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Observational study

# Healthcare resource use and costs of opioid-induced constipation among non-cancer and cancer patients on opioid therapy: A nationwide register-based cohort study in Denmark

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## HIGHLIGHTS

- Opioid-induced constipation (OIC) identified from Danish national health registries.
- 25% higher total healthcare costs for cancer patients with versus without OIC.
- 34% higher total healthcare costs for non-cancer patients with versus without OIC.
- Along with OIC, strong and long-term opioid treatment are important cost drivers.
- Reducing OIC has potential cost savings for the healthcare system.

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## ABSTRACT

**Background and aim:** Opioid analgesics are often effective for pain management, but may cause constipation. The aim of this study was to determine healthcare resource use and costs in non-cancer and cancer patients with opioid-induced constipation (OIC).

**Methods:** This was a nationwide register-based cohort study including patients ≥18 years of age initiating ≥4 weeks opioid therapy (1998–2012) in Denmark. A measure of OIC was constructed based on data from Danish national health registries, and defined as ≥1 diagnosis of constipation, diverticulitis, mega colon, ileus/subileus, abdominal pain/acute abdomen or haemorrhoids and/or ≥2 subsequent prescription issues of laxatives. Total healthcare resource utilization and costs (including pharmacy dispense, inpatient-, outpatient-, emergency room- and primary care) were estimated according to OIC status, opioid treatment dosage and length, gender, age, marital status, and comorbidities using Generalised Linear Model.

**Results:** We identified 97 169 eligible opioid users (77 568 non-cancer and 19 601 patients with a cancer diagnosis). Among non-cancer patients, 15% were classified with OIC, 10% had previous constipation, and 75% were without OIC. Patients characteristics of non-cancer OIC patients showed a higher frequency of strong opioid treatment (69% versus 41%), long-term opioid treatment (1189 days versus 584 days), advanced age (73 years versus 61 years), and cardiovascular disease (31% versus 19%) compared to those without OIC ($P < 0.001$ for all comparisons). Non-cancer patients with OIC had 34% higher total healthcare costs compared to those without OIC ($P < 0.001$) after adjusting for age, gender, opioid usage, marital status and comorbidities. Among cancer patients, 35% were classified with OIC, 14% had previous constipation, and 51% were without OIC. A higher proportion of cancer patients with OIC were continuous opioid users (85% versus 83%) and strong opioid users (97% versus 85%), compared to those without OIC ($P < 0.001$ for both comparisons). Further, the mean number of days on opioids were higher for cancer patients with versus without OIC (329 days versus 238 days, $P < 0.001$). Total healthcare costs were 25% higher for cancer patients with versus without OIC ($P < 0.001$) after adjusting for age, gender, opioid usage, marital status and comorbidities.

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**Conclusions:** The results of this nationwide study based on real life data suggested that both non-cancer patients and cancer patients suffering from opioid-induced constipation (OIC) may have higher healthcare resource utilization and higher associated costs compared to those without OIC.
**Implications:** Reducing the number of OIC patients has potential cost savings for the health care system. Special attention should be on patients at potential high risk of OIC, such as strong and long-term opioid treatment, advanced age, and concomitant cardiovascular disease.


## 1. Introduction

### 1.1. Background

Opioids are frequently used for chronic pain but they are not often effective [1]. The majority of opioid users in Denmark are individuals with acute pain, while the highest consumption is attributable to users with non-malignant chronic pain [1]. A well-known and common side effect of opioid use is bowel dysfunction which can lead to constipation. The frequency of opioid-induced constipation (OIC) ranges from 33 to 94% in non-cancer and cancer patients [2–4]. Results from a population-based survey of 322 patients with chronic pain in the US and EU, showed that 33% of the patients reported that they had missed doses, decreased the dose of or stopped using opioid medication in order to relieve bowel-related side effects [5,6].

OIC may lead to opioid dose reduction, non-adherence, and treatment discontinuation resulting in possible inadequate analgesia [6]. In addition, persistent constipation may lead to serious medical conditions, such as bowel obstruction and faecal impaction, and consequently to increased use of healthcare services, decreased work productivity, and reduced quality of life [7–10].

Previous studies have shown that OIC imposes a substantial economic burden for patients, however without differentiating between the underlying indications for opioid treatment, such as cancer versus non-cancer pain [7,11–13]; and only a few studies have evaluated constipation after opioid therapy in patients with non-cancer pain [14,15]. There is thus a substantial need for population-based studies assessing the economic and health-related burden of OIC, focusing on differentiating between patients with non-cancer and cancer pain.

### 1.2. Objectives

The objectives of this nationwide register-based cohort study was to determine healthcare resource use and cost among non-cancer and cancer patients with OIC, with a focus on treatment and general management of opioid therapy and OIC in Denmark.

## 2. Methods

### 2.1. Study design

This is an observational cohort study on opioid-induced constipation (OIC) identified from national health registries in Denmark during 1998–2012.

### 2.2. Setting

Denmark have a tax funded healthcare system providing all inhabitants free health care access (including both general practices and hospitals) irrespective of socioeconomic status [16]. All Danish citizens are registered in the Danish civil Registration system and assigned a unique civil registration number, which is utilized in all national registers thus enabling accurate register linkage. In this study, healthcare resource utilization and costs included hospitalizations, outpatient visits, drugs, and visits to general practitioners and practising specialists in the public and private health care sector in Denmark. The following data sources were utilized:

- The Danish National Patient Registry [17], including data on all somatic hospitalizations (since 1977) and outpatient visits (including emergency room visits) since 1995. Hospital discharge and outpatient contact diagnoses are according to the International Classification of Diseases (ICD version 10 from 1994 onwards).
- Cost of hospitalization and outpatient cost were based on diagnosis-related group tariffs from the Danish Ministry of Health.
- The use and costs of drugs were based on data from the National Danish Medicine Agency, which includes the retail price of the drug (including dispensing costs) multiplied by the number of transactions. The Danish National Prescription Registry [18] keeps records on all drug prescriptions issued from Danish pharmacies since 1995. Due to partial reimbursement of drug expenses by the Danish health care system, all pharmacies in Denmark are required to register each prescription issue in the national prescription registry, ensuring complete registration. Each issued drug prescription is registered according to the Anatomical Therapeutic Chemical (ATC) system [19].
- The frequency and costs of consultations with general practitioners and other specialists were based on data from the National Health Security.
- Data on socioeconomic status was retrieved from the Danish Income Statistics. Classification of education and employment status were performed on individual level (Table 1).

### 2.3. Study population

All patients aged 18 years or older who had issued a prescription for opioids, with a minimum total daily dose of 30 mg of oral morphine, or equianalgesic dosing of one or more opioid therapies (ATC: N02 [analgesics] except N07BC [drugs used in opioid dependence] and N02AC [diphenylpropylamine derivatives]) during the study inclusion period 01.01.1998 to 30.06.2012 were identified in the Danish National Prescription Registry.

Eligible patients had: (1) treatment with opioids for at least four weeks and at least two prescriptions issued with known opioid coverage of at least 70% (defined as number of daily doses dispensed divided by the total number of days between prescription issue); (2) at least 12 months opioid free period prior to the index date (defined as the date of first of at least two opioid prescriptions issued); (3) at least 6 months of follow-up after index date; (4) no cancer diagnosis (ICD10: C00-C99) after study entry (due to the complexity of symptoms prior to a cancer diagnosis as well as the long study period); (5) no missing information on socioeconomic status or duration of opioid treatment.