Therapeutic potential of Opioid-Cannabinoid Interactions

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Disclosures

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CAMH
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Narsad

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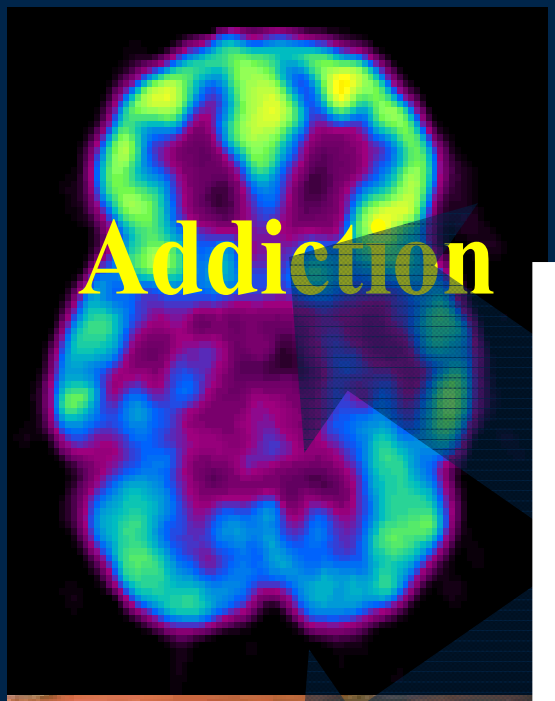
Outline

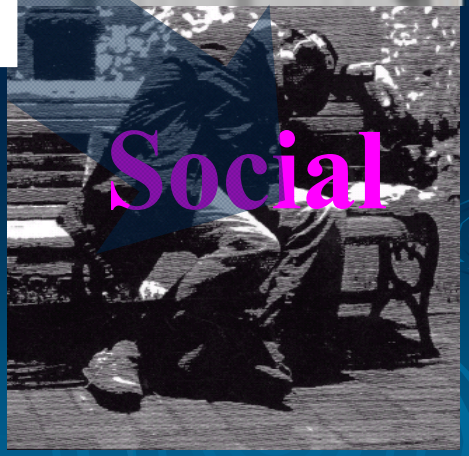
1. The Opioid Crisis
2. Therapeutic potential of cannabinoid/opioids interactions
   - To help with problems related to opioid drugs
   - To help with problems related to cannabis

VERY HIGH RISK

OVERDOSE, INFECTIONS



OPIOIDS



Canada: one of the highest user of opioids

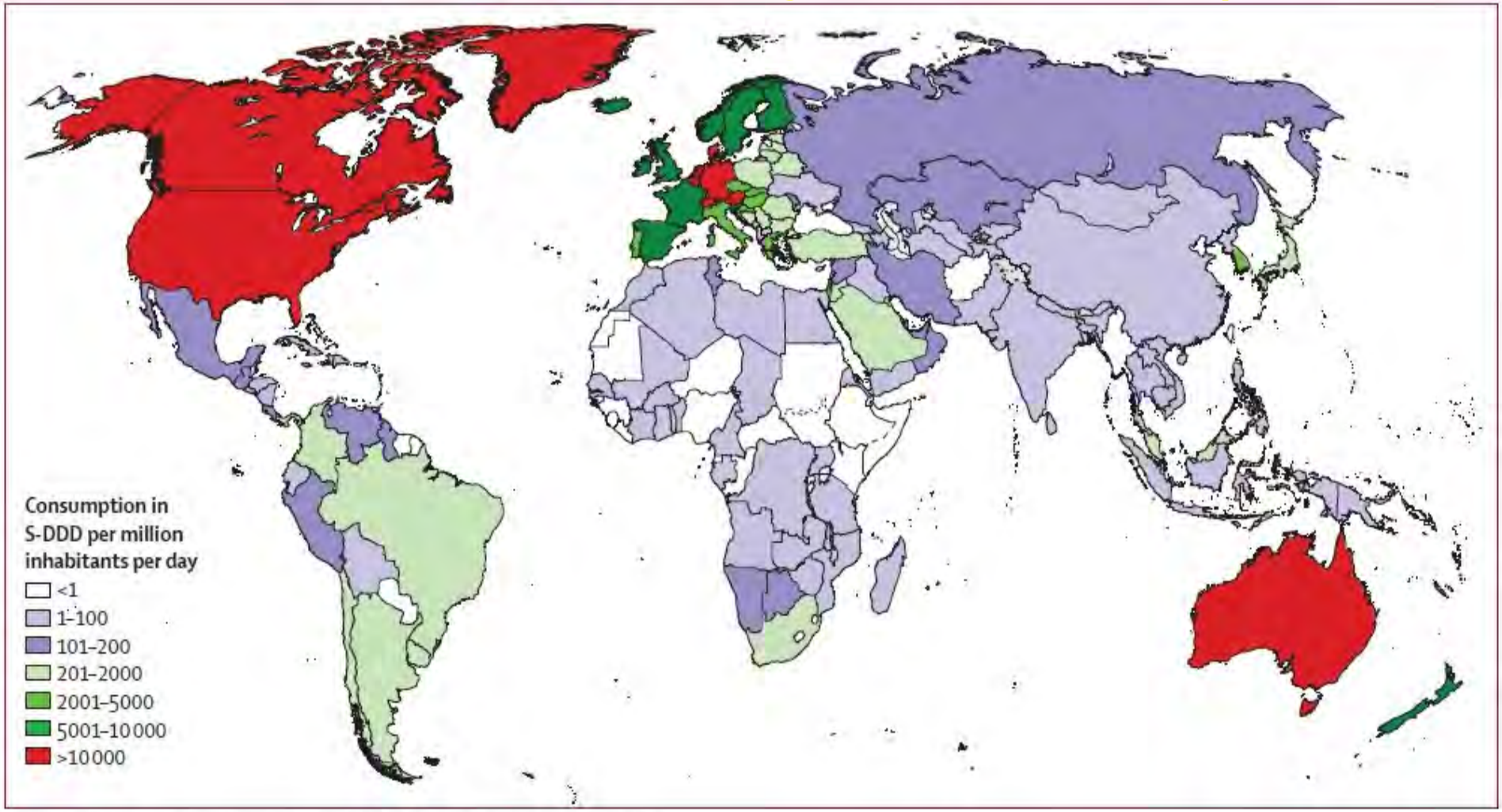
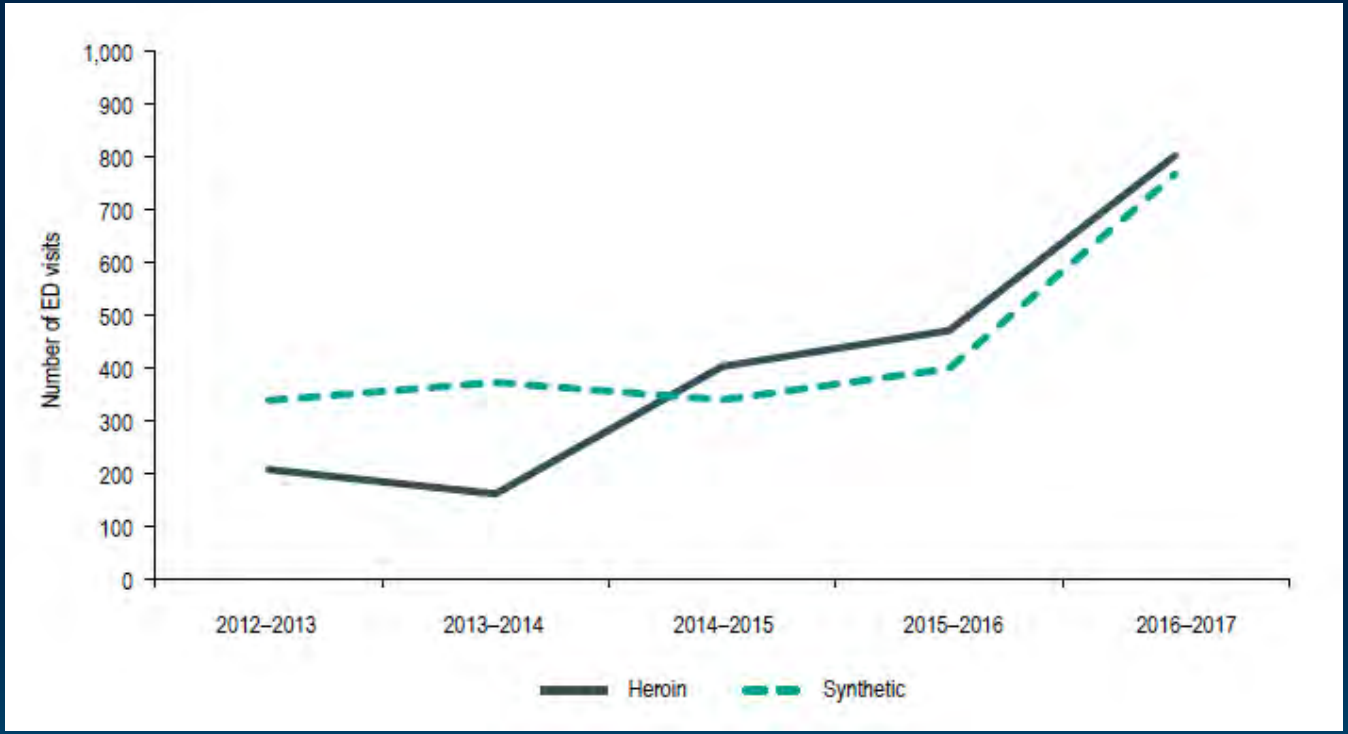


Figure 2: Mean availability of opioids for pain management in 2011–13

From WHO

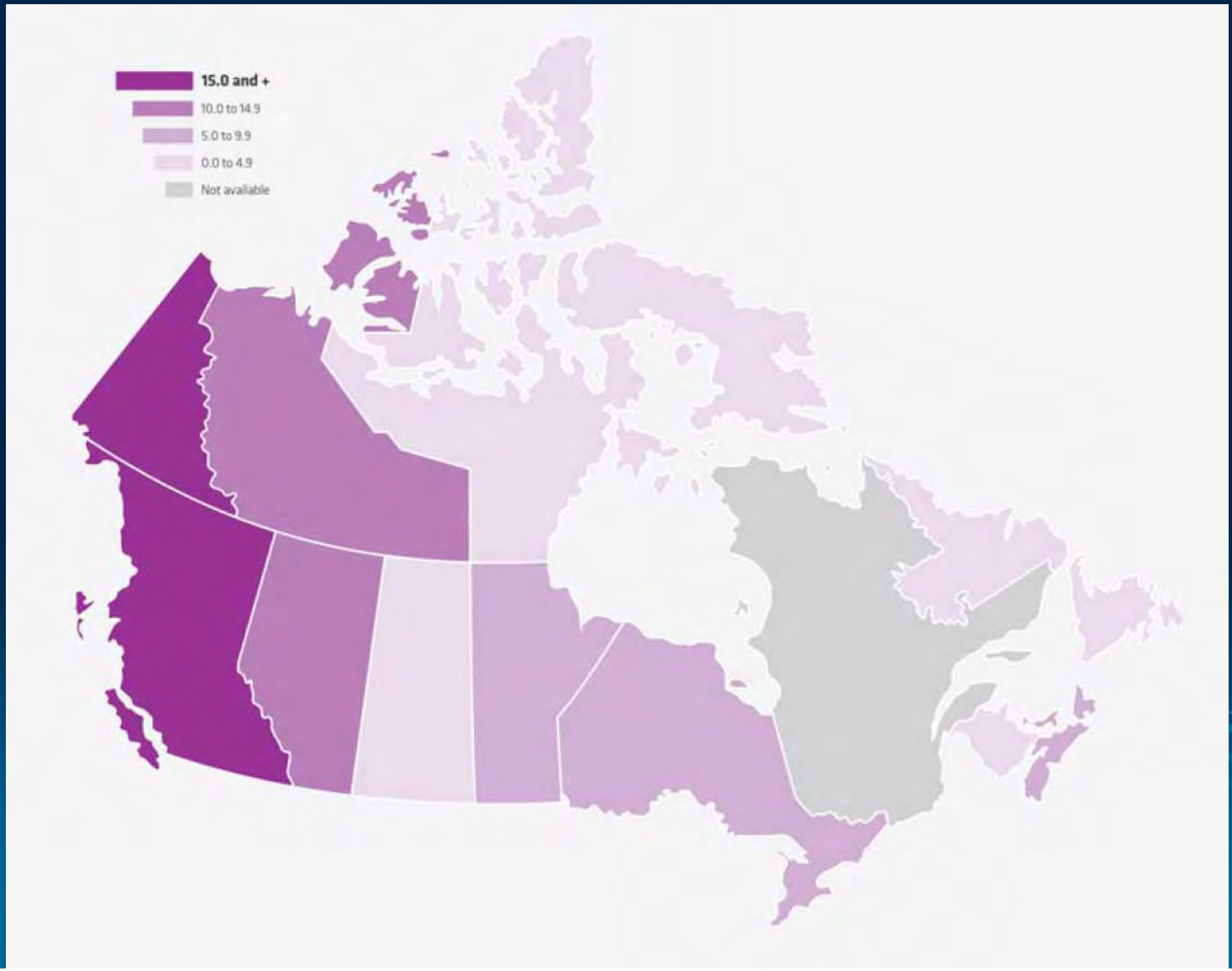
ED visits due to heroin and synthetic opioid poisoning, Ontario, 2012-2013 to 2016-2017



In Ontario, over the past 5 years, the number of ED visits increased almost four-fold for heroin poisonings and more than double for synthetic opioids.

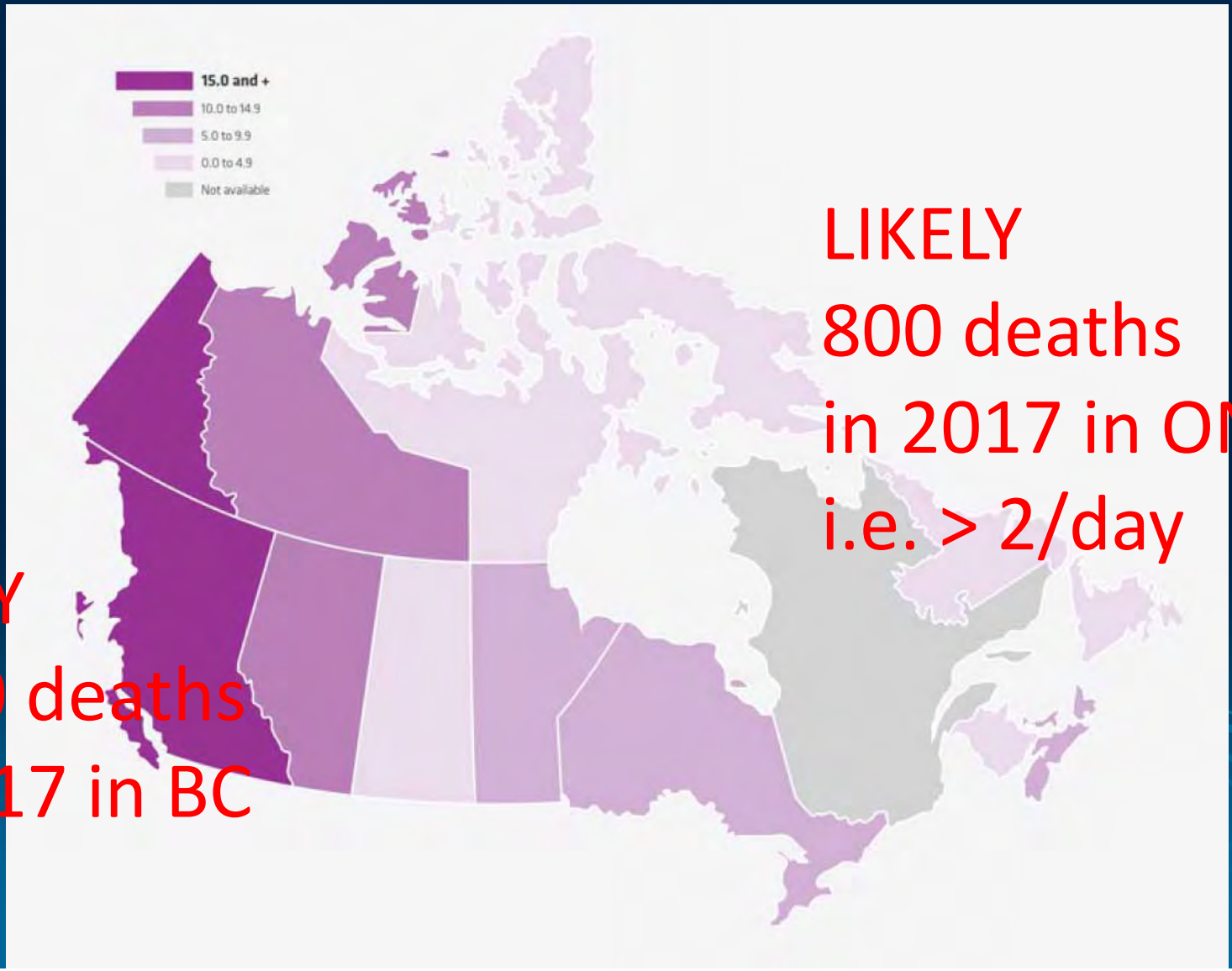
From CIHI Report, 2017

Apparent opioid related deaths in Canada, 2006 (per/100,000)



From Health Canada

Apparent opioid related deaths in Canada, 2006 (per/100,000)

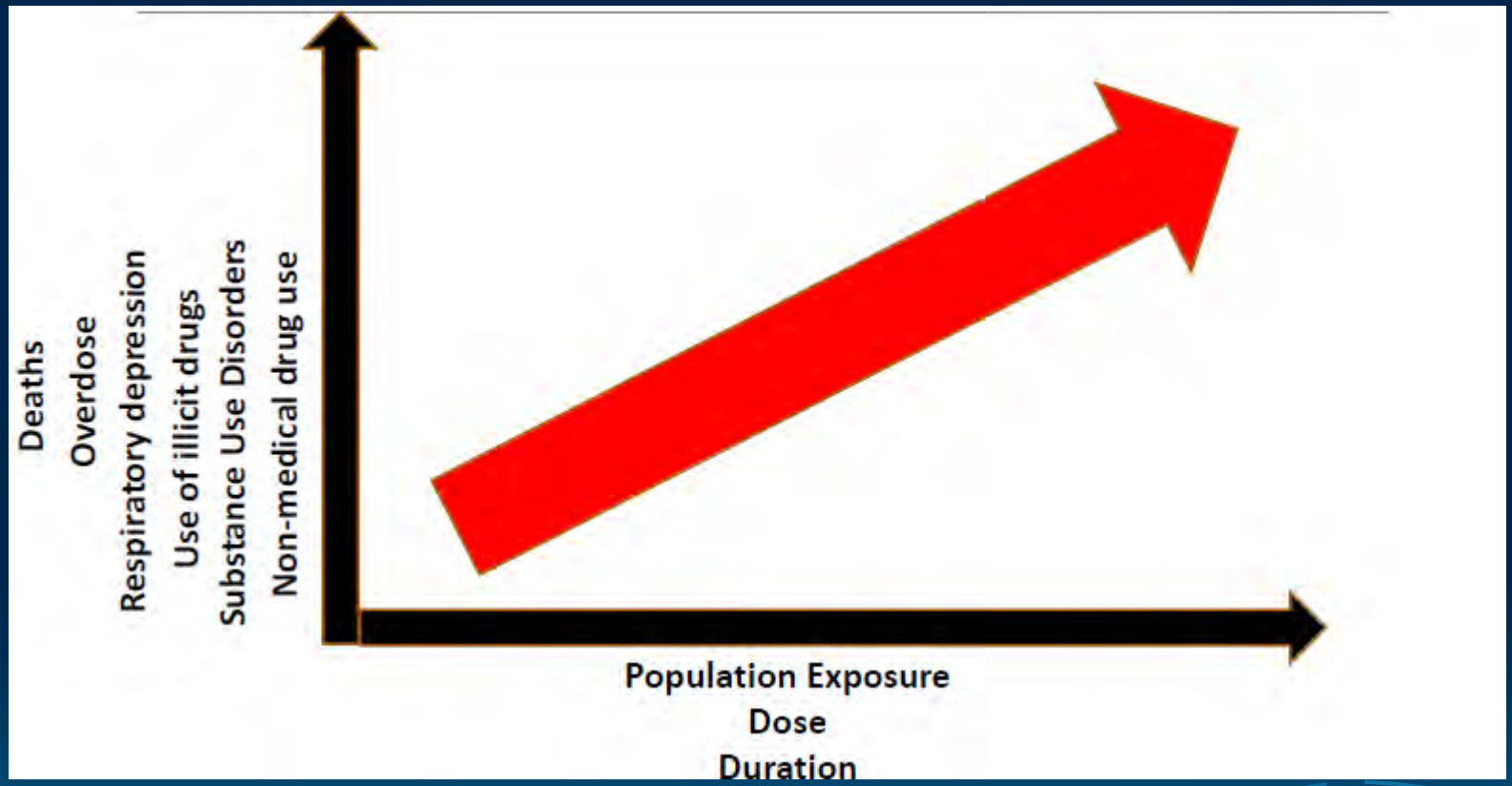


LIKELY
800 deaths
in 2017 in ON
i.e. > 2/day

LIKELY
1,400 deaths
In 2017 in BC

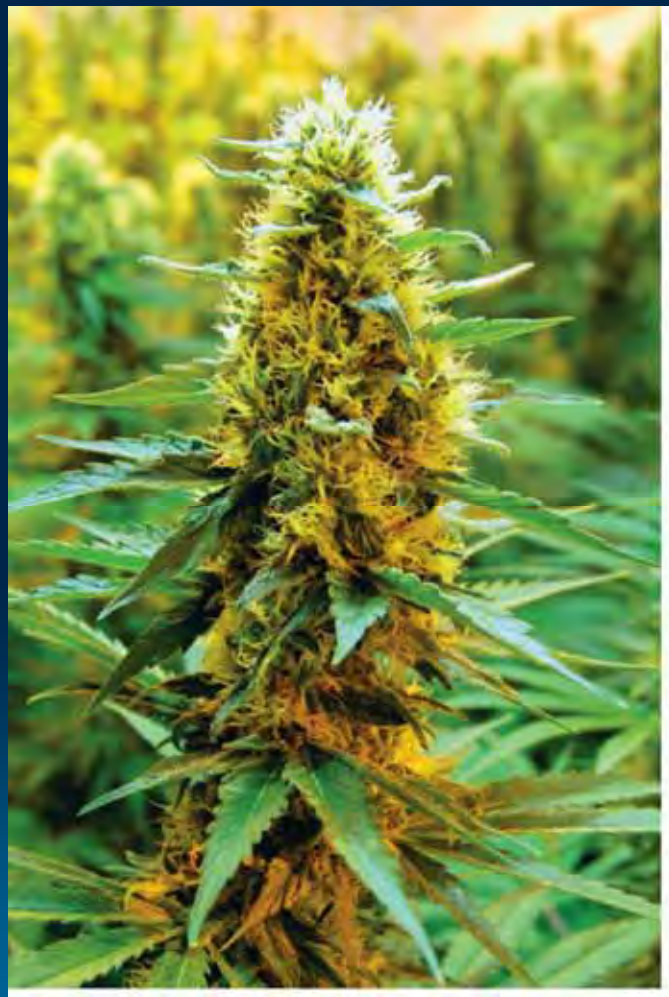
From Health Canada

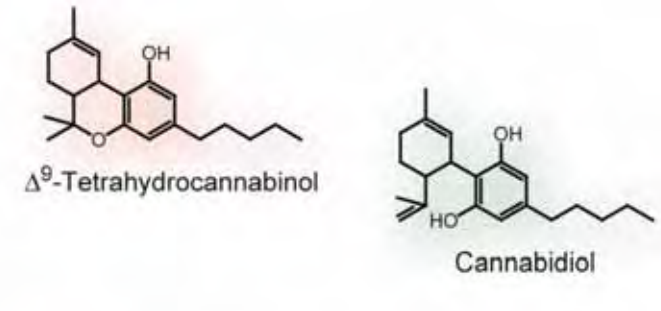
Opiate Use in population is directly linked with negative consequences

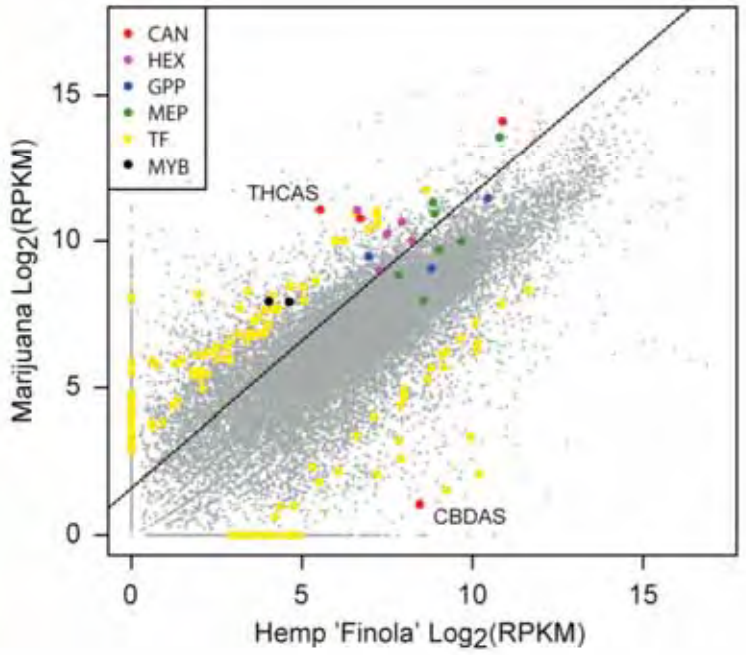


However, It is hard to cut safely opioid doses

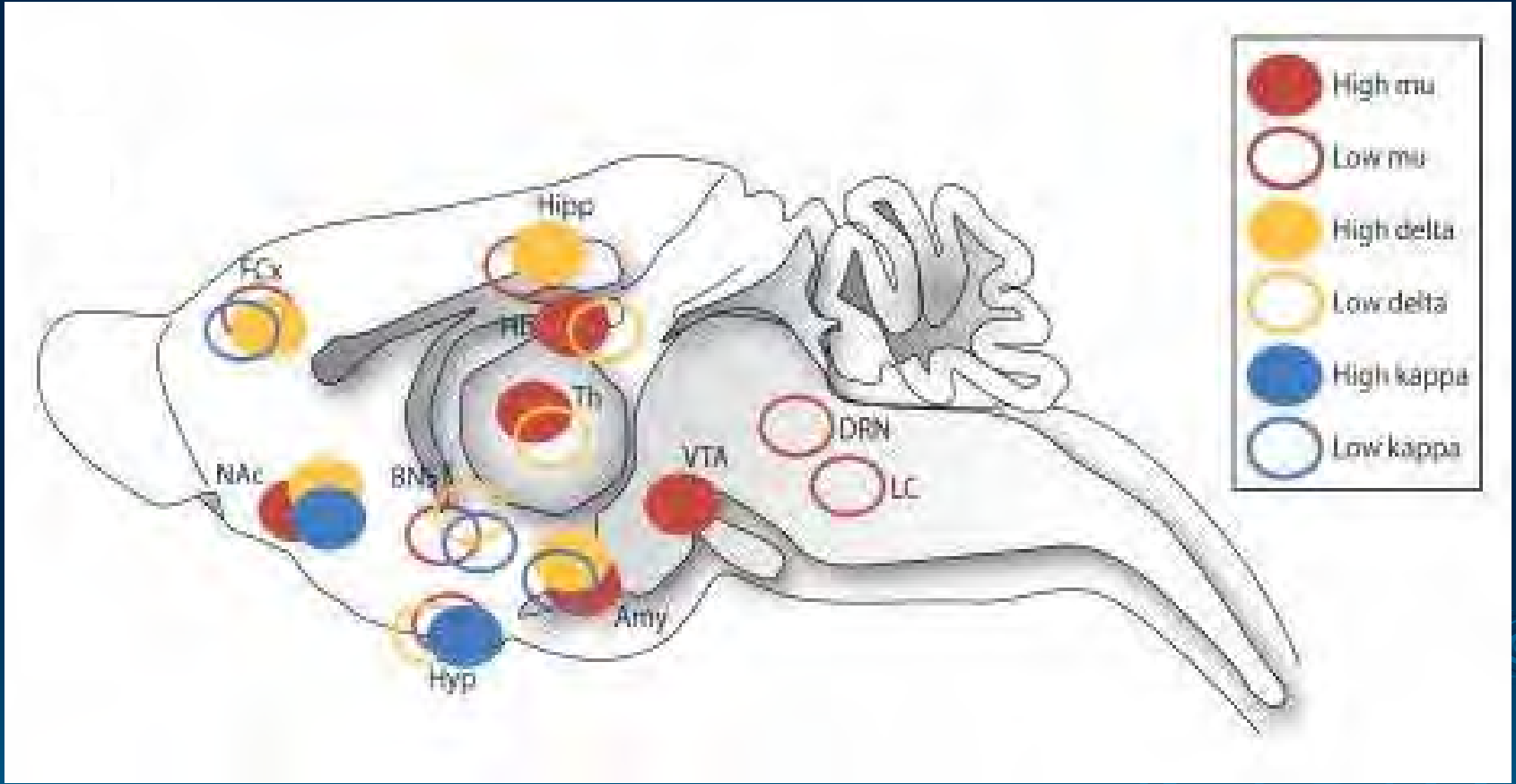
Would the cannabinoid system be a useful target ?





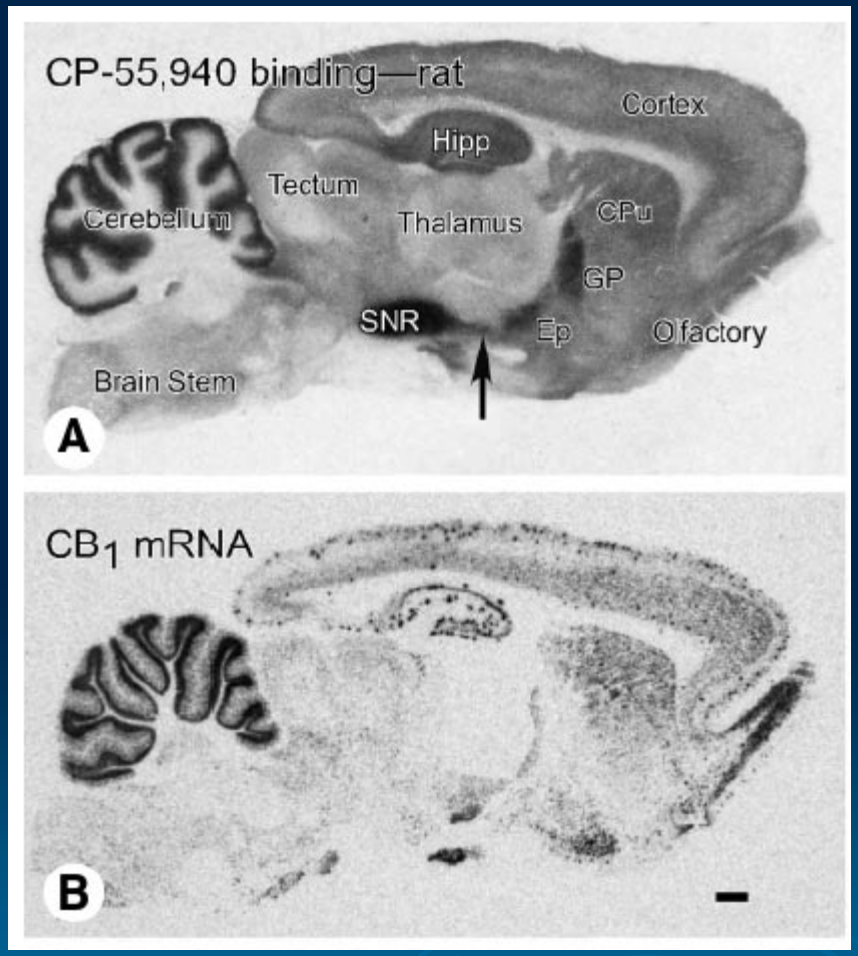


Opioid Receptors are widely distributed in the brain



Lutz and Kieffer Trends Neurosci 2013;36(3):195-206

CB1 Receptors are widely distributed in the brain



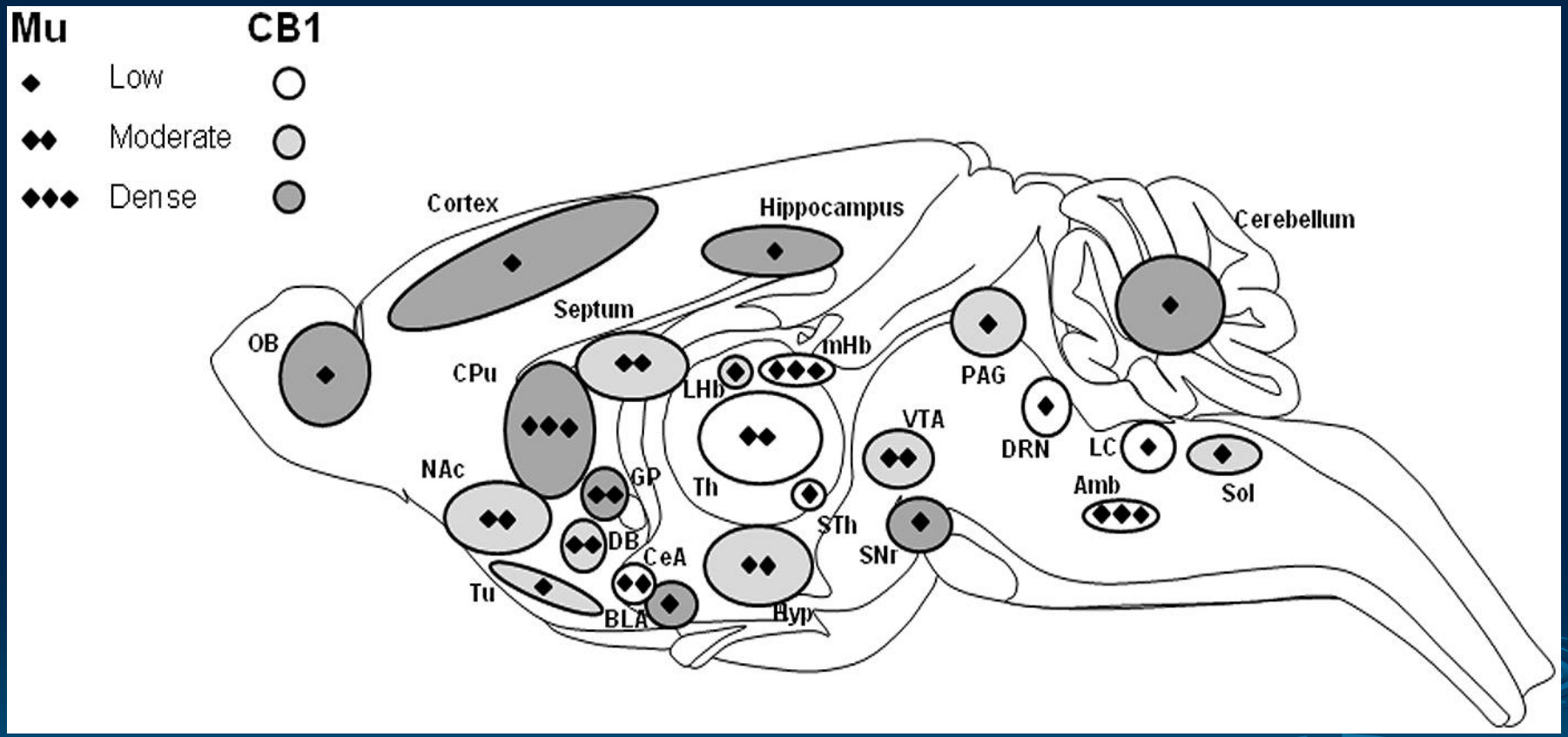
High density in brain areas concerned with memory, cognition, motor coordination, mood, anxiety and reward and pain

Express in spinal cord

Express in lipocytes in fat tissue, liver, pancreas…

From Freund et al., 2003

Overlapped distribution of Opioid and Cannabinoid Receptors



Befort Frontiers in Pharmacology 2015;(5):6-6

opioid-cannabinoid interactions can occur through multiple mechanisms

- Release of opioid peptides by cannabinoids or endocannabinoids by opioids
-
- Existence of a direct receptor-receptor interaction when the receptors are co-expressed in the same cells
- Interaction of their intracellular pathways
- Cross-regulation of receptor density
- Cross-tolerance/sensitization
- Mutual potentiation (e.g. antinociceptive synergy)

Cannabinoid involvement in analgesic effects of morphine

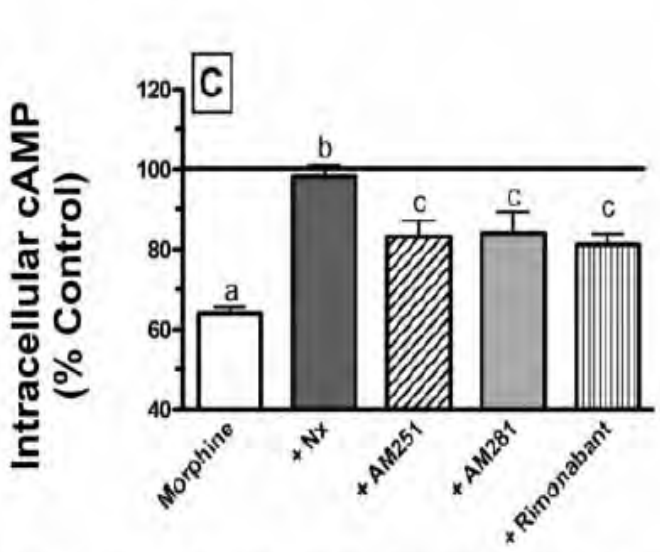


Figure 7. Modulation of forskolin-stimulated adenylyl cyclase activity by acute administration of test compounds in intact CHO-hMOR cells. C) Inhibition of adenylyl cyclase activity produced by 10 nM morphine was significantly attenuated by co-incubation with either the neutral MOR antagonist naloxone (1 µM), AM-251 (10 µM), rimonabant (10 µM) or AM-281 (10 µM). Values designated with different letters above the error bars are significantly different (P<0.05, one-way ANOVA followed by a Newman-Keuls post-hoc test, mean ± SEM).

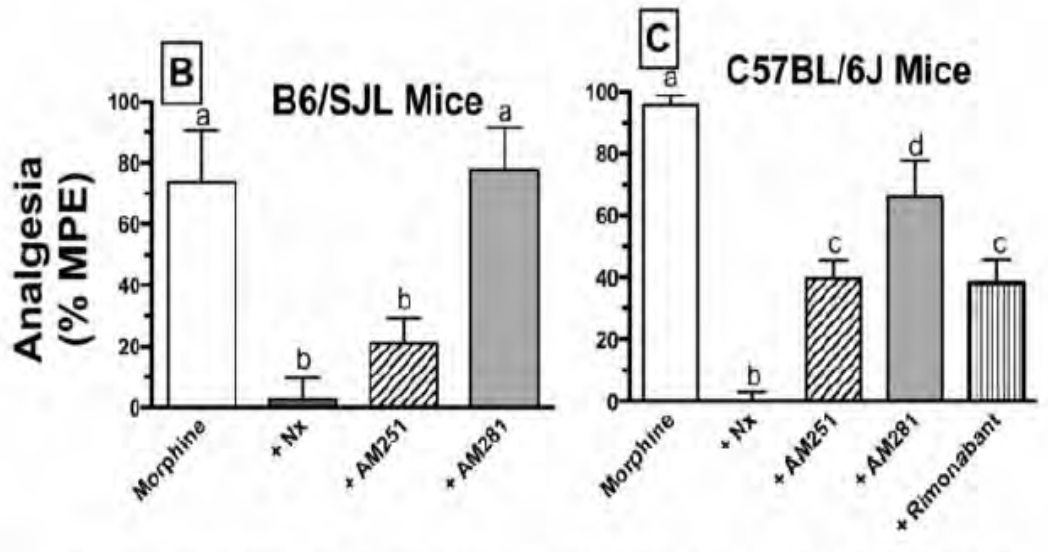
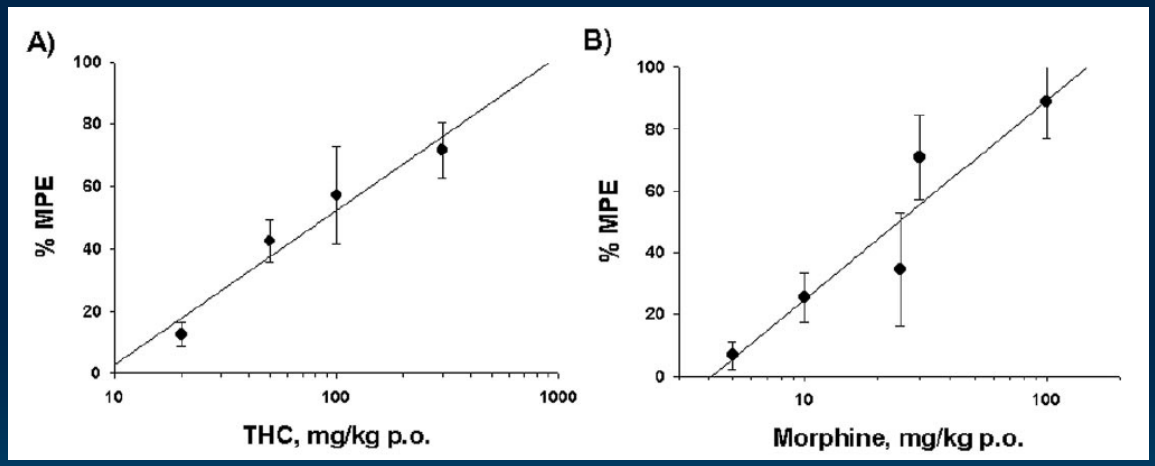
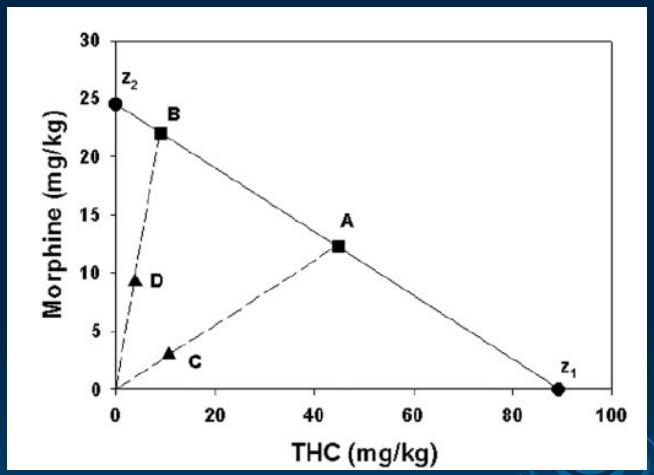


Figure 9. Antagonism of in vivo morphine analgesia in two different strains of mice by test compounds utilizing the tail-flick procedure. B) B6SJL or C) C57BL/6J mice by intra-peritoneal (i.p.) injection of naloxone (4 mg/kg) or AM-251 (10 mg/kg), but not AM-281 (10 mg/kg) significantly reduced analgesia produced by 5 mg/kg morphine. The test doses of naloxone, AM-251, rimonabant or AM-281 had no effect on basal tail-flick latencies when administered alone (data not shown). All data are expressed as the percent of maximum possible effect (% MPE). Values designated with different letters above the error bars are significantly different (P<0.05, one-way ANOVA followed by a Newman-Keuls post-hoc test, mean ± SEM).

Kathryn et al., Neuroharmacol 2012(63):905-15

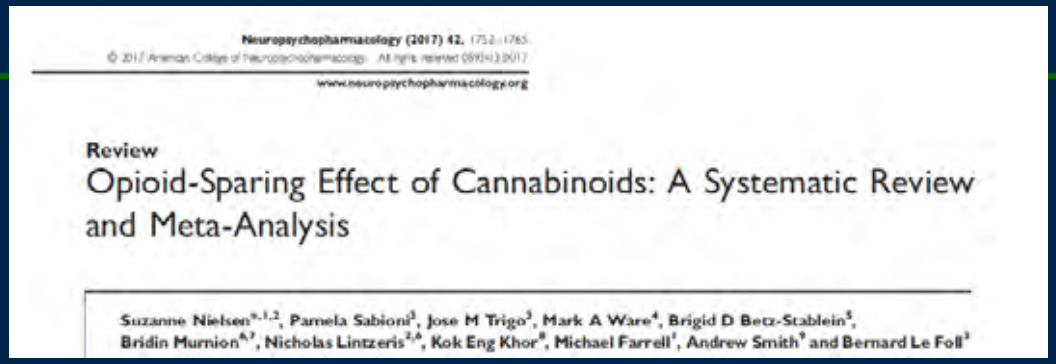
Δ^9 THC and morphine analgesic effects synergize: a isobologram analysis





Cichewicz and McCarthy, JPET, 304, 1010-1015, 2003

‘Opioid sparing effect of cannabinoids ?



Neuropsychopharmacology (2017) 42, 1752–1765

www.neuropsychopharmacology.org

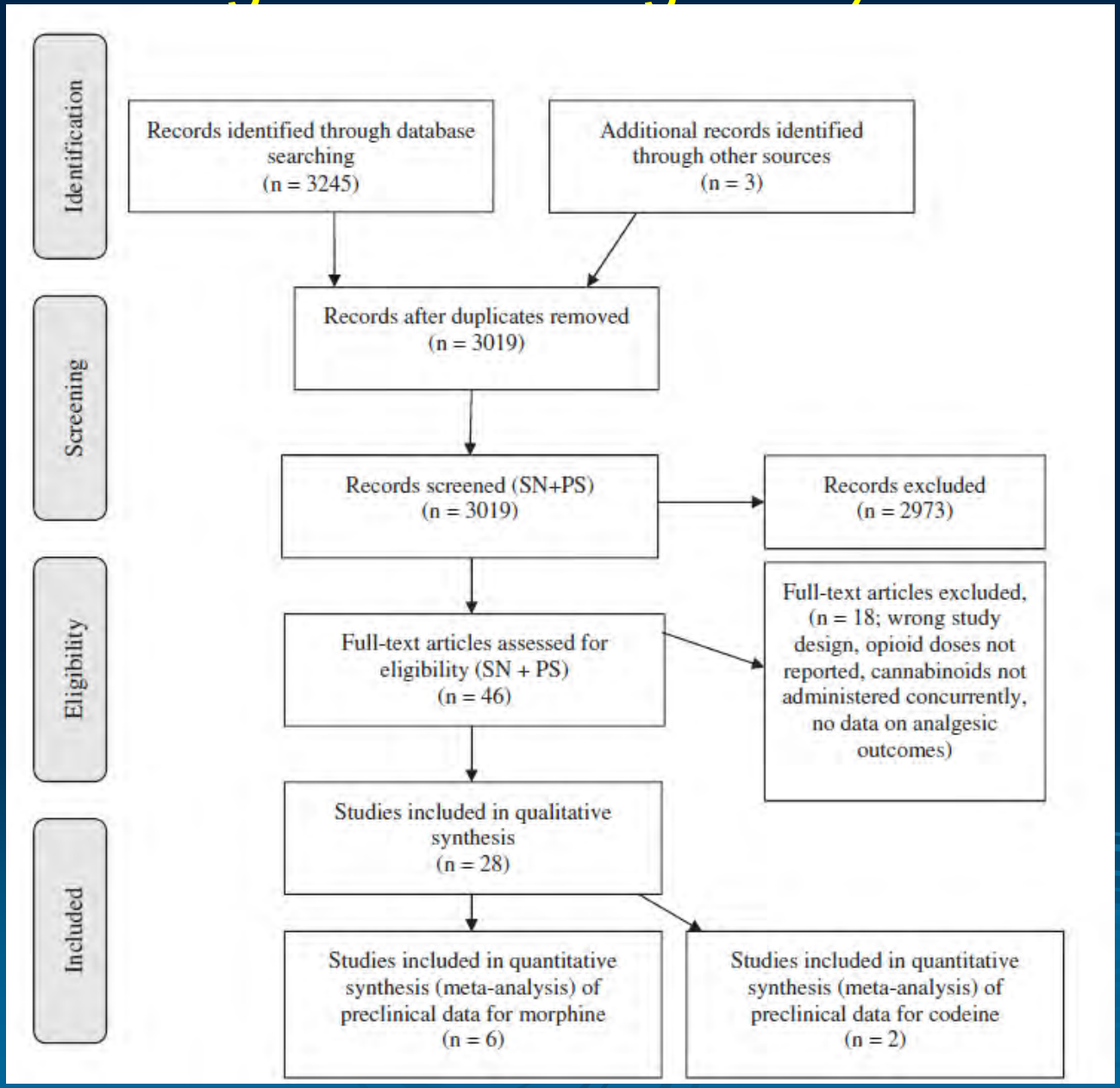
Review

Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

Suzanne Nielsen[1,2], Pamela Sabioni[3], Jose M Trigo[3], Mark A Ware[4], Brigid D Betz-Stablein[5], Bridin Murnion[6,7], Nicholas Lintzeris[2,6], Kok Eng Khor[8], Michael Farrell[1], Andrew Smith[9] and Bernard Le Foll[3]

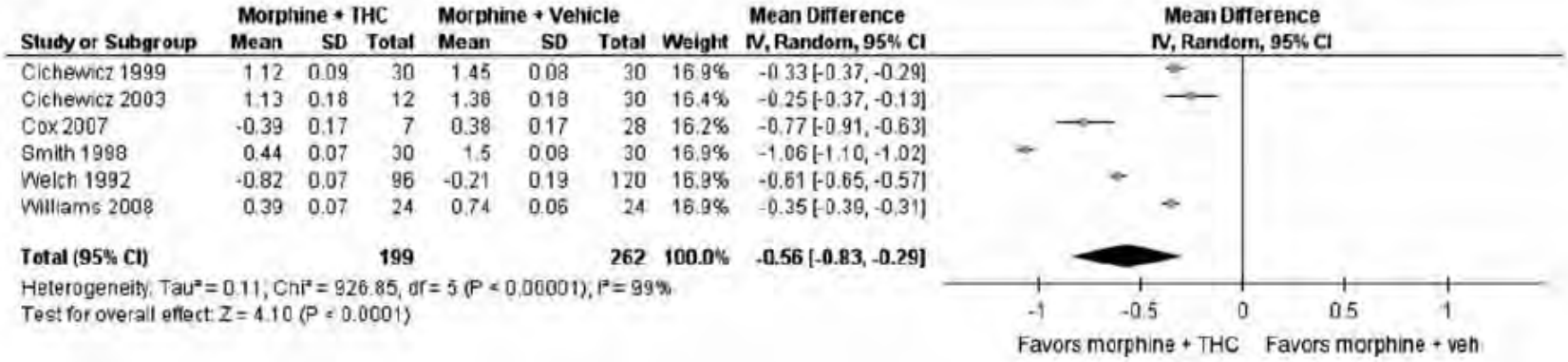
- Systematic search according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
- No date limits, search run on 29 Oct 2015
- Eligible studies:
- - Human or animal studies
- - Outcomes for either pain/analgesia or opioid requirements/opioid-sparing effects from concurrently administered opioids and cannabinoids
- - Controlled clinical studies and case series

PRISMA diagram showing study identification



Pre-Clinical Results

Meta-Analysis 6 studies: Morphine/THC



Study or Subgroup	Morphine + THC Mean	SD	Total	Morphine + Vehicle Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cichewicz 1999	1.12	0.09	30	1.45	0.08	30	16.9%	-0.33 [-0.37, -0.29]
Cichewicz 2003	1.13	0.18	12	1.38	0.18	30	16.4%	-0.25 [-0.37, -0.13]
Cox 2007	-0.39	0.17	7	0.38	0.17	28	16.2%	-0.77 [-0.91, -0.63]
Smith 1998	0.44	0.07	30	1.5	0.08	30	16.9%	-1.06 [-1.10, -1.02]
Welch 1992	-0.82	0.07	96	-0.21	0.19	120	16.9%	-0.61 [-0.65, -0.57]
Williams 2008	0.39	0.07	24	0.74	0.06	24	16.9%	-0.35 [-0.39, -0.31]
Total (95% CI)			**199**			**262**	**100.0%**	**-0.56 [-0.83, -0.29]**

Heterogeneity: Tau² = 0.11; Chi² = 926.85, df = 5 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.10 (P < 0.0001)

Mean Difference
IV, Random, 95% CI

-1 -0.5 0 0.5 1

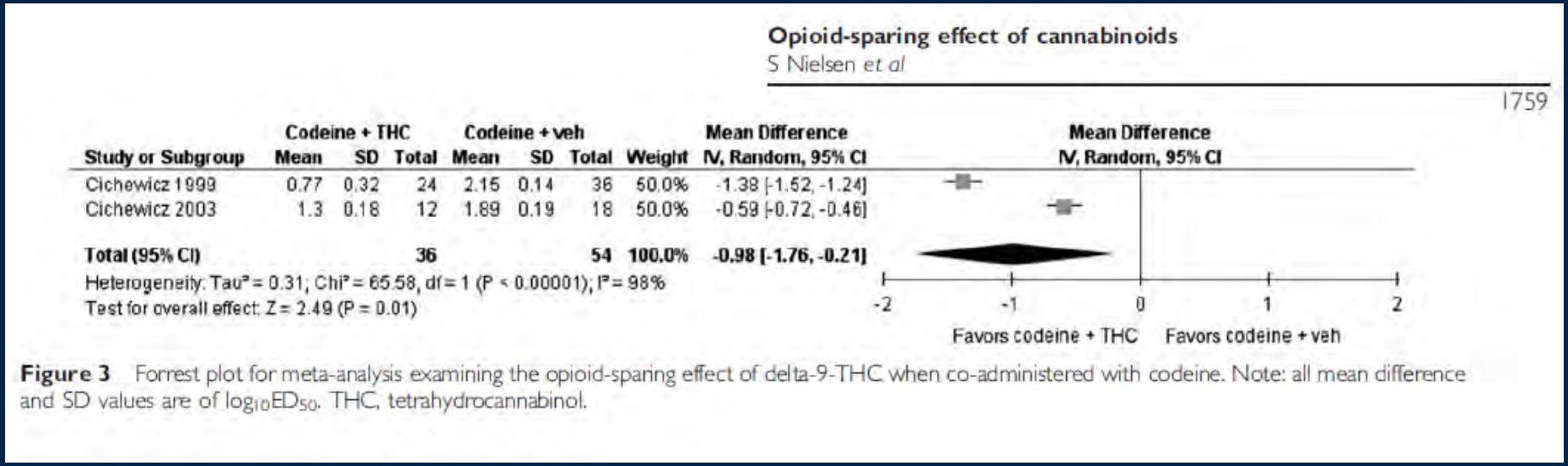
Favors morphine + THC Favors morphine + veh

Figure 2 Forrest plot for meta-analysis examining the opioid-sparing effect of delta-9-THC when co-administered with morphine. Note: all mean difference and SD values are of $\log_{10}ED_{50}$. THC, tetrahydrocannabinol.

Neuropsychopharmacology

Pre-Clinical Results

Meta-Analysis 2 studies: Codeine/THC



Opioid-sparing effect of cannabinoids
S Nielsen *et al*

1759

Study or Subgroup	Codeine + THC Mean	SD	Total	Codeine + veh Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cichewicz 1999	0.77	0.32	24	2.15	0.14	36	50.0%	-1.38 [-1.52, -1.24]
Cichewicz 2003	1.3	0.18	12	1.89	0.19	18	50.0%	-0.59 [-0.72, -0.46]
Total (95% CI)			**36**			**54**	**100.0%**	**-0.98 [-1.76, -0.21]**

Heterogeneity: Tau² = 0.31; Chi² = 65.58, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.49 (P = 0.01)

Figure 3 Forrest plot for meta-analysis examining the opioid-sparing effect of delta-9-THC when co-administered with codeine. Note: all mean difference and SD values are of $\log_{10}ED_{50}$. THC, tetrahydrocannabinol.

Conclusion: strong preclinical support for opioid sparing effects of cannabinoids

Clinical studies results

Table 2 Summary of Evidence of Opioid-sparing Effects from Clinical Studies

(a) Study reference	Study design	Population	Follow-up period	Opioid used	Cannabinoid used	Effect of cannabinoid on opioid dose	Outcome on analgesia observed	GRADE evidence rating and other notes
Laboratory studies								
Abrams et al, 2011	Clinical laboratory study of self-reported pain under observed conditions (also measured pharmacokinetic effects of concurrent administration)	People ($n=24$) receiving chronic opioid treatment (mixed pain conditions)	5 days	Morphine sulfate (mean daily dose 62 mg, $n=13$) or oxycodone hydrochloride (mean daily dose 53 mg, $n=11$)	Vaporized cannabis dose of 0.9 g of 3.56% delta-9-THC or as much as they could tolerate, administered three times per day.	Opioid dose held constant to examine effect of delta-9-THC on opioid pharmacokinetics (ie, no reduction from baseline opioid dose possible).	Mean pain score reduction, from 34.8 (95% CI 29.4, 40.1) at baseline to 24.1 (95% CI 18.8, 29.4) on day 5 with morphine, and from 43.8 (95% CI 38.6, 49.1) at baseline to 33.6 (95% CI 28.5, 38.6) on day 5 with oxycodone. Significant reduction overall.	Cannabis inhalation produced a subjective 'high'. GRADE rating 'low' quality. Downgraded as study did not have a placebo condition, so placebo effects cannot be excluded Note: no pharmacokinetic interaction observed.
Naef et al, 2003	Experimental heat, cold, pressure, single and repeated transcutaneous electrical stimulation pain, randomized, placebo-controlled, double-blinded, crossover study.	Healthy cannabis naive volunteers ($n=12$)	Four study sessions with at least 7 days washout between sessions	Morphine (30 mg) daily	Dronabinol (20 mg)	No significant analgesic effect of dronabinol or morphine–dronabinol combination on heat, pressure, or cold tests. Additive effect of morphine on transcutaneous electrical stimulation test.	Potentiation of analgesia not observed in this experimental pain study.	GRADE rating 'moderate'. Placebo-controlled, blinded study. Downgraded due to indirect evidence as use of experimental pain measures.
Roberts et al, 2006	Experimental thermal pain. Double-blinded, four treatment crossover design.	Healthy volunteers ($n=13$) with no recent opioid or cannabinoid use	Four lab sessions	Morphine (0.02 mg/kg IV, 1.4 mg dose for 70 mg adult, ie, sub-analgesic)	Dronabinol (5 mg)	NA (opioid dose held constant)	Combination of delta-9-THC and morphine did not have an effect on pain intensity. The combination resulted in lower ratings of unpleasantness of pain compared with either drug alone.	GRADE rating 'moderate'. Placebo-controlled, blinded study. Downgraded due to indirect evidence as use of experimental pain measures.
Case series								
Lynch and Clark, 2003	Observational case series	Mixed pain conditions ($n=3$) (peripheral neuropathy, multiple sclerosis, lower back pain)	1–9-month observation period	Morphine (75–360 mg daily)	Smoked cannabis plant, unknown content	Mean baseline morphine dose of 195 mg (SD 147 mg) compared with 35 mg (SD 31 mg) after commencing smoked cannabis. Opioid dose reduction or cessation in each case.	Improved pain control described, with patients either reducing or ceasing morphine dose.	GRADE rating 'very low'.

Clinical studies results

(b) Study reference	Study design	Population	Follow-up period	Opioid used	Cannabinoid used	Effect of cannabinoid on opioid dose	Outcome on analgesia observed	GRADE evidence rating and other notes
Controlled trials								
Johnson *et al*, 2010	Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial.	Patients with cancer pain ($n=177$), with inadequate analgesia despite chronic opioid dosing.	2 weeks	Varied opioids reported as OME (IQR) 120 mg (50–213)	Patients randomized to delta-9-THC : CBD, delta-9-THC, or placebo Delta-9-THC (mean 9 sprays per day)	No change in median amount of breakthrough opioid medication in any group.	Change in pain NRS (out of 10) from baseline was statistically significantly in favor of delta-9-THC : CBD compared with the placebo −1.01 ($p=0.245$) −1.37 ($p=0.014$)	GRADE rating 'high'. Placebo-controlled and randomized.
				80 mg (30–180)	Delta-9-THC : CBD (mean 10 sprays per day)			
				120 mg (40–240)	Placebo (mean 11 sprays/day)		−0.69 (reference group)	
Lissoni *et al*, 2014	Two groups (not randomized): cannabinoid tincture or melatonin	Patients with untreatable metastatic solid tumor ($n=26$)	Not stated	Oxycodone, median dose of 30 mg (10–60 mg), twice per day	Cannabis flos (19% delta-9-THC) was given as an infusion. 100 ml (500 mg/l water) three times per day	5/12 patients (42%) achieved control of pain without opioid dose increase compared to the control group, where 2/14 (14%) achieved pain control	The number that achieved pain control was not significantly different between groups	GRADE rating 'low'. Non-randomized design, no allocation concealment described. Control group received melatonin (20–100 mg). Greater disease progression documented in the cannabis group
Narang *et al*, 2008	Phase 1: randomized, single-dose, double-blinded, placebo-controlled, crossover trial. Primary outcome measures TOTPAR score	Patients on opioids for chronic pain; BPI ⩾ 4 ($n=30$). Pain diagnosis: neuropathic ($n=7$), nociceptive ($n=7$), mixed neuropathic and nociceptive ($n=11$), and uncategorized ($n=5$)	Phase 1: three 8-h lab sessions with 3 days washout	OME mean 68.1 mg (SD 57.2, range 7.5–228). Participants were taking oxycodone, morphine, methadone hydrocodone, and hydromorphone	Phase 1: single-dose placebo, dronabinol 10 and 20 mg	One subject took rescue pain medication in all conditions, one subject took rescue medication during the placebo and 10 mg dronabinol condition, and six subjects took rescue medication only with placebo.	In single-dose studies, 10 and 20 mg dronabinol significantly increased the amount of analgesic relief reported compared to placebo	GRADE rating 'moderate'. Randomized and placebo-controlled. Downgraded a only a single dose was examined. TOTPAR 31.1 in placebo group, compared with 39.7 with dronabinol 10 mg and 41. with dronabinol 20 mg
	Phase 2: open-label (no placebo) extension. Primary outcome measure change in pain intensity		Phase 2: open label for 4 weeks		Phase 2: flexible dose schedule, dronabinol 5 mg daily – 20 mg three times per day.	Opioid dose not reported	Mean baseline NRS of 6.9 compared with 5.2 after 4 weeks of dronabinol. This represents a statistically significant reduction	GRADE rating 'low'. Open label study. Significant improvements ($p<0.05$) i sleep, energy, pain relief, and social functioning. Lac of placebo control means effects may be non-specifi or placebo
Portenoy *et al*, 2012	Randomized, 4-arm placebo-controlled, graded-dose study	Patients with active cancer and chronic pain on a stable oral morphine regimen, plus fentanyl ($n=360$)	5 weeks of medication administration	Morphine and fentanyl Median 120 mg OME Median 120 mg OME Median 180 mg OME Median 120 mg OME	Nabiximols 1–4 sprays Nabiximols 6–10 sprays Nabiximols 11–16 sprays Placebo	No change in median amount of breakthrough opioid medication in any group. Note that patients were discouraged from reducing their opioid dose, so the opioid-sparing effect could not be observed	Treatment difference (change from baseline pain score): −0.75 points (95% CI −1.28, −0.22, $p=0.06$ compared to placebo) −0.36 points (95% CI −.089, 0.18 points, $p=0.19$ compared to placebo). −0.09 points (95% CI: −0.62, 0.44 points, $p=0.75$ compared to placebo) Not reported (reference group)	GRADE rating 'high'. Placebo-controlled, randomized controlled tri Opioid composite measure showed better improvements in the low-dose group. 1–4 spray group had significant improvements in analgesi Lower tolerability of delta-9-THC : CBD in higher dose groups
Seeling *et al*, 2006	Randomized, controlled trial (two groups)	Prostate cancer patients <70 y.o. ($n=105$). $N=53$ in intervention and 52 in control	From the day prior to surgery to two days post operation	Piritramide 1.5 mg/ml, bolus 2 mg (no continuous infusion) via patient-controlled analgesia for 48 h post operation	Dronabinol 5 mg × 8 doses over 48 h (perioperatively)	Median dose of piritramide alone was 74 mg (IQR 44–90) compared with 54 mg (IQR 46–88) when administered with dronabinol	The difference between the intervention (dronabinol) group and control group was not significant. No evidence was found of synergistic antinociceptive interaction between delta-9-THC and piritramide for acute postoperative pain	GRADE rating 'high'. Placebo-controlled, randomized controlled tri Patients administered thei own opioid doses

Clinical Results (summary)

Very-low-quality evidence: 1
Low-quality evidence: 3
Moderate-quality evidence: 2
High-quality evidence: 3 RCTs

None of the 3 high-quality studies provided evidence of an opioid-sparing effect.

Evidence of an opioid-sparing only in 1 very low-quality study

Reduced use of opioid in subjects using medical cannabis

American Pain Society
RESEARCH
EDUCATION
TREATMENT
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Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

Kevin F. Boehnke,* Evangelos Litinas,† and Daniel J. Clauw‡,§

64 % reduction in opioid dose (n=118), decreased number of and side effects of medication, improved quality of life

The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain

A Prospective Open-label Study

Simon Haroutounian, PhD,† Yael Ratz, PharmD,* Yehuda Ginosar, MD,‡ Karina Furmanov, MSc,§ Fayez Saifi, MD,*‡ Ronit Meidan, RN,* and Elyad Davidson, MD*‡*

44 % reduction in opioid dose (n=176), decreased pain

However, lack of control !!

Am J Public Health. 2017 Nov;107(11):1827-1829

AJPH RESEARCH

Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000–2015

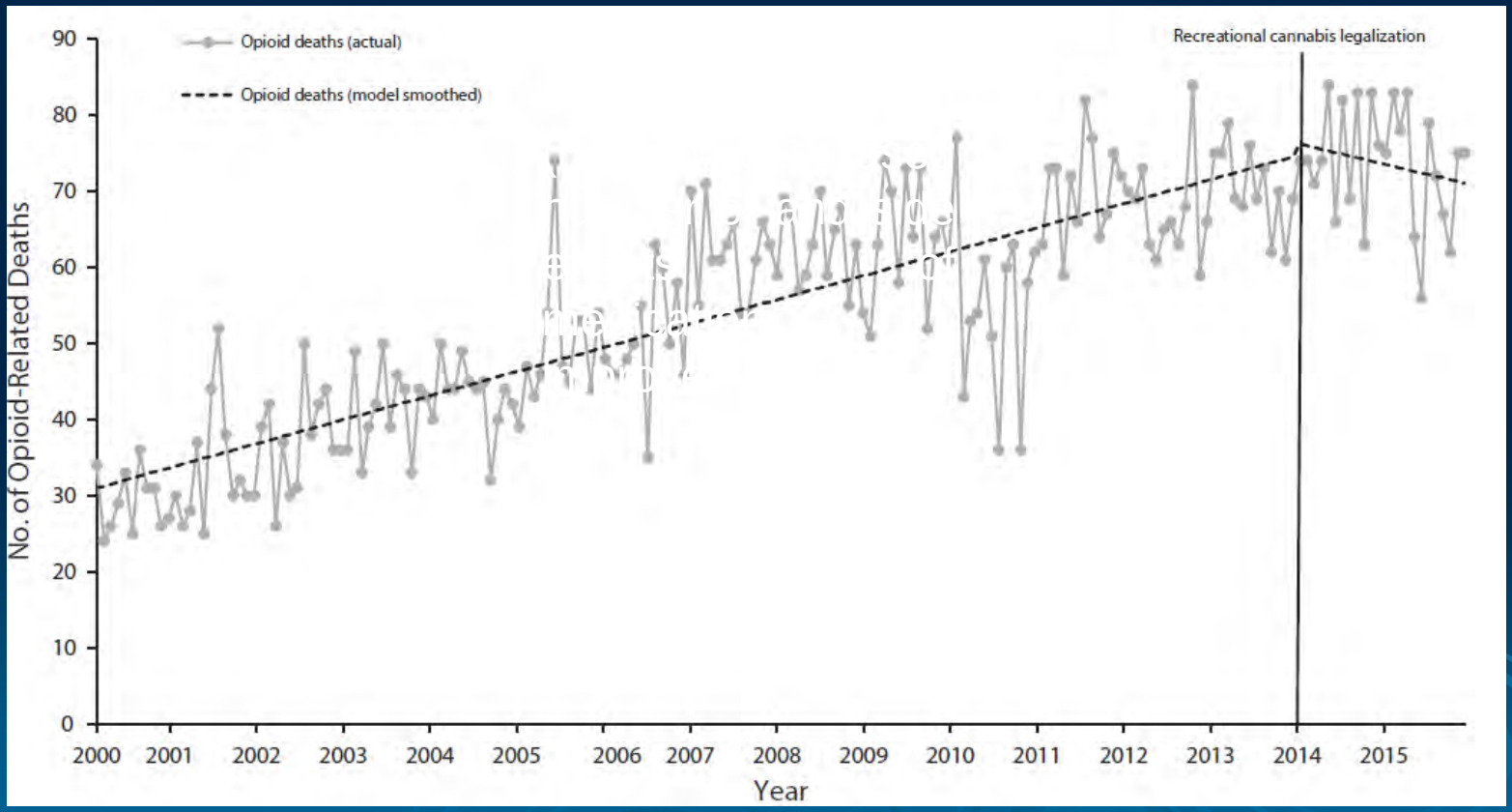
Melvin D. Livingston, PhD, Tracey E. Barnett, PhD, Chris Delcher, PhD, and Alexander C. Wagenaar, PhD

Interrupted time-series design (2000–2015) to compare changes in level and slope of monthly opioid-related deaths before and after Colorado stores began selling recreational cannabis.

Also describes the percent change in opioid-related deaths by comparing the unadjusted model-smoothed number of deaths at the end of follow-up with the number of deaths just prior to legalization

Results

Colorado's legalization of recreational cannabis sales and use resulted in a 0.7 deaths per month (b = –0.68; 95% confidence interval = –1.34, –0.03) reduction in opioid-related deaths.



Am J Public Health. 2017 Nov;107(11):1827-1829

Interim conclusion

- THC can produce analgesia in different animal models and can also potentiate the effects of opioid drugs
- Preclinical evidence support an opioid sparing effects of cannabinoid drug
- There is limited evidence so far supporting the opioid sparing effects of cannabinoids in humans
- However, more and more uncontrolled studies support the opioid sparing effect and potential utility of increased access to cannabinoid drug to reduce mortality related to opioids

Potential of the opioid system for Cannabis Use Disorder

Cannabis as a typical Addictive Substance

- Cannabis Withdrawal is very well characterized now (Thanks to Dr Budney work and others)
- 8 – 9 % of ever users will develop cannabis dependence, an ever larger fraction will develop cannabis use disorder

Psychosocial interventions for cannabis use disorder (Review)

Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L

THE COCHRANE COLLABORATION®

Gates et al., 2016 Cochrane Review

Pharmacotherapies for cannabis dependence (Review)

Marshall K, Gowing L, Ali R, Le Foll B

Marshall et al., 2014 Cochrane Review

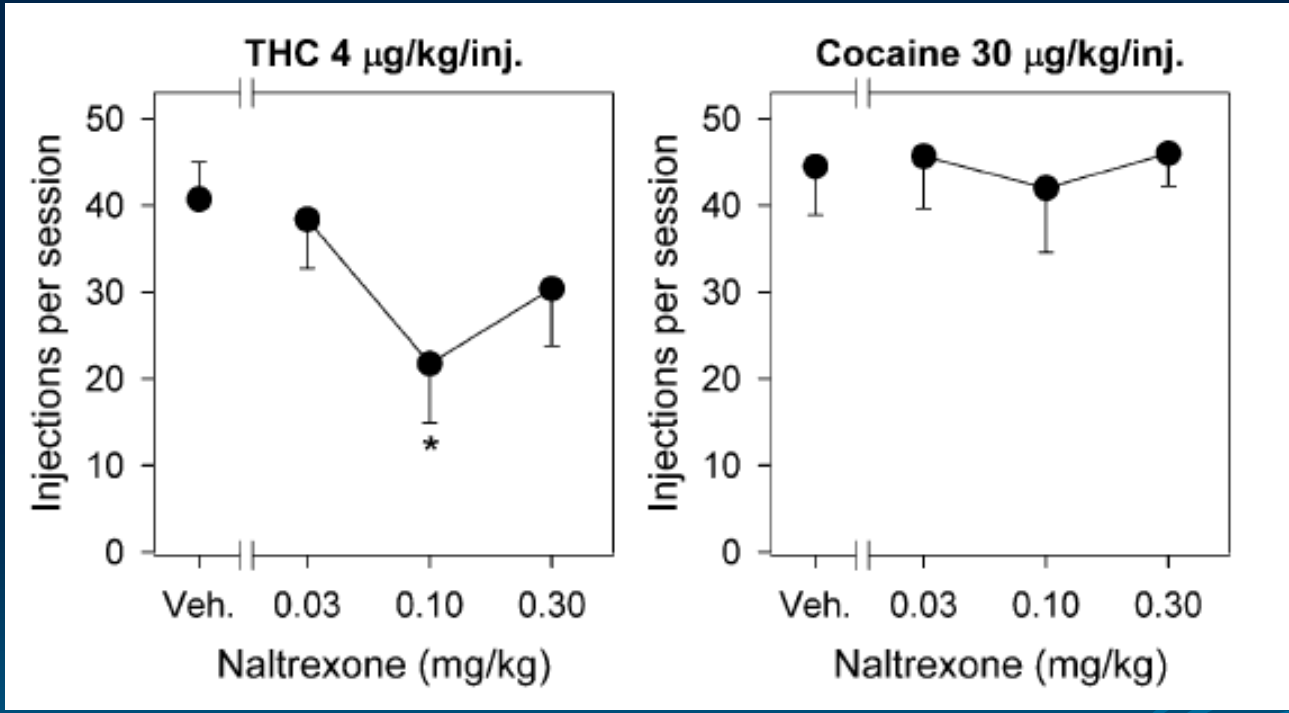
Pharmacotherapies for cannabis dependence (Review)

Marshall K, Gowing L, Ali R, Le Foll B

No Pharmacological treatment available !

Marshall et al., 2014 Cochrane Review

The opioid antagonist naltrexone reduces the reinforcing effects of THC in squirrel monkeys



Justinova et al Psychopharmacology 2004;(1-2):186-94

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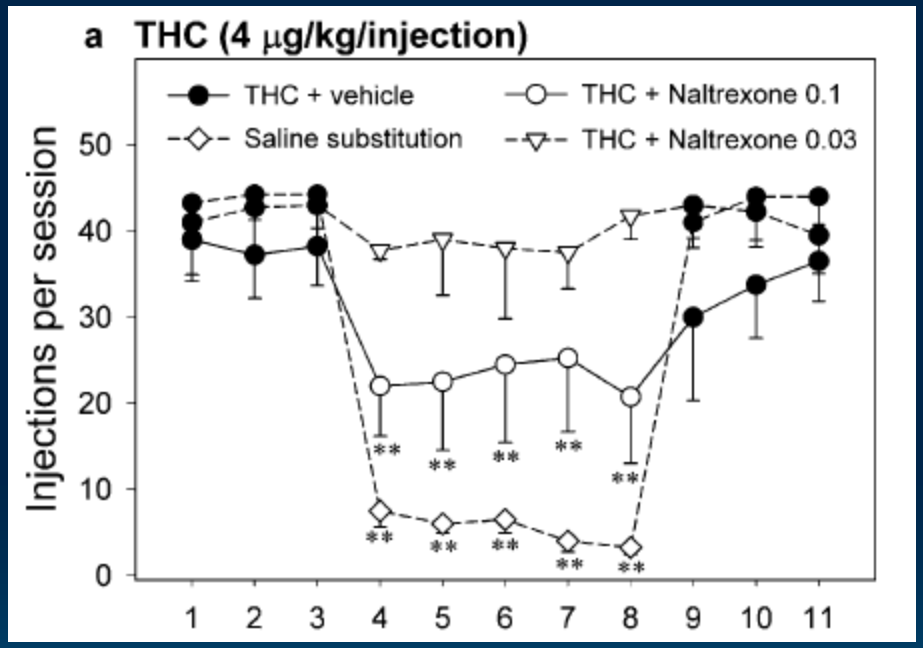
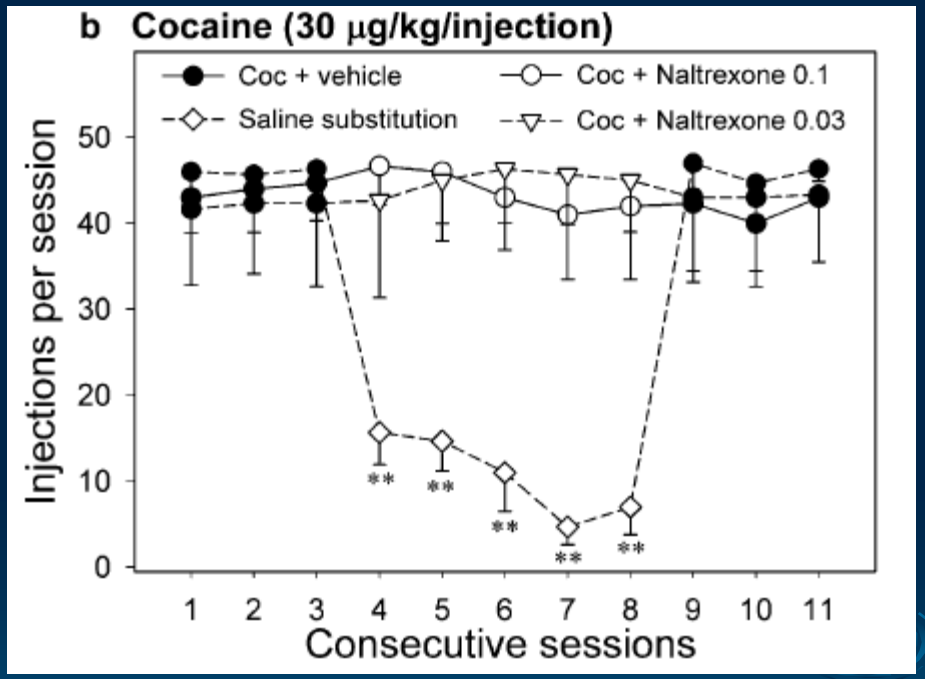
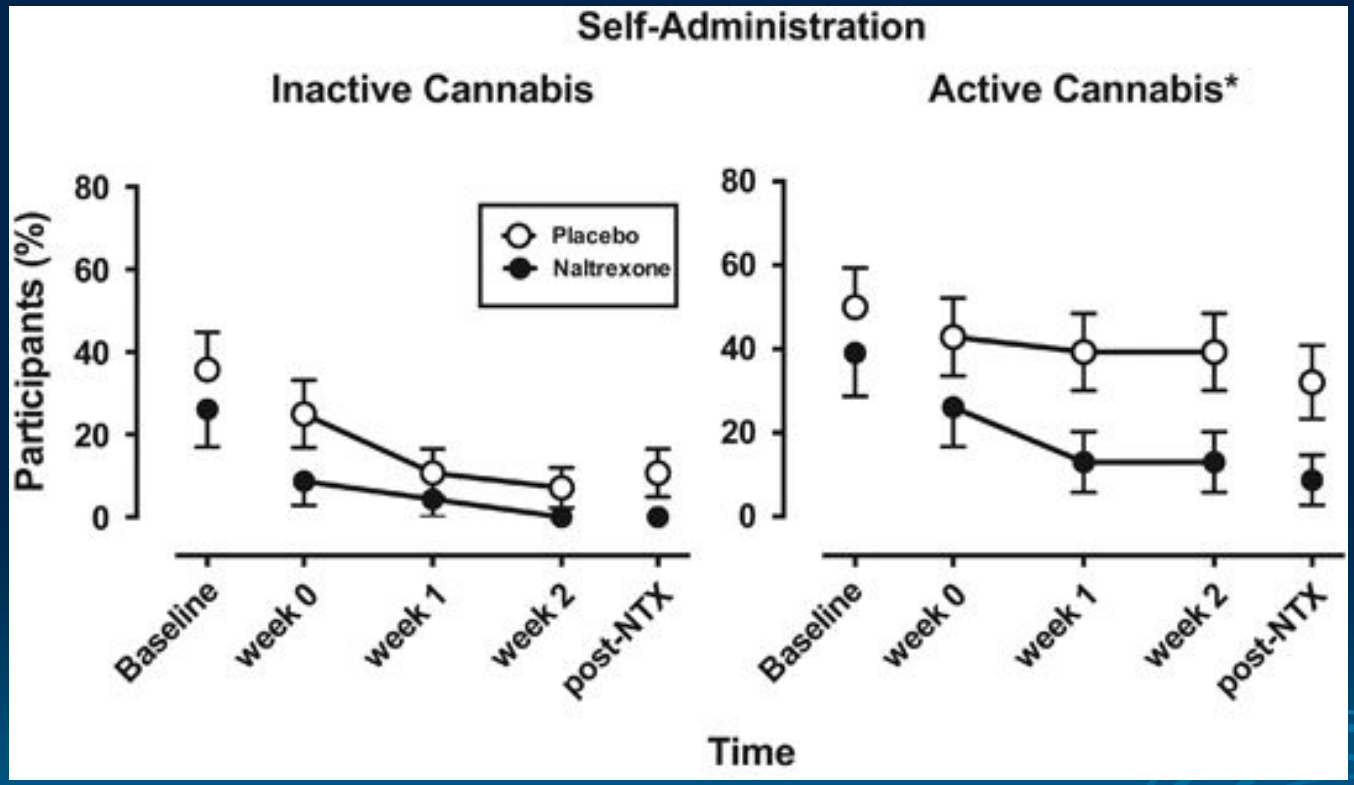




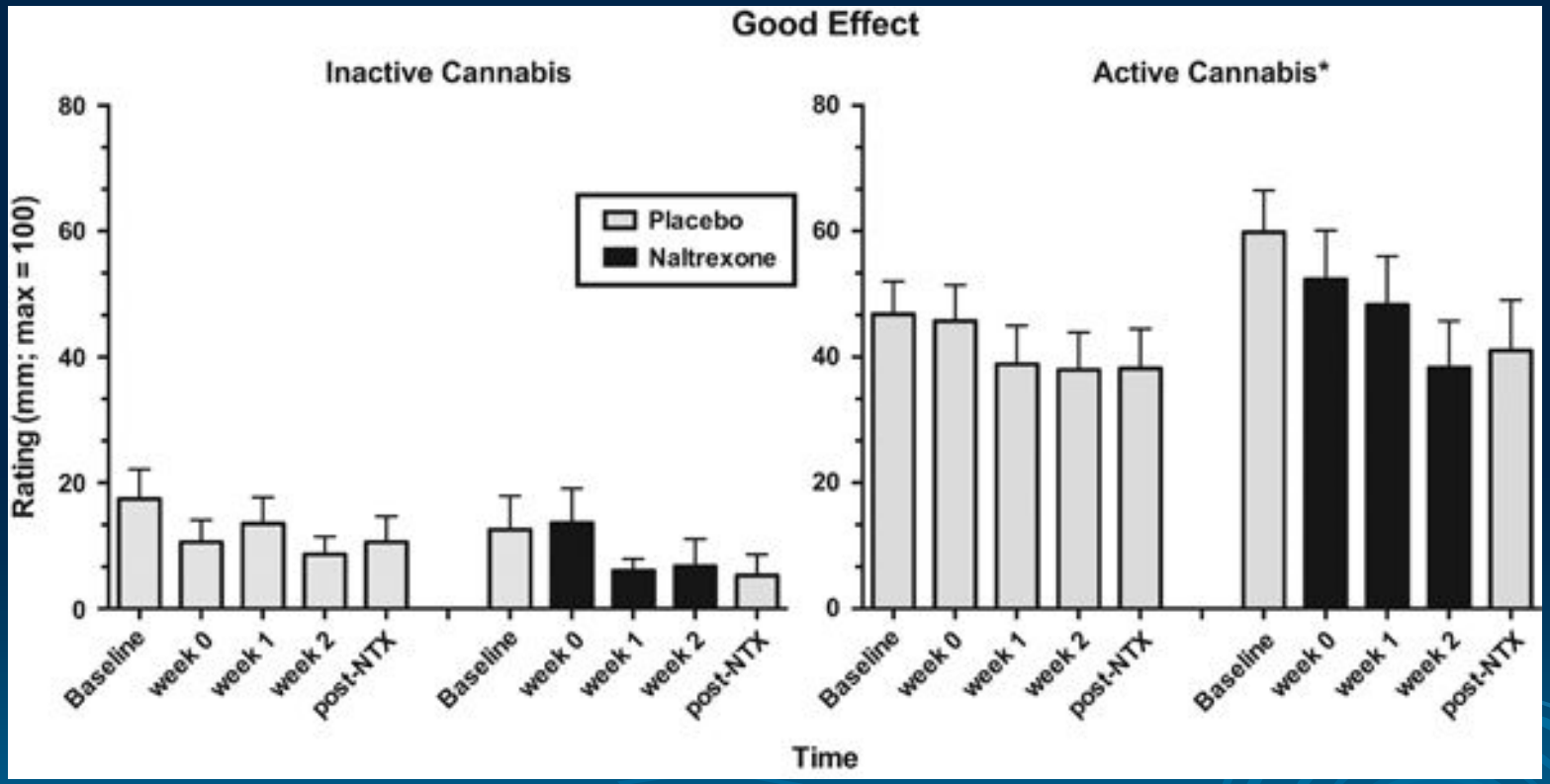
Justinova et al Psychopharmacology 2004;(1-2):186-94

Naltrexone Maintenance Decreases Cannabis Self-Administration in Daily Cannabis Smokers



Haney et al Neuropsychopharmacology 2015;(11):2489-98

Naltrexone Maintenance Decreases Cannabis Subjective Effects in Daily Cannabis Smokers



Haney et al Neuropsychopharmacology 2015;(11):2489-98

CONCLUSION

- Opioid crisis is a phenomenon that affect countries that are high prescribers of opioid medications (US, Canada)
- The Cannabinoid and opioid receptors are co-localized in some areas of the brain/spinal cord and they functionally interact
- Cannabinoids have clear analgesic properties in preclinical models and allow for opioid sparing effects. However, there is so far limited validation of those effects in humans
- For addiction treatment: Blocking the opioid system could decrease motivation for cannabis. Validation RCTs are needed

Priorities for research

- Performing RCT testing cannabis for pain
- Performing RCT testing the opioid sparing effect of cannabis in patients with chronic pain
- Performing clinical trials for pharmacotherapies interventions for cannabis use disorders

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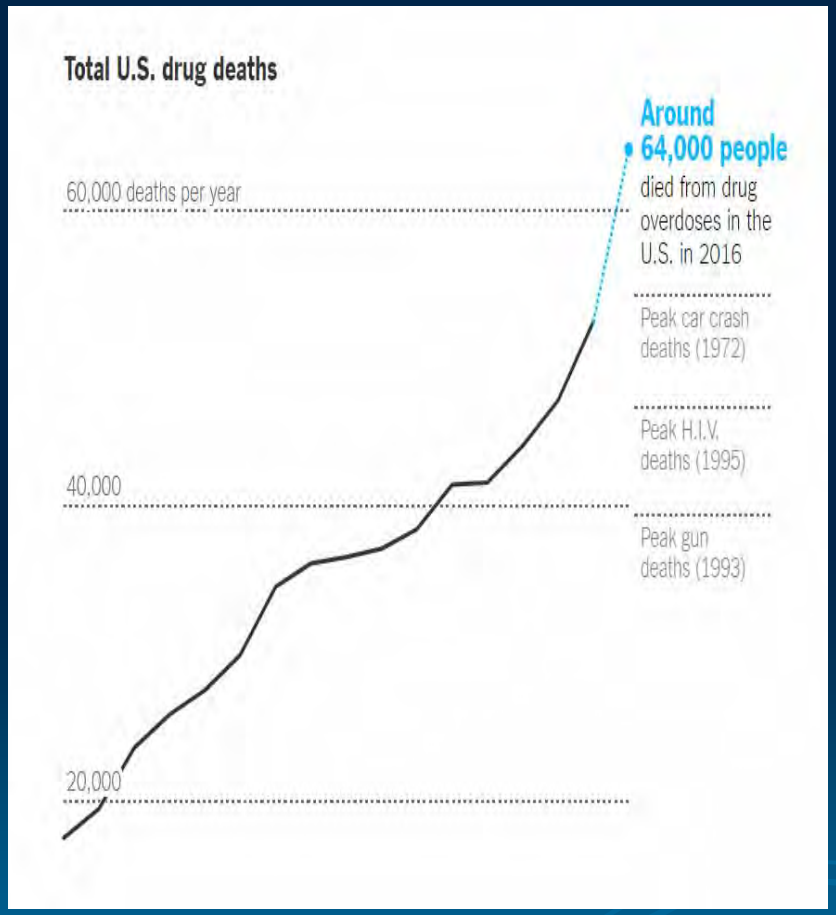
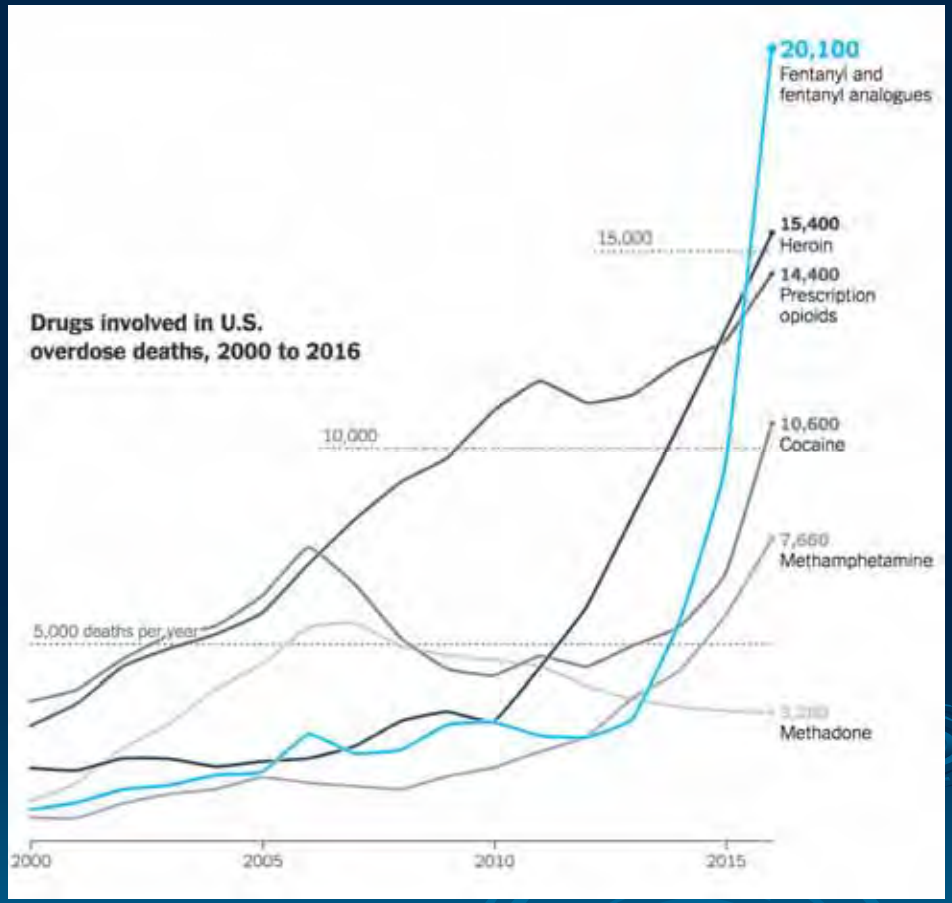
Canadian Institutes of Health Research

Estimate of Total U.S. Drug Deaths in 2016



Fentanyl-Related Deaths Surpassed Heroin or Rx Opioids in 2016



Graphs from NY Times Article based on CDC MMWR Report 2017