

Opioids and Non-opioids in the Management of Pain: Time for Change

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Disclosures

- **Relationships with for-profit interests**
 - None, not allowed
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Objectives

1. Brief outline of 'opioid epidemic' in Canada and how it impact our patients
2. Review the best evidence on comparative effectiveness and safety of opioids versus non-opioids for pain
3. Discuss approach to managing pain and opioids

Example Case

Mr HD, a 78 yr man with COPD, chronic pancreatitis, hypertension, diabetes, GERD. Admitted with flare in abdominal pain. Home meds include hydromorphone Contin 9 mg bid plus 2-4mg IR q4h prn, hydrochlorothiazide, metformin, PPI, metoprolol, ramipril, lorazepam, inhalers.

Nothing concerning is found on CT abdomen.

1. *What would you prescribe for his Pain?*
 - a. Discontinue hydromorphone, substitute non-opioid
 - b. Increase the dose of hydromorphone only
 - c. Add acetaminophen
 - d. Add NSAID
 - e. Add Anticonvulsant
2. *What if the pain was back pain? Or knee pain or headache?*

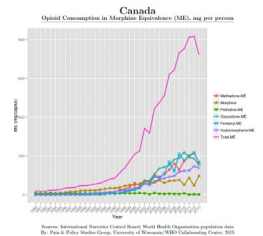
Practice Reflection

Thinking of all of the patients you have seen who were taking high doses of opioids for chronic non-cancer pain:

By the time you finished seeing them or discharged them, what percentage of patients had started tapering or had a specific plan in place to taper the opioids?

- a) > 70%
- b) 40-70%
- c) 10-40%
- d) < 10%

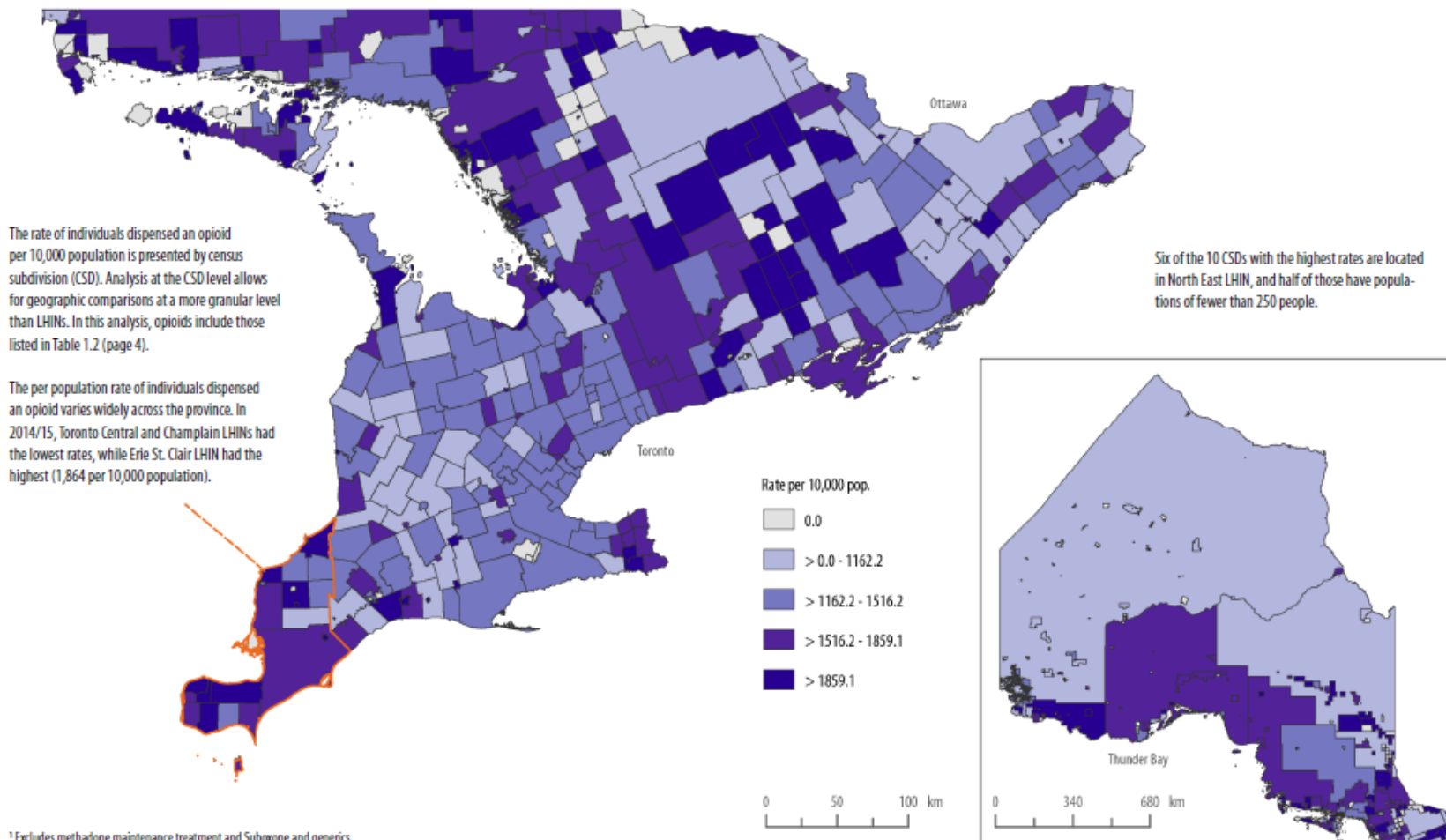
Opioid Utilization: Background



- ❑ Canadians are second highest opioid users per capita in the world
 - ❖ 1 in 8 Canadians filled opioid prescription in 2018
 - 1 in 5 seniors
- ❑ Approx. 4400 opioid-related deaths annually
- ❑ The elderly have the highest rate of high potency opioid use, chronic use, and opioid-related hospitalization
- ❑ Opioids now the leading cause of death in age group 30 to 39 years
 - ❖ Contributing to a recent drop in Canadian life expectancy

Regional Variation in Utilization

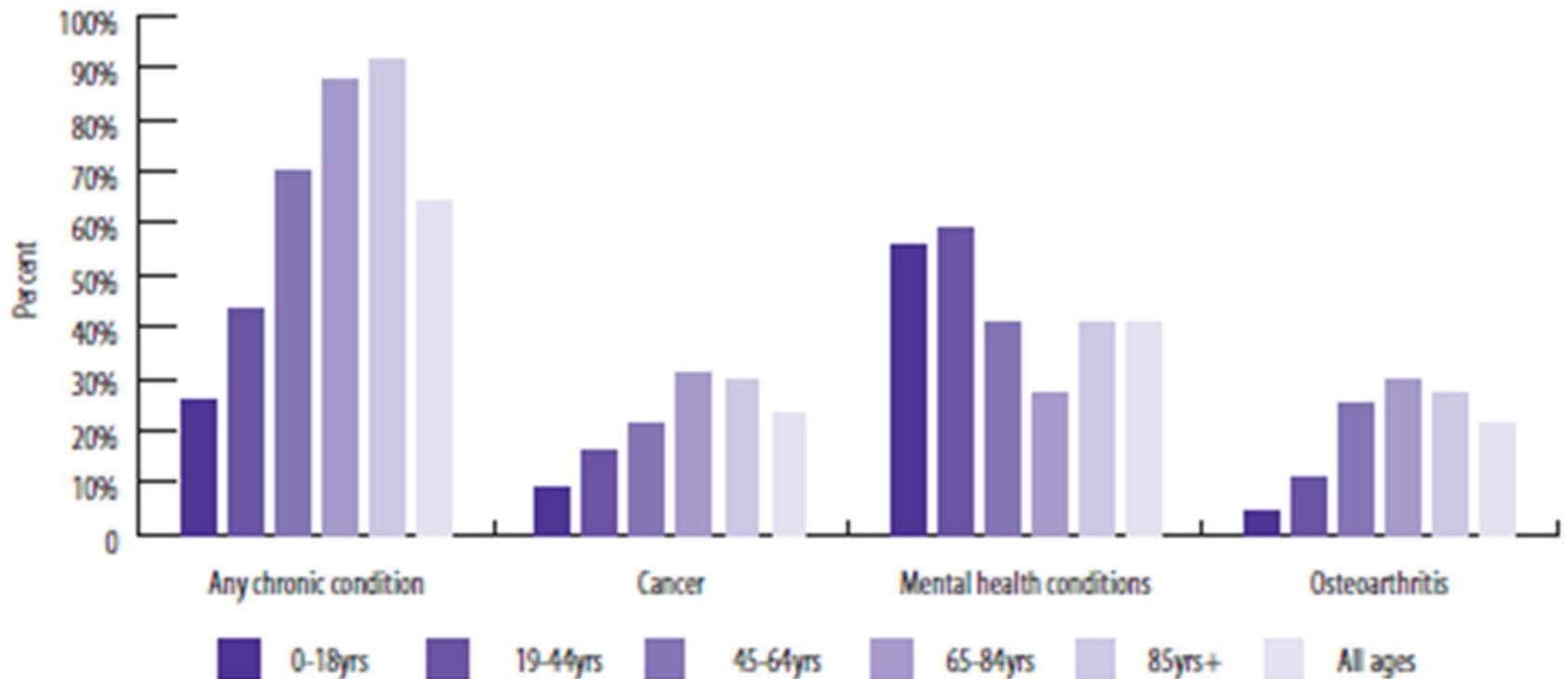
Figure 1.7: Rate of individuals dispensed an opioid¹ per 10,000 population, by CSD, FY 2014/15



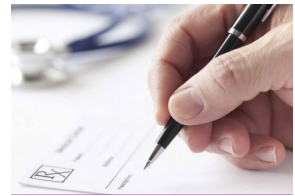
¹ Excludes methadone maintenance treatment and Suboxone and generics.
Data source: Narcotics Monitoring System (NMS), MOHLTC, 2014/15.

What are Opioids Used for?

Figure 1.4: Percent of all opioid recipients having chronic conditions, by age group, FY 2014/15

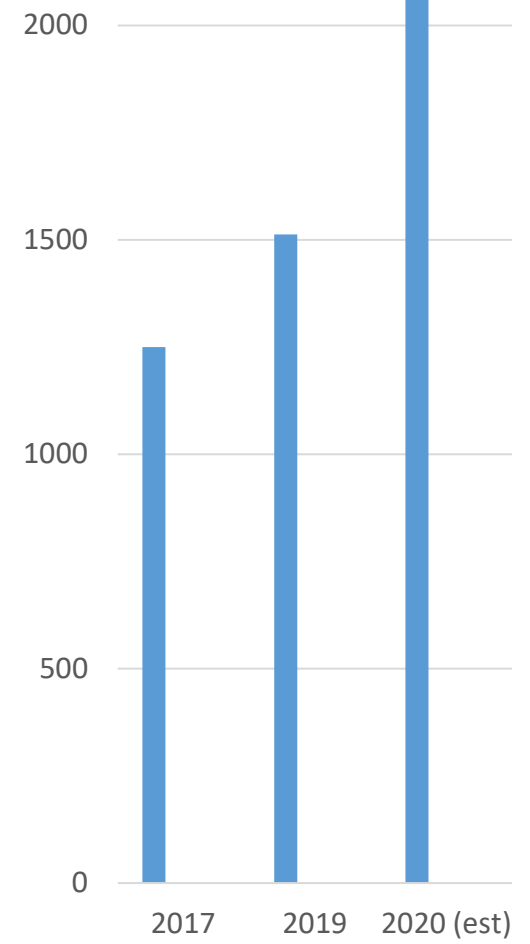
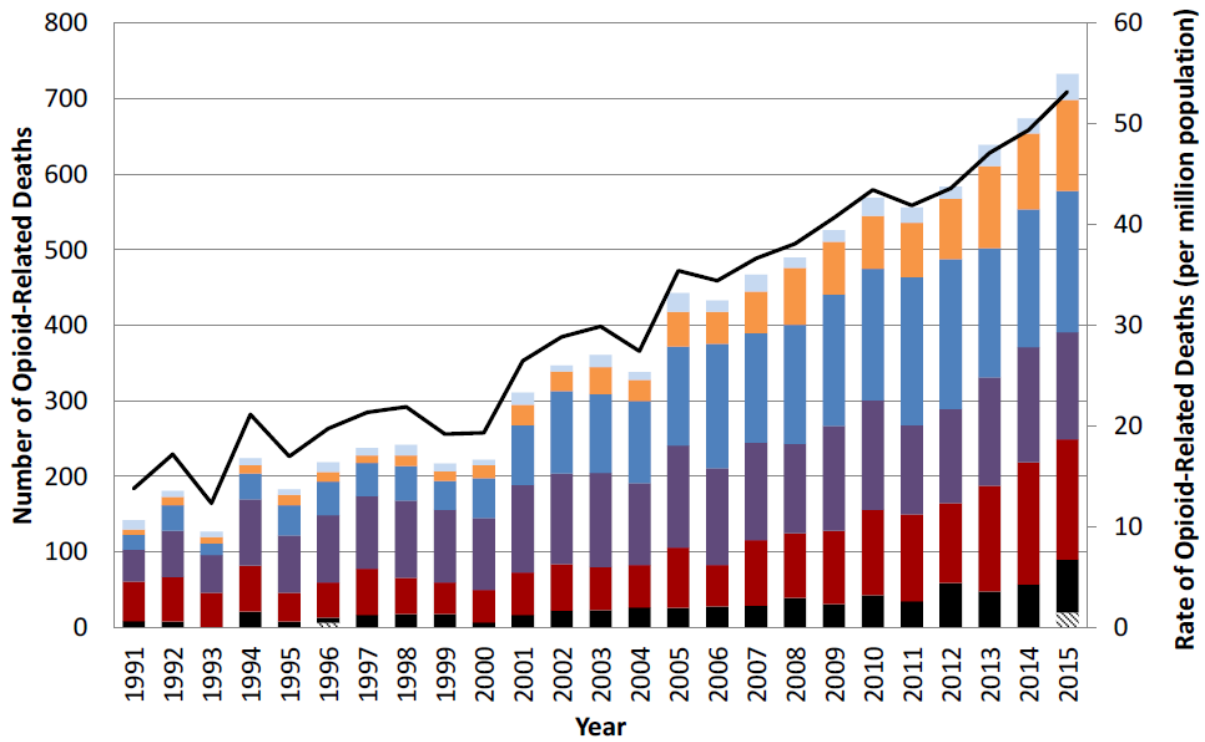


Opioid-related Harm



- ❑ Use disorder (addiction, dependence, abuse)
 - ❖ Prevalence reported at 3-26%, CCSA says 9.6% in 2018
 - ❖ Associated with younger age, other substance use disorder, depression, use of other psychotropic meds
 - ❖ Illicit drug use, criminal behaviour
- ❑ Fatal and non-fatal overdose
- ❑ Fracture, falls, driving crashes, hypogonadism, nausea/vomiting/constipation, amnesia, cognitive changes, drowsiness, sleep apnea, urinary retention, pruritis, infection risk, weight gain, hyperalgesia
- ❑ Additional direct health care costs of approx. \$20K/patient/yr

Opioid-related Deaths in Ontario

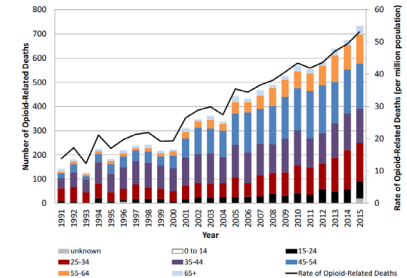


unknown (hatched) 0 to 14 (white) 15-24 (black)
 25-34 (red) 35-44 (purple) 45-54 (blue)
 55-64 (orange) 65+ (light blue) Rate of Opioid-Related Deaths (black line)

Drug Poisonings at SJHH

- Dovetale-EPIC review 2018-2020
- N = 2983
 - ❖ mean age 38.3, 54.7% women
 - ❖ 1236 (41.4%) considered non-intentional
 - ❖ 866 (29.0%) mental health diagnosis
- 853 (28.6%) involve opioids
 - ❖ 238 (8.0%) involve fentanyl

Opioid-related Harm: Mortality Predictors

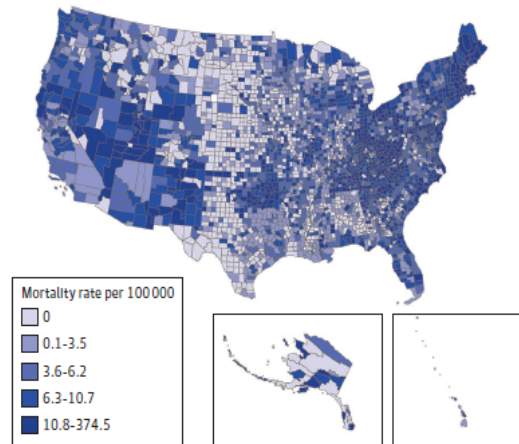


- Opioid dose in morphine mg equivalents
 - ❖ Especially beyond 50 MME
- Long-acting opioids – at least new use
- Concomitant use:
 - ❖ Other sedatives – benzodiazepines, alcohol, gabapentin, pregabalin, etc
 - ❖ Illicit opioids
- Depression
- Pharmaceutical marketing of opioids to physicians

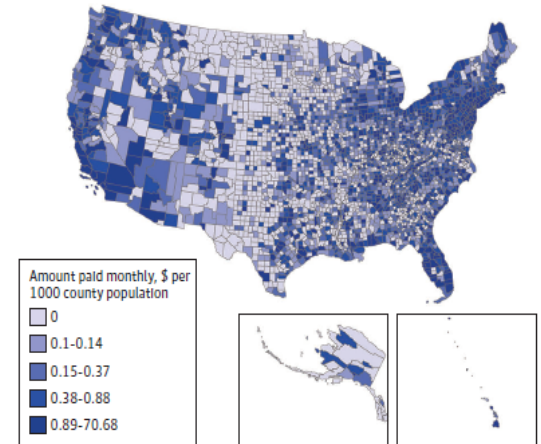
Pharmaceutical Marketing and Opioid-related Mortality

- 434,754 non-research payments to 67,507 physicians 2013-15
- Marketing opioids increased prescribing rates then opioid-related mortality

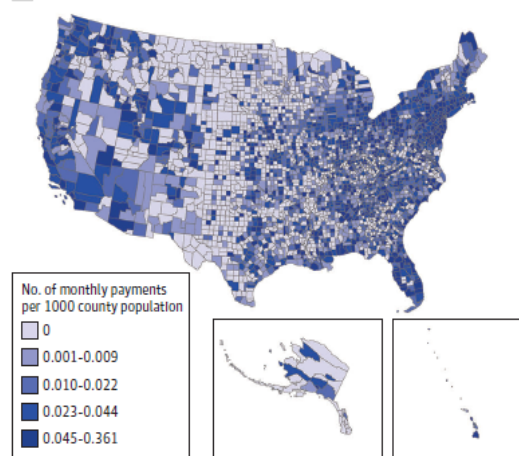
A Mean mortality rate from prescription opioid overdoses across US counties (2014-2016)



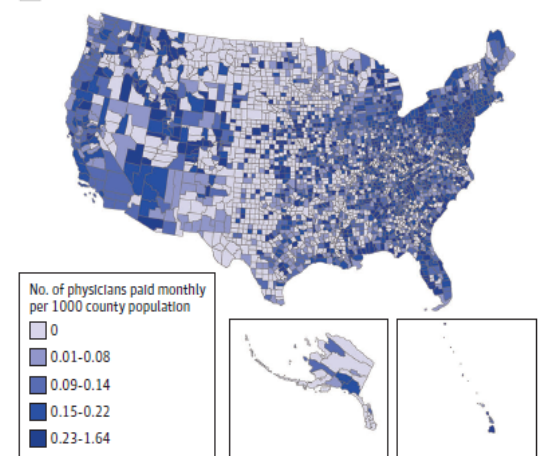
B Marketing value in dollars (2013-2015)



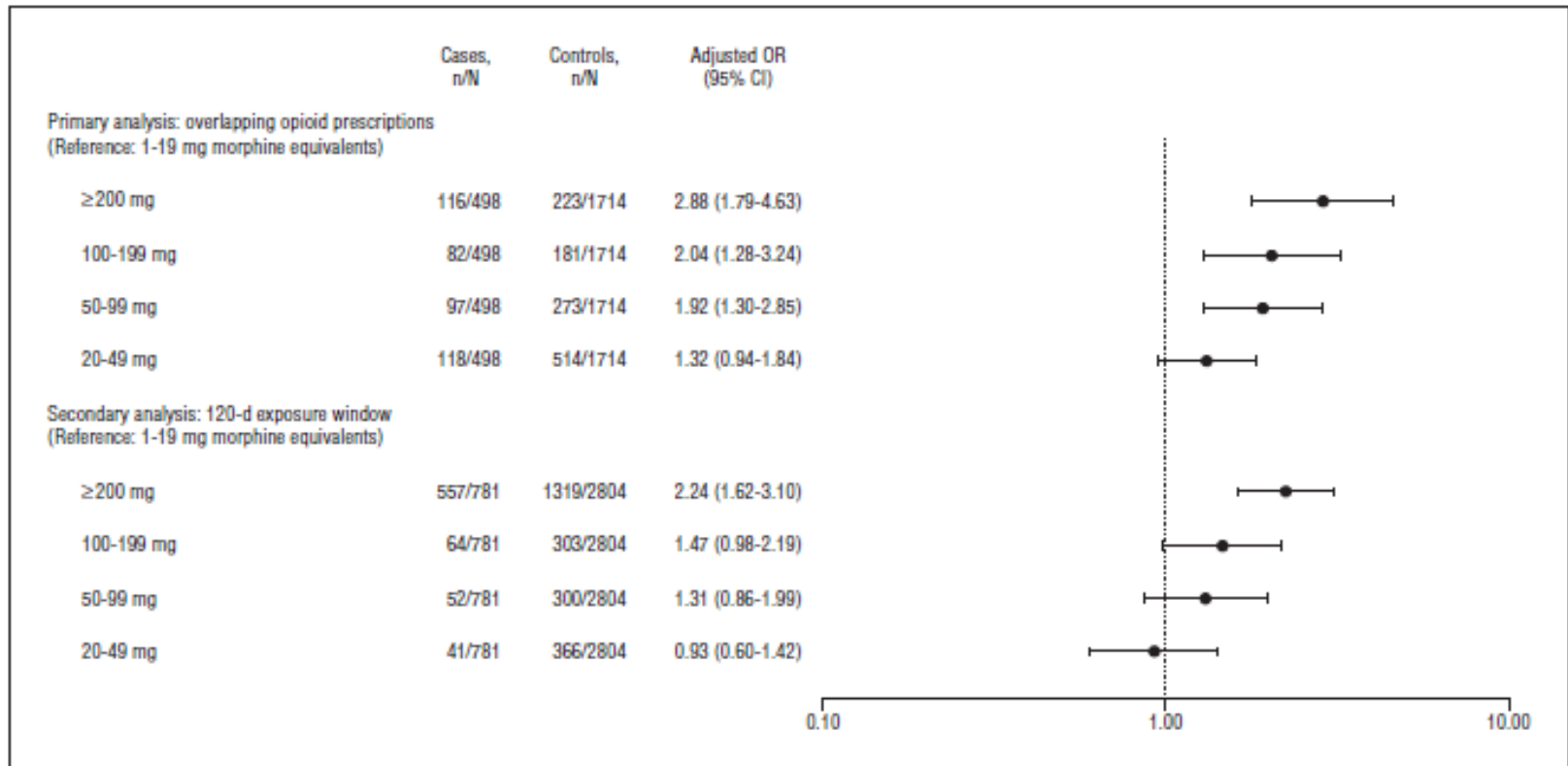
C Payments to physicians (2013-2015)



D Physicians receiving marketing (2013-2015)

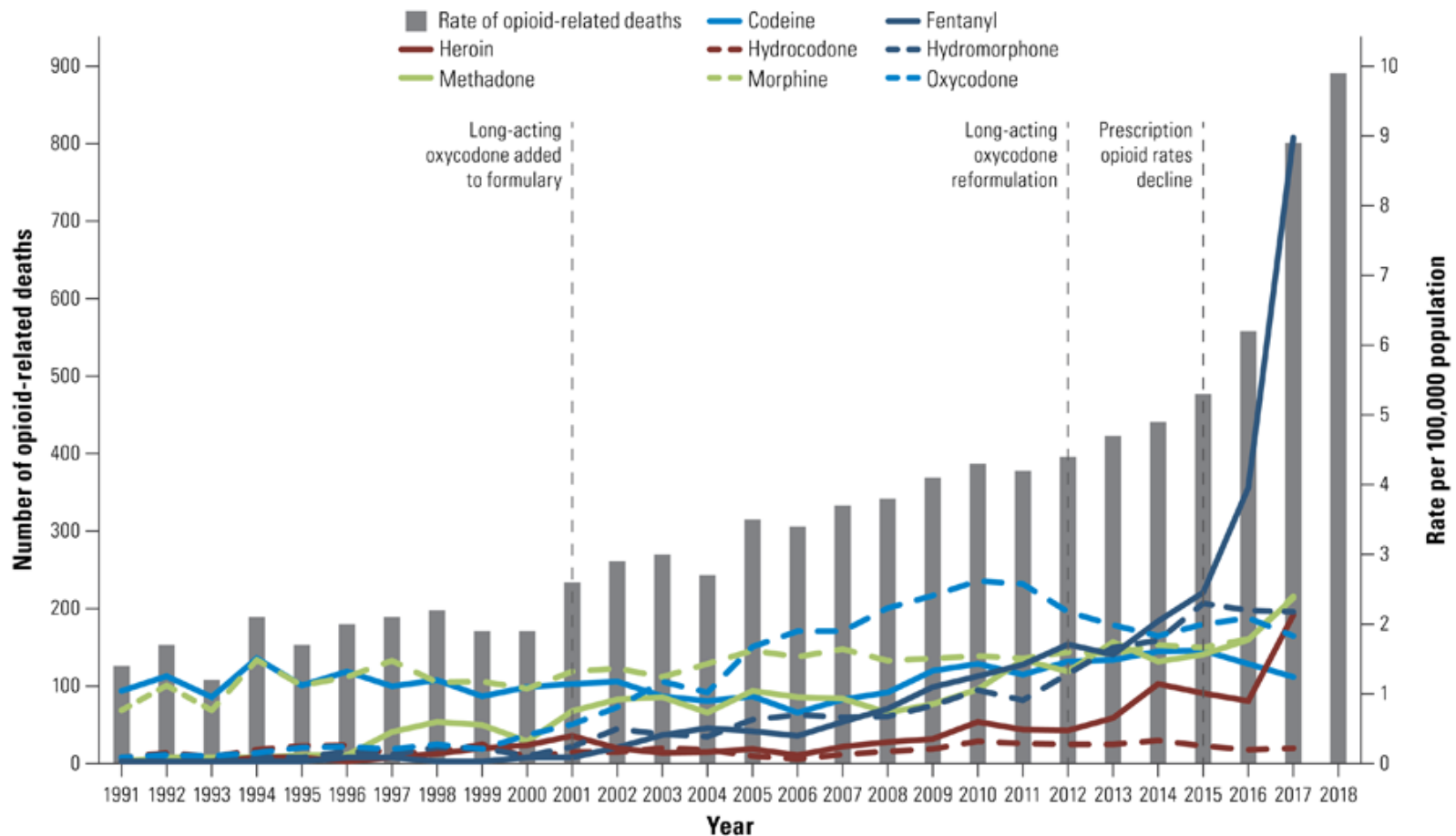


Opioid Dose and Mortality

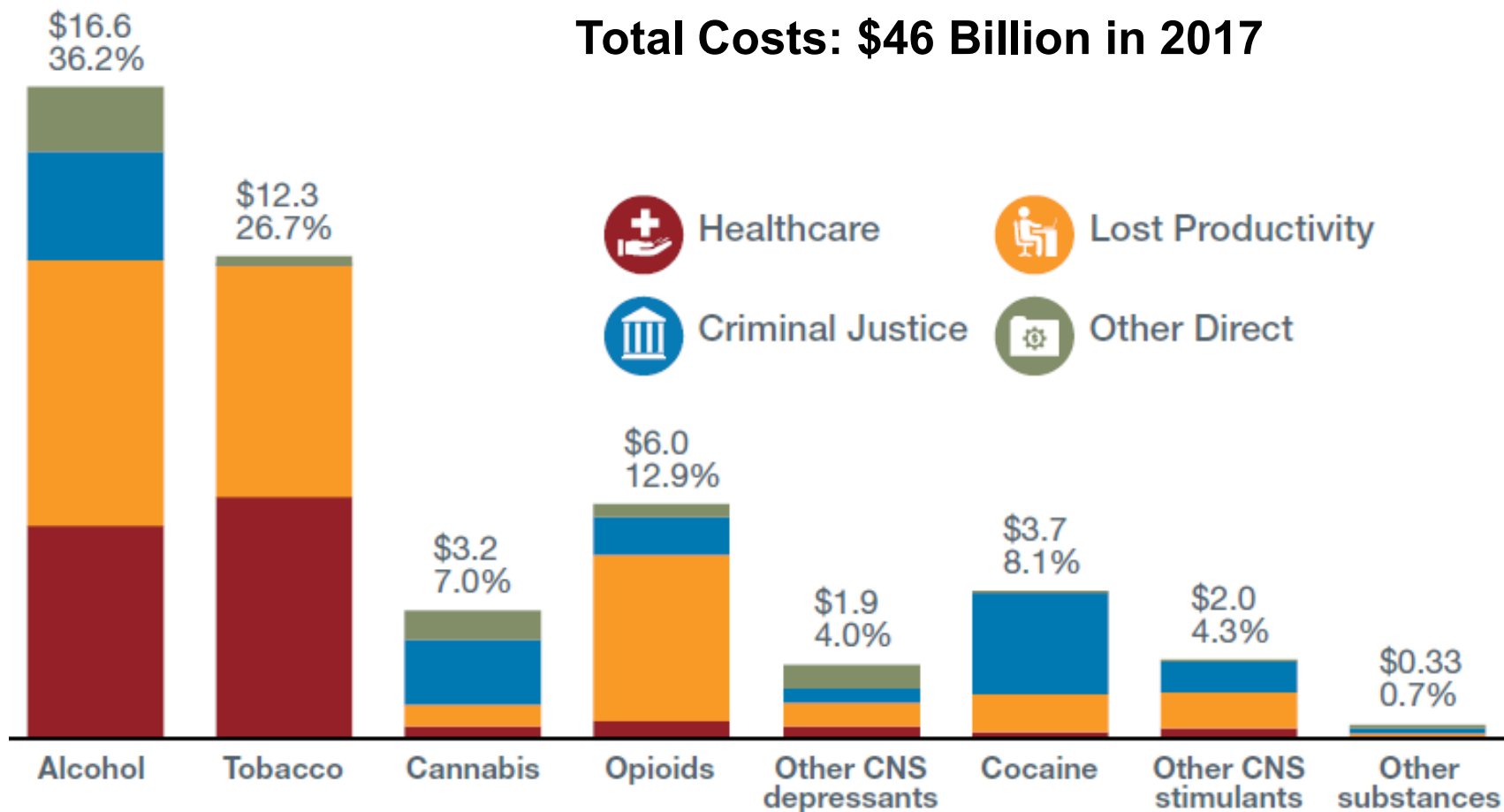


- ❑ Meta-regression shows no dose effect for pain, physical function

Overdose Deaths Not Declining



Costs of Substance Use: Canada



PEARL: Learn Morphine Mg Equivalents (MME)

Opioid (Equivalent Oral Dose , mg)†	30 mg Morphine	50 mg Morphine
Codeine	200	333
Hydromorphone	6	10
Morphine	30	50
Oxycodone	20	33
Tramadol	150	250
Fentanyl patch	6-12mcg/h	15mcg/h
Methadone	7	12

† *First 6 opioids account for 96% all opioid prescriptions in Canada*

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3. Approach to managing pain and opioids

Opioids for Chronic Noncancer Pain: Best Evidence

- Systematic review of 96 RCTs
 - ❖ n = 26,169 (61% female, median age 58 yr)
 - 25 trials neuropathic pain, 32 trials nociceptive pain, 33 trials central sensitization, 6 mixed
 - 79% industry-funded
 - Median MME 45 mg/day, median duration 60 days
 - Primary outcomes pain severity, physical function
 - Secondary outcomes - Emotional/role/social function, sleep quality, adverse events (AEs)

Opioids for Chronic Noncancer Pain

Outcome Measure	No. of Trials (N = 96)	No. of Patients (N = 26 169)	Follow-up, mo	Serious Risk of Bias? ^a	I ² (95% CI), % ^b	Serious Indirectness or Imprecision? ^c	P Value for Publication Bias ^d	No. (%) of Patients Who Achieved the MID		Risk Difference for Achieving the MID (95% CI), %		Quality of Evidence
								Placebo	Opioids	WMD (95% CI)		
Pain ^e	42	16 617	3-6 ^f	No	70.4 (59.5 to 78.4)	No	.07	3232 (48.7)	6048 (60.6)	11.9 (9.7 to 14.1)	-0.69 cm (-0.82 to -0.56)	High
Physical functioning ^g	51	15 754	1-6	No	65.7 (53.9 to 74.4)	No	.06	2992 (46.1)	5058 (54.6)	8.5 (5.9 to 11.2)	2.04 points (1.41 to 2.68)	High
Emotional functioning ^h	23 ⁱ	8962	1-4	No	47.2 (14.0 to 67.6)	No ^j	.86	1141 (35.0)	1899 (33.3)	-1.7 (-4.2 to 0.8)	-0.44 points (-1.09 to 0.20)	High
Role functioning ^k	16 ⁱ	5329	1-4	No	18.3 (0 to 54.6)	No ^j	.89	1113 (48.0)	1475 (49.0)	1.0 (-0.7 to 2.6)	0.87 points (-0.54 to 2.28)	High
Social functioning ^l	29	7623	1-4	No	19.7 (0 to 49.4)	No	.84	1527 (43.8)	1920 (46.4)	2.6 (0.7 to 4.5)	1.58 points (0.45 to 2.70)	High
Sleep quality ^m	15	6585	3-6 ^f	No	60.3 (30.0 to 77.5)	No	.06	1232 (47.2)	2111 (53.1)	5.9 (2.8 to 9.1)	3.42 mm (1.58 to 5.26)	High
Vomiting ⁿ												
Enrichment trials	18	5961	1.5-4	No	0 (0 to 41.3)	No	.65	68 (2.3) ^o	179 (5.9) ^o	3.6 (2.1 to 5.4)	RR, 2.50 (1.89 to 3.30)	High
Nonenrichment trials	33	11 268	1-6	No	0 (0 to 36.4)	No	.23	96 (2.3) ^o	667 (9.4) ^o	7.1 (5.4 to 9.3)	RR, 4.12 (3.34 to 5.07)	High

- ❖ No benefit outcome met Minimal Important Difference vs placebo
- ❖ More vomiting, constipation, drowsiness, dizziness, pruritis
- ❖ Opioids similar benefit to NSAIDs, TCAs, anticonvulsants but more adverse events
- ❖ No difference by pain type

Opioids MSK Pain in Elderly

- SR people > 60 yr with MSK pain
 - ❖ 23 RCTs placebo-controlled
 - ❖ small effect decreasing pain intensity and improving function
 - Not associated with dose or duration
 - ❖ Adverse events 3 X higher
- SR with NMA, non-low back acute MSK pain
 - ❖ 207 RCTs, n = 32,959, med-mean age 34 yr, mean pain score 6.5/10
 - ❖ For pain, function, satisfaction – topical NSAIDs best then oral NSAIDs then ACM
 - ❖ Opioids less effective, more adverse effects, particularly GI and neurologic

Opioids vs Non-opioids for Musculoskeletal Pain



- 240 patients of US VA clinics (SPACE RCT)
 - ❖ Mean age 58.3, 13% women, 97.5% completed trial
 - Moderate to severe chronic back pain or hip or knee OA despite analgesia
 - Pre-randomization patient perception of effectiveness for opioids 7.8/10 vs non-opioids 5.7/10;
 - ❖ Comparing IR opioids then SR opioids then TD fentanyl to max 100 MME vs ACM and NSAIDs then adjuvant TCAs and transdermals then pregabalin/duloxetine/ tramadol
- Results:
 - Pain-related function not different between groups over 12 months
 - Pain intensity improved more for non-opioid strategy with half the adverse events, half the rate of discontinuation (p=0.03)

Opioids for Acute Pain: SR

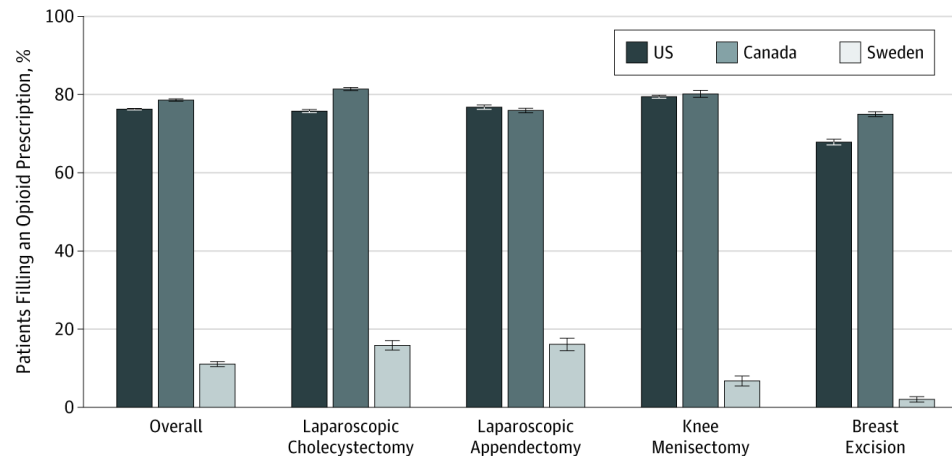


□ SR ED/EMS settings

- ❖ 52/65 were RCTs, 51 from ED, all low to moderate quality evidence
- ❖ $N < 7000$ patients with acute pain $\geq 7/10$
- ❖ IV opioids NOT superior to IV acetaminophen or IV NSAIDs or IV ketamine
- ❖ $> 50\%$ patients receiving opioids have AE
- ❖ Opioids more harmful than ACM or NSAIDs

Opioids and Surgery

- Opioid-naïve patients 16-64 yr undergoing 4 low risk surgeries in Ontario, USA, Sweden 2013 to 2016 (N = 223,834)



% Patients Filling an Opioid Prescription During First 7 Days After Surgery

- USA tended to use much more potent opioids

Opioids Peri-operatively



- SR codeine vs NSAIDs for same day surgery
 - ❖ 40 RCTs, n = 5116
 - ❖ NSAIDs superior at 6 and 12 hours, with fewer adverse effects, including bleeding
- PANSAID RCT on Opioid Sparing
 - ❖ N = 556 pts hip arthroplasty, mean age 67 yr, 50% women, all receiving morphine PCA
 - ❖ Acetaminophen or ibuprofen alone or combinations
 - ❖ Ibuprofen 400 mg qid alone was best
 - PCA morphine reduced by 10 mg/d by 24 hours
 - No difference in adverse events between groups

Cancer Pain Question

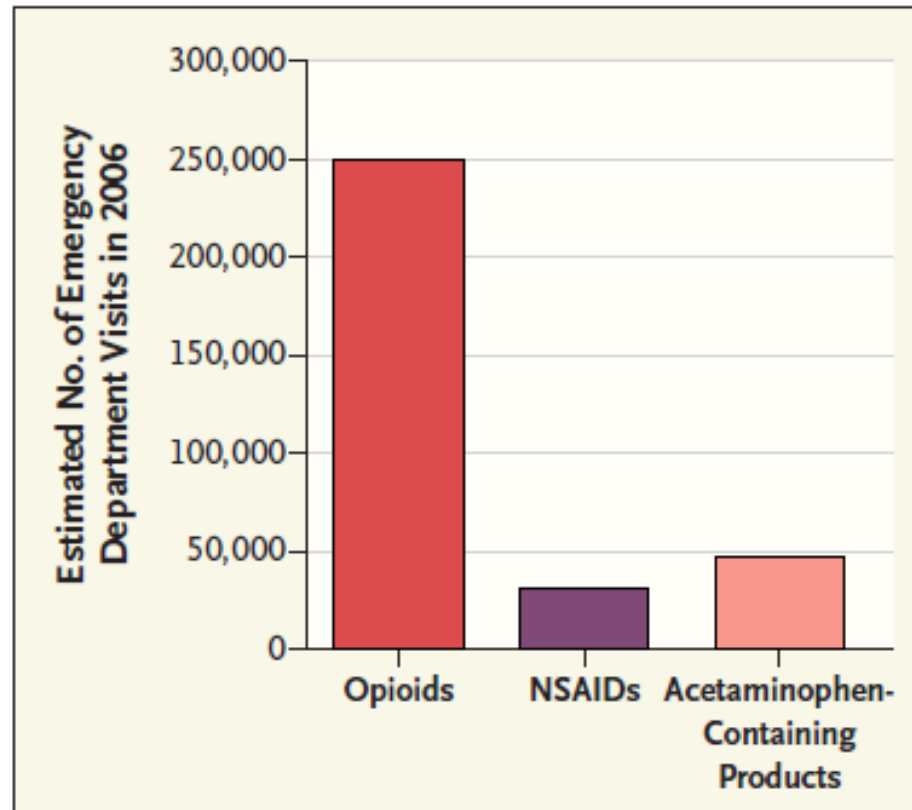
We treat cancer-related pain differently from non-cancer pain because:

- a. Cancer means a short life expectancy so the harms of opioid use don't matter.
- b. It is well known that other families of analgesics are ineffective for cancer pain.
- c. Convention – there is no good evidence that cancer-related pain responds differently than non-cancer pain

Analgesic Comparative Safety

- Which analgesic drug family was responsible for the most serious adverse drug events requiring ED visits in 2006?
 - a. Acetaminophen
 - b. NSAIDs
 - c. Opioids

Analgesics Comparative Safety



Number of Emergency Department Visits in 2006 for Cases Involving Exposure to Opioids, NSAIDs, or Acetaminophen-Containing Products.

Non-opioid Analgesic CES

- ❑ Acetaminophen minimally effective
 - ❖ But safe in therapeutic doses
- ❑ Anticonvulsants and tricyclics
 - ❖ Modest effect pregabalin, gabapentin for neuropathic pain, not effective for back pain,
 - ❖ high withdrawal rates, safer than opioids
- ❑ Ketamine
 - ❖ Needs more research
- ❑ Cannabis, cannabinoids
 - ❖ No good evidence of benefit, some harm

NSAID Safety



- ❑ Opioids sig increase in hospitalization (HR 1.7), death (HR 1.9-3.7), total AE (aHR 2.0) compared to NSAIDs in multiple studies
- ❑ Key NSAID safety outcomes (all chronic use)
 - ❖ BP increase mild - mean of 2/0.5 mmHg, onset > 6 weeks chronic therapy
 - ❖ Cardiovascular events - 0.4% at 6 mo for low risk; up to 5.5% at 18 mo for high risk pt
 - ❖ Renal toxicity - AKI in 0.2% low risk; 4.5% additional AKI in high risk
 - Opioids higher risk for CKD pts compared to NSAIDs, including for kidney outcomes
 - ❖ GI Bleeding - Celecoxib plus PPI at 18 mo - rate of 5.6% in very high risk pts
 - Recent study suggesting opioids associated with higher bleeding risk

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Interventions to Change Opioid Prescribing

- SR interventions targeting opioid prescribing
 - ❖ 116 studies (5 RCTs) with 95 interventions
 - Mostly low quality studies
 - > 50% prescription monitoring programs
 - Others CME, legislation, multidisciplinary clinics, etc
 - Outcome mostly prescription rates
 - No good evidence on clinical outcomes or appropriate use

Patient Assessment: Risk of Benefit vs Harm

PEG Scale Assessing Pain Intensity and Interference (Pain, Enjoyment, General Activity)

1. What number best describes your pain on average in the past week?

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

Opioid Risk Tool (ORT)

Date:				
Patient name:				
		Mark each box that applies	Item score (female)	Item score (male)
1. Family history of substance abuse	■ Alcohol	[]	1	3
	■ Illegal drugs	[]	2	3
	■ Prescription drugs	[]	4	4
2. Personal history of substance abuse	■ Alcohol	[]	3	3
	■ Illegal drugs	[]	4	4
	■ Prescription drugs	[]	5	5
3. Age (mark box if 16 to 45)		[]	1	1
4. History of preadolescent sexual abuse		[]	3	0
5. Psychological disease	■ Attention deficit disorder	[]	2	2
	■ Obsessive compulsive disorder			
	■ Bipolar			
	■ Schizophrenia			
	■ Depression	[]	1	1
TOTAL:			_____	_____
Total score risk category: <ul style="list-style-type: none"> ■ Low risk: 0 to 3 ■ Moderate risk: 4 to 7 ■ High risk: ≥8 				

Reproduced from: Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. *Pain Medicine* 2005; 6(6):432-442, by permission of Oxford University Press on behalf of the American Academy of Pain Medicine, and Lynn R. Webster, MD, author of "The Painful Truth: What Pain is Really Like and Why it Matters to Each of Us."

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Nonpharmacologic Options: Back Pain

Intervention	Pain			Function		
	Magnitude of Effect	Evidence	SOE	Magnitude of Effect	Evidence	SOE
→ Exercise vs. usual care	Small	1 SR (19 RCTs) + 1 SR	Moderate	Small	1 SR (17 RCTs) + 1 SR	Moderate
MCEs vs. minimal intervention	Moderate (short to long term)	1 SR (2 RCTs)	Low	Small (short to long term)	1 SR (3 RCTs)	Low
Tai chi vs. wait list or no tai chi	Moderate	2 RCTs	Low	Small	1 RCT	Low
Yoga vs. usual care	Moderate	1 RCT	Low	Moderate	1 RCT	Low
Yoga vs. education	Small (short term) and no effect (longer term)	5 RCTs (short term) + 4 RCTs (longer term)	Low	Small (short term) and no effect (longer term)	5 RCTs (short term) + 4 RCTs (longer term)	Low
→ Mindfulness-based stress reduction vs. usual care or education	Small	3 RCTs	Moderate	Small	3 RCTs	Moderate
Progressive relaxation vs. wait-list control	Moderate	1 SR (3 RCTs)	Low	Moderate	1 SR (3 RCTs)	Low
Electromyography biofeedback vs. wait list or placebo	Moderate	1 SR (3 RCTs)	Low	No effect	1 SR (3 RCTs)	Low
Operant therapy vs. wait-list control	Small	1 SR (3 RCTs)	Low	No effect	1 SR (2 RCTs)	Low
Cognitive-behavioral therapy vs. wait-list control	Moderate	1 SR (5 RCTs)	Low	No effect	1 SR (4 RCTs)	Low
Multidisciplinary rehabilitation vs. no multidisciplinary rehabilitation	Moderate	1 SR (3 RCTs)	Low	Small	1 SR (3 RCTs)	Low
→ Multidisciplinary rehabilitation vs. usual care	Moderate (short term), small (long term), and favors rehabilitation	1 SR (9 RCTs) (short term) + 1 SR (7 RCTs) (long term)	Moderate	Small (short and long term)	1 SR (9 RCTs) (short term) + 1 SR (7 RCTs) (long term)	Moderate
Acupuncture vs. sham acupuncture	Moderate	1 SR (4 RCTs) + 5 RCTs	Low	No effect	1 SR (4 RCTs) + 5 RCTs	Low
→ Acupuncture vs. no acupuncture	Moderate	1 SR (4 RCTs)	Moderate	Moderate	1 SR (3 RCTs)	Moderate
Spinal manipulation vs. sham manipulation	No effect	1 SR (3 RCTs) + 1 RCT	Low	Unable to estimate	1 RCT	-
Spinal manipulation vs. inert treatment	Small	7 RCTs	Low	-	-	-
Massage vs. usual care	No effect	1 RCT	Low	Unable to estimate	2 RCTs	Insufficient

Opioid Tapering: SR



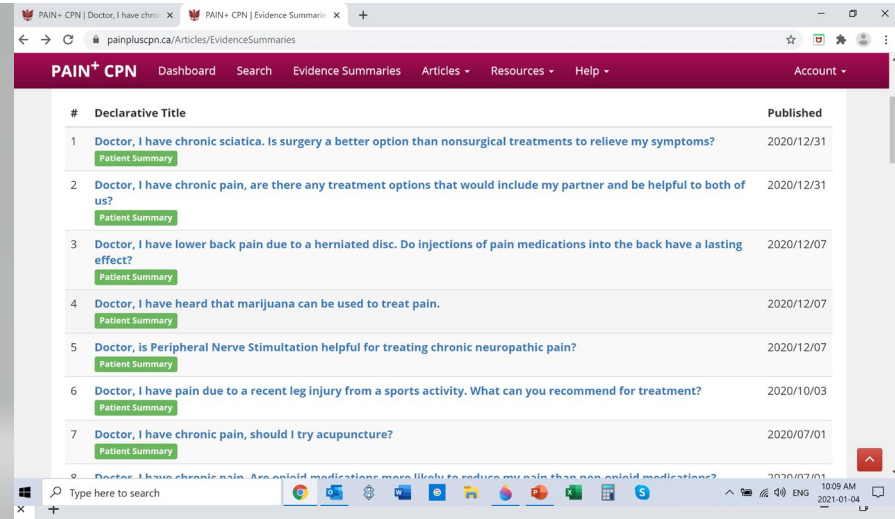
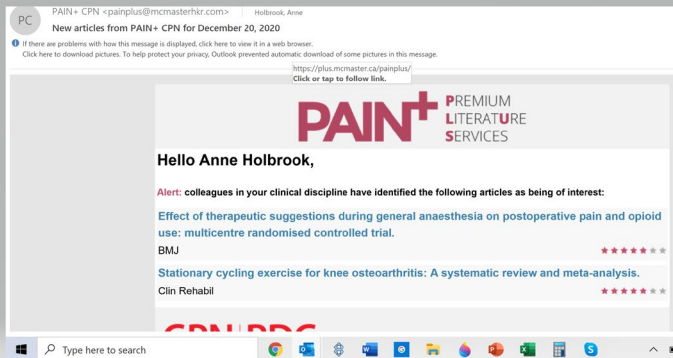
- 67 studies (11 RCTs, 56 observational)
 - ❖ N = 12,546
- 8 types of intervention to reduce or discontinue chronic opioid use
 - ❖ Pain programs, behavioural, buprenorphine
- 40 studies examining patient outcomes
 - ❖ Improvement in pain severity, function and quality of life in all fair-quality studies
 - ❖ Quality of evidence very low

Opioid Agonist Therapy

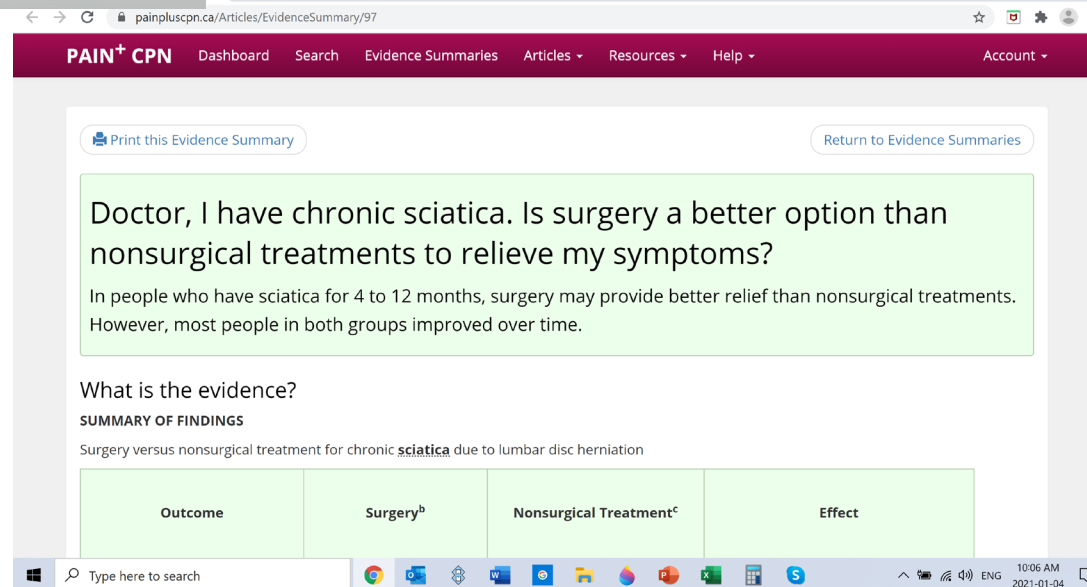


- ❑ SRs of methadone (11 RCTs, n = 1169) or buprenorph/naloxone (31 trials, n=5430) for OUD compared to placebo
 - ❖ Superior retention in treatment, less opioid use
- ❑ SR of 11 trials of heroin users, n = 1592
 - ❖ Psychological therapies added to methadone or buprenorphine decrease dropouts, use of other opioids
- ❑ Retrospective cohort in BC, n = 55,347 from 1996-2018, all pts on opioid agonist therapy (OAT)
 - ❖ Mortality rate overall 17.5 per 1000 person-years
 - ❖ SMR 7.2 overall, 4.6 on OAT vs 9.7 off OAT, lower on Bup/Nal than methadone
 - ❖ OAT more protective in presence of fentanyl

Learning Resources



https://machealth.ca/programs/opioids_clinical_primer



Analgesia Principles

1. Assess pain, function, risk of harm
2. Keep expectations reasonable – analgesics have limited benefits, not curative
3. Use every non-opioid option
4. Avoid prescribing opioids for chronic pain, acute back pain, arthritis, fibromyalgia, neuropathic pain, etc
5. Learn morphine mg equivalents
6. Do not prescribe doses greater than 50 MME/d
7. Avoid long-acting opioids
8. Always try to taper to discontinue opioids

Summary

- Opioids are poor analgesics
- The harm of opioids outweighs their benefit even at low dose
- Opioid dependence and addiction are very hard to treat
- There are no highly effective, safe analgesics
 - ❖ This is a top research priority