Cannabinoids act on many of the same pain pathways as opioids

Endogenous neurotransmitters
- opioids (enkephalins) -> opioid receptors
- endocannabinoids (anadamide) -> cannabinoid receptors

Similar locations of these receptors:
- Peripheral nociceptive nerves (source of pain)
- In the sensory neuron transduction pathway
- In the descending modulatory pathways

With a key difference…
although CB receptors are found in similar pain circuits as opioids, their absence in the brainstem makes them safer than opioids.

Roques BP, et al. Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain, 2012
http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.htm
Cannabinoid agonists are effective in all peripheral neuropathic pain models

- Nerve Injury
  - Sciatic nerve ligation (SNL and PSN)
  - Sciatic nerve injury (CCI, SNI)
- Diabetes
  - Streptozotocin
- Chemotherapy
  - Paclitaxel, Cisplatin
- HIV neuropathy

Bouhassira D, Attal N. Translational neuropathic pain research: A clinical perspective. Neuroscience (2016), http://dx.doi.org/10.1016/j.neuroscience.2016.03.029
Cannabis provide an adjunct for opioids for treatment of pain

Individuals with chronic pain requiring opioids (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, migraine, MS, sickle cell disease, TOS).

Synergistic effects with opioids, providing pain relief with lower opioid doses and with less side effects. Did not change opioid blood levels.

GW pharmaceuticals phase 3 trials of nabiximols (Sativex) show benefit for cancer pain

- Randomized 360 subjects to placebo or one of three experimental groups
- Best results with 4 sprays per day (10mg THC / 10 mg CBD)
- Higher doses were not well-tolerated
  - more adverse events
  - higher drop-out rates.

**Figure 4.** Analysis of change from baseline in NRS average pain score.

JAMA meta-analysis = highest level of evidence for cannabis in treatment of chronic pain

- Meta-analysis provides compilation of data from randomized clinical trials (RCTs) comparing cannabinoids to placebo for chronic pain and other conditions.
- Also provides best available information about potential for adverse events (AEs) with cannabis [1].
- Includes 28 studies of chronic pain (63 reports, 2454 individual participants)
Patients with chronic pain successfully substitute medical cannabis for opioids

- Online survey of 244 medical cannabis patients with chronic pain to examine whether medical cannabis changed individual patterns of opioid use
- N=184 analyzed
- Found that cannabis was associated with
  - Decrease in opioid use (64%)
  - Improved quality of life (45%)

<table>
<thead>
<tr>
<th>Medication type</th>
<th>Use before initiation of cannabis (n/N)</th>
<th>Use after initiation of cannabis (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>119/184 (65%)</td>
<td>33/184 (18%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>115/184 (62%)</td>
<td>38/184 (21%)</td>
</tr>
<tr>
<td>Disease-modifying antirheumatic drugs (DMARDs)</td>
<td>15/184 (8%)</td>
<td>3/184 (2%)</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>72/184 (39%)</td>
<td>25/184 (14%)</td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors (SNRIs)</td>
<td>13/184 (7%)</td>
<td>3/184 (2%)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>34/184 (18%)</td>
<td>8/184 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>69/184 (38%)</td>
<td>40/184 (22%)</td>
</tr>
</tbody>
</table>

NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis.

Cannabis is considered an beneficial adjuvant at all steps of analgesic ladder

- Synergistic actions between cannabinoids and opioids can lower dose of opioids needed to control pain
- Cannabis-based medicine containing both THC and CBD appears to be more effective and better tolerated than synthetic THC (dronabinol)
- Modified WHO analgesic ladder includes cannabinoids as adjuvant medications that may be considered at all steps of treatment of cancer or other chronic pain [1]

States with medical cannabis laws have significantly lower state-level opioid overdose mortality rates

- A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.
- Reported age-adjusted opioid analgesic overdose death rate per 100,000 population in each state.
- Regression models were developed including state and year fixed effects, the presence of 3 different policies regarding opioid analgesics, and the state-specific unemployment rate.
- Results showed states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; \( P = .003 \)) compared with states without medical cannabis laws.
- The association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law strengthened over time.
- Concluded that medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates.

**Mean Age-Adjusted Opioid Analgesic Overdose Death Rate.** States with medical cannabis laws compared with states without such laws in the United States, 1999-2010.

**Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010.** Point estimate of the mean difference in the opioid analgesic overdose mortality rate in states with medical cannabis laws compared with states without such laws; whiskers indicate 95% CIs.

States with medical cannabis laws have fewer fatal crashes involving opioids

- States that passed medical marijuana laws saw an overall reduction in fatal crashes involving drivers who tested positive for opioids.
- Authors expect the adverse consequences of opioid use to decrease over time in states where medical marijuana use is legal, as individuals substitute marijuana for opioids in the treatment of severe or chronic pain.