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Cannabinoids: Reviewing the evidence and future potential

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Definitions

Cannabis
Hemp plant from which marijuana is derived
3 species (C. sativa, C. indica, C. ruderalis)

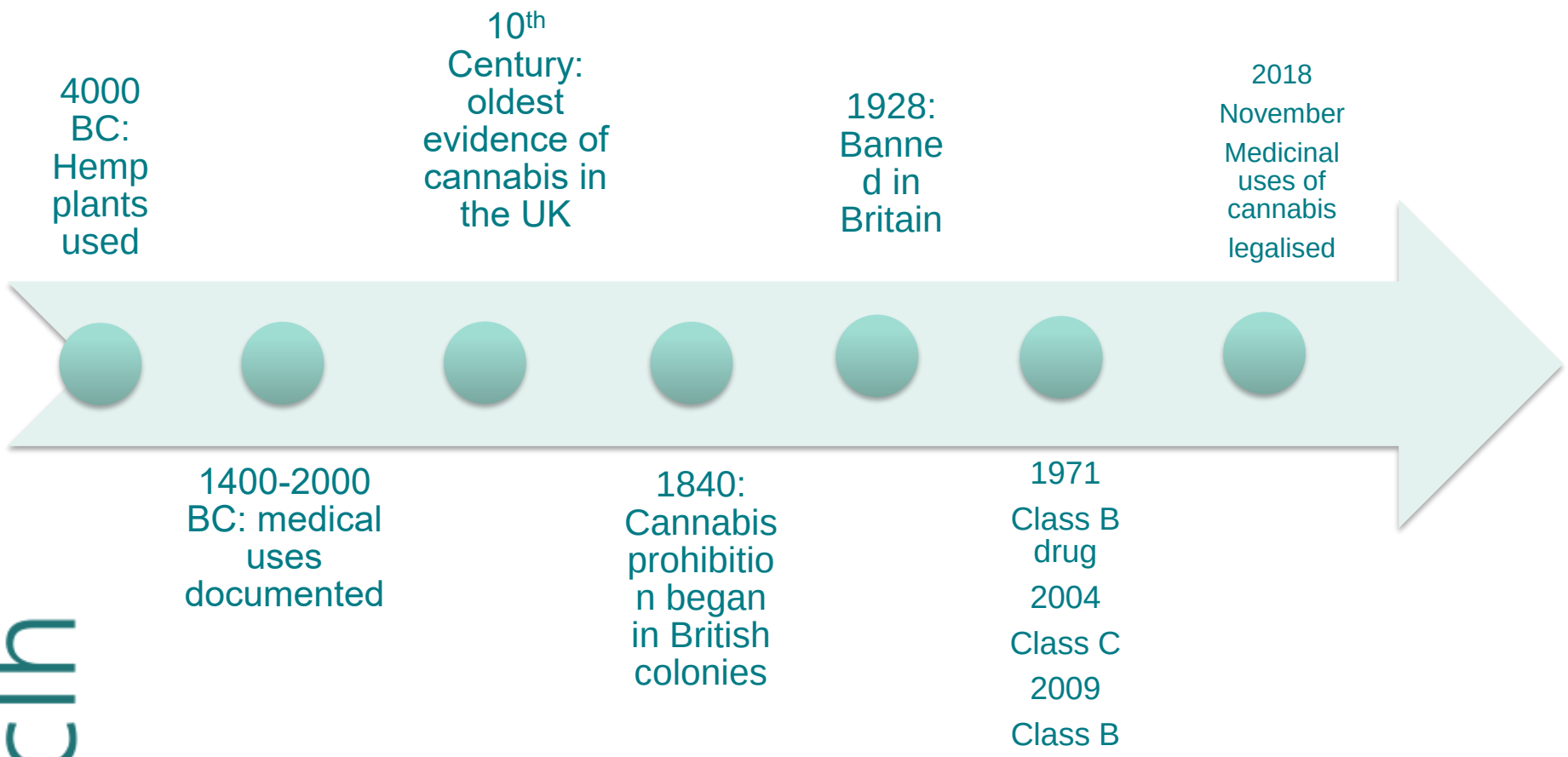
Marijuana
Dried leaves, flowers, stems, and seeds from the hemp plant

Cannabinoid
various naturally occurring, biological active, chemical constituents (such as cannabidiol or cannabinol) of hemp or cannabis including some that possess psychoactive properties

Medical cannabis (Dept of Health and Social Care)

“Cannabis-based products are defined as being a preparation or product which contains cannabis, cannabis resin, cannabinol or a cannabinol derivative that is produced for medicinal use in humans, and is a medicinal product, or a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product.”

Timeline of cannabis in the UK



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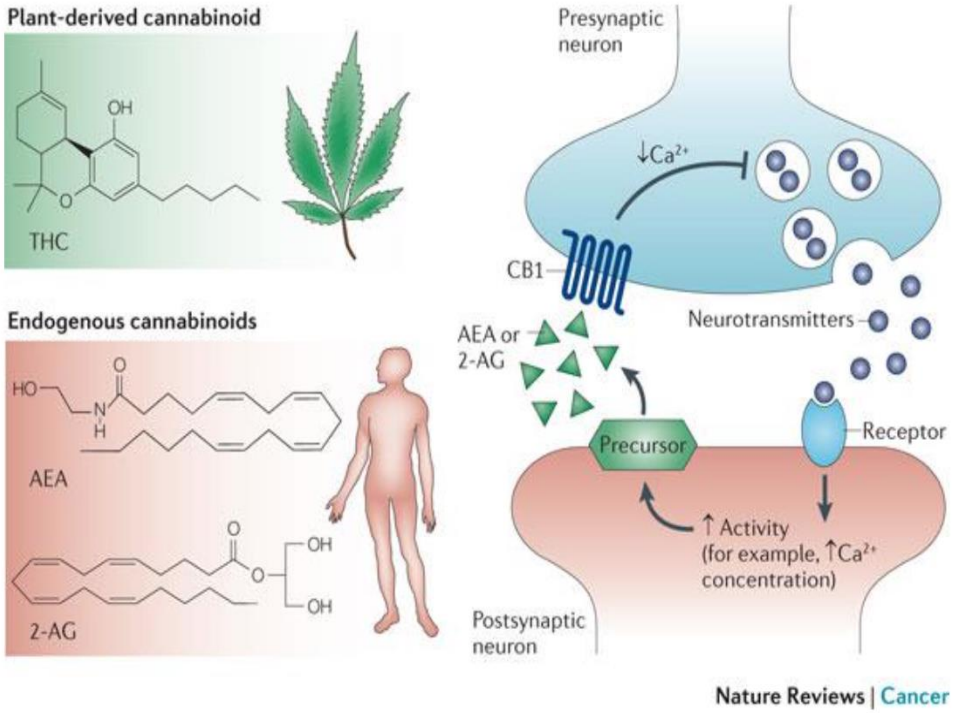
Cannabis and cannabinoids

- Cannabis Sativa L produces key cannabinoids such as THC and CBD
- Up to 142 other cannabinoids, typically low quantities
- Terpinoids (eg limonene an a-pinene)

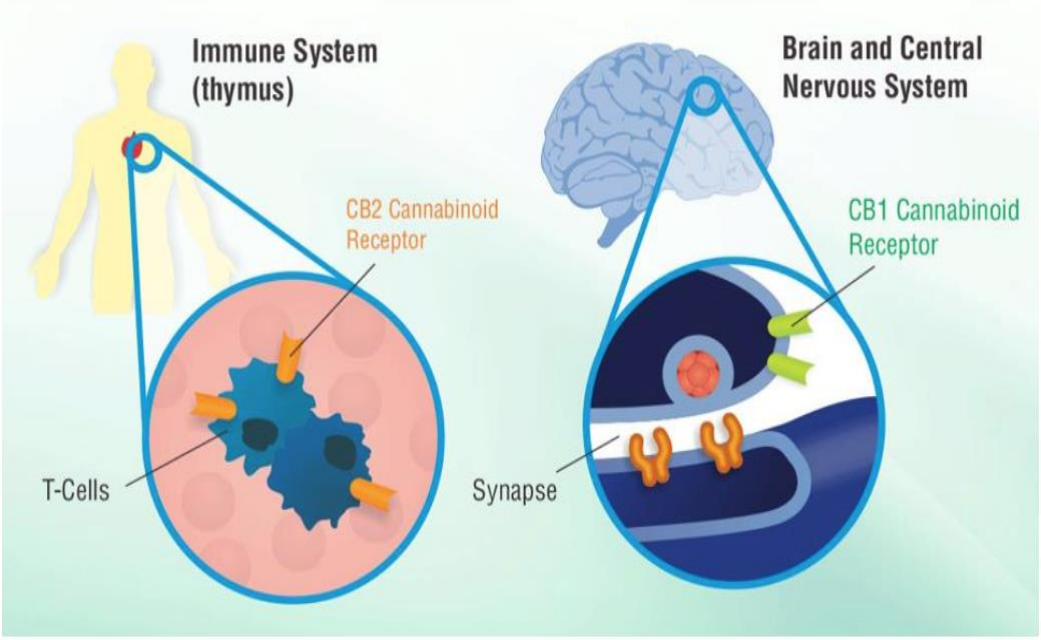
- Almost all clinical research focuses on THC and CBD

Cannabis and cannabinoids Velasco et al 2012



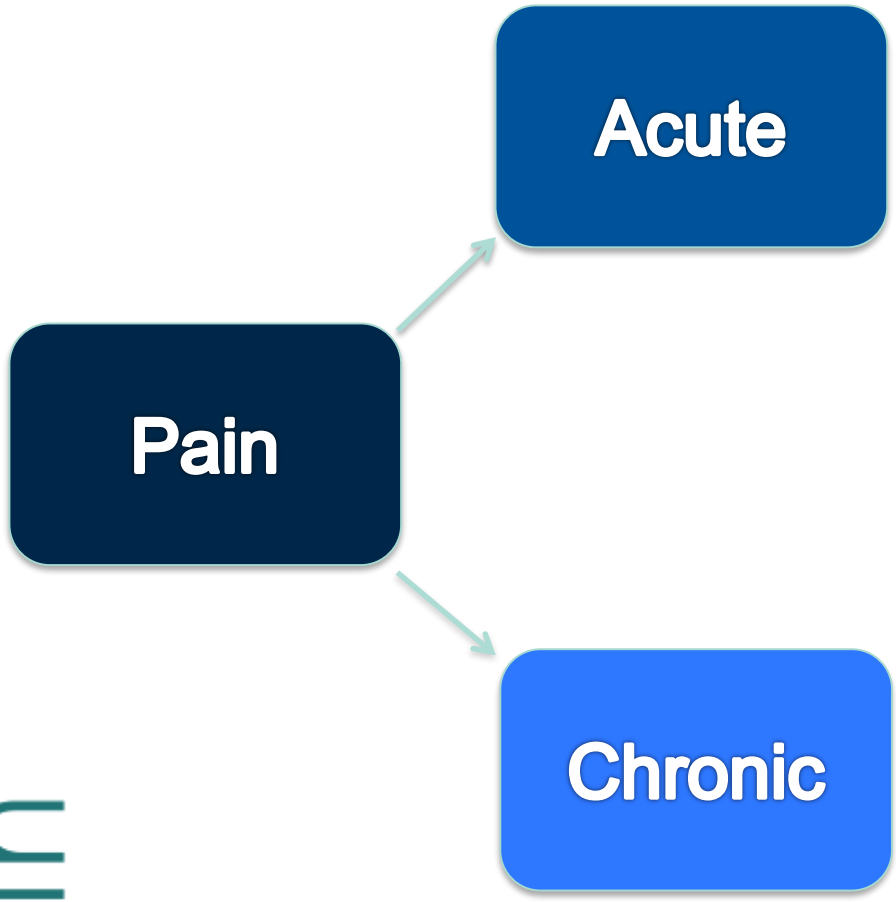
Endocannabinoids produced on demand and play a modulatory role in pain, appetite, movement, cognition and reward

Cannabis and cannabinoids



Pleasure, memory concentration, sensory and time, coordination, movement, appetite

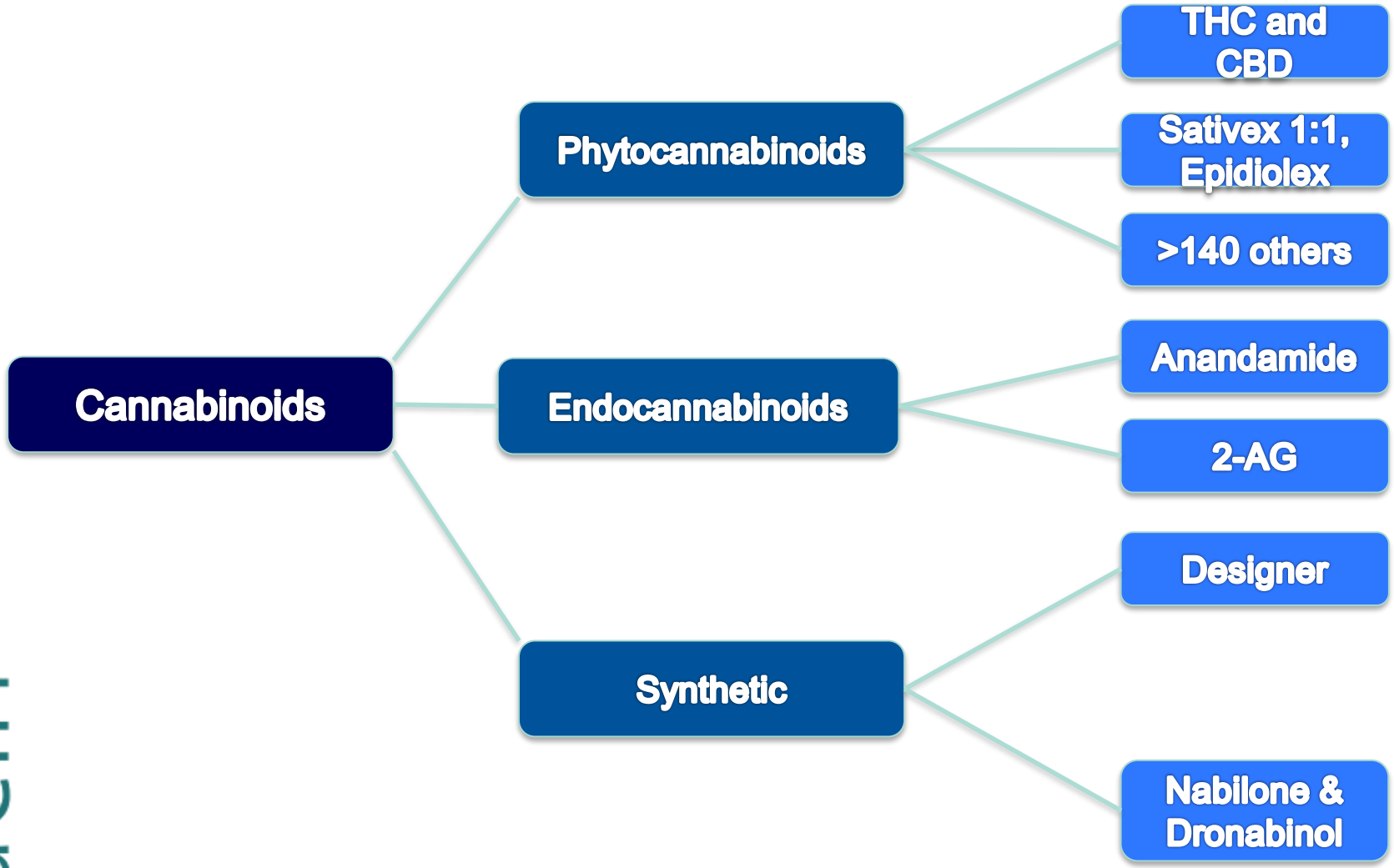
Types of pain



International Classification of chronic pain for ICD-11

- Cancer
- Neuropathic
- Primary chronic
- Musculoskeletal
- Visceral
- Headache & Orofacial
- Post surgical & traumatic

Cannabinoids



Medicinal cannabis

Cannabis based products for medicinal use consist of:

- THC
- +/- CBD
- Terpenoids

Administration

- Inhaled (vaporizer)
- Oral

	Medicinal products					
	Cannabis based products for medicinal use				Synthetic cannabinoids for medicinal use	
Example	**Bedrocan**	**Tilray**	**Sativex**	**Epidiolex**	**Dronabinol**	**Nabilone**
Cannabinoid profile	THC +/–CBD	THC +/–CBD	THC:CBD ratio 1:1	CBD	THC	THC
Formulation	Herbal cannabis	Oil	Oromucosal spray	Oral solution	Capsule or liquid	Capsule
Licensed indications (UK)	None	None	Multiple sclerosis	None	None	Chemotherapy induced nausea and vomiting
Quality standards	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice
Affected by rescheduling (UK) on 1 November 2018?	Yes	Yes	No	No	No	No

Freeman et al. (2019) *BMJ*

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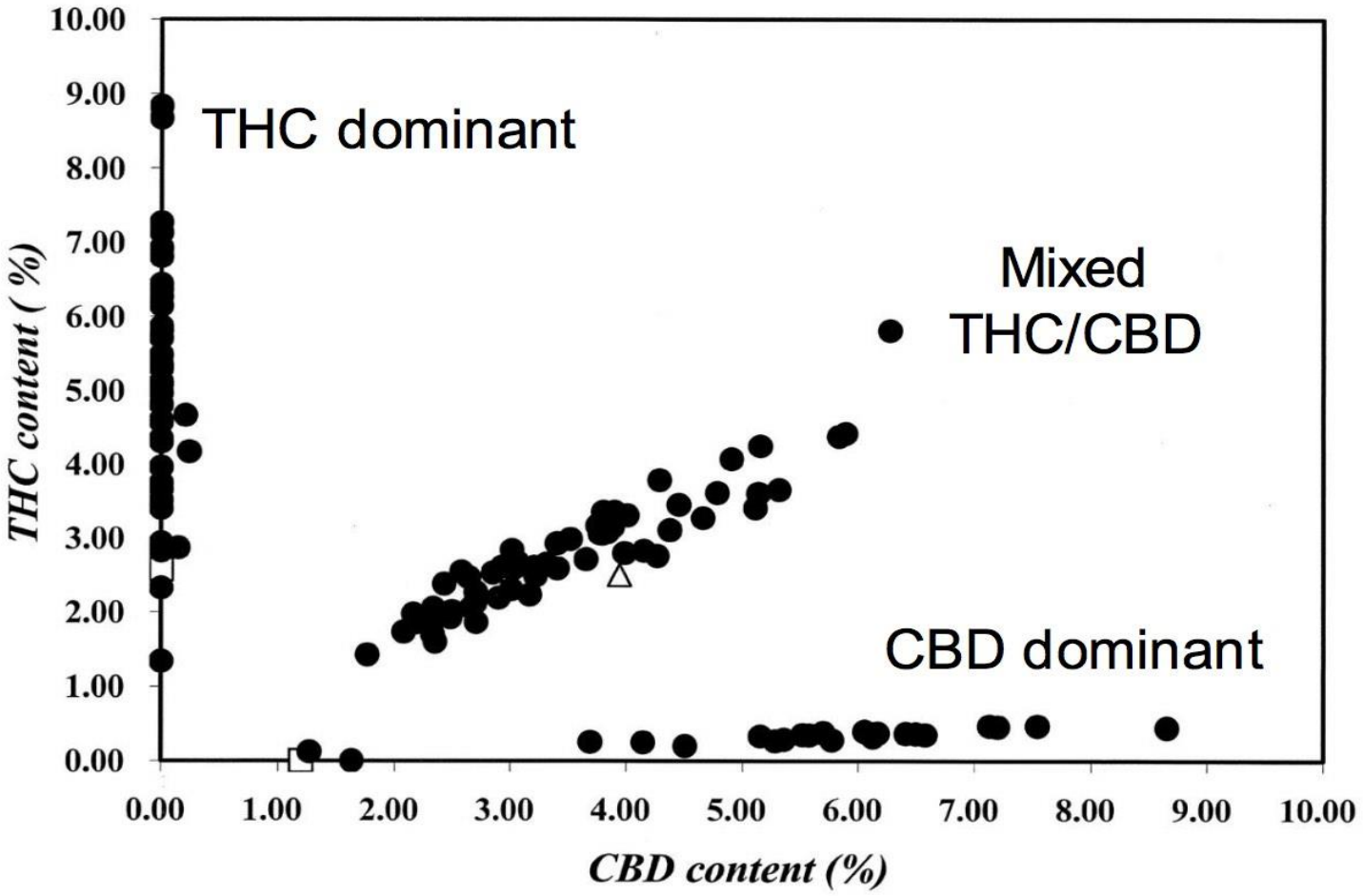

THC dominant
Mixed
THC/CBD
CBD dominant
THC content (%)
CBD content (%)
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
10.00

Effects of THC and CBD

Table 2| **Summary of evidence for medicinal use of cannabis based products and cannabinoids.**

Indication	Number of studies (participants)	Primary products tested	Comparator	Outcome	Summary estimate (95% confidence interval)	GRADE certainty rating
Chronic pain[23]	9 (1734)	Sativex (THC+CBD)	Placebo	30% reduction in pain	Odds ratio: 1.46 (1.16 to 1.84). More effective than placebo	⊕⊕⊕◯ Moderate
Multiple sclerosis[11]	5 (1244)	Sativex (THC+CBD)	Placebo	Ashworth spasticity scale	Weighted mean difference: −0.12 (−0.24 to 0.01). Not more effective than placebo	⊕⊕⊕◯ Moderate
Treatment resistant epilepsy[24]	2 (291)	Epidiolex (CBD)	Placebo	50% reduction in seizure frequency	Relative risk: 1.74 (1.24 to 2.43). More effective than placebo	⊕⊕◯◯ Low
Nausea and vomiting due to chemotherapy[11]	3 (102)	Dronabinol (THC)	Placebo	Complete response in nausea and vomiting	Odds ratio: 3.82 (1.55 to 9.42). More effective than placebo	⊕⊕◯◯ Low

Grading of recommendations, assessment, development, and evaluations (GRADE)[25]

⊕⊕⊕⊕ High, the authors have a lot of confidence that the true effect is similar to the estimated effect

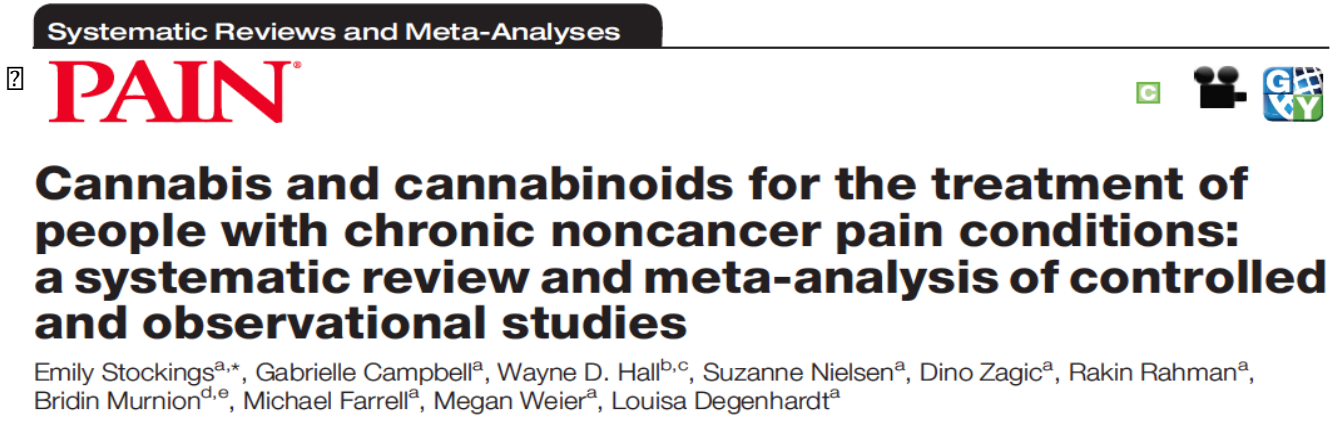
⊕⊕⊕◯ Moderate, the authors believe that the true effect is probably close to the estimated effect

⊕⊕◯◯ Low, the true effect might be markedly different from the estimated effect

⊕◯◯◯ Very low, the true effect is probably markedly different from the estimated effect

Freeman et al. (2019) *BMJ*

Chronic non-cancer pain



Systematic Reviews and Meta-Analyses

PAIN

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

Reduction in pain?

- Aim for 30% pain reduction
  - 29.0% patients in cannabinoid groups vs 25.9% in placebo group (NNT=24)
- VAS scale: cannabinoids reduced pain by 2.9mm on a 100mm
- Patient subjective assessment as ‘much’ to ‘very much’ improved.
  - 18.9% in cannabinoid group vs 11.8% in placebo (NNT = 38)

Improvement in function?

- QOL — no change
- Physical function — no change
- Depression and anxiety — no change
- Sleep — reduction in sleep problems

Placebo effect

- 1 in 4 patients in placebo group had 30% pain relief overall
- 2 in 3 patients in placebo group reported adverse effects
- Adverse effects:
  - Depression
  - Cognitive impairment
  - Thought disturbance
  - Confusion

Adverse Effects of THC and CBD

- Adverse effects of THC
- Disorientation, dizziness, euphoria, drowsiness

- Adverse effects of CBD
- Sedation, diarrhea, abdominal discomfort, headache

- Addiction

- Whiting et al (2015)

Summary of findings

- Does not support cannabinoids as more effective analgesic agents than established medications
- Limited evidence due to trial designs
- Number Needed to Treat to Benefit (NNTB): 24
  - Gabapentin: 7.7, TCAs: 3.4, Strong opioid: 10.4
- Number Needed to Treat to Harm (NNTH): 6
- Some benefit for neuropathic pain and MS-related spasticity

Cochrane Library: Cannabis-based medicines for neuropathic pain in adults 2018

- 16 studies with 1750 patients included
- Primary outcome : Achieving 50% or greater pain relief (21% vs 17%) –low quality studies
- Evidence for Patient Global Impression of change with cannabis very low
- High withdrawal rate due to adverse event
- Secondary outcomes : > 30% pain relief in 39 vs 33% , adverse events increased, psychiatric disorder occurred in 17%
- No information on longterm risk
- Conclusion: Potential benefit in chronic neuropathic pain might be outweighed by harm

Cannabis to reduce opioid use

- Small studies: access to legalising marijuana reduced prescription opioids (Bachhuber at al; JAMA Internal medicine 2015)
- 6%-14% fewer opioids ie 39 fewer prescriptions per 1000 people
- Fewer side effects than opioids in the elderly (The Europaen Journal of Internal Medicine)
- Basic Science
- Interactions between Cannabinoid and opioid receptors
- CB1 in amygdala: emotional response to pain

Cannabis and cancer pain

- No compelling evidence of benefit
- 40% of cancer pain is neuropathic
- CB1 receptor expression increased in dorsal root ipsilateral to cancer sites
- Treatment of cancer itself and other cancer related side effects anecdotal

- **Why medical cannabis is still out of patients' reach—an essay by David Nutt (***BMJ* 2019;365:l1903)

- 1998 House of Lords has asked to allow cannabis to be a medicine

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FACULTY OF PAIN MEDICINE
of the Royal College of Anaesthetists

Faculty Position Statement on the medicinal use of Cannabinoids in Pain Medicine

- Lack of good quality evidence
- Warned of parallels with the opioid crisis
- Supports setting up robust trials and databases
- Only used after conventional interventions have failed
- Limited number to secondary care MDT specialist pain services and nationally audited

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NICE Cannabis-based medicinal products: published 11.11.2019 Draft

- What is the clinical and cost effectiveness of cannabis-based medicinal products for people with chronic pain?

- What are the adverse effects or complications of cannabis-based medicinal products for people with chronic pain?

Eligibility criteria : cannabis-based product for medicinal use

- Is or contains cannabis, cannabis resin, cannabinol or derivates
- Is produced for medicinal use in humans
- Is a medicinal product
- A substance or preparation for the use as an ingredient of a medicinal product

- Synthetic compound which is identical in structure to the naturally occuring cannabinoids such as delta9THC ie dronabinol
- Licensed products such as Sativex and Nabilone
- Plant-derived cannabinoids such as pure cannabidiol

Methods

- PICO analysis

- Excluded Studies that used level 1, smoked cannabis
- 9341 references screened
- 20 RCT (14 parallel and 6 crossover) included
- Fewer than 5 RCT's found for children
- No studies for pregnant women, hepatic, renal disease
- 5 studies looked at cancer pain
- Studies were graded (GRADE)

Interventions

- 5 cancer pain:Oromucosal spray (2.7mg THC/2.5mCBD)
- Oromucosal spray (2.7mg THC)

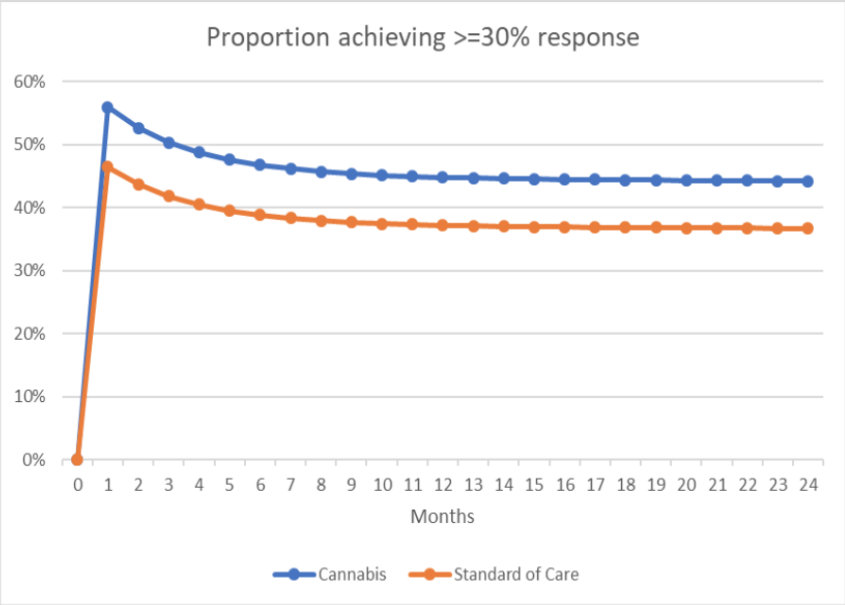
- 7 neuropathic pain: (oromucosal spray (THC/CBD); oral delta THC –dronabinol)

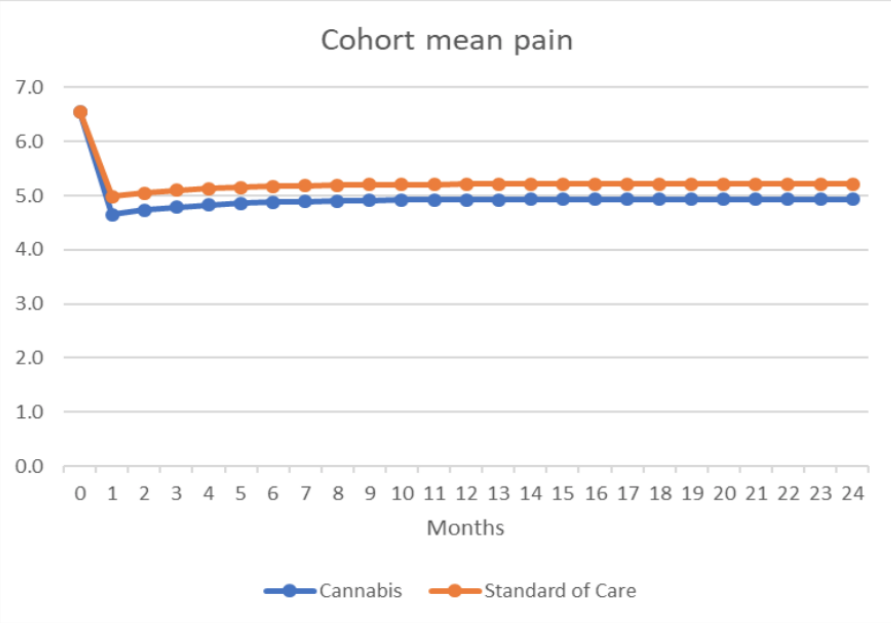
- 3 musculosceletal pain (THC/CBD, delta9THC, nabilone)
- 3 visceral pain (delta9THC)
- 2 widespread pain (nabilone, vapourisedTHC different quantities)

The outcomes that matter most: benefits

- CBMP reduce chronic pain : nabilone in fibromyalgia,THC reduced mean functional impairment in 96 participants
- Benefit is small
- High quality study did not differentiate reduction in pain intensity dronabinol/placebo in 389 participants
- No difference THC/CBD in functional pain, change in opioid use

Pain outcomes projected





Cost effectiveness

- Modelling the health economic impact de novo

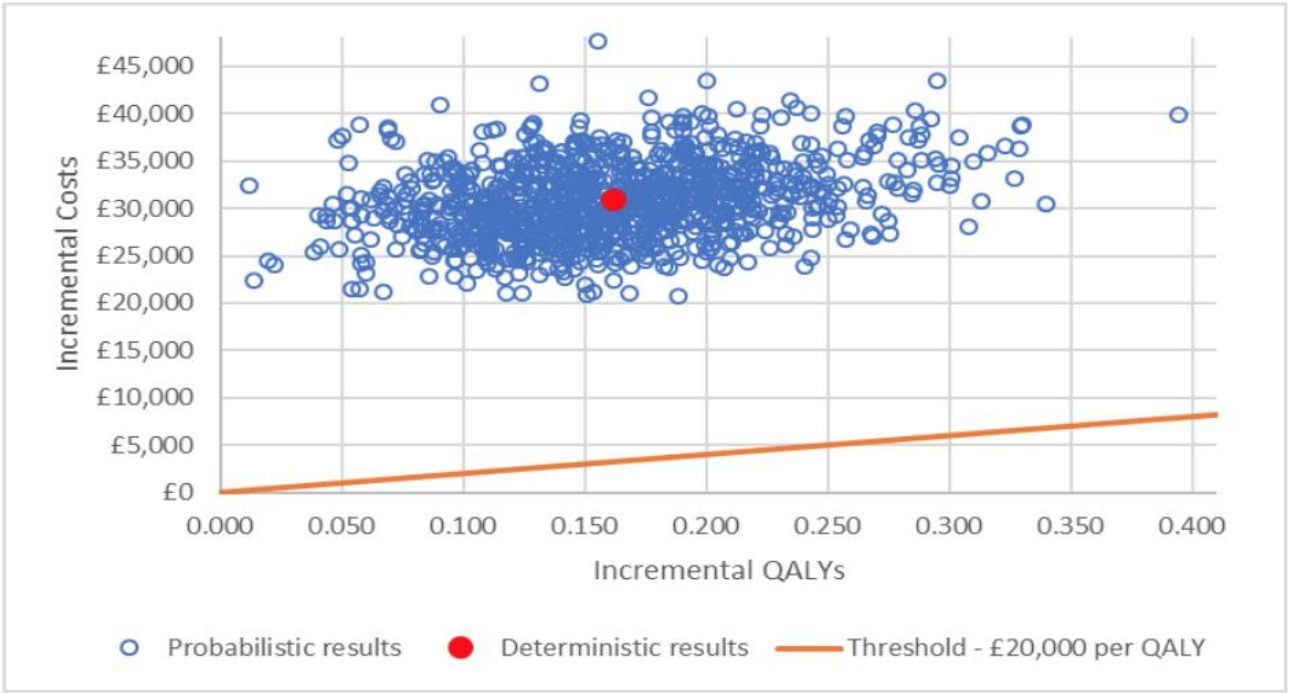


Figure 6: Probabilistic Sensitivity Analysis Scatterplot

Recommendation : Chronic Pain

- Do not offer the following to manage chronic pain in adults
- Nabilone
- Dronabinol
- THC (delta-9-tetracannabidiol
- Combination of CBD/THC
- Do not offer CBD to manage chronic pain in adults unless in a clinical trial

Future of cannabinoid research

Trial Designs

- **Well conducted RCTs**
- **NICE recommendation**
- **Multiple arms**
  - Placebo AND current best practice
- **Duration > 3 month**
- **Unified outcome measures**

Target areas

- **Guided by basic science**
- **Improve understanding of the role of the endocannabinoid system in pain**
- **THC vs CBD**

Acknowledgement

- Dr Tom Freemann Senior Lecturer University of Bath
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- Prof Celia Morgan, University of Exeter
- Drugscience.org

Thank you for listening!