Therapeutic potential of Opioid-Cannabinoid Interactions

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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

Addiction

Economic

OPIOIDS

Medical

Social

OVERDOSE, INFECTIONS
Canada: one of the highest user of opioids

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

From WHO
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 1,400 deaths in 2017 in BC
- LIKELY 800 deaths in 2017 in ON i.e. > 2/day

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

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) B6/SJL or C) C57BL/6J mice by intraperitoneal (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., Neuropharmacol 2012(63):905-15
Δ⁹ THC and morphine analgesic effects synergize: a isobologram analysis

Cichewicz and McCarthy,JPET,304,1010-1015,2003
‘Opioid sparing effect of cannabinoids?

- 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

- Records identified through database searching (n = 3245)
- Additional records identified through other sources (n = 3)

- Records after duplicates removed (n = 3019)

- Records screened (SN+PS) (n = 3019)

- Full-text articles assessed for eligibility (SN + PS) (n = 46)
  - Full-text articles excluded, (n = 18; wrong study design, opioid doses not reported, cannabinoids not administered concurrently, no data on analgesic outcomes)
  - Studies included in qualitative synthesis (n = 28)

- Studies included in qualitative synthesis (meta-analysis) of preclinical data for morphine (n = 6)
- Studies included in quantitative synthesis (meta-analysis) of preclinical data for codeine (n = 2)
Pre-Clinical Results

Meta-Analysis 6 studies: Morphine/THC

Figure 2: Forest 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

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

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study design</th>
<th>Population</th>
<th>Follow-up period</th>
<th>Opioid used</th>
<th>Cannabinoid used</th>
<th>Effect of cannabinoid on opioid dose</th>
<th>Outcome on analgesia observed</th>
<th>GRADE evidence rating and other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams et al, 2011</td>
<td>Clinical laboratory study of self-reported pain under observed conditions (also measured pharmacokinetic effects of concurrent administration)</td>
<td>People (n = 24) receiving chronic opioid treatment (mixed pain conditions)</td>
<td>5 days</td>
<td>Morphine sulfate (mean daily dose 62 mg, n = 13) or oxycodeone hydrochloride (mean daily dose 53 mg, n = 11)</td>
<td>Vaporized cannabis dose of 0.9 g of 3.5% delta-9-THC or as much as they could tolerate administered three times per day</td>
<td>Cannabinoid dose held constant to examine effect of delta-9-THC on opioid pharmacokinetics (ie, no reduction from baseline opioid dose possible).</td>
<td>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 36.6, 49.1) at baseline to 35.6 (95% CI 28.3, 38.6) on day 5 with oxycodeone. Significant reduction overall. Potential of analgesia not observed in this experimental pain study.</td>
<td>Cannabis inhalation produced a subjective &quot;high&quot;. GRADE rating: low quality. Downgraded as study did not have a placebo condition, so placebo effects cannot be excluded. Note: no pharmacokinetic interaction observed.</td>
</tr>
<tr>
<td>Naef et al, 2003</td>
<td>Experimental heat, cold, pressure single- and repeated transcutaneous electrical stimulation pain, randomized, placebo-controlled, double-blinded, crossover study.</td>
<td>Healthy cannabis naive volunteers (n = 12)</td>
<td>Four study sessions with at least 7 days washout between sessions</td>
<td>Morphine (30 mg) daily</td>
<td>Dronabinol (20 mg)</td>
<td>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.</td>
<td>NA (opioid dose held constant)</td>
<td>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.</td>
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<td>Roberts et al, 2006</td>
<td>Experimental thermal pain. Double blinded, four treatment crossover design.</td>
<td>Healthy volunteers (n = 15) with no recent opioid or cannabinoid use</td>
<td>Four lab sessions</td>
<td>Morphine (0.02 mg/kg IV, 1.4 mg dose for 70 kg adult, ie, sub-analgesic)</td>
<td>Dronabinol (5 mg)</td>
<td>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.</td>
<td>NA (opioid dose held constant)</td>
<td>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.</td>
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<td>Lynch and Clark, 2003</td>
<td>Observational case series</td>
<td>Mixed pain conditions (n = 3) (peripheral neuropathy, multiple sclerosis, lower back pain)</td>
<td>1-3 month observation period</td>
<td>Morphine (75-360 mg daily)</td>
<td>Smoked cannabis plant, unknown content</td>
<td>Mean baseline-morphine dose of 195 mg (SD 14.7 mg) compared with 35 mg (SD 31 mg) after commencing smoked cannabis. Opioid dose reduction or cessation in each case.</td>
<td>Improved pain control described, with patients either reducing or ceasing morphine dose.</td>
<td>GRADE rating: very low.</td>
</tr>
</tbody>
</table>
Clinical studies results

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<th>(b) Study reference</th>
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<td>Johnson <em>et al.</em>, 2010</td>
<td>Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial</td>
<td>Patients with cancer pain (n = 177), with inadequate analgesia despite chronic opioid dosing</td>
<td>2 weeks</td>
<td>Varied opioids reported as OME (OR), 120 mg (30–213)</td>
<td>Patients randomized to delta-9-THC: CBD, Delta-9-THC or placebo</td>
<td>Delta-9-THC (mean 9 sprays per day)</td>
<td>No change in median amount of breakthrough opioid medication in any group</td>
<td>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 = 0.024)−1.37 (p = 0.001)</td>
</tr>
<tr>
<td>Liason <em>et al.</em>, 2014</td>
<td>Two groups (not randomized), cannabidiol extract or melatonin</td>
<td>Patients with unrelenting metastatic solid tumor (n = 26)</td>
<td>Not stated</td>
<td>Oxycodone, median dose of 30 mg (10–60 mg), twice daily</td>
<td>Cannabis oil (10% THC:10% CBD) was given up an infusion, 100 mg over 30 minutes</td>
<td>S2 patients (42%) achieved control of pain without opioid dose, increase compared to the control group, where 2/14 (14%) achieved pain control</td>
<td>The number that achieved pain control was not significantly different between groups</td>
<td>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.</td>
</tr>
<tr>
<td>Narang <em>et al.</em>, 2008</td>
<td>Phase I: randomized, single-dose, double-blinded, placebo-controlled crossover trial. Primary outcome measure: TOTPAIN score</td>
<td>Patients on opioids for chronic pain (n = 30). Pain diagnosis: neuropathic (n = 7), non-neuropathic (n = 23).</td>
<td>Phase 1: three 8-h lab sessions with 3 days washout</td>
<td>OME mean 68.1 mg (SD 57.2, range 24–228)</td>
<td>Opioid doses (mean 21 mg), placebo (mean 15 mg)</td>
<td>One subject took rescue pain medication in all conditions, one subject took rescue medication during the placebo and 0 mg condition, and six subjects took rescue medication only with placebo</td>
<td>The mean baseline NRS of 6.9 compared with 5.2 after 4 weeks of cannabis. This represents a statistically significant reduction</td>
<td>GRADE rating low; Open-label study. Significant improvements (p&lt;0.05) in sleep, energy, pain relief, and social functioning. Use of placebo control means effects may be non-specific or placebo.</td>
</tr>
<tr>
<td>Portenoy <em>et al.</em>, 2012</td>
<td>Randomized, 4-arm placebo-controlled, graded-dose study</td>
<td>Patients with active cancer and chronic pain on a stable oral morphine regimen, plus fentanyl (n = 360)</td>
<td>3 weeks of medication administration</td>
<td>Morphine and fentanyl Median: 120 mg OME, Median: 120 mg OME</td>
<td>Nabilone: 2–4 sprays</td>
<td>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</td>
<td>Treatment difference (change from baseline pain score): −0.25 points (95% CI: −0.39, 0.18 points, p = 0.19 compared to placebo)</td>
<td>GRADE rating high; Placebo-controlled, randomized controlled trial. Opioid composite measure showed better improvements in the low dose group (4–4 sprays per day) compared to placebo. Improvements in analgesia, lower tolerance of delta-9-THC: CBD in higher dose groups.</td>
</tr>
<tr>
<td>Seeling <em>et al.</em>, 2006</td>
<td>Randomized, controlled trial (two groups)</td>
<td>Prostate cancer patients n = 70 vs. n = 103, N = 53 in intervention and 52 in control</td>
<td>From the day prior to surgery to two days post operation</td>
<td>Piritramide 1.5 mg/ml, bolus 2 mg (no continuous infusion) by patient-controlled analgesia for 48 h post operation</td>
<td>Dronabinol 5 mg x 8 doses 10 mg 48 h postoperatively</td>
<td>Median dose of piritramide alone was 7.94 mg (IQR 6.94–90) compared with 54 mg (IQR 48–68) when administered with dronabinol</td>
<td>The difference between the treatment (dronabinol) and control group was not significant. No evidence was found of synergistic antinociceptive interaction between delta-9-THC and piritramide for acute postoperative pain</td>
<td>GRADE rating high; Placebo-controlled, randomized controlled trial. Patients administered their own opioid doses</td>
</tr>
</tbody>
</table>
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

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

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

However, lack of control!!
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.

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
Pharmacotherapies for cannabis dependence (Review)

Pharmacotherapies for cannabis dependence (Review)


No Pharmacological treatment available!
The opioid antagonist naltrexone reduces the reinforcing effects of THC in squirrel monkeys

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

Naltrexone Maintenance Decreases Cannabis Self-Administration in Daily Cannabis Smokers

Naltrexone Maintenance Decreases Cannabis Subjective Effects in Daily Cannabis Smokers

CONCLUSION

- Opioid crisis is a phenomenon that affects 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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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