

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.

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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.

2.4. Variables

2.4.1. Cancer status

Cancer status was defined by primary and secondary diagnoses at index date and admissions up to 12 months before index date (ICD10: C00–C99).

2.4.2. Opioid-induced constipation status

A measure of OIC was constructed based on data from Danish national health registries. A patient had to meet at least one of the following criteria at or after index date:

- (1) A minimum of two subsequent prescriptions for laxatives (ATC code: A06A) issued, with no more than two daily doses dispensed between two prescribing events.
- (2) At least one of the following diagnoses: constipation (ICD10: K59.0), diverticulitis (ICD10: K57), mega colon (ICD10: K59.3), ileus/subileus (ICD10: K56.6–7), abdominal pain/acute abdomen (ICD10: R10.0–R10.4) or haemorrhoids (ICD10: K64).

Patients defined as having previous constipation had to meet at least one of the above criteria prior to index date.

2.4.3. Opioid treatment patterns

Opioid treatment patterns were classified according to: (1) Duration of opioid use during follow up period (1–3 months, 3–6 months, 6–12 months, >12 months); (2) Level of perceived opioid coverage defined as continuous opioid users (opioid coverage of $\geq 70\%$ until end of follow-up) and periodic opioid user (opioid coverage of $\geq 70\%$ for at least 4 weeks, after which the coverage percentage drops but with continuous prescription issue for opioids); and (3) Strength of opioids defined as strong opioids (ATC: N02AA01–55, N02AB, N02AE, N02AF, N02AG) and weak opioids (ATC: N02AA59, N02AX).

2.4.4. Covariates

Other baseline medication included redeemed prescriptions on nonsteroidal anti-inflammatory drugs (ATC: M01A), paracetamol (ATC: N02BA), acetylsalicylic acid (ATC: N02BA) or anti-rheumatics (ATC: M01C) 12 months before index date.

Selected baseline comorbidities included cardiovascular disease (ICD10: I00–I52; I60–I99), osteoarthritis (ICD10: M15–19, M47), rheumatoid arthritis (ICD10: M05–M06), back pain (ICD10: M54), migraine (ICD10: G43), soft tissue disorders (ICD10: M79) 12 months before index date.

Socioeconomic status was measured according to: marital status (married, not married), educational status (primary school, secondary school, vocational, short college, bachelor/medium college, master or PhD, unknown), employment status (age retirement, disability pension, early retirement, employed, not in labour force, sick leave, social welfare, student, unemployed, unknown).

2.4.5. End point and follow up

The primary endpoint was the total healthcare cost, including costs for inpatient-, outpatient-, emergency room-, and primary care as well as costs for prescribed medication issued at pharmacy. All costs were presented per patient per year adjusted to 2014 prices using the consumer price index and measured in Danish Kroner (DKK) and converted into Euros (EUR; € = DKK 7.45). Patients were followed from index date until discontinuation, death or end of the study period.

2.5. Statistical methods

The statistical methods used in the descriptive analysis were Chi-square for the categorical variables and for continuous

variables; *t*-test for parametric tests and Wilcoxon for non-parametric tests. The statistical method used to estimate the impact of OIC status and opioid treatments patterns on total healthcare cost was 2-step one-model regression, the Generalised Linear Model, with log link function and gamma distribution [20]. We use backward stepwise variable selection to select the covariates that needed to be controlled for (i.e., age, gender, marital status, and comorbidity).

3. Results

Approximately 1.4 million patients over 18 years of age initiated opioid therapy during January 1998 to June 2012 and 119 922 of these patients were in treatment with opioids for ≥ 4 week and had ≥ 2 prescriptions issued with known opioid coverage of $\geq 70\%$ (Fig. 1). For the current analyses, the following exclusions were made: 9814 patients with <6 months of follow-up; 8457 patients diagnosed with cancer during the study period; 4482 patients missing information on socioeconomic status and opioid duration.

Of the 97 169 patients eligible of analyses 77 568 patients were non-cancer patients and 19 601 patients had a cancer diagnosis prior to study entry. Among the non-cancer patients, 15% were classified with OIC, 10% with previous constipation, and 75% without OIC, while for the cancer patients the corresponding figures were 35%, 14%, and 51%, respectively.

3.1. Non-cancer patients

Mean age was 61 years (standard deviation [SD] 18), 73 years (SD 16), and 75 years (SD 16) for the non-cancer patients without OIC, with OIC, and with previous constipation, respectively (Table 1). Irrespective of which OIC status definition was met, the majority were women (Table 1). A higher proportion of non-cancer patients with OIC were periodic (41%) or strong opioid users (69%), compared to those without OIC (31% and 41%, respectively). Further, the mean number of days on opioids were higher for patients with OIC (1189 days [SD 1164]) than for both without OIC (584 days [SD 898]) or with previous constipation (573 days [SD 782]). The overall most prevalent co-morbidity was cardiovascular disease, more commonly seen for the patients with current or previous constipation (31% and 36%, respectively), than for non-cancer patients without OIC (19%) (Table 1). Primary school was the most prevalent educational level in all three OIC status definitions (Table 1). In the OIC and previous constipation patient groups, more than 70% of patients were retired due to age compared to only about 40% of the no OIC patient group.

There were approximately four hospital admissions per patient year in all three constipation status definitions for the non-cancer patients (Table 2). The length of hospital stay was about 7 days per patient year for patients with current or previous constipation and about 4 days per patient year for patients without OIC. Among non-cancer patients with OIC and previous constipation, the absolute total healthcare cost were 9654 Euros and 10 249 Euros per patient year, respectively. Among non-cancer patients without OIC the total healthcare cost were 6986 Euros per patient year. In all three OIC status definitions, total costs were mostly driven by costs from inpatient visits and prescribed medication costs.

The multivariable regression analysis (Table 3) shows that non-cancer patients with OIC showed 34% higher costs compared to those without OIC ($P < 0.001$), whereas costs were 20% higher in non-cancer patients with previous constipation than in those without OIC ($P < 0.001$), after adjusting for age, gender, opioid usage, marital status, and comorbidity. The use of strong opioids and short-term opioid treatment were also important cost drivers among non-cancer patients. Strong opioid users had 76% higher

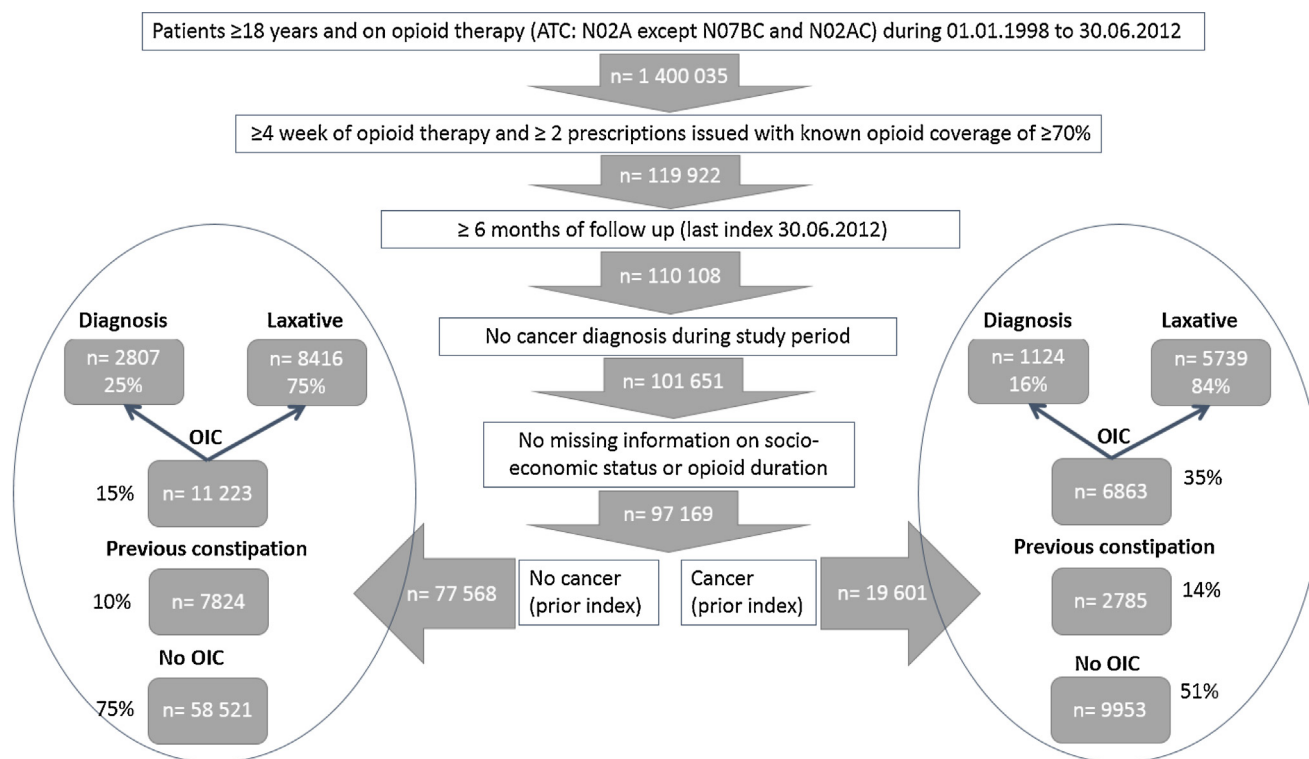


Fig. 1. Flow chart of cohort selection and sample size (abbreviations: OIC = opioid-induced constipation, n = number).

costs compared to weak opioid users, whereas short-term opioid users (1–3 months and 4–6 months) had more than two-fold higher costs compared to long-term opioid users (above 12 months).

3.2. Cancer patients

The mean age among cancer patients varied from 67 years (SD 12) in the no OIC and OIC groups to 71 years (SD 13) in the previous constipation group (Table 1a – Appendix A). A minority were women in all three constipation status definitions (Table 1a). A higher proportion of cancer patients with OIC were continuous opioid users (85%) and strong opioid users (97%), compared to cancer patients without OIC (83% and 85%, respectively). Further, the mean number of days on opioids were higher for cancer patients with OIC (329 days [SD 523]) than without OIC (238 days [SD 447]). For all three constipation status definitions, cardiovascular disease was the most prevalent co-morbidity and primary school was the most prevalent educational level. In the previous constipation group, approximately three out of four patients were retired due to age compared to about half of the cancer patients with OIC and without OIC.

OIC and previous constipation cancer patients, had 21 and 20 hospital admissions per patient year, respectively. Cancer patients without OIC had 17 hospital admissions per patient year (Table 2). The length of hospital stay was 23 days per patient year for patients with current or previous constipation, and 18 days per patient year for patients without OIC. The absolute total healthcare costs among cancer patients with current OIC, previous constipation, and without OIC were: 32 060 Euros, 29 961 Euros, 24 925 Euros per patient year, respectively.

The results from the multivariable regression (Table 3) shows that cancer patients with OIC had 25% higher costs compared to patients without OIC ($P < 0.001$), whereas costs were 7% higher in patients with previous constipation than in those without OIC ($P < 0.001$) after accounting of age, gender, opioid usage, marital

status, and comorbidity. The use of strong opioids and short-term opioid treatment were also important cost drivers among cancer patients, showing an 81% higher cost among strong compared to weak opioid users and a two-fold higher cost among short-term versus long-term opioid users.

4. Discussion

4.1. Key results

This study showed that patients on opioid therapy suffering from OIC had higher healthcare resource utilization and higher associated costs compared to those without OIC. The total costs were mostly driven by costs from inpatient visits and prescribed medications. Further, strong and long-term opioid treatment, advanced age, and cardiovascular disease were more frequent among patients suffering from OIC, regardless of cancer status.

4.2. Limitations

This study has several limitations and the findings should be interpreted with caution. The measure of OIC based on ICD10 codes and ATC codes in the Danish national health registries does not capture all OIC patients. An internet-based survey study of patients who had issued prescribed opioids for non-cancer pain, confirmed that there is a high degree of self-management of OIC with over-the-counter medications without healthcare contacts [21]. On the other hand, some patients that issue prescriptions for laxatives do not necessarily have OIC, because it is recommended for all patients to prevent OIC [22]. Further, diagnoses such as diverticulites and haemorrhoids are also not specific for patients with OIC. Thus, we cannot rule out the risk of misclassification bias in this study. Most clinical trials regarding OIC have relied on objective measures such as bowel movement frequency, and in addition included patient-reported outcome measures such as, “feeling of incomplete bowel

Table 1

Baseline characteristics and opioid use patterns according to opioid-induced constipation (OIC) status among non-cancer patients.

Non-cancer patients	No OIC			OIC			Previous constipation			P-value
<i>n</i> = 77 568	<i>n</i> = 58 521			<i>n</i> = 11 223			<i>n</i> = 7824			
Characteristics										
Age at the index date, mean (SD), median	61.3	(17.6)	62	72.7	(16.2)	77	75.4	(15.8)	80	0.000
Gender, <i>n</i> (%)										
Female	31 882	(54.5)		7412	(66.0)		5146	(65.8)		0.000
Male	26 639	(45.5)		3811	(34.0)		2678	(34.2)		0.000
Opioid usage post index date										
Strong opioids, <i>n</i> (%)	24 026	(41.1)		7762	(69.2)		4566	(58.4)		0.000
Weak opioids, <i>n</i> (%)	34 495	(58.9)		3461	(30.8)		3258	(41.6)		0.000
Continuous users, <i>n</i> (%)	40 399	(69.0)		6657	(59.3)		5388	(68.9)		0.000
Periodic users, <i>n</i> (%)	18 122	(31.0)		4566	(40.7)		2436	(31.1)		0.000
Opioid treatment length (days), mean (SD), median	584.2	(897.9)	189	1189.1	(1164.3)	806	572.6	(782.0)	244	
Diseases, <i>n</i> (%)										
Cardiovascular disease	11 040	(18.9)		3462	(30.8)		2822	(36.1)		0.000
Osteoarthritis	4541	(7.8)		671	(6.0)		355	(4.5)		0.000
Rheumatoid arthritis	654	(1.1)		156	(1.4)		81	(1.0)		0.028
Back pain	1938	(3.3)		405	(3.6)		272	(3.5)		0.241
Migraine	92	(0.2)		22	(0.2)		15	(0.2)		0.551
Soft tissue disorders	904	(1.5)		185	(1.6)		124	(1.6)		0.711
Other medication, <i>n</i> (%)										
Nonsteroidal anti-inflammatory drugs	30 349	(51.9)		5147	(45.9)		3289	(42.0)		0.000
Paracetamol	16 757	(28.6)		5113	(45.6)		5111	(65.3)		0.000
Acetylsalicylic acid	2042	(3.5)		477	(4.3)		305	(3.9)		0.000
Antireumatics	34	(0.1)		8	(0.1)		2	(0.0)		0.411
Socioeconomic status										
Marital status, <i>n</i> (%)										
Married	27 876	(47.6)		3614	(32.2)		2204	(28.2)		0.000
Educational status, <i>n</i> (%)										
Primary school	23 810	(40.7)		4730	(42.1)		3100	(39.6)		0.000
Secondary school	1358	(2.3)		167	(1.5)		90	(1.2)		0.000
Vocational	17 588	(30.1)		2201	(19.6)		1367	(17.5)		0.000
Short college	1411	(2.4)		144	(1.3)		68	(0.9)		0.000
Bachelor/medium college	4826	(8.2)		561	(5.0)		339	(4.3)		0.000
Master or PHD	1449	(2.5)		153	(1.4)		127	(1.6)		0.000
Unknown	8079	(13.8)		3267	(29.1)		2733	(34.9)		0.000
Employment status, <i>n</i> (%)										
Age retirement	24 833	(42.4)		8088	(72.1)		6059	(77.4)		0.000
Disability pension	7262	(12.4)		1284	(11.4)		962	(12.3)		0.000
Early retirement	2365	(4.0)		207	(1.8)		100	(1.3)		0.000
Employed	9535	(16.3)		523	(4.7)		214	(2.7)		0.000
Not in labour force	1223	(2.1)		123	(1.1)		39	(0.5)		0.000
Sick leave	9754	(16.7)		652	(5.8)		273	(3.5)		0.000
Social welfare	2747	(4.7)		287	(2.6)		148	(1.9)		0.000
Student	258	(0.4)		16	(0.1)		12	(0.2)		0.000
Unemployed	530	(0.9)		39	(0.3)		16	(0.2)		0.000
Unknown	14	(0.0)		4	(0.0)		1	(0.0)		0.000

Abbreviations: OIC, opioid-induced constipation; *n*, number; SD, standard deviation.

evacuation" [23,24]. However, there is no generally accepted definition for OIC.

The arbitrary threshold chosen for the opioid coverage (at least 70% in the first four weeks) is likely to influence patient eligibility, but is based on the commonly seen slow escalation of dispensed opioid daily dose in the beginning of an opioid treatment period. The physician should, according to international guidelines [25], closely monitor the opioid treatment by for example initiating treatment with low dose opioids and increasing the dosage depending on patient response.

Healthcare utilization and cost data should be interpreted carefully, as these are not limited to admissions, visits, and costs resulting only from OIC. The OIC-related costs are only related to the ICD10 codes for OIC, likely covering the more severe OIC patients. OIC-related costs in primary care are not known. Further, due to availability of over-the-counter laxatives, calculation of the complete prescribed medication cost related to OIC is not possible. OIC is also likely to be associated with costs to the society such as productivity loss, which was not assessed in the present study. Hjalte et al. [7] examined costs associated with OIC among patients treated with strong opioids in Sweden and concluded that OIC imposed

substantial costs to society, especially for patients with severe OIC. Further, patients may have other medications, have limited mobility, or dietary habits that could contribute to constipation and associated higher costs. Although the present study setup allowed control of several important potential confounders, these may not be sufficient to completely avoid residual confounding.

4.3. Interpretation

Our findings are in line with previous studies showing that reducing OIC among patients treated with opioids has potential cost savings for the health care system [7,11–15]. The most recent study by Wan et al. [14] identified a substantial economic burden of gastrointestinal events among users of opioids for non-cancer pain in a US setting, but only included patients on long-term opioid treatment (≥ 90 days).

Our study adds to the present scarce knowledge on the consequences of both short-term and long-term opioid treatment by also differentiating between patients with and without cancer, using national register data obtained from all adult patients treated with opioids for more than four weeks over a 13-year period in Denmark.

Table 2
Healthcare utilization and costs for total-, inpatient-, outpatient-, emergency room-, primary-care and pharmacy dispense per patient per year among non-cancer patients and cancer patients.

Healthcare use and costs	Non-cancer patients				Cancer patients			
	No OIC n = 58 521	OIC n = 11 223	Previous constipation n = 7824	Total ^a n = 77 568	No OIC n = 9953	OIC n = 6863	Previous constipation n = 2785	Total ^a n = 19 601
Total care								
Number of admissions (pr. patient year)	4.12	4.65	4.68	4.30	16.68	20.90	19.72	18.85
Number of days (pr. patient year)	4.43	7.52	7.26	5.47	18.39	23.43	22.80	21.08
Total cost (€ pr. patient year)	6985.86	9654.16	10 248.62	7951.47	24 925.45	32 059.70	29 961.44	28 588.02
Total cost OIC (€ pr. patient year)	2.05	180.61	208.40	65.63	13.73	405.08	555.38	245.54
Inpatient care								
Number of admissions (pr. patient year)	0.83	1.28	1.39	0.99	3.67	4.76	4.70	4.26
Number of days (pr. patient year)	4.43	7.52	7.26	5.47	18.39	23.43	22.80	21.08
Inpatient cost (€ pr. patient year)	3810.90	5486.98	5703.07	4403.90	15 315.01	19 479.76	17 888.83	17 410.48
Inpatient cost OIC (€ pr. patient year)	0.00	110.39	93.28	36.36	0.00	247.82	380.61	151.18
Outpatient care								
Number of visits (pr. patient year)	2.93	2.88	2.73	2.90	12.55	15.61	14.43	14.09
Outpatient cost (€ pr. patient year)	845.63	842.40	791.62	840.15	6023.62	7096.20	6370.95	6526.55
Outpatient cost OIC (€ pr. patient year)	0.00	15.49	13.66	5.15	0.00	17.23	25.16	10.36
Emergency room (ER) care								
Number of visits (pr. patient year)	0.35	0.49	0.56	0.41	0.46	0.53	0.58	0.51
ER cost (€ pr. patient year)	39.07	51.02	58.81	43.83	50.07	55.55	59.87	53.57
ER cost OIC (€ pr. patient year)	0.00	0.73	0.57	0.24	0.00	1.13	1.18	0.62
Primary care								
Primary care cost (€ pr. patient year)	554.61	720.69	899.66	626.94	711.81	867.83	1 038.28	817.10
Pharmacy								
Cost of prescribed medication (€ pr. patient year)	1735.64	2553.06	2795.45	2036.64	2824.93	4560.37	4603.52	3780.32
Cost of prescribed OIC medication (€ pr. patient year)	2.05	54.00	100.89	23.89	13.73	138.90	148.43	83.38

^a Geometric averages.

Abbreviations: OIC, opioid-induced constipation; n, number.

Table 3
Results from multivariable regression analysis for total healthcare costs among non-cancer patients and cancer patients.

	Total healthcare cost							
	Non-cancer patients				Cancer patients			
	Exp (estimate)	Lower CL	Upper CL	P-value	Exp (estimate)	Lower CL	Upper CL	P-value
Intercept	4410.41	4278.35	4546.56	0.000	42 744.60	38 580.64	47 357.97	0.000
OIC status								
No OIC	Reference				Reference			
OIC	1.34	1.31	1.37	0.000	1.25	1.21	1.29	0.000
Previous constipation	1.20	1.17	1.22	0.000	1.07	1.02	1.12	0.002
Dosage of opioids								
Weak	Reference				Reference			
Strong	1.76	1.74	1.79	0.000	1.81	1.73	1.90	0.000
Opioid treatment length								
1–3 months	2.79	2.75	2.84	0.000	2.20	2.12	2.29	0.000
4–6 months	2.20	2.15	2.25	0.000	1.94	1.86	2.03	0.000
7–12 months	1.68	1.64	1.72	0.000	1.62	1.54	1.69	0.000
>12 months	Reference				Reference			
Gender								
Female	0.92	0.91	0.94	0.000	0.91	0.89	0.94	0.000
Male	Reference				Reference			
Age	1.00	1.00	1.00	0.000	0.98	0.98	0.98	0.000
Marital status								
Married	1.03	1.01	1.04	0.000	1.16	1.13	1.20	0.000
Not married	Reference				Reference			
Diseases								
Cardiovascular disease	1.48	1.45	1.50	0.000	1.05	1.02	1.09	0.002
Back pain	1.06	1.02	1.10	0.006	0.98	0.88	1.09	0.670
Osteoarthritis	1.18	1.15	1.21	0.000	1.00	0.91	1.09	0.995
Rheumatoid arthritis	1.25	1.17	1.33	0.000	1.04	0.89	1.22	0.627
Migraine	0.93	0.78	1.10	0.395	0.77	0.50	1.19	0.239
Soft tissue disorders	1.10	1.04	1.16	0.002	0.98	0.84	1.15	0.838

Abbreviations: OIC, opioid-induced constipation; CL, confidence limit.

It is already emphasized in clinical guidelines that continuous opioid-use should be accompanied by laxatives, this is not always done. A prior Danish study indicated that only a small proportion (28%) of patients with a prescription for opioids remembered

having received information on risk for potential OIC, or any recommendation on how to use laxatives to prevent constipation [26]. Further, in multinational longitudinal study almost half of patients reported sufficient laxative [27]. However, the majority of these

patients were inadequate laxative responders (indicated by <3 bowel movements per week or ≥ 1 moderate to very severe constipation symptom). Hence, for some OIC patients, laxatives alone are likely to be insufficient. Besides emphasizing the relevance of laxatives to physicians, and that they should frequently inform and ask opioid users about constipation, there is a need for increased focus on patients at high risk of developing opioid-induced constipation. As it has previously been shown that constipation is relatively frequent among patients with cardiovascular disease [28], the present study, showing an increased frequency of OIC among patients with cardiovascular disease, may further reflect that this patient group could be more vulnerable to the constipation effects of opioids and thus could benefit from an increased attention.

4.4. Generalizability

The nationwide setting, with a study database covering the complete Danish population, makes selection bias and loss to follow up of negligible magnitude in this study. However, selection bias might occur for other reasons. Users of codeine were not included in our study, because the distribution between the different indications (i.e., pain, coughing, and diarrhoea) for this drug is unknown. Codeine has as monotherapy received ATC code R05DA04 and is therefore not classified together with opioids. However, since codeine converts into morphine regardless of indication, users of codeine could have been included. Thus, the study population identified in this study might not be a complete representative sample of the actual patients at risk of OIC in the general population. Further, representativeness will always be a historical concept because it is time- and place-specific [29,30]. Generalization of results for this study population should be made with caution.

5. Conclusion

The results of this nationwide study based on real life data suggested that patients with OIC, regardless of cancer or non-cancer status, have higher healthcare resource utilization and higher associated costs compared to patients without OIC. The total healthcare costs were mostly driven by costs from inpatient visits and prescribed medications.

Implications

Reducing the number of OIC patients has potential cost savings for the health care system. Special attention should be given to patient groups who might be at high risk of opioid-induced constipation, such as users of strong opioids, patients on long-term opioid treatment, at advanced age, and with concomitant cardiovascular disease.

Ethical issues

The study was approved by the Danish Data Protection Agency (No. 2013-54-0414). All data was anonymized, and did not permit identification of individual patients. According to Danish legislation, ethics approval is not required for register-based studies.

Conflicts of interest

J.S. and J.K. have received compensation from AstraZeneca for their work on this report. H.N.C. holds a full time position at AstraZeneca as epidemiologist. The other authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.sjpain.2017.01.006>.

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