Current knowledge of opioid addiction and relevance to clinical practice

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Review

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

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Here we provide the updated version of the guidelines of the European Association for Palliative Care (EAPC) on the use of opioids for the treatment of cancer pain. The update was undertaken by the European Palliative Care Research Collaborative. Previous EAPC guidelines were reviewed and compared with other currently available guidelines, and consensus recommendations were created by formal international expert panel. The content of the guidelines was defined according to several topics, each of which was assigned to collaborators who developed systematic literature reviews with a common methodology. The recommendations were developed by a writing committee that combined the evidence derived from the systematic reviews with the panellists' evaluations in a co-authored process, and were endorsed by the EAPC Board of Directors. The guidelines are presented as a list of 16 evidence-based recommendations developed according to the Grading of Recommendations Assessment, Development and Evaluation system.

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WHO analgesic ladder: a good concept gone astray

Ballantyne and Kalso, BMJ 2016

"The success of opioid treatment in terminally ill cancer patients set the stage for extending the same moral imperative and treatment principles to the treatment of chronic pain, where previously opioids were considered too risky or not effective"

"Over the past 30 years, in much of the developed world, we have seen more patients treated with opioids at higher doses than ever before. The extent to which the more liberal use of opioids would cause harm was not predicted".

The Washington Post

Post Politics

Trump declares the opioid crisis a public health emergency

By Jenna Johnson and John Wagner

President Trump said Thursday that the opioid epidemic — which is killing more than 100 people each day — is the "worst drug crisis in American history" and said his administration is declaring it a public health emergency, pledging the nation's full resolve in overcoming it.

The opioid epidemic in United States

The Opioid Epidemic in the United States—Overview, Origins, and Potential Solutions

- Approximately 65,000 deaths in 2016, a 21% increase from the previous year
- A 4-fold increase in US opioid analgesics related deaths 1999-2010 associated with a 4-fold increase in opioid prescriptions 1999-2010
- In the same period, admissions for the treatment of substance use disorder increased 6-fold
- The opioid epidemic cost the United States $504 billion in 2015, which represents 2.8% of the nation's total gross domestic product
- The drug manufacturers have paid only $35 billion in fraud settlements out of $711 billion in worldwide net revenue

Identification of the US opioid crisis

Prospective population-based studies have:

1. provided the warnings of opioid-related abuse (> 20%) and deaths in the US
2. demonstrated that the long-term analgesic and health effects of long-term opioid therapy are poor due to
   - lenght of studies
   - mixed population groups
   - variations in practice
   - open environment

Paulozzi et al. Pain Med. 2012; Gomes et al., Arch Intern Med 2011; Dunn et al., Ann Intern Med 2010; Bohnert et al., JAMA 2011; Højsted et al., Pain 2013; Boscarino et al., J Addict Dis 2011.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

The Role of Science in Addressing the Opioid Crisis

Nora D. Volkow, M.D., and Francis S. Collins, M.D., Ph.D.

Opioid misuse and addiction is an ongoing and rapidly evolving public health crisis, requiring innovative scientific solutions. In response, and because no existing medication is ideal for every patient, the National Institutes of Health (NIH) is joining with private partners to launch an initiative in three scientific areas: developing better overdose-reversal and prevention interventions to reduce mortality, saving lives for future treatment and recovery; finding new, innovative medications and technologies to treat opioid addiction; and finding safe, effective, nonaddictive interventions to manage chronic pain. Each of these areas requires a range of short-, intermediate-, and long-term research strategies (Fig. 1).

in blood naloxone levels equivalent to those achieved with parenteral administration; it was approved by the Food and Drug Administration (FDA) in 2015. The NIH will now work with private partners to develop stronger, longer-acting formulations of antagonists, including naloxone, to counteract the very-high-potency synthetic opioids that are now claiming thousands of lives each year.

In the intermediate and longer term, alternative interventions against opioid-induced respiratory depression, such as 5-hydroxytryptamine type 1A (5-HT_{1A}) agonists, ampakines, and phrenic-nerve-stimulation devices, could protect persons at particularly high risk for overdose. Research is also under way to characterize the physiological

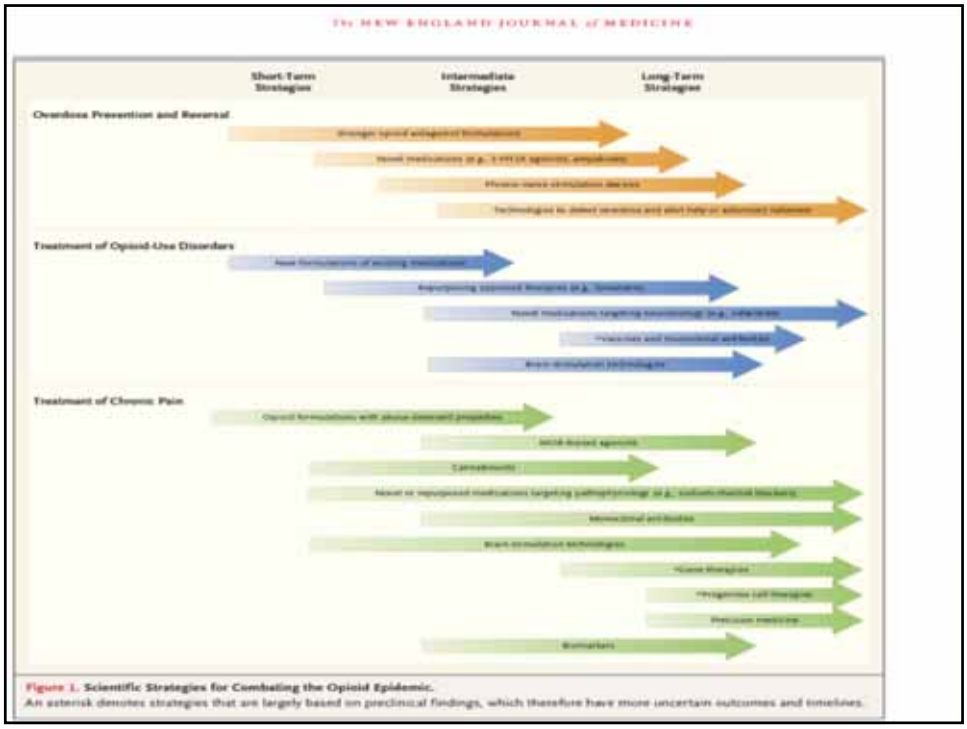

Figure 1. **Scientific Strategies for Combating the Opioid Epidemic.**
An asterisk denotes strategies that are largely based on preclinical findings, which therefore have more uncertain outcomes and timelines.

Opioid consumption: Why Denmark?

- One of the highest per capita comsumption 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

Estimate of opioid users and consumption in Denmark

Based ond three databases:

Numbers of users:

- Acute pain: 55%
- Cancer Pain: 13%
- CNCP: 32%

Consumption:

- Acute pain: 1%
- Cancer pain: 30%
- CNCP: 69%

The Board of Health estimated that 170.000 CNCP patients used opioids regularly (more than one prescription in 6 months) in 2017.
A decline of 14.000 since 2015 has been noted.

Jarlbaek et al., Ugeskr Læg 2010; The Board of Health Opioid Report 2016

The Danish Health and Morbidity Surveys

The Danish Health and Morbidity Surveys have been carried out in 1987, 1994, 2000, 2005, 2010, 2013 and 2017

The purpose is to describe and monitor the status and trends in health and morbidity in the adult Danish population

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?”

PAIN

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www.elsevier.com/locate/pain

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 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 fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity.

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

Conclusions from Danish Health and Morbidity Surveys

Long-term/regular opioid use in 4-5% of the Danish population was associated with reporting:

- High pain intensity, low functional capacity and poor quality of life
- Poor self-rated health and sleep
- Enhanced smoking behavior
- Lower odds of recovery from chronic pain
- Higher risk of all-cause mortality
- Higher risk of injuries and poisoning resulting in hospital admissions
- Lack of/low sexual desire

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; Kurita et al., Pain 2012; Ekholm et al., Pain 2014; Birke et al., Eur J Pain 2017 ; Birke et al., Pain Med 2018.

Critical issues on opioids

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

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

Eriksen et al., Pain 2006; Manchikanti et al., Pain Physician 2012; Dowell et al. MMWR Recomm 2016

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

Højsted et al., Pain 2013

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

Conclusion:

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

*Long-term users: individuals who in the previous year have used at least one prescription/month for six months.

The role of benzodiazepines in opioid treatment of CNCP

- Studies from Norway, the United States, and Denmark have consistently showed that persistent opioid use is strongly associated with co-medication of BZD
- Additionally, strong association between high doses of opioid and high doses of concurrent use of BZD has been demonstrated

Skurtveit et al., Pain Med 2010; Morasco et al., Pain 2010; Melbye et al., Acta Anaesthesiol Scand 2012; Fredheim et al., Pain 2013; Birke et al., Acta Anaesthesiol Scand 2016.

Other concepts and definitions surounding opioid addiction

- Psychological dependence
- Opioid abuse
- Opioid dependence
- Aberrant opioid behaviour
- Problematic opioid use
- Pharmaceutical opioid use disorder
- Chemical coping

Addiction - ICD - 10

A cluster of behavioral, cognitive and physiological phenomena, which may develop after repeated substance use and that typically include:

- A strong desire to take the drug
- Difficulties in controlling its use
- Persisting in its use despite harmful consequences
- A higher priority given to the drug use than to other activities and obligations
- Increased tolerance
- Sometimes a physical withdrawal state

WHO, 2003

Addiction – Portenoy's criteria

Addiction is a psychological and behavioural syndrome characterized by

- Evidence of psychological dependence
  - (A) An intense desire for the drug and (B) overwhelming concern about its continued availability
- Evidence of compulsive drug use
  - Unsanctioned dose escalation
  - Continued dosing despite significant side effects
  - Use of drug to treat symptoms not targeted by therapy
  - Unapproved use during periods of no symptoms
- Evidence of other aberrant drug-related behaviours
  - Manipulation of the treating physician or medical systems for the purpose of obtaining additional drugs (ex. altering prescriptions)
  - Acquisitions of drugs from other medical or non-medical sources
  - Drug-hoarding or sales
  - Unapproved use of other drugs (sedatives, hypnotics) or alcohol

Portenoy, JPSM 1990

Prevalence of opioid addiction in a multidisciplinary pain centre

252 patients with chronic pain (235 non-cancer, 17 cancer) were screened for addiction ICD-10 and Portenoy's criteria (PC) by the treating physician and nurse and filled in the Pain Medication Questionnaire (PMQ). 74% were treated with opioids.

Prevalence of addiction to opioids:
- ICD-10: 14.4%
- PC: 19.3%

Inter-rater agreement:
- ICD-10: 95%
- PC: 93%

PMQ (response rate 78%):
- PMQ had acceptable construct and criterion validity and high reliability
- Patients in the high-risk group used higher opioid doses, drank more alcohol, smoked more tobacco, used more benzodiazepines and displayed more anxiety and depression than those in the low risk group

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

Prevalence of opioid and medicinal cannabis addiction in two multidisciplinary pain centers

888 patients with chronic pain were screened for addiction using among other instruments DSM-IV and PC. Response rate was 57%. Opioid treatment: 53.4%; MC-treatment: 37.3%; Mixed treatment: 8.7%.

Prevalence of addiction to opioids:
- DSM-IV: 52.6%
- PC: 17.3%

Prevalence of addiction to MC:
- DSM-IV: 21.2%
- PC: 10.6%

Problematic use of opioids and cannabis was more common in individuals using medications for longer periods of time, reporting higher levels of depression and anxiety, and using alcohol or drugs.

Feingold et al., Pain Med 2017

Predicting the risk for aberrant opioid use behavior in patients receiving outpatient supportive care consultation at a comprehensive cancer center

751 opioid treated patients with cancer referred to supportive care were screened with SOAPP-14 and CAGE-AID for aberrant drug behaviour (ADB). Response rate was 97%.

Prevalence of ADB :

- SOAPP-14: 19.6%
- CAGE-AID: 10.5%

Men and patients who have anxiety, financial distress, and a prior history of alcoholism/illicit drug use are at increased risk of ADB.

Yennurajalingam et al., Cancer 2018

Tapering off opioids in chronic non-cancer pain (CNCP) and cancer patients

Studies	Design	Patients and treatments	Intervention	Assessments	Outcomes
Sullivan et al., J Pain 2017	RCT	CNCP patients (N=35). Oral opioids.	CBT program plus 10% opioid dose reduction per week; however, pausing the taper was allowed. Control: Usual care.	Baseline and 22 and 34 weeks after randomization. Measures: Pain, abuse, health, anxiety, sleep and QoL	The intervention: Improved self-reported pain interference and decreased prescription opioid problems at 22 weeks.
Kurita et al., Eur J Pain 2018	RCT	CNCP patients (N=75; N=35). Oral opioids.	Phase 1: Stabilization of opioid dose Phase 2: 10% opioid tapering of opioid dose every 1-2 weeks until discontinuation up to 6 months. Control: Stabilization opioid treatment	Phase 1: Months Measures: cognitive function, pain, sleep, rest, quality of life, depression, anxiety, opioid misuse and opioid withdrawal symptoms	Phase 1: Improved psychomotor function, sleep, opioid withdrawal symptoms, QoL and misuse scores. Phase 2: Improved sleep.
Arthur et al., The Oncologist 2018	Controlled study	Cancer patients with aberrant opioid-related behavior (AB) (N=30) vs patients without AB (N=70).	The Compassionate High Alert Team (CHAT)	Observation period 3 months Measures: Number of AB, opioid use, ESAS, Memorial Delirium Assessment Scale and CAGE-AID score.	The intervention: Reduced number of ABs and opioid use.

Over-all conclusions and future directions

- Substantial risks of addiction/problems in chronic pain patients treated with long-term opioids
- Further development and validation of instruments to identify problematic opioid use
- Use and implementation of guidelines for responsible opioid prescribing:
  - Dowell et al. CDC guideline for prescribing opioids for chronic pain. JAMA 2016
  - 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. www.cfpc.ca/2017-canadian-opioid-prescribing-guideline
  - The Norwegian Directorate of Health. National recommendation for opioid treatment for chronic non-cancer pain [Internet]. [cited 2016 Sep 1]. Available from: https://helsedirektoratet.no/retningslinjer/opioider
- More research in opioid addiction in cancer: Curatively intended therapy, palliative care and cancer survivors

A research agenda

Projects:

1) The association between long-term opioid use, morbidity, mortality, life style behavior and use of health care services in a Danish population
   - Cohorts of CNCP patients from 2010 and 2013
   - Postoperative initiation/maintenance of long-term opioid use

2) Iatrogenic opioid addiction in patients with cancer and non-cancer chronic pain
   - Prevalence of opioid addiction by the PMQ among opioid treated patients with CNCP and cancer-related pain
   - Associations between genetic variations and addiction risk
   - Test an opioid taper off program in a pilot group

3) The immune and endocrine systems in CNCP pain patients treated with long-term opioids: effects on cognition, pain and QoL
   - Explorative comparison study

Reflections on pain management with opioids

- A pandemic lack of availability and accessibility of opioids for patients with advanced cancer!
- Those CNCP patients who benefits from long-term opioid treatment!
- Opiophobia and regulatory restrictions contribute to undue suffering for millions!
- Too liberal use of opioids cause harm to millions!

Carmona-Bayonas et al., Clin Transl Oncol 2017