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Division of Pharmacy Practice & Policy

The rise and fall of opioids

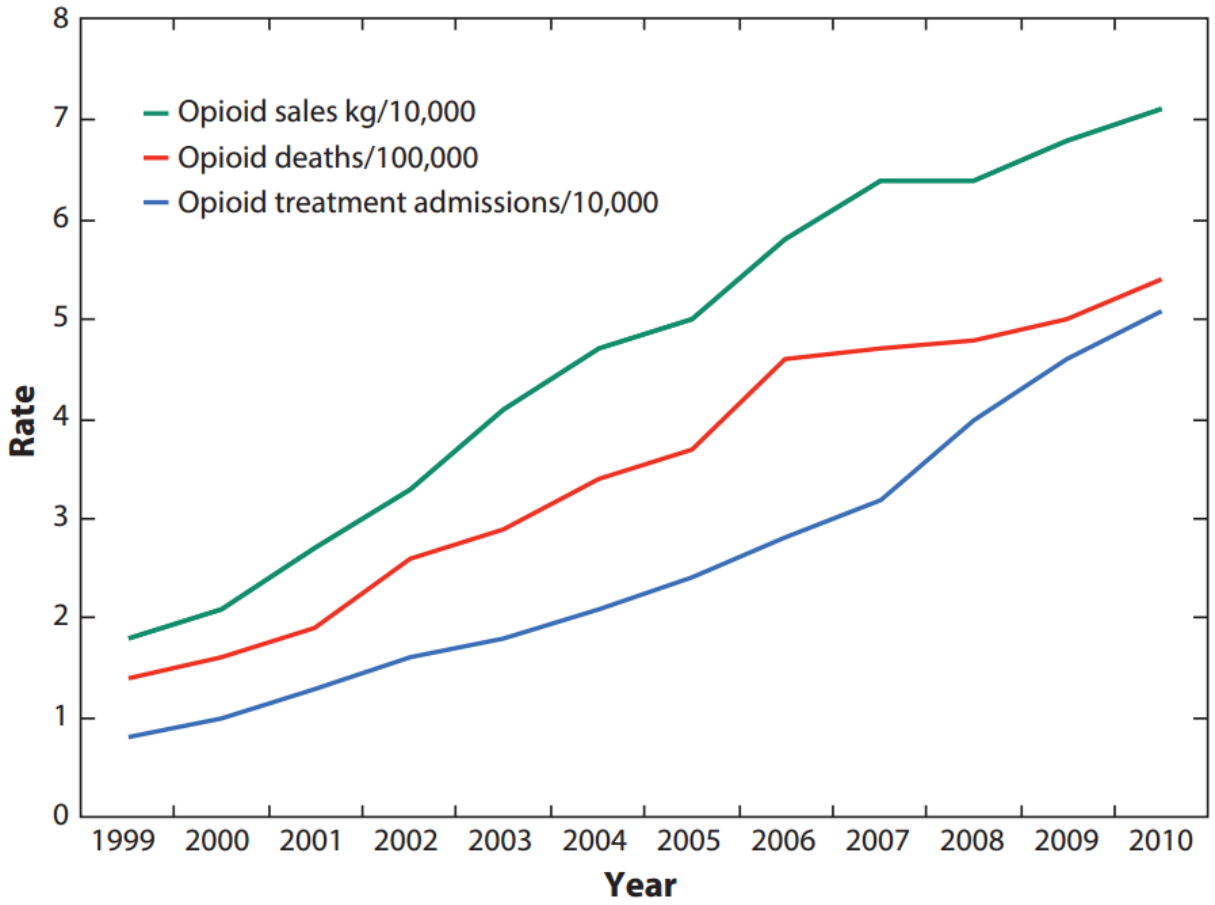
Palliative Care Advanced Course

June 2018

Overview

- Why we are where we are?
- Prescribing trends
- Opioid effectiveness for long-term pain
- Opioid harms
  - Pyschiatric comorbidities
  - Misuse
  - Addiction
  - Mortality
- Deprescribing

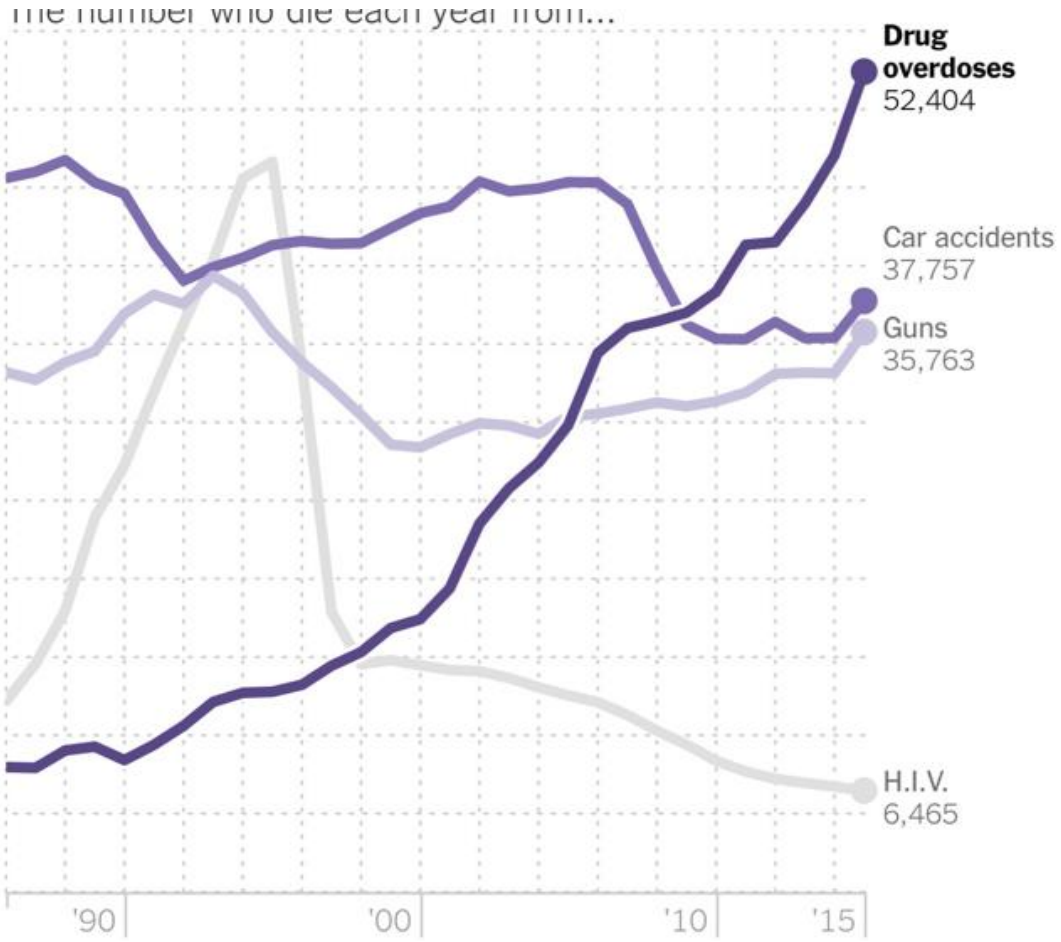
Impact of opioid prescribing



Rates of opioid pain reliever overdose death, treatment admissions and kilograms sold - United States, 1999-2010. Morbidity and mortality weekly report (MMWR). Centers for Disease Control and Prevention.

Mortality in the US

Since 1990, the number of Americans who have died every year from

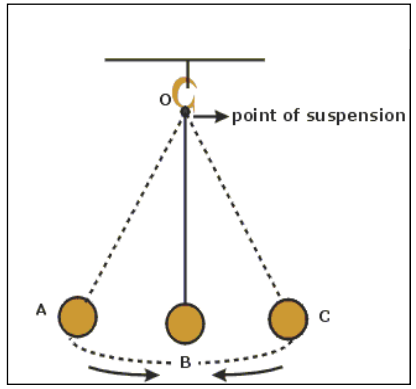


New York Times. 14 April 2017.

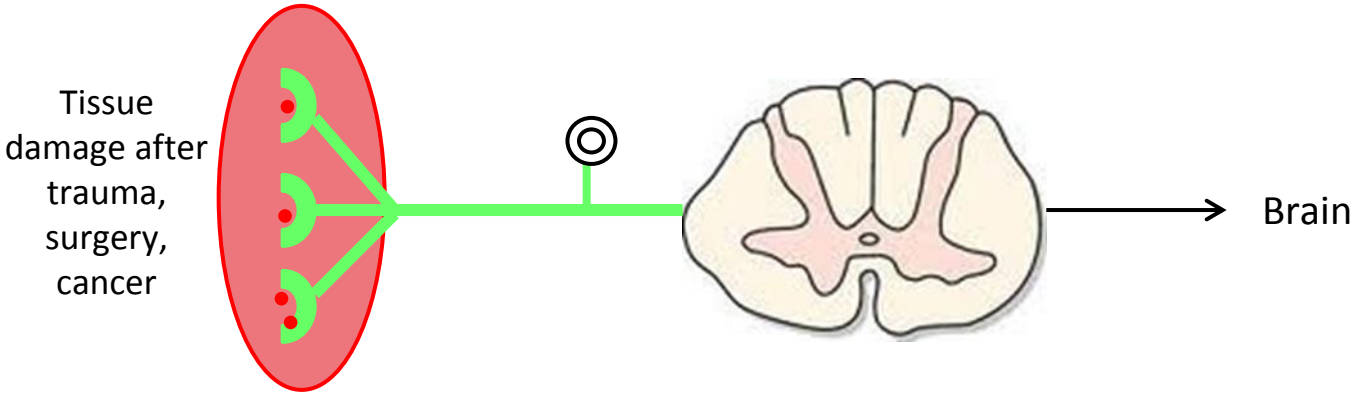
A public health emergency

History (the short version)

- Mid 1980's cancer patients dying in pain
- Late 1990's pain relief as a universal human right
  - role of Pharma and patient advocacy groups
- Undertreatment of pain seen as malpractice
- Pain as 5th vital sign
- Small trials showing efficacy of opioids in non-cancer pain
- Early 2000's escalation of opioid prescribing paralleled by misuse, diversion and deaths
- Recognition of limitations of trial data
- Systematic reviews of efficacy
- Recognition of dose related harms



Acute and cancer pain



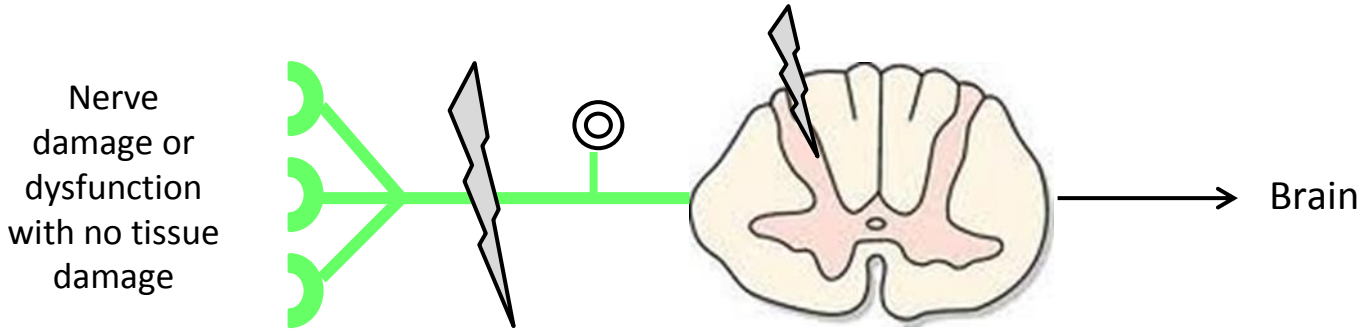
- Appropriate pain reflecting ongoing tissue damage

- Treatment includes
  - Paracetamol
  - NSAIDs
  - **Opioids**

- Opioids are an effective and important part of acute and cancer pain management

- After surgery and trauma, opioids must be weaned and stopped as inflammatory processes cease and pain decreases (**within 3 months**)

Persistent pain

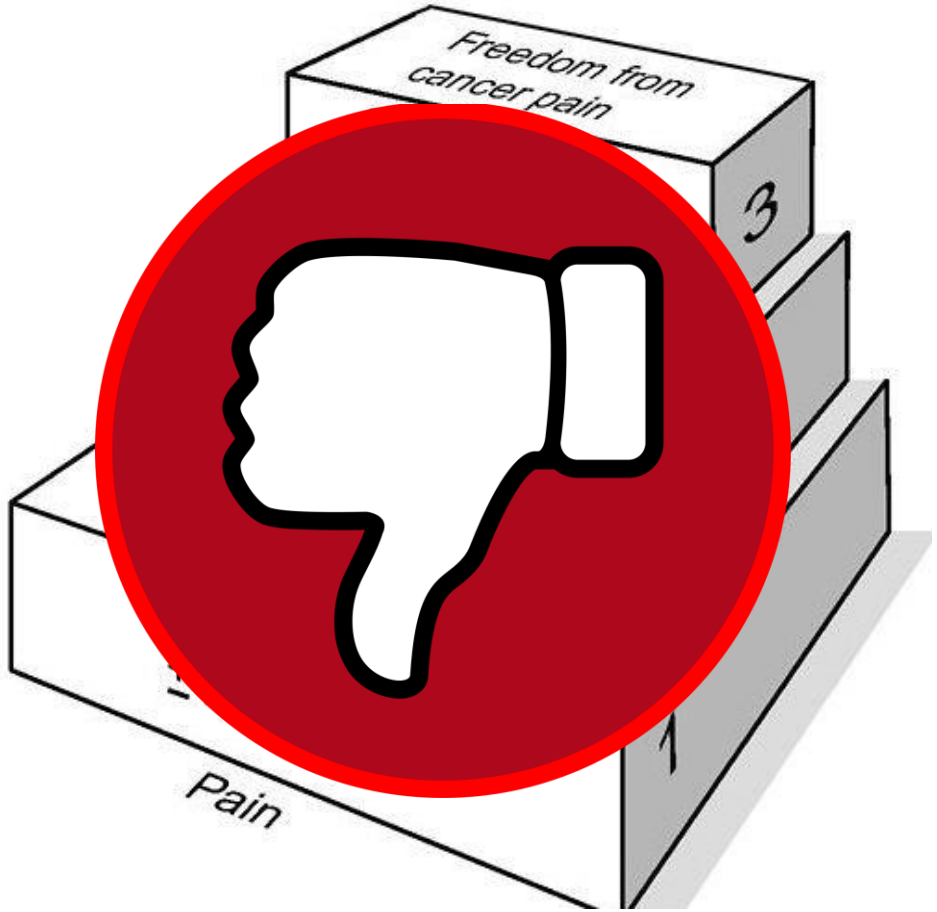


- Disease or damage of the somatosensory system
- Inappropriate response with no tissue injury
- Pain continues despite healing with ongoing pain signalling

- Treatment includes:
  - Drugs to reduce nerve excitability
  - Physiotherapy to increase mobility
  - Psychological support for help with associated anxiety and depression
  - Emphasis on self management and living with the chronic pain

- **Opioids are neither safe nor effective for the majority of patients with chronic pain**

WHO analgesic ladder

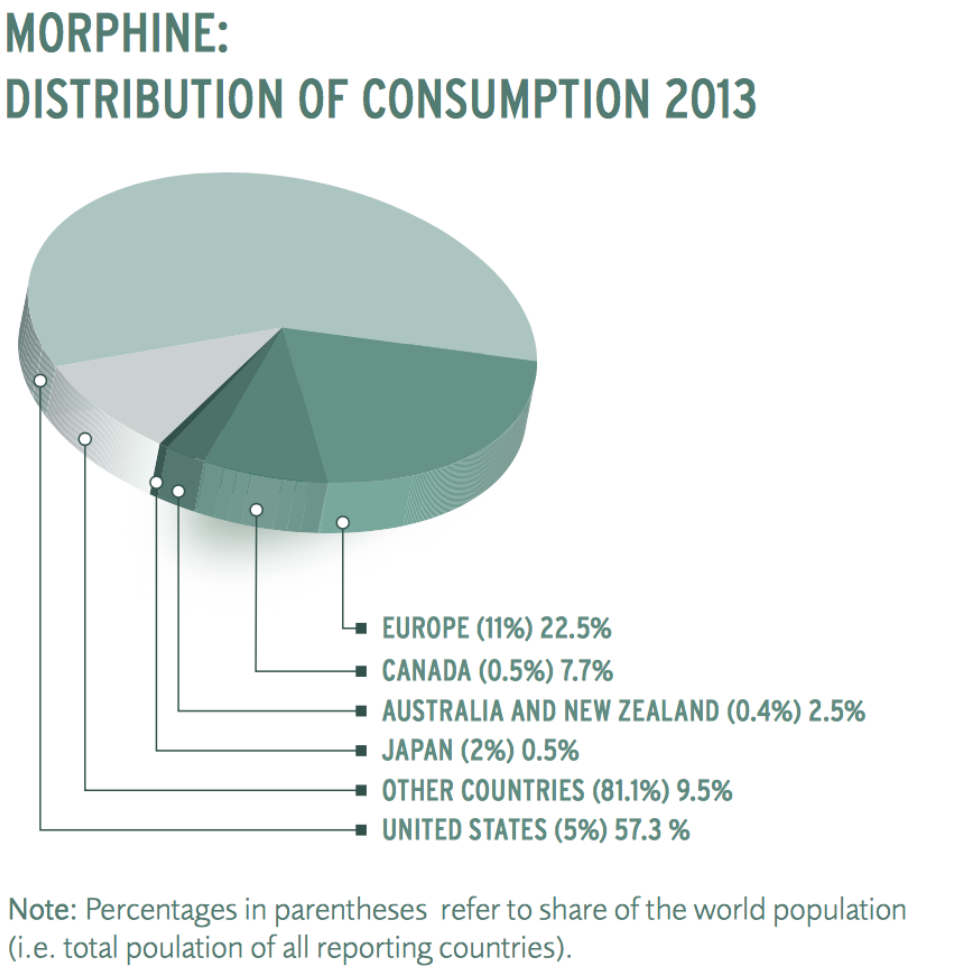


World Health Organisation 1986

Balancing undersupply and overconsumption

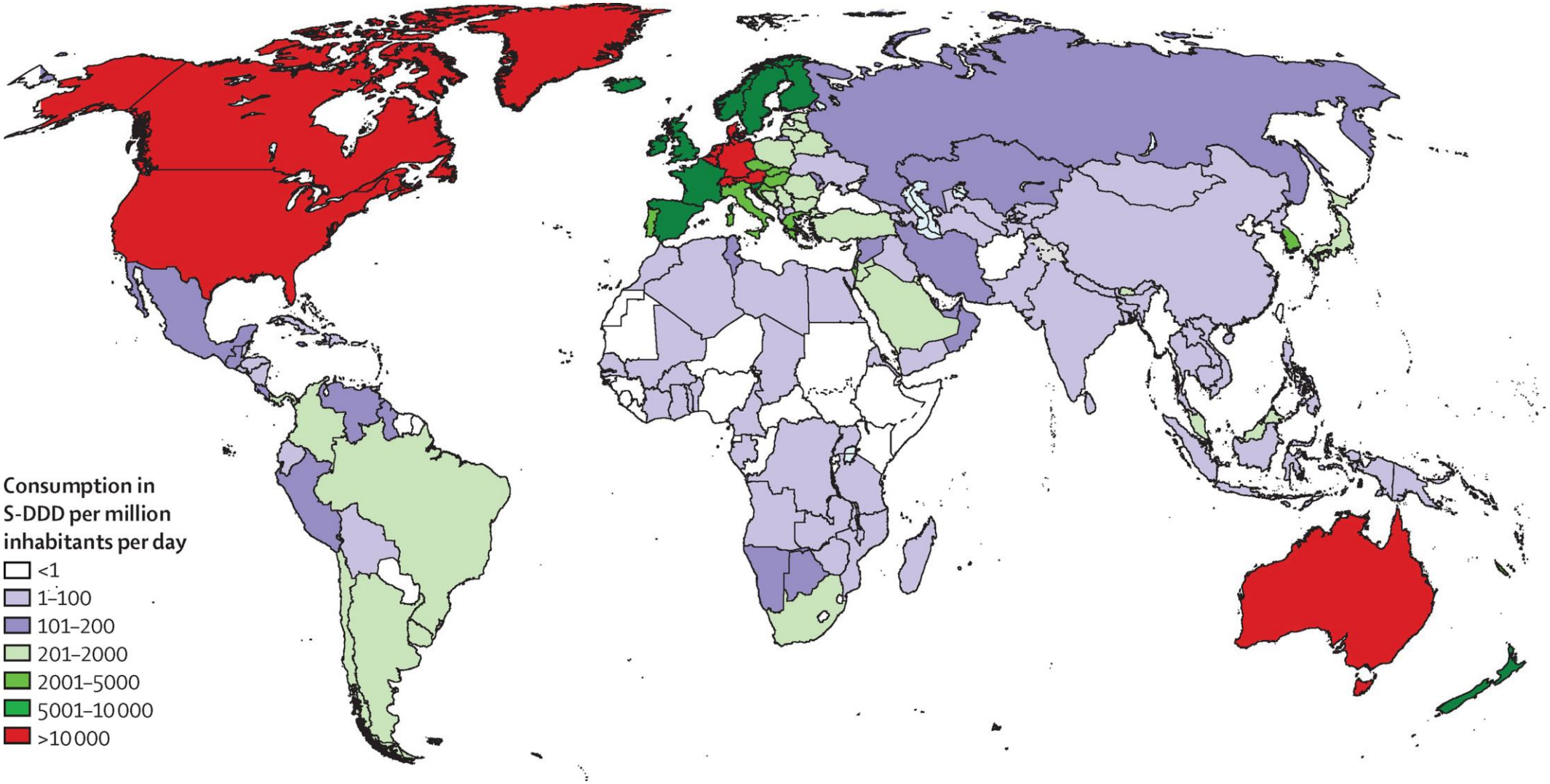
- Over 75% of the world's population (over 5.5 billion) have poor-to-nonexistent access to adequate analgesics, in particular morphine

- Just 17% of the entire population, mostly in northern countries, consume 92% of the global supply



Global Commission on Drug Policy. The negative impact of drug control on public health: The global crisis of avoidable pain. 2015.

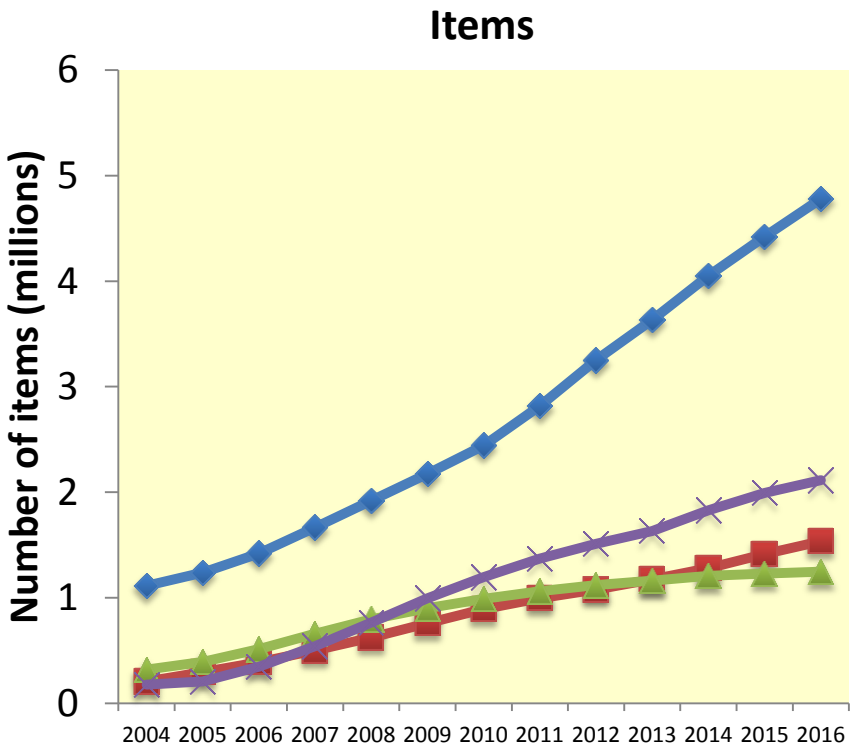
Balancing undersupply and overconsumption

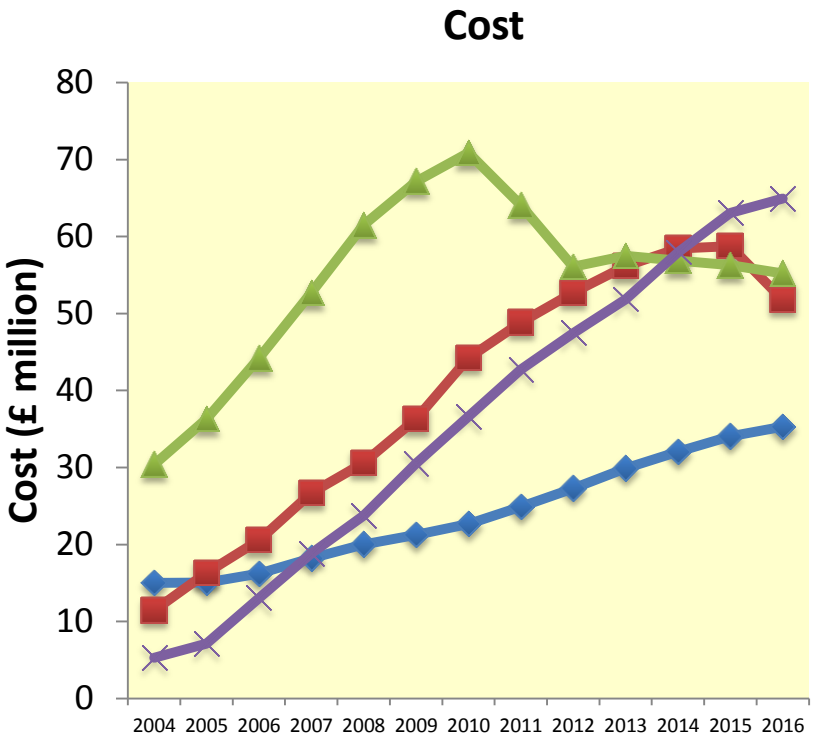


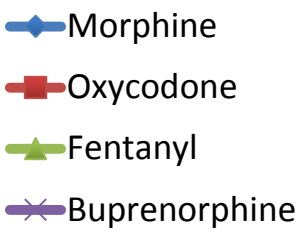
Berterame S, et al. Lancet 2016; 387: 1644-1656.

Opioid prescribing in the UK

- In 2016, 23.9 million prescriptions were dispensed in England costing £292.1 million







BNF classification 4.7.2 (opioid analgesics)
Compiled from Prescription Cost Analysis. NHS Digital (formerly Health and Social Care Information Centre.

How many patients are prescribed opioids?

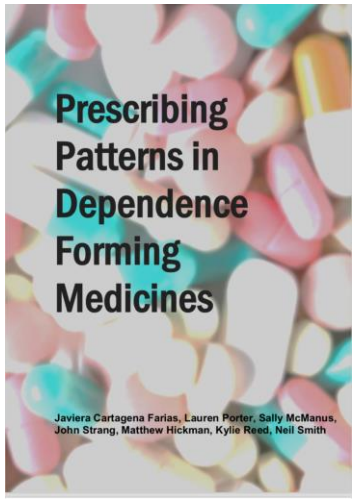
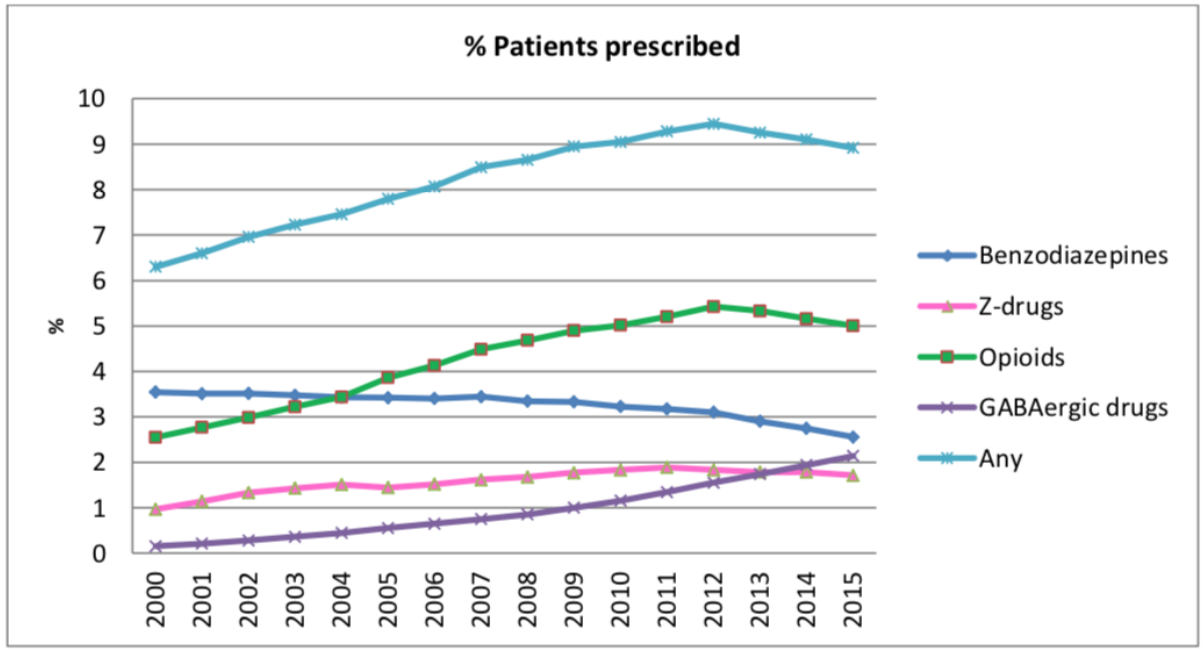


Figure 6.1: Proportion of patients prescribed benzodiazepines, Z-drugs, opioids, GABAergic medicines, and any of these drugs, 2000 to 2015



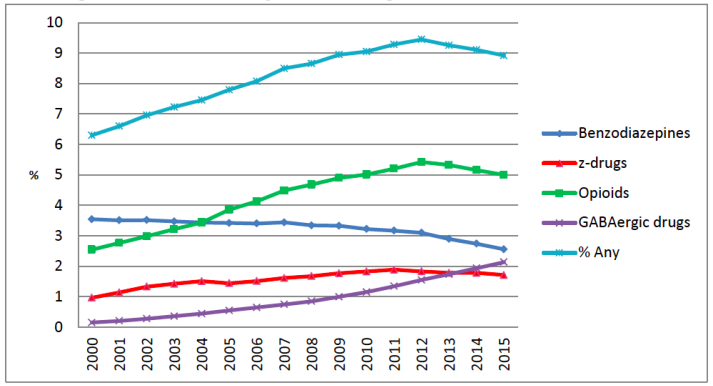
Source: CPRD. Figures presented in Appendix 3. Base: 15.8 million patients.

Cartagena Farias J et al. Prescribing patterns in dependence forming medicines. 2017. London: NatCen.

Duration of opioid prescribing

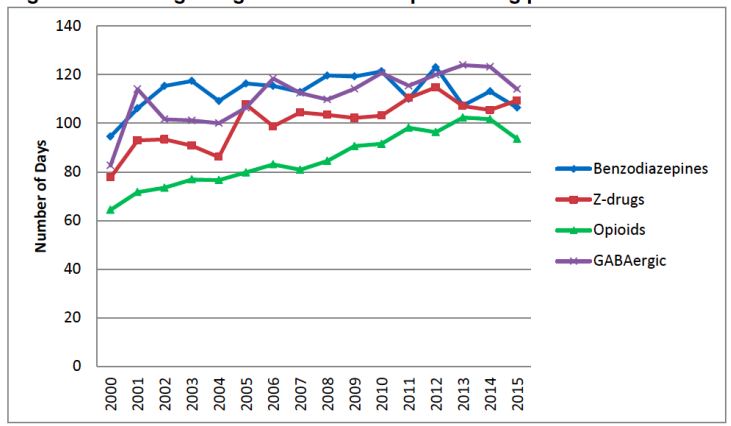
- CPRD between 2000 and 2014
- Opioids
  - Length of continuous prescribing increased
    - 2000: 64 days
    - 2014: 102 days
- Dependence forming medicines prescribed for longer in areas of deprivation

Figure 1.1: Proportion of patients prescribed benzodiazepines, Z-drugs, opioids, GABAergic medicines, and any of these drugs, 2000 to 2015

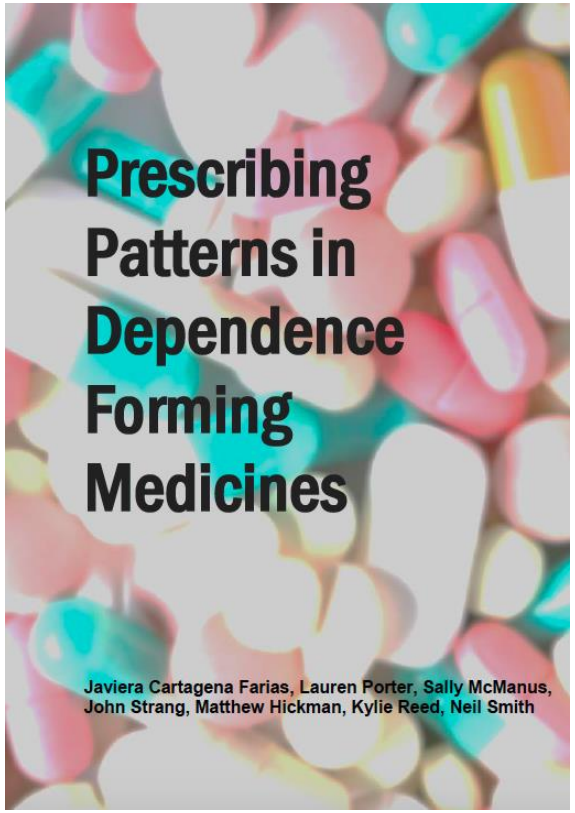


Source: CPRD. Figures presented in Appendix 3. Base: 15.8 million patients.

Figure 1.3: Average length of continuous prescribing periods

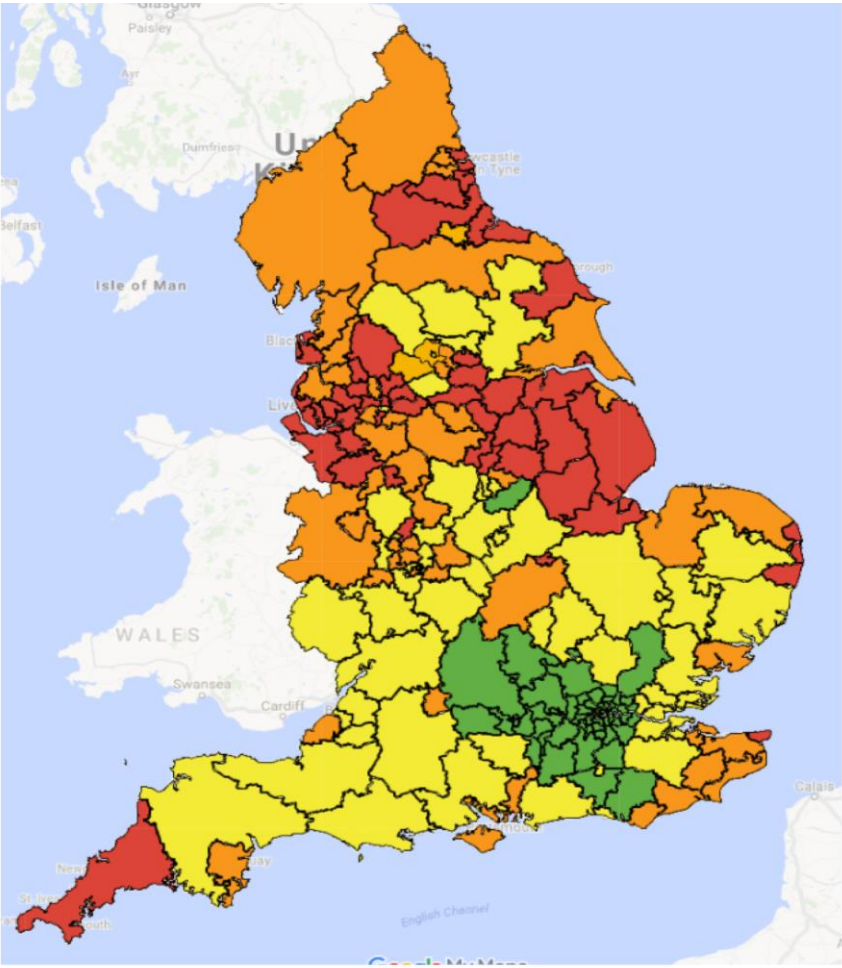


Source: CPRD (see Appendix 6).



Cartagena Farias J et al. Prescribing patterns in dependence forming medicines. 2017. London: NatCen.

Regional variation in opioid prescribing

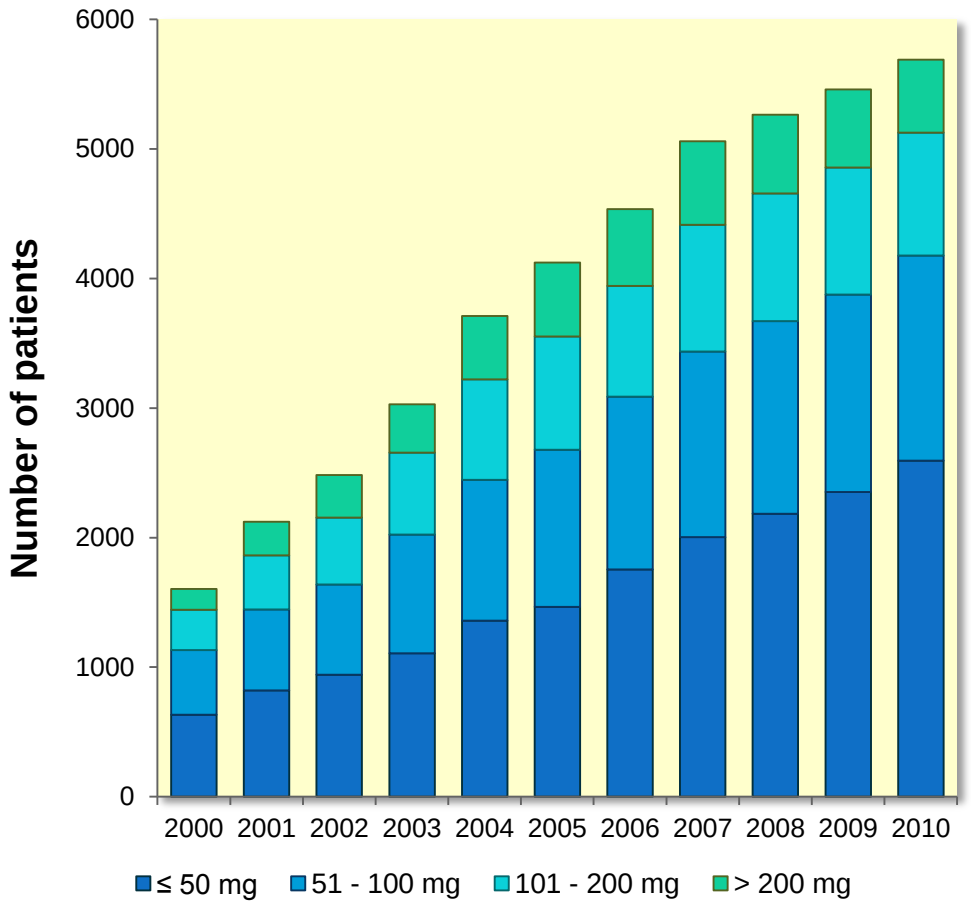


	Upper (fourth) quartile – Opioid DDD per 1000 inhabitants per year > 18,775.57
	Third quartile – Opioid DDD per 1000 inhabitants per year 14,414.95 – 18,775.57
	Second quartile – Opioid DDD per 1000 inhabitants per year 10,726.82 – 14,414.95
	Lower (first) quartile – Opioid DDD per 1000 inhabitants per year < 10,726.82

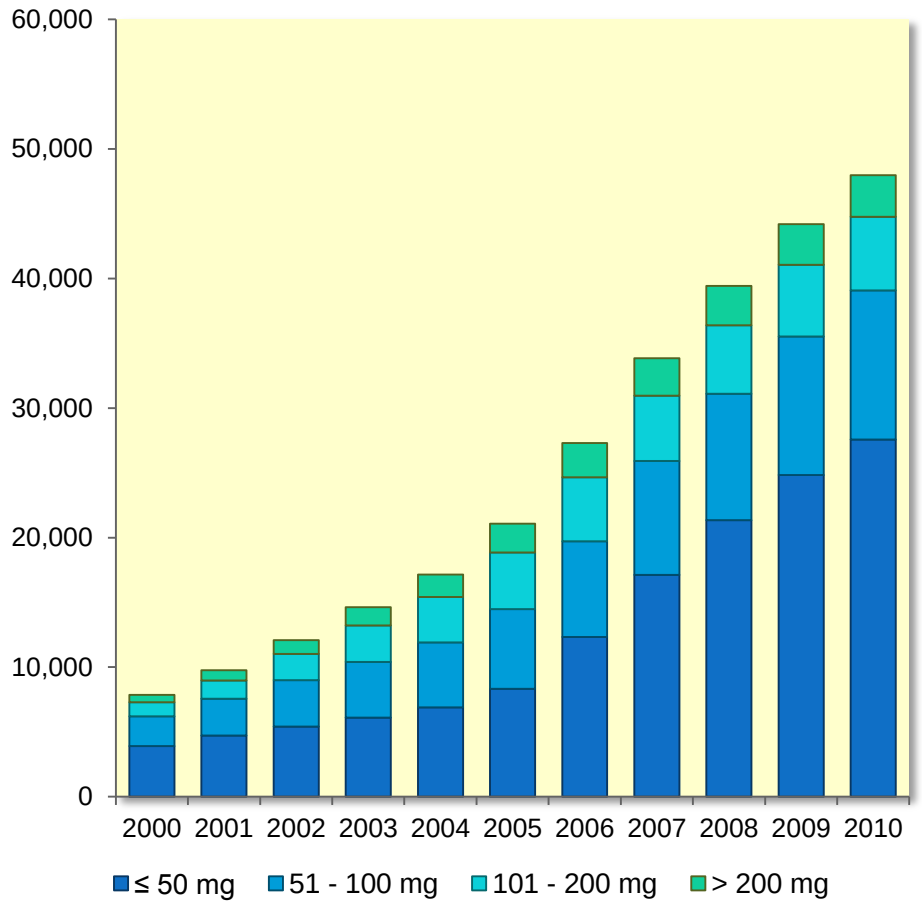
Chen T-C et al. Int J Drug Policy Submitted.

Opioid doses in the UK

Cancer



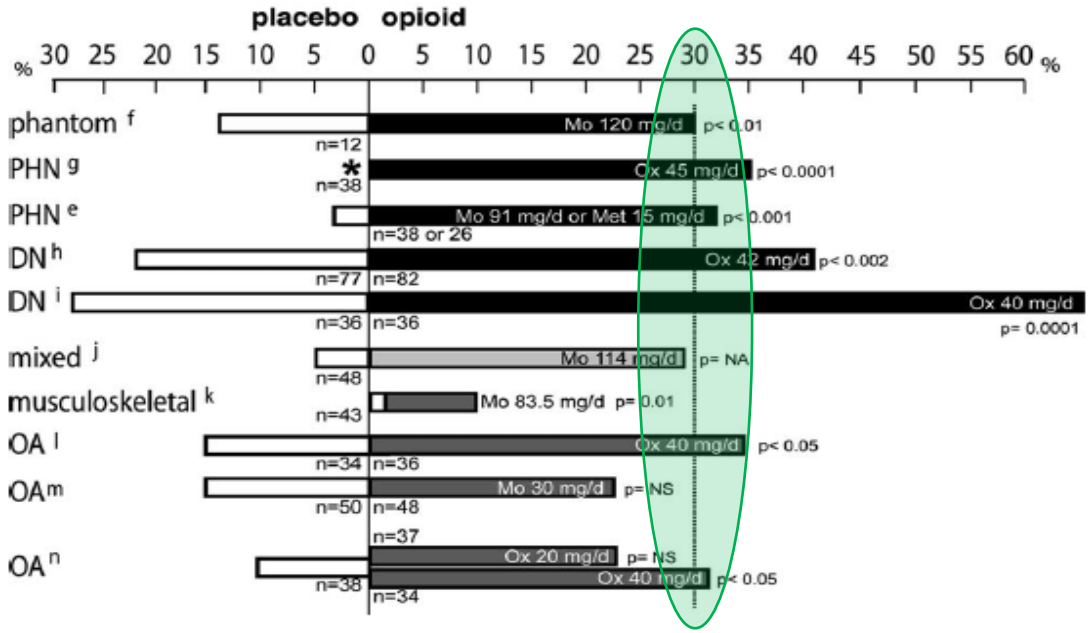
Non-cancer



Zin CS et al. Eur J Pain 2014; **18**: 1343.

Opioid effectiveness

- Opioids are very good analgesics for acute pain and for pain at the end of life but there is little evidence that they are helpful for long-term pain



- No study of opioid therapy versus placebo, no opioid therapy, or non-opioid therapy evaluating long-term (>1 year) outcomes related to pain, function, or quality of life

Kalso E *et al*. *Pain* 2004; **112**: 372. Chou R *et al*. *Ann Intern Med* 2015; **162**: 276.

REVIEW
Annals of Internal Medicine

The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop

- No evidence relating to:
  - different dosing strategies
  - short versus long acting
  - continuous versus as needed
  - opioid rotation

- Dose dependent risk for serious harms

- Increased risk of:
  - Sexual dysfunction [OR 1.45 (CI -1.87)]
  - Fractures [OR 1.27 (CI 1.21-1.33)]
  - Myocardial infarction [OR 1.28 (CI 1.19-1.37)]
  - Abuse [wide range – up to 37%]
  - Overdose [HR 5.2 (CI 2.1-12.5)]
  - Motor vehicle accident [OR 1.24-1.42]

Chou R *et al*. *Ann Intern Med* 2015; **162**: 276.

Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain

The SPACE Randomized Clinical Trial

- 12-month pragmatic randomised clinical trial (n = 240 patients)
- Compared the use of opioid vs nonopioid treatment for LBP and OA

- No improvement in pain-related function over 12 months (3.4 vs 3.3 points on an 11-point scale at 12 months, respectively)

- Pain intensity was significantly better in the nonopioid group over 12 months (mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5 [95% CI, 0.0 to 1.0])
- medication-related adverse symptoms were significantly more common in the opioid group over 12 months (overall $P = 0.03$)

Krebs EE, Gravely A, Nugent S, et al. JAMA. 2018;319(9):872–882.

Opioids in trials and in practice

- Finite duration
- Selected populations
- Discrete diagnoses
- Closely supervised and supported
- Active management of side effects
- Rescue medicines as necessary

Long-term opioids and outcomes

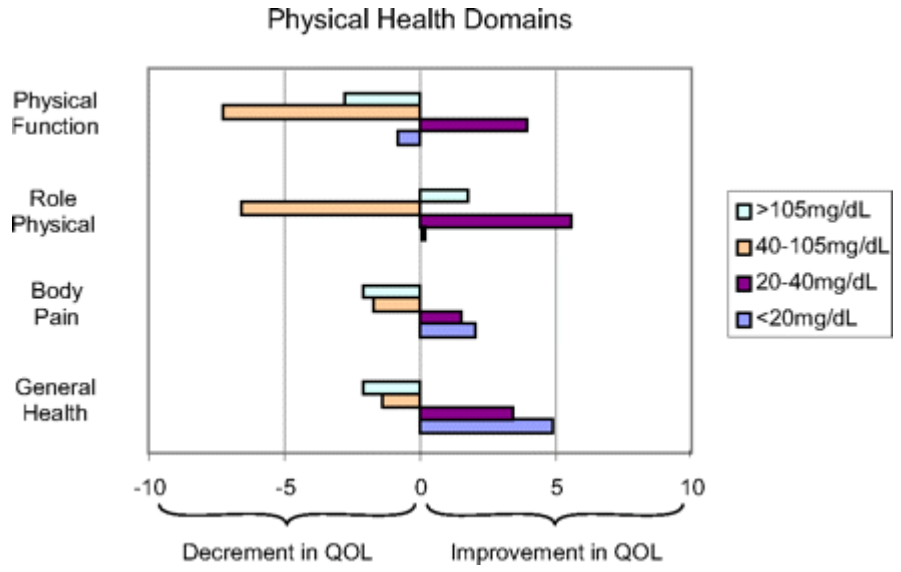
- 228 opioid users compared with 1,678 non-opioid users

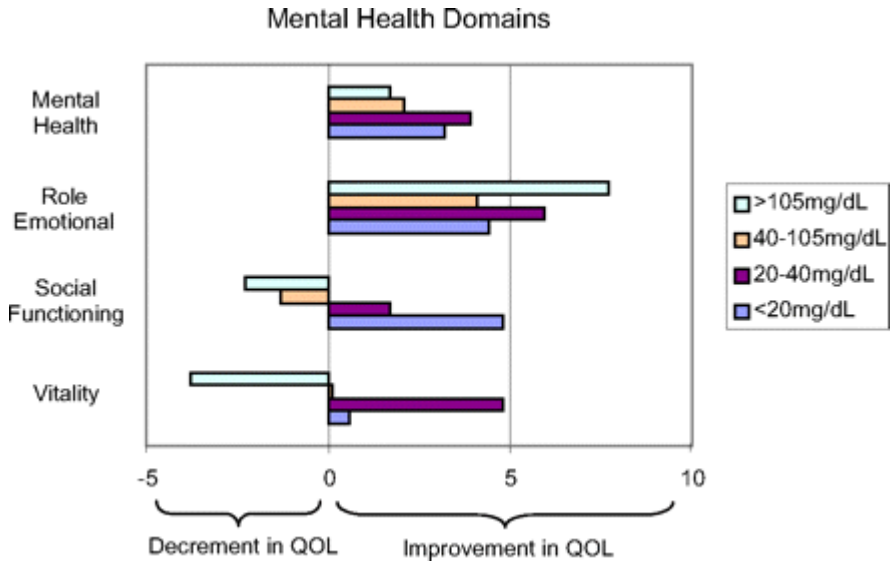
- Opioids usage significantly associated with:
  - reporting of severe pain
  - poor self-rated health
  - inactivity during leisure
  - unemployment
  - higher healthcare utilization
  - poor health orientated quality of life

Eriksen et al. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. Pain, 2006;125:172-9

QoL associated with opioid therapy in primary care

- 801 daily opioid users vs 93 non-opioid chronic pain patients from the practices of 235 PCPs, divided into low, moderate and high-dose groups
- Propensity score adjusted difference in SF-36 physical and mental health domain scores vs. non-opioid users





Dillie et al. J Am Board Fam Med 2008;21:108-17

Psychiatric co-morbidities

- Patients with mood disorders more likely to be started on opioid treatment than those without
- Patients with depression almost twice as likely to continue taking those opioids long term
- Opioids being used to treat insomnia and stress – symptoms accompanying chronic pain – rather than the pain itself
- Dysregulation of the endogenous opioid system in borderline personality disorder, depression, stress

Halbert B, Davis R, Wee CC. Pain 2016;157:2452. Sullivan MD. Pain 2016:157:2395. Prossin AR, Love TM, Koeppe RA et al. Am J Psychiatry 2010;167:925.

Comprehensive Review
PAIN

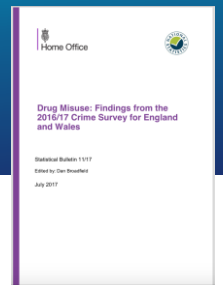
Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis

Kevin E. Vowles[a,*], Mindy L. McEntee[a], Peter Siyahhan Julnes[a], Tessa Frohe[a], John P. Ney[b], David N. van der Goes[c]

- Problematic use ranged from < 1 – 81%
- Misuse
  - 21 – 29% (95% CI 13 – 38%)
- Addiction
  - 8 – 12% (95% CI 3 – 17%)

Vowles K et al. Pain 2015; 156: 569 – 576.

Crime Survey for England and Wales 2016-17



- In the last year 7.6% of adults aged 16 to 59 years had taken a prescription-only painkiller not prescribed to them for medical reasons
- Only 0.2% said it was just for the feeling or experience it gave them

- 83% reported not having taken another drug in the last year, suggesting that those who misuse painkillers do not tend to use other drugs. This is in contrast with users of NPS, of whom the majority (74.5%) had used another drug in the last year

- Use of non-prescribed prescription-only painkillers for medical reasons **decreases as life satisfaction increases**;
  - 12.5% of those with low levels of life satisfaction reported use in the last year, compared with 6. % of those with very high levels of life satisfaction
  - Over twice as many people with a long-standing illness or disability reported use of non - prescribed prescription-only painkillers for medical reasons (13.9%) compared with those with no long-standing illnesses (6.5%)

Drug Misuse: Findings from the 2016/17 Crime Survey for England and Wales.

Common misconception: Addiction thought to be rare

ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER
HERSHEL JICK, M.D.
Boston Collaborative Drug Surveillance Program
Boston University Medical Center
Waltham, MA 02154

1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

Porter J, Jick H. New Engl J Med 1980; 302:123.

Retraction July 2017

Retraction Watch

Tracking retractions as a window into the scientific process

NEJM issues unusual warning for readers about 1980 letter on opioid addiction

with 12 comments

This week, the *New England Journal of Medicine* issued a type of editor's note we've never seen before, on a highly influential letter published nearly 40 years ago.

Above the one-paragraph letter, which reports data suggesting pain medications are not likely to cause addiction, the journal has added a note warning readers that the letter has been "heavily and uncritically cited" by sources using it to suggest opioids are not addictive.

In essence, the journal isn't commenting on the merits of the letter — the problem is how it's been used by others.

The same issue of the journal includes a letter by researchers based in Canada who analyzed how the 1980 letter had been cited, noting:

> In conclusion, we found that a five-sentence letter published in the *Journal* in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy…Our findings highlight the potential consequences of inaccurate citation and underscore the need for diligence when citing previously published studies.

Pages

- Help us: Here's some of what we're working on
- How you can support Retraction Watch
- Meet the Retraction Watch staff
  - About Adam Marcus
  - About Ivan Oransky
- The Center For Scientific Integrity
  - Board of Directors
- The Retraction Watch FAQ, including comments policy
  - The Retraction Watch Transparency Index
- The Retraction Watch

http://retractionwatch.com/2017/06/02/nejm-issues-unusual-warning-readers-1980-letter-opioid-addiction/

IASP
PAIN® 154 (2013) 2677–2683
PAIN®
www.elsevier.com/locate/pain

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

Jette Højsted [a,*], Ola Ekholm [b], Geana Paula Kurita [a,c], Knud Juel [b], Per Sjøgren [c,d]

- Six potential addictive behaviours
  - daily smoking
  - high alcohol intake
  - illicit drug use
  - obesity
  - long-term BDZ use
  - long-term BDZ-like drug use

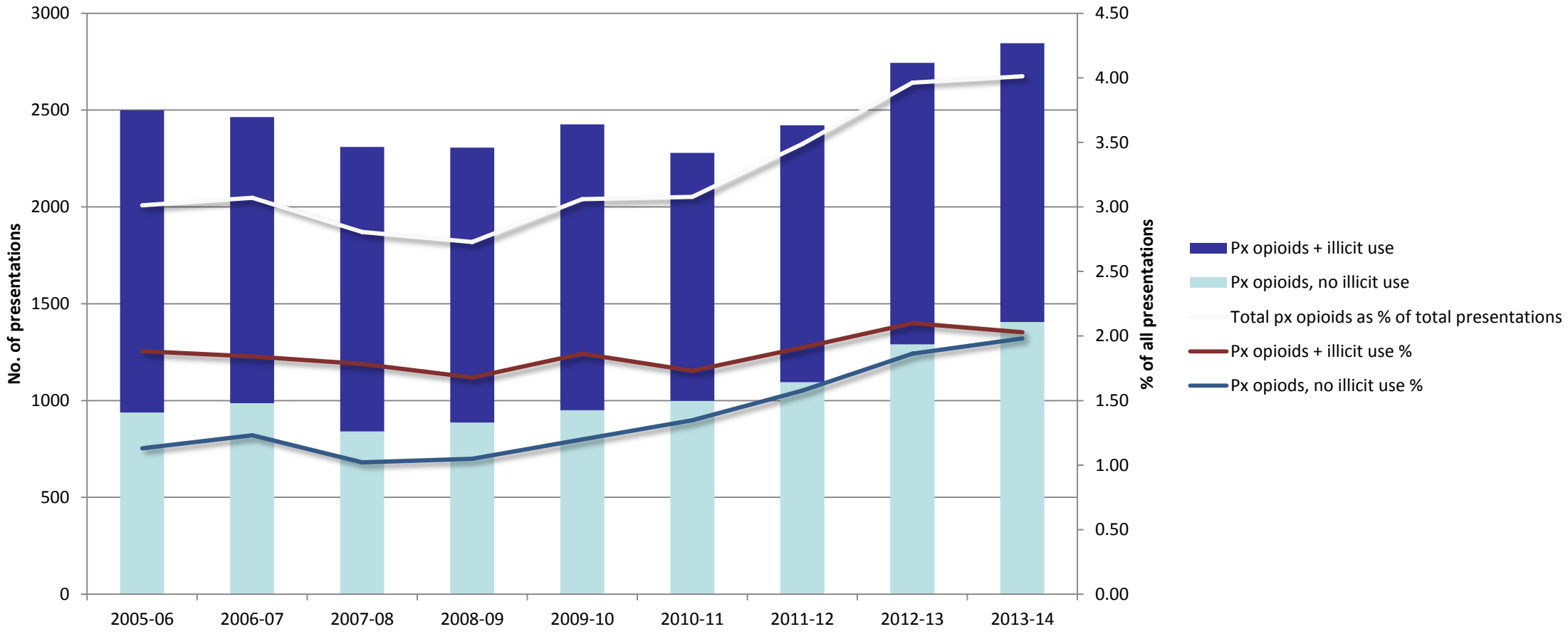
At least two behaviours

- 22.6 % long-term opioid users
- 11.5 % chronic pain but not taking opioids
- 8.9% individuals without chronic pain

Thus, a strong association was demonstrated between long-term opioid use and the clustering of addictive behaviors. An intricate relationship between chronic pain, opioid use, and addictive behaviors was observed in this study

Højsted J et al. Pain 2013; 154: 2677.

Addiction to medicines



National Drug Treatment Monitoring Service.

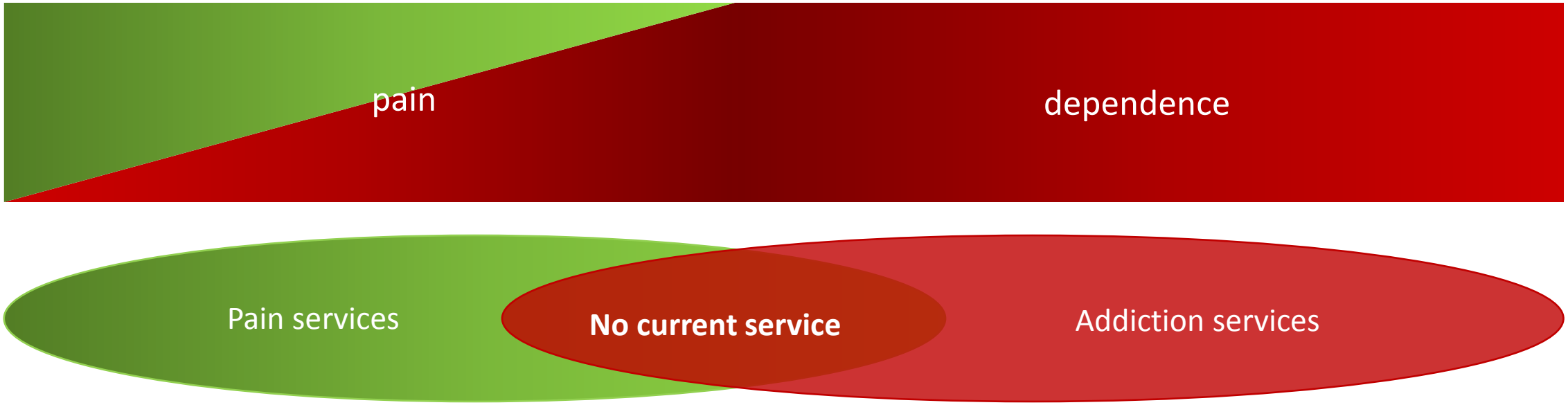
Prevalence of opioid use disorders

- Germany
  - 1- year prevalence 0.008%
- UK
  - 714 699 person years exposure
  - 5 year prevalence 0.05%
  - Incidence 6.51 (95% CI 5.93 – 7.13) patients per 10000 patient-years exposed
  - Morphine increasing

Marschall U et al. Eur J Pain 2016; 20: 767. Cooper AJM et al. Pain Ther 2017; 6: 73.

Spectrum of prescribed opioid use

Chronic pain	Chronic pain	No pain but pain reported	*No pain*
Stable prescribed opioids	Increasing dose of opioids	Prescribed drug seeking	*Diverted opioids*
Risk of dependence	Dependence and problem opioid use	Addiction	*Addiction*



Risks of running into problems with opioids

- Patient factors
  - Depression/common mental health diagnoses
  - Alcohol misuse/non-opioid drug misuse
  - Opioid misuse

- Drug factors
  - High doses
  - Multiple opioids
  - More potent drugs
  - Concurrent benzodiazepines/sedative drugs

Wilsey et al. Pain Med 2008; 9: 1107. Gudin et al. Postgrad Med 2013; 125:115. Fishbain et al. Pain Med 2008; 9: 444. Chou et al. Ann Int Med 2015; 162: 276.

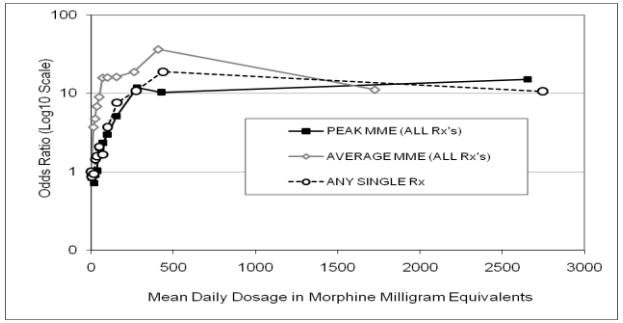
Who gets long-term opioid therapy?

- Patient factors
  - Depression/common mental health diagnoses (x3-4)
  - Alcohol misuse/non-opioid drug misuse (x4-5)
  - Opioid misuse (x5-10)

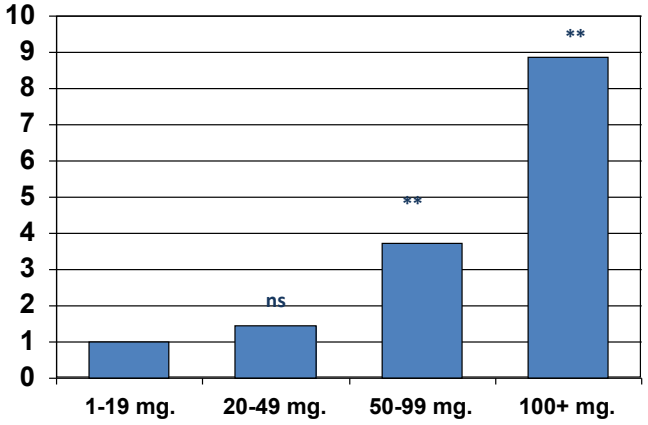
- At risk patients are more likely to receive
  - High doses
  - Multiple opioids
  - More potent drugs
  - Concurrent benzodiazepines/sedative drugs

Edlund et al. Clin J Pain 2010; 26: 1. Morasco Pain 2010; 151: 625. Sullivan (2010) Pain, 151(3), 567-568.

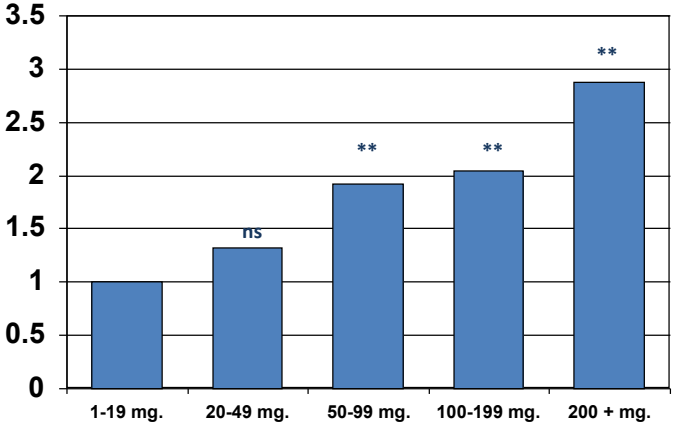
High opioid doses and deaths: a case for a dose limit



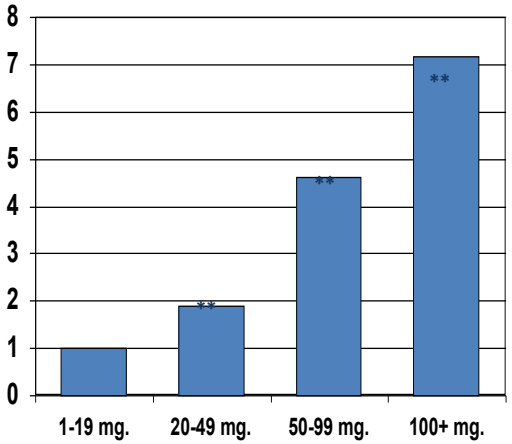
Paulozzi et al. Pain Med 2012.



Dunn et al. Ann Int Med 2010.



Gomes et al. Arch Int Med 2011.



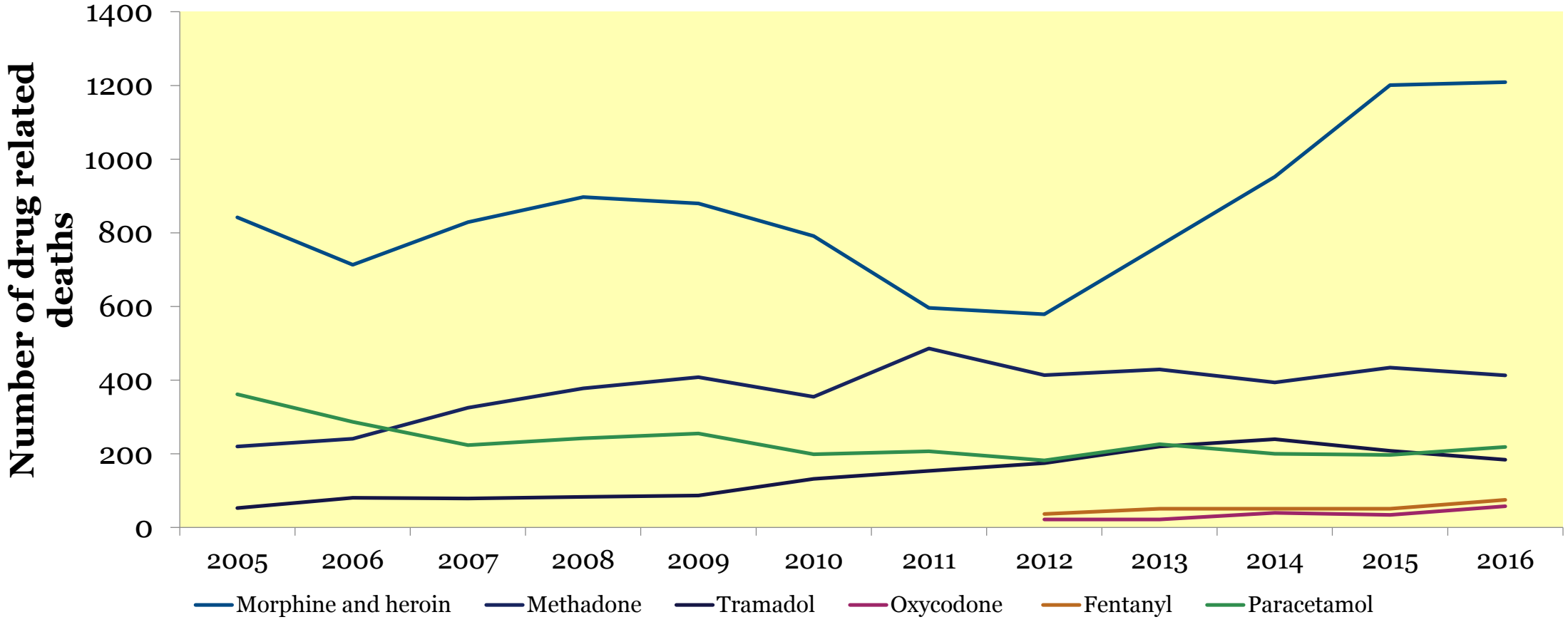
Bohnert et al. JAMA 2011.

International maximum recommended daily doses

- Australia: max 60mg MED
- USA: max 90mg MED
- UK & Germany: max 120mg MED

https://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware
Dowell D, et al.. MMWR Recomm Rep 2016; 65 (No. RR-1): 1–49.
Häuser W et al. Dtsch Arztebl Int 2014; 111: 732–40.

Deaths related to drug poisoning in England



Office of National Statistics Deaths Related to Drug Poisoning in England and Wales, 2009 – 2016.

Gabapentin and opioids

- Prescription opioid use associated with risk of opioid-related death:
- 1 in 550 chronic opioid users dying within 2.5 years of first opioid prescription
- Co-prescription of benzodiazepines with opioids increased the risk of overdose death 4 fold
- Concomitant gabapentin use (> 900mg per day) was associated with a 60% increase in the risk of opioid-related death
- Very high doses gabapentin associated with 2 fold increase

Kaplovitch E et al. PLoS ONE 2015; 10(8): e0134550. Gomes T et al. PLoS Med 2017; 14(10): e1002396.

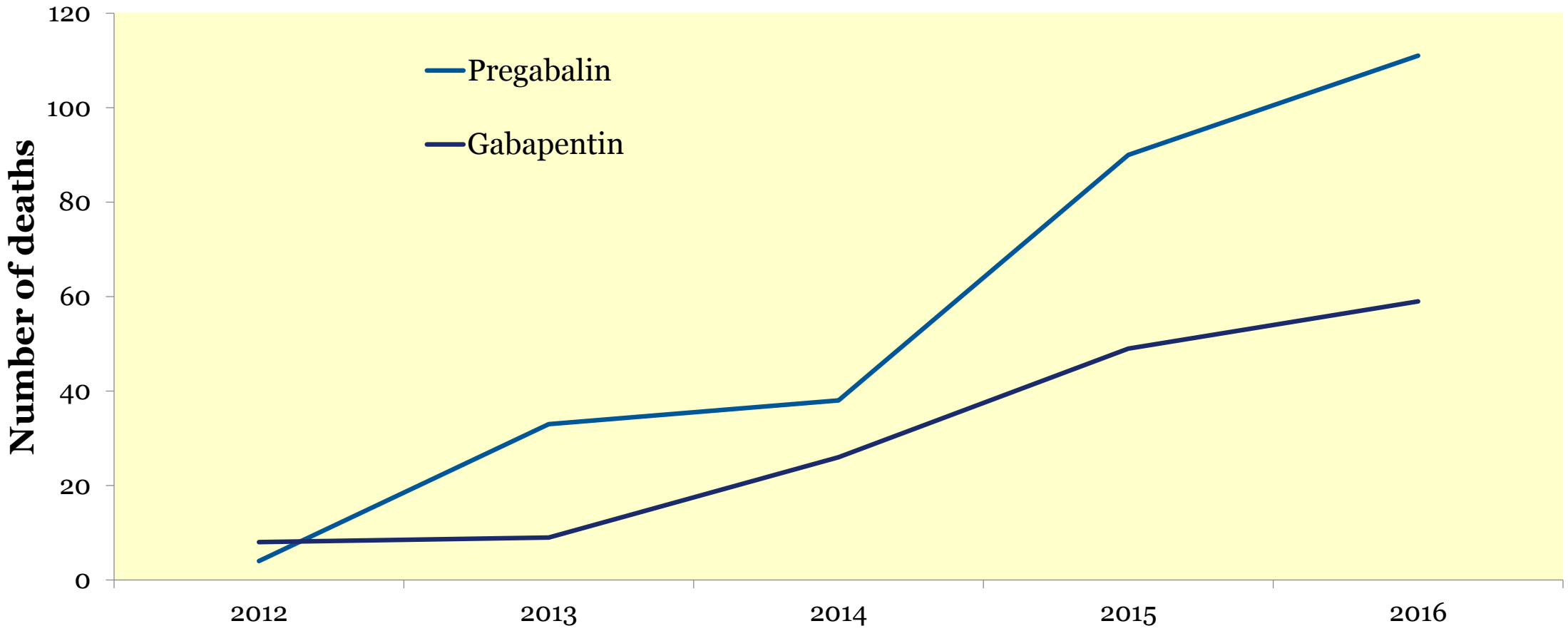
Increasing safety concerns

- 12.1 % of all urine specimens from patients with opioid addiction found to be positive for pregabalin. None of the patients concerned had a medical indication for using pregabalin

- More likely to be prescribed gabapentin or pregabalin if
  - previous substance use disorder treatment or diagnosis (aOR 1.41, 95 % CI 1.31–1.52)
  - previously been dispensed high doses of drugs with abuse potential (aOR 1.77, 95 % CI 1.62–1.94)

Grosshans M et al. Eur J Clin Pharmacol 2013; Boden R et Eur J Clin Pharmacol 2014.

Gabapentinoid related deaths in UK



Office for National Statistics. Deaths related to drug poisoning.

Deprescribing: you know it makes sense

+

PAIN + MEDICINES

Poor sleep	Brain fog
Fatigue	Inability to drive
Depression	Constipation
Loss of role	More lack of libido
Lack of libido	Unsteadiness

Deprescribing: you know it makes sense

+

PAIN

Poor sleep
Fatigue
Depression
Loss of role
Lack of libido

Opioids Aware

Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain

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Public Health England

A Public Health England funded project

Good practice in prescribing opioid medicines for pain should reflect fundamental principles in prescribing generally. The decision to prescribe is underpinned by applying best professional practice; understanding the condition, the patient and their context and understanding the clinical use of the drug. This resource, developed by UK healthcare professionals and policymakers, provides the information to support a safe and effective prescribing decision.

1. Opioids are very good analgesics for acute pain and for pain at the end of life but there is little evidence that they are helpful for long term pain.
2. A small proportion of people may obtain good pain relief with opioids in the long-term if the dose can be kept low and especially if their use is intermittent (however it is difficult to identify these people at the point of opioid initiation).
3. The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day, but there is no increased benefit.
4. If a patient is using opioids but is still in pain, the opioids are not effective and should be discontinued, even if no other treatment is available.
5. Chronic pain is very complex and if patients have refractory and disabling symptoms, particularly if they are on high opioid doses, a very detailed assessment of the many emotional influences on their pain experience is essential.

About the Resource

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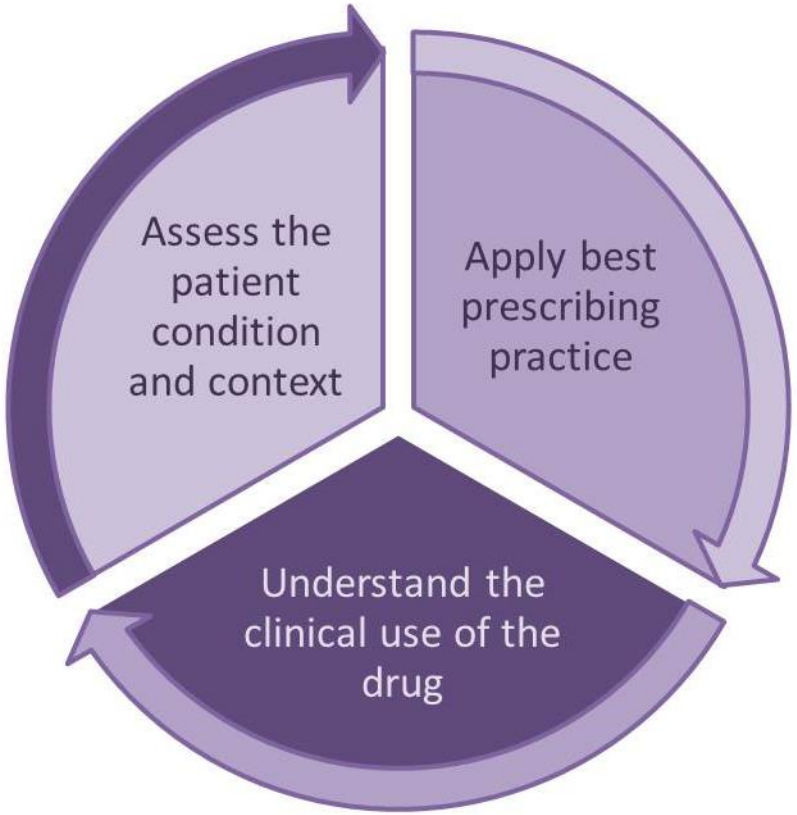
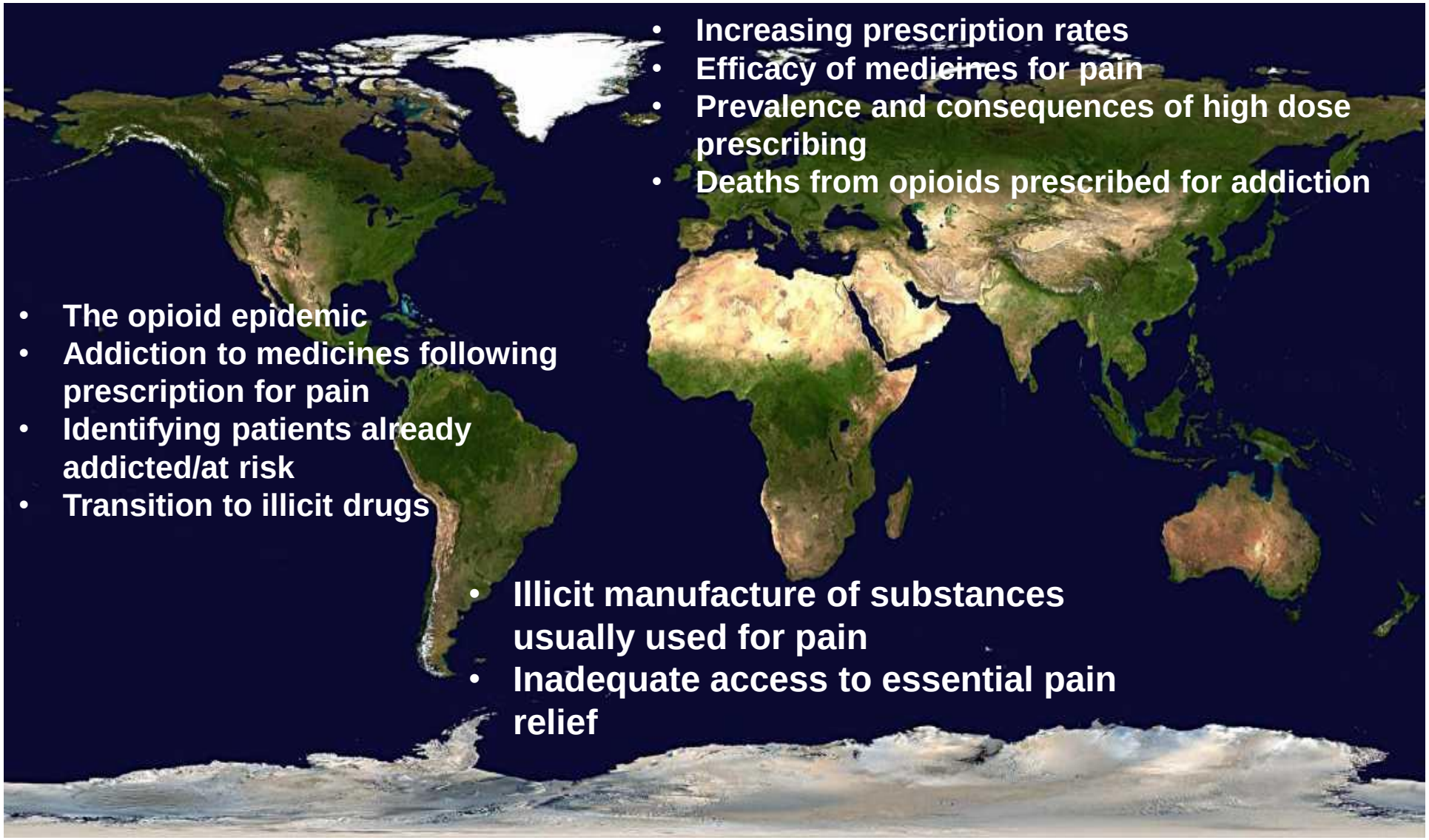


http://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

The opioid conversation: pieces of the picture



- Increasing prescription rates
- Efficacy of medicines for pain
- Prevalence and consequences of high dose prescribing
- Deaths from opioids prescribed for addiction

- The opioid epidemic
- Addiction to medicines following prescription for pain
- Identifying patients already addicted/at risk
- Transition to illicit drugs

- Illicit manufacture of substances usually used for pain
- Inadequate access to essential pain relief

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Any questions?

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