KU LEUVEN

New evolutions in pain medication, myths & facts of opioids

BVOT congres , Orthopaedica Belgica 2018
Minne Casteels, met dank aan Johan De Coster
3 mei 2018

New evolutions in pain medication, myths & facts of opioids

This talk:

- not an exhaustive overview
- adressing some issues and some literature/data

DOI
Chair MFC UZ Leuven
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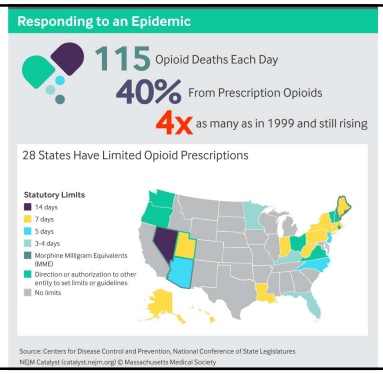
Member SAWP Ema

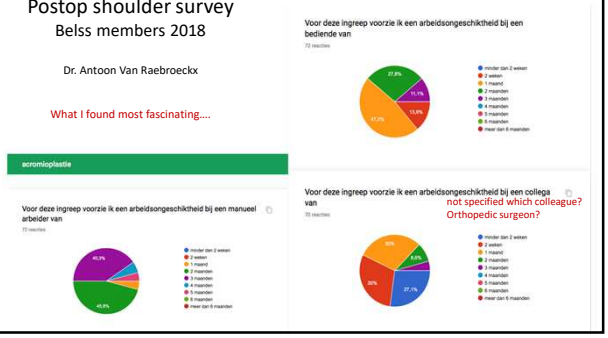
http://www.ema.europa.eu/docs/en_GB/document_library/contacts/mcasteels_DI.pdf



Postop shoulder survey
Belss members 2018

Dr. Antoon Van Raebroeckx

What I found most fascinating....

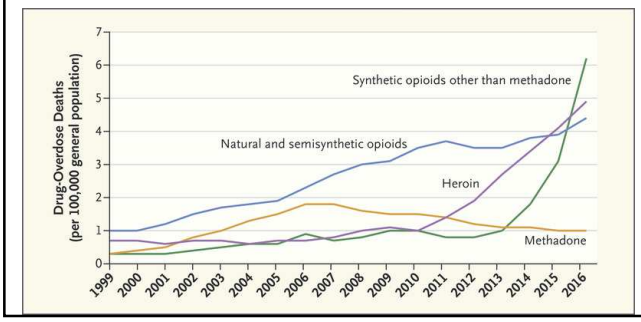


N Engl J Med 2018; 378:1565-1567 DOI: 10.1056/NEJMp1800216

From 1999 through 2015, drug-overdose deaths approximately tripled in the United States, and the majority of such deaths now involve an opioid. In 2016 alone, there were 64,000 drug-overdose deaths in the United States — more than the total number of U.S. military deaths during the Vietnam War. As a result, and despite gains in other areas of medicine and public health, the United States recently experienced its first major decline in life expectancy since 1993.

The origins of the opioid epidemic can be traced to overprescription of narcotic analgesics. But in recent years, deaths due to illicit synthetic opioids have outstripped deaths due to heroin and prescription painkillers. According to the Centers for Disease Control and Prevention, deaths involving synthetic opioids (excluding methadone) doubled between 2015 and 2016. This upsurge can largely be attributed to the emergence of fentanyl and related analogues in the illegal-drug supply. An examination of data from 10 U.S. states found that more than half the people who died of opioid-related overdoses during the second half of 2016 tested positive for fentanyl.

US N Engl J Med 2018; 378:1565-1567 DOI: 10.1056/NEJMp1800216



Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study
BMJ 2018;360:j5790 http://dx.doi.org/10.1136/bmj.j5790

US -retrospective – observational study

Orthopedic surgeons alone were responsible for 7,7% opioid prescriptions in 2007.

What this study adds:

- Each refill and additional week of opioid prescription is associated with a large increase in opioid misuse among opioid naive patients
- The duration of a prescription rather than opioid dosage was more strongly associated with ultimate misuse in the early postsurgical period

Suicide: A Silent Contributor to Opioid-Overdose Deaths

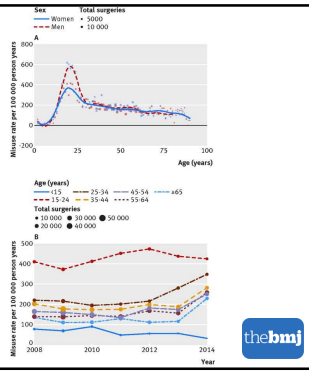
N Engl J Med 2018; 378:1567-1569 DOI: 10.1056/NEJMp1801417

In 2016, the Centers for Disease Control and Prevention (CDC) reported 42,000 opioid-overdose fatalities, including an unknown number of suicides. Notably, two populations that are more likely than others to receive opioid prescriptions — patients with chronic pain and those with mood disorders — are also at greater risk for suicide.

…… these data suggest that the true proportion of suicides among opioid-overdose deaths is somewhere between 20% and 30%, but it could be even higher.

…… The significant increases in both opioid-overdose deaths and suicide rates in our country have contributed to reduced life expectancy for Americans. These two epidemics are intermingled, and solutions to address the opioid crisis require that we tailor interventions to preventing opioid-overdose deaths due to suicidal intent.

Misuse of and prescription rates for opioids per 100 000 person years across ages and sex over time by cohort.



Gabriel A Brat et al. BMJ 2018;360:bmj.j5790

Actions taken, e.g.:

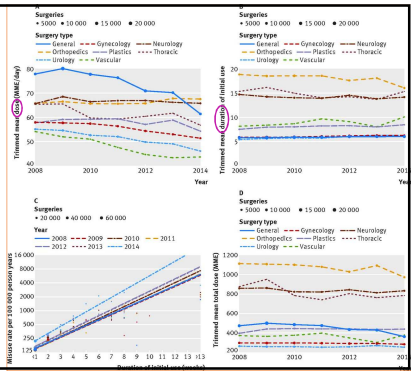
- Canada: naloxone available without a prescription
- Prescription limits, cf. US (varying between states)
- Another focus is chronic pain treatment: overprescription of opioid medications reflects in part the limited number of alternative medications for chronic pain. Thus, we cannot hope to prevent opioid misuse and overdose without addressing the treatment needs of people with moderate-to-severe chronic pain. Though more cautious opioid prescribing is an important first step, there is a clear need for safer, more effective treatments.

thebmj

orthopedics

Temporal effects and sensitivity analysis for opioid use.

MME= morphine mg equivalent



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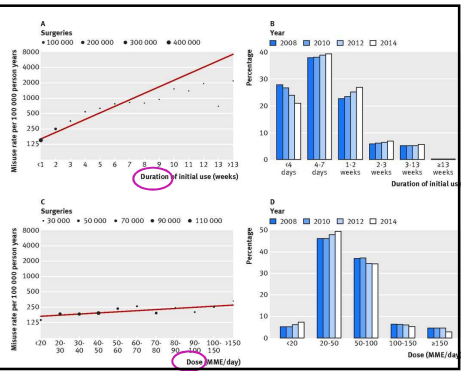
Postsurgical rates of misuse by dosage and duration of opioid prescription.



thebmj

Gabriel A Brat et al. BMJ 2018;360:bmj.j5790

We focused on typical surgical patients without a history of misuse or ongoing opioid use and estimated an adjusted 44% increase in misuse for every refill fulfilled, or 20% increase for every week of prescription.

A second finding was that duration of use rather than dosage of equivalent opioids was more strongly associated with subsequent misuse of post-discharge prescriptions.

These findings suggest a more nuanced understanding of the relation between duration and dosage, with a **focus on early appropriate treatment of pain (including higher doses) for a limited time**.
Such findings imply that optimal postoperative prescribing, which maximizes analgesia and minimizes the risk of misuse, may be achieved with moderate to high opioid dosages at shorter durations, a combination that merits further investigation in population based and clinical studies.

BMJ 2018;360:j5790

Pijnstillers: opvallende stijging van het verbruik van 5 opioïden

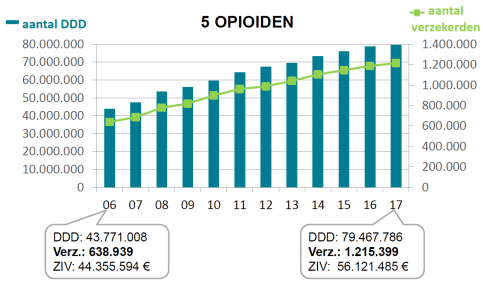
https://www.riziv.fgov.be/nl/pers/Paginas/opioden-opvallende-stijging.aspx#.WuchJnkUmUk

Hoog chronisch verbruik van opioïden

Het controleonderzoek omschrijft een verzekerde die meer dan 365 DDD per jaar afhaalde, als een 'chronisch grote verbruiker'. Deze verbruikt dus theoretisch gemiddeld 1 dagdosis per dag gedurende een jaar.

In 2016 waren er 30.353 'chronisch grote verbruikers'. Dit beperkt aantal verzekerden (2,6% van de 1.186.943 verzekerden) haalde maar liefst 34% af van de 78,6 miljoen afgeleverde DDD's. Het aantal 'chronisch grote verbruikers' is met 28% gestegen ten opzichte van 2010. Dit bevestigt dat zowel het sporadische verbruik als het chronische grote verbruik is toegenomen. Één op de 5 grote chronische verbruikers was in 2016 jonger dan 50 jaar. Hun verbruik zal in de komende jaren wellicht nog meer stijgen, gelet op hun jonge leeftijd en de gewenning.

Evolution of use 2006-2017



Pijnstillers: opvallende stijging van het verbruik van 5 opioïden

https://www.riziv.fgov.be/nl/pers/Paginas/opioden-opvallende-stijging.aspx#.WuchJnkUmUk

De Dienst voor geneeskundige evaluatie en controle (DGEC) van het RIZIV stelt een opvallende stijging vast van het verbruik van 5 opioïden. Dat verbruik heeft gevolgen voor de patiënt zelf, de ziekteverzekering (verzekering voor geneeskundige verzorging) en de samenleving in het algemeen.

De 5 opioïden, een omschrijving

…….De DGEC opende een multidisciplinair onderzoek naar het verbruik van 5 opioïden: fentanyl (pleisters), tramadol, oxycodone, tilidine, en piritramide.

Een zorgwekkende stijging van het verbruik van de 5 bestudeerde opioïden

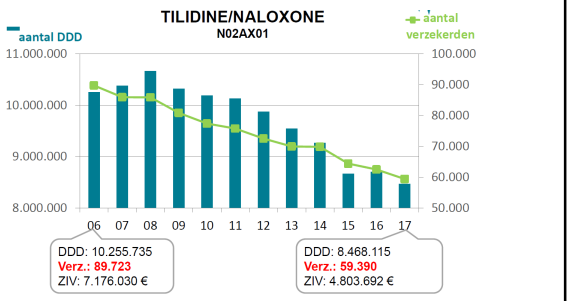
Tussen 2010 en 2016 is het verbruik sterk gestegen. Het aantal verzekerden die minstens 1 verpakking van één van de 5 onderzochte opioïden afhaalden, steeg met 32%. De afgehaalde hoeveelheid nam eveneens met 32% toe.

In 2016 haalden 1.186.943 verzekerden minstens 1 verpakking af voor in totaal 78,6 miljoen DoorsneeDagDosissen of DDD's. Dat is 10% van de Belgische bevolking. Een DDD is de veronderstelde onderhoudsdosis per dag, zoals de WHO dat voor elk geneesmiddel heeft bepaald. Dat verbruik kostte de ziekteverzekering 55,4 miljoen euro.

Evolution of use 2006-2017

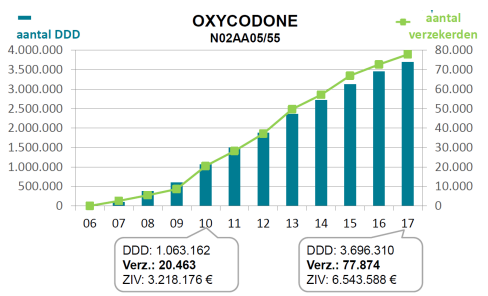
- decrease
  - tilidine/naloxone (DDD en verzekerden)
  - piritramide (verzekerden)
- increase of both DDD and number of users
  - oxycodone
  - fentanyl (lichte daling in 2017)
  - tramadol + tramadol/paracetamol

Evolution of use 2006-2017



Verbruik en mogelijk misbruik van opioïden in België
Willems, De Mooter - DGEC

Evolution of use 2006-2017



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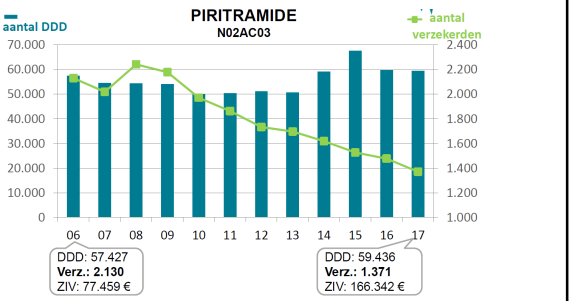

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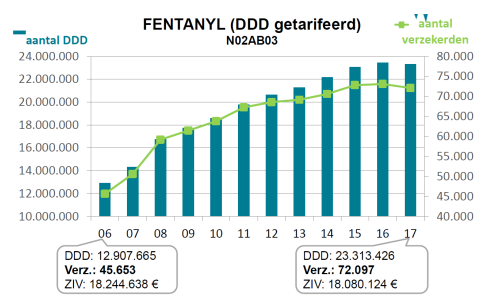

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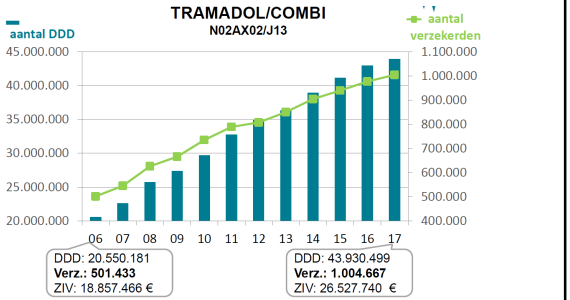

Verbruik en mogelijk misbruik van opioïden in België
Willems, De Mooter - DGEC

Evolution of use 2006-2017

- 1.215.399 verzekerden in 2017:

	# verzekerden
tramadol	↗ 1.004.667
fentanyl	72.097
tilidine	↘ 59.390
oxycodone	↗ 77.874
piritramide	↘ 1.371

# verzekerden	2010	2017	% stijging
Totaal (5 opioïden)	898.367 →	1.215.399	35 %

Verbruik en mogelijk misbruik van opioïden in België
Willems, De Mooter - DGEC

Present practices in postoperative analgesia

In all cases where opioids are administered need for regular measurement of:

- sedation score
- respiration rate
- blood pressure

postoperative pain

- Basis: step 1 medication for 48 to 72 hours at defined time points.
  Beware of CI and AE — paracetamol / NSAID
- If insufficient pain control (NRS≥ 4) in spite of systematic basic analgesia:
  administer step 2-3 according to prescription — tramadol / morphine/oxycodone
- Systematic administration of paracetamol as long as opioids are needed

Taradyl -ketorolac

- Concern over the high incidence of reported adverse effects with ketorolac has led to its withdrawal in some countries while in others its permitted dosage and maximum duration of treatment have been reduced.
- Not longer than 48 hours
- Adverse effects: GI, haematological, renal, bleeding, hypersensitivity, neurological reactions, pulmonary edema, hepatotoxicity…….think of CI for NSAIDs!
- From 1990 to 1993, 97 reactions with a fatal outcome were reported worldwide.
- Ketorolac should be used with caution in heart failure, hepatic impairment and conditions leading to reduction in blood volume or in renal blood flow. Dose should be reduced in elderly and <50 kg.
- Is a potent NSAID and is indicated only for the short-term management of moderate to severe pain and not for minor or chronic painful conditions
- Used mainly because of availability of injectable form – switch to other when PO possible

Patient controlled analgesia maximalised when/where feasible

- PCIA patient controlled intravenous analgesia
- PCEA patient controlled epidural analgesia
- PCRA patient controlled regional analgesia (patient can leave the hospital with PCRA in place for the next few days)
- ketamine-drip (via PCA pump) + benzo
- clonidine

Paracetamol

- Dosing! Toxicity at lower dose in children, low weight patients, alcohol use, anorexia, elderly people, chronically underfed, kidney and liver insufficiency
- Normal postoperative dose: IV 15 mg/kg/6 hours with a maximum of 1 gram
- Systematically administered as long as there is a need for step 2 or 3 pain medication

Tramadol (step 2)

- For minor interventions: in combination with paracetamol and/or NSAID
- As alternative when patient has a CI for morphine (e.g. sleep apnea, day surgery…)
- Can be administered in combination with PCRA when peripheral block is insufficient
- Nausea is frequent AE (>25%); provide anti-emetics
- Do not combine with morphine, piritramide, PCIA and PCEA with fentanyl

PK morphine

	onset	peak	duration
po	unknown	60 min	4-5 hrs
sc	20 min	50-90 min	4-5 hrs
iv	rapid	20 min	4-5 hrs

sc morphine can be replaced by oxycodone (dosing and dosing interval similar to morphine)

October 2016: Dipidolor®(piritramide): stock rupture because of worldwide production stop

UZ Leuven made a full switch to morphine

Take care

- Intravenous administration of morphine for acute pain is not allowed in non-ICU or non-PACU.
- Initially sc administration. Subsequently switch versus oral (e.g. oxycodon).
- Avoid sending postoperative patients home with strong opioids (or prescriptions thereof), but one has to admit that the short stay policy makes this challenging.
- If switch from PCA to transdermal fentanyl: be aware of time delay before full effect of fentanyl TTS

Morphine

- Dose of SC morphine: 0,1 to 0,2 mg/kg up to a maximum of 15mg SC
- 5 mg SC may suffice for less painful interventions
- Take care with obese, cardiopulmonary compromised patients
- CI: sleep apnea
- Minimum dosing interval of 4 hours (up to 6-8 hours)
- In surgery when no PCIA or PCEA is foreseen, in combination with basic scheme (paracetamol and/or NSAID)
- Can be combined with PCRA when this does not provide sufficient analgesia
- Before administration: evaluate respiration rate, BP, sedation score
- Not together with piritramide, tramadol, PCEA with fentanyl or PCIA

Sufentanil tablets (15 µg) for sublingual use, in a handheld device?

SmPC

- Zalviso is indicated for the management of acute moderate to severe post-operative pain in adult patients.
- Zalviso is to be administered in a hospital setting only. Zalviso should only be prescribed by physicians who are experienced in the management of opioid therapy, particularly opioid adverse reactions such as respiratory depression.
- Zalviso sublingual tablets are to be self-administered by the patient in response to pain using the Zalviso administration device. The Zalviso administration device is designed to deliver a single sufentanil 15 micrograms sublingual tablet, on a patient-controlled as needed basis, with a minimum of 20 minutes (lockout interval) between doses, over a period of up to 72 hours, which is the maximum recommended treatment duration.

Belgium: not reimbursed.

If used: patient should be informed beore (and offered ICF).

Sufentanil tablets (15 µg) for sublingual use, in a handheld device?

Anaesthesia 2018, 73, 143–159

Editorial

https://clinicaltrials.gov; search term: 'sublingual sufentanil': this company had completed 16 clinical trials with SSTS since March 2008.

According to 'ClinicalTrials.gov', 7 of these studies were still to be published (last accessed 9 April 2017) while nine appeared in the seven original articles found in the described PubMed search.

https://doi.org/10.1111/anae.14132

"The major advantage of the sublingual sufentanil tablet system is improved mobility, which may be an advantage for some patients."

Solid RCT lacking.

A TRP channel trio mediates acute noxious heat sensing

Ine Vandewauw, Katrien De Clercq, Marie Mulier , Katharina Held , Silvia Pinto , Nele Van Ranst , Andrei Segal , Thierry Voet , Rudi Vennekens , Katharina Zimmermann , Joris Vriens & Thomas Voets

Nature **volume 555**, pages 662–666 (29 March 2018)doi:10.1038/nature26137

Thomas Voets and Joris Vriens demonstrated that 3 ion channels play a crucial role in pain sensation.....

April 09, 2018 – Grünenthal, the KU Leuven's Centre for Drug Design and Discovery (CD3) and the Laboratory of Ion Channel Research (LICR) announced today that they have entered into a research collaboration for the development of novel non-opioid drug candidates for the treatment of painful diseases with a high unmet medical need.

- Sufficient pain relief
- Take care of what patient goes home with (pills/prescriptions)
- Limit duration of opioid treatment
- Opioids are no household medicines "in case of"
- Additional research is needed : how can initial postoperative treatment minimise misuse and addiction?

Thank you