



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

Jørgen Eriksen <sup>a</sup>, Per Sjøgren <sup>a,\*</sup>, Eduardo Bruera <sup>b</sup>, Ola Ekholm <sup>c</sup>, Niels K. Rasmussen <sup>c</sup>

<sup>a</sup> *Multidisciplinary Pain Centre, H:S Rigshospitalet, Copenhagen, Denmark*

<sup>b</sup> *Department of Palliative Care and Rehabilitation Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA*

<sup>c</sup> *National Institute of Public Health, Copenhagen, Denmark*

Received 5 October 2005; received in revised form 7 June 2006; accepted 8 June 2006

### 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 16,684 individuals (>16 years of age), 10,066 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 medications. Participants reporting pain were divided into opioid and non-opioid users. The analyses were adjusted for age, gender, concomitant use of anxiolytics 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.

© 2006 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

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

### 1. Introduction

During the last two decades a significant increase in the use of opioids for chronic non-cancer pain has been observed as the result of the combined efforts of clinical needs, recommendations from pain clinicians of different kinds and not least impressive sales promotion activities from the pharmaceutical companies. Interestingly, this has taken place without the availability of scientifically relevant long-term studies focussing on extremely important clinical issues such as physical dependency,

tolerance development, cognitive disorders, abnormal pain sensitivity and potential dysfunction of the immune and reproductive systems (Jaffe, 1992; Sees and Clark, 1993; Savage, 1996; Sjøgren et al., 2000; Mao, 2002; Rajagopal et al., 2004; Vallejo et al., 2004). Although the risk of addiction has been addressed in several articles the extent of this problem is virtually unknown as well as the impact of diversion of opioid drugs. The newly published systematic review on long-term opioid use by Kalso et al. (2004) includes only studies having a maximal length of 8 weeks – a time period without specific interest considering chronic use. At the moment best available evidence for “real” long-term effects of opioids is probably found in prospective cross-sectional

\* Corresponding author. Tel.: +45 3545 7384; fax: +45 3545 7349.  
E-mail addresses: rh12244@rh.dk, p.sjogren@mail.dk (P. Sjøgren).

studies in patients being treated for years or in open follow-studies (Becker et al., 1997, 2000; Sjogren et al., 2005).

Within the last years international and national guidelines on long-term use of opioids have been published (Kalso et al., 2003; The Pain Society, 2004) – one of them unfortunately supported editorially and economically by a pharmaceutical company (Kalso et al., 2003). The guidelines stress that opioids may be indicated in some chronic non-cancer conditions and that the treatment goal should be not only pain relief, but also an improved quality of life and functional capacity (Ballantyne and Mao, 2003; Kalso et al., 2003; The Pain Society, 2004; Kalso, 2005).

Denmark has for years had an extremely high usage of opioids (Joranson, 2004), mainly prescribed for chronic non-cancer pain conditions (Clausen et al., 1995; Jarlbæk et al., 2004). New epidemiological data excluding cancer patients have shown that about 3% of the Danish population uses opioids on a regular or continuous basis. Long-term/chronic pain (>6 months) is reported by 19% of the adult population and among these 12% used opioids (Eriksen et al., 2003). Based on data from the 2000 Danish Health and Morbidity Survey this study aims epidemiologically to investigate if the essential goals of long-term opioid treatment – pain improvement, quality of life and functional capacity – are achieved.

## 2. Methods

The 2000 Danish Health and Morbidity Survey is the fourth in a series of health surveys conducted in Denmark every sixth to seventh year (Kjøller et al., 1995; Kjøller and Rasmussen, 2002). The aim of the surveys is to evaluate the general health status and morbidity in the Danish population and to monitor health status over time.

In the 2000 survey, a National random sample of 16,684 persons over 16 years of age and representative of the Danish population was drawn from the Danish Central Personal Register and asked to participate.

Data were collected via face-to-face interviews carried out by a professional interview staff from the Danish National Institute of Social Research and through a self-administered questionnaire, which included the Short Form 36 (SF-36). Only those who took part in the interview and filled in the postal questionnaire were included in the study.

Participants suffering from chronic pain were identified through the question ‘Do you have chronic/long-lasting pain lasting 6 months or more?’ that was included in the self-administered questionnaire. Positive responders constitute the pain group (PG) and negative responders the control group (CG). Responders with a self-reported earlier or present cancer diagnosis were excluded.

Age was categorized into four groups: 16–24, 25–44, 45–66 and  $\geq 67$  years. Cohabitation status was assembled into four groups: married; cohabitating; single (divorced/separated or widowed); and single (never married). The International

Standard Classification of Education (ISCED), which combines school- and vocational education, was used to describe educational status (Hansen and Kühl, 1994). ISCED was categorized into three levels: <10 years, 10–12 years and  $\geq 13$  years. Self-rated health status was evaluated on a 5-item scale: 1, really good health; 2, good health; 3, fair health; 4, bad health and 5, very bad health and dichotomized into really good/good and fair/bad/very bad health. Bodily pain is derived from the six-point verbal rating pain scale included in the SF-36 and dichotomized into none/very mild/mild and moderate/severe/very severe pain according to Jensen et al. (2004). A supplementary question on satisfaction/dissatisfaction with the medical treatment offered for their pain condition was forwarded to the PG.

Health-related disability was evaluated as physical activity in leisure-time (all age groups); quitting job because of ill health; and self-reported absences due to illness. The variable ‘quitting job’ was constructed from two variables: ‘quitted job for health reasons’ and ‘changing job and later quitted because of ill health’. The analysis was performed among persons younger than 67 years. Self-reported absence due to illness was measured among those actively engaged in employment as the number of absent days during the 14-day period before interview.

Use of the health care system is registered as contact to a medical doctor (unspecified) within the last three months. Usage of medications was obtained by an open-ended question asking whether the respondent used analgesics (non-opioids, opioids), anxiolytics or antidepressants regularly or continuously. In case of a positive response, the type of medication was coded according to Anatomical Therapeutic Chemical Classification System (<http://www.whocc.no/atcddd/>). Satisfaction with medical treatment was assessed in the PG by the questions: ‘Are you satisfied with the pain treatment you have been offered till now?’ Answers were categorized as ‘Yes’ or ‘No’.

Data on the Danish opioid consumption during the period 1981–2002 were obtained from the Danish Pharmaceutical Information, which provides information on the quantity of opioids sold to the Danish pharmacies and hospitals. Equi-Analgesic Daily Doses (EADD) were calculated according to Clausen et al. (1995).

### 2.1. Statistical analyses

Logistic regression analysis was used to analyse the association between opioid usage (the dependent variable) and different sociodemographic variables, self-perceived health and pain intensity. Logistic regression analysis was also used to investigate the association between opioid usage (independent variable) and functional capacity, satisfaction with medical treatment and consulting a doctor within the last three months. The results from the logistic regression analyses are presented as odds ratios (OR<sup>a</sup>: adjusted for sex and age; OR<sup>b</sup>: adjusted for sex, age and concomitant use of benzodiazepines and antidepressants; OR<sup>c</sup>: adjusted for sex, age and concomitant use of benzodiazepines and antidepressants, and bodily pain severity within the past four weeks) with 95% confidence intervals (CI). Goodness of fit of the models was assessed by the Hosmer-Lemeshow test (Hosmer and Lemeshow, 2000). The tests indicated that the models fit the

data adequately. Age adjusted mean scores were estimated for each of the SF-36 subscales. The mean scores were standardized by the age distribution characteristics of Danes in 2000. To compare the self-reported use of pain medication between the pain group and the control group, we used the  $\chi^2$  test.

### 3. Results

The study flow chart is presented in Fig. 1. The study population comprised 10,066 individuals. Comparing the sociodemographics and self-perceived health of those who completed the interview with the investigated sample, only small differences were observed (Table 1). Table 1 also demonstrates sociodemographic data, self-perceived health and reports on pain in the PG and CG. Chronic pain is associated with female gender age >45 years, living alone (divorced/separated or widowed), short education and poor self-perceived health (Eriksen et al., 2003). Almost identical numbers of individuals in the PG report none/very mild/mild or moderate/severe/very severe pain. Data on use of pain medication in the Danish population are shown in Table 2 (Eriksen et al., 2003). Nine per cent of the Danish population used some kind of analgesics. Almost one-third of the PG used analgesics, compared with 4% of the CG. Opioids were used regularly or continuously by 12% of the PG: 3% used the so-called “strong” opioids and 9% used the “weak” opioids (tramadol, codeine and dextropropoxyphene). Prevalence of opioid use was 20% among those in the PG who reported moderate/severe or very severe pain, compared with 3% among those who reported none/very mild or mild pain (OR<sup>a</sup> 8.37; OR<sup>b</sup> 8.10). Prevalence of opioid use among those who reported fair, bad or really bad self-perceived health was 18%, compared with 4% among those who rated

their health as really good or good (OR<sup>a</sup> 5.21; OR<sup>b</sup> 4.95; OR<sup>c</sup> 2.84).

The PG was divided into the group of opioid users and the group of non-opioid users and Table 3 shows the corresponding prevalence rates for various sociodemographic groups, self-perceived health and reporting of pain. Opioid usage is significantly associated with reporting of moderate/severe or very severe pain, poor self-rated health, and living alone (being separated/divorced or widowed). Data on health-related quality of life (SF-36) are shown in Fig. 2. In all eight subscales, opioid users had a lower mean score than non-opioid users.

Table 4 shows that opioid usage is associated with not being physically active in leisure time (OR<sup>b</sup> 1.55) and not being engaged in employment (OR<sup>b</sup> 0.37). In addition, individuals using opioids have 2.68 higher odds (OR<sup>b</sup>) of being a disability pensioner compared with the non-opioid individuals. Compared with non-opioid users, opioid users had 2.52 higher odds (OR<sup>b</sup>) of using the health care system within the last three months. Satisfaction/dissatisfaction with treatment was similar among the opioid and non-opioid using group of pain patients.

The opioid consumption in Denmark was relatively stable during the period 1981–1984. However, the use of opioids has increased from 340,000 EADDs/million inhabitants in 1984 to 2,523,000 EADDs in 2002 (Fig. 3). The 2002-usage includes transdermal fentanyl, oxycodone and hydromorphone, which were not available in Denmark until 3–5 years ago. The consumption of the so-called weak opioids: codeine, tramadol and dextropropoxyphene are not included.

### 4. Discussion

The Danish experience with opioids in the treatment of chronic non-cancer pain goes back several years. As the most opioid-consuming country in the world (Joranson et al., 2000), Denmark has often been considered a model for pain treatment in patients with cancer. Yet most of the prescription opioids are used for chronic non-cancer pain, and less than 33% are used for cancer patients (Clausen et al., 1995; Jarlbæk et al., 2004).

During the last two decades the use of opioids for treatment of chronic non-cancer pain has increased considerably: more than 600% in Denmark (Eriksen, 2004). Several studies, mostly small series, have demonstrated beneficial effects, but complications and side effects are rarely reported in these studies. Chronic non-cancer pain patients are not a homogeneous group, and the patients may demonstrate a wide range of biological, psychological and social symptoms often complicated by depression, anxiety, somatoform disorders, as well as substance abuse disorders (Dworkin et al., 1990; Schofferman, 1993; Becker et al., 1997; Kouyanou

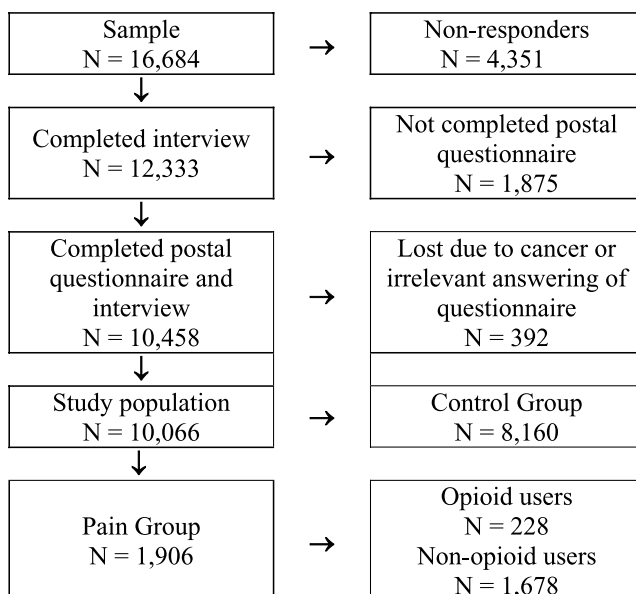


Fig. 1. Study flow chart. National epidemiology.

Table 1

Sociodemography, self-perceived health and reporting of pain in the various investigation groups derived from the 2000 Danish Health and Morbidity Survey

Variables	Completed interview % (n)	Study population % (n)	No pain control group % (n)	Pain group % (n)
Gender				
Men	49 (6,011)	48 (4,842)	50 (4,047)	42 (795)
Women	51 (6,322)	52 (5,224)	50 (4,113)	58 (1,111)
Age				
16–24	14 (1,627)	13 (1,292)	14 (1,165)	7 (127)
25–44	36 (4,304)	37 (3,620)	38 (3,132)	27 (488)
45–66	35 (4,460)	36 (3,771)	35 (2,886)	46 (885)
67+	16 (1,942)	14 (1,383)	12 (977)	21 (406)
Education				
≤10 y	25 (3,172)	22 (2,348)	22 (1,736)	30 (612)
11–12 y	24 (3,003)	24 (2,451)	24 (1,909)	29 (542)
≥13+ y	51 (5,886)	54 (5,052)	54 (4,330)	40 (722)
Cohabitation status				
Married	52 (6,451)	54 (5,516)	55 (4,424)	57 (1,092)
Cohabiting	16 (1,939)	16 (1,574)	16 (1,323)	14 (251)
Single (separated/divorced or widowed)	13 (1,612)	11 (1,157)	10 (815)	18 (342)
Single (unmarried)	19 (2,235)	18 (1,745)	19 (1,538)	11 (207)
Self-perceived health				
Really good/good	80 (9,607)	80 (8,042)	88 (7,190)	45 (852)
Fair/bad/very bad	20 (2,726)	20 (2,021)	12 (968)	55 (1,053)
Bodily pain				
None/very mild/mild	Data not available	84 (8,473)	92 (7,537)	49 (936)
Moderate/severe/very severe		16 (1,593)	8 (623)	51 (970)

et al., 1998). In this context it is noteworthy that only observed non-verbal pain behaviour but not pain severity, objective physical pathology, duration of pain or demographic characteristics seem to influence the physicians opioid prescribing (Turk and Okifuji, 1997).

In this cross-sectional population study about 90% of the opioid users in the PG reported moderate, severe or very severe pain compared with 46% in the non-opioid PG. Obviously the opioid treatment did not alleviate this group of individuals sufficiently to achieve similar

functional status, quality of life and pain control as compared to individuals not receiving opioids, or the general population. The failure of opioids to achieve this outcome in a “real world” study has not been reported before. In Table 3 the association between bodily pain within the past four weeks and opioid use indicates that if opioids had adequate analgesic effects a higher number of opioid users should have none/very mild/mild pain. Furthermore, the table shows associations between various background variables at different levels of

Table 2

Self-reported use of pain medication in the study population, pain and control groups derived from the Danish Health and Morbidity Survey in 2000

Regular use of medicine	2000 Danish Health and Morbidity Survey			
	Study population (N = 10,066, %)	Pain group (N = 1,906, %)	Control group (N = 8,160, %)	p
Analgesics	9	30	4	<0.01
Non-opioids <sup>a</sup>	9	30	4	
Opioids	3	12	1	<0.01
Weak <sup>b</sup>	2	9	1	<0.01
Strong <sup>c</sup>	1	3	0	<0.01
No analgesic used	91	70	96	<0.01
Anxiolytics	1	3	1	<0.01
Antidepressants	2	4	2	<0.01

<sup>a</sup> Acetylsalicylic acid, paracetamol and non-steroid anti-inflammatory drugs.

<sup>b</sup> Codeine, tramadol, dextropropoxyphene.

<sup>c</sup> All other opioids.

Table 3

Results from multivariate logistic regression analyses showing the associations between usage of opioids and various socioeconomic variables, self-rated health and bodily pain within the last 4 weeks among individuals with self-reported chronic pain

Variables	Opioid users % (n)	Odds ratio <sup>a</sup> (95% CI)	Odds ratio <sup>b</sup> (95% CI)	Odds ratio <sup>c</sup> (95% CI)
<b>Gender</b>				
Men	11 (795)	1.00	1.00	1.00
Women	12 (1111)	1.16 (0.87–1.56)	1.12 (0.84–1.51)	0.94 (0.69–1.28)
<b>Age</b>				
16–24 y	4 (127)	0.29 (0.12–0.70)	0.32 (0.13–0.78)	0.32 (0.13–0.80)
25–44 y	11 (488)	0.83 (0.59–1.17)	0.88 (0.62–1.24)	0.89 (0.62–1.27)
45–66 y	13 (885)	1.00	1.00	1.00
≥67 y	10 (406)	0.74 (0.51–1.09)	0.74 (0.51–1.09)	0.72 (0.49–1.08)
<b>Education</b>				
≤10 y	14 (612)	1.59 (1.11–2.28)	1.51 (1.05–2.18)	1.33 (0.92–1.94)
11–12 y	12 (542)	1.29 (0.89–1.86)	1.27 (0.88–1.84)	1.06 (0.72–1.56)
≥13 y	9 (722)	1.00	1.00	1.00
<b>Cohabitation status</b>				
Married	12 (1,092)	1.88 (0.97–3.62)	2.01 (1.04–3.89)	1.79 (0.91–3.51)
Cohabiting	9 (251)	1.35 (0.65–2.80)	1.44 (0.69–2.98)	1.16 (0.55–2.46)
Single (separated/divorced or widowed)	15 (342)	2.52 (1.23–5.17)	2.50 (1.21–5.16)	2.10 (1.00–4.39)
Single (unmarried)	6 (207)	1.00	1.00	1.00
<b>Self-perceived health</b>				
Really good/good	4 (852)	1.00	1.00	1.00
Fair/bad/very bad	18 (1,054)	5.21 (3.55–7.65)	4.95 (3.36–7.29)	2.84 (1.89–4.26)
<b>Bodily pain within the past four weeks</b>				
None/very mild/mild	3 (936)	1.00	1.00	–
Moderate/severe/very severe	20 (970)	8.37 (5.49–12.74)	8.10 (5.32–12.34)	–

<sup>a</sup> OR adjusted for gender and age.  
<sup>b</sup> OR adjusted for gender, age, and concomitant use of benzodiazepines and antidepressants.  
<sup>c</sup> OR adjusted for gender, age, concomitant use of benzodiazepines and antidepressants, and bodily pain within the past four weeks.  
 \*  $p < 0.05$ .  
 \*\*  $p < 0.01$ .

control (OR<sup>a,b,c</sup>). Table 4 shows clear associations between opioid use and some behavioural outcome variables as frequent use of the health care system and not being engaged in employment. Including bodily pain within the past four weeks in the multivariate logistic regression analyses the association between opioid use and sedentary leisure-time physical activity vanished.

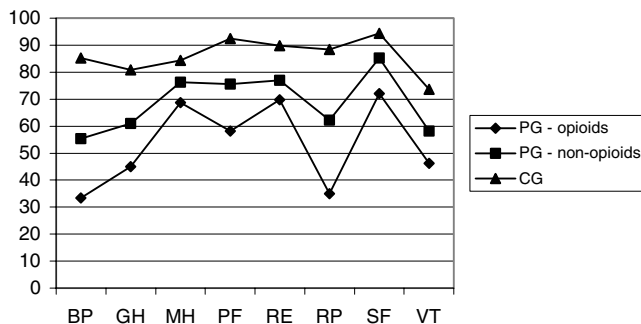


Fig. 2. SF-36 scores in the various investigation groups. PG, pain group; CG, control group. BP, bodily pain; GH, general health; MH, mental health; PF, physical function; RE, role emotional; RP, role physical; SF, social function; VT, vitality.

Because of the cross-sectional nature of this epidemiological study a causative relationship between pain relief, quality of life and functional capacity and regular or continuous use of opioids cannot be ascertained. However, it is remarkable that opioid treatment of chronic non-cancer pain does not seem to fulfil any of the key outcome goals: pain relief, improved quality of life and improved functional capacity. One can argue that these outcomes would have been even poorer without opioids, but another plausible explanation may be that opioids are not very helpful or even deleterious in the long-run. There exist no longitudinal randomised controlled trials on long-term effects and consequences of opioid use in non-cancer patients and best available data should be extracted from prospective controlled cross-sectional and open follow-up studies. It may be hypothesized that opioids could have relatively short-run (months) benefits, which in the long-run (years) may turn into opposite and deleterious effects as previously described by Schofferman (1993) as “the opioid downhill spiral”. In a retrospective comparison performed among chronic pain patients referred to a tertiary pain clinic Ciccone et al. (2000) also found that opioid users were more likely to report more pain, having more

Table 4

Results from multivariate logistic regression analyses showing the associations between usage of opioids and functional status, satisfaction with medical treatment, and use of the health care system among subjects reporting chronic pain

Variable	Pain group	Prevalence % (n)	Odds ratio (OR <sup>a</sup> ) (95% CI)	Odds ratio (OR <sup>b</sup> ) (95% CI)	Odds ratio (OR <sup>c</sup> ) (95% CI)
Sedentary leisure-time physical activity	Opioid users	31 (228)	1.68 (1.21–2.32)**	1.55 (1.11–2.15)**	1.34 (0.95–1.88)
	Non-opioid users	21 (1,678)	1.00	1.00	1.00
Engaged in employment <sup>d</sup>	Opioid users	32 (182)	0.35 (0.25–0.49)**	0.37 (0.26–0.53)**	0.45 (0.31–0.65)**
	Non-opioid users	55 (1,318)	1.00	1.00	1.00
Disability pension <sup>d</sup>	Opioid users	37 (182)	2.91 (2.03–4.19)**	2.68 (1.85–3.89)**	2.03 (1.38–2.99)**
	Non-opioid users	17 (1,318)	1.00	1.00	1.00
Satisfied with the medical treatment offered	Opioid users	52 (217)	0.85 (0.64–1.15)	0.85 (0.63–1.15)	1.05 (0.77–1.43)
	Non-opioid users	56 (1,514)	1.00	1.00	1.00
Use of health care system <sup>e</sup>	Opioid users	81 (223)	2.66 (1.86–3.81)**	2.52 (1.75–3.62)**	1.98 (1.36–2.87)**
	Non-opioid users	63 (1,675)	1.00	1.00	1.00
Absence due to illness within the last two weeks ( $\geq$ one day) <sup>f</sup>	Opioid users	20 (51)	1.13 (0.56–2.28)	1.08 (0.53–2.21)	0.77 (0.37–1.61)
	Non-opioid users	17 (727)	1.00	1.00	1.00

<sup>a</sup> OR adjusted for gender and age.

<sup>b</sup> OR adjusted for gender, age, and concomitant use of benzodiazepines and antidepressants.

<sup>c</sup> OR adjusted for gender, age, concomitant use of benzodiazepines and antidepressants, and bodily pain within the past four weeks.

<sup>d</sup> Only persons < 67 years are included.

<sup>e</sup> Contact to the health care system (a medical doctor) within the last three months.

<sup>f</sup> Only persons engaged in employment are included.

\*\*  $p < 0.01$ .

pain locations, being more depressed and physically disabled than non-opioid users. However, having adjusted for concomitant use of benzodiazepines the differences disappeared. This was not the case in the present study in which adjusting for concomitant use of benzodiazepines and antidepressants did not influence the results obtained. The Danish Morbidity and Health Survey relies solely on the respondents' self-reporting of pain, symptoms, complaints, health perceptions without any validation through a clinical examination. Several

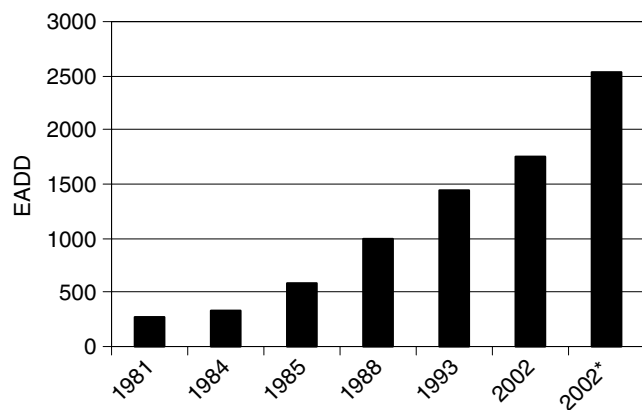


Fig. 3. Danish opioid consumption (EADD × 10<sup>3</sup>) during the period 1981–2002. Opioid usage comprises morphine, buprenorphine, pentazocine, methadone, pethidine, dextromoramide, ketobemidone and nicomorphine. \*2002: include transdermal fentanyl, oxycodone and hydromorphone. EADD, Equi-analgesic daily doses.

studies including analyses on data from the Danish 1994 survey have shown that self-reported and self-assessed health status information have a high predictive validity in relation to mortality and hospitalisation (Helweg-Larsen et al., 2003; Sha et al., 2005). Studies have also shown rather high levels of concordance between self-reported and registered hospitalisations and drug use (Reijneveld and Stronks, 2001).

Opioid treatment does have some inherent risks, which in a long-term perspective may give rise to serious treatment problems, and may be responsible for maintaining or worsening the pain condition. Among these physical dependence, tolerance development, abnormal pain sensitivity, addiction, abuse, and cognitive impairment are well known, but sometimes overlooked in a population in which problems are particularly likely to arise because life expectancy is much longer than that of many cancer patients. Furthermore, increasing evidence also suggests that long-term opioid treatment may have detrimental effects on the immune system (Sacerdote et al., 1997; Vallejo et al., 2004) and the reproductive system (Rajagopal et al., 2004).

Epidemiology of patients referred to and treated at specialized pain units should not be interpreted as representative for a general pain population, however, they may represent the tip of an iceberg. Therefore an increasing number of this category of patients (70–80%) is treated with opioids already at referral (Buckley et al., 1986; Becker et al., 1997; Kouyanou et al., 1997; Nissen et al., 2001). This is reflected also

in our multidisciplinary pain unit in which 68% were treated with opioids at referral – often several types at the same time – in a mean dose equivalent of 75 mg of morphine daily (Eriksen, 2004). Current estimates indicate that between 3% and 19% of chronic pain patients suffer an addictive disorder (Hoffmann et al., 1995; Kouyanou et al., 1997, 1998), which, however, parallels the lifetime prevalence rates of addictive diseases in the general population (Regier et al., 1990). However, among the more stigmatized groups higher rates of substance abuse should be expected (Savage, 1996; Joranson et al., 2000).

The fact that opioids can improve pain, functional capacity and quality of life in selected patients with chronic non-cancer pain should not be ignored. However, our research, both in the general population and in patients referred to our pain center, suggests reasons for concern. The findings of our study strongly suggest that caution should be used with long-term opioid treatment of pain, at least until there is better evidence on efficacy and outcomes.

## References

- Ballantyne JC, Mao J. Opioid therapy for chronic pain. *New Engl J Med* 2003;349:1943–53.
- Becker N, Thomsen AB, Olsen AK, Sjøgren P, Bech P, Eriksen J. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. *Pain* 1997;73:393–400.
- Becker N, Sjøgren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain* 2000;84:203–11.
- Buckley FP, Sizemore WA, Charlton JE. Medication management in patients with chronic non-malignant pain. A review of the use of a drug withdrawal protocol. *Pain* 1986;26:153–65.
- Clausen TG, Eriksen J, Borgbjerg FM. Legal opioid consumption in Denmark in 1981–1993. *Eur J Clin Pharmacol* 1995;48:321–5.
- Ciccone DS, Just N, Bandilla EB, Reimer E, Ilbeigi MS, Wu W. Psychological correlates of opioid use in patients with chronic non-malignant pain: A preliminary test of the downhill spiral hypothesis. *J Pain Symptom Manage* 2000;20:180–92.
- Dworkin SF, Von Korff M, LeResche L. Multiple pains and psychiatric disturbance. An epidemiological investigation. *Arch Gen Psychiatry* 1990;47:239–44.
- Eriksen J, Jensen MK, Sjøgren P, Ekholm O, Rasmussen NK. Epidemiology of chronic non-malignant pain in Denmark. *Pain* 2003;106:221–8.
- Eriksen J. Long-term/chronic non-cancer pain. Epidemiology, health-care utilization, socioeconomic and aspects of treatment. University of Copenhagen. Thesis 2004.
- Hansen A, Kühl K. Dansk Uddannelses Nomenklatur (Danish Educational Nomenclature). Copenhagen: Danish Statistics and Ministry of Education; 1994.
- Helweg-Larsen M, Kjoller M, Thoning H. Do age and social relations moderate the relationship between self-rated health and mortality among adult Danes? *Soc Sci Med* 2003;57:1237–47.
- Hoffmann NG, Olufsson O, Salen B, Wickström L. Prevalence of abuse and dependency in chronic pain patients. *Int J Addict* 1995;30:919–27.
- Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 2000.
- Jaffe J. Opiates: clinical aspects. In: Lowinson JH, Ruiz P, Millman RG, editors. Substance Abuse. A Comprehensive Textbook. Baltimore: Williams and Wilkins; 1992. p. 186–94.
- Jarlbæk L, Andersen M, Kragstrup J, Hallas J. Cancer patients' share in a population's use of opioids. A linkage study between a prescription database and the Danish Cancer Registry. *J Pain Symptom Manage* 2004;27:36–43.
- Jensen MK, Sjøgren P, Ekholm O, Rasmussen NK, Eriksen J. Identifying a long-term/chronic, non-cancer pain population using a one-dimensional verbal pain rating scale. An epidemiological study. *Eur J Pain* 2004;8:145–52.
- Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA* 2000;283:1710–4.
- Joranson DE. Improving availability of opioid pain medications: testing the principle of balance in Latin America. *J Pall Med* 2004;7:105–14.
- Kalso E, Allan L, DelleMijn PLI, Faura CC, Ilias WK, Jensen TS, et al. Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain* 2003;7:381–6.
- Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004;112:372–80.
- Kalso E. Opioids for persistent non-cancer pain. *BMJ* 2005;330:156–7.
- Kjøller M, Rasmussen NK, Keiding L, Petersen HC, Nielsen GA. The Danish Health and Morbidity Survey, 1994. Copenhagen: The Danish Institute of Clinical Epidemiology, 1995. English summary available at: [www.niph.dk](http://www.niph.dk).
- Kjøller M, Rasmussen NK, editors. The Danish Health and Morbidity Survey 2000 and Trends Since 1987. Copenhagen: National Institute of Public Health; 2002.
- Kouyanou K, Pither CE, Wessely S. Medication misuse, abuse and dependence in chronic pain patients. *J Psychosom Res* 1997;43:497–504.
- Kouyanou K, Pither CE, Rabe-Hesketh S, Wessely S. A comparative study of iatrogenesis, medication abuse, and psychiatric morbidity in chronic pain patients with and without medically explained symptoms. *Pain* 1998;76:417–26.
- Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain* 2002;100:213–7.
- Nissen LM, Tett SE, Cramond T, Williams B, Smith MT. Opioid analgesic prescribing and use - an audit of analgesic prescribing by general practitioners and The Multidisciplinary Pain Centre at Royal Brisbane Hospital. *Br J Clin Pharmacol* 2001;52:693–8.
- Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to morphine. *Cancer* 2004;100:851–8.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;19:2511–8.
- Reijneveld SA, Stronks K. The validity of self-reported use of health care across socioeconomic strata: a comparison of survey and registration data. *Int J Epidemiol* 2001;30:1407–14.
- Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. *Br J Pharmacol* 1997;121:834–40.
- Savage SR. Long-term opioid therapy: assessment of consequences and risks. *J Pain Symptom Manage* 1996;11:274–86.
- Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of non-malignant origin. *J Pain Symptom Manage* 1993;8:279–88.
- Sees KL, Clark HW. Opioid use in the treatment of chronic pain: assessment of addiction. *J Pain Symptom Manage* 1993;8:257–64.

- Sha MC, Callahan CM, Counsell SR, Westmoreland GR, Stump TE, Kroenke K. Physical symptoms as a predictor of health care use and mortality among older adults. *Am J Med* 2005;118:301–6.
- Sjogren P, Olsen AK, Thomsen AB. Impaired neuropsychological performance in chronic non-malignant pain patients receiving long-term oral therapy. *J Pain Symptom Manage* 2000;19:100–8.
- Sjogren P, Christrup LL, Petersen M Aa, Hojsted J. Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. *Eur J Pain* 2005;9:453–62.
- The Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain. A consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists. March 2004. [www.britishpainsociety.org/pdf/opioids\\_doc\\_2004.pdf](http://www.britishpainsociety.org/pdf/opioids_doc_2004.pdf).
- Turk DC, Okifuji A. What factors influence physicians' decisions to prescribe opioids for chronic non-cancer pain patients. *Clin J Pain* 1997;13:330–6.
- Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression. A review. *Am J Ther* 2004;11:354–65.