CANNABIS FOR THE RHEUMATOLOGIST

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Disclosures

- None
Overview

- The history of cannabis use
- Anecdotal use of cannabis in chronic pain
- The biology of cannabinoids
- Types of medical cannabis / cannabinoid medication
- Evidence for the use of cannabinoids in diseases
- Evidence for the use of cannabinoids in chronic pain

The history of cannabis use

- First use 5000 years ago by early Chinese as a treatment for malaria, constipation, rheumatic pains and an analgesic during childbirth
- W.B. O’Shaughnessy, a doctor with the Bengal army and professor of chemistry in 1843 demonstrated its use in various indications
- Sir John Russell Reynolds, physician to Queen Victoria and president of RCP London wrote in Lancet in 1890 about its medicinal uses
- Adopted into US and UK pharmacies until 1940s
- Although currently illegal in the US, certain states have legalised its use for medical reasons such as for severe pain
Opioid related deaths in the US rose from 1999-2014
Opioid prescriptions are decreased in states with legalised cannabis

- 23.08 million daily doses of opioid dispensed each year per state on average
- 3.742 million fewer daily doses in states with dispensaries
- 1.792 million fewer daily doses in states with legal home cultivation

JAMA Intern Med. 2018;178(5):667-672

CANNABIS 101
### Types of cannabis available from US dispensaries

- Marijuana – dried plant product – smoked or vaporised
- Hashish – resin cake that can be ingested or smoked
- Tincture – liquid that is taken sublingually
- Hashish oil – oil obtained from plant by solvent extraction
- Infusion – plant material mixed with butter or cooking oil to be ingested

### Biology of cannabinoids

- Marijuana contains over 60 active cannabinoids

- Activate 2 GPCRs
  - CB1 – mainly in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord and peripheral nerves
  - CB2 – mainly on immune cells

- Can directly inhibit release of
  - Acetylcholine
  - Dopamine
  - Glutamate

- Indirectly affects
  - GABA
  - NMDA
  - Opioid receptors
  - Serotonin receptors
Primary cannabinoids in marijuana

- Δ⁹-tetrahydrocannabinol – THC
  - Euphoric and psychotic effects

- Cannabidiol – CBD
  - Not psychoactive and may have anti anxiety and anti psychotic effects

- Ratios of THC to CBD can be different in various strains of marijuana

Physiological effects of cannabinoid receptor activation

- Euphoria
- Psychosis
- Impaired memory and cognition
- Reduced locomotor function
- Increased appetite

- Other effects such as antiemetic, pain relieving, anti-spasticity, sleep-promoting effects
Types of cannabinoid medication

- Herbal cannabis – phytocannabinoids
  - Nabiximols, Cannador
  - THC
  - CBD

- Endocannabinoids – endogenous compounds made by mammals
  - Anandamide
  - 2-arachidonylethanolamine (2-AG)

- Synthetic analogues
  - Dronabinol
  - Levonantradol
  - Nabilone

EVIDENCE FOR USE OF CANNABINOID MEDICATIONS IN CHRONIC PAIN
Evidence for the use of cannabis-derived medication in chronic pain

- Systematic review of 79 trials involving 6462 participants

**Chronic Pain**

- Assessed in 28 studies – 2454 participants
  - 13 studies nabiximols
  - 4 smoke THC
  - 5 nabulone
  - 3 THC oromucosal spray
  - 2 dronabinol
  - 1 vaporised cannabis
  - 1 ajuvencic acid
  - 1 oral THC

- One trial compared nabulone with amitriptyline
- One trial nabulone was an adjunct to gabapentin

- Conditions
  - 12 neuropathic pain
  - 3 cancer pain
  - 3 diabetic peripheral neuropathy
  - 2 fibromyalgia
  - 2 HIV associated sensory neuropathy
  - 1 for RA and others

Whiting et al. JAMA. 2015;313(24):2456-2473

Greater reduction in pain of at least 30% is greater with cannabinoids than placebo
Increased risk of adverse events with cannabinoids

- Any adverse event – **OR 3.03** (2.42-3.80)
- Serious adverse event – **OR 1.41** (1.04-1.92)
- Withdrawal due to adverse event – **OR 2.94** (2.18-3.96)
- Dizziness **OR 5.09** (4.10-6.32)
- Dry mouth, nausea, fatigue, somnolence

An overview of systematic reviews of cannabinoids for chronic pain suggests there are inconsistencies

- 10 SRs were included
- 4 high quality, the rest moderate

**Conclusion**

Inconsistent findings of the efficacy, tolerability and safety of cannabis-based medicines for the management of cancer and non-cancer pain

However it is becoming more widespread and consideration should be made about driving ability especially with THC containing products and also the possible ingestion by children

Challenges in this area

The Health Effects of Cannabis and Cannabinoids:
Implications for Public Health

The Health Effects of Cannabis and Cannabinoids Implications for Public Health

In 2013, between 499,000 and 721,000 units of medical and recreational cannabis products were sold per month in Colorado (Colorado DOH, 2013, p. 32). Pain patients also use topical forms (e.g., transdermal patches and creams). Thus, the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products, as much as the efficacy, more research is needed on the various forms, routes of administration, and combination of cannabinoids.

CONCLUSION 8: There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

CANNABINOID MEDICATIONS IN EXPERIMENTAL PAIN
Association of cannabinoid administration with experimental pain in healthy adults

- Systematic review and meta-analysis
- 18 placebo controlled studies with 442 participants
- Although meta-analyses have shown evidence for the use of cannabinoids in chronic pain, there are often no objective experimental measures of pain

Cannabinoids cause a small increase in the pain threshold

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Substance administered</th>
<th>Route</th>
<th>Dose</th>
<th>Endpoint</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al. (1974)</td>
<td>Cannabis (1% THC)</td>
<td>Intravenous</td>
<td>10 mg/kg</td>
<td>Threshold</td>
<td>0.0502 (1.504 vs 0.355)</td>
</tr>
<tr>
<td>Liberman and Stern (1985)</td>
<td>Cannabis (5 mg THC)</td>
<td>Intraoral</td>
<td>5 mg</td>
<td>Threshold</td>
<td>0.0216 (1.773 vs 1.351)</td>
</tr>
<tr>
<td>Koett et al. (1978)</td>
<td>Cannabis extract (15 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0191 (1.605 vs 0.381)</td>
</tr>
<tr>
<td>Radosevitch et al. (2001)</td>
<td>Cannabis (20 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0021 (0.005 vs 0.001)</td>
</tr>
<tr>
<td>Cooper et al. (2013)</td>
<td>Cannabis (60 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0021 (0.004 vs 0.001)</td>
</tr>
<tr>
<td>Wolkowicz et al. (1997)</td>
<td>Cannabis (600 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0564 (1.046 vs 0.630)</td>
</tr>
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<td>Wolkowicz et al. (1997)</td>
<td>Cannabis (600 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0751 (0.086 vs 0.090)</td>
</tr>
<tr>
<td>Killibride et al. (2015)</td>
<td>Nabilone (1 mg)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0042 (0.004 vs 0.004)</td>
</tr>
<tr>
<td>Killibride et al. (2015)</td>
<td>Nabilone (2.5 mg)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0151 (0.015 vs 0.010)</td>
</tr>
<tr>
<td>Cooper and Liberman (1974)</td>
<td>Cannabis (600 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0214 (1.112 vs 0.531)</td>
</tr>
<tr>
<td>Cooper et al. (1985)</td>
<td>Cannabis (20 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0219 (0.021 vs 0.016)</td>
</tr>
<tr>
<td>Cooper et al. (1985)</td>
<td>Cannabis (60 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0590 (0.216 vs 0.167)</td>
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<tr>
<td>Wolkowicz et al. (1997)</td>
<td>Nabilone (20 mg)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0830 (0.083 vs 0.083)</td>
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<tr>
<td>Cooper and Liberman (1974)</td>
<td>Cannabis (600 mg THC)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0352 (0.342 vs 0.305)</td>
</tr>
<tr>
<td>Liberman and Stern (1985)</td>
<td>THC 20 mg (intravenous)</td>
<td>Intravenous</td>
<td>Combined</td>
<td>Combined</td>
<td>0.0081 (0.008 vs 0.008)</td>
</tr>
</tbody>
</table>

De Vita et al. JAMA Psychiatry. 2018;75(11):1118-1127
Cannabinoids do not reduce intensity of ongoing experimental pain

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Subject Group/Study</th>
<th>Outcome</th>
<th>Median (95% CI)</th>
<th>F mean</th>
<th>Hypergeometric</th>
<th>F exact</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hof et al., 2005</td>
<td>Dronabinol (0.375 mg/kg, i.v.)</td>
<td>Intensity</td>
<td>−0.745 (−1.490 to 0.025)</td>
<td>−1.14</td>
<td>−</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Maldonado et al., 2007</td>
<td>Cannabinoids (100 mg/kg THC, i.v.)</td>
<td>Intensity</td>
<td>−0.076 (−0.008 to 0.140)</td>
<td>−</td>
<td>−</td>
<td>0.08</td>
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</tr>
<tr>
<td>Hof et al., 2005</td>
<td>Dronabinol, 5 mg</td>
<td>Intensity</td>
<td>−0.029 (−0.015 to 0.037)</td>
<td>−</td>
<td>−</td>
<td>0.35</td>
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<tr>
<td>Richer et al., 2005</td>
<td>Dronabinol, 5 mg</td>
<td>Intensity</td>
<td>−0.275 (−0.347 to 0.325)</td>
<td>−</td>
<td>−</td>
<td>0.35</td>
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<tr>
<td>Forimoto et al., 2008</td>
<td>Meperidine, 1 mg/kg (i.v.)</td>
<td>Intensity</td>
<td>−0.293 (−0.361 to 0.368)</td>
<td>−</td>
<td>−</td>
<td>0.38</td>
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<tr>
<td>Kolliparki et al., 2012</td>
<td>Dronabinol, 5 mg (i.v.)</td>
<td>Intensity</td>
<td>−0.881 (−0.950 to 0.614)</td>
<td>−</td>
<td>−</td>
<td>0.47</td>
<td></td>
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<tr>
<td>Lent et al., 2011</td>
<td>THC, 15 mg</td>
<td>Intensity</td>
<td>−0.823 (−0.863 to 0.270)</td>
<td>−</td>
<td>−</td>
<td>0.47</td>
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<tr>
<td>Kolliparki et al., 2011</td>
<td>Δ9-THC (5 μg/kg, i.v.)</td>
<td>Intensity</td>
<td>−0.168 (−0.207 to 0.046)</td>
<td>−</td>
<td>−</td>
<td>0.08</td>
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<tr>
<td>Richer et al., 2008</td>
<td>Cannabinoids, 20 mg of Δ9-THC (i.v.)</td>
<td></td>
<td>−0.002 (−0.003 to 0.012)</td>
<td>−</td>
<td>−</td>
<td>0.87</td>
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<tr>
<td>Maldonado et al., 2007</td>
<td>Cannabinoids, 100 mg of Δ9-THC (i.v.)</td>
<td></td>
<td>−0.024 (−0.030 to 0.034)</td>
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<tr>
<td>Cooper and Haney, 2011</td>
<td>Cannabis, 0.05 mg, 1 3:1:100 THC (i.v.)</td>
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<td>−0.820 (−0.849 to 0.543)</td>
<td>−</td>
<td>−</td>
<td>0.35</td>
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<td>Cooper et al., 2011</td>
<td>Dronabinol, 10 mg (i.v.)</td>
<td></td>
<td>−0.021 (−0.023 to 0.012)</td>
<td>−</td>
<td>−</td>
<td>0.49</td>
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<tr>
<td>Kolliparki et al., 2012</td>
<td>Meperidine, 2 mg/kg (i.v.)</td>
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<td>−0.380 (−0.400 to 0.340)</td>
<td>−</td>
<td>−</td>
<td>0.89</td>
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<td>Cooper et al., 2012</td>
<td>Dronabinol, 15 mg (i.v.)</td>
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<td>Kolliparki et al., 2013</td>
<td>Δ9-THC (5 μg/kg, i.v.)</td>
<td></td>
<td>−0.051 (−0.056 to 0.034)</td>
<td>−</td>
<td>−</td>
<td>0.44</td>
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<td>Cooper et al., 2013</td>
<td>Cannabis, 0.1 mg, 1 3:1:100 THC (i.v.)</td>
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<td>−0.304 (−0.350 to 0.274)</td>
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<td>0.046</td>
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<td>Cooper et al., 2013</td>
<td>Cannabis, 0.1 mg, 1 3:1:100 THC (i.v.)</td>
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<td>0.408 (0.350 to 0.905)</td>
<td>−</td>
<td>−</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Maldonado et al., 2007</td>
<td>Cannabinoids, 100 mg of Δ9-THC (i.v.)</td>
<td></td>
<td>0.403 (0.350 to 0.905)</td>
<td>−</td>
<td>−</td>
<td>0.22</td>
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<tr>
<td>Wolkin et al., 2003</td>
<td>THC, 10 mg</td>
<td></td>
<td>0.521 (0.450 to 1.270)</td>
<td>−</td>
<td>−</td>
<td>0.19</td>
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<tr>
<td>Reuter et al., 2002</td>
<td>HI-2210, 10 mg, solution (p.o.)</td>
<td></td>
<td>0.614 (0.512 to 1.076)</td>
<td>−</td>
<td>−</td>
<td>0.009</td>
<td></td>
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<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.307 (0.250 to 0.364)</td>
<td>−</td>
<td>−</td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>

De Vita et al. JAMA Psychiatry. 2018;75(11):1118-1127

Cannabinoids reduce perception of ongoing pain unpleasantness

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<tr>
<td>Roberts et al., 2005</td>
<td>Dronabinol, 1 mg</td>
<td></td>
<td>−0.403 (−0.330 to 0.129)</td>
<td>−</td>
<td>−</td>
<td>0.64</td>
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<tr>
<td>Cooper et al., 2005</td>
<td>Dronabinol, 1 mg (i.v.)</td>
<td></td>
<td>−0.823 (−0.944 to 0.255)</td>
<td>−</td>
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<td>0.58</td>
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<tr>
<td>Wolkin et al., 2006</td>
<td>THC, 20 mg</td>
<td></td>
<td>−0.241 (−0.215 to 0.330)</td>
<td>−</td>
<td>−</td>
<td>0.05</td>
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<tr>
<td>Lent et al., 2011</td>
<td>THC, 15 mg</td>
<td></td>
<td>−0.321 (−0.349 to 0.779)</td>
<td>−</td>
<td>−</td>
<td>0.32</td>
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Nabilone is effective in improving sleep in patients with fibromyalgia

- Randomised, double blind, active control crossover
- Each drug given for 2 weeks with a 2 week washout
- 31 subjects – 29 completed
- Sleep improved by both medications but nabilone superior
  - Insomnia severity index difference - 3.2 (1.2-5.3)
  - More adverse effects for nabilone - dizziness, nausea, dry mouth

Evidence for the use of Cannabidiol in Drug-Resistant seizures in Dravet syndrome

- Dravet syndrome – loss of function mutation in the SCN1A gene
- Randomised double-blind, placebo controlled trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cannabidiol</th>
<th>Placebo</th>
<th>Adjusted Median Difference (% 95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of convulsive seizures per month — median (range)</td>
<td>12.4 (1.9 to 12.7)</td>
<td>14.9 (1.7 to 7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td>5.9 (2.9 to 12.5y)</td>
<td>4.1 (1.9 to 10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change in seizure frequency — median (range)</td>
<td>-88.8 [-100 to 35]</td>
<td>-59.4 [-100 to 35]</td>
<td>-30.8 [-11.3 to -41.4]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval
† The P values were calculated with the use of a Wilcoxon rank sum test with the Hodges-Lehmann approach.
Labeling accuracy of CBD extracts sold online

- 84 products from 31 companies were purchased and analysed blindly by HPLC
  - Products included oil, tincture and vaporisation liquid
  - Accurately labeled - 90-110% labeled value
  - Overlabeled - <90%
  - Underlabeled - >110%

- CBD
  - 30.95% accurately labeled
  - 26.19% overlabeled
  - 42.85% underlabeled

- Oil tended to be better than vaporisation liquid
- THC was detected in 18/84 samples

Conclusions

- Inconsistent evidence for efficacy in chronic pain
- Associated with significant adverse events including dizziness
- Studies of whether cannabinoid medications can reduce opioid use are ongoing
- There may be significant differences in over the counter preparations

Bonn-Miller et al. JAMA. 2017. 318(17): 1708-1709