Burden of disease is often aggravated by opioid treatment of chronic pain patients: Etiology and prevention

For more than two decades, Danish doctors have prescribed opioids for chronic noncancer pain more liberally than have doctors in the neighboring countries. We have been looking to Denmark for the long-term effects of this liberal practice [4] that, as early as 2003, Jørgen Eriksen called “working in a minefield” [4,11]. In this issue of Pain, Ekholm and coworkers in Per Sjøgren’s research group report data from the ongoing health surveys in Denmark: They followed 13,127 persons from the 2000 and 2005 surveys for up to 11 years. In all, 20% (2557) had chronic pain, and 7% of these (167) were on long-term and 15% (375) on short-term opioid therapy at baseline [10]. Their data are from face-to-face interviews of the cohorts in 2000 and 2005 and from the Danish national registries of drug prescriptions, hospital admissions, and causes of death.

Patients with chronic pain not on opioids and those on short-term opioid therapy had increased risk of all cause mortality compared with persons without chronic pain (odds ratio [OR] = 1.4, P < .01). These findings agree with other cohort studies that followed up participants for as many as 17 years [18,20,24,33]. Those participants treated long term with opioids in the year preceding the surveys in 2000 and 2005 had almost double the risk of death (OR = 1.8; 95% confidence interval [CI] = 1.3–2.4) up until end of 2011 compared with pain-free persons, but were not significantly different from chronic pain patients without opioids or those on short-term opioid treatment. When corrected for possible confounding factors (age, gender, education, co-habitation, smoking, alcohol intake, body mass index, Charlson Co-morbidity Index), the risk of death was slightly less (OR = 1.7). The investigators did not find any specific causes of death. Previously reported increased risk of death from cancer [20] or cardiovascular disease [20,24,33] in chronic pain patients was not found in chronic pain patients with or without opioid treatment by Ekholm et al. [10]. They did not report any overdose deaths or suicides in the long-term opioid-using group. Suicides occurred in 1/10,000 person-years among those with chronic pain (not using opioids) and those without.

Thus, Ekholm et al. [10] documented that opioid treatment does not significantly increase the already high risk of death among chronic pain patients in Denmark. With only 167 patients on long-term opioid treatment at baseline, there is a real risk of underestimating the increased risk of death by opioid therapy. Unfortunately, in this study there are no data on diversion and overdose deaths among other users of opioids in Denmark. Our impression of the Scandinavian scene is that it is nothing like the mega-numbers of prescription opioid overdose statistics from the United States [25]. It may well be that the robust health care system in Denmark, and the focus on ill effects of uncritical opioid prescribing during the last 10 years in Denmark [11] and the other Nordic countries [4], appear to have prevented such opioid-misuse catastrophes that now are highly visible in the United States [25].

1. Opioids can aggravate the burden of disease of chronic pain patients

The risk of being hospitalized for injuries or intoxication was higher among chronic pain patients not on opioid treatment, compared with pain-free persons [10]. The long-term opioid treated pain patients had even higher risk of injuries or intoxication than the chronic pain patients who were not on opioid treatment, but not significantly different from those who were treated short-term with opioids [10].

Chronic pain patients have a poor quality of life [19,34], high risk of disability [19,23], depression [22], and an increased risk of suicide attempts [31]. Inactivity, economic ruin, social isolation, stigma, and co-morbidities all probably contribute to the increased risk of injuries and intoxication compared with that in persons without chronic pain [10].

Inappropriate long-term opioid treatment obviously can aggravate the already-high burden of disease in chronic pain patients. We do not know the long-term outcome of pain management with opioids in the 167 patients on long-term opioid treatment at baseline in 2000 and 2005, or what happened to those on short-term opioids, or those not on opioid treatments at baseline [10]. The results of this study would be more valuable if we had information on what happened to opioid treatment during the 6- to 11 years after baseline. In an analysis in 2005 of some of the sample from 2000, it appears that more than 9% recovered annually, 4 times more often in persons not on opioids than those on opioid therapy in 2000 [30]. So how did this changing therapy affect the results in 2011? Clearly one cannot assume that the treatment regimens at baseline were constant during these long years with chronic pain. Unfortunately, there is no information about dose or how many of the 542 patients exposed to opioids in 2000 and in 2005 developed problematic opioid use or iatrogenic opioid addiction.

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2. Opioid treatment can increase the already high risk of serious outcomes of chronic pain

Opioids have a number of well-known dose-related and potentially fatal adverse effects, such as respiratory depression and cardiac arrhythmias (QT prolongation). Less well known, but also potentially life-threatening adverse effects are the serotonin syndrome [2], the endocrinopathies [27], immunosuppression [29], and malnutrition [21].

Potentially dangerous interactions can occur between opioids and other drugs prescribed for chronic pain or for other health problems. Opioids can cause QT prolongation, well known during methadone treatment [7], but this can occur with other opioids as well, for example, oxycodone [13]. Drugs that can increase the risk of QT prolongation and polymorphic ventricular arrhythmias from opioids are antidepressants, antibiotics, and a long list of other drugs [8]. Benzodiazepines and alcohol increase the sedative effects of opioids, increasing the risk of pneumonia in older adults [9].

Interference with metabolism of potent opioids, again best documented for methadone [7], can be caused by many drugs (psychotropic drugs, antibiotics, anticonvulsants, antihistamines, and antiretroviral drugs). A case report illustrates well how ciprofloxacin can cause accumulation of methadone, severe sedation, and respiratory depression [17].

Serious serotonin syndrome can be caused by several opioids, tramadol in particular, but also fentanyl [26], especially when interacting with serotoninergic antidepressants prescribed for chronic pain or for the depression that is present in up to 100% of chronic pain patients [22]. These serotoninergic complications are dangerous because many doctors still do not recognize in time the typical triad with the following:

(a) mental symptoms (nervous, anxious, agitated, poor-quality sleep),
(b) increased sympathetic nervous system activity (high blood pressure, tachycardia, diaphoresis, mydriasis, lively intestinal motility),
(c) and the most typical—augmented tendon reflexes with inducible myoclonus [2,3].

Treatment involves stopping all serotoninergic drugs. However, once hyperpyrexia appears, the serotonin syndrome is rapidly fatal unless intensive medical care is applied, with serotonin-antagonists and life-saving cardio-respiratory support [2,26]. This diagnosis is easily missed in a post mortem examination.

Reports of tramadol-related deaths are increasing in countries where tramadol is prescribed for chronic pain [15]. These deaths cannot be due to respiratory depression from this weak opioid agonist [32]; rather, they may be caused by unrecognized and untreated serotonin syndrome from tramadol, potentiated by other serotoninergic medications [2,3,26]. Denmark has a higher use of tramadol for chronic pain than the other Nordic countries [16].

3. Should Denmark and the Western medical world stop long-term opioid treatment?

The Danish experience during more than 2 decades has documented that long-term opioid treatment may increase the burden of ill health of chronic pain patients [10,11]. The “flood of opioids” has caused “a rising tide of death” in the United States [25]. This rising tide of prescription opioid–related overdose deaths has not reached the Nordic countries. This is true also for Denmark, with its long history of liberal prescription of opioids. This may be due to the warnings from Jørgen Eriksen, Per Sjøgren, and others about dangers of too liberal opioid prescribing during the last decade [11]. Still, the U.S. experience may cause the opioid policy pendulum to swing back (again!) to the restrictive opioid regulations that we had before the 1980s. The many mitigating actions in that direction taken by the authorities in the United States appear to have limited effects on abuse, while already reducing access to opioids for chronic opioid-sensitive pain [1,12]. Finding the right balance between too liberal and too restrictive opioid regulations will continue to be a major challenge in pain medicine for a long while [12].

4. Are the opioids per se the culprit, or is it the way that we treat our patients with opioids?

Safe and effective treatment of opioid-sensitive pain is possible [14] but continues to be a double-edged sword that is difficult to handle [5]. It requires deep pharmacological knowledge, experience, resources, considerable patience, and mental energy from a group of helpers who are able to take care of the whole bio-psycho-social conundrum of the chronic pain patient [5,28]. GPs should not start long-term opioid treatment without being in collaboration with a pain center. Torsten Gørdh’s pain center in Uppsala, Sweden, in collaboration with the addiction medicine department, documented that it is possible to rehabilitate opioid-misusing chronic pain patients back to long-term satisfactory pain relief and quality of life [28]. They accomplish this by converting the failed opioid treatment to methadone, in addition to helping the patients with other aspects of their chronic disease [28].

It is difficult to predict who will eventually develop problematic opioid use. Therefore, all chronic patients with opioid-sensitive pain who are offered long-term opioid treatment must have a strict regimen from day 1: Collaboration with 1 pharmacy, 1 pain management group, with 1 responsible pain specialist (with a stand-in), and with the patient’s general practitioner. Frequent evaluation of effects and adverse effects is mandatory. Opioid therapy must be discontinued as soon as it is clear that lack of pain relief and adverse effects are detrimental to the patient’s health. This is the difficult part of long-term opioid therapy for chronic pain. It is demanding for patients as well as for health care providers. Starting is easy; stopping becomes increasingly difficult with time. The reward system is involved from the first dose; tapering and stopping inappropriate opioid treatment may be difficult already after a few months. This is in part due to withdrawal causing increased pain sensitivity, with break-through pain aggravating the original pain condition. The easy way, when pain relief is not satisfactory, is to escalate the dose. This brings the patients and their health care providers into the “minefield” described by Jørgen Eriksen more than 10 years ago [4,11].

Howard Fields expressed a “glimmer of hope” that we will have safer opioids in the future by combining a MOP-receptor agonist, responsible for analgesia, reward, and addiction, with a DOP receptor antagonist, reducing the undesirable effects while retaining the analgesic effects of the MOP-agonist [12]. There are also ongoing clinical trials with a NOP (nociceptin-orphanin) receptor agonist, cebranopadol, that has a profile of effects different from MOP agonists (www.clinicaltrials.gov). The art of helping chronic pain patients with opioid-sensitive pain has become even more challenging in recent years by the frequent adverse interactions with other drugs that now are commonly prescribed for chronic pain. Still, going back to the intense opiophobic conditions of the 20th century is not possible. Long-term, double-blind, placebo-controlled RCTs on opioid treatment are difficult and costly. However, a 6-month (+1 month follow-up after unblinding) RCT showed that it is possible to maintain blind- ing with opioid doses in a safe and effective dose range [6]. It also showed how the positive “context-sensitive therapeutic effect” continued to have a strong and increasing effect on subjective pain...
from hip and knee osteoarthritis during the entire double-blinded period of half a year [6]. A pharmaceutical company sponsored that study. It is time that our health care authorities sponsor investigator-initiated, large studies to determine the true cost–benefit profile of long-term opioid treatment. Otherwise, we will continue to fumble our way forward, depending on the best possible indirect epidemiological outcome studies, like the Ekholm et al. study reported in this issue of *Pain* [10].

**Conflict of interest statement**

The authors have no conflicts of interest regarding this commentary.

**References**


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