclusion with cancer diagnosis



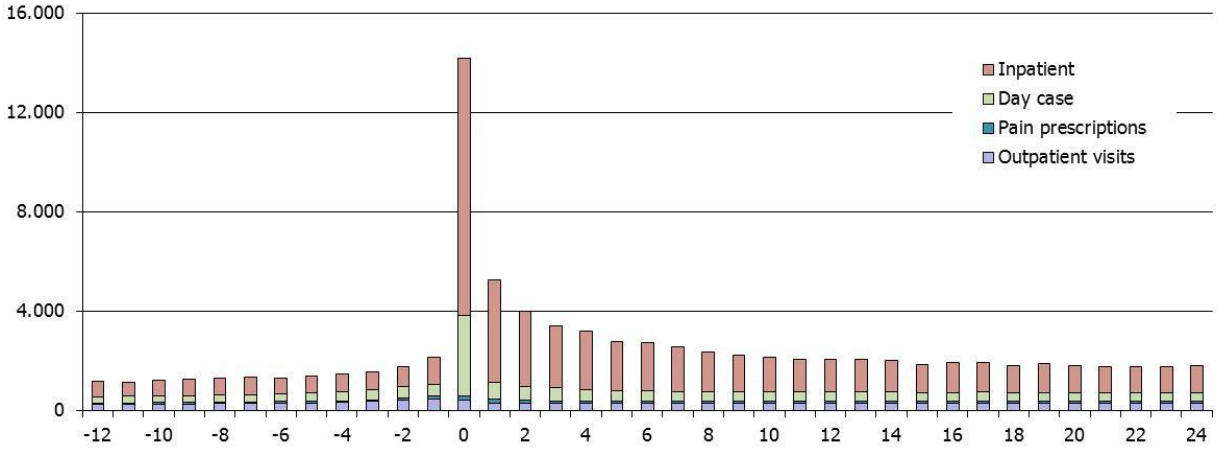
The same picture is seen for specific back pain conditions although the costs in months zero are much less than for the cancer group (DKK 17,000 on average). Again the costs drop the following months, and approach the level before the inclusion.

Figure B 33: Monthly costs (2010 DKK) from inclusion with specific back conditions



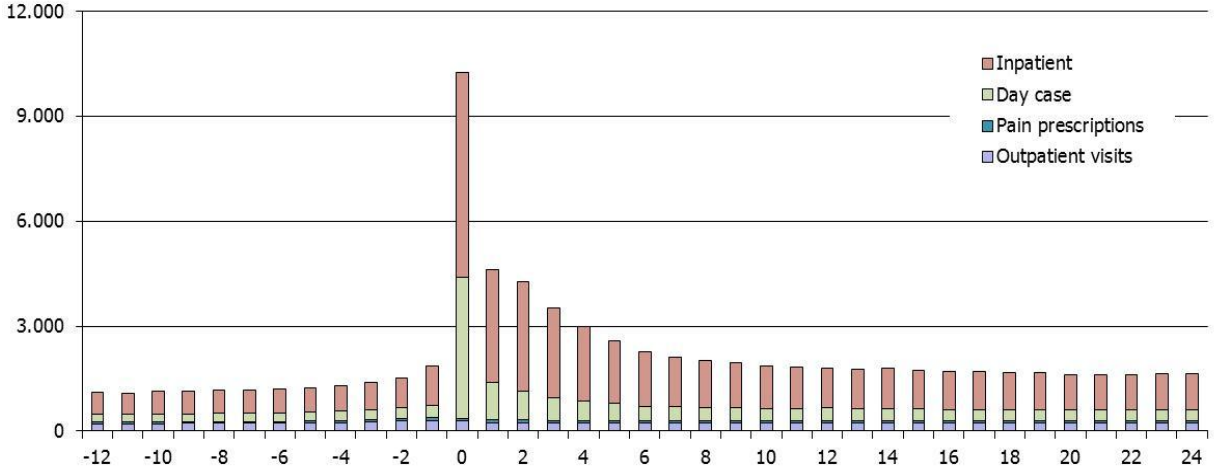
The treatment of patients with intervertebral disc pain disorders costs approximately DKK 14,200 on average during the inclusion month. Costs then drop down to approximately DKK 5,000 the following month, to DKK 4,000 in month three and keeps dropping but never down to the level before the inclusion.

Figure B 34: Monthly costs (2010 DKK) from inclusion with intervertebral disc disorders



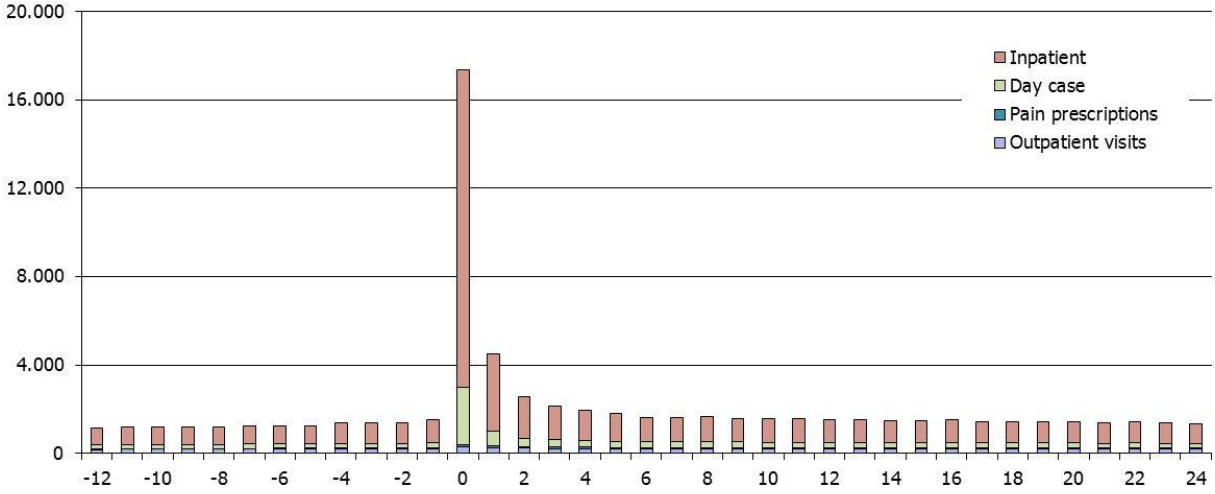
With arthritis below, costs are almost DKK 10,200 on average during the inclusion month, then drop to near DKK 4,300, in month 9 it reaches a level of about DKK 2,000 per month, and remains higher than before the inclusion in the following months.

Figure B 35: Monthly costs (2010 DKK) from inclusion with arthritis



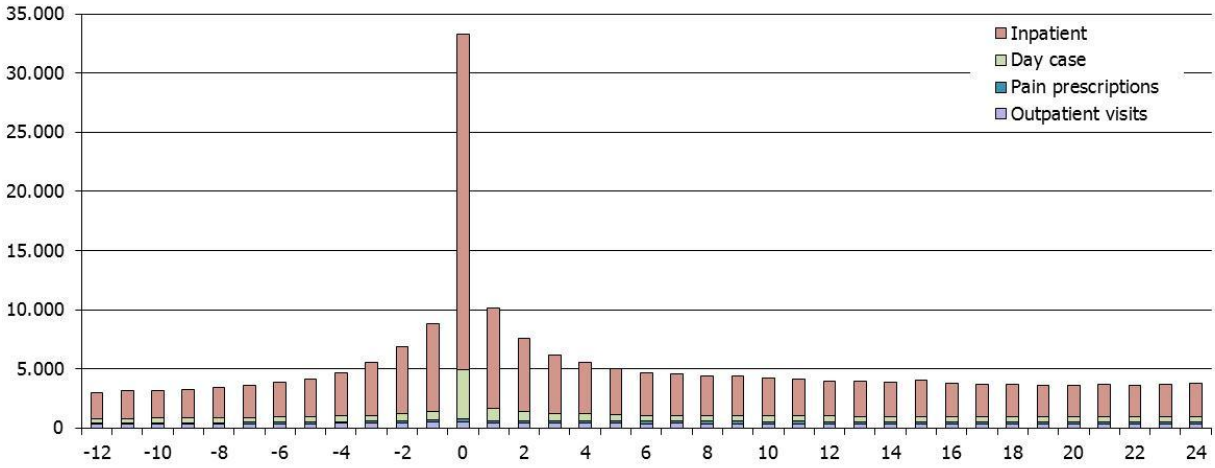
For posttraumatic fracture, the costs are highest in month 0 (DKK 17,000 on average), and drops to DKK 4,200 the following month. After 5-6 months the average monthly healthcare costs are the same as before the hospital treatment – the inclusion.

Figure B 36: Monthly costs (2010 DKK) from inclusion with posttraumatic fracture diagnosis



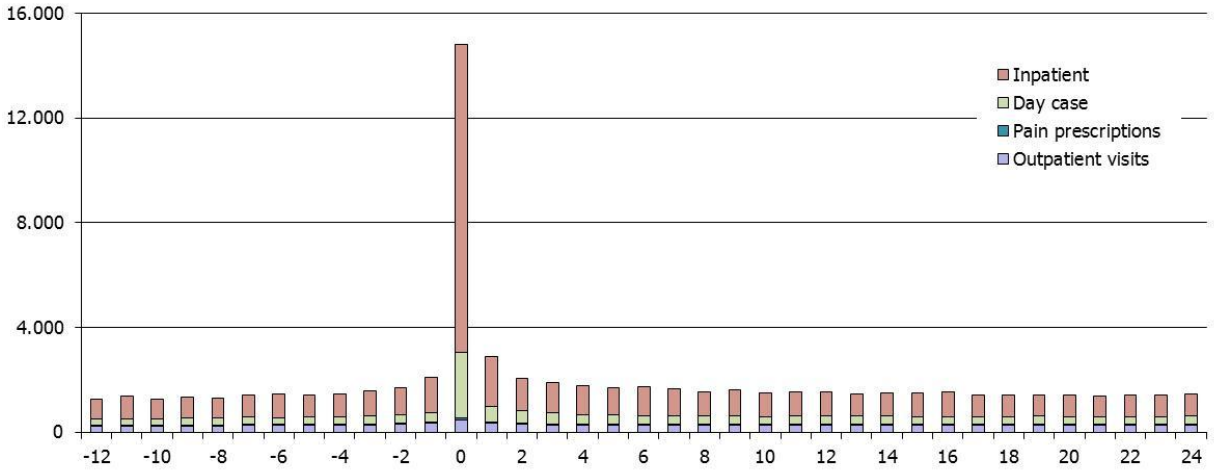
Patients with multi-morbidities below had higher costs than patients included in the other eight diagnosis groups before the inclusion, with costs ranging from DKK 2,000 to 9,000 during the months before the inclusion month, where costs raise to approxiamately DKK 33,000. In the following months costs drop, but remain higher than for those of the other diagnoses, except cancer.

Figure B 37: Monthly costs (2010 DKK) from inclusion with multi-morbidities



Patients with headache incur approximately DKK 15,000 in healthcare costs the month of inclusion at a hospital. In the subsequent months costs drop, but remain slightly higher than before the inclusion.

Figure B 38: Monthly costs (2010 DKK) from inclusion with headache diagnosis



The picture for neuropathic patients shows that costs increase before the inclusion, peak to more than DKK 20,000 on average during month 0 and drop again down to previous levels after a couple of months.

Figure B 39: Monthly costs (2010 DKK) from inclusion with neuropathies

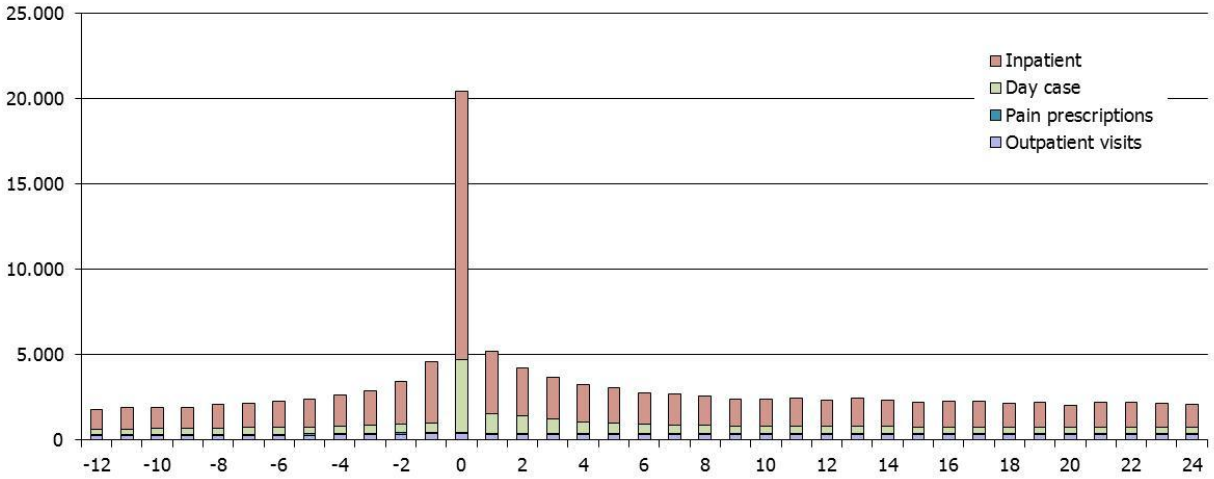
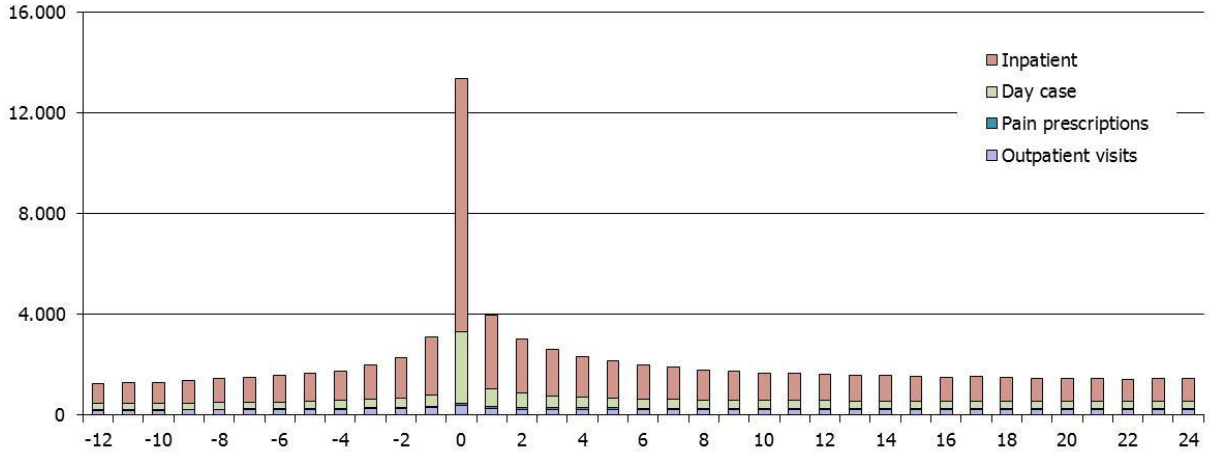


Figure B 40: Monthly costs (2010 DKK) from inclusion with a non-specified chronic pain diagnosis

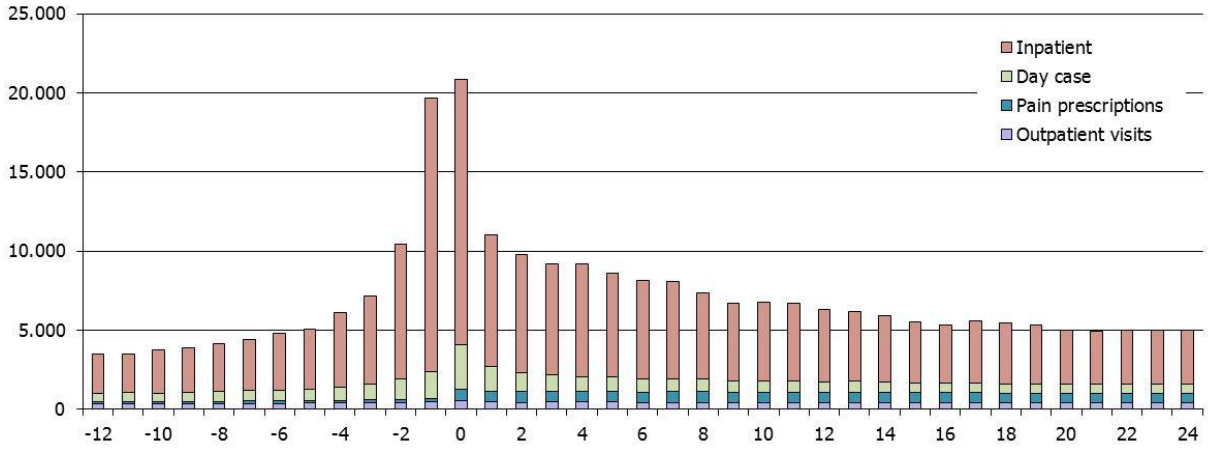


For non-specific chronic pain, costs also peak at month 0 up to DKK 13,500 per patient, drops again after 8 months to a level which is slightly higher than before the inclusion.

Appendix 6: Cost over time by SRSO continuation

In the figures below, we calculated the average monthly costs for patients who had a first line slow-release strong opioid prescription, 12 months back in time and 24 months forward from the month of the prescription (month 0). As a general tendency, health care costs are lower before the prescription, peak during the month of the prescription, then drop the following months, but never reaches the same level as before the prescription.

Figure B 41: Healthcare costs of strong opioid continuers before and after 1st line prescription



Costs are higher among continuers of the slow-release strong opioid treatment than discontinuers.

Figure B 42: Healthcare costs of strong opioid discontinuers (alive) before and after 1st line prescription

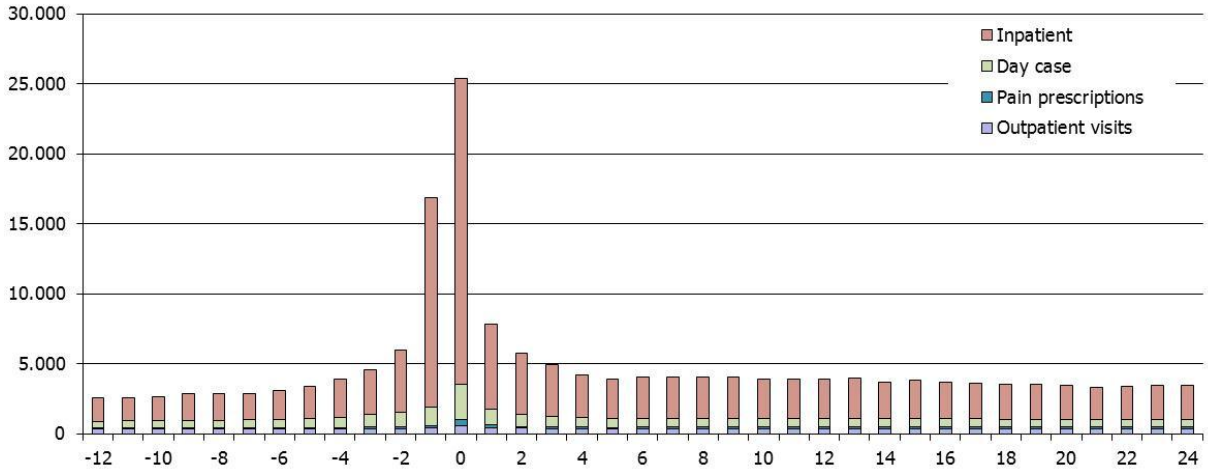
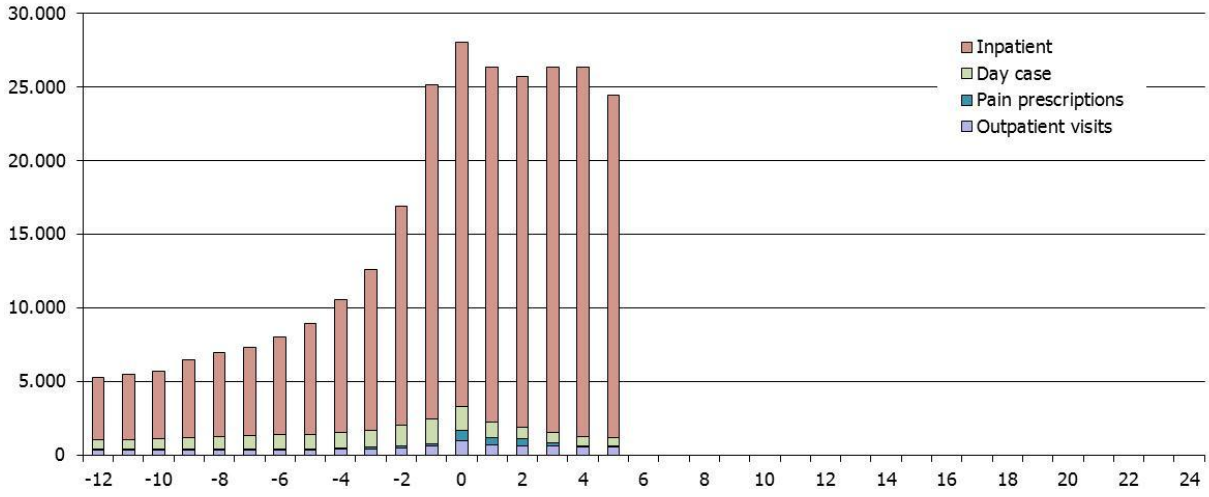


Figure B 43: Healthcare costs of strong opioid discontinuers (dead) before and after 1st line prescription



For the patients who die within 3-6-months from the prescription healthcare costs remain high – above DKK 25,000, during the terminal months.

Appendix 7: Cost over time by NPP treatment continuation

The figures show the average monthly costs for patients who had a first line neuropathic pain prescription, 12 months before and 24 months after the month of the prescription (month 0). As a general tendency, health care costs are lower before the prescription, peak the month before of the prescription, then drop from month 3, but never reaches the same level as before the prescription. They are lower on average than for patients on first line slow release, e.g. at a maximum DKK 11,000 per month.

For the patients who die (figure 3-45) costs remain high: DKK 25,000-32,000 per month during the last 6 months before death.

Figure B 44: Healthcare costs of neuropathic pain prescription continuers before and after 1st line prescription

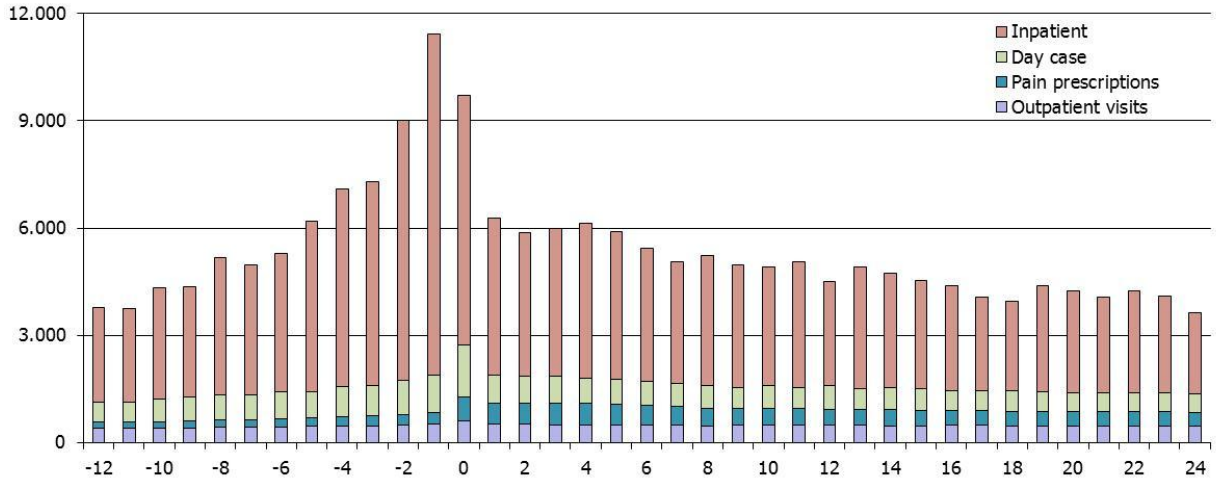


Figure B 45: Cost of neuropathic pain discontinuers (alive) before and after 1st line prescription

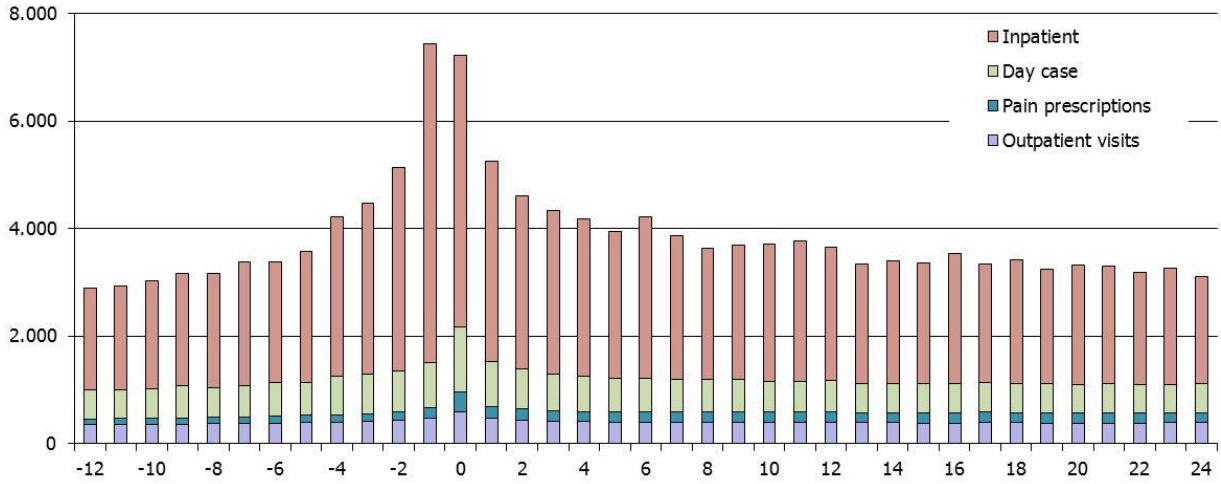


Figure B 46: Cost of neuropathic pain discontinuers (dead) before and after 1st line prescription