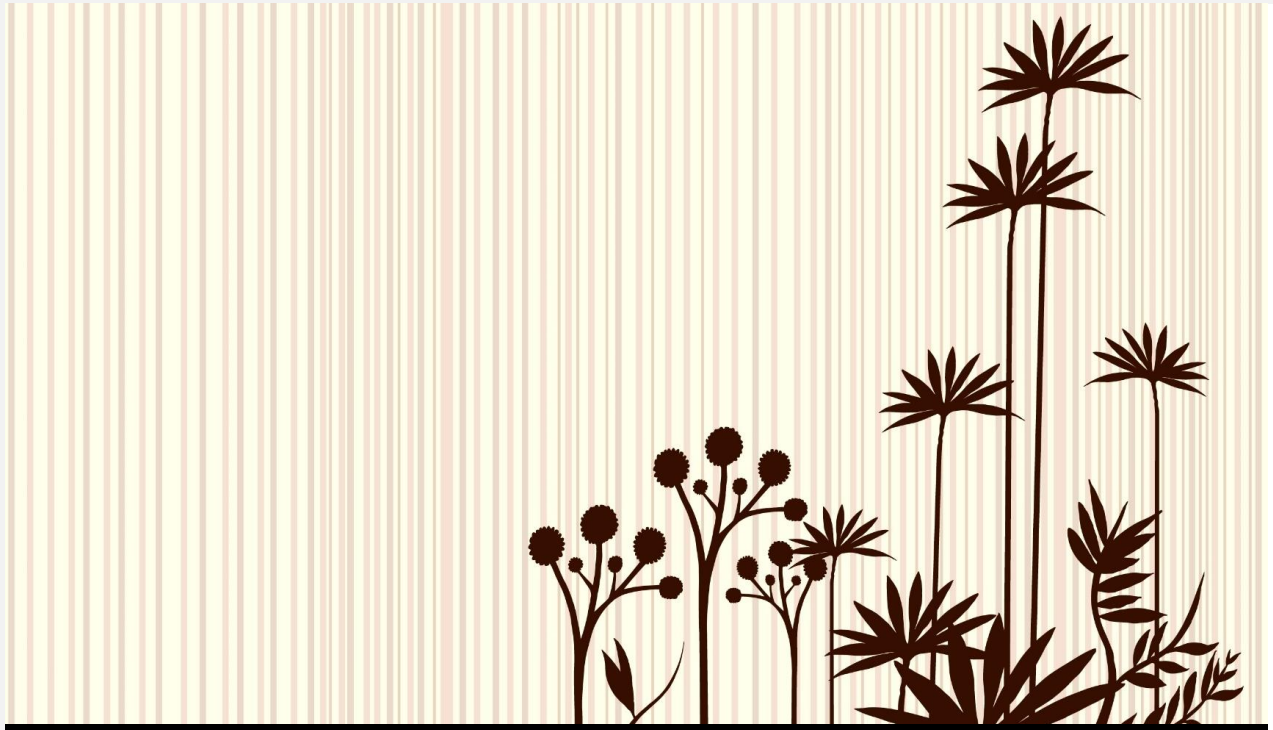
Alternative analgesia

Dr Gigi Yeung

Nephrologist, Wollongong Hospital



Case

Mrs LM, 72yo F

Referral to RSC for neuropathic pain

Background:

- ESKD secondary to biopsy-proven FSGS (2009), commenced HD in 2016 via left thigh AV graft
- Breast cancer
  - Lt radical mastectomy with axillary dissection 2003
  - Local recurrence in Lt breast + detection of Rt breast Ca in 2014 -> Rt mastectomy and adjuvant RTx
- Right upper lobe lung nodule detected on CT in April 2020 (? new primary vs met)
- COPD (smoker)
- Hypertension
- Hyperlipidaemia

Medications

- Warfarin 3mg daily
- Metoprolol XL 95mg daily
- Crestor 10mg daily
- Renagel 800mg TDS with meals
- Calcium 600mg BD
- Calcitriol 0.25mcg daily
- Vitamin D 1 daily
- Resonium 15g on non-dialysis days
- Acimax 20mg BD
- Aromasin 25mg daily
- Gabapentin 200mg nocte (dialysis days) and 100mg nocte (non-dialysis days)
- Dolased (paracetamol, codeine phosphate and doxylamine) 2-4 daily
- Serepax 30mg nocte
- Symbicort
- Aranesp 80mcg weekly

Initial RSC review (Sep 2020)

- Severe neuropathic pain in legs/feet – felt like “walking on broken glass”, with allodynia
- Bilateral shooting pain radiating down both arms with paraesthesia (cervical nerve root compression on CT)
- Prescribed pregabalin 75mg BD by GP – resulted in hallucinations

Plan:

- Pregabalin reduced to 50mg BD
- Commenced methadone 2.5mg TDS

Progress

September 2020

- Self-ceased pregabalin with no further hallucinations
- Stopped taking methadone as “not working” (taking on PRN basis rather than regular)
- Commenced on CBD50 oil 0.1ml TDS (0.1mg)

November 2020

- Multiple issues: difficult vascular access, intra-dialytic hypotension, lung nodule
- CBD oil resulted in good effect on arm pain – switched to 0.3ml nocte with PRN 0.1-0.2ml
- Discussed ACP – patient had no wish to withdraw from dialysis

December 2020

- Arm pain well-controlled on CBD oil 0.3ml nocte
- Gabapentin reduced to 100mg 3x/week post-dialysis

Progress

February 2021

- New painful leg ulcers
- Fall at home – sustained left humeral fracture
- Unable to afford CBD oil – discussed linking with research study for subsidized supply
- Added tapentadol SR 50mg BD with IR 50mg q8h PRN

March 2021

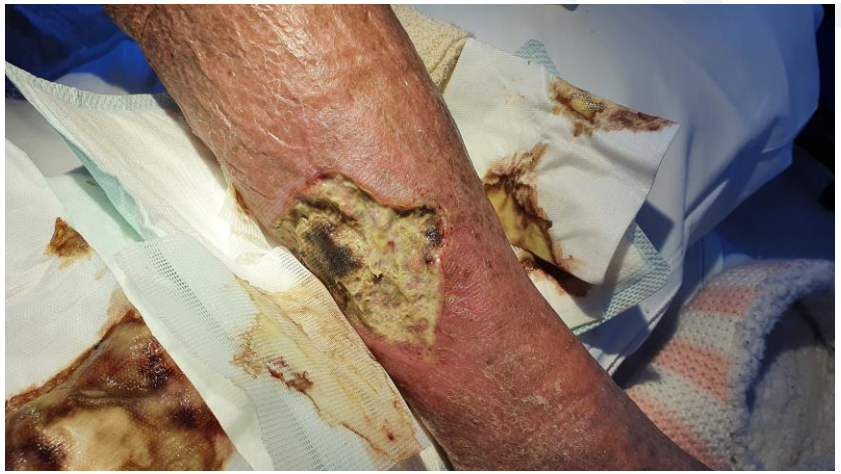
- Admitted to hospital with infected left LL ulcers
- Biopsy performed – no evidence of calciphylaxis
- Concern re: ischaemic steal from thigh fistula

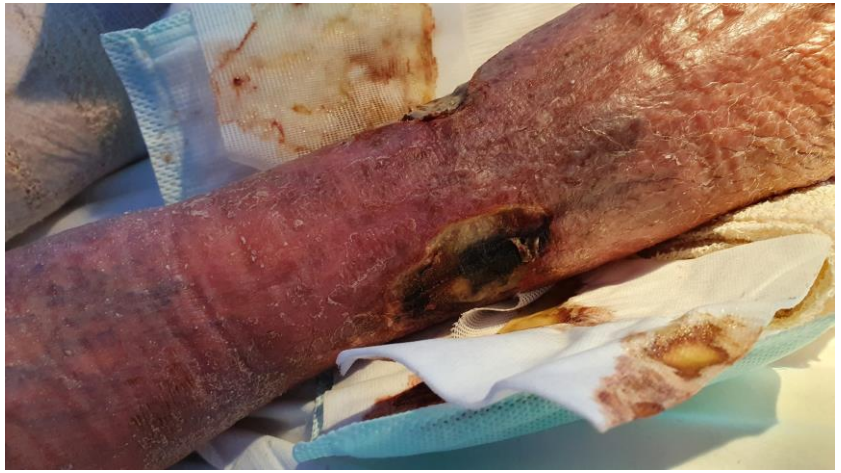
May 2021

- Severe 10/10 pain in both legs
- On review – left LL ulcers had progressed in size with new ulcers developing on right leg
- Admitted for Abx and vascular review

May 2021 admission

- Commenced on IV Tazocin
- Underwent debridement of ulcers + Lt LL angiogram:
  - Heavily calcified iliacs and femoral arteries
  - Thigh loop graft patent
  - Slow flow through native and patent SFA – appears to have steal syndrome from fistula





Pain management:

- Described sharp pain around ulcers, with feeling of ants crawling on her legs
- Tapentadol ceased, switched to SC hydromorphone 0.5mg q8h and PRN 0.5mg q6h
- Gabapentin increased to 100mg nocte
- Aperients charted

May 2021 admission

- Decision made to ligate thigh fistula
- LIJ tunnelled vascath inserted (RIJ occluded)
- Ongoing issues with intradialytic hypotension despite midodrine
- Poor flows through new vascath

RSC review:

- Pain better controlled on hydromorphone
- Switched to Norspan patch 10mcg/hr weekly and PRN Temgesic
- Ongoing issues with constipation as patient reluctant to take aperients because of fear of needing to open her bowels whilst on dialysis
- Advanced care planning discussions

Medical Cannabis

Cannabis

- Derived from the hemp plant *Cannabis Sativa* and its subspecies
- Cannabis plants and extracts have been used for medicinal purposes for thousands of years

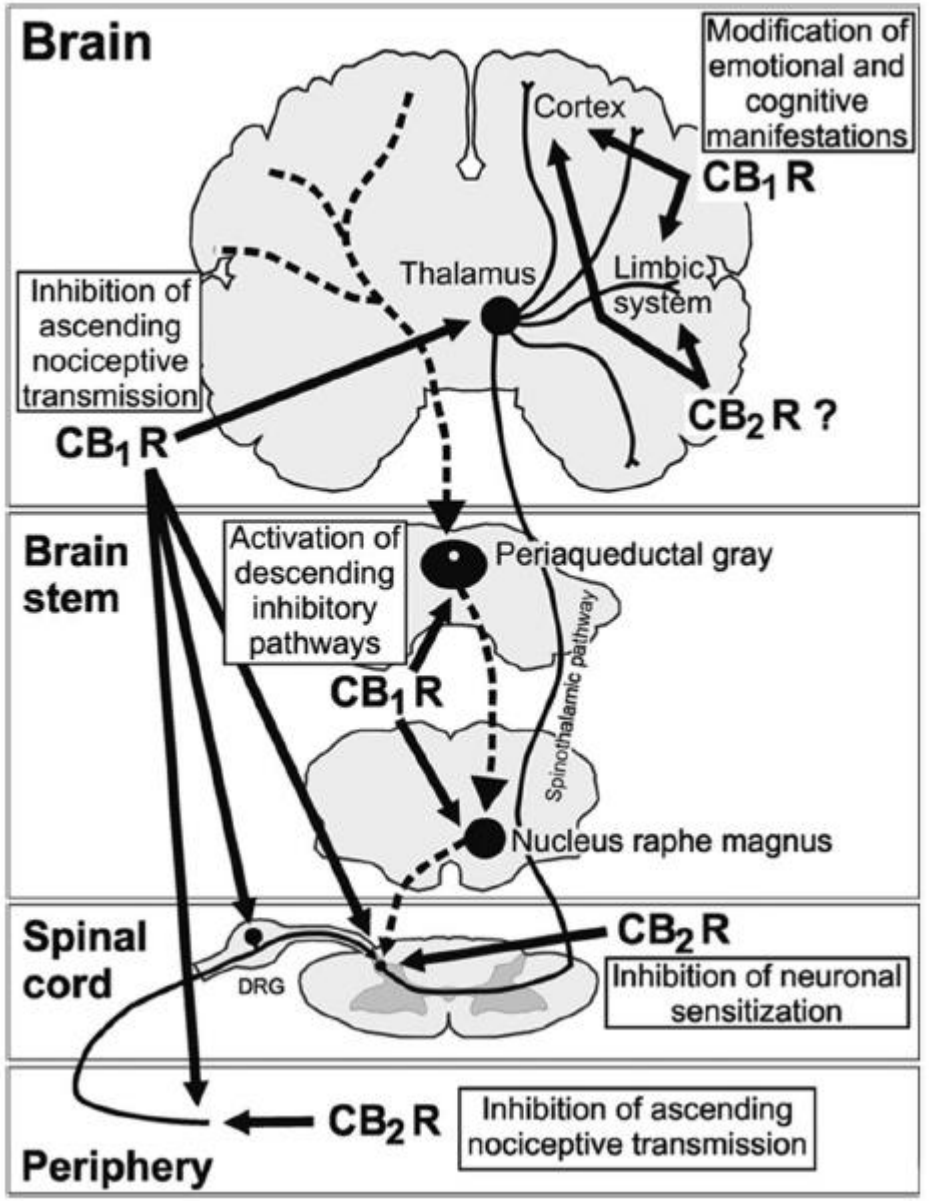
- Comprised of more than 500 compounds with >100 phytocannabinoids identified (e.g. Δ^9-THC and CBD)
- Multiple purported therapeutic actions: analgesic, anti-emetic, anti-inflammatory, anti-convulsive, anti-anxiety / anti-depressant, sleep assistance, appetite stimulation, neuroprotective

Endocannabinoid system

Many of the effects of cannabinoids are mediated by two G protein-coupled receptors:

- **CB1R** are present in high levels in the **CNS** (and GIT)
- **CB2R** are most in peripheral organs, mainly immune cells

The ECS plays a crucial role in the inhibitory control of the nociceptive stimuli by acting at peripheral, spinal, and supraspinal levels



Maldonado R, Baños JE, Cabañero D. The endocannabinoid system and neuropathic pain. Pain. 2016 Feb;157 Suppl 1:S23-S32.

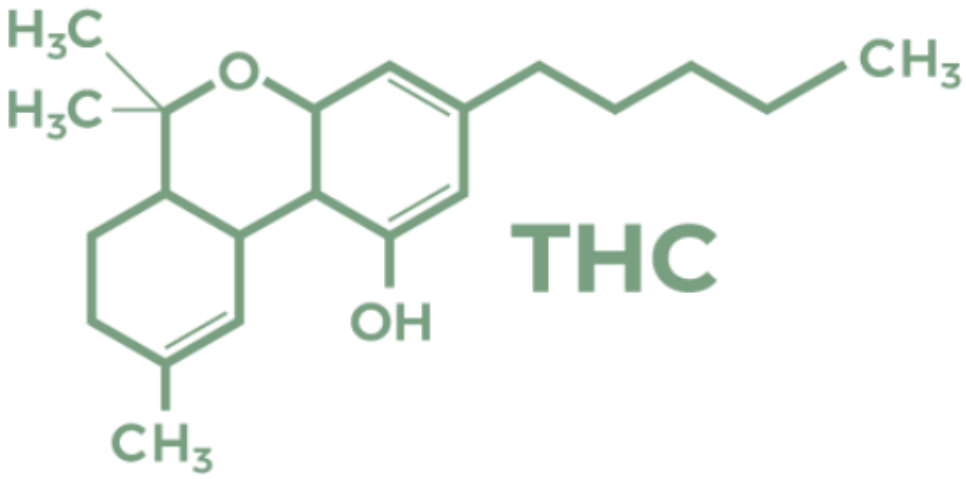
Delta-9-tetrahydrocannabinol (THC)

Partial agonist of both CB1R and CB2R

- **Psychoactive effects**
- Anti-emesis, may improve appetite
- Anti-convulsant
- Analgesic

Adverse effects:

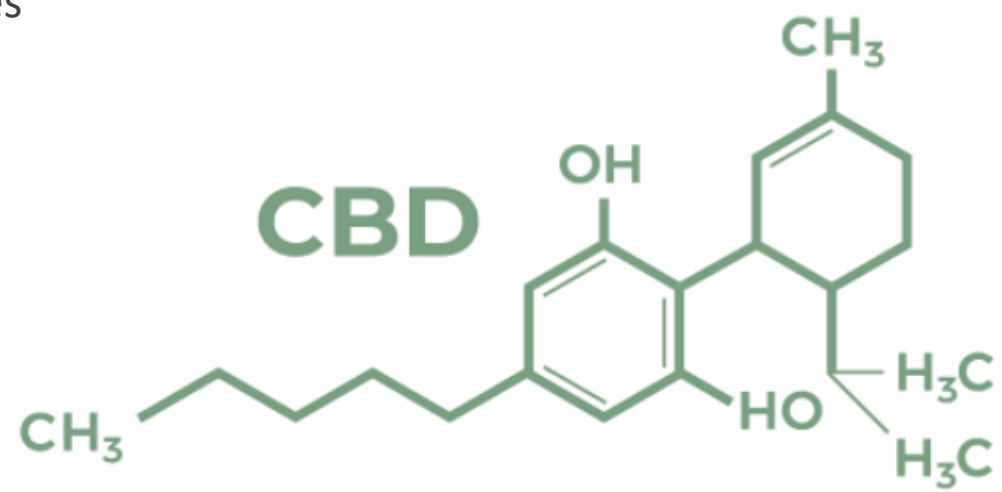
- Dizziness, euphoria, paranoia, somnolence, amnesia, anxiety, confusion, hallucination
- Generalised weakness
- Palpitations, tachycardia, vasodilation / flushing
- Abdominal pain, nausea, vomiting



Cannabidiol (CBD)

Inhibits the metabolism of THC into its psychoactive metabolite 11-hydroxyTHC – mitigates THC-induced paranoia and anxiety and potentiates the non-psychoactive effects of THC through its indirect mechanism

- Analgesic
- Sedation
- Anti-convulsant – used in refractory paediatric epilepsy syndromes
- Anti-psychotic
- Anxiolytic
- Anti-emetic



Adverse effects:

- Vomiting, diarrhoea, decreased appetite
- Somnolence

Pharmacokinetics

Table 1 Comparison between inhaled and oral cannabis' PK and efficacy in chronic pain

Parameter	Inhaled	Oral (oromucosal)
Onset of effect	Minutes	Hours
Peak effect	1 h	Several hours (2–4 h)
Duration of effect	3–5 h	Variable, 8 to > 20 h
Self-titration to achieve desirable effects within tolerable ranges	Could be implemented relatively easy	Not recommended due to unpredictable appearance of side effects
Scientific evidence for chronic non-cancer neuropathic pain treatment	Conclusive or substantial for pain intensity	Moderate for short-term sleep improvement

- THC and CBD are both highly **lipophilic** with **low oral bioavailability** (6-20%)
- Oral formulations exhibit variable absorption and undergo extensive hepatic first-pass metabolism
- Primarily **cleared by the liver** and the minority of inactive metabolites are excreted in the urine, accounting for 20-30% of metabolite elimination
- Note - CYP450 and CYP2D6 inhibitor (need to watch for drug interactions)

Romero-Sandoval et al. Cannabis and Cannabinoids for Chronic Pain. Curr Rheumatol Rep 19, 67 (2017).
Lucas et al. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol*. 2018 Nov;84(11):2477-2482.

Commercially available products

Current product range: LGP CLASSIC OIL

This product range is locally produced using full plant extract medicinal cannabis. Our Classic range has a variety of THC and CBD ratios presented in a simple oil formulaion. For assistance on which product to consider please contact our Medical team.

PRODUCT NAME	THC/CBD	SCHEDULE	THC (MG/ML)	CBD (MG/ML)	BOTTLE SIZE	TOTAL CANNABINOIDS	RRP TO PATIENTS
LGP CLASSIC CBD 50	CBD	4	<0.2 mg	50 mg	50 mL	2500 mg	$265
LGP CLASSIC 1:100	CBD	8	<1.5 mg	100 mg	50 mL	5050 mg	$325
LGP CLASSIC 1:20	CBD dominant	8	1 mg	20 mg	50 mL	1050 mg	$195
LGP CLASSIC 10:10	Balanced	8	10 mg	10 mg	50 mL	1000 mg	$195
LGP CLASSIC 20:5	THC dominant	8	20 mg	5 mg	50 mL	1250 mg	$245

Table 1: Summary of cannabinoid products used in studies of medicinal cannabis in CNCP

Cannabinoid product	Definition	Preparation	Administration	Standardised
Nabiximols	Whole plant extract with specific concentration: each mL contains 2.7 mg THC and 2.5 mg CBD. Also reported as "Sativex".	Liquid	Oromucosal spray	Yes
THC:CBD extracts	Combination of THC extract and CBD. Studies were classified as THC:CBD if no specific concentration or ratio of THC:CBD was provided.	Liquid	Sublingual spray	Yes
		Capsule	Oral	Yes
Dronabinol	Synthetic cannabinoid derivate that mimics THC. Also referred to as "Marinol"; "oral THC"	Capsule	Oral	Yes
THC extract	The active cannabinoid part of the cannabis plant. Also reported as "Cannabis extract"; "cannabis sativa extract".	Liquid	Sublingual spray	Yes
		Capsule	Oral	Yes
Nabilone	Synthetic delta 9 THC	Capsule	Oral	Yes
CBD extract	Active cannabinoid part of cannabis that does not have psychoactive effects. Also reported as cannabidiol	Liquid	Spray	Yes
Cannabis sativa	Any plant-based cannabis product with variable THC %. Also reported as "herbal cannabis", "smoked cannabis", Bedrocan (THC high), Bedrobinal (THC medium) and Bediol (THC low)	Herbal leaf	Smoked, vapourised, eaten	Not specified
Ajulemic acid	Synthetic cannabinoid derivative of the non-psychoactive THC metabolite 11-nor-9 carboxy- THC. Also reported as CT-3, AB-III, HU-239, IP-751, CPL 7075 and Resunab.	Capsule	Oral	Yes

Reference: TGA review 2017

Serpell et al. 2014

- Randomised, double-blind, placebo-controlled parallel group study
- **246 adults** (mean age 57) with **peripheral neuropathic pain associated with allodynia**
  - Recruited from 21 sites in the UK, Belgium, Canada, Czech Republic, and Romania
- Randomised to **nabiximols (Sativex) THC:CBD spray** self-titrated up to a maximum dosage of 24 sprays/day (n=128) vs placebo (n=118) over **15 weeks**
- Primary efficacy endpoints:
  - 30% responder rate in PNP 0-10 numerical rating scale
  - Mean change from baseline to the end of treatment in this score

Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, *et al.* A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *European Journal of Pain* 2014; 18: 999-1012.

Results

- 34 patients (28%) receiving THC/CBD spray were classified as responders at the 30% level compared with 19 patients (16%) on placebo

- Most common treatment-related AEs: dizziness, nausea, change in taste, fatigue, psychiatric symptoms
- 33 patients stopped receiving study medication due to AEs, 25 in the THC/CBD spray arm and 8 in the placebo group

Table 2 Summary of the analysis of all primary and secondary efficacy endpoints (ITT and PP analysis sets). Treatment differences between THC/CBD spray and placebo are presented using change from baseline to the end of treatment data for each endpoint, unless otherwise stated.

Endpoint	ITT analysis set			PP analysis set		
Primary endpoints						
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
30% responder analysis (PNP 0–10 NRS)	1.970	1.049 to 3.702	0.034	2.266	1.124 to 4.568	0.021
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
PNP 0–10 NRS	−0.34 (0.230)	−0.79 to 0.11	0.139	−0.48 (0.303)	−1.08 to 0.12	0.116
Secondary endpoints						
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
NRS	−2.86 (2.211)	−7.22 to 1.50	0.198	−5.26 (2.873)	−10.94 to 0.41	0.069
Sleep quality 0–10 NRS	−0.83 (0.306)	−1.43 to −0.23	0.007	−0.91 (0.369)	−1.63 to −0.18	0.015
BPI-SF (pain severity composite score)	−0.25 (0.236)	−0.72 to 0.21	0.288	−0.27 (0.291)	−0.85 to 0.30	0.349
BPI-SF (average pain)	−0.34 (0.237)	−0.81 to 0.12	0.148	−0.47 (0.299)	−1.06 to 0.13	0.122
BPI-SF (worst pain)	−0.30 (0.265)	−0.82 to 0.22	0.255	−0.39 (0.322)	−1.02 to 0.25	0.234
BPI-SF (pain interference composite score)	−0.32 (0.241)	−0.80 to 0.15	0.183	−0.39 (0.304)	−0.99 to 0.21	0.204
Dynamic allodynia test	0.08 (0.305)	−0.52 to 0.68	0.795	−0.27 (0.359)	−0.98 to 0.44	0.460
Punctate allodynia test	−0.14 (0.118)	−0.37 to 0.09	0.233	−0.06 (0.150)	−0.35 to 0.24	0.701
EQ-5D (weighted health status index VAS)	−0.01 (0.024)	−0.06 to 0.04	0.617	–	–	–
EQ-5D (self-rated health status VAS)	−0.75 (2.459)	−5.60 to 4.09	0.760	–	–	–
Use of rescue analgesia	−0.38 (0.237)	−0.85 to 0.09	0.112	0.40 (0.316)	−1.02 to 0.23	0.211
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
50% responder analysis (PNP 0–10 NRS)	1.699	0.645 to 4.476	0.280	2.045	0.750 to 5.576	0.157
SGIC (end of treatment only)	1.762	1.080 to 2.876	0.023	2.988	1.661 to 5.378	0.0003

BPI-SF, Brief Pain Inventory (short form); CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; NRS, numerical rating scale; PNP, peripheral neuropathic pain; PP, per protocol; SGIC, Subject Global Impression of Change; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

Serpell et al. *European Journal of Pain* 2014; 18: 999-1012.

Nurmikko et al. 2007

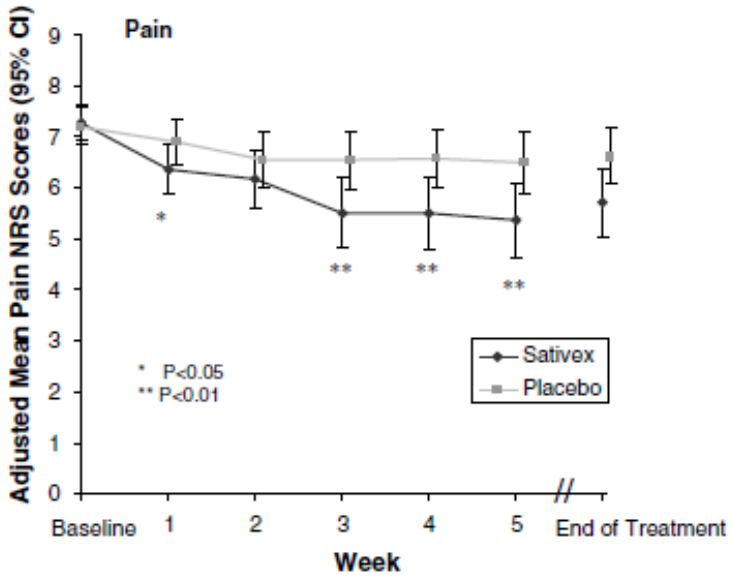
- Multi-centre, randomised, double-blind, placebo-controlled, parallel design trial
- **125 adults** (mean age 53) with **unilateral peripheral neuropathic pain and allodynia**
  - Baseline severity score of >4 on NRS, >6 months of pain due to a clinically identifiable nerve lesion
- Randomised to **Sativex THC:CBD spray** (n=63) or placebo (n=62) for **5 weeks**
- **Primary outcome:** change from baseline on NRS of mean intensity of global neuropathic pain (0 to 10)
  - Secondary measures included the composite score calculated from the Neuropathic Pain Scale (NPS), tests for mechanical allodynia, a four-step verbal rating scale for sleep disturbance, the Pain Disability Index (PDI), the Patient Global Impression of Change (PGIC) of both pain and allodynia, and the General Health Questionnaire (GHQ-12)

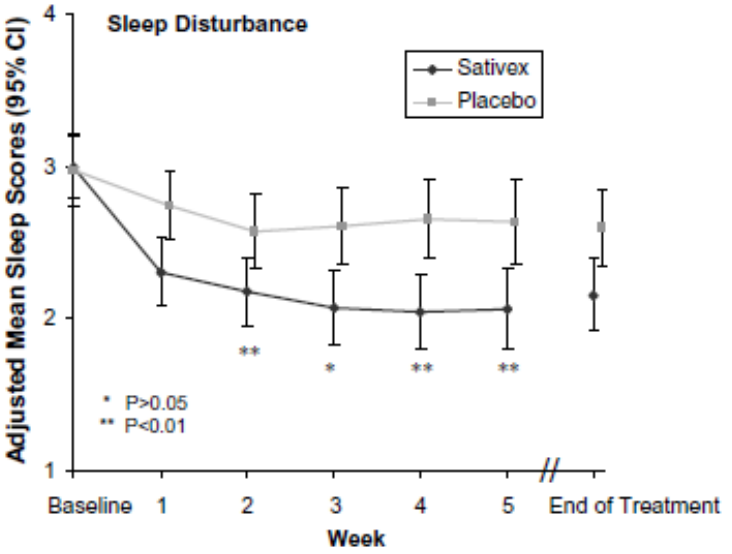
Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007; 133: 210-20.

Results

- The mean reduction in pain intensity score was greater in patients receiving sativex than placebo (-1.48 vs. -0.52 points on NRS)
- Improvements in Neuropathic Pain Scale composite score, sleep NRS, dynamic allodynia, punctate allodynia, Pain Disability Index and Patient's Global Impression of Change were greater on Sativex

- Sedative and gastrointestinal side effects were reported more commonly by patients on active medication
- 18% on sativex and 3% on placebo withdrew during the study





Nurmikko et al. *Pain* 2007; 133: 210-20.

Toth et al. 2012

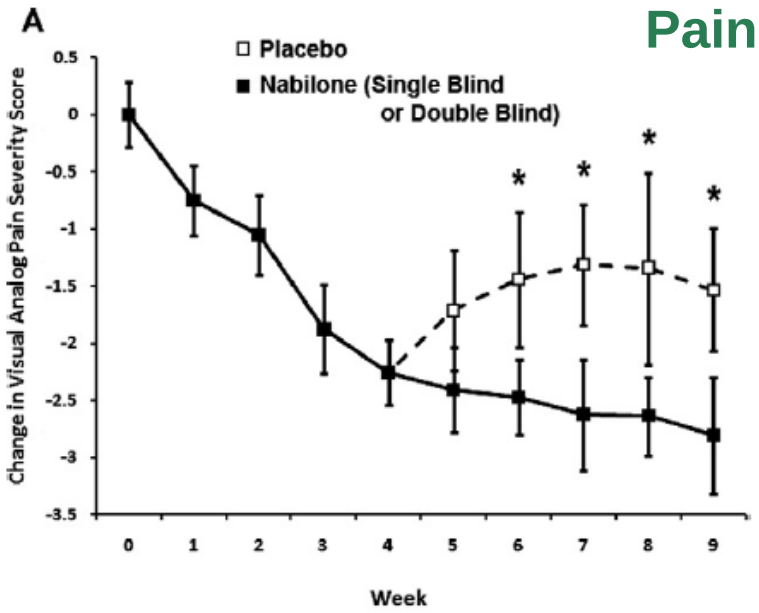
- Single-centre, randomised, double-blind, placebo-controlled, flexible-dose study with enriched enrolment
- **26 adults** (mean age 61) with **refractory diabetic peripheral neuropathic pain**
  - Subjects with a pain score ≥ 4 continued regular pain medications and were administered single-blinded adjuvant nabilone for 4 weeks. Subjects achieving ≥ 30% pain relief (**26/37**) were then randomized.
- Randomised to **flexible-dose nabilone 1-4 mg/day** (n=13) or placebo (n=13) for **5 weeks**
  - Nabilone is a synthesised CB1 predominant receptor agonist
- **Primary outcome:** mean difference in average daily pain score
  - Based on mean pain score in final week, compared to baseline week prior to run-in phase
  - Pain severity and sleep disruption severity over the preceding 24 hours were rated daily using an 11-point NRS from 0 to 10

Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, *et al.* An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 2012; 153: 2073-82.

Results

- 11/13 (85%) in the nabilone group, compared to 5/13 (38%) in the placebo group achieved ≥30% pain reduction compared to baseline
- Improvement in the change in mean end-point neuropathic pain with nabilone vs placebo (mean treatment reduction of 1.27; 95% CI 2.29-0.25, P = 0.02)
- Improvements in anxiety scores, sleep disruption and EQ-5D

- **Adverse events:** dizziness, dry mouth, drowsiness, confusion or impaired memory, lethargy, euphoria, headache, and increased appetite
- 2 subjects discontinued the drug in the single-blind phase due to confusion



Toth C et al. *Pain* 2012; 153: 2073-82.

Frank et al. 2008

- Randomised, double blind, crossover trial
- **96 adults** with **chronic neuropathic pain**
  - Mean baseline pain score >4
- Randomised to **nabilone** up to 2mg/day (n=13) or **dihydrocodeine** up to 240mg/day (n=13) for **6 weeks**, with a 2-week washout between treatment periods.
- **Primary outcome:** difference in mean visual analogue score computed over the last 2 weeks of each treatment period
  - Secondary outcomes were changes in mood, quality of life, sleep, and psychometric function

Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ Case Reports* 2008; 336: 199-201.

Results

- Dihydrocodeine was a significantly better analgesic than nabilone
- Assuming a drop in VAS score of 1 is clinically relevant:
  - 3/64 patients had a clinically relevant response on nabilone compared with 12/64 on dihydrocodeine
  - 49 patients had no clinically relevant drop in their pain score on either treatment

- Secondary outcomes – SF-36
  - Nabilone superior for physical role (p=0.03)
  - Dihydrocodeine superior for bodily pain (p=0.03)

- Adverse events:
  - Nabilone – sickness/nausea
  - Dihydrocodeine – tiredness, nightmares

Frank et al. *BMJ Case Reports* 2008; 336: 199-201.

Cochrane Library

Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

- 16 studies (n=1750)
  - THC:CBD combination oromucosal spray (10 studies)
  - Nabilone (2 studies)
  - Inhaled herbal cannabis (2 studies)
  - Dronabinol (2 studies)

- Study duration: 2 to 26 weeks

Mücke et al. *Cochrane Database of Systematic Reviews* 3 (2018).

Summary of results

- All cannabis-based medicines (at any dose) pooled together were superior to placebo for:
  - Substantial pain relief (>50%) (low-quality evidence)
  - Moderate pain relief (>30%) pain relief (moderate-quality evidence)
  - Global improvement (very low-quality evidence)
  - Reduction of mean pain intensity (low-quality evidence)
  - Sleep problems (low-quality evidence)
  - Psychological distress (low-quality evidence)

- More people dropped out due to adverse events with cannabis-based medicines compared to placebo
- More people reported adverse events of the central nervous system and psychiatric disorders with all cannabis-based medicines
- No difference in SAE or improvement in HRQOL

Frank et al. *BMJ Case Reports* 2008; 336: 199-201.

Patient or population: adults with chronic neuropathic pain

Settings: outpatient study centres and hospitals in Europe and North America

Intervention: cannabis-based medicines (smoked cannabis; oral plant-based (dronabinol) or synthetic tetrahydrocannabinol (THC) (nabilone); oromucosal spray of THC and cannabidiol (CBD))

Comparison: placebo

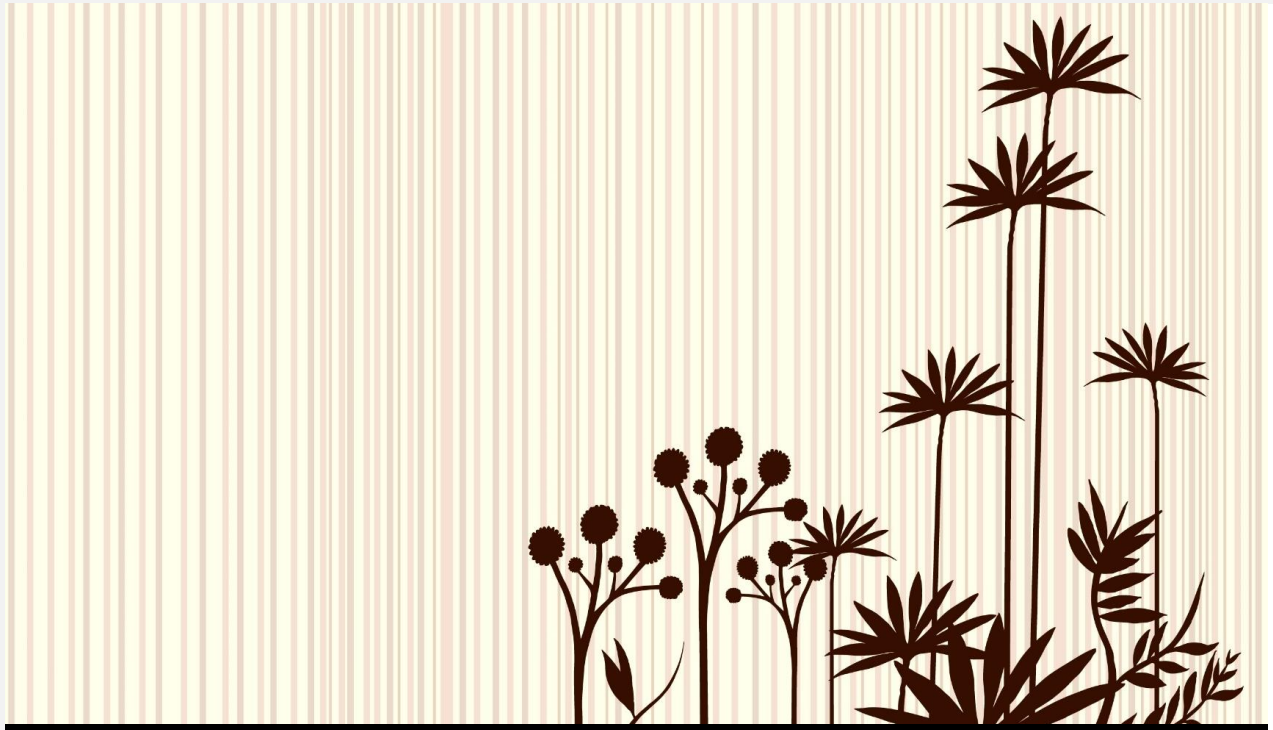
Outcomes	Probable outcome with intervention 95% CI	Probable outcome with placebo	Relative effect Risk difference (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain relief of 50% or greater	209 per 1000 (196 to 222)	173 per 1000	0.05 (0.00 to 0.09)	1001 (8 studies)	⊖⊖⊖⊖ **low** [1,2]	NNTB 20 (11 to 100)
Patient Global Impression of Change much or very much improved	261 per 1000 (246 to 276)	211 per 1000	0.09 (0.01 to 0.17)	1092 (6 studies)	⊖⊖⊖⊖ **very low** [1,3,4]	NNTB 11 (6 to 100)
Withdrawals due to adverse events	104 per 1000 (99 to 107)	47 per 1000	0.04 (0.02 to 0.07)	1848 (13 studies)	⊖⊖⊖⊖ **moderate** [1]	NNTH 25 (16 to 50)
Serious adverse events	66 per 1000 (63 to 69)	52 per 1000	0.01 (-0.01 to 0.03)	1876 (13 studies)	⊖⊖⊖⊖ **low** [1,2]	NNTH not calculated
Participant-reported pain relief of 30% or greater	377 per 1000 (358 to 396)	304 per 1000	0.09 (0.03 to 0.15)	1586 (10 studies)	⊖⊖⊖⊖ **moderate** [1]	NNTB 11 (7 to 33)
Specific adverse events: nervous system disorder	611 per 1000 (576 to 644)	287 per 1000	0.38 (0.18 to 0.58)	1304 (9 studies)	⊖⊖⊖⊖ **low** [1,3]	NNTH 3 (2 to 6)
Specific adverse events: psychiatric disorders	165 per 1000 (156 to 174)	49 per 1000	0.10 (0.06 to 0.15)	1314 (9 studies)	⊖⊖⊖⊖ **low** [1,3]	NNTH 10 (7 to 16)

Abbreviations:
CI: Confidence interval; **NNTB**: number needed to treat for an additional beneficial outcome; **NNTH**: number needed to treat for an additional harmful outcome; **RD**: risk difference

Discussion

- No high-quality evidence for efficacy of cannabis-based medicine for chronic neuropathic pain
- Adverse events (esp. CNS) may limit the clinical usefulness
- No long-term efficacy and safety data
- Unclear publication bias
- Small study size
  - 5/10 studies reporting outcome >30% pain relief had treatment group sizes below 50
- Most studies selected statistical methods that bias towards exaggerating efficacy of the drugs

Frank et al. *BMJ Case Reports* 2008; 336: 199-201.



Summary

- No high-quality evidence for efficacy of cannabis-based medicine for chronic neuropathic pain
- Small percentage of patients may derive benefit
- Risk of short-term adverse events (CNS / GI)