Non-CME Webinar Series
designed with the trainee in mind

second Tuesdays of odd-numbered months

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Efficacy and Side Effects

Lynn Kohan M.D.

9/8/2020

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Faculty Disclosure

	Nothing to disclose
	Yes, as follows: x

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Off-Label Product Use

Will you be presenting or referencing off-label or investigational use of a therapeutic product?	
x	No
	Yes, as follows:

Learning objectives

By the end of this session, the participants will be able to:

- *Analyze the efficacy of opioid therapy*
- *Describe adverse effects associated with opioid therapy*

Effectiveness of short term opioid therapy

- 62 randomized controlled trials
  - In 61 duration <16 weeks
  - Opioid more effective than placebo for nociceptive and neuropathic pain
  - Max dose < 180 MME (except in 3 studies)

Furlan et al. Pain Res Management 2011.

Original Investigation

Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain
A Systematic Review and Meta-analysis

Christina Abdel Shaheed, PhD; Chris G. Maher, PhD; Kylie A. Williams, PhD; Richard Day, MD; Andrew J. McLachlan, PhD

Key Points

Question What is the efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain?

Findings In this systematic review we found that recommended doses of opioid analgesics (range 40.0-240.0-mg morphine equivalents/day) did not provide clinically meaningful pain relief (> 20 points on a 0-100 point pain scale) in people with chronic low back pain.

Meaning For people with chronic low back pain who tolerate the medicine, opioid analgesics provide modest short-term pain relief, but the effect is not likely to be clinically important within guideline-recommended doses.

JAMA Intern Med. 2016;176(7):958-968.
doi:10.1001/jamainternmed.2016.1251
Published onlineMay 23, 2016.

Efficacy

- No long term ($\geq$ 1 year) outcomes in pain/function
- Most placebo-controlled studies $\leq$ 6 weeks
- No differences in pain/function with dose escalation

Long term efficacy

- Cochrane Review
  - 26 studies > 6 months
    - 25 of these were case series or uncontrolled trials
  - Some evidence that pts on LOT have pain relief
  - BUT..
    - Many discontinued bc of side effects (23%) or poor pain relief (10%)

Noble et al. Cochrane Database Syst Rev 2010

Other problems

Function

- Effect on function smaller than impact on pain
- No improvement in function

Pt exclusion

- Often excluded pt's with medical comorbidities, psychiatric comorbidities, or at risk for misuse/use disorder

Limited evidence for common conditions

- Low back pain, fibromyalgia, headache, etc.

Efficacy

- Limited evidence for long-term opioids
  - Lack of evidence vs no efficacy?
- SPACE TRIAL

Question: For patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use, does opioid medication compared with nonopioid medication result in better pain-related function?

Findings In this randomized clinical trial that included 240 patients, the use of opioid vs nonopioid medication therapy did not result in significantly better pain-related function over 12 months (3.4 vs 3.3 points on an 11-point scale at 12 months, respectively).

Meaning This study does not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Krebs EE. JAMA 2018; 319 ((): 872-882.

Efficacy

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 00, No 00 (), 2018: pp 1–10
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Effectiveness of Opioids for Chronic Noncancer Pain: A Two-Year Multicenter, Prospective Cohort Study With Propensity Score Matching

Dalila R. Veiga,[*,†,‡] Matilde Monteiro-Soares,[‡,§] Liliane Mendonça,[¶,‖] Rute Sampaio,[‖,**,††] José M. Castro-Lopes,[‖,**,††,‡‡] and Luís F. Azevedo[‡,§,‖,‡‡]

No improvement regarding pain relief, functional outcomes and quality of life over 2 years of follow-up.

Conclusion
Limited effectiveness of opioids in long-term CNCP management

Veiga D. J of Pain 2018; 00:1-10.

Adverse Effects

Tolerance, physical dependence, abuse, and addiction

Cardiac adverse events

Sleep disturbances

GI side effects

Immunologic

Bladder Dysfunction

Endocrine effects

Hyperalgesia

Fracture

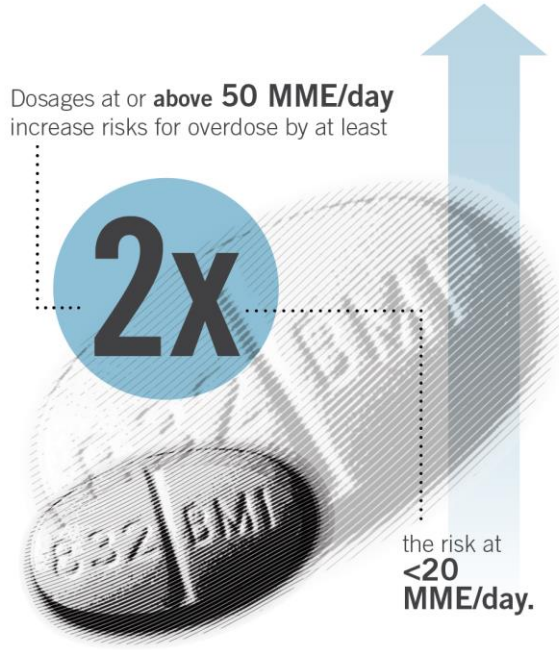
Khademi H, Kamangar F, Brennan P, Malekzadeh R. Opioid Therapy and its Side Effects: A Review. Arch Iran Med. 2016; 19(12): 870 – 876.
Benyamin R. Opioid complications and side effects. Pain Physician: Opioid special issue 2008; 11: S105-S120.
Baldini A, Von Korff M, Lin EH. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. *Prim Care Companion CNS Disord*. 2012;14(3):PCC.11m01326. doi:10.4088/PCC.11m01326

Side effects

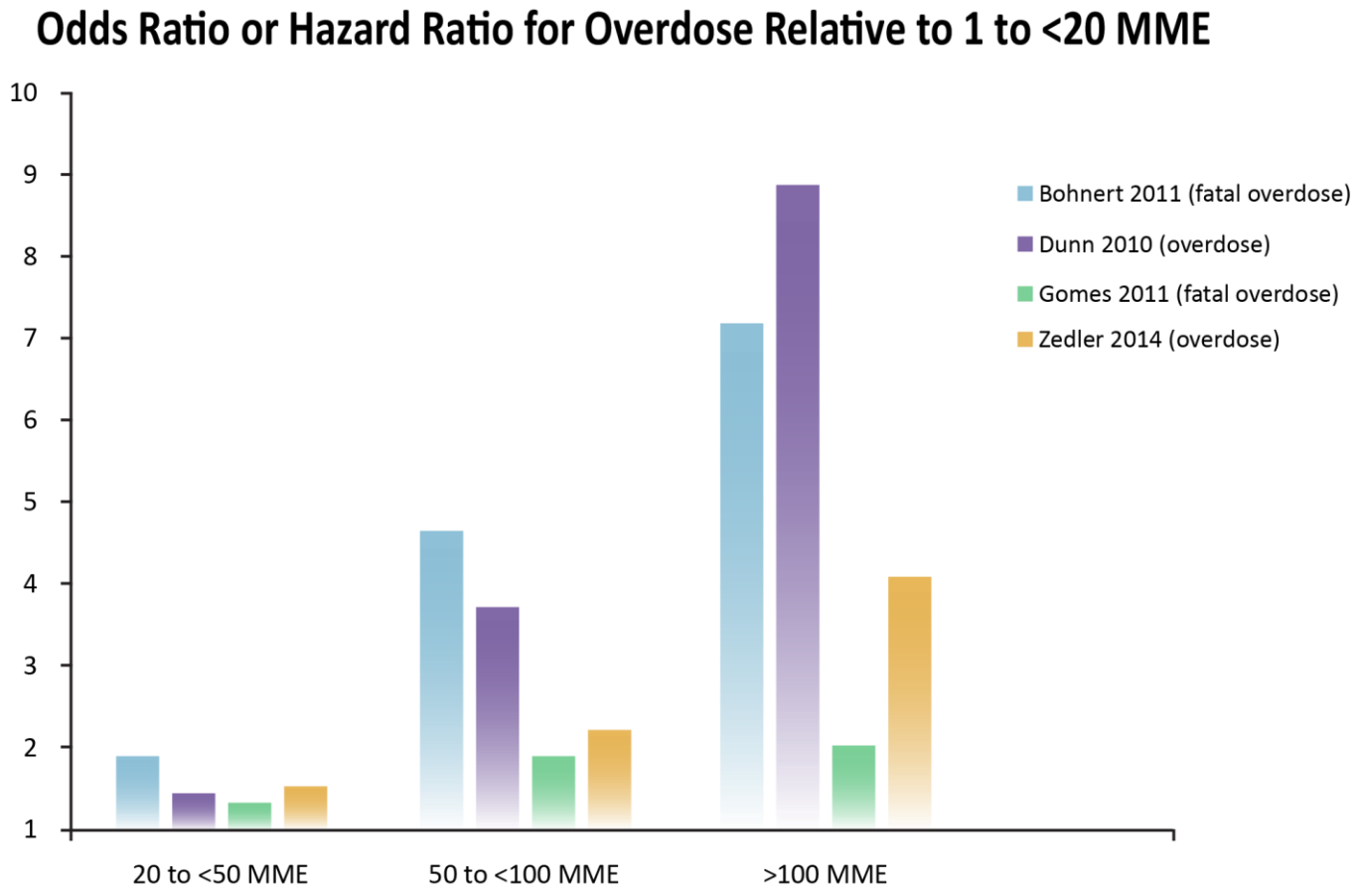
- Risk assessment tools unable to accurately classify at risk pt’s
- Dose dependent association with risk of overdose/harms
- Starting LA/ER opioids associated with increased risk of overdose
- Increased risk of long term use when opioids used for acute pain

Factors that increase risk of harm

- Pregnancy
- Older age
- Comorbid renal or hepatic insufficieny
- Mental health disorder
- Substance use disorder
- History of overdose
- Sleep-disordered breathing
- Multiple prescriptions from different providers
- Concurrent benzodiazepine use
- Increased dose



Prescribed MME and overdose Risk



https://www.slideshare.net/OPUNITE/rx16-clinical-tues1115group

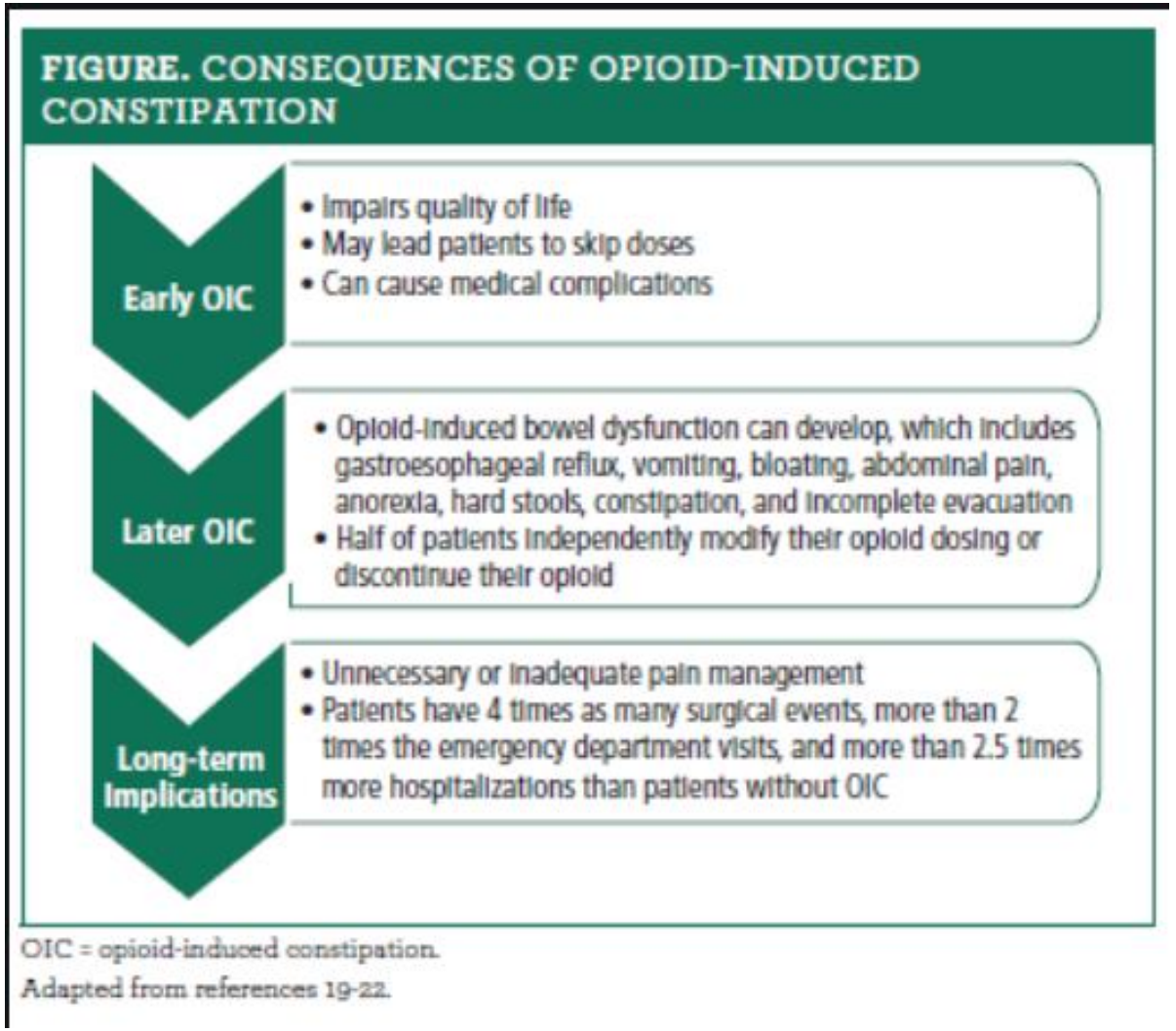
Constipation

Table 1. Diagnosis of Opioid-Induced Constipation[a]

1. Fewer than 3 bowel movements per week
2. Hard or lumpy stools
3. Sensation of incomplete evacuation
4. Sensation of anorectal obstruction
5. Straining with defecation
6. Bloating and abdominal pain relieved with bowel movements
7. Small stools
8. GERD (potentially)

[a] Adapted from Rome III Criteria for Diagnosis of Functional Constipation. Based on reference 9.
GERD, gastroesophageal reflux disease

https://www.practicalpainmanagement.com/opioid-induced-constipation-causes-treatments

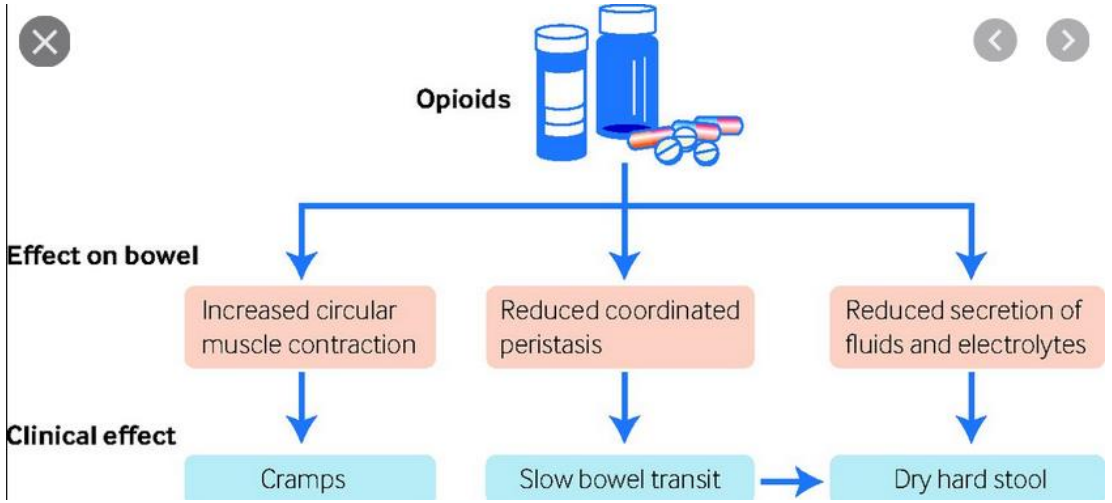


https://www.pharmacytimes.com/publications/issue/2016/july2016/opioids-and-constipation

Constipation

Largely mediated by mu opioid receptors on myenteric and submucosal neurons in the gut

- Suppress forward peristalsis
- Raises sphincter tone
- Increase fluid absorption
- Reduces intestinal secretions



https://www.bmj.com/content/358/bmj.j3313

Table 2. Categories of Anti-constipatory Agents	
Category	**Mechanisms of Action**
Bulk-producing agents	*Bulking agents* work in both the small and large bowel, with an onset of action of 12 to 72 hours. They bulk up the stool so that it retains more water, making peristalsis easier. Examples include psyllium, methylcellulose, and dietary fiber.
Stool softeners	*Stool softeners* soften stool and make it "slippery," making the stool easier to pass. These work in the colon and take from 6 to 8 hours to work.
Lubricants or emollients	*Lubricants/emollients,* such as mineral oil, softens and coat feces, thus preventing colonic water absorption. Vegetable-oil enemas act as lubricants.
Hydrating agents	*Hydrating agents* increase the water content in the stool, which makes the stool softer and easier to pass. Some of these work by increasing the bowl lumen osmolality. Examples include Fleet phospho-soda and Miralax.
Stimulants	*Stimulants* stimulate colonic contractions that propel stools forward. These agents irritate the lining of the intestine. Examples include cascara, bisacodyl, and senna.
Others: prostaglandin analogues or prokinetics	*Prostaglandins, prokinetic drugs, and other agents* change the way the intestine absorbs water and electrolytes, and increase the weight and frequency of stools while reducing transit time.

https://www.practicalpainmanagement.com/opioid-induced-constipation-causes-treatments

Cardiovascular effects

Original Investigation

Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain

Wayne A. Ray, PhD; Cecilia P. Chung, MD, MPH; Katherine T. Murray, MD; Kathi Hall, BS; C. Michael Stein, MB, ChB

IMPORTANCE Long-acting opioids increase the risk of unintentional overdose deaths but also may increase mortality from cardiorespiratory and other causes.

OBJECTIVE To compare all-cause mortality for patients with chronic noncancer pain who were prescribed either long-acting opioids or alternative medications for moderate to severe chronic pain.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study between 1999 and 2012 of Tennessee Medicaid patients with chronic noncancer pain and no evidence of palliative or end-of-life care.

EXPOSURES Propensity score–matched new episodes of prescribed therapy for long-acting opioids or either analgesic anticonvulsants or low-dose cyclic antidepressants (control medications).

MAIN OUTCOMES AND MEASURES Total and cause-specific mortality as determined from death certificates. Adjusted hazard ratios (HRs) and risk differences (difference in incidence of death) were calculated for long-acting opioid therapy vs control medication.

RESULTS There were 22 912 new episodes of prescribed therapy for both long-acting opioids and control medications (mean [SD] age, 48 [11] years; 60% women). The long-acting opioid group was followed up for a mean 176 days and had 185 deaths and the control treatment group was followed up for a mean 128 days and had 87 deaths. The HR for total mortality was 1.64 (95% CI, 1.26-2.12) with a risk difference of 68.5 excess deaths (95% CI, 28.2-120.7) per 10 000 person-years. Increased risk was due to out-of-hospital deaths (154 long-acting opioid, 60 control deaths; HR, 1.90; 95% CI, 1.40-2.58; risk difference, 67.1; 95% CI, 30.1-117.3) excess deaths per 10 000 person-years. For out-of-hospital deaths other than unintentional overdose (120 long-acting opioid, 53 control deaths), the HR was 1.72 (95% CI, 1.24-2.39) with a risk difference of 47.4 excess deaths (95% CI, 15.7-91.4) per 10 000 person-years. The HR for cardiovascular deaths (79 long-acting opioid, 36 control deaths) was 1.65 (95% CI, 1.10-2.46) with a risk difference of 28.9 excess deaths (95% CI, 4.6-65.3) per 10 000 person-years. The HR during the first 30 days of therapy (53 long-acting opioid, 13 control deaths) was 4.16 (95% CI, 2.27-7.63) with a risk difference of 200 excess deaths (95% CI, 80-420) per 10 000 person-years.

CONCLUSIONS AND RELEVANCE Prescription of long-acting opioids for chronic noncancer pain, compared with anticonvulsants or cyclic antidepressants, was associated with a significantly increased risk of all-cause mortality, including deaths from causes other than overdose, with a modest absolute risk difference. These findings should be considered when evaluating harms and benefits of treatment.

-Prolo
-Clinic
from b
-At ris
from b

- CYP3A
and va
- Hypok
- Dimin
- Cocain
- Tricycl
- Halope
- Drope

Ray et al JAMA 2016.
Benyamin R. et al Painp Psyician 2008.

All cause mortality

Häuser *et al. BMC Medicine* (2020) 18:162
https://doi.org/10.1186/s12916-020-01644-4

BMC Medicine

All-cause mortality in patients with long-term opioid therapy compared with non-opioid analgesics for chronic non-cancer pain: a database study

Winfried Häuser[1,2*], Tino Schubert[3], Tobias Vogelmann[3], Christoph Maier[4], Mary-Ann Fitzcharles[5] and Thomas Tölle[6]

Conclusion

Increased risk of all cause mortality

Opioid group had higher risk of heart failure and higher use of antithrombotic and antiplatelet (also higher use of antipyschotics)

Immune effects

Table 1. *Central immunologic effects of opioids.*

Receptor	Effect
MOR	Decreases NK cell activity (central) Macrophage phagocytosis (central) Inhibits T-cell proliferation (central) Nitric oxide release (peripheral)
DOR	Increases NK cell activity (central) Potentiates humoral immune response (MOR dependent) Decreases PFC response
DOR antagonist	At low dose inhibits DHR
KOR	Pronounced suppression of humoral immunity
KOR antagonist	Increases PFC Suppression of humoral immune response (MOR dependent)

PFC=plaque forming cells; DHR=delayed hypersensitivity reaction; NK=natural killer

Benyamin R et al Painp Psyician 2008.

Different opioids have different impact

Tramadol may enhance NK cell activity, lymphocyte proliferation, and Il-2 release

Buprenorphine has no immune response

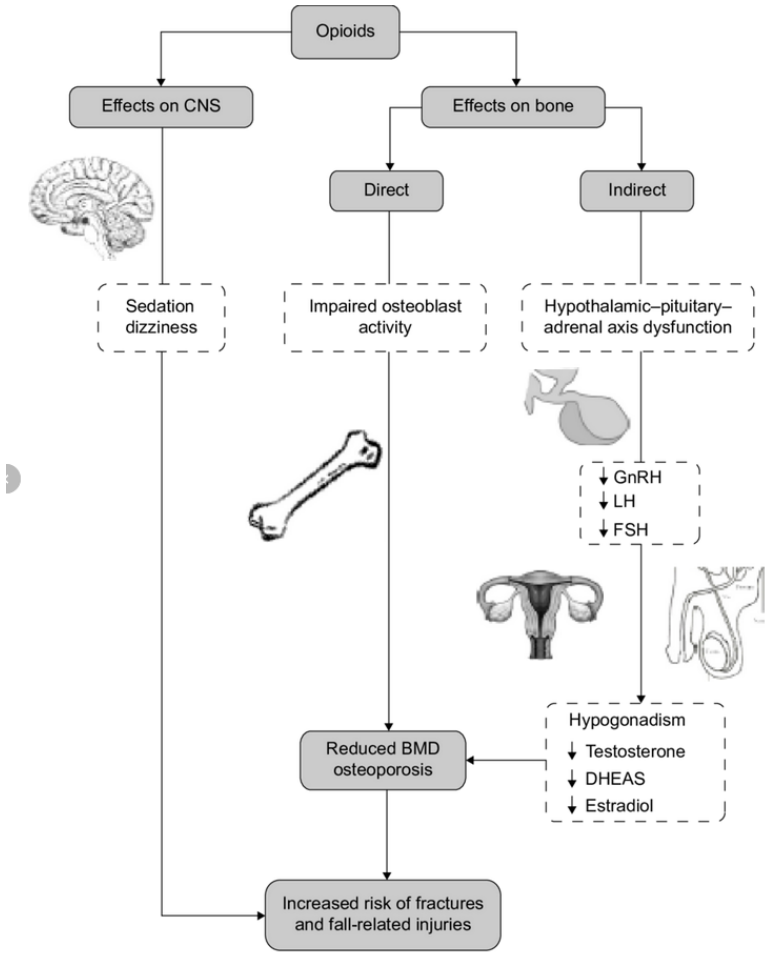
Opioid Endocrinopathy

Table 2. *Opioid-induced hormonal changes.*

Hormone	Opioid Effect	Potential symptom linkage
Testosterone	decrease	decreased libido erectile dysfunction reduced energy
Estrogen	decrease	sexual dysfunction reduced bone mineral density osteoporosis
Cortisol	decrease	secondary hormonal alterations
Luetenizing hormone	decrease	secondary reduced androgen hormone levels amenorrhea hypomenorrhea
Gonadotropin releasing hormone	decrease	secondary reduced androgen hormone levels

Benyamin R. et al Painp Psyician 2008.

Opioid Endocrinopathy



Mechanisms by which opioids may increase the risk of fracture and fall-related injuries. Abbreviations: CnS, central nervous system; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; BMD, bone mass density.

Table 8. Major Characteristics of Opioid Endocrinopathy[a]

- History of good opioid pain control that later ceases
- Low testosterone
- Low estradiol
- Amenorrhea/oligomenorrhea (females)
- Gynecomastia (males)
- Impotence

[a] Unless there is evidence of gonadal hormone suppression, uncontrolled pain and not opioids should be suspected as the major contributor to low serum levels.

https://www.practicalpainmanagement.com/resources/diagnostic-tests/hormone-abnormalities-uncontrolled-chronic-pain-patients-use-hormone

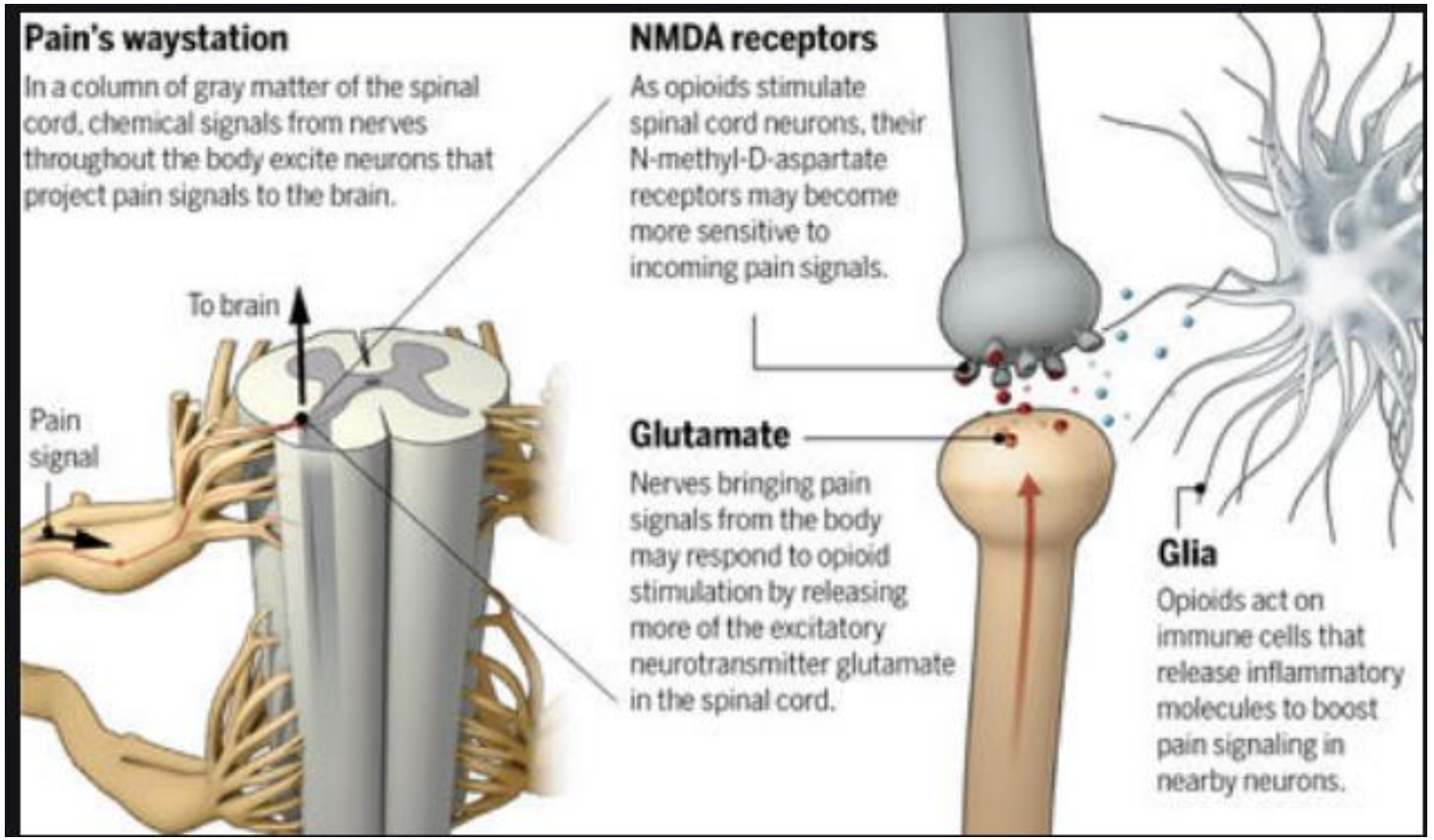
Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. *Ther Clin Risk Manag*. 2015;11:515-523
https://doi.org/10.2147/TCRM.S79409

Opioid induced hyperalgesia

Worsening pain over time in spite of and b/c of increased opioid doses

Areas of pain more diffuse

Pain of lesser quality and harder to pinpoint



https://www.sciencemag.org/news/2016/11/why-painkillers-sometimes-make-pain-worse

Opioid induced hyperalgesia

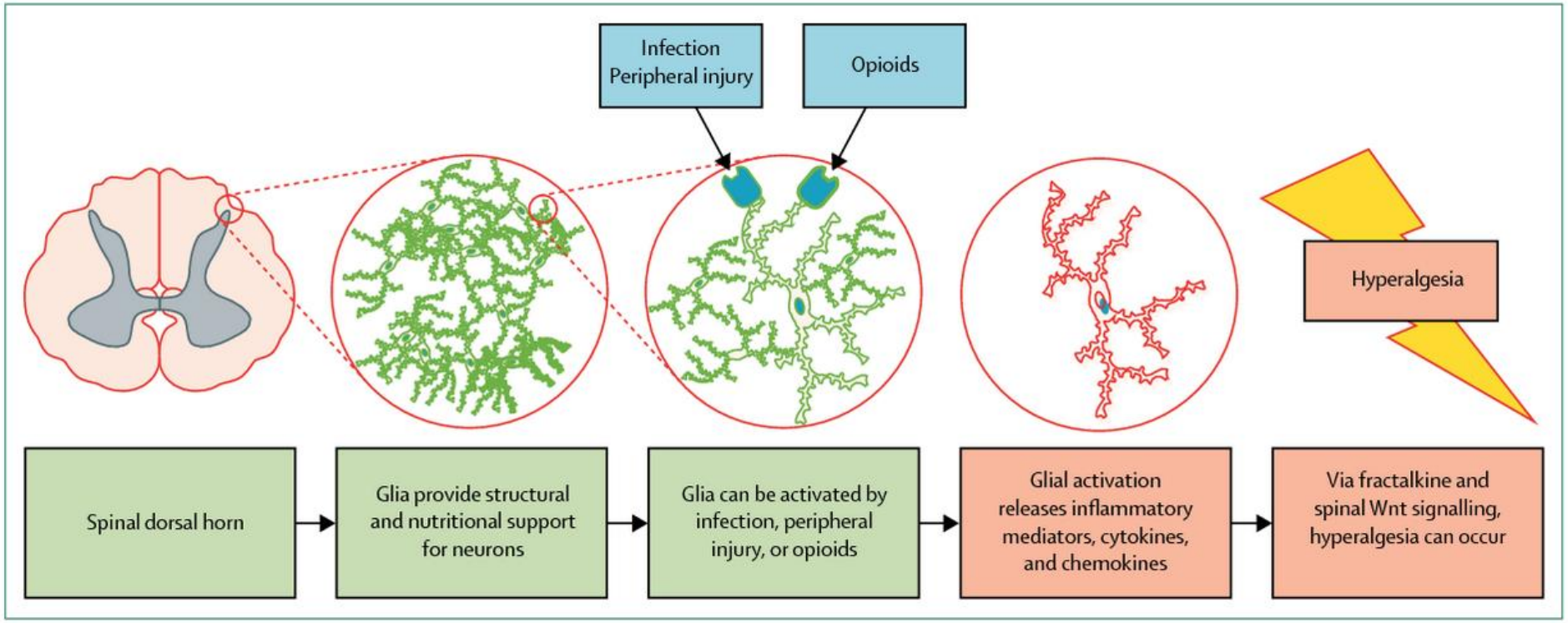


Figure 3: Proposed mechanism of opioid-induced hyperalgesia Spinal dorsal horn glial inflammatory processes are mediated in part by chemokines, such as fractalkine, and result in hyperalgesia.

Published in The lancet. Gastroenterology & hepatology 2017

Narcotic bowel syndrome.

A. Farmer, J. Gallagher, C. Bruckner-Holt, Q. Aziz

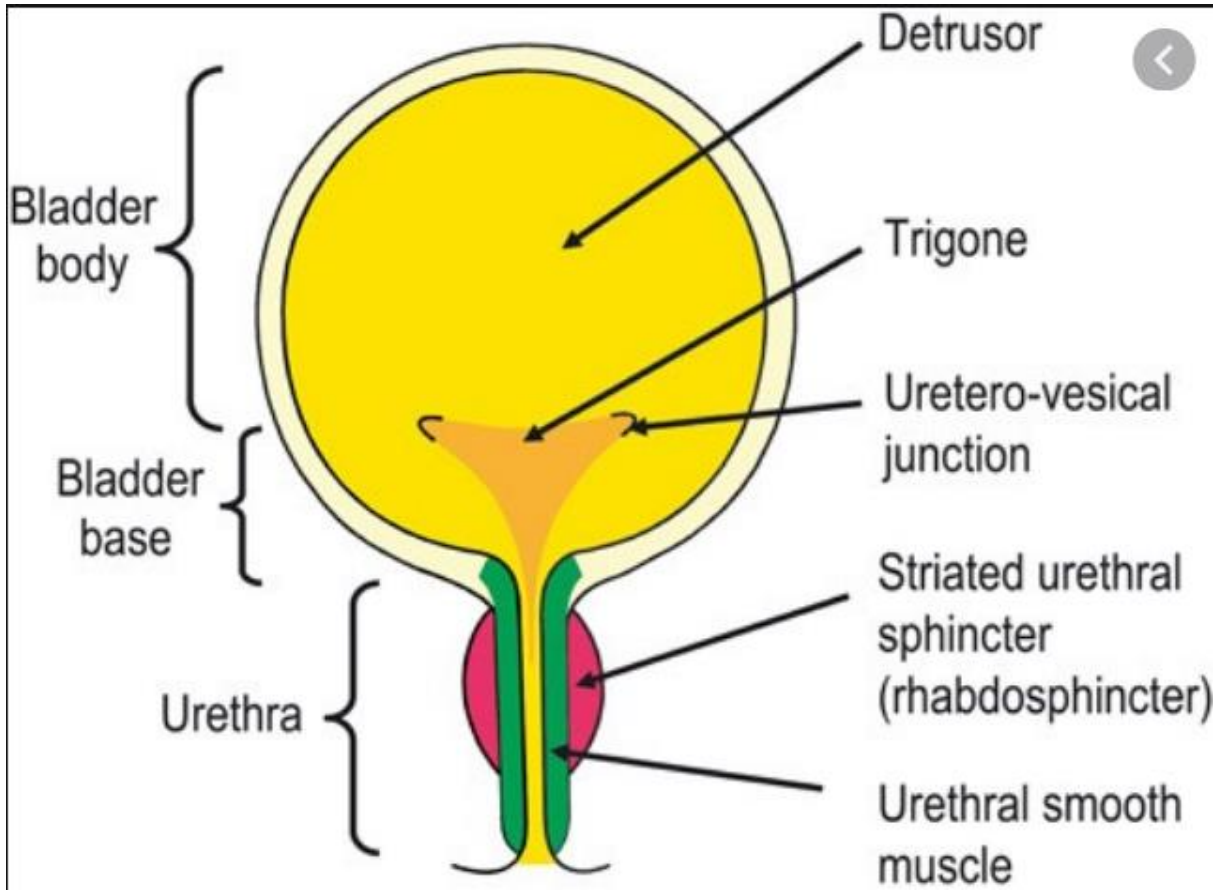
Bladder dysfunction

Spasm of wall muscle and internal sphincter

Increased ADH release

Inhibition of urinary voiding reflex

Increased tone of of external sphincter—increased bladder volume



Westerling D., Andersson KE. (2007) Opioids and Bladder Pain/Function. In: Schmidt R., Willis W. (eds) Encyclopedia of Pain. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-29805-2_2975

Sleep Disturbance

- Increased number of shifts in sleep waking states
- Decrease total sleep time
- Decrease sleep efficiency
- Decrease delta sleep
- Decrease REM sleep

https://www.medpagetoday.com/neurology/sleepdisorders/83530

Conclusions

- Need more evidence to support the use of long term opiods
- May be beneficial in small set of select pts

- Educate and monitor pts for opioid related adverse effects
- Opioid induced adverse effects can impact multiple systems

Krebs EE, Gravely A, Nugent S, et al. 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. *JAMA.* 2018;319(9):872–882. doi:10.1001/jama.2018.0899

Veiga D. et al. Effectiveness of opioids for chronic noncancer pain: A two-year multicenter, prospective cohort study with propensity score matching. The J of Pain 2018; 00:1-10.

Shaheed C, et al. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain. A systematic review and metanalysis. JAMA Int Med 2016; 176(&): 958-968.

Benyamin R. Opioid complications and side effects. Pain Physician: Opioid special issue 2008; 11: S105-S120.

Hauser W. All-cause mortality in patients with long-term opioid therapy compared with non-opioid analgesics from chronic non-cancer pain: a database study. BMC Medicine 2020; 18: 162.