



Use of opioids in chronic non-malignant pain: the Danish experience
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Clinical consequences of long-term opioid use



JAMA™ Opioid Analgesics—Risky Drugs, Not Risky Patients

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- Considered the backbone of analgesia, however at a price...
- Sleep apnoea, cognitive impairment, hyperalgesia, immuno-suppressive/carcinogenic etc.....
- Fourfold increase in US opioid analgesics related deaths 1999-2010, (N= 4030 to 16.651)
 Fourfold increase in opioid prescriptions 1999-2010
- The highest risk of dependence and death does not come from patient-related factors, but from opioid use

Opioid side effects

Wanted effects

- analgesia
- sedation
- anti-dyspnoe
- anti-salivation



Unwanted effects

- respiratory depression
- sedation
- constipation
- itching
- nausea/vomiting
- dry mouth
- sweating
- dizziness
- sleep disturbance
- difficult micturition
- mood changes
- *cognitive dysfunction*
- *hyperalgesia/allodynia*
- *hallucinations/delirium*
- *myoclonus/seizures*

Long-term consequences of long-term opioid treatment

- Dysfunction of the immune and reproductive systems
- Addiction
- Cognitive dysfunction
- Tolerance
- Opioid-induced hyperalgesia (OIH)

Savage, JPSM 1993; Fecho et al, J Pharmacol Exp Ther 1995; Mitchell et al, Nat Neurosci 2000; Abs et al, J Clin Endocrinol Metab 2000; Mao, Pain 2002; Sjögren et al, Eur J Pain 2005

Opioids and the endocrine system

- Opioids may lower testosterone and LH levels in men
- Opioids may lower oestradiol, progesterone, LH and FSH levels in women
- Substitution therapy is discussed
- Hypothalamic-pituitary-adrenal axis (HPA) is influenced by opioid use:
 - Mood disorders
 - Cognitive deficits
 - Chronic fatigue syndrome
 - Stress
 - Insomnia

Abs et al., J Clin Endocrinol Metabol 2000; Rajgopal et al., Cancer 2004; Vuong et al., Endocrinol Rev 2010

Opioids (morphine) and the immune system

- Suppression of NK cells and T and B lymphocytes
- Inhibition of pro-inflammatory cytokines (monocytes) and interleukin-2 (T lymphocytes)
- Stimulating tumor growth by cell cycle progression, cell migration and angiogenesis (antagonized by naloxone/methylnaltrexone)
- Not all opioids induce the same immunosuppressive effects
- Clinical trials are underway to assess the effectiveness of naltrexone in metastatic breast cancer and gliomas
- Population-based studies are underway to assess breast cancer recurrence related to opioid use

Lennon et al., Anesthesiology 2012

Opioid consumption: Why Denmark?

- One of the highest per capita consumption of prescribed opioids in the world
- Many countries are moving in the same direction
- Comprehensive and accurate healthcare statistics and databases
- Not constrained by unmonitored private sector or by privacy sensibilities
- Few controlled studies of short duration

Højsted and Sjøgren, Curr Opin Anaesthesiol 2007

Estimate of opioid users and consumption in Denmark

Based on three databases:

Number of users:

- | | |
|--------------------------------|-----|
| 1. Acute pain: | 55% |
| 2. Cancer pain: | 13% |
| 3. Chronic non-malignant pain: | 32% |

Consumption:

- | | |
|--------------------------------|-----|
| 1. Acute pain: | 1% |
| 2. Cancer pain: | 30% |
| 3. Chronic non-malignant pain: | 69% |

Jarlbæk et al, Ugeskr Læg 2010

Epidemiology of chronic pain

“Epidemiology of chronic pain is hampered by the problems of case definition and identification, and epidemiological research on pain has to rely on self-report and on rather simple measures”

(Smith et al., 1996; Crombie, 1997)

The Danish Health and Morbidity Surveys

The Danish Health and Morbidity Surveys have been carried out in 1987, 1994, 2000, 2005, 2010 and 2013

The purpose is to describe and monitor the status and trends in health and morbidity in the adult Danish population (>16 years)

The surveys are nationally representative and administered by the National Institute of Public Health

The letter of introduction invited the selected individuals either to fill out the questionnaire online or to complete the mailed questionnaire

Chronic pain was characterized by the question: “Do you have long-term/chronic pain of more than six months duration?”



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Critical issues on opioids in chronic non-cancer pain: An epidemiological study

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Abstract

The aim of the study was epidemiologically to evaluate the long-term effects of opioids on pain relief, quality of life and functional capacity in long-term/chronic non-cancer pain. The study was based on data from the 2000 Danish Health and Morbidity Survey. As part of a representative National random sample of 10,684 individuals (>16 years of age), 93,995 took part in an interview and completed a self-administered questionnaire. Cancer patients were excluded. The interview and the self-administered questionnaire included questions on chronic/long-lasting pain (>6 months), health-related quality of life (SF-36), use of the health care system, functional capabilities, satisfaction with medical pain treatment and regular or continuous use of medication. Participants reporting pain were divided into opioid and non-opioid users. The analyses were adjusted for age, gender, concurrent use of analgetics and antidepressants and pain intensity. Pain relief, quality of life and functional capacity among opioid users were compared with non-opioid users. Opioid usage was significantly associated with reporting of moderate/severe or very severe pain, poor self-rated health, not being engaged in employment, higher use of the health care system, and a negative influence on quality of life as registered in all items in SF-36. Because of the cross-sectional nature causative relationships cannot be ascertained. However, it is remarkable that opioid treatment of long-term/chronic non-cancer pain does not seem to fulfil any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity.

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Keywords: Epidemiology; Chronic non-cancer pain; Opioids; Quality of life; Functional capacity

Conclusions from Danish Health and Morbidity Surveys in 2000 and 2005

Opioid use in chronic non-malignant pain was associated with reporting:

- high pain intensity
- poor self-rated health, quality of life and sleep
- low functional capacity
- attenuated alcohol behaviour
- enhanced smoking behaviour
- reduced oral health

Further, a cohort study demonstrated:

- the use of strong opioids was significantly associated with increased mortality

Eriksen et al, Pain 2006; Sjøgren et al, Eur J Pain 2009; Ekholm et al, Eur J Pain 2009; Sjøgren et al, Clin J Pain 2010

Critical issues on opioids

Opioid treatment of chronic non-malignant pain did not seem to fulfil any of the key outcomes recommended by international guidelines:

- Pain relief
- Improved quality of life
- Improved functional capacity

Manchikanti et al, Pain Physician 2012

Methods of the Danish Health and Morbidity Survey in 2010

- The survey included data from the Danish National Prescription Registry, the Danish National Patient Register and the Danish Register of Causes of Death.
- The survey was based on a simple random sample of 25,000 individuals (16 years or older) living in Denmark using the Danish Civil Registration System.
- In all, 15,165 individuals (60.7%) completed the questionnaire

Prevalence of chronic pain and associations with potential risk

Variables	%	OR	95% CI	N
Total of chronic pain individuals	26.8			14,925
Sex and age		<i>p<0.0001</i>		
Men 16-24 y:	8.9	0.37	(0.29-0.49)	722
Men 25-44 y:	17.0	1		1,856
Men 45-64 y:	28.3	1.63	(1.41-1.88)	2,705
Men 65-79 y:	30.6	1.67	(1.39-2.00)	1,336
Men ≥80 y:	34.2	1.92	(1.40-2.63)	256
Women 16-24 y:	18.9	0.78	(0.63-0.96)	931
Women 25-44 y:	22.3	1.44	(1.24-1.67)	2,323
Women 45-64 y:	38.4	2.67	(2.32-3.09)	2,983
Women 65-79 y:	38.5	2.01	(1.67-2.41)	1,442
Women ≥80 y:	53.6	3.2	(2.45-4.15)	371
Marital status		<i>p=0.0027</i>		
Married	28.1	1		8,308
Cohabiting	20.9	0.96	(0.84-1.08)	2,070
Single (divorced, separated, widowed)	39.0	1.44	(1.08-1.97)	1,789
Single (unmarried)	18.1	0.94	(0.82-1.07)	2,368
Education		<i>p<0.0001</i>		
Basic school	33.5	2.17	(1.94-2.44)	4,149
Upper secondary or vocational school	27.5	1.65	(1.49-1.82)	6,228
Higher education	18.7	1		4,465
Country of origin		<i>p<0.0001</i>		
Denmark	26.4	1		14,033
Other western	27.1	1.13	(0.92-1.39)	395
Non-western	32.8	1.68	(1.41-1.98)	497
Body mass index		<i>p<0.0001</i>		
18.5	30.7	1.91	(1.18-1.92)	364
18.5-25	21.9	1		7,266
25-30	28.3	1.29	(1.17-1.41)	5,001
≥30	38.1	1.88	(1.68-2.12)	1,893

Medicine use during 90 days prior to survey

Kjaersgaard et al.

Medicine	Chronic pain %			Without chronic pain %		
	Dk	Other western	Non-western	Dk	Other western	Non-western
Opioids	13.4	1.6	5.6	1.4	1.2	2.0
Strong	4.2	0.0	1.5	0.4	0.3	0.3
Weak	9.2	1.6	5.6	1.0	0.9	1.7
Anxiolytics	4.0	2.4	1.5	0.9	1.6	1.2
Antidepressants	11.4	8.2	12.0	3.9	1.8	1.2
Not respondents	3,065	99	141	9,429	257	311

- In all, 4.5% of the study population were prescribed opioids
- The highest opioid use was in current cancer followed by cardiovascular disease and COPD
 - Opioid use was higher in Dk background than western or non-western ($p<0.0001$)
 - Anxiolytic was higher in Dk background than in a non-western ($p=0.0454$)

Mortality in opioid treated in chronic non-malignant pain: a population-based cohort study

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- A cohort from the Danish Health and Morbidity Surveys 2000 and 2005 were followed from the interview date until death, emigration, or 31 December 2011 (end of follow-up)
- Individuals with a known cancer history at baseline were excluded
- Long-term users: individuals who in the previous year have used at least one prescription/month for six months.
- Short-term users: individuals who in the previous year have used at least one prescription

Results

The cohort (N=13,127 individuals) was further divided into four groups:

- long-term opioid users with chronic pain (n=167)
- short-term opioid users with chronic pain (n=375)
- non-opioid users with chronic pain (n=2,015)
- individuals without chronic pain (and no opioid use) (n=10,570).

Number of deaths, death rates (per 1,000 person years) and hazard ratio (HR) of all cause mortality according to chronic pain status and opioid use.

	Chronic pain			No chronic pain	p-value
	Long-term opioid users	Short-term opioid users	Non-opioid users		
N	167	375	2,025	10,570	
Person-years of follow up	1,456	3,428	19,102	104,679	
Number of deaths	47	76	303	769	
Death rates (per 1,000 person years)	32	22	16	7	
Age-adjusted HR (95% CI)	1.77 (1.32-2.39)	1.36 (1.07-1.72)	1.39 (1.22-1.59)	1	<0.01
Multivariable adjusted HR (95% CI) ^a	1.72 (1.28-2.41)	1.22 (0.93-1.59)	1.28 (1.10-1.49)	1	<0.01

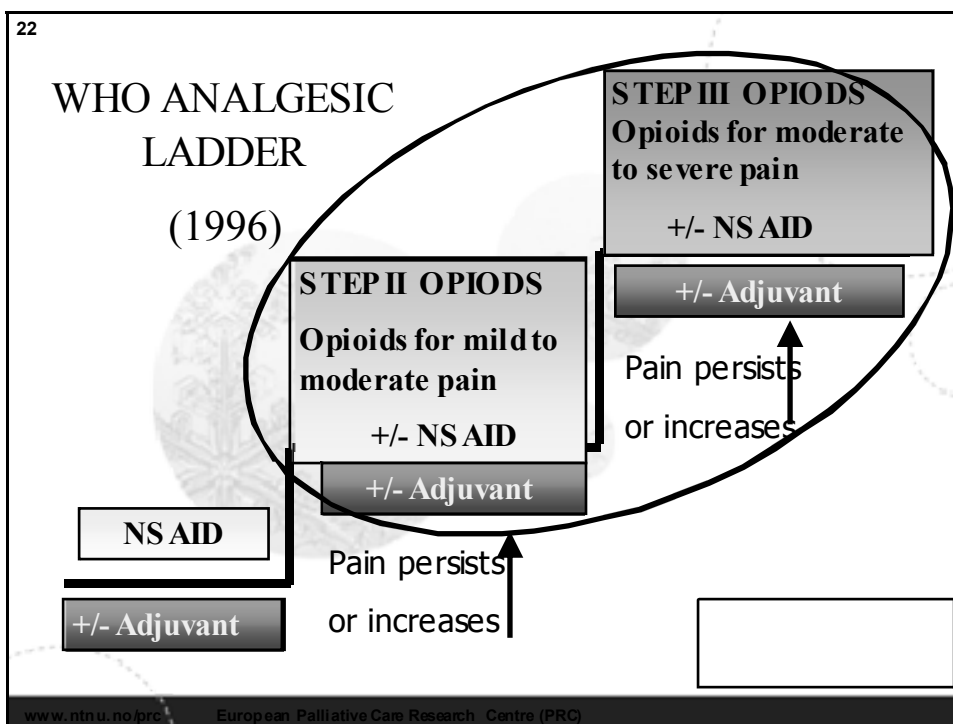
^aAdjusted for age, sex, education, comorbidity status, smoking behaviour, high alcohol intake, BMI and Charlson Comorbidity Index.

Number of deaths, death rates (per 1,000 person years) and hazard ratio (HR) of cardiovascular, cancer and other mortality (underlying cause) according to chronic pain status and opioid use.

	Chronic pain			No chronic pain	p-value
	Long-term opioid users	Short-term opioid users	Non-opioid users		
Cardiovascular mortality					
Number of deaths	22	22	93	252	
Death rates (per 1,000 person years)	8	6	5	2	
Age-adjusted HR (95% CI)	1.28 (0.70-2.35)	1.04 (0.67-1.63)	1.28 (0.99-1.65)	1	0.27
Cancer mortality					
Number of deaths	22	20	83	250	
Death rates (per 1,000 person years)	8	6	4	2	
Age-adjusted HR (95% CI)	1.48 (0.81-2.68)	1.28 (0.81-2.03)	1.28 (0.99-1.65)	1	0.11
Other mortality					
Number of deaths	23	34	107	265	
Death rates (per 1,000 person years)	16	20	7	2	
Age-adjusted HR (95% CI)	2.42 (1.67-3.51)	2.74 (1.92-3.93)	1.68 (1.39-2.01)	1	<0.001

Conclusions

- The risk of all-cause mortality was significantly associated with long-term opioid use
- There were no associations between long-term opioid use and either cancer morbidity or cancer mortality
- Both long- and short-term opioid users had a markedly higher risk of injuries and poisoning resulting in hospital inpatient admissions (data not shown)
- No deaths among long-term opioid users were due to suicides was found (data not shown)



Opioids and Breast Cancer Recurrence (BCR): A Danish Population-Based Cohort Study

Prevalence of opioid use in breast cancer patients

METHODS:

- We investigated the association between post-diagnosis opioid use and BCR among stage I-III breast cancer patients.
- We identified incident stage I-III breast cancer cases diagnosed 1995–2008 in Denmark (DBCG registry)
- Follow-up began on the date of breast cancer primary surgery and continued until the first of BCR, death, emigration, or 31 December 2012
- Completeness of the DBCG has increased over time from 87% in 1986 to 96% in 1997

Opioids and Breast Cancer Recurrence (BCR): A Danish Population-Based Cohort Study

Prevalence of opioid use in breast cancer patients

RESULTS:

- We identified 34,188 patients. Overall, 47% of patients were ever users of opioids
- Ever use of opioids was not associated with the rate of BCR in both crude and adjusted analyses
- Use of strong, weak, or both did not influence the rate of BCR
- Opioid type and exposure (time, doses) did not influence the rate of BCR

Addictive behaviors related to opioid use for chronic pain: a population-based study

Wise et al, 2012

Six potential addictive behaviors were identified:

- daily smoking
- high alcohol intake
- illicit drug use in the past year
- obesity
- long-term use of benzodiazepines
- long-term use of benzodiazepine-related drugs

At least 2 of the 6 addictive behaviors were observed in:

- 23 % of the long-term opioid users with chronic pain
- 12 % of those with chronic pain not using opioids
- 9 % of individuals without chronic pain

A strong association was demonstrated between long-term opioid use and the clustering of addictive behaviors

Prevalence of addiction in a multidisciplinary pain centre

Chronic pain patients on opioids (N=252) were evaluated for addiction by the treating physician and nurse:

Prevalence of addiction to opioids:

- ICD-10: 14.4%
- Portenoy's criteria: 19.3%

Inter-rater agreement:

- ICD-10: 95%
- Portenoy's criteria: 93%

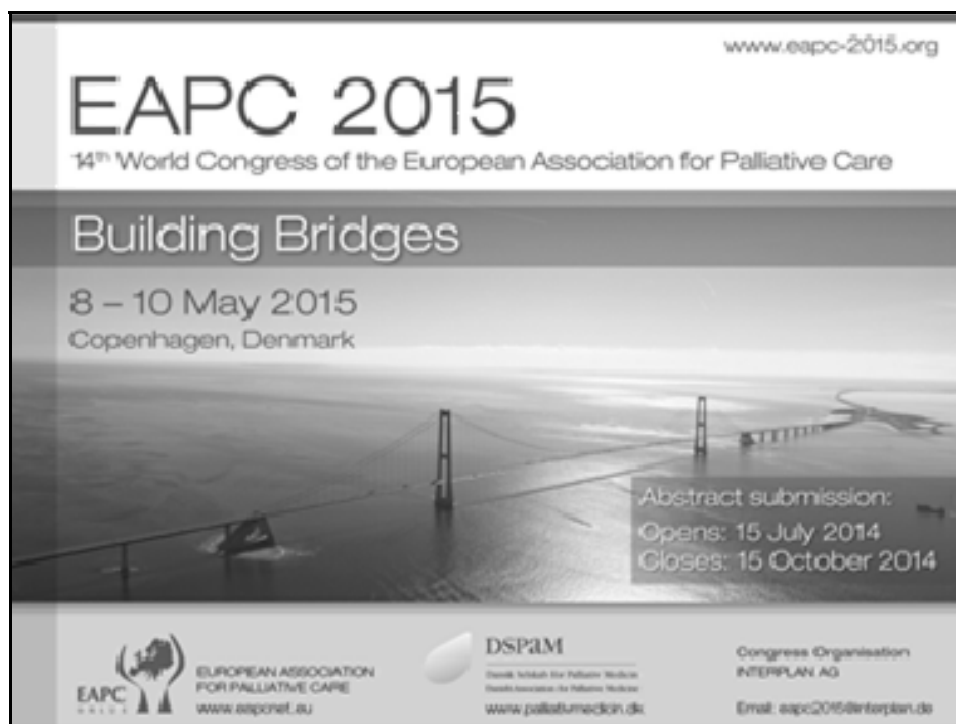
Højsted et al, Eur J Pain 2010; Højsted et al, Acta Anaesth Scand 2011

The "Danish experience" with opioids for chronic non-malignant pain

- The key outcomes recommended by international guidelines were not fulfilled
- 4-5 % of the population were prescribed opioids regularly
- The risk of all-cause mortality were significantly associated with long-term opioid use
- There were no associations between long-term opioid use and either cancer morbidity or cancer mortality
- There were no association between post-diagnosis opioid use and BCR
- There seemed to be a considerable risk of development of addiction in relation to the legal medical long-term opioid use

Future perspectives

- Manchikanti et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I--evidence assessment. Pain Physician 2012.
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