Do Cannabinoids have a role in cancer pain?
A short history of cannabis
“The decoction of the root eases the pains of the gout, the hard humours of knots in the joints, the pains and shrinking of the sinews, and the pains of the hips.”
8000 BC Hemp cultivation.

2800 BC China *Pen ts’ao Ching*.

2000 BC India *Atharva Veda*.

4 AD Obstetric analgesia.

60+ AD Dioscorides and Galen.

1653 Culpepper.

1842 O’Shaughnessy.

1860s Queen Victoria.
The Science
Cannabinoid Receptors

\( \text{CB}_1 \)

Neurons

- Inhibit adenylate cyclase.
- Activate K\(^+\) channels.
- Inactivate Ca\(^{++}\) channels.

\( \text{CB}_3 \)

GPR55

\( \text{CB}_2 \)

Immune cells

- Inhibit adenylate cyclase.

Cayman Chemical
Brain

Herkenham et al 1991; Egertová et al 2003
Spinal Cord
Reported effects of cannabis and $\Delta^9$THC

- **CNS:**
  - Euphoria/”high”.
  - Heightened sensory perception.
  - Impaired cognition and psychomotor performance.
  - Distortion of space & time sense.
  - Memory impairment.
  - Fragmentation of thoughts.
  - Antinociception and analgesia.
  - Anti-emesis.
  - Increased appetite.
  - Altered thermoregulation.
  - Schizophrenia-like syndrome.
Pertinent pre-clinical data
Cannabinoid Analgesia in Pain Models

- Visceral inflammatory pain and referred hyperalgesia  
  (Jaggar et al 1998a,b, Farquhar-Smith et al 2001, 2002)

- Formalin  

- Carrageenan  
  (Richardson et al 1998)

- Cystitis  
  (Wang et al 2013)

- Collagen-induced arthritis  
  (Malfait et al 2000)

- Complete Freund’s Adjuvant  
  (Martin et al 1999, Smith et al 1999)

- Chemotherapy induced neuropathic pain  
  (Burgos et al 2012, Guindon et al 2013, Khasabova et al 2012)

- Tumour induced bone pain  
Cannabinoid binding

Vehicle

Capsaicin

Opioid Binding

Lamina I,II

Hohmann & Herkenham 1998

Farquhar-Smith et al 2000

Bridges et al 2001

Chronic Constriction Injury

Partial Sciatic Nerve Ligation

Spinal Nerve Ligation

L4 L5 L6

CB₁

IB4

100 µm.

L4 L5 L6

Conininoid binding

Cannabinoid binding

Vehicle Capsaicin

Hohmann & Herkenham 1998
Evidence in humans
Meta-analysis of clinical evidence
(17 years ago)

- All clinical trials published prior to 1999.
- 9 trials included
  - 5 cancer pain (119 patients analysed)
  - 2 chronic non-malignant pain (2 patients)
  - 2 acute pain (72 patients)
- THC (5-20 mg p.o.) ~ equi-analgesic to 50 –120 mg codeine
- Dose related and dose limiting CNS adverse events common.

Campbell et al 2001 BMJ
More recent meta-analysis

- Meng et al 2017 Anesthesia Analgesia – chronic neuropathic pain
  - 11 RCT n=1219 NRS 0.65 – weak recommendation
- Whiting et al 2015 JAMA – Medical use
  - Portnoy (2012), Johnson (2010)
- Aviram et al 2017 Pain Physician -
<table>
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<tr>
<th>Study name</th>
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<td>Noyes 1975e</td>
<td>THC 15mg vs. Placebo</td>
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<td>Wads 2003a</td>
<td>THC 2.5mg vs. Placebo</td>
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<td>-1.066</td>
<td>0.488</td>
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<td>Wads 2003b</td>
<td>CBG 2.5mg vs. Placebo</td>
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<td>Wads 2003c</td>
<td>THC/CBG 2.5mg vs. Placebo</td>
<td>-0.158</td>
<td>-0.932</td>
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<td>0.689</td>
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<td>Berma 2004a</td>
<td>GW 2000-02 (THC) vs. Placebo</td>
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<td>-0.773</td>
<td>-0.173</td>
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<td>GW 1000-02 (sativax) vs. Placebo</td>
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<td>Wads 2004</td>
<td>Sativax vs. Placebo</td>
<td>-0.303</td>
<td>-0.945</td>
<td>0.340</td>
<td>0.356</td>
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<td>Rog 2005*</td>
<td>Sativax vs. Placebo</td>
<td>-0.492</td>
<td>-0.980</td>
<td>0.004</td>
<td>0.487</td>
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<tr>
<td>Wissel 2006</td>
<td>Nabilone 1mg vs. Placebo</td>
<td>0.309</td>
<td>1.118</td>
<td>0.500</td>
<td>0.454</td>
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<tr>
<td>Blake 2006</td>
<td>CBM vs. Placebo</td>
<td>0.629</td>
<td>1.151</td>
<td>0.107</td>
<td>0.486</td>
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<tr>
<td>Numis 2007*</td>
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<td>0.982</td>
<td>0.196</td>
<td>0.003</td>
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<tr>
<td>Frank 2008</td>
<td>Nabilone 2mg vs. Dihydrocodeine</td>
<td>0.652</td>
<td>0.154</td>
<td>1.150</td>
<td>0.010</td>
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<td>Skrabe 2008</td>
<td>Nabilone 0.5mg vs. Placebo</td>
<td>0.937</td>
<td>1.535</td>
<td>-1.138</td>
<td>0.019</td>
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<tr>
<td>Wilsy 2008</td>
<td>3.5%+7% cannabis cigarette vs. Placebo</td>
<td>0.402</td>
<td>-0.727</td>
<td>0.078</td>
<td>0.015</td>
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<tr>
<td>Ware 2010a</td>
<td>2.5% cannabis cigarette vs. Placebo</td>
<td>0.082</td>
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<td>Ware 2010b</td>
<td>6% cannabis cigarette vs. Placebo</td>
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<td>0.355</td>
<td>0.786</td>
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<td>Ware 2010c</td>
<td>9.4% cannabis cigarette vs. Placebo</td>
<td>0.451</td>
<td>-0.884</td>
<td>-0.017</td>
<td>0.042</td>
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<tr>
<td>Selvaraj 2010*</td>
<td>Sativax vs. Placebo</td>
<td>0.445</td>
<td>-0.272</td>
<td>1.162</td>
<td>0.224</td>
</tr>
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<td>Johnson 2010b*</td>
<td>THC 2.5mg/CBG 2.5mg vs. Placebo</td>
<td>-0.499</td>
<td>-0.897</td>
<td>-0.102</td>
<td>0.014</td>
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<tr>
<td>Rintala 2003</td>
<td>Dronabinol vs. Dihydrocodeine</td>
<td>0.975</td>
<td>0.224</td>
<td>2.173</td>
<td>0.111</td>
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<tr>
<td>Toth 2012</td>
<td>Nabilone 1-4mg vs. Placebo</td>
<td>-1.210</td>
<td>-2.203</td>
<td>-0.401</td>
<td>0.003</td>
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<td>Piris 2012</td>
<td>Nabilone 0.5mg vs. Ibuprofen 400mg</td>
<td>-0.431</td>
<td>-0.973</td>
<td>0.111</td>
<td>0.119</td>
</tr>
<tr>
<td>Langford 2013</td>
<td>THC 2.5mg/CBG 2.5mg vs. Placebo</td>
<td>-0.103</td>
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Fixed 0.411  
Random 0.541

Fig. 2. Meta-analysis- without acute postoperative pain.

All pain (without acute post-operative pain)  
Aviram et al 2017
Chronic neuropathic pain

Aviram et al 2017

**Fig. 6. Meta-analysis- cannabinoids effects on chronic NP.**

<table>
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<tr>
<th>Model</th>
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<td>Wade 2003a</td>
<td>THC 2.5mg vs. Placebo</td>
<td>-0.299</td>
<td>-1.066</td>
<td>0.489</td>
<td>0.406</td>
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<td>Wade 2003b</td>
<td>CBD 2.5mg vs. Placebo</td>
<td>-0.190</td>
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<td>-0.844</td>
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<td>Wallace 2015b</td>
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<td>7% THC vaporizer vs. Placebo</td>
<td>-2.869</td>
<td>-4.000</td>
<td>-2.003</td>
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</table>

**Fixed**   0.381  
**Random**  0.528
Yes, but what about cancer pain?
### Cancer pain

Aviram et al 2017

*“Alarming adverse reactions were also observed at this dose”*

---

### Study outcomes

<table>
<thead>
<tr>
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<th>Study name</th>
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* = Parallel design

**Fig. 7. Meta-analysis- cannabinoids effects on cancer pain.**
### Meta-analysis for CNS-related AEs

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<th>Model</th>
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<th>Comparison</th>
<th>Outcome</th>
<th>Risk ratio</th>
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<th>Upper limit</th>
<th>p-Value</th>
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<tbody>
<tr>
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<td>Aviram et al 2017</td>
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<td>Combined</td>
<td>2.842</td>
<td>0.584</td>
<td>6.762</td>
<td>0.2718</td>
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</table>

*= Parallel design; **= Postoperative pain.

*Fig. 10. Meta-analysis for CNS-related AEs.*

CNS-related adverse effects

Aviram et al 2017
Cancer Pain

- Patients with uncontrolled cancer pain (NRS 5)
- N=117, (Sativex 60, THC 58, placebo 59)
- NRS -1.37 (Vs. -0.69) (THC NS)
- 30% reduction from baseline in 43% (c.f. 23%)
- No change opioid dose or breakthrough
- N&V increased (85% AE, c.f. 75% placebo)

Johnson et al 2010 J Pain Symptom Manage
Cancer Pain

- N=263 (360 randomised), Nabiximols (a.k.a. Sativex)
- 5 weeks low, medium (up to 10 sprays/day) and high dose spray
- 1° outcome: 30% responder, no difference
- But low/medium more ‘analgesed’ (average daily pain)
- No differences side effects

Portenoy et al 2012 J Pain
Cancer pain (not included in meta-analyses)

- N=397
- Self titration Sativex over 2 weeks
- 10.7% improvement (compared to 4.5% control) in NRS – not significant
- Subgroup analysis for QOL
- From US

Lichtman et al 2017 J Pain Symptom Manag
Cancer pain (not included in meta-analyses)

- 2) RCTs Refractory pain, 15% >90mg/day/mean morphine (≥4≤8)
- N=399 (64/200 withdrew in Sativex group)
- Median improvement from baseline average NRS 7.2% (c.f. 9.5% placebo)
- Subgroup US <65y 11.2% vs. 4.8%
- PGIC better by 0.27 at week 5

Fallon et al 2017 Br J Pain
The other problem
Long Term CNS Adverse Effects

- Historical cohort study 1969-70 Swedish conscripts
- n=50,087 (97% of Swedish 18-20 yr. olds)
- Questionnaire of drug use
- National register of psychiatric admissions 1970-1996
- Dose dependent increase risk of developing schizophrenia with cannabis use (30% increased risk of schizophrenia [OR: 6.7 (2.1-21.7)])

Zammit et al 2002 BMJ
The bottom line

‘May be beneficial’
(but potential of side effects)
The future?
**Pros**
- Major receptor system
- Wealth of animal data
- Some human data

**Cons**
- Long term issues
- Central side effects
- Legal issues
- Herbal CBs wrong drug?
Pros

- More human data
- Major receptor system
- Wealth of animal data
- Some human data

Cons

- Legal issues
Transdermal CB2 agonist

- Chemically favourable
- No central side effects
- Anti-inflammatory with no NSAID problems
Do Cannabinoids have a role in cancer pain?

- Yes
- No
- Maybe