Chronic non-cancer pain and opioid use:

Population-based studies

PhD Thesis

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List of papers

My thesis is based on the following papers referred to by their roman numerals:

Paper I   Birke H, Kurita GP, Sjøgren P, Højsted J, Simonsen MK, Juel K, Ekholm O. **Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013.** Acta Anaesthesiol Scand. 2016; 60: 623–633.

Paper II   Birke H, Ekholm O, Sjøgren P, Kurita GP, Højsted J. **Long-term opioid therapy in Denmark: A disappointing journey.** Eur J Pain. 2017; 21: 1516-1527.

Paper III   Birke H, Ekholm O, Sjøgren P, Højsted J, Kurita GP. **Chronic pain, opioid use, and sexual desire and satisfaction with sex life.** Pain Med. 2018; 0: 1-9.

Paper IV   Birke H, Ekholm O, Sjøgren P, Fredheim O, Mahic M, Clausen T, Skurtveit S. **Tramadol use in Norway: A register-based population study.** Pharmacoepidemiol Drug Saf. 2018;1–8

Abbreviations

CNCP	Chronic non-cancer pain
DDD	Defined Daily Doses
OMEQ	Oral morphine equivalent
BMI	Body Mass Index
BZD	Benzodiazepine
L-TOT	Long-term opioid therapy
DANCOS	Danish National Cohort Study
NorPD	Norwegian Prescription Database
OR	Odds Ratio
HR	Hazard Ratio
HRQOL	Health-related quality of life

Definitions

In paper I, II, and III

Chronic non-cancer pain:	Pain lasting 6 months or more
Long-term opioid user:	Individuals, who use at least one opioid prescription per month in six separate months within one year
Short-term opioid user:	Individuals, who have use at least one prescription in one year

In paper IV

Opioid naïve tramadol users:	Individuals, who did not receive any prescription of opioids, during the previous two years
Former weak opioid users:	Individuals, who received prescriptions of only weak opioids including tramadol, during the previous two years
Former strong opioid users:	Individuals, who received prescriptions of strong opioids, during the previous two years. This group includes patients who had received both strong and weak opioids.
Users in palliative care:	Individuals who received reimbursement of opioids for palliative treatment, during the previous two years.
Recurrent opioid users:	Individuals who received opioids at least once during each of the four 365 day's periods.
Consistent recurrent users:	Individuals, who met the criteria for recurrent opioid use and received more than five prescriptions of opioids during the fourth one-year period.
Possible concurrent drug users:	Individuals, who met the criteria for recurrent opioid use and received one or more prescriptions of BZDs or Z-hypnotics during the fourth one-year period.
Possible problematic drug users:	Individuals, who met the criteria for recurrent opioid use and received, during the fourth one-year period, prescriptions of ≥365 DDD opioids, ≥100 DDD BZDs, and ≥100 DDD Z-hypnotics.

Table 1: A brief overview of the four papers

Paper	Objectives	Data source and study populations	Results	Conclusions
I	From 2000 to 2013 in Denmark, the prevalence of CNCP, prescription patterns of opioids and concurrent use of BZDs and BZD-related drugs among opioid users according to CNCP status.	In 2000: n= 9,892 In 2005: n= 5,188 In 2010: n= 14,099 In 2013: n= 13,063 Cross-sectional surveys in 2000, 2005, 2010 and 2013 based on data from DANCOS.	Increase in: CNCP prevalence (18.9% to 26.8%), number of opioid users (users of L-TOT 1.3% to 1.8%, users of short-term opioid use 2.8% to 3.9%), and number of dispensed opioids (492 to 964 OMEQ/1000 individuals/day) Women had a higher use of opioids (especially the elderly) and a higher prevalence of L-TOT than men. A decrease in the concurrent use of BZD and BZD-related drugs among users in L-TOT (60% to 33%).	During 2000-2013, the prevalence of CNCP and opioid use increased, particularly among elderly women, in 2013 one-third of users in L-TOT had a concurrent use of BZDs and/or BZD-related drugs.
II	Incidence of long-term opioid users and predictors associated with initiating L-TOT Changes in self-rated health, and pain interference with physical activities during follow-up in individuals starting L-TOT according to CNCP status.	Cross-sectional surveys in 2000, 2005 based on data from DANCOS. In 2000 + 2005: n=12,145 The panel study: In 2000: n=2,015	Significant predictors for initiating L-TOT: female sex, short education, tobacco smoking, sedentary lifestyle, overweight, and obesity. L-TOT users were more likely to report negative changes in self-rated health, pain interference with normal activities, and moderate physical activities compared with non-opioid users, longer duration of L-TOT increased the odds of negative changes.	L-TOT did not seem to be effective in achieving the key treatment goals: pain relief, improved quality of life and functional capacity. A possible dose-response relationship between treatment duration and the risk of experiencing negative changes.
III	Associations between CNCP status, opioid use, sexual desire and satisfaction in sexual life, communication with health professionals about sexual-related issues, and sexual activity according to CNCP status and opioid use.	Cross-sectional survey in 2013 based on data from DANCOS. In 2013: n=11,517 (aged 18-74).	More men than women reported dissatisfaction with sex life and more women than men reported a lack of/low sex sexual desire. CNCP patients were more likely to report dissatisfaction with sex life and low sexual desire compared to no-CNCP patients, and L-TOT further increased the odds of reporting a negative impact on sexual desire. A low prevalence of no-CNCP patients had talked to health professionals during the past five years about sexually related problems (around one-tenth). The prevalence only changed slightly in individuals with CNCP using or not using opioids. L-TOT users with CNCP had the lowest prevalence of individuals, who had sexual intercourse during the past year (56,7%), no-CNCP patients not using opioids the highest prevalence (76,5%).	CNCP was associated with higher odds of reporting dissatisfaction with sex life and low sexual desire, L-TOT seems independently to generate an additional negative impact on sexual desire. Few individuals have talked to health professionals about sexually related problems. L-TOT and CNCP seems to be associated with low prevalence of reporting sexual intercourse during the past year.
IV	Prevalence of tramadol users, the pattern of opioid use and co-medication with BZDs and Z-hypnotics among recurrent opioid users in four different study population groups (opioid naïve tramadol users, former users of weak opioids, former users of strong opioids, and users in palliative care) during four years of follow-up.	A register-based population study. Data from NorPD. Individuals (>=18 years), who received prescription(s) of tramadol in 2012 (N=154,042) were stratified into four groups according to previous opioid use two years before their first tramadol prescription in 2012.	6% of opioid naïve tramadol users became recurrent users and almost doubled their mean opioid consumption (66-108 DDD). 1/4 proceeded to strong opioids or was co-medicated with BZDs, 1/3 with Z-hypnotics. In former weak opioid users; 39.8% became recurrent users, 18.7% proceeded to strong opioids, mean opioid consumption increased slightly, 1/3 used BZDs or Z-hypnotics concurrently. In former strong opioid users and users in palliative care; 61 % and 70% became recurrent users had a similar prescription pattern (high increasing mean opioid consumption, 301 to 318, 413 to 430 DDD, respectively); 1/2 proceeded to strong opioids and/or used BZDs or Z-hypnotics concurrently.	Many patients who developed recurrent opioid use received prescriptions, which substantially conflicted with existing national guidelines and might involve problematic opioid use.

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Danish summary

Baggrund

I vesten er et stort antal patienter med kroniske non-maligne smerter i stigende grad blevet behandlet med opioider gennem de sidste årtier. I 2010 havde næsten 27% af den voksne befolkning i Danmark kroniske non-maligne smerter. En epidemisk stigning i opioidforbruget er også bekræftet i Danmark: en stigning på 63% i mængden af udskrevne stærke opioider fra 1997 til 2013, en stigning på 30% af brugere af stærke opioider og en stigning på 70% af tramadol brugere fra 2001 til 2013. Danmark har dermed et af de højeste forbrug af legale opioider i verden og det højeste forbrug i Skandinavien. Et betydeligt antal kroniske non-maligne smertepatienter behandlet med opioider vil udvikle et langtidsopioidforbrug med alvorlige negative konsekvenser for individet og samfundet. En af de sparsomt undersøgte bivirkninger til opioidbehandling, er opioiders påvirkning på det endokrine system, som kan medføre en nedgang i produktionen af kønshormoner. Hos begge køn har et lavt niveau af testosteron en negativ indflydelse på seksuel lyst og fertilitet, og dette fald i kønshormonniveauet kan negativt påvirke patienternes sexliv. Alligevel er der få undersøgelser af sammenhængen mellem kroniske non-maligne smerter, opioidforbrug og sexliv.

I Skandinavien er tramadol et af de mest almindelige anvendte opioider til kroniske non-maligne smerter. Både Norge og Danmark har i de sidste 10 år oplevet en stigning i tramadol forbruget med en tredobbelt stigning i den årlige forekomst af tramadolbrugere blandt voksne i Norge (1,7% i 2004 til 4,7% i 2014) og Danmark har haft en 17% stigning i tramadolbrugere (fra 2009 til 2014). Det stigende tramadolforbrug bør udforskes yderligere, da brug af tramadol kan være lige så bekymrende i forhold til udvikling af et problematisk opioidforbrug og -overforbrug som ved andre opioider, selvom det oprindeligt blev markedsført som et mere "sikkert" smertestillende middel med lavere risiko for afhængighed.

Formålet med ph.d. studiet var at undersøge:
I Danmark:

- forekomsten af kroniske non-maligne smerter, forbrug af udskrevet opioider og det samtidige forbrug af udskrevet BZDer- og BZD-relaterede lægemidler blandt opioidbrugere i forhold til deres kroniske non-maligne smertestatus.

- incidensen af langvarige opioidbrugere i den voksne befolkning, prædiktorer associeret med initiering af langtidsopioidforbrug og ændringerne i selvvurderet helbred, smerte

indflydelse på normale arbejdsaktiviteter og moderate fysiske aktiviteter i løbet af en follow-up periode.

- sammenhænge mellem kroniske non-maligne smerte status, opioidforbrug, sexlyst og tilfredshed i sexlivet, kommunikation med sundhedspersonale om seksuelle problemer og seksuel aktivitet i relation til kronisk mon-maligne smertestatus og opioidforbrug.

I Norge:

- forekomsten af tramadolbrugere, mønsteret i opioidforbrug og samtidige forbrug af benzodiazepiner (BZDer) og Z-hypnotika blandt langtidsopioidbrugere i fire forskellige studiepopulationer (opioid naive tramadolbrugere, tidligere brugere af svage opioider, tidligere brugere af stærke opioider og brugere i palliativ behandling) gennem fireårs follow-up periode.

Metoder

Artikel I, II og III: Data fra de nationale repræsentative danske sundhed- og sygelighedsundersøgelser (2000, 2005, 2010 og 2013) blev kombineret med Lægemiddelstatistikregisteret på individuelt niveau. Studiepopulationerne varierede mellem 5.000 og 13.000 individer $\geq$16 år (svarprocenten: 51-63%). Respondenter udfyldte selv et spørgeskema, herunder spørgsmål om kroniske non-maligne smerter ($\geq$6 måneder).

En panelundersøgelse blev gennemført i en subpopulation, der både deltog i undersøgelsen i 2000 og i 2013. Inklusionskriterier: personer, uden en kræft diagnose, uden brug af udskrevne opioider i et år før baseline (undtagen i artikel I) og som har besvaret spørgsmål om kroniske non-maligne smerter i spørgeskemaet, og desuden i studie III: personer i alderen 18-74 år.

I hvert undersøgelsesår blev forekomsten af kroniske non-maligne smerter, befolkningskarakteristika, forekomsten af opioidbrugere og opioidforbrug undersøgt. Discrete time survival models og logistiske regressionsmodeller blev brugt til at identificere prædiktorer for at starte et langtidsopioidforbrug og til at undersøge ændringer i selvvurderet helbred, samt smerteindflydelse på den fysiske kapacitet.

Sammenhæng mellem behandlingsvarighed og ændringer i out-comes samt sammenhænge mellem kroniske non-maligne smerter, opioidforbrug og mangel på/eller lav sexlyst og

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utilfredshed med sexlivet blev undersøgt. Resultaterne blev vist som hazard ratios og odds ratios med 95% konfidensintervaller.

Artikel IV: Data blev udtrukket fra den norske receptpligtige database NorPD. Personer ≥18 år, der indløste mindst en recept på tramadol i 2012, blev inkluderet, og data på alle udskrevne analgetiske opioider, herunder tramadol på individuelt niveau blev udtrukket i perioden 2010-2016. Den endelige studie population på 154.042 individer blev stratificeret i fire forskellige grupper ud fra tidligere opioidforbrug. Studiepopulationskarakteristika, brugen af opioider (mængde, type og antal recepter) blev analyseret i en toårig periode før baseline. Blandt langtids-opioidbrugerne blev i hvert år i den fireårige opfølgningsperiode, opioid-forbrug og samtidig forbrug af BZDer og Z-hypnotika undersøgt. I det fjerde år i follow-up perioden blev forekomsten blandt langtidsbrugere af et samtidigt brug af benzo-diazepiner og Z-hypnotika, konsistente langtidsforbrugere af opioider, og potentielle brugere af et problematisk medicinforbrug undersøgt.

Resultater

Artikel I: Fra 2000 til 2013 fandt vi stigninger i forekomsten af kroniske non-maligne smerter (fra 18,9 % til 26,8 %), kortvarige opioidbrugere (fra 2,8 % til 3,9 %), langvarige opioidbrugere (fra 1,3 % til 1,8 %) og i antallet af udskrevne opioider (fra 492 til 964 Oral morphine equivalent (OMEQ)/1000 individer/dag). En større andel blandt kvinder end blandt mænd havde kroniske non-maligne smerter og højere brug af opioider. I 2013 havde 33 % af langtidsopioidbrugere et samtidig brug af BZDer og/eller BZD-relaterede lægemidler. *Artikel II:* Kvinder, kort uddannelse, tobaksrygning, stillesiddende livsstil, overvægt/fedme var signifikante prædiktorer for udviklingen af langtidsopioidforbrug. Flere patienter (med eller uden kroniske non-maligne smerter ved baseline) med langtidsopioidforbrug rapporterede negative ændringer i selvvurderet helbred, smerteforstyrrelser ved normale aktiviteter og moderate fysiske aktiviteter sammenlignet med ikke-opioidbrugere. Der var indikationer på et dosis-responsforhold mellem opioidbehandlingsvarigheden og risikoen for at opleve negative ændringer. *Artikel III*: Kroniske non-maligne smertepatienter havde højere sandsynlighed for at opleve utilfredshed med sexliv og lav sexlyst sammenlignet med dem uden kroniske non-maligne smerter. Blandt kroniske non-maligne smerte patienter oplevede en større andel blandt mænd end blandt kvinder utilfredshed med sexlivet. Til gengæld oplevede en større andel blandt kvinder end blandt mænd manglende lyst til sex. Generaliserede smerter øgede forekomsten hos begge køn. Brug af opioider forværrede yderligere den seksuelle sundhed hos kroniske non-maligne smertepatienter. *Artikel IV*: I 2012

modtog 3,9 % af den norske voksne befolkning (≥18 år) mindst en recept på tramadol (154.042 ud af 3.932.250 individer) og de blev stratificeret i fire grupper: opioid naive tramadolbrugere (64.792), tidligere brugere af svage opioider (76.712), tidligere brugere af stærke opioider (9.313), og brugere i palliativ behandling (3.225). Kvinder var overrepræsenteret i alle fire grupper. I løbet af den fireårige follow-up periode blev 5,8 % af de opioid naive tramadolbrugere langtidsbrugere med en gennemsnitlig årlig fordobling af opioiddosis (66 DDD til 108 DDD), 23,3 % begyndte på stærke opioider, 40,3 % blev langtidsbrugere, 25,3 % blev samtidigt medicineret med BZDer og 34,0 % med Z-hypnotika, og 11,9% blev samtidigt medicineret med begge lægemidler. I gruppen af tidligere brugere af stærke opioider og patienter i palliativ behandling udviklede 5,5 % og 6,8 % et muligt problematisk mønster i medicinforbrug.

Konklusioner og perspektiver

I 2000-2013 steg brugen af opioider blandt kroniske non-maligne smertepatienter i Danmark, især blandt ældre kvinder, og en tredjedel af langvarige opioidbrugere havde et samtidig brug af BZDer og/eller BZD-relaterede lægemidler. Det ser ikke ud som om at et langtidsopioidforbrug er effektivt til at opnå de vigtigste behandlingsmål: smertelindring, forbedret livskvalitet og funktionel kapacitet. Kroniske non-maligne smertepatienter havde højere sandsynlighed for seksuelle problemer, og opioidforbrug forøgede yderligere risikoen for at have seksuelle problemer, især blandt langtidsopioidbrugerne. Blandt tramadolbrugere i Norge modtog et stort antal af dem, som udviklede et langtidsopioidforbrug, recepter der i væsentlig grad strider imod de nationale anbefalinger.

Opioidbehandling til kroniske non-maligne smerter, især langtidsopioidforbrug, kræver særlig opmærksomhed fra sundhedsmyndighederne på grund af dets potentiale for udvikling af et problematisk opioidforbrugsmønster. Opioidbrugere bør regelmæssigt overvåges for effekt og bivirkninger og monitoreres for udvikling af seksuelle problemer. Evidensbaserede farmakologiske såvel som ikke-farmakologiske tværfaglige behandlingsmodaliteter bør i højere grad være mere tilgængelige for kroniske non-maligne smertepatienter, således som det anbefales i de opdaterede internationale vejledninger.

English summary

Background

In western countries, an immense number of chronic non-cancer pain (CNCP) has increasingly been treated with opioids during the past decades. In 2010, nearly 27% of adults in Denmark suffered from CNCP. An epidemic increase in the opioid consumption has also been noted in Denmark; an increase of 63% in the volume of dispensed strong opioids from 1997 to 2013, an increase of 30% in strong opioid users, and an increase of 70% in tramadol users from 2001 to 2013. Thus, Denmark has one of the highest consumption of legal opioids in the world and the highest use in Scandinavia. A substantial number of CNCP patients treated with an opioid will develop long-term opioid use, with severe adverse consequences for the individual and for the society. One of the under-investigated adverse effects of opioid treatment is the impact of opioids on the endocrine system, which can cause a decline in the production of sex hormones. As a low level of testosterone, in both genders, negatively influence sexual desire and fertility, this decline in the level of sex-hormones can cause a negative effect on patients' sex life. Yet, studies addressing associations between CNCP, opioid use, and sex life are sparse.

In Scandinavia, tramadol is among the most commonly used opioid for CNCP. Both Norway and Denmark have, during the last 10 years, experienced an increase in tramadol use e.g. a threefold increase in the one-year periodic prevalence of tramadol users has been noted among adults in Norway (1.7% in 2004 to 4.7% in 2014) and Denmark has experienced a 17% increase of tramadol users (from 2009 to 2014). This increasing use of tramadol use needs further exploration as tramadol use may elicit similar concerns about the development of problematic opioid use and overdoses as demonstrated for other opioids, even though it was marketed as a "safer" painkiller with lower addiction risk.

The aims were to investigate:

In Denmark:

- the prevalence of CNCP, prescription patterns of opioids and concurrent use of BZD and BZD-related drugs among opioid users according to CNCP status.
- the incidence of long-term opioid users in the general adult population, predictors associated with initiating L-TOT and the changes in self-rated health, pain interference

with normal work activities and moderate physical activities during follow-up in individuals starting L-TOT according to CNCP status.

- associations between CNCP status, opioid use and libido and satisfaction in sexual life, communication with health professionals about sexual-related issues, and sexual activity according to CNCP status and opioid use.

In Norway:

- prevalence of tramadol users, the pattern of opioid use and co-medication with BZDs and Z-hypnotics among recurrent opioid users in four different study population groups (opioid naïve tramadol users, former users of weak opioids, former users of strong opioids, and users in palliative care) during four years of follow-up.

Methods

Study I, II, and III: Data from the national representative Danish Health and Morbidity Surveys (2000, 2005, 2010, and 2013) were combined with The Danish National Prescription Registry at an individual level. The study populations varied between 5,000 and 13,000 individuals ≥16 years (response rates: 51–63%). Respondents completed a self-administered questionnaire including identification of chronic pain (≥6 months). A panel study was conducted in a subsample, who participated both in the survey in 2000 and in 2013, respectively. Inclusion criteria: individuals without a cancer history, with no dispensed opioid use during the baseline year (except for study I), and who answered the CNCP question, and additionally in study III: individuals in the age between 18 - 74 years old.

The prevalence of CNCP, study population characteristics, the prevalence of opioid users, and opioid consumption were investigated in each survey year. Discrete time survival models and multiple logistic regression models were used to identify predictors for starting L-TOT and furthermore to examine changes in self-rated health, pain interference with physical function. Also, associations between duration of treatment and changes in outcomes were examined as well as associations between CNCP, opioid use, and lack of/low sexual desire and dissatisfaction with sexual life. The results were shown as hazard ratios and odds ratios with 95% confidence intervals.

Study IV: Data were drawn from the Norwegian prescription database (NorPD). Individuals ≥18 years, who received at least one prescription of tramadol in 2012 were included and data were retrieved for the period of 2010-2016 on all dispensed analgesic opioids including tramadol at an individual level. The final study population of 154,042 individuals was stratified into four different groups according to previous opioid use. Study population characteristics, the use of

opioids (amount, type, and the number of prescriptions) were analyzed in a two-year period before baseline. Among recurrent opioid users, during each year of the four-year follow-up period, opioid consumption, and concurrent use of BZDs or Z-hypnotics was calculated. In the fourth year of follow-up, among recurrent users, the prevalence of concurrent users of BZDs and Z-hypnotics, consistent recurrent opioid users, and possible problematic drug users was calculated.

Results

Study I: From 2000 to 2013, we found increases in the prevalence of CNCP (from 18.9% to 26.8%), short-term opioid users (from 2.8% to 3.9%), long-term opioid users (from 1.3% to 1.8%), and in the number of dispensed opioids (from 492 to 964 OMEQ/1000 individuals/day). More women than men had CNCP and higher use of opioids. In 2013, 33% of long-term opioid users had a concurrent use of BZD and/or BZD-related drugs. *Study II:* Female sex, short education, tobacco smoking, sedentary lifestyle, overweight/obesity were significant predictors for developing L-TOT. More patients (with or without CNCP status at baseline) in L-TOT reported negative changes in self-rated health, pain interference with normal activities, and moderate physical activities compared with non-opioid users. A dose–response relationship between opioid treatment duration and the risk of experiencing negative changes was indicated. *Study III:* CNCP patients had higher odds of experiencing dissatisfaction with sex life and low sexual desire compared to those without CNCP. Among CNCP patients, more men than women experienced dissatisfaction with sex life, and more women than men experienced a lack of/low sex sexual desire. Widespread pain increased the prevalence in both genders. Using opioids added an additional negative impact on sexual health in CNCP patients. *Study IV:* In 2012, 3.9% of the Norwegian adult population (≥18 years) received at least one prescription of tramadol (154,042 out of 3,932,250 individuals) and were stratified into four groups: opioid naïve tramadol users (64,792), former users of weak opioids (76,712), former users of strong (9,313), and users in palliative care (3,225). More women than men were represented in all four groups. During the four-year study period: 5.8% of opioid naïve tramadol users became recurrent users with a mean annual opioid dose doubling (66 DDD to 108 DDD), 23.3% shifted to strong opioids, 40.3% had a high recurrent use, 25.3% were co-medicated with BZDs and 34.0% with Z-hypnotics, and 11.9% were co-medicated with both drugs. In former strong opioid users and users in palliative care 5.5% and 6.8% developed a possible problematic drug use pattern.

Conclusions and perspectives

During 2000-2013, the use of opioids among CNCP patients in Denmark increased, particularly among elderly women, and one-third of long-term opioid users had a concurrent use of BZDs and/or BZD-related drugs. L-TOT did not seem to be effective in achieving the key treatment goals: pain relief, improved quality of life and functional capacity. CNCP patients had higher odds of sexual problems and opioid use added further negatively to sexual problems, especially in those on L-TOT. In a cohort of tramadol users in Norway, many of those, who developed recurrent opioid use, received prescriptions which substantially conflicted with the national guideline.

Opioid therapy for CNCP, especially L-TOT, requires special attention from health authorities due to its potential for the development of problematic opioid use. Opioid users should regularly be monitored for efficacy and side effects including the development of sexual problems. Evidence-based pharmacological as well as non-pharmacological interdisciplinary treatment options for CNCP patients should be more accessible in accordance with updated international guidelines.

Introduction

The prevalence of chronic non-cancer pain

Chronic non-cancer pain (CNCP) represents a profound public health problem with a huge social and economic impact on society. CNPC is acknowledged as a complexed biopsychosocial phenomenon in which biological, psychological, and social factors interact dynamically with each other (1). Prevalence estimates of CNPC vary widely due to different chronic pain definitions as well as a variety of assessments methods and population dissimilarities presented in epidemiological studies (2). Typical CNPC estimates range from 10-30 % (3). The Danish prevalence of CNCP among adults seems to be increasing during the recent decades and reached nearly 27% in 2010 (4–6). In a large scale internet based European survey (United Kingdom, France, Spain, Italy, Germany), one in five of the estimated adult population of 250 million persons reported having experienced moderate or severe pain in the last month (7). Another pan-European survey found a 19% prevalence among adults, wherein two-thirds reported pain of moderate intensity and one-third of severe intensity. Nearly 60% had experienced pain lasting from 2-15 years and 21 % had suffered from pain for 20 years or more. Among those with CNCP, only 2%

were managed by pain specialists, 40% received inadequate pain management, and one-third did not receive treatment, which causes a huge negative effect on the quality of life (8). Two of the largest pan-European surveys have both stated that the most common chronic pain conditions are chronic back pain and arthritis, particularly osteoarthritis (7,8). Although CNCP is a very common disorder, valid and reliable epidemiological data are limited. One of the most comprehensive epidemiological literature review of CNCP in Europe found, despite substantial data from many individual European countries, limited high-quality pan-European data on chronic pain (2).

Opioids

For millennia, acute and chronic pain states have been treated with opioids. Around 3400 B.C, the opium poppy was cultivated in lower Mesopotamia by Sumerians, who called it a "joy plant" due to its euphoric effect (9). Opium was mentioned as a pain treatment medication in ancient Egyptian papyrus records (10), and later in 1170, the first book of western surgery described the use of opium for surgical procedures (11).

Today, the opioid class of drugs includes natural opiates (e.g., morphine, codeine), semi-synthetic opioids (e.g., tramadol, oxycodone), and synthetic opioids (e.g., methadone, buprenorphine, and fentanyl) (12). Traditionally, opioids are divided into weak (e.g. codeine, tramadol) or strong opioids (e.g. morphine, oxycodone). If this is an appropriate division is questionable as the potency of opioids is equal whether low doses of a strong opioids or high doses of a weak opioid is being prescribed. In addition, several opioids have been developed as short-acting or long-acting formulations.

Tramadol is the most frequently used weak opioid for CNCP in Scandinavia, in which Denmark has the highest use (13). Both Norway and Denmark have, during the last 10 years, experienced an increase in the use of tramadol. From 2004 to 2014, Norway has had a threefold increase in the one-year periodic prevalence of tramadol users among adults (1.7% - 4.7%), and from 2009 to 2014, Denmark has experienced a 17% increase of tramadol users, whereas Sweden and Iceland have had a decrease and Finland a stable consumption of tramadol (13).

One explanation for the extensive increase in tramadol use is because of the way tramadol has been marketed since the 80ties; as an opioid drug with less addictive effect compared to other opioids.

In the WHO guidelines for cancer pain relief, tramadol is mentioned as a step-2 analgesic (14). Tramadol has a multimode of actions on serotonergic and noradrenergic nociception and its metabolite O-desmethyltramadol acts on the µ-opioid receptor (15). Yet, symptoms of tramadol intoxication are like other opioid analgesics. Fatal intoxications because of tramadol use seem to be rare and are associated with large overdoses of tramadol and concurrent use of other drugs or alcohol (15). In line with a long-term use of other opioids, there is little evidence for effective pain relief when using tramadol for more than three months in individuals with CNCP. Because of tramadol´s serotonin receptor agonist effect, it has, as the only opioid drug, an inherent risk of causing serotonergic syndrome (16,17,18). In general, tramadol is to some extent still considered as an opioid drug with a lower potential for addiction compared to other opioids e.g. morphine. This increasing use of tramadol use needs further exploration as tramadol use may elicit similar concerns about the development of problematic opioid use and overdoses as demonstrated for other opioids (15).

The well-known physiological effects of opioids are multiple such as; providing analgesia, altering of body temperature, causing sedation, depressing respiration, inducing appetite, decreasing gastrointestinal transit, affecting urinary output, inducing hyperalgesia, and producing either euphoria or dysphoria (18–21). These effects are primarily produced through actions at the three opioid receptor subtypes: µ, κ, and δ, of which the µ-opioid receptor is the most well-known and studied. Initiating of the G protein-coupled µ receptor leads to acute changes in neuronal excitability. It is primarily the agonist actions of opioids at µ receptors that are thought to provide analgesia, suppress coughing, and ease diarrhea. Unfortunately, µ receptors also seem to be involved in the abuse potential of many opioid drugs (22). However, genetic vulnerability or predisposition of addictive behaviors, substance, and non-substance related, may likely be in play in some individuals suffering from CNCP (23).

Despite that opioid treatment is connected with a substantial series of negative consequences, opioids still play a central role in the treatment of cancer patients (14,24), and is crucial in providing pain relief especially in patients with advanced disease. The success of opioid therapy in patients with advanced cancer set has the stage for extending the same treatment principles to the treatment of all chronic pain conditions including CNCP and chronic pain in cancer, where survival and chronic disease trajectories are getting more prevalent due to increased survival rates (25). However, the markedly increased prescribing of opioid analgesics in the United States beginning in the 1980s has also set the stage for the current US epidemic of prescription opioid addiction and

deaths (26). Also, carefully selected and closely monitored patients with non-cancer diseases and with verified opioid-responsive pain conditions might benefit from opioid treatment if non-opioid treatment has been exhausted (27).

The use of opioids for chronic non-cancer pain

In recent decades, opioid therapy for CNCP has increased dramatically (8,28–32) and accordingly, in Denmark, more than 80% of the volumes of dispensed opioids are today used for CNCP (13). Danish data have demonstrated an increase of 63 % in the volume of dispensed strong opioids from 1997 to 2013 (33). Contemporarily, the number of strong opioid users has increased with 30 % from 2001 to 2013 and a substantial increase in the number of weak opioid users has also been noted; such as an increase of 70 % in the number of tramadol users (34). In 2013, 168,000 individuals in Denmark were estimated to be long-term opioid users, out of which one quarter for more than five years and one third shifted from weak to strong opioids (13).

A study in 2016 found a substantially higher use of both weak and strong opioids in Denmark compared to the use of opioids in Sweden, Norway, Iceland, and Finland. In all Scandinavian countries, tramadol is the most used weak opioid for CNCP (13). Although several factors like prescription and reimbursement policies differ between the Scandinavian countries, no such differences exist that could explain the different amount of opioid consumption for CNCP (35). In Norway and Sweden prescribers of opioids must follow special precautions, and the Danish Medicines Agency has recently changed the directions so that prescription of both strong and weak opioids, except for codeine combination drugs, must be monitored. All the Scandinavian countries, except in Iceland, have to use a special prescription form to prescribe opioids; In Denmark for strong opioids and some weak, in Finland for strong opioids, and in Norway and Sweden for both strong and weak opioids (35). Also, control by authorities and difficulties in filling special prescription forms may altogether influence physicians' choices regarding opioid prescriptions. This may be the case in Finland where a lot of weak opioids and non-steroidal anti-inflammatory analgesics are prescribed (36).

Denmark has recently changed the regulation of opioid prescriptions after an ongoing debate both in the media and in professional fora about specifically the addiction potential of tramadol (37). Thus, since 2017, opioid prescribers were imposed to report all side effects of tramadol in a two-year period (38). These initiatives have been taken as the Danish authorities have recognized that the consumption of tramadol in Denmark was too high and required increased control (37).

Still today, the best existing evidence indicates a major gap between an increasingly sophisticated understanding of the pathophysiology of pain and common insufficiency of its treatment (39). The highest and most harmful opioid doses are likely to be prescribed for patients in the greatest distress, who at the same time are those most at risk of adverse effects – a phenomenon called "adverse selection" (40,41). This concept was promoted by the WHO stepladder by recommending higher doses and continuously use for high pain intensity (42). The somatosensory component of CNCP is to a higher degree influenced by cognitive and affective elements than in acute or cancer-related pain, thus the use of WHO stepladder approach to CNCP may be inappropriate (43). Accordingly, CNCP becomes more related to emotional and psychosocial factors and less related to nociception (43), which may explain why CNCP is not responding well to opioids in the long run (44). Ballantyne et al. have questioned how pain intensity in individuals with CNCP should be interpreted and to what degree the reporting of pain is an attempt of communicating bodily distress – a condition to which opioids are ineffective (25). An epidemiological study in Denmark concluded that social and psychological factors were not only risk factors for the development of CNCP but also predictors for recovery from CNCP (6).

Usually, opioid-responsive chronic pain only responds well to opioids in the early course of the treatment, as CNCP does not follow a predictable or linear trajectory as acute pain often does. The reporting and experience of chronic pain are altered by mood, environment, stress, duration, meaning, acceptance, expectation, and fear. Accordingly, chronic pain scores do not respond in a predictable way to opioids. On the contrary, an attempt to lower chronic pain scores has caused an adverse overuse of opioids (44). The WHO stepladder approach for CNCP patients created the idea that opioid use could unfailingly reduce pain and improve patients' quality of life. This approach may not only expose CNCP patients to harm but simultaneously gives them unrealistic and false expectations, as well as disappointed clinicians due to ineffective treatment outcomes (25).

Long-term opioid therapy for chronic non-cancer pain

CNCP patients are often treated with L-TOT (45–47). A review which presented 3 follow-up studies from 7 to 24 months duration showed that 44% were still being treated with L-TOT at the end of the follow-up (48). A study using data from the NorPD found that 24 % of new strong opioid users continued opioid treatment at follow-up 5 years later (49).

Currently, the sparse available evidence of the effectiveness of L-TOT for CNCP is primarily based on population-based studies. Long-term investigation of the effectiveness of opioid treatment using RCT design is unrealistic because of the short time to follow-up. Further, RCT of L-TOT can be difficult to conduct because of ethical concerns due to the very common occurrence of side effects related to the opioid use and an expected large number of drop-outs (50–52).

Noble et al. concluded in a review, that data describing long-term safety and efficacy of opioids for CNCP is limited regarding quantity and quality. Two studies of L-TOT versus alternative treatments also found limited advantages in favor of opioids (53,54). To conclude, no strong evidence supported that L-TOT sufficiently relieves pain and/or improves the quality of life (48,53,55–59).

An increased risk of dose escalation during L-TOT has been found in several studies (49,60,61). From a societal perspective, higher-dose regimens account for the majority of opioids dispensed, so cautious dosing may reduce both the diversion potential and risks of adverse effects (62).

Adverse effects and long-term consequences of long-term opioid therapy

An updated Cochrane review of the analgesic efficacy of opioids in neuropathic pain described the most common reported adverse events to be constipation, drowsiness, nausea, followed by dizziness and vomiting (63). Especially prolonged use of opioids for CNCP may have serious adverse effects on respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine and central nervous systems (62,64). These adverse effects include drug tolerance, hyperalgesia (65), hypogonadism, sexual dysfunction (66), and immunosuppression (9).

Former epidemiological studies from Denmark have found several negative outcomes of L-TOT for CNCP; opioid use was significantly associated with moderate/severe or very severe pain, poor self-rated health, unemployment, higher use of the health care system, a negative influence on quality of life (58), significantly higher risk of all-cause mortality among long-term opioid users, increased risk of injuries and toxicity/poisoning resulting in hospital inpatient admissions (67), and individuals not using opioids had an almost four times higher odds of recovery from chronic pain compared with individuals using opioids (59).

An under-investigated adverse effect of opioid treatment is the impact of opioids on the endocrine system (69–72), which has been shown to happen immediately after intake of opioids (73). This opioid-induced suppression of adrenal-related hormones can, in the long run, cause

hypogonadotropic hypogonadism (66,72,74), and hypocorticism (66). As a consequence, many CNCP patients using opioids may experience endocrine dysfunction caused by opioid-induced inhibition of the hypothalamic-pituitary-function (72,74). The decline in production of sex-hormones can cause a negative effect on patients' sex life since a low level of testosterone, in both genders, negatively influence sexual desire and fertility (72). Yet, studies addressing associations between CNCP, opioid use, and sex life are sparse.

A population-based study concluded that higher daily doses of prescribed opioids were associated with higher risks of overdose and other severe sequelae such as addiction, fractures, intestinal blockages, and sedation (50). Negative cardiovascular effects such as increased risk of myocardial infarction or heart failure, as well as increased risk of pneumonia among the elderly, probably associated with immunosuppression, have also been demonstrated (75–77).

A review of the potential adverse effects of L-TOT concluded that increasing numbers of deaths were due to opioid overdose among CNCP patients (64). Benyamin et al. showed that the increased number of drug deaths from opioids generally matched the increase in sales for each type of opioid. From 1990 to 2002, the number of opioid analgesic poisonings on death certificates increased by 91.2%. (9). Similarly, Gilson et al. showed a 71% increase in abuse of prescription opioids between 1997 and 2002 in the U.S. (78). Prescription opioid abuse is the second most common type of illicit drug abuse after marijuana in the United States (79). With reason, experts advocate for the use of opioids in only carefully selected group of patients (48,80,81). Lastly, it is crucial to provide an early and proper identification besides cautious monitoring for signs of opioid addiction in CNCP patients.

Opioid treatment of acute or cancer pain is rarely associated with the development of opioid abuse/dependence, whereas L-TOT for CNCP has been shown to result in opioid misuse/dependence in 3% to 19% of patients (82–84). It is likewise striking that as many as 40% of long-term opioid users develop aberrant patterns of opioid use e.g.: obtaining opioids from multiple prescribers, falsifying prescriptions, stealing opioids, and intranasal or intravenous use of oral opioids (85).

The predictors for opioid misuse still remain a topic of debate, since little epidemiologic data exist which clearly define risk factors for opioid abuse by CNCP patients (86). However, commonly accepted risk factors for opioid abuse and misuse are; personal or family history of drug or alcohol abuse (87–89), use of cannabis (90), psychosocial comorbidity (89), psychiatric morbidity (41,91),

young age (54), back pain, multiple pain complaints, higher degree of subjective pain, greater pain influence on functional capacity (92–95) and probably genetics (96).

Co-medication with benzodiazepine and benzodiazepine-related drugs

As BZDs is a psychotropic drug prescription of BZDs medications are indicated for the treatment of patients suffering from anxiety and insomnia. BZD-related drugs - also called Z-drugs and melatonin receptor agonist agents have also to some extent been used for insomnia instead of BZDs medications. Long-term use of BZDs can cause sedation, nervousness, and cognitive impairment due to a downregulation of the GABA receptor (97,98). Even after short-term use, patients may be at risk of falls, suicide, vehicle crashes, and overdose when using these drugs (99). Only some weeks of treatment can be enough to develop BZD dependence, and cessation may be difficult due to a complex mix of withdrawal and rebound symptoms, and recurrence of underlying anxiety (100).

As opioids and BZD interact with one another, co-abuse is widespread and frequent. Several studies have shown preclinical evidence that BZDs increase the rewarding and reinforcing effects of opioids, which can explain the mechanism underlying opioid and BZD co-abuse (101,102).

A high prevalence of BZD use has been shown not only among opioid users, but also among CNCP patients. As many as 40–60% of CNCP pain patients has been shown to be regular users of BZD (103). The doses of BZDs exceeded the recommended doses, which highlights the need for guidance of this population concerning the possible risk of combining opioids with BZDs, along with awareness among prescribers for abusive patterns of use (104). BZDs have a well-documented addictive potential, but have no analgesic effect (100,105), although it unknown whether the use of BZD by CNCP patients is primarily recreational or therapeutic (106). It is noteworthy that a prospective follow-up study (over 4-7 years) of patients, who initially reported no history of opioid use, found that BZD use was a stronger predictor of future prescription opioid use than musculoskeletal pain/chronic pain (105).

Guideline recommendations

New updated guidelines for prescribing opioids for CNCP have been published recently, and a consistent trend is that recommendations have become more strict and more cautious (107,108).

The guidelines have been developed using systematic reviews of evidence and the evidence for each recommendation was judged based on the strength of the evidence and the degree of harm

(99,109,110). The principles were straightforward: non-opioid therapy is now the main and most important recommendation, opioids should be prescribed only when necessary and only to verified opioid-sensitive pain conditions at the lowest effective dose. Further, the patient should be assessed for the previous history of opioid/or other addictive drugs and be currently monitored for harmful effects and the drug discontinued if ineffective or harmful. The guidelines underpin the importance of communication involving the patient and of informed consent. If opioid use is initiated pain specialists warn against the concurrent use of BZDs and endorse a shared treatment goal agreement between patient and prescriber with close monitoring of adverse effects, patient education, and a plan for tapering off. Further, it is recommended to avoid long-acting opioids and instead prescribe low dose short-acting drugs. Only in specific circumstances with severe intractable pain long-acting or high dose opioids is recommended. L-TOT should be prescribed only to patients with proven medical necessity and stability followed by improvement in pain and function, independently or in combination with other treatment modalities. The new key focus of the opioid treatment is to accomplish improvements in quality of life and functional capacity more than focusing on pain relief (99,109,110). At prolonged opioid treatment, the clinicians should evaluate benefits and harms together with the patients at least every three months. If possible, review of data from prescription drug monitoring programs for high-risk combinations or doses should be done (99). Most importantly, realistic expectations of the long-term analgesic effect of opioids need to be discussed in the open and clarified (99,109). Lastly, the updated American Society of Interventional Pain Physicians (ASIPP) Guidelines recommends before, during, and after initiation to consider and evaluate respiratory instability, acute psychiatric instability, former or present alcohol or substance abuse, confirmed allergy to opioid agents and any life-threatening drug interactions and simultaneous use of BZDs (109).

In April 2018, new Danish recommendations regarding the use of opioids to CNCP were published by the Danish Health Authority in their website (111). Their recommendations are in line with the above-mentioned international guidelines and underpin the importance of frequent monitoring of patients who initiate opioid treatment and a maximum dose of morphine of 90 mg daily. Further, poly- opioid drug use is only acceptable during an opioid rotation (111). Therefore, a formal guideline about opioid prescribing to patients with CNCP is very recent in Denmark and their impact on opioid use among individuals with CNCP may be negligible.

Unlike Denmark and Sweden, Norway has had a comprehensive national guideline including recommendations for pain management and opioid use for CNCP with the latest update in 2016.

The Norwegian guideline for opioid use for CNCP is strict, emphasizing that opioid treatment should only be prescribed to a small minority of patients and only after detailed evaluation and close monitoring (110). Furthermore, The Norwegian Directorate of Health states that opioid treatment should only involve one single opioid drug/formulation and co-medication with BZDs should be avoided (110). Norway has also more strict criteria to be met before patients can receive reimbursement for the expenses associated with opioid treatment compared to Denmark and Sweden (13,112).

Based on the developing "opioid epidemic" in western countries, we find it highly justified to monitor different aspects of opioid prescribing for CNCP patients in Denmark and in the Nordic countries as such. The present thesis has followed a long research tradition in Denmark for monitoring the consumption and added new knowledge to former studies. Further, as a result of a newly established Nordic collaboration based on identical prescription databases, we have also found it justified to address the critical issues of a rapid increase in tramadol use in Norway, which hopefully soon will be followed by population-based studies in the other Nordic countries.

The overall aim

The overall aim of this thesis is to study the prescription patterns of opioids in two Scandinavian countries; Denmark and Norway. We aimed, more specifically, to study the consequences of L-TOT for CNCP in population-based studies in Denmark and the drug use pattern in a cohort of tramadol users in Norway.

The specific aims of each of the four papers were:
Paper I *(Using Danish data)*
- To investigate the prevalence of CNCP in Denmark
- To investigate to the pattern of dispensed opioids according to CNCP status
- To investigate the concurrent use of BZD and BZD-related drugs among opioid users

Paper II *(Using Danish data)*
- To investigate the incidence of long-term opioid users in the Danish adult population
- To investigate predictors associated with initiating L-TOT according to CNCP status
- To investigate changes in self-rated health, pain interference with normal work activities and moderate physical activities according to CNCP status and L-TOT

Paper III *(Using Danish data)*

- To investigate associations between CNCP status, opioid use and libido and satisfaction in sexual life.
- To investigate CNCP patients` communication with health professionals about sexual-related issues
- To investigate sexual activity according to CNCP status and opioid use

Paper IV *(Using Norwegian data)*

- To investigate the prevalence of tramadol users in the adult population (≥18 years) in Norway
- To investigate the pattern of opioid use in different study populations (opioid naïve tramadol users, former users of weak opioids, former users of strong opioids, and users in palliative care) in four years of follow-up
- To investigate the pattern of co-medication with BZDs and Z-hypnotics among recurrent opioid users

Materials and methods

Data source

Paper I, II, and III:

Data were obtained from the Danish National Cohort Study (DANCOS), a nationally representative health survey based on linkage of information in the Danish Health and Morbidity surveys to official Danish health and socioeconomic, individual-based registers. DANCOS is administered by the National Institute of Public Health, University of Southern Denmark (113). The main purpose of the surveys was describing trends and status in health and morbidity among the adult Danish population (16 years or older) and factors including health behavior, lifestyles, environmental and occupational health risks and health resources that could have an impact on the health status. The Danish Health and Morbidity surveys further aimed to highlight several specific topics e.g. parent-reported child health, exposure to detrimental environmental factors and assessment of the associated health-related risks, use of illicit drugs, dental status, chronic pain, violence and sexual assault, and suicidal behavior (114). The self-administered questionnaire in each survey year: 2000, 2005, 2010, and 2013 contained questions about CNCP ("Do you have chronic/long-lasting pain

lasting more than 6 months or more?"). In 2010 and 2013, the questionnaires were supplemented with questions about locations of chronic pain (115).

Paper IV:

Data were drawn from the prescription database NorPD administered by the Norwegian Institute of Public Health for the period of 2010-2016. The following variables were used from NorPD: unique personal identity number, sex, age, dispensing date, and drug information including ATC code, drug quantity measured in Defined Daily Doses (DDD) and the reimbursement code for opioids (116).

Data collection

In paper I-III: All selected individuals received a letter of introduction with a brief description of the purpose and content of the survey. It was also underlined that participation was voluntary. In 2000 and 2005, data were collected via the face-to-face interview at the respondent's home, with a minimum of four contact attempts. All respondents were asked to fulfill a self-administered questionnaire following the interview in 2000 and in 2005. The reasons for adding a self-administered questionnaire to the interview were because questions with a more sensitive nature such as sexual behavior and use of illicit drugs were added and a wish for a reduction of the length of the face-to-face interview. In 2010 and 2013, data were collected solely via self-administered questionnaires (117). In 2000 and 2005, the samples were restricted to Danish citizens; subsequent surveys included all persons living in Denmark (117). Further, a panel study was conducted, where a subsample of individuals invited to the survey in 2000 and still alive and living in Denmark was invited to participate in each of the following surveys. Information about the prescription of opioids was identified by the ATC codes: N02A, N02BE51, N02BA51 and R05DA04 and drawn from the Danish National Prescription Registry (115). The Danish National Patient Register was used to identify individuals with a cancer diagnosis (ICD codes C00–D49 excluding C44) (118).

Paper IV: Data from the NorPD were used in this study. Since 2004, NorPD covers all prescription drugs dispensed by pharmacies in Norway. Medicines supplied to hospitals and nursing homes are also partly included, though, not at an individual level. NorPD contains information on sex, age, dispensing date, drug quantity measured in DDD, and the reimbursement code for opioids (116). By using a unique encrypted personal identity number in the NorPD database, individuals who received at least one prescription of tramadol in 2012 were identified. Thereafter, data were retrieved for the period of 2010-2016 on all dispensed analgesic

opioids (ATC code N02A) including tramadol (N02AX02, N02AX52) at an individual level used in Norway (116).

Study populations

Paper I, II, and III: Cross-sectional surveys in 2000, 2005, 2010, and 2013 based on a random sample of adults (16 years or older) living in Denmark. A panel study was also conducted based on a subsample of respondents who were completed both the face-to-face interview and the self-administered questionnaire in 2000 and alive and living in Denmark in 2013. These individuals were invited to participate in 2013; however, in 2013, data were only collected via self-administered questionnaires.

Individuals with a (self-reported) history of cancer and/or with a cancer diagnosis (ICD codes C00–D49 excluding C44) in The Danish National Patient Register were excluded (118).

The sample sizes:
In 2000: 16,684 individuals (response rate: 63%)
In 2005: 10,916 individuals (response rate: 51%)
In 2010: 25,000 individuals (response rate: 61%)
In 2013: 25,000 individuals (response rate: 57%)
The sample size in the panel study:
In 2000: 5,912 individuals

Paper IV:

The Norwegian population in 2012 counting 5.2 million individuals.

The final study populations

Paper I:

Respondents of the survey in 2000, in 2005, in 2010, and in 2013 in the age of 16 years or more were included. Exclusion of individuals, who had a cancer history and/or had been dispensed opioids during the baseline year, and who did not answer the question about chronic pain in the questionnaire. Thus, the final study populations were:

In 2000: **9,892 individuals**
In 2005: **5,188 individuals**
In 2010: **14,099 individuals**

In 2013: **13,063 individuals**

Paper II:

Respondents of the survey in 2000 and/or 2005 were included in this study only once to avoid duplicates. Exclusion of individuals, who had a cancer history, had been dispensed opioids during the baseline year, and individuals who did not answer the chronic pain question.

To answer aim 1+2:   In 2000+2005 = **12,145 individuals** (Figure 1)

To answer aim 3:   In 2000 = **2,015 individuals (the panel study)** (Figure 1)

Figure 1: flow-chart
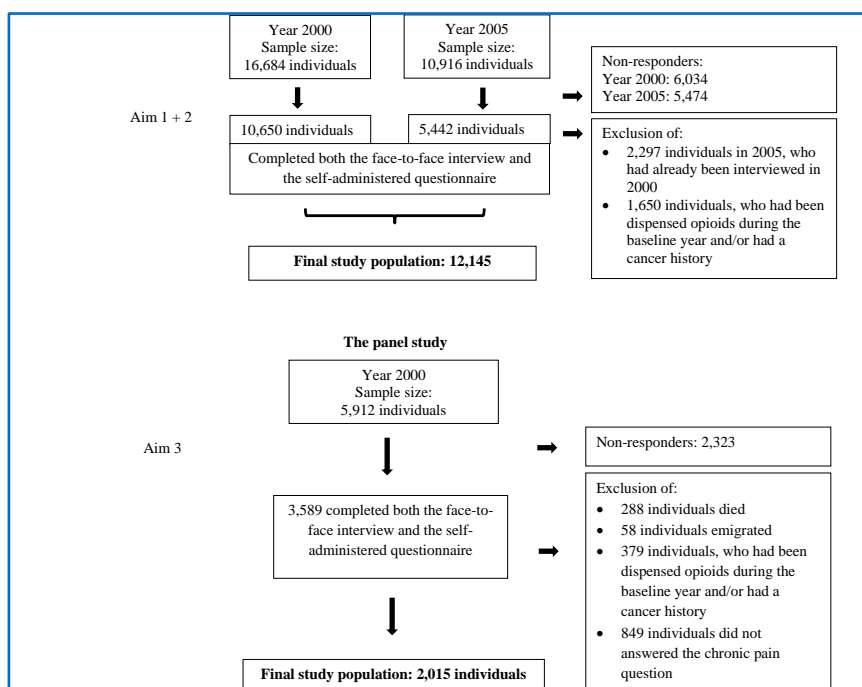
Paper III:

In 2013, due to a high item non-response rate on the outcome variables among those under 18 years and those older than 74 years, the study population was restricted to individuals aged 18-74 without a cancer history (n= 20,597). The final study population was **11,517 individuals**, who completed the self-administered questionnaire.

Paper IV:

In 2012, out of 5.2 million individuals in Norway (the total population), the final study population was **154,042 individuals** (≥18 years), who had redeemed at least one prescription of tramadol in 2012.

Data permission

Paper I, II, and III: All surveys were approved by the Danish Data Protection Agency (reference numbers: 2001-54-0894, 2009-54-0832 and 2012-54-0272).

Paper IV: The use of anonymous population data from NorPD does not require permission from the Regional Committee for Medical Research Ethics according to Norwegian legislation.

Assessments of chronic pain status and opioid use

Paper I, II, and III:

CNCP: The question 'Do you have chronic/long-lasting pain lasting 6 months or more?' identified respondents suffering from chronic pain.

Long-term opioid users were classified as individuals, who had been dispensed at least one prescription in six separate months within a year. This definition was recommended by the Danish Health and Medicines Authority and has been used in previous studies (67,119).

Short-term opioid users were classified as individuals, who have been dispensed at least one prescription in the previous year. These definitions have been used by the Danish Health and Medicines Authority and have been used in previous studies (67,119).

Assessments of prescribed drugs

Paper I, II, and III:

Information about prescription drugs dispensed in Denmark was drawn from the Danish National Prescription Registry (120).

Opioids were identified by the ATC codes: N02A, N02BE51, N02BA51 and R05DA04.

BDZs were identified by the ATC codes N05BA and N05CD.

BZD-related drugs were identified by the ATC code N05CF.

DDD and/or OMEQ were used to analyze the use of opioids;

- The DDD is defined as the expected average maintenance dose per day for a drug used for its main indication among adults by the World Health Organization (WHO). Only drugs classified according to the ATC (Anatomical Therapeutic Chemical) system is assigned a DDD. As the DDD is a unit of measurement, it does not necessarily reflect the recommended or prescribed Daily Dose. Despite that information about drug consumption presented in DDDs only provide a rough estimate of consumption, DDDs offer a fixed unit of

measurement independent of package size, strength, price, and currencies. Thus, DDD
enables the researcher to examine trends in drug consumption and make comparisons
between population groups possible. In population studies, DDD is often represented as
DDD/1000 inhabitants/ day (121,122).

- OMEQ measures the analgesic potency in each opioid (122). DDD can be converted to the
corresponding mg OMEQ by multiplying the mg per DDD with the morphine equianalgesic
ratio (123). (Table 2).

Table 2. DDD values and equianalgesic ratio for various opioids

Opioid (ATC code)	Administration route	DDD (mg)	Equianalgesic ratio
Morphine (N02AA01)	PO	100	1
Morphine (N02AA01)	PA	30	3
Oxycodone (N02AA05)	PO	75	1.5
Buprenorphine (N02AE01)	TD	1.2	110
Buprenorphine (N02AE01)	SL	1.2	50
Hydromorphone (N02AA03)	PO	20	6
Fentanyl (N02AB03)	TD	1.2	100
Oxycodone combinations (N02AA55)	PO	Equivalent to 75 mg oxycodone	1.5
Pethidine (N02AB02)	PO	400	0.1
Tramadol (N02AX02)	PO	300	0.2
Tapentadol (N02AX06)	PO	400	0.4
Codeine (R05DA04)	PO	100	0.1
Codeine, combinations excluding psychoepileptica (N02AA59)	PO	100	0.1
Dextropropoxyphene (N02AC04)	PO	200/300*	0.15
Ketobemidone (N02AB01)	PO	50	1
Ketobemidone and antispasmodics (N02AG02)	PO	50	1
Ketobemidone and antispasmodics (N02AG02)	PA	50	3
*Chloride/napsylate			
Per Oral (PO), Transdermal (TD), Sublingual (SL), Parentera (PA)			

Paper IV:

Information about prescription drugs dispensed in Norway was drawn from the NorPD.

- *Opioids* were identified by the ATC codes: N02A
- *BZDs* were identified by the ATC codes: N05BA, N05CD, and N03AE01
- *Z-hypnotics* were identified by the ATC codes: N05CF01 and N05CF02
- Drug quantity was measured in DDD

Tramadol users in 2012 were stratified into four different groups according to previous opioid use
(opioid naïve tramadol users, former users of weak opioids, former users of strong opioids, and
users in palliative care). Study population characteristics, the use of opioids (amount, type, and the
number of prescriptions) were analysed in a two-year period before baseline. Amongst recurrent

opioid users, during each year of the four-year follow-up period, opioid consumption, and concurrent use of BZDs or Z-hypnotics was calculated.

At the fourth year of follow-up, among recurrent users, we calculated;

- the prevalence of possible concurrent users of BZDs and Z-hypnotics
- the prevalence of consistent recurrent opioid users
- the prevalence of possible problematic drug users

Assessments of demographic factors

Paper I, II, and III:

Sex and age: Complete data on sex and age on all respondents were obtained from the Danish Civil Registration System (124).

Education: The Danish Education Registers were used to obtain data on the highest completed education (125). Highest completed education level was categorized as basic school, upper secondary or vocational school, or higher education. Missing data on highest completed education were complemented with self-reported data from the survey (<5%).

Cohabitation status: Data on cohabitation status were obtained by combining survey and register data from the Danish Civil Registration System and were categorized as married, cohabiting, single (divorced, widowed or unmarried), or single (unmarried) in paper I, in paper II-III cohabitation status was categorized only as married/cohabiting or single (divorced, widowed or unmarried).

BMI: self-reported height and weight were used to calculate body mass index (BMI) (weight in kilograms divided by height in meters squared).

Assessments of lifestyle factors

Smoking behavior: was assessed by asking the respondent whether they smoked or not, and smokers were asked about their average daily number of smoked cigarettes. Heavy smokers were defined as individuals smoking at least 15 cigarettes a day (126,127).

Alcohol intake: high alcohol intake was classified as an intake of more than 14/21 standard drinks for women and men per week, respectively (128). The question 'How many alcoholic drinks did you have each day last week? We'll start with yesterday and take one day at a time' was used in the

research year 2000 and 2005 to assess the amount of alcohol intake measured in a number of standard drinks, with one drink equivalent to approximately 12 g (or 15 mL) of pure alcohol.

Cannabis use: use of cannabis was assessed based on the recommendations by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (129). Thus, the use of cannabis was assessed by the question: 'Have you ever tried to use cannabis? The possible answer categories were: Yes, within the past month; Yes, within the past year; Yes, previously; No, I have never tried cannabis.'

Physical activity: physical activity in leisure time was measured using the 4-level Saltin-Grimby Physical Activity Level Scale (SGPALS) (130).

Assessments of health status

Three questions were selected from *The Short-Form Health Survey* SF-12 questionnaire, which was considered adequate and useful measures of general health status related to physical, psychological, functional and social well-being (131). Data were obtained from the panel study.

Overall self-rated health status: the question: 'In general, would you say that your health is excellent, very good, good, fair or poor?' (131) was used to examine changes in overall self-rated health status in individuals starting L-TOT between 2000 and 2013. The responses were coded from 1 (poor) to 5 (excellent). A negative change was defined as any negative change on the 5-point scale in the follow-up period.

Pain interference with physical activities: changes in pain interference with physical activities between 2000 and 2013 were assessed by the question: 'During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?' (131). The responses were coded from 1 (extremely) to 5 (not at all). A negative change was defined as any negative change on the 5-point scale in the follow-up period.

Moderate physical activities: changes in moderate physical activities between 2000 and 2013 were assessed by the question regarding activities during a typical day (moving a table, pushing a vacuum cleaner, bowling or playing golf, climbing several flights of stairs) (131). The responses were coded from 1 (yes, limited a lot) to 3 (no, not limited at all). A negative change was defined as any negative change on the 3-point scale in the follow-up period.

Charlson Comorbidity Index: The index is based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes and is used to adjust for comorbidity. Based on the adjusted risk of mortality each comorbidity category has a weighted score from 1 to 6. The total sum of all the weights gives a single comorbidity score—the higher the score, the more possible the predicted outcome will cause mortality (132). The Charlson Comorbidity Index has shown to be a valuable tool to adjust for confounders in studies based on data from administrative databases (133).

Assessments of sexual health status

Paper III:

Sexual outcomes were assessed by four closed-ended questions related to satisfaction with sex life (SL):

Satisfaction with SL: 'How satisfied are you with your sex life in the past year?': very satisfied; satisfied; neither satisfied nor dissatisfied; dissatisfied; very dissatisfied; don't know. The outcome for dissatisfaction with SL was dichotomized as either dissatisfied (dissatisfied or very dissatisfied) or other (very satisfied; satisfied; neither satisfied nor dissatisfied; don't know)

A lack of or low sexual desire: 'Have you experienced a lack or decreased sexual desire within the past year?': yes, always; yes, often; yes, sometimes; yes, but rarely; no, never. The outcome for a lack of or decreased sexual desire was dichotomized as a lack of or low sex desire (yes, always; yes, often) or other (yes, sometimes; yes, but rarely; no, never).

Communication about sexual-related issues with the health care system: 'Have you talked to a health professional about sexually related issues during the past five years?': yes, on my own initiative; yes, on the initiative by a health professional; no.

Sexual activity: 'Did you have sexual intercourse in the past year?': yes; no.

Statistical analyses

Paper I
Prevalence of CNCP
Prevalence of CNCP in the adult Danish population according to gender and age-groups (16–24 years, 25–44 years, 45–64 years, 65–79 years, and ≥80 years), cohabitation status, education, and

BMI was calculated in each survey year (2000, 2005, 2010, and 2013), expect of country of origin which was only calculated in 2010 and 2013.

Prevalence of opioid prescriptions in each survey year (2000, 2005, 2010, and 2013)

Prevalence of long-term and short-term opioid users, and dispensed opioids by gender, age groups (16-44 years, 45-64 years, and ≥ 65 years) and chronic pain status were calculated. Dispensed opioids were represented as both DDD/1000 individuals/day and OMEQ/1000 individuals/day and increase/decrease change since 2000 was presented as a percentage.

Paper II

Incidence rates for initiating L-TOT during follow-up were calculated. Follow-up was continued until initiating L-TOT, death, emigration, a cancer diagnosis or end of follow-up (31st December 2012). Person-years (the total sum of the observation-years of everyone) were calculated as the sum of individual follow-up times until initiating L-TOT, censoring for death, emigration or cancer, or the end of follow-up. Crude incidence rates of starting treatment are presented as events per 1,000 person-years.

Predictors for initiating L-TOT

The predictors of starting L-TOT were analyzed in accordance to CNCP status at baseline and the results shown as hazard ratios (HR) with 95% confidence intervals (CI). Discrete time survival models to identify predictors for initiating L-TOT was used as the individual's long-term opioid status. Sex, cohabitation status, education, smoking behavior, alcohol intake, use of cannabis, and physical activity in leisure time, BMI, dispensed BZDs, and a dummy variable for survey year was included in the regression models. Age was used as the underlying time scale treating age at the interview as the time of delayed entry. Graphically check of Cox's proportional hazards assumptions were made.

Changes in self-rated health, pain interference, and physical function.

Multiple logistic regression analyses were used to examine changes in self-rated health, pain interference and physical function between 2000 and 2013 in the panel study. The two groups (CNCP patients or individuals without CNCP) were also combined in these analyses to investigate the association between duration of treatment and changes in outcomes. The results are shown as sex- and age-adjusted odds ratios (OR) with 95% confidence intervals.

Paper III

The associations between CNCP, opioid use, and lack of/low sexual desire and dissatisfaction with sexual life

Multiple logistic regression models were used to examine the associations between CNCP, opioid use, and lack of/low sexual desire and dissatisfaction with sexual life. The models were adjusted for gender, age, cohabitation status, education, smoking behaviour, high alcohol intake, physical activity in leisure time, BMI, dispensed BZD and/or BZD - related drugs and comorbidity. The Charlson Comorbidity Index was used to adjust for comorbidity. The results are shown as odds ratios (OR) with 95% confidence intervals.

Study IV

We made calculations of the drug use (opioids, BZDs, and Z-hypnotics) among tramadol users (≥18 years), in 2012, according to the four study populations groups. We analyzed the use of opioids (amount, type, and the number of prescriptions) in a two-year period before baseline. Amongst recurrent opioid users, during each year of the four-year follow-up period, we studied opioid consumption, and concurrent use of BZDs or Z-hypnotics. At the fourth year of follow-up, among recurrent users, we calculated; the prevalence of possible concurrent users of BZDs and Z-hypnotics; the prevalence of consistent recurrent opioid users, and the prevalence of possible problematic drug users.

Main results

Paper I:

In the period from 2000 to 2013, the prevalence of CNCP, the number of opioid users and the number of dispensed opioids increased. In total, the prevalence of CNCP increased from 18.9% to 26.8%, with clear gender and age differences – a higher proportion among women than among men had CNCP and increasing age was associated with higher prevalence of CNCP, especially among the elderly women (Table 3).

Table 3. Prevalence of chronic non-cancer pain in the adult Danish population. 2000-2013

		2000	2005	2010	2013
Total		18.9	20.2	26.2	26.8
Men					
	16-24 y.	7.3	4.7	8.7	8.4
	25-44 y.	12.2	15.5	16.5	18.7
	45-64 y.	20.5	20.0	26.4	27.0
	65-79 y.	22.8	22.6	28.7	26.8
	≥80 y.	34.1	22.0	32.0	33.5
	All men	16.4	17.7	22.3	22.8
Women					
	16-24 y.	11.5	12.1	16.1	15.6
	25-44 y.	14.6	15.7	20.9	21.3
	45-64 y.	25.8	28.9	35.9	35.0
	65-79 y.	35.7	26.6	35.6	39.4
	≥80 y.	42.5	32.7	52.3	46.7
	All women	21.3	22.4	29.6	30.2

Overall, from 2000 to 2013, we found an increasing prevalence of short- and long-term opioid users (Figure 2), as well as an 38% increase in the number of dispensed opioids (from 492 to 964 OMEQ/1000 individuals/day) (Table 4) and the highest increase (+97%) found among elderly women (OMEQ/1000 individuals/day) (Table 5).

Figure 2. Prevalence of long-term and short-term opioid users in 2000-2013
among individuals with chronic pain.
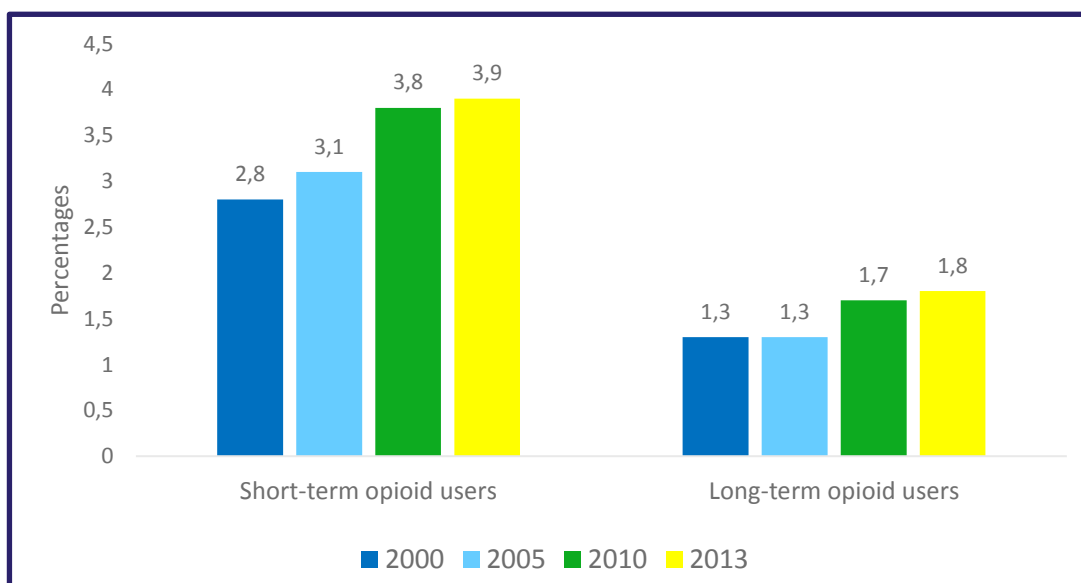
Table 4. Dispensed opioids in 2000-2013 by chronic pain status. OMEQ/1,000 individuals/day (percentage change since 2000)

		2000	2005		2010		2013	
All								
	Chronic pain	2,350	1,692	*(-28%)*	3,021	*(+29%)*	3,243	*(+38%)*
	No chronic pain	49	98	*(+100%)*	102	*(+102%)*	128	*(+161%)*
	All respondents	492	664	*(+35%)*	867	*(+76%)*	964	*(+96%)*

Table 5. Dispensed opioids in 2000-2013 by gender and age among individuals with chronic non-cancer pain. OMEQ/1,000 individuals/day (percentage change since 2000)

		2000	2005		2010		2013	
				Chronic pain				
Men								
	16-44 y.	1,052	1,319	*(+25%)*	1,391	*(+32%)*	1,578	*(+50%)*
	45-64 y.	3,365	3,814	*(+13%)*	2,624	*(-22%)*	2,825	*(-16%)*
	≥65 y.	3,097	6,685	*(+115%)*	4,100	*(+32%)*	3,811	*(+23%)*
Women								
	16-44 y.	1,027	1,518	*(+47%)*	1,000	*(-3%)*	1,151	*(+12%)*
	45-64 y.	2,633	2,282	*(-13%)*	3,008	*(+14%)*	3,228	*(+23%)*
	≥65 y.	2,947	3,106	*(+5%)*	6,320	*(+114%)*	5,808	*(+97%)*

In addition, individuals with CNCP had a higher consumption of weak opioids compared to strong opioids and a substantial increase in the use of weak opioids (35.8 - 39.9 DDD/ 1000 individuals/day), whereas the use of strong opioids was stable (26.7 - 26.6 DDD/ 1000 individuals/day). The concurrent use of BZDs decreased whereas the concurrent use of BZD-related drugs remained stable. However, 33% still had a concurrent use of BZD and/or BZD-related drugs (Figure 3).

Figure 3. Co-medication with benzodiazepines and/or Benzodiazepine-related drugs among long-term opioid users.
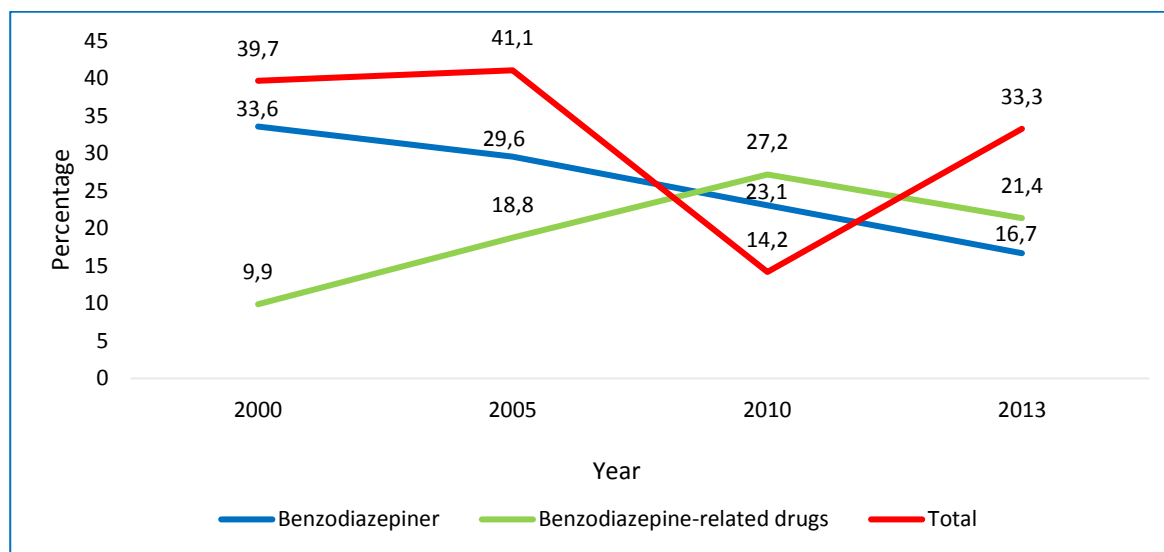
Paper II:

The long-term opioid incidence rate was substantially higher in CNCP patients at baseline (9/1000 person-years) than among others (2/1000 person-years) (Table 6)

Table 6. Study population according to chronic pain status at baseline and the number of new long-term opioid users and number of new users per 1000 person-years.

	Chronic pain	Not chronic pain
No. of individuals at baseline	1,997	10,148
Person-years of follow-up	17,900	98,260
No. of cases	159	200
Incidence rate (per 1,000 person-years)	9	2

Female sex, short education, tobacco smoking, sedentary lifestyle, overweight, and obesity was found to be significant predictors for initiating L-TOT (Table 7).

Table 7. Hazard ratios (HR)* and 95% confidence intervals (CI) for long-term opioid use. Results from Cox's proportional hazards analysis with age as the underlying time scale.

		Chronic pain at baseline			No chronic pain at baseline		
		HR	95% CI	P-value	HR	95% CI	P-value
Sex				0.096			0.006
	Men	1			1		
	Women	1.40	(0.94-2.08)		1.74	(1.27-2.40)	
Cohabitation status				0.842			0.969
	Married/cohabiting	1			1		
	Single	1.04	(0.70-1.56)		1.01	(0.72-1.41)	
Education				0.126			0.028
	Basic school	1.69	(0.90-3.17)		1.79	(1.14-2.80)	
	Upper secondary or vocational school	1.90	(1.02-3.51)		1.33	(0.85-2.07)	
	Higher education	1			1		
Smoking behaviour				0.002			<0.001
	Heavy smoker	2.38	(1.41-4.03)		3.12	(2.04-4.79)	
	Daily (not heavy) smoker	1.64	(0.94-2.85)		1.96	(1.25-3.09)	
	Occasional smoker	3.03	(1.03-8.95)		1.17	(0.42-3.28)	
	Ex-smoker	0.97	(0.57-1.63)		1.34	(0.89-2.04)	
	Never smoker	1			1		
High alcohol intake				0.774			0.758
	Yes	0.92	(0.50-1.67)		1.08	(0.68-1.70)	
	No	1			1		
Use of cannabis				0.939			0.864
	Within last year	1.25	(0.36-4.31)		1.25	(0.54-2.87)	
	Previously	1.04	(0.57-1.89)		1.07	(0.67-1.69)	
	Never	1			1		
Physical activity in leisure time				0.144			0.007
	Heavy or moderate	1			1		
	Light	1.67	(0.82-3.39)		1.27	(0.81-1.98)	
	Sedentary	2.14	(0.99-4.63)		2.11	(1.26-3.55)	
BMI				0.119			0.013
	<25	1			1		
	25-<30	1.26	(0.84-1.89)		1.29	(0.92-1.79)	
	≥30	1.72	(1.02-2.89)		1.94	(1.24-3.02)	
Dispensed benzodiazepines during the baseline year				<0.001			0.022
	Yes	2.62	(1.71-4.01)		1.70	(1.08-2.67)	
	No	1			1		
*HR adjusted for the variables in the table + survey year							

There was a higher proportion of individuals who initiated L-TOT in the follow-up period who reported negative changes in self-rated health (53.9% vs. 29.6%), pain interference with normal activities (83.3% vs. 36.1%), and moderate physical activities (50.0% vs. 24.2%) compared with non-opioid users (with/without CNCP). Likewise, individuals who initiated L-TOT in the follow-up period had higher likelihood of experiencing negative changes in self-rated health (OR 2.0, 95% CI 1.1-3.9), pain interference with normal activities (OR 8.2, 95% CI 3.6-19.0), and moderate physical activities (OR 5.3, 95% CI 2.6-10.8) compared with those not using opioids (with/without CNCP). Our results also indicated a dose-response relationship between L-TOT duration among those who initiated L-TOT during follow-up and risk of experiencing negative changes.

Paper III:

Among individuals with CNCP, a higher proportion of men than women reported dissatisfaction with sex life, whereas women more frequently than men reported a lack of/low sex sexual desire. A higher number of pain locations increased the prevalence of dissatisfaction and lack of/low sexual desire in both genders.

Going from one to two to three pain locations increased the prevalence of those, who had a lack of/low sexual desire: men: 9.6% (1 pain location), 11.0% (2 pain locations), 19.7% (≥3 pain locations), and women: 23.8% (1 pain location), 31.0% (2 pain locations) and 34.4% (≥3 pain locations) (Table 8). Likewise, going from one to two pain locations increased the prevalence of those being dissatisfied with their sex life (men: 21.2% to 30.5%, women: 12.8% to 18.7%), whereas three or more pain locations did not further alter the prevalence (Table 9).

Table 8. Prevalence of reporting a lack/or low sexual desire according to chronic pain location and number of pain locations stratified by gender and age.

	Prevalence of a lack/or low sexual desire									
	Men (%)					Women (%)				
	18-44 years	45-64 years	65-74 years	All men	No. of respondents	18-44 years	45-64 years	65-74 years	All women	No. of respondents
Number of pain locations										
1	10.6	5.5	18.1	9.6	449	21.8	25.5	23.8	23.8	570
2	5.4	9.3	30.2	11.0	335	22.9	32.2	45.0	31.0	488
≥3	14.0	19.0	31.5	19.7	348	32.4	34.4	37.9	34.4	607
No chronic pain	4.7	7.4	16.2	7.0	3,973	15.9	21.5	29.5	19.1	4,132

Table 9. Prevalence of reporting dissatisfaction with sex life according to chronic pain location and number of pain locations stratified by gender and age.

Prevalence of dissatisfaction with sex life										
	Men (%)					**Women (%)**				
	18-44 years	45-64 years	65-74 years	All men	No. of respondents	18-44 years	45-64 years	65-74 years	All women	No. of respondents
Number of pain locations										
1	22.4	19.7	21.4	21.2	419	13.5	12.8	9	12.8	528
2	30.5	27.3	41.3	30.5	313	21.7	17.7	13.1	18.7	431
≥3	27.8	26.9	39.8	29.1	315	17.8	19.4	19	18.8	537
No chronic pain	20.6	17.3	17.6	19.1	3,827	14.9	12.4	7.9	13.5	3,852

CNCP patients had higher odds of reporting low sexual desire (Table 10) and dissatisfaction with sex life (Table 11) compared to those without CNCP; OR 1.46 (95% CI 1.28-1.67), OR 1.38 (95% CI 1.22-1.58), respectively. Using opioids increased the odds; both short- and long-term opioid users with CNCP were more likely to report a lack of/low sexual desire OR 1.82 (95% CI 1.39-2.38), and OR 2.64 (95% CI 1.80-3.88) (Table 10) as well as sexual dissatisfaction (OR 1.35; 95% CI 1.00-1.82, and OR 1.69; 95% CI 1.07-2.67, respectively) (Table 11) than individuals without CNCP.

Table 10. Crude prevalence and odds ratio of a lack of or low sexual desire according to chronic pain status and opioid use.

A lack of or low sexual desire			
	%	OR*	95% CI
Chronic pain - long-term opioid user	39.3	2.64	(1.80-3.88)
Chronic pain - short-term opioid user	29.6	1.82	(1.39-2.38)
Chronic pain - no opioids	20.5	1.46	(1.28-1.67)
No chronic pain	12.6	1	
OR* adjusted for gender, age, education, cohabitation status, smoking behaviour, high alcohol intake, leisure-time physical activity, BMI, dispensed benzodiazepine-related drugs in the previous year, and Charlson Comorbidity Index			

Table 11. Crude prevalence and odds ratio of being dissatisfied with sex life according to chronic pain status and opioid use.

Dissatisfaction with sex life			
	%	OR*	95%CI
Chronic pain - long-term opioid user	24.8	1.69	(1.07-2.67)
Chronic pain - short-term opioid user	21.4	1.35	(1.00-1.82)
Chronic pain - no opioids	21.0	1.38	(1.22-1.58)
No chronic pain	16.6	1	
OR* adjusted for gender, age, education, cohabitation status, smoking behaviour, high alcohol intake, leisure-time physical activity, BMI, dispensed benzodiazepine-related drugs in the previous year, and Charlson Comorbidity Index			

We found a low prevalence among individuals without CNCP, who had talked to health professionals about sexually related problems during a past five-year period (men: 10.3 %, women: 15.3%). Having CNCP and using opioids did not alter much the prevalence.

Paper IV:

In 2012, 3.9% of the Norwegian adult population (≥18 years) received at least one prescription of tramadol (154,042 out of 3,932,250 individuals) (134). When we stratified the total study population of tramadol users into four groups according to their previous use of opioids, 64,792 were defined as opioid naïve tramadol users (group 1), 76,712 were former users of weak opioids (group 2), 9,313 were former users of strong opioids (group 3), and 3,225 users in palliative care (group 4). We found a clear gender difference as the proportion of women was higher compared to men in all four groups. In total, 5.8% (N= 3,476) of opioid naïve tramadol users, 39.8% (N= 27,765) of former users of weak opioids, 60.7% of former users of strong opioids, and 70.0% of users in palliative care became recurrent users. Among the recurrent opioid uses, we found a high increase in opioid doses in all four groups during the four-year study period, especially among the opioid naïve tramadol users, who almost doubled their mean opioid consumption from 66 DDD to 108 DDD from the first to the fourth year (Table 12).

Table 12. Use of opioids in total and use of strong opioids among the four study population groups, who have used opioids in each of all 4 years of follow-up from 2012 to 2016 (recurrent opioid users) in a 2-year period before baseline and in a 4-year follow-up period

	Group 1: Opioid naïve tramadol users N = 3,476	Group 2: Former weak opioid users N = 27,765	Group 3: Former strong opioid users N = 4,664	Group 4: Users in palliative care N = 1,251
Opioid use	**DDD Mean**			
- 2 years	-	157	275	420
- 1 years	-	156	277	405
+ 1 year	66	173	301	413
+ 2 years	81	183	311	413
+ 3 years	95	190	318	415
+ 4 years	108	191	318	430
Strong opioids	**N (%), DDD Mean**			
- 2 years	-	-	2,917 (62.5%), 80	499 (39.9%), 274
- 1 years	-	-	3,419 (73.3%), 77	554 (44.3%), 255
+ 1 year	494 (14.2%), 50	2,660 (9.6%), 45	2,452 (52.6%), 125	528 (42.2%), 283
+ 2 years	598 (17.2%), 81	3,393 (12.2%), 77	2,368 (50.8%), 173	579 (46.3%), 302
+ 3 years	745 (21.4%), 99	4,375 (15.8%), 98	2,520 (54.0%), 197	595 (47.6%), 334
+ 4 years	809 (23.3%), 140	5,183 (18.7%), 114	2,551 (54.7%), 222	633 (50.6%), 379

Group 1: Individuals, who did not receive any prescription of opioids in 2010-2012 (opioid naïve tramadol users)
Group 2: Individuals, who received prescriptions of only weak opioids in 2010-2012 (former weak opioid user group)
Group 3: Individuals, who received prescriptions of strong and/or weak opioids in 2010-2012 (former strong opioid user group)
Group 4: Individuals, who received palliative care and prescriptions of opioids in 2010-2012 (users in palliative care group)
DDD= Defined Daily Doses

During the four years of follow-up, the opioid naïve tramadol users did not only experience an escalation in opioid doses, 23.3% proceeded to use strong opioids (Table 12, Figure 4), 40.3% met the criteria for a consistent recurrent use (at least one prescription each research year and at least six or more prescriptions of opioids during the fourth 1- year period), 25.3% were co-medicated with BZDs, 34.0% were co-medicated with Z-hypnotics, and 11.9% were co-medicated with both drugs (Table 13). More than haft of former strong opioid users and users in palliative care had shifted to the use of strong opioids in the fourth year of follow-up (Figure 4).

Former strong opioids users had a prescription pattern like the users in palliative care; mean DDD 300 and 410, respectively; (Table 12) half of them had a possible concurrent use of BZDs

or Z-hypnotics; one quarter had a possible use of all three drugs concurrently (Table 13); and 5.5% and 6.8% had a possible problematic drug use pattern, respectively.

Table 13: The possible concurrent drug use of opioids, benzodiazepines, and Z-hypnotics, at the fourth year of follow-up, in recurrent opioid users (who have used opioids in each of all four years from 2012-2016), stratified into four different study population groups.

	Group 1: Opioid naïve tramadol users	Group 2: Former weak opioid users	Group 3: Former strong opioid users	Group 4: Users in palliative care
	n = 413 (11.9%)	n = 5,070 (18.3%)	n = 1,239 (26.6%)	n = 319 (25.5%)
	DDD Mean, Median (IQR)			
Opioids, in total	175, 67 (75-164)	246, 163 (65-328)	400, 254 (103-493)	453, 309 (143-588)
Benzodiazepines	150, 65 (20-192)	188, 99 (25-239)	238, 120 (40-300)	241, 122 (40-275)
Z-hypnotics	284, 241 (90-400)	352, 300 (125-432)	379, 330 (150-500)	411, 357 (200-500)

DDD = Defined Daily Doses
IQR = Interquartile range

Figure 4. The periodic prevalence of receiving a strong opioid in each of the one-year periods according to four different study populations
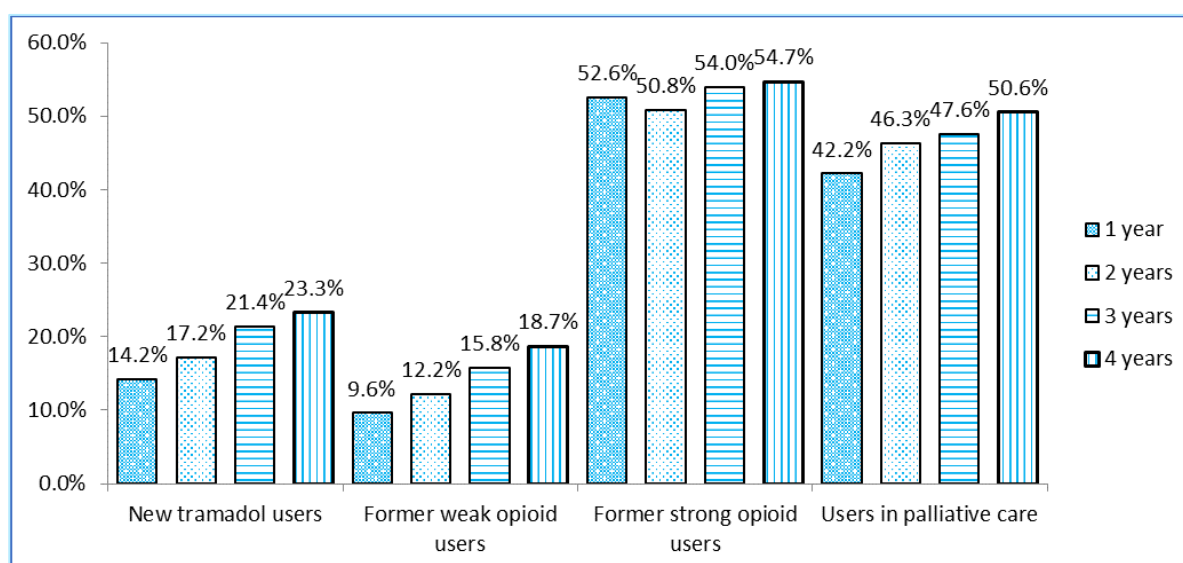
Discussion

In this section first, central issues in the research field are discussed, second, findings of the four papers are discussed individually in view of the existing literature and third, important limitations and strengths in all four papers are discussed.

This thesis highlights prevalent consumption of opioids for CNCP, strong associations between L-TOT and adverse changes in HRQOL, prevalent use of co-medications as BZDs or BZD-related drugs, dose escalations in long-term opioid users demonstrated clearly in a cohort of tramadol users, who also had a concurrent prevalent use of co-medications as BZDs or Z-hypnotics.

It is well-known that western countries are struggling with an increasing use of opioids due to an extensive use of opioids for CNCP. The United States and Canada are experiencing a real opioid crisis causing momentous suffering, overdose-related deaths and addiction (135,136). Likewise, though not to the same dramatic extent, a widespread and liberal use of opioid therapy for CNCP has created an epidemic increase in Scandinavia (13,35,68,137–139). This increasing use has been followed by reports of contemporarily increasing rates of fatal opioid overdoses (139). Studies addressing these severe consequences of opioid use together with the rising prevalence of CNCP in the gradually aging populations are emerging (8,69). A recent Danish report from the Board of Health concluded, that Denmark had a significantly higher consumption of opioids (>2/3 generated by individuals with CNCP) compared to the rest of the Scandinavian countries and estimated that 168.000 individuals were L-TOT users (13).

Not only the risk of addiction and the over-dose related causalities have been worrying, but also a relatively new awareness of the adverse effects, long-term consequences, and poor pain relief outcomes when using opioids long-term for CNCP has arisen. It has become obvious that changes in opioid prescription are urgently needed. President Trump has recently declared a united combat to the opioid crisis in the United States (140) and in the Scandinavian countries, journalists and pain specialists have focused on the increasingly problematic opioid use, especially regarding the liberal use of tramadol and its negative consequences (141,142). In Denmark, the health authorities have recently announced new recommendations for the use of opioids for CNCP (111), and new updated guidelines have become increasingly more restrictive in their recommendations compared to previous guidelines (107–109).

The following four papers will be discussed individually.

Paper I:

In paper I, we examined the prevalence of CNCP and use of opioids and co-medication in CNCP patients from 2000 to 2013 in Denmark. The increasing prevalence of CNCP found in this study (18.9% in 2000 to 26.8% in 2013) could to some extent be caused by methodological variances in the surveys e.g. more detailed questions about pain locations were added to the questionnaire from 2010. Still, the increasing CNCP prevalence is in line with other studies (4,143–145). A previous study in Denmark also found an increasing annual incidence rate for development of CNCP - from 1.8% in 2004 (6) to 2.7% in 2010 (68).

CNCP prevalence is often reported to be higher in older age groups, in lower income groups, among those with low education, among women, among obese, and among tobacco smokers (31,138,146–148) (Breivik 2006), which corresponds well with our findings (149). In addition, we found a higher prevalence of CNCP among those with a non-Western background. This population group has shown not only to have more widespread pain but also higher pain intensity than native Danes in a previous Danish study (150). Another epidemiological survey of CNCP has discussed whether cultural background and local traditions may influence the reporting of CNCP in different European countries (8).

The fact that women have demonstrated higher biological sensitivity and a lower threshold for pain stimuli than men, possibly mediated and modulated by gonadal hormonal factors, may explain the gender differences found in our as well as in other studies (8,74,145,151–154).

This study showed an increased use of opioids for CNCP, with the highest consumption among women, which has also been found in a former epidemiological study (155), but men have also been found to use more potent opioids (156) and at higher doses than women (157). The increasingly widespread and liberal use of opioids for CNCP - has increased to epidemic proportions - in the western part of the world is well-acknowledged in the literature (158–160). From 1980 to 2000, Denmark experienced more than a 600% increase in the use of opioids for treating CNCP (58). In our study we found an increase in the dispensed amount of opioids of 38% among CNCP patients and 161% among no-CNCP patients from 2000 to 2013 (OMEQ/1000 individuals/day). We also showed an increasing prevalence of long-term users among individuals with CNCP, despite a lack of strong evidence supporting that long-term opioid treatment adequately relieves pain (30,56,143).

Long-term opioid use is strongly associated with adverse biological consequences, addiction, opioid misuse, unintended opioid overdose, polydrug abuse, and a cluster effect of addiction behaviours (119,161,162). Our study found a huge decrease in the concurrent use of BZD and BZD- related drugs among long-term opioid users from 60% to 33% (2000–2013) and a shift in the drug use pattern from BZD to BZD-related drugs. A growing alertness in the Danish health care system of the negative side effects of BZD and BZD- related drugs has probably caused this decrease (163). However, still, one-third of the long-term opioid users had a concurrent use of either BZD or BZD-related drugs. BZD and BZD-related drugs were more frequently used by individuals with CNCP compared to individuals without CNCP, even though sedative drugs interact adversely with opioids and should be avoided (164). The increased risk of concurrent use of BZD in long-term and high dose opioid users has also been shown in previous studies (49,119,161,165).

Paper II:

In our second paper, we found that women, short education, tobacco smoking, sedentary lifestyle, overweight, and obesity were significant predictors for initiating L-TOT. Likewise, a Norwegian cohort study have also showed that 62.7% of new long-term opioid users were women (49) as psychological, biological, cultural and social factors may cause gender differences in pain responses, reporting and management (166), especially among the middle-aged women (45–64 years), who have been shown to use significantly more health care services than men (167). Also, lifestyle factors such as smoking, sedentary lifestyle, obesity have been found to be predictors of L-TOT in other studies (58,168,169). Notably, smoking has been shown to be strongly associated with L-TOT. In a large-scale study of 26,014 low back pain patients, more than 50% of the L-TOT users were current or recent smokers and 50 % were over-weighty (169). Low education is a well-known predictor of L-TOT (170,171), and additionally lower educated patients have been found to be three times more likely to be prescribed opioids for acute pain conditions than higher educated patients – even after adjusting for age, sex, income and pain severity (172). An explanation might be that low education level has been associated with low medication knowledge and consequently low knowledge of potential drug side effects plus lower self-efficacy regarding recovery (173). Also, use of BZDs has been found to be associated with initiating L-TOT. The use of BZDs has previously been found to be a stronger predictor of future opioid prescriptions than musculoskeletal pain/chronic pain (105). The concurrent use of BZDs is concerning as BZDs have no established analgesic effects (174), but a well-documented addictive and abusive potential (100,105), as it increases the rewarding and reinforcing effects of opioids (101,102,175).

Long-term opioid users have both higher frequency and increased likelihood for developing poor self-rated health, higher pain interference with normal activities and moderate physical activities compared with those not using opioids with or without CNCP. Longer duration of L-TOT seems further to increase the risk of experiencing these negative effects. Also, severe adverse effects, dose escalation and co-medication of BZDs and hypnotics are common during L-TOT. Consequently, due to non-evidence supported treatment, CNCP patients who are co-medicated with high doses of opioids and BZDs may already have or are at risk of developing problematic opioid use (176). These results are alarming as improved HRQOL, pain relief and improved physical functioning are the key goals for opioid therapy for CNCP (177). Eriksen et al. have previously found an indication of recurrent opioid therapy for CNCP did not seem to improve HRQOL, pain relief or functional capacity (58). A causal relationship between pain relief, HRQOL, functional capacity and recurrent use of opioids could not be assessed because of the cross-sectional nature of that study (63). Since we could characterize new users of L-TOT and follow them up to 13 years by using information from the prescription database, our results could more strongly indicate a potential causal relationship. Another pharmaco-epidemiological study found indications of insufficient pain relief in most opioid users as more than two-thirds of persistent opioid users still reported severe or very severe pain (143). Lastly, a comprehensive review concluded that the evidence for the effectiveness of L-TOT in terms of achieving pain relief and improving functional capacity was weak (178). When investigating the prevalence of new opioid users, who are developing L-TOT, a wide range of prevalences have been found in population-based studies. One study found that nearly half of new strong opioid users became L-TOT, wherein 7% were still using opioids five years later (49), another study found a very low percentage (0.3% and 0.08%) among new users of weak opioids, who developed recurrent or problematic opioid use during three years of follow-up (179). In contrast, a population-based study found that 21% of short-term opioid users (≤90 days of prescribed opioids) progressed to periodic opioid use (>90 days and <120 DDD or >10 prescriptions in total) and 6% progressed to long-term use (>90 days and ≥120 DDD or ≥10 prescriptions) (168). These prevalence differences for developing L-TOT between studies may partly be explained using different inclusion criteria and study population groups.

The fact that L-TOT users are often being prescribed high opioid doses (180), is concerning since high opioid doses have an increased risk of opioid-related mortality, toxicity, fractures, and road trauma (52,181–183).

The opioid prescription pattern for CNCP in Denmark seems to conflict with recommendations for responsible opioid use for CNCP (99,108,111).

Paper III:

In paper III, we investigated the relation between chronic pain, opioid use and problems with satisfaction with sex life and sexual desire. Chronic pain, and especially widespread pain has been shown to be strongly associated with emotional suffering and physical limitations interfering with the quality of life, as well as sexual life (8,184–186). Accordingly, our results indicated that widespread pain increases the prevalence of experiencing a lack of or low sexual desire. In a population-based study, 73% of patients with chronic pain reported sexual difficulties associated with their pain condition (187). Also, women suffering from widespread chronic pain have been found to have more sexual pain and sexual distress compared with healthy women (188). A systematic review examining sexual dysfunction in women found an average of one-quarter of the respondents reported sexual pain disorders (189).

CNCP patients using opioids may develop endocrine dysfunction caused by opioid-induced inhibition of the hypothalamic-pituitary function (72,74). As soon as an opioid is taken it has an impact on the endocrine system (73) and can, in long-term opioid users, cause hypogonadotropic hypogonadism (70,72,74) and hypocorticism (70). A decline in the level of testosterone has a significant impact on both genders' sexual desire and infertility, therefore sexual problems are most likely mediated by the reduced level of testosterone in opioid users (72). CNCP patients are already, independently of opioid use status, at increased risk of having sexual problems, and opioid treatment may exacerbate and accelerate development of difficulties in their sex life.

Despite it was not possible, in the present survey, to assess whether opioid-induced hormone deficiency was causative of low sexual desire and dissatisfaction with sex life, our results are in line with several other studies showing correlations between opioid use, hypogonadism, and sexual problems. A recent study of the impact of opioids on the hypothalamic–pituitary–gonadal axis found that the degree of being unsatisfied with sex life was positively correlated with opioid dose (190). Insufficient clinical management is still very present (191), even though this opioid-induced influence on the endocrine system have been acknowledged for decades (192–194) and present evidence recommends regular screening of opioid users for indicators of hypogonadism and for assessments of gonadal function (191). Lastly, evidence suggests that hypogonadism may increase pain sensation and therefore potentially counteract the analgesic effect of opioids (192). To reverse opioid-induced endocrine dysfunction, hormone substitution, a decreasing opioid dose, or cessation of opioid therapy can be necessary steps to take (70,74).

Gender, age, and lifestyle have been found to be three important factors playing a role in a satisfactory sex life. Decreased sexual desire has been the most frequent female sexual disorder, with a mean frequency of 64% (189,195) more prevalent in women than in men (196–199) and increasing with age (189,195–199). Our results also found gender and age differences, which might be associated with women´s menopausal decline in oestrogen production (195,198,200) plus the fact that many medical conditions and lifestyle behaviours representing risk factors for a sexual disorder are strongly related to age (184). Accordingly, our result showed that women more frequently reported a lack of/low sexual desire compared to men, whereas men more often were dissatisfied with their sex life than women.

It appears that sexual-related problems have a low priority in the health care system, often remains unnoticed, undertreated and unspoken (201). Even though 90% in an epidemiological study considered a satisfactory sex life important (196) and the majority of chronic pain patients preferred to have a choice of information and/or discussion about their sex life with a health professional (187), in present study, only approximately one out of ten reported having talked to a health professionals during the past five years about sexual-related problems. However, sexual dissatisfaction appears to be frequent in a "normal" population. One-quarter of men and more than half of women have been found to experience periods of declining interest in sexual activity (200). Notable, couples who identified themselves being in happy relationships reported these types of sexual-related problems (202). In our study, a causative relationship could not be assessed between CNCP, opioids, and having sexual problems. We do not know if the respondents' report of a low sexual desire and/or dissatisfaction with sexual life affected their quality of life – it might be either a disturbing or an acceptable part of life.

Since the functioning of one's sex life is a multifactorial determined condition, a precise estimation of the absolute influence of risk factors can be problematic to estimate (184). However, in our study suffering from CNCP was associated with higher odds of dissatisfaction with sex life and low sexual desire and L-TOT independently generates an additional negative impact on sexual desire. These results call for a careful monitoring of opioid user's sexual health in a multidisciplinary setting to prevent the development of sexual problems.

Paper IV:

In paper IV, we investigated the drug use pattern in a cohort of tramadol users in Norway during a four-year period. Previously, new opioid users' drug use pattern has been investigated in studies based on the NorPD (49,179). One study found that seven % of new weak opioid users developed

recurrent opioid use (received an opioid prescription at least once during each of four years) and only 0.08% developed a prescription pattern indicating problematic opioid use (>365 DDD of opioids during each of four years, opioid prescriptions from >3 clinicians, and >100 DDDs of BZDs simultaneously) (179). Except that we found higher proportions of recurrent users (0.5-6.8%) with a possible problematic drug use, these results are in line with ours. Precise comparisons between pharmaco-epidemiological studies can be a challenge due to different study designs and criteria for problematic opioid use (203).

Norway has experienced an increasing use of opioids and a rise in the number of drug-induced deaths, in which opioids have been most frequently involved (204). In 2015, 17% of the Norwegian population were treated with opioids and the rate of high-risk opioid users was 2.7/1.000 in 2013 (204). In 2014, the Norwegian average of drug-induced mortality rate, among adults (aged 15-64 years), was 75.6 deaths/million, compared to the European average of 20.3 deaths/million (204). However, mortality rate assessments may differ substantially between the European countries (205).

In the present study, former strong opioids users had a prescription pattern like the users in palliative care, even though recommendations and treatment principles for opioids in these two patient populations differ substantially (25). CNCP should not be treated as acute pain conditions, as acute pain represent a predictable and linear trajectory and usually respond well to opioids in contrast to chronic pain were opioids only initially provides pain relief (25,44). Further, as bio-psycho-social factors influence the experience, perception, and report of chronic pain, it may explain why L-TOT for CNCP does not provide expected pain relief, and why it is inappropriate, in most cases, to offer the simple WHO stepladder approach (25,44).

Compared to non-opioid users, opioid users, especially long-term high dose opioid users, have increased risks for co-medication with BZDs or Z-hypnotics (49,119,161,165,174,206). Our results emphasize this association as high-dose opioid users were also high-dose users of sedatives. In former strong opioid users and users in palliative care, who developed recurrent opioid use, a very high proportion was co-medicated - almost half used BZDs or Z-hypnotics, and one-quarter used both drugs. Frequently occurrence of sleep difficulties and anxiety among CNCP patients may contribute to the high prevalence of concurrent use of sedative-hypnotics (207,208). BZDs or Z-hypnotics act as central nervous system depressants and increases the risk of addictive behavior, drug toxicity, mortality, and overdose-related deaths (175,176,209). Users in palliative care may, though, continue this polydrug pattern if it is crucial for relieving pain, distress, and anxiety despite severe adverse effects.

Because problematic opioid use by definition is described in terms of behavioral patterns, not drug consumption, it is not possible to accurately identify persons with problematic opioid use based on prescription register data alone. Some of the recurrent users may not have received tramadol for CNCP but for separate acute pain episodes, and some of the possible concurrent drug users may not have used BZDs and/or z-hypnotics simultaneously with opioids. Yet, our findings highlight that those who became recurrent users among the group of naïve opioid tramadol users, they received prescriptions conflicting with existing guidelines which might lead to problematic opioid use. The results from two new studies observing the risk of opioid misuse and pain relief among opioid naïve CNCP patients does not support initiating opioid treatment for CNCP. They found an association between each refill and week of opioid use with large increases in opioid misuse, as well as a higher pain influence on functional capacity during 12 months using opioids compared to non-opioid medication (210,211).

Methodological considerations

Strengths of the studies are that they are based on data from national administrative registers; the three Danish studies were based on a combination of large representative surveys data, with adequate response rates, linked with register-based detailed information on prescription medicines. The Norwegian study was also based on the national prescription database similarly providing detailed information of drug use. Recall- and information bias is reduced using register-based data, as data are pre-collected and independently of our studies e.g. information about highest completed education, cohabitation status, and dispensed medicine. Another main strength is the availability to follow opioid use in large populations over prolonged time, making subgroup analysis possible – although small sample sizes may still be problematic in paper II. As we could characterize new long-term opioid users and follow them up to 13 years due to information from the prescription database we had the possibility to examine potential causality between L-TOT and negative changes in HRQOL in paper II. Since randomized clinical trials are not possible to conduct because of ethical considerations – studies in opioid use using population-based data is a major advantage to investigate consequences of opioid use with long follow-ups.

Main limitations of the studies are the lack of assessments of compliance and adherence to the pharmacological treatment in all four studies as we only have register-based data on dispensed medicine, and limited information about pain and health status in paper I-III. A lack of information about whether the dispensed medicine is taken can have weakened the results.

When using register-data, we were not able to ask for more relevant data for our studies, as data might be collected with other research and administrative goals than our research questions alone (212). Another potential limitation using register-data is misclassification in the recording of ICD-codes, missing coding, delated coding or under-coverage of some of the variables e.g. the measurements of co-morbidity can be affected by the fact that an illness can progress, and consequently the diagnosing of the disease might occur at a later stage (212). In paper I-III, one important issue of concern is that the pain variable contains very limited information. More detailed information about duration, intensity, mechanisms etc. would have improved the analysis and outcomes.

However, pain intensity and physical functioning have been shown to be modestly associated and therefore it is recommended (213) to include measurements of functional capacity in chronic pain clinical trials. Also, implementation of pain interference in functional capacity assessments as a core outcome measure has also been advised to be included in trials (The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)) and in The Brief Pain Inventory (BPI) measurement instruments (214,215). Thus, pain interference measurements may be of even higher clinical relevance than simple measures of pain intensity.

Another possible limitation was that non-Danish citizens living in Denmark were excluded from the surveys in 2000 and 2005, which could be a possible source of bias as the prevalence of CNCP seems to be higher in this subpopulation (150). Also, the highest obtained educational level among immigrants is often missing in Danish registers as well as educational attainment is often missing for persons with educations taken abroad (212). Non-responders can also cause possible bias in the analysis.

Also lost to follow-up due to death, emigration or non-response could, in paper II, have weakened the analysis. It can be difficult to calculate the characteristics of those lost to follow-up in more detailed analysis e.g. lost to follow-up was associated with a lower level of education but was not associated with gender in paper II.

Some of the results in paper II should be interpreted with caution because of the limited number of subjects within each subgroup. Also, the estimates in paper II and III could be to some extent subject to sample-to-sample variation. Lastly, the lack of an international definition of L-TOT as well as different study populations across studies may have influenced the external validity of paper II.

In paper III, lack of/low sexual desire and dissatisfaction with sexual life was assessed by non-validated standard questions, which though are used in numerous studies, despite that the wording of the questions, the answer categories, and/or the reference period might be slightly different (216–219). Furthermore, we have adjusted our regression models in paper III with known confounders, however, other potential confounders correlated to sexual problems in CNCP patients such as pain types and intensity (220), disabilities (221), psychological factors (222), and patients' history of sexual abuse (223) were not possible to adjust for, which might have affected our analysis.

In paper IV, NorPD does not deliver data about drug use during hospitalization/stay at other institutions, which may have caused a minor underestimation of the real drug use. As hospitalization increases with age, underestimation is most prevalent among the elderly (224), among sick hospitalized patients and thus in users of palliative care. Also, a potential inaccurate stratification could have occurred due to the use of reimbursement code to stratify the study population between palliative care treatment and acute pain/CNCP. Furthermore, inaccurately use of the code can have occurred when distinguishing cancer patients' palliative care from those in curatively intended treatment or in complete remission. It is also important to recognize that patients were stratified according to baseline status in 2012. Some of the patients, who were stratified as non-palliative at baseline, may have developed a life-limiting disease and become palliative care patients during follow-up. This may explain some cases of dose-escalation and co-medication in the three non-palliative groups in our study. An inadequate use of reimbursement code could have caused an inaccurate stratification when stratifying the study population between palliative care and acute pain/CNCP treatment, and when separating cancer patients' palliative care from those in curatively intended treatment or in complete remission. Another concern to recognize is that patients were stratified according to baseline status in 2012, and some patients, who were stratified as non-palliative at baseline, may have developed a life-limiting disease and turned out to be palliative care patients during follow-up. This might explain some cases of dose-escalation and co-medication in the three non-palliative groups in paper IV. Often registers only contain limited and unspecific confounder information (212). This limitation together with the fact that register-based studies often have great statistical power to detect small effect sizes makes register-based studies disposed of confounding (225). Not all potential confounder variables are possible to adjust for in the analysis.

Another concern in pharmaco-epidemiological studies is the potential healthy drug-use effect and health drug-adherer effect; individuals who comply with their physician's advice when given a prescription are different and healthier than individuals who do not (225).

Conclusions

During 2000-2013, the prevalence of CNCP and the use of opioids in Denmark increased, particularly among elderly women, and in 2013 one-third of long-term opioid users had a concurrent use of BZDs and/or BZD-related drugs. L-TOT did not seem to be effective in achieving the key treatment goals: pain relief, improved quality of life and functional capacity as users in L-TOT had increased odds for experiencing poorer self-rated health and increased pain interference during physical activities compared to those with or without CNCP not using opioids. CNCP patients had higher odds of sexual problems and opioid use added further negatively to sexual problems, especially in those on L-TOT. In a cohort of tramadol users in Norway, many of those, who developed recurrent opioid use, received prescriptions which substantially conflicted with existing guidelines. Even though only a minority of opioid naïve tramadol users became recurrent users (5.8%), these patients developed a potential problematic drug use with a high increase in annual doses, a high number proceeded to the use of strong opioids and/or was co-medicated with BZDs and/or Z-hypnotics. Finally, it is concerning that former strong opioids users had a prescription pattern like the users in palliative care using high doses of opioids, half of them was co-medicated with BZDs or Z-hypnotics and one quarter was co-medicated with all three drugs concurrently.

Perspectives

New winds blow in Denmark regarding the attention to opioid use for CNCP. More restrictive rules in prescribing opioids have emerged from the Danish health authorities during the past year (68), with increased surveillance of prescription of tramadol and other opioids, requirements of monthly face-to-face consultations with opioid users, and reporting of any tramadol-related side effects in a two-year period.

In the future treatment of CNCP, it is essential to have in mind that the principles for the treatment of chronic pain are fundamentally different from treatment of acute pain and to some extent cancer-related pain. Due to the limited effect and the high risk of harmful consequences of L-TOT for

CNCP, patients should instead receive other pharmacological treatments and learn to cope with their situation, as CNCP often have a major impact on the patient state of mind. Patients with CNCP are at risk of several severe consequences such as a high risk of developing an addiction, depression, sleep disturbances, stress conditions, fatigue, isolation, anxiety and becoming physical inactive – factors that can interfere and reinforce each other in a negative way (226). According to pain specialists, passive treatments modalities should be avoided as patients may develop passive coping strategies for handling their chronic pain condition (227,228). Notable, a current study concludes that most CNCP patients, including individuals severely affected, were ready to practice active self-care methods (229).

Currently, an expansion of the Danish database (PainData) is being considered. The PainData registry contains patient-specific data across a number of bio-psycho-social domains of CNCP before the first consultation at a pain clinic, immediately and 12 months after treatment including information about standardized pain sensitivity tests and pain diagnosis from six pain centres across the country (230). This example with monitoring and collection of big pain data may contribute to improved research data, a better understanding of CNCP conditions, greater knowledge on how various psychological, physical, social and existential factors influence the experience of pain and disability in a patient with CNCP (230). Also, focusing on establishing a shared commitment between patient and practitioner on a strategy for the pain management, a clarification of realistic expectations, and using evidence-based pain treatment modalities would, most likely, raise the quality of the chronic pain treatment (109).

Today, some of the major challenges for CNCP patients is limited access to specialized pain treatment; long waiting time – around up to one and a half year – in starting treatment at a public multidisciplinary pain clinic, and a general lack of medical practitioners with pain education. Potential consequences of delayed accessibility to qualified pain management might be that CNCP patients in distress are buying illegal opioid analgesics or cannabis, have difficulties in returning to work, increased disability and decreased quality of life (144,231), which all together induce human suffering and are costly for the individual as well as for the society (8,144,231,232). More resources allocated to pain research and management to increase the accessibility to treatment facilities are needed.

Prospectively, and in line with recommendations from The Danish Health Authority, interdisciplinary non-pharmacological treatment should be included as a central and integrated part of the treatment of all patients with CNCP conditions. Chronic pain patients would benefit from

treatment modalities involving not only specialized pain clinicians but also physiotherapists and psychologists trained in different therapies including e.g. cognitive behavioral therapy and mindfulness. Physiotherapists have the professional expertise to help the patient to rebuild and maintain muscle strength and body movements despite the pain condition by using patient-activating strategies. Bio-psycho-social factors should be addressed as these factors have shown to have an important role in the rehabilitation of chronic pain patients (226).

In general, a lack of knowledge about how to treat CNCP is apparent. More education of the complex CNCP conditions in the future medical education would be beneficial - maybe a medical training round at a multidisciplinary pain clinic should be a part of the medical student's education, as this patient group can be a complex and difficult task for the medical practitioners. Non-pain physicians prescribed the vast majority of the opioids and have been shown to prescribe opioids more liberally than pain clinics and centres (49,161,165).

The way that pain management is organized may also have significance to the follow-up procedures in opioid users. As several healthcare sectors are taking care of the prescription of opioids there is uncertainty about responsibility for the opioid treatment when admitted to or discharged from a hospital. More collaboration, including addiction-medicine specialists, and standardized structural approaches between healthcare sectors are needed.

Lastly, more studies are needed to investigate the long-term influence of opioid use in large population-based studies with several years of follow-up regarding drug use pattern, morbidity, mortality, use of health care services and genetics. These research questions cannot be answered in randomized clinical trials, but will largely depend on longitudinal study designs based on population-based register data.

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Appendices

Paper I	Birke H, Kurita GP, Sjøgren P, Højsted J, Simonsen MK, Juel K, Ekholm O. **Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013.** Acta Anaesthesiol Scand. 2016; 60: 623–633.

Paper II	Birke H, Ekholm O, Sjøgren P, Kurita GP, Højsted J. **Long-term opioid therapy in Denmark: A disappointing journey.** Eur J Pain. 2017; 21: 1516-1527.

Paper III	Birke H, Ekholm O, Sjøgren P, Højsted J, Kurita GP. **Chronic pain, opioid use, and sexual desire and satisfaction with sex life.** Pain Med. 2018; 0: 1-9.

Paper IV	Birke H, Ekholm O, Sjøgren P, Fredheim O, Mahic M, Clausen T, Skurtveit S. **Tramadol use in Norway: A register-based population study.** Pharmacoepidemiol Drug Saf. 2018;1–8

Questionnaire Susy, 2010 (in Danish)

Paper I - IV er ikke med i denne udgave. Kontakt venligst forfatteren, hvis du ønsker at vide mere.