

Opioid use after surgical treatment in the Danish population— Protocol for a register-based cohort study

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Abstract

Background: Over the past 25 years, global opioid consumption has increased. Denmark ranks fifth in opioid use globally, exceeding other Scandinavian countries. Postsurgical pain is a common reason for opioid prescriptions, but opioid use patterns after patient discharge from the hospital are unclear. This study examines trends in opioid prescription among Danish surgical patients over a year.

Methods: This register-based cohort study will use data from Danish governmental databases related to patients undergoing the 10 most frequent surgical procedures in 2018, excluding cancer-related and minor procedures. The primary outcome will be the dispensed postoperative opioid prescriptions at retail pharmacies over four quarters. Secondary analyses will include associations with sex, age, education attainment, and oral morphine equivalent quotient. Surgical treatments and diagnoses will be identified using NOMESCO procedure codes and ICD-10 codes. Opioids will be identified by ATC codes N02A and R05DA04. Subjects will be classified as preoperative opioid consumers or non-opioid consumers based on opioid prescriptions redeemed in the 6 months before surgery.

Discussion: The study will use extensive national register-based data, ensuring consistent data collection and enhancing the generalizability of the findings to similar healthcare systems. The study may identify high-risk populations for long-term opioids and provide information to support opioid prescribing guidelines and public health policies.

KEYWORDS

epidemiological studies, opioid epidemic, postoperative period

1 | INTRODUCTION

Over the past 25 years, there has been a significant global rise in opioid consumption, particularly in Western countries.^{1–3} Despite a recent decrease in the number of opioid users, Denmark currently

ranks fifth in global opioid consumption (measured in milligram morphine equivalents per 1000 inhabitants/day), with consumption rates approximately 10%–30% higher than countries with similar healthcare systems as Norway (ranks 9th) and Sweden (ranks 13th).^{4,5} The possible effects of opioid use extend beyond the classical side effects

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(e.g., constipation, sedation, nausea, and vomiting, etc.).^{6,7} Long-term opioid consumption has been associated with no pain improvement, poor self-rated health, unemployment, increased healthcare utilization, opioid misuse/addiction, and a negative impact on overall quality of life.^{8,9}

A survey with 18 hospitals across Europe showed that the mean incidence of chronic postsurgical pain at 6 months was 10.5%, with variations depending on the type of surgery.¹⁰ The occurrence of postoperative pain resulting from surgical handling, which may cause nerve injury or inflammation, negatively impacts the patient's well-being and can impede early mobilization, affecting recovery time and increasing the risk of complications.^{11–13} Opioids are frequently used in the pre-, peri-, and postoperative periods due to their efficacy in providing pain relief, although patients are typically expected to discontinue opioid therapy shortly after surgery.¹⁴

Studies have shown that a significant proportion (55%–75%) of patients undergoing surgical treatment receive opioid prescriptions for postoperative pain management.^{15,16} In addition, the prevalence of long-term opioid use (more than 6 months) after orthopedic surgeries have been reported as 12.5% in the Netherlands, 4%–10% in Australia, and 24% in the USA.^{17–19} With more than 2 million surgical procedures performed in Denmark annually (2023),²⁰ surgical treatments may constitute one of the most used reasons for opioid prescriptions.²¹

Danish population-based studies regarding trends of postoperative opioid prescription redeemed at retail pharmacies after surgical treatment are sparse and are limited to single procedures in a few subspecialties.^{22–28} Thus, an updated comprehensive picture of postoperative opioid dispensation patterns across the most frequent surgical specialties can be useful to raise awareness and improve opioid prescribing practices, presumably reducing the risks associated with long-term opioid consumption postoperatively.

2 | AIM

The primary aim is to investigate the trends of postoperative opioid prescriptions redeemed at retail pharmacies during 1 year for patients submitted to the 10 most frequent non-cancer surgical treatments at Danish hospitals. The secondary aim is to analyze associations between the frequency of redeemed postoperative opioid prescriptions regarding sex, age, educational attainment, and oral morphine equivalent (OMEQ).

3 | METHODS AND ANALYSIS

3.1 | Study design

This is a register-based cohort study. Data will be collected from the Danish governmental databases and will comprise data on postoperative opioid prescriptions redeemed at retail pharmacies 6 months before surgical treatment performed in 2018 and 1 year after.

3.2 | Data source

Individual-level data from national administrative registers will be accessed through Statistics Denmark's research platform. All individuals living in Denmark have a personal identification number and, thus, the registers can be linked at the individual level with this number. The registers are (Table 1):

1. The Danish National Patient Registry (DNPR) contains information on diagnoses (ICD-10 codes), treatments, and examinations (The Nordic Medico-Statistical Committee Classification of Surgical Procedures [NOMESCO] codes) among others in every hospital in Denmark (including private hospitals/clinics).²⁹
2. The Danish National Prescription Registry (NPR) contains data information on dispensed drugs (including its Anatomical Therapeutic Chemical [ATC] classification code), drug dosage, quantity dispensed, and the date of dispensation among others.³⁰
3. The Danish Civil Registration System (CRS) records current and historical information on all persons living in Denmark, such as sex, date of birth, civil status, and citizenship, among others.³¹
4. Danish Education Register (ER), which contains detailed information on individuals' educational attainment.³²

3.3 | Sample selection

The study population inclusion criteria are Danish citizens undergoing surgical treatment at a Danish hospital in 2018. Exclusion criteria: All subjects with cancer-related surgeries and/or with a current cancer diagnosis (ICD-10: C00-C97 [ICD-8: 140-208]) registered in DNPR at the index time of the surgical treatment in 2018. Minor surgical procedures, endoscopies, and removal of tissue for transplantation will also be excluded.

3.4 | Variables

Data on surgical treatments in 2018 will be extracted from the DNPR and contemplate NOMESCO procedure codes, ICD-10 codes, and date of surgical treatment (Table 2). The date of (the first) surgical treatment will be Day 0 (the index date). If an individual has more than one surgical treatment during 2018 only the first surgery will be considered for main analysis. However, the number of surgeries per individual in the period will be registered for complementary analysis. The surgical treatments will be grouped by specialty, and the top 10 according to frequency in 2018 will be selected for this study.

Data on opioid prescriptions redeemed at retail pharmacies 6 months before and 1 year after surgery will be drawn from NPR. This information before surgery will allow the classification of patients as preoperative opioid consumers and preoperative non-opioid consumers in the period from 1 to 180 days (6 months) before surgery. Preoperative opioid consumers will be those who had redeemed at

TABLE 1 Data variables.

Data source	Variables	Variables categories	Assessment window
The Danish National Patient Registry	Surgical treatment (NOMESCO codes)	Date of surgery	Year 2018 (index date)
		The 10 most prevalent surgeries	Year 2018
The Danish National Prescription Registry	Dispensed opioids (ACT codes: N02A and R05DA04)	All opioids (% OMEQ)	180–1 day before Index date
			0–90 days after index date
			91–180 days after index date
			181–270 days after index date
			271–365 days after index date
The Danish Civil Registration System	Sex	Female	At index date
		Male	At index date
		Age	Numeric
The Danish Education Register	Educational attainment	Lower secondary school or less	At index date
		Upper secondary school	At index date
		Higher education	At index date

Abbreviations: NOMESCO, The Nordic Medico-Statistical Committee Classification of Surgical Procedures; OMEQ, oral morphine equivalent.

least one opioid prescription in that period. Opioids will be identified by the following ATC codes: N02A and R05DA04 (Table 3). Data on postoperative dispensed opioids will be reported in quarters of a year from the index date (i.e., first quarter: 0–90 days [3 months], second quarter: 91–180 days [6 months], third quarter: 181–270 days [9 months], fourth quarter: 271–365 days [12 months]) to determine the trends of postoperative opioid prescription redeemed at retail pharmacies.

Individuals' sociodemographic characteristics will comprise sex (male/female) and age (number of years in whole number at index date) obtained from the DCRS.³¹

Educational attainment will be obtained from the ER, which classifies it as follows: basic school/no information (individuals who have not undergone formal education or completed the compulsory 9–10 years of schooling), secondary/vocational education (individuals who have surpassed basic education but have not achieved a bachelor's degree; this includes those with secondary education, high school diplomas, or vocational training), and higher education (individuals with a bachelor's degree from a college or university, or those who have obtained advanced degrees such as master's, doctoral, or other postbachelor qualifications).

OMEQ standardizes and compares different opioid formulations based on their morphine equivalent potency. This approach allows for a more accurate assessment of total opioid exposure across various types of opioids, including those with different potencies and durations of action. OMEQ is calculated by applying the drug-specific conversion factor to the total amount of opioids dispensed.³¹ The official OMEQ conversion factors are found in the World Health Organization (WHO) index³² (Table 4).

3.5 | Statistical analysis

Statistical analysis will be performed using SAS version 9.4 (SAS Institute, NC, USA).

The initial step in the data analysis will involve identifying the 10 most common surgical treatments in 2018. Subjects undergoing these surgeries will be classified as preoperative opioid consumers or non-opioid consumers based on their opioid use in the 6 months preceding surgery. For each quarter postsurgery, the primary outcome will be the total amount of postoperative opioid prescriptions redeemed at retail pharmacies, comparing opioid consumers to non-opioid consumers. The secondary outcome will analyze associations between the frequency of redeemed postoperative opioid prescriptions and variables such as sex, age, educational attainment, and OMEQ to identify high-risk groups by quantifying their overall opioid exposure and enhancing targeted pain management strategies.

4 | DISCUSSION

Limited research has been conducted on the utilization of postoperative opioid prescriptions redeemed at retail pharmacies in Denmark.^{22–28} Unlike previous investigations focusing on prolonged opioid therapy following specific orthopedic procedures (defined by ICD-10 and NOMESCO codes) such as hip, knee, or spine surgery, the present study will encompass the top 10 most frequent surgical interventions in Denmark, thus representing a comprehensive exploration across various surgical specialties. While prior studies predominantly utilized national registries,^{25–28} some narrowed their focus to regional

TABLE 2 NOMESCO procedure codes.

NOMESCO procedure codes	Surgical treatments
KA Operations on the nervous system	KAA Operations on the skull and intracranial structures KAB Operations on the spinal cord and nerve roots KAC Operations on peripheral nerves KAD Operations on the autonomic nervous system KAE Other operations on the nervous system KTA Minor neurosurgical procedures KAW Reoperations after surgery on the nervous system
KC Operations on the eye and around the eye	KCA Operations on the eye socket KCB Operations on eyelids KCC Operations on lacrimal apparatus KCD Operations on the eyeball KCE Operations on eye muscles KCF Operations on the conjunctiva KCG Operations on the cornea and sclera KCH Operations in the anterior chamber of the eye, chamber angle, iris and ciliary body KCJ Operations on the lens of the eye KCK Operations for diseases of the choroid, corpus vitreum and retina KTC Minor surgical procedures on the eye and surrounding areas KCW Reoperations after surgery on the eye and surrounding areas
KE Operations on the lips, teeth, jaws, mouth and throat	KEA Operations on lips KEB Operations on teeth KEC Operations on gums and processus alveolaris KED Operations on the lower jaw KEE Operations on the upper jaw and cheekbones KEF Other operations on jaws and facial bones KEG Surgeries on the jaw joint KEH Operations on the palate KEJ Operations on the tongue and floor of the mouth KEK Cheek operations KEL Operations on salivary glands KEM Operations on tonsils and adenoid tissue KEN Operations on the throat and surrounding soft tissues KTE Minor surgical procedures on the lips, teeth, jaws, mouth and throat KEW Reoperations after surgery on the lips, teeth, jaws, mouth and throat
KJ Operations on digestive organs and spleen	KJA Operations on the abdominal wall, peritoneum, mesentery and omentum KJB Operations on the diaphragm and operations for gastroesophageal reflux KJC Operations on esophagus KJD Operations on the stomach and duodenum KJE Operations on the appendix KJF Operations on the small intestine and large intestine KJG Operations on the rectum KJH Operations on the rectal opening and perianal tissue KJJ Operations on the liver KJK Operations on bile ducts KJL Operations on the pancreas KJM Operations on the spleen KTJ Minor gastroenterological procedures KJW Reoperations after gastroenterological surgery
KK Operations on the urinary tract, male genitalia and retroperitoneal tissue	KKA Operations on the kidney and renal pelvis KKB Operations on the ureter KKC Operations on the urinary bladder KKD Urethral operations KKE Operations on the prostate and seminal vesicles KKF Operations on the scrotum and scrotal contents KKG Operations on the penis KKK Operations on retroperitoneal tissue KTK Minor urological procedures KKW Reoperations after urological operations

TABLE 2 (Continued)

NOMESCO procedure codes	Surgical treatments
KL Operations on female genitalia	KLA Operations on the ovary KLB Operations on salpinx KLC Operations on the uterus and parametries KLD Operations on the cervix KLE Operations on the vagina KLF Operations on the vulva and perineum KLG Female sterilisations KTL Minor gynaecological procedures KLW Reoperations after gynaecological operations
KM Obstetric operations	KMA Operations before and during birth KMB Operations after birth and spontaneous abortion KMC Caesarean sections and obstetric laparotomies KTM Minor obstetric procedures KMW Reoperations after obstetric operations
KN Operations on the musculoskeletal system	KNA Operations on the back and neck KNB Operations on the shoulder and upper arm KNC Operations on elbow and forearm KND Operations on the wrist and hand KNE Pelvic operations KNF Operations on the hip and thigh KNG Operations on knees and lower legs KNH Operations on ankle and foot
KP Operations on peripheral vessels and lymphatic system	KPA Operations on arteries departing from the aortic arch and their branches KPB Operations on arteries in the upper limb KPC Operations on suprarenal aorta and visceral arteries KPD Operations on the infrarenal aorta and iliac arteries and distal connections KPE Operations on the femoral artery and its branches KPF Operations on the popliteal artery and arteries in the lower leg and foot KPG Extra-anatomic bypass operations KPH Operations on veins KPJ Operations on the lymphatic system KPX Operations on both arteries and veins KTP Minor surgical procedures on vessels and the lymphatic system KPW Reoperations after surgery on peripheral vessels and the lymphatic system
KQ Operations on the skin and subcutaneous tissue	KQA Operations on the skin and subcutaneous tissue of the head and neck KQB Operations on the skin and subcutaneous tissue of the truncus KQC Operations on the skin and subcutaneous tissue of the upper limb KQD Operations on the skin and subcutaneous tissue of the lower limb KQX Operations on the skin and subcutaneous tissue without specifying the location KTQ Minor surgical procedures on the skin and subcutaneous tissue KQW Reoperations after surgery on the skin and subcutaneous tissue

or hospital-based populations.²²⁻²⁴ The data collection periods varied from 1 to 12 years, spanning from 2005 to 2020.²²⁻²⁸

Our study benefits from extensive national register-based data, offering detailed insights into pharmaceutical prescriptions and surgical interventions. This methodology enhances internal validity by ensuring consistent data collection nationwide, mitigating potential biases or inaccuracies. Moreover, the use of national registers enhances external validity, facilitating the extrapolation of findings to countries with comparable healthcare systems, such as those in Scandinavia or other European regions.

By concentrating on data from 2018 and extending follow-up into 2019, we will exploit the most recent and reliable dataset available before the COVID-19 pandemic, capturing healthcare practices and patient outcomes unaffected by pandemic-related disruptions in Denmark.

The study is expected to significantly contribute by offering insights into opioid prescribing patterns following surgery, which can refine guidelines and reduce unnecessary prescriptions. The study aims to identify high-risk populations for prolonged opioid use, allowing for targeted interventions and monitoring. The findings may raise awareness, optimize pain management strategies, enhance patient

TABLE 3 Anatomical therapeutic chemical code for opioids.

Opioids N02A and R05DA04	N02AA natural opium alkaloids	
	N02AA01	Morphine
	N02AA05	Oxycodone
	N02AB phenylpiperidine derivatives	
	N02AC diphenylpropylamine derivatives	
	N02AD benzomorphan derivatives	
	N02AE oripavine derivatives	
	N02AF morphinan derivatives	
	N02AG opioids in combination with antispasmodics	
	N02AJ opioids in combination with non-opioid analgesics	
	N02AX other opioids	
	N02AX02	Tramadol
	R05DA04	Codeine

TABLE 4 Overview of ATC codes, mg/DDD, equianalgesic ratios, and mg/OMEQ of included opioids.³³

ATC	Drug	Opioid groups	Adm. route	mg/DDD	Equianalgesic ratio	MG/OMEQ
N02AA01	Morphine	Morphine	Oral	100.0	1.0	100.0
N02AA03	Hydromorphone	Other opioids	Oral	20.0	1.5	30.0
N02AA04	Nicomorphine	Other opioids	Oral	30.0	1.0	30.0
N02AA05	Oxycodone	Oxycodone	Oral	75.0	1.5	112.5
N02AA55	Oxycodone and naloxone	Oxycodone	Oral	75.0	1.5	112.5
N02AB01	Ketobemidone	Other opioids	Oral	50.0	1.0	50.0
N02AB02	Pethidine	Other opioids	Oral	400.0	0.1	40.0
N02AB03	Fentanyl	Other opioids	Transdermal	1.2	100.0	120.0
N02AC04	Dextropropoxyphene	Other opioids	Oral	250.0	0.19	47.5
N02AD01	Pentazocine	Other opioids	Oral	200.0	0.6	120.0
N02AE01	Buprenorphine	Other opioids	Transdermal	1.2	110.0	132
N02AG02	Ketobemidone, antispasmodics	Other opioids	Oral	25.0	2.0	50.0
N02AJ06	Codeine, paracetamol	Codeine	Oral	90.0009	0.1	9.0009
N02AJ07	Codeine, acetylsalicylic acid	Codeine	Oral	57.5988	0.1	5.75988
N02AX02	Tramadol	Tramadol	Oral	300.0	0.2	60.0
N02AX06	Tapentadol	Other opioids	Oral	400.0	0.4	160.0
N02BA75	Codeine, salicylamide, combinations with psycholeptics	Codeine	Oral	57.5988	0.1	5.75988
R05DA04	Codeine	Codeine	Oral	100.0	0.1	10.0

Abbreviations: ATC, Anatomical Therapeutic Chemical code; Adm. route, route of administration; DDD, defined daily dose; OMEQ, oral morphine equivalent.

recovery, and minimize adverse effects. In addition, the study may inform national public health policies and support appropriate opioid use, highlighting the need for educational interventions for healthcare providers and patients and guiding future research on postoperative opioid use.

A limitation present in this protocol is the lack of information on opioid treatment compliance due to the absence of data on actual

medication usage following prescriptions. In addition, information regarding factors influencing opioid prescriptions beyond postoperative pain management, such as chronic pain or other medical conditions, is not available in the databases. However, the data from an extensive national registers database and our focus on the top 10 most frequent surgeries are robust enough to ensure relevant findings and inspire further investigations.

4.1 | Ethical considerations

The current study has been approved by the Research and Innovation Organization of the University of Southern Denmark (SDU RIO) (notification number 11.807). SDU RIO processes and approves all scientific and statistical projects at the University of Southern Denmark according to the Danish Data Protection Regulation. Ethical approval is not required for data register study according to Danish legislation.

AUTHOR CONTRIBUTIONS

All the authors discussed the concept of the study, the methods and the analysis. All authors have approved the final manuscript of the protocol.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data were created or analyzed in this protocol.

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