Do Cannabinoids have a role in cancer pain?

A short history of cannabis

Culpepper

"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.

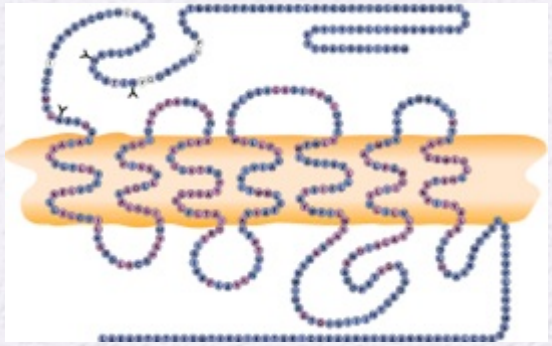
The Science

Cannabinoid Receptors

CB_1

Neurons

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



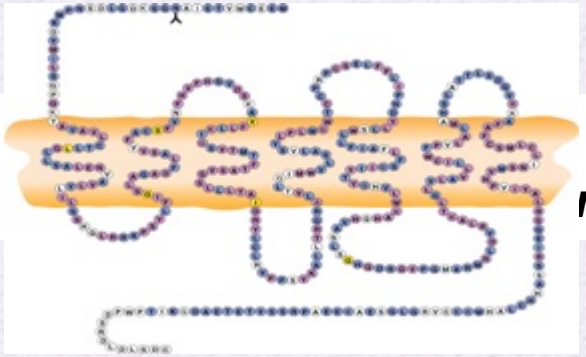
CB_3

GPR55

CB_2

Immune cells

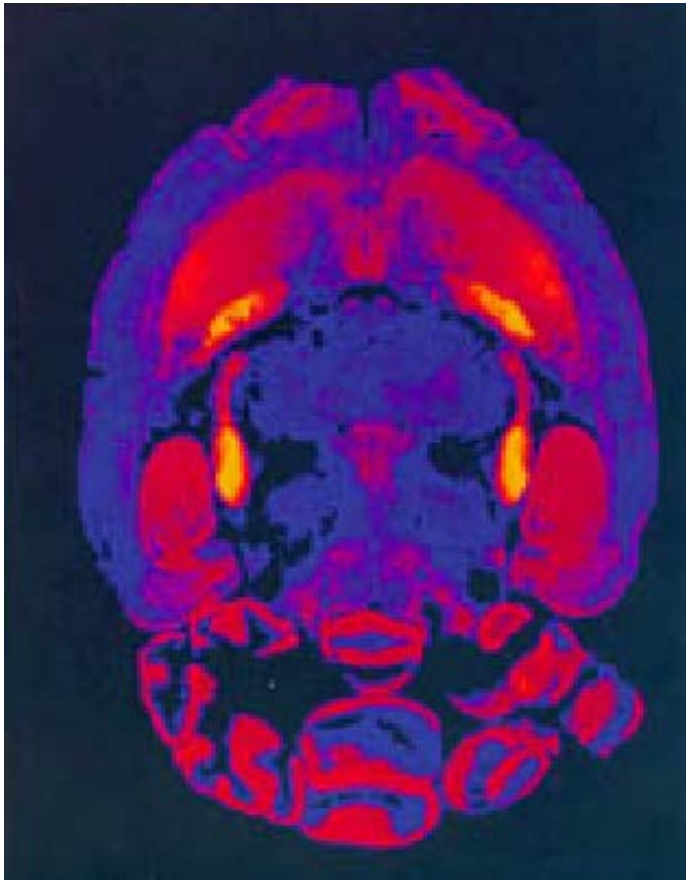
- Inhibit adenylate cyclase.

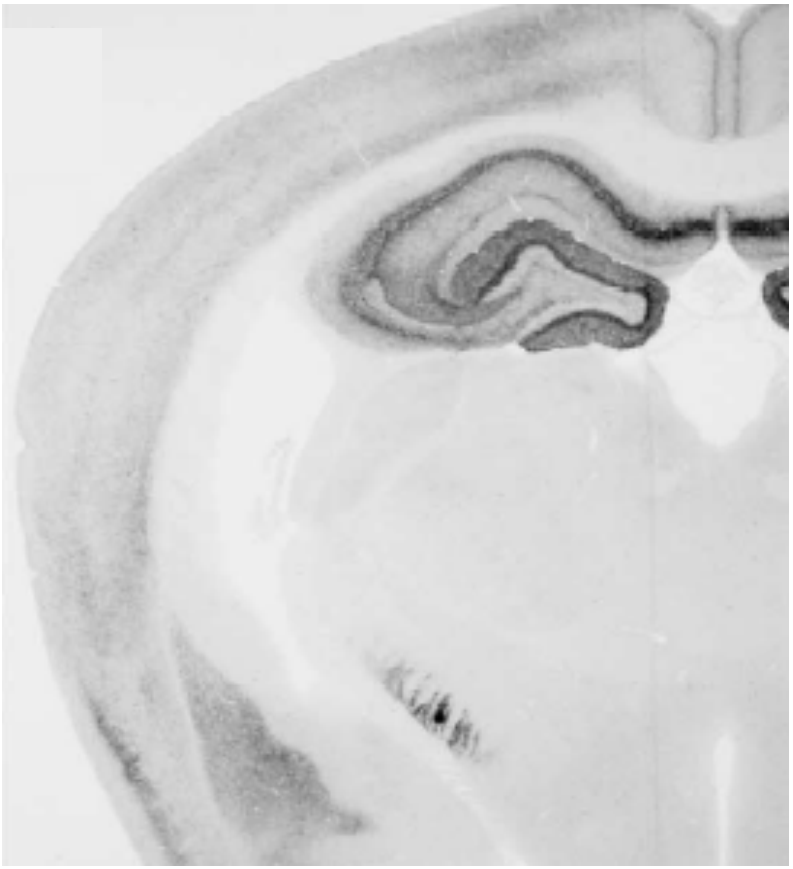


ns)

Cayman Chemical

Brain





Herkenham et al 1991; Egertová et al 2003

Spinal Cord

Farquhar-Smith et al 2000

Reported effects of cannabis and Δ^9THC

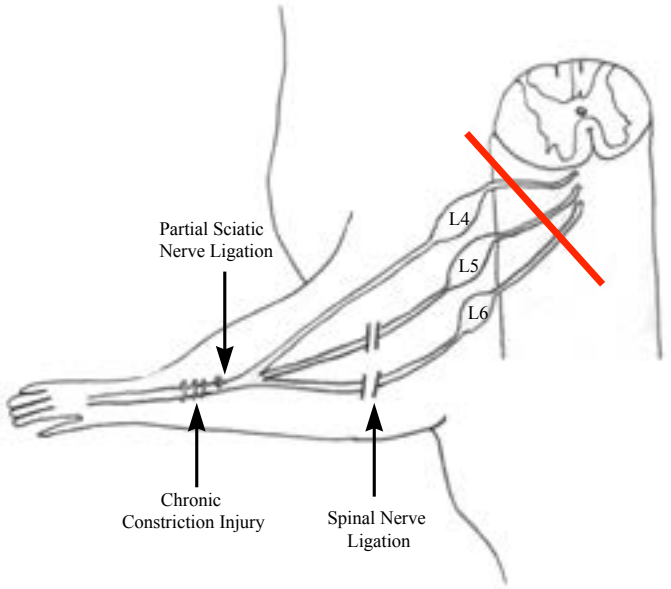
- **CNS:**
  - Euphoria/"high".
  - Heightened sensory perception.
  - Impaired cognition and pyschomotor performance.
  - Distortion of space & time sense.
  - Memory impairment.
  - Fragmentation of thoughts.
  - Antinociception and analgesia.
  - Anti-emesis.
  - Increased appetite.
  - Altered thermoregulation.

  - Schizophrenia-like syndrome.

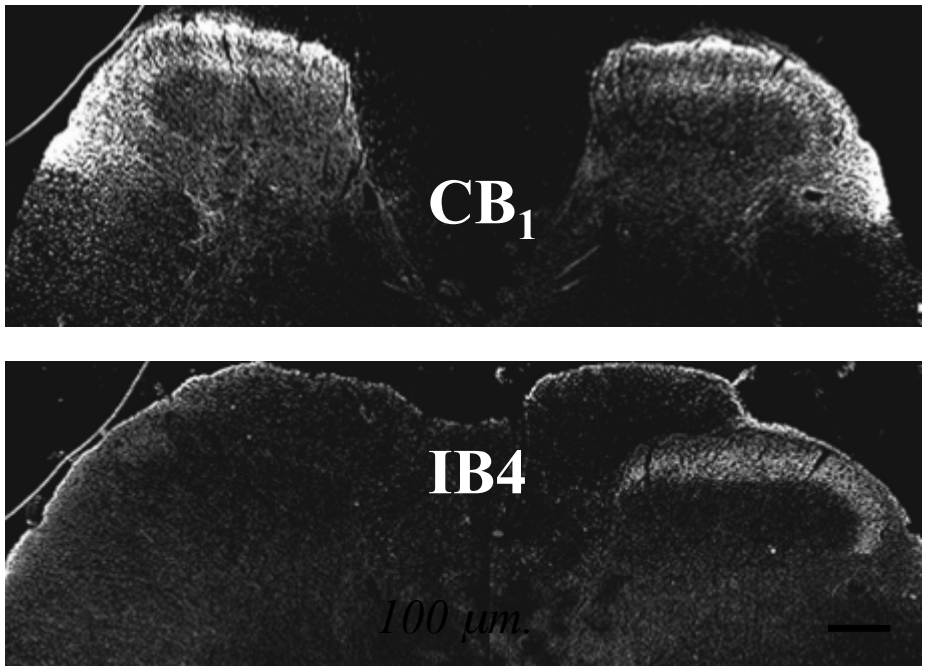
Pertinent pre-clinical data

Cannabinoid Analgesia in Pain Models

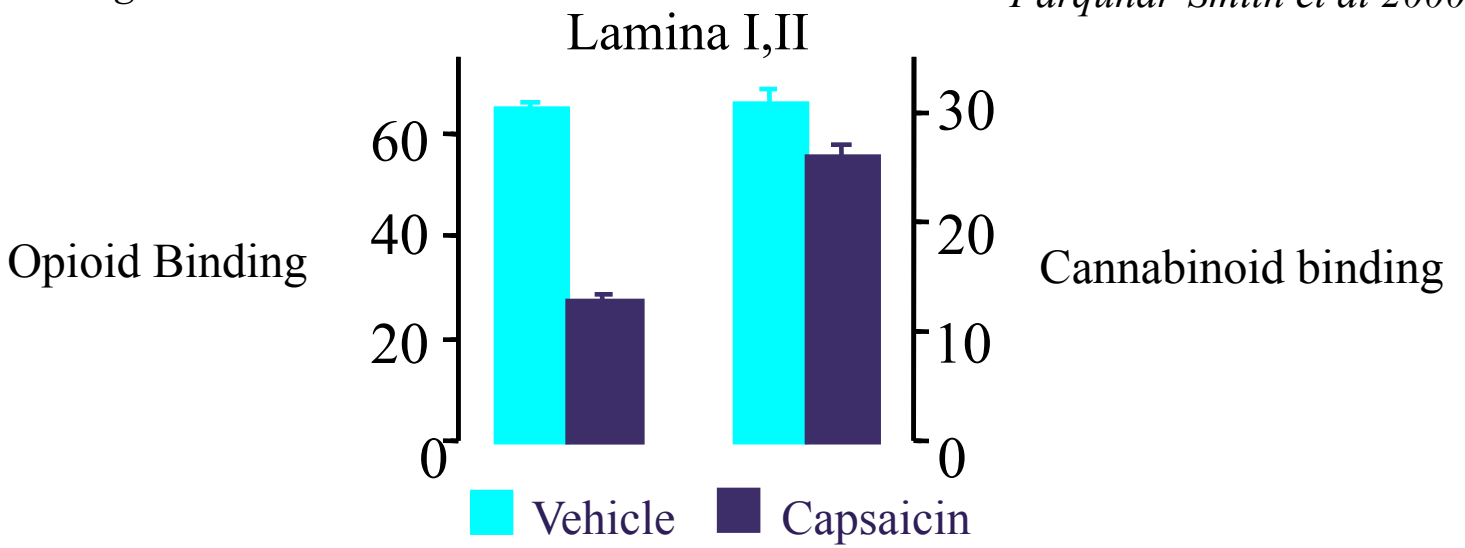
- Visceral inflammatory pain and referred hyperalgesia *(Jaggar et al 1998a,b, Farquhar-Smith et al 2001, 2002)*
- Formalin *(Tsou et al 1996, Jaggar et al 1998a, Calignano et al 1998, Hanus et al 1999, Schreiber et al 2012))*
- Carrageenan *(Richardson et al 1998)*
- Cystitis *(Wang et al 2013)*
- Collagen-induced 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 *(Kehl et al 2003, Wang et al 2012, Khasabova et al 2011)*



Bridges et al 2001



Farquhar-Smith et al 2000



Hohmann & Herkenham 1998

Evidence in humans

Meta-analysis of clinical evidence (17 years ago)

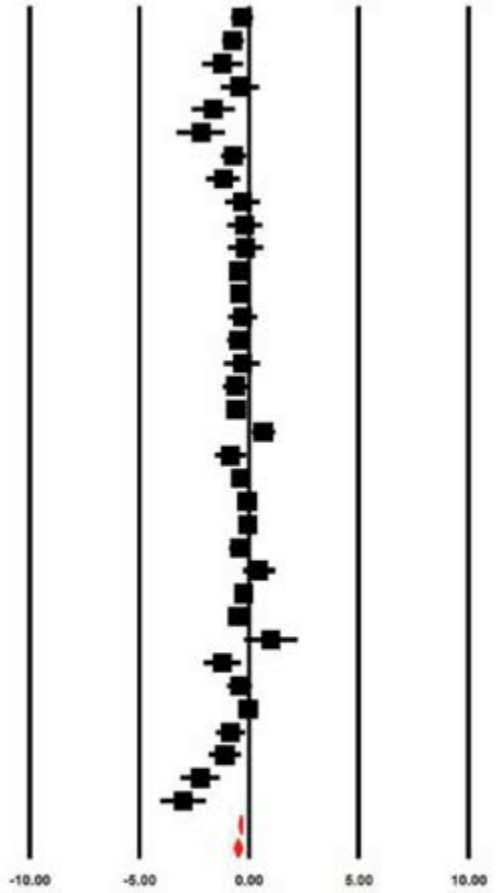
- All clinical trials published prior to 1999.
- 9 trials included
  - 5 cancer pain (119 patients analysed)
  - 2 chronic non-malignant pain (2 patients)
  - 2 acute pain (72 patients)
- THC (5-20 mg p.o.) ~ equi-analgesic to 50 –120 mg codeine
- Dose related and dose limiting CNS adverse events common.

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 -

Model	Study name	Outcome	Statistics for each study			
			Hedges's g	Lower limit	Upper limit	p-Value
	Noyes 1975al	THC10mg vs. Placebo	-0.316	-0.789	0.157	0.190
	Noyes 1975all	THC 20mg vs. Placebo	-0.753	-1.240	-0.266	0.002
	Noyes 1975bl	THC 5mg vs. Placebo	-1.202	-2.120	-0.283	0.010
	Noyes 1975bll	THC 10mg vs. Placebo	-0.418	-1.267	0.432	0.335
	Noyes 1975bIII	THC 15mg vs. Placebo	-1.622	-2.600	-0.643	0.001
	Noyes 1975bIV	THC 20mg vs. Placebo	-2.196	-3.276	-1.115	0.000
	Staquet 1978a	NIB 4mg vs. Placebo	-0.716	-1.254	-0.177	0.009
	Staquet 1978b	NIB 4mg vs. Placebo	-1.183	-1.941	-0.425	0.002
	Wade 2003a	THC 2.5mg vs. Placebo	-0.289	-1.066	0.488	0.466
	Wade 2003b	CBD 2.5mg vs. Placebo	-0.190	-0.964	0.585	0.631
	Wade 2003c	THC\CBD 2.5mg vs. Placebo	-0.158	-0.932	0.616	0.689
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.473	-0.773	-0.173	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.419	-0.712	-0.125	0.005
	Wade 2004	Sativax vs. Placebo	-0.303	-0.945	0.340	0.356
	Rog 2005*	Sativax vs. Placebo	-0.492	-0.980	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.309	-1.118	0.500	0.454
	Blake 2006	CBM vs. Placebo	-0.629	-1.151	-0.107	0.018
	Nurmikko 2007*	Sativax vs. Placebo	-0.589	-0.982	-0.196	0.003
	Frank 2008	Nabilone 2mg vs. Dihydrocodeine 240mg	0.652	0.154	1.150	0.010
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.837	-1.535	-0.138	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.402	-0.727	-0.078	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.082	-0.494	0.330	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.057	-0.469	0.355	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.451	-0.884	-0.017	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.445	-0.272	1.162	0.224
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.237	-0.636	0.162	0.244
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.499	-0.897	-0.102	0.014
	Rintala 2010	Dronabinol vs. Diphenhydramine	0.975	-0.224	2.173	0.111
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.216	-2.030	-0.401	0.003
	Pini 2012	Nabilone 0.5mg vs. Ibuprufen 400mg	-0.431	-0.973	0.111	0.119
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.411	-0.494	-0.327	0.000
Random			-0.541	-0.715	-0.367	0.000



Fixed 0.411
Random 0.541

x*= Parallel design.

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

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

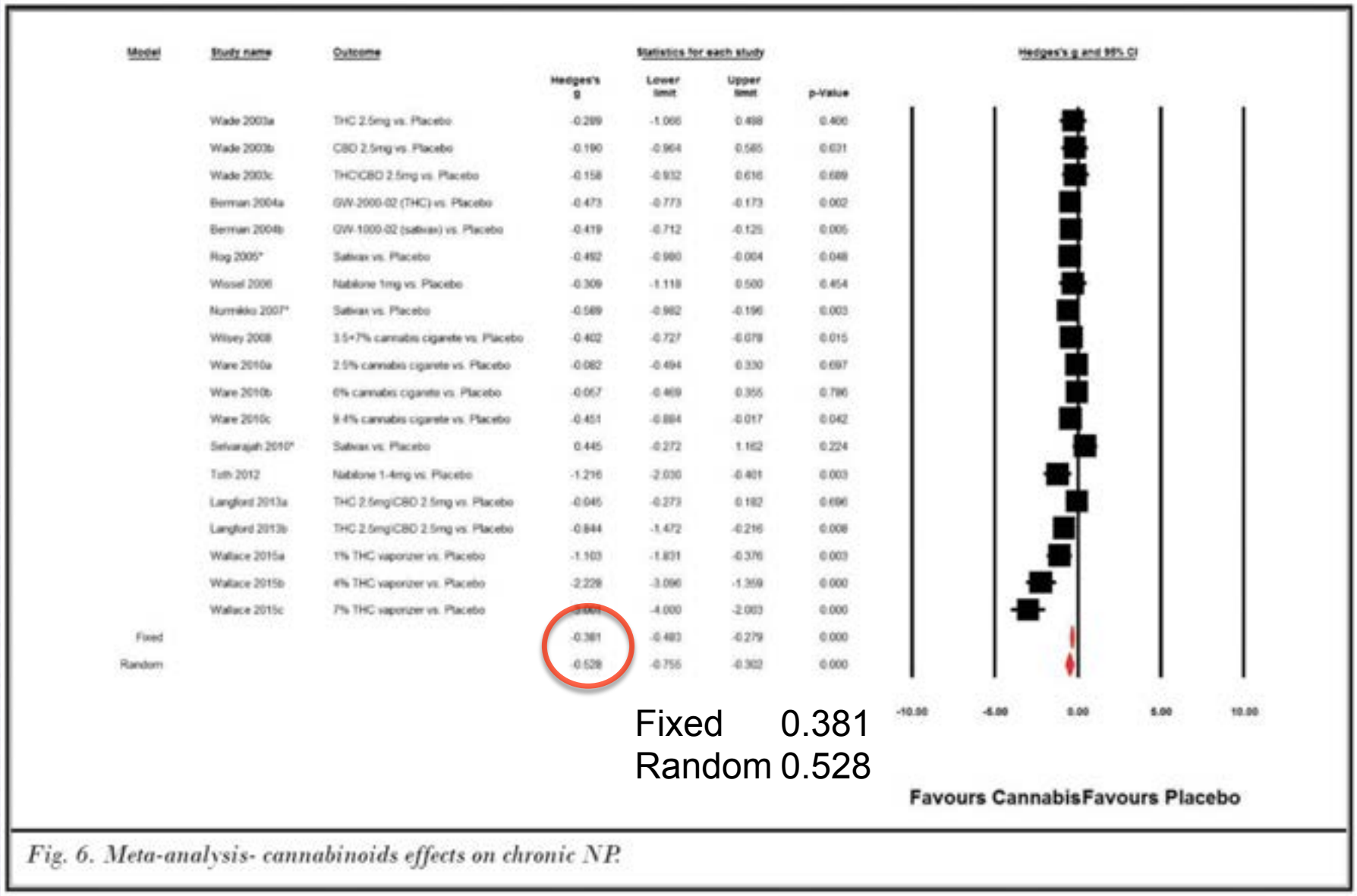


Fig. 6. Meta-analysis- cannabinoids effects on chronic NP.

Chronic neuropathic pain

Aviram et al 2017

Yes, but what about cancer pain?

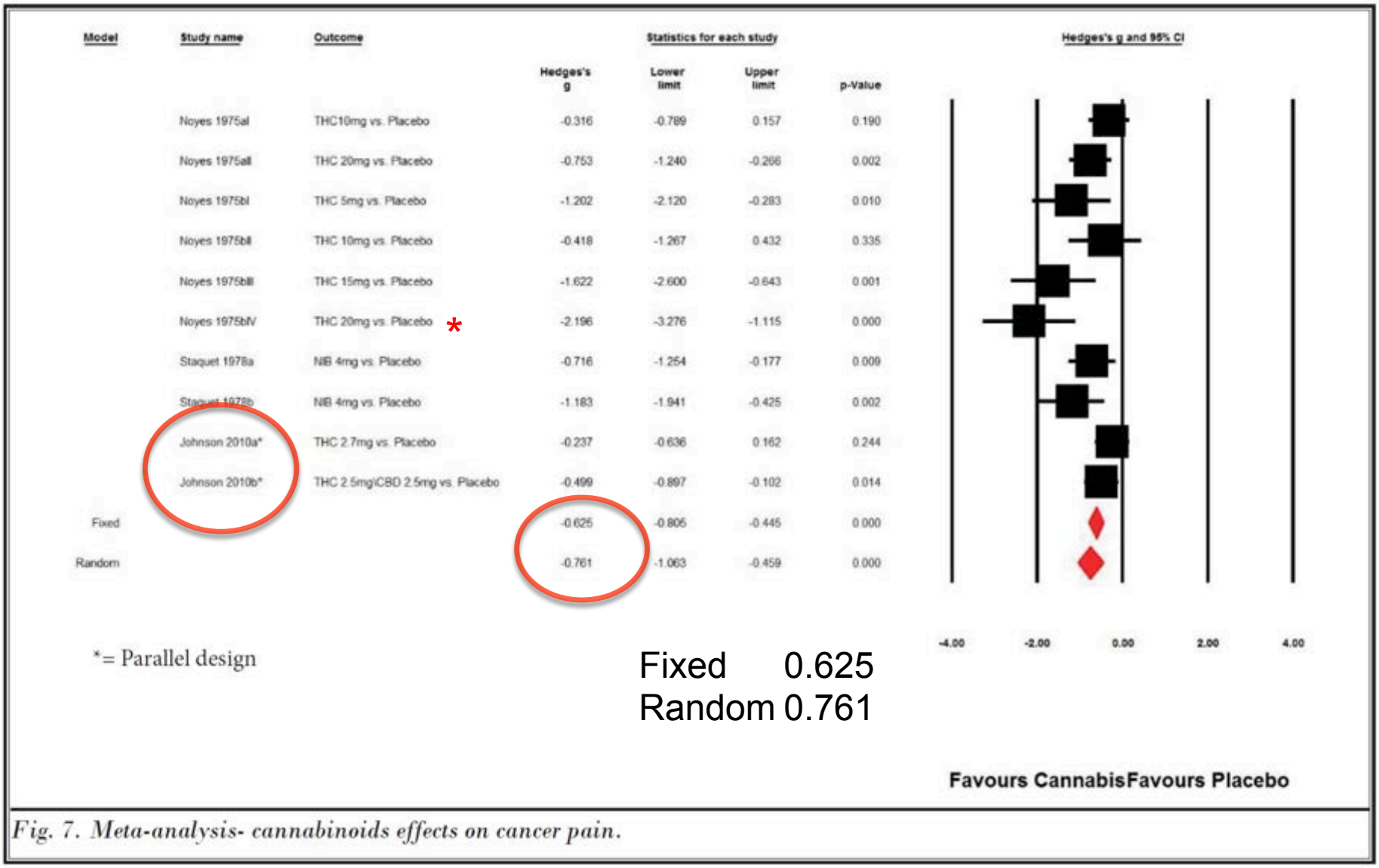


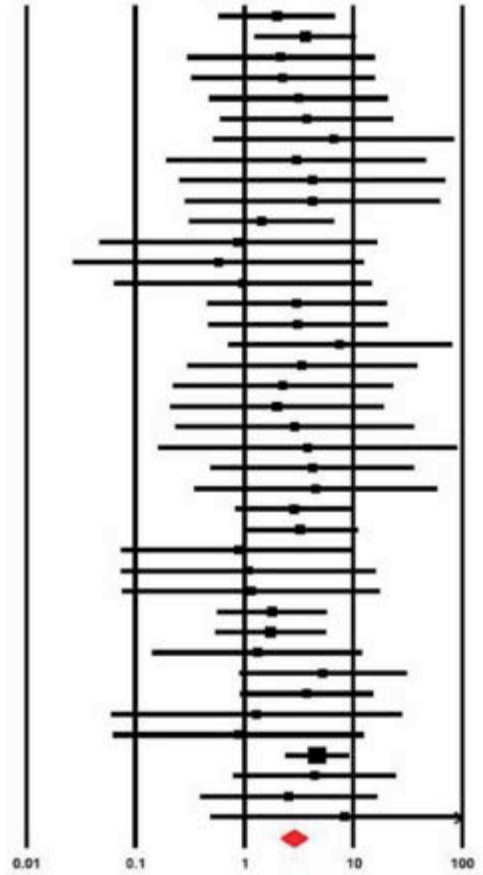
Fig. 7. Meta-analysis- cannabinoids effects on cancer pain.

Aviram et al 2017

Cancer pain

*** "Alarming adverse reactions were also observed at this dose"**

Model	Study name	Comparison	Outcome	Statistics for each study: Risk ratio	Lower limit	Upper limit	p-Value
	Noyes 1975al	THC 10mg vs. placebo	Combined	1.987	0.584	6.762	0.2718
	Noyes 1975all	THC 20mg vs. placebo	Combined	3.642	1.248	10.629	0.0180
	Noyes 1975bl	THC 5mg vs. placebo	Combined	2.156	0.297	15.643	0.4474
	Noyes 1975bll	THC 10mg vs. placebo	Combined	2.254	0.323	15.716	0.4120
	Noyes 1975bllI	THC 15mg vs. placebo	Combined	3.127	0.474	20.640	0.2363
	Noyes 1975blV	THC 20 mg vs. placebo	Combined	3.707	0.601	22.876	0.1583
	Jain 1981**l	Levonantradol 1.5mg vs. placebo	Combined	6.633	0.523	84.174	0.1444
	Jain 1981**ll	Levonantradol 2mg vs. placebo	Combined	3.000	0.192	46.795	0.4332
	Jain 1981**lll	Levonantradol 2.5mg vs. placebo	Combined	4.217	0.254	69.956	0.3152
	Jain 1981**lV	Levonantradol 3mg vs. placebo	Combined	4.243	0.288	62.393	0.2920
	Buggy 2003**	THC 5mg vs. placebo	Combined	1.446	0.315	6.626	0.6351
	Wade 2003a	THC 2.5mg vs. placebo	Combined	0.873	0.047	16.389	0.9279
	Wade 2003b	CBD 2.5mg vs. placebo	Combined	0.577	0.027	12.519	0.7264
	Wade 2003c	THC 2.5mg\CBD 2.5 mg vs. placebo	Combined	0.968	0.063	14.802	0.9812
	Berman 2004a	GW-1000-02 vs. placebo	Combined	3.049	0.460	20.232	0.2482
	Berman 2004b	GW-2000-02 vs. placebo	Combined	3.097	0.466	20.573	0.2420
	Wade 2004	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	7.555	0.708	80.638	0.0941
	Svendsen 2004	Dronabinol vs. placebo	Combined	3.374	0.299	38.102	0.3254
	Rog 2005*	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	2.256	0.221	22.980	0.4921
	Wissel 2006	Nabilone 1mg vs. placebo	drowsiness	2.000	0.211	18.981	0.5460
	Blake 2006	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	2.886	0.233	35.671	0.4087
	Abrams 2007*	Cannabis 3.56% vs. placebo	dizziness	3.783	0.162	88.578	0.4083
	Nurmikko 2007*	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	4.209	0.489	36.244	0.1908
	Skrabek 2008 (4w)	Nabilone vs. placebo	Combined	4.534	0.351	58.577	0.2469
	Narang 2008a	Dronabinol 10mg vs. placebo	Combined	2.847	0.826	9.822	0.0976
	Narang 2008b	Dronabinol 20mg vs. placebo	Combined	3.276	0.969	11.068	0.0561
	Ware 2010a	Cannabis 2.5% vs. placebo	Combined	0.876	0.074	10.413	0.9164
	Ware 2010b	Cannabis 6% vs. placebo	Combined	1.091	0.075	15.945	0.9490
	Ware 2010c	Cannabis 9.4% vs. placebo	Combined	1.154	0.076	17.562	0.9176
	Johnson 2010a*	THC 2.7mg vs. placebo	Combined	1.794	0.563	5.718	0.3229
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. placebo	Combined	1.734	0.544	5.533	0.3522
	Rintala 2010	Dronabinol vs. diphenhydramine	Combined	1.312	0.143	12.000	0.8103
	Corey-Bloom 2012	Cannabis 4% vs. placebo	Combined	5.292	0.900	31.123	0.0653
	Portenoy 2012*	Nabiximol 11-16 sprays vs. placebo	Combined	3.725	0.928	14.954	0.0637
	Pini 2012	Nabilone 0.5mg vs. placebo	Combined	1.291	0.060	27.911	0.8706
	Huggins 2012	PF-04457845 vs. placebo	Combined	0.886	0.063	12.474	0.9287
	Zajicek 2012	Cannabis extract vs. placebo	Combined	4.659	2.385	9.102	0.0000
	Langford 2013a	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	4.415	0.798	24.431	0.0889
	Serpell 2014*	Sativax vs. placebo	Combined	2.536	0.395	16.266	0.3265
	Lynch 2014	Sativax vs. placebo	Combined	8.363	0.483	144.928	0.1445
Fixed				2.842	2.163	3.734	0.0000



*= 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, >90mg/day morphine (≥4≤8)
  Enriched enrolment, 15% improvement NRS
- 1) N=206 (from 540)
  N=399 (64/200 withdrew in Sativex group)
- Mean average pain score from 3.2 to 3.7 (3.1 to 3.6 placebo
  Median improvement from baseline
  7.2% (c.f. 9.5% placebo)
- 68% adverse effects (64% placebo)
- Sub group 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

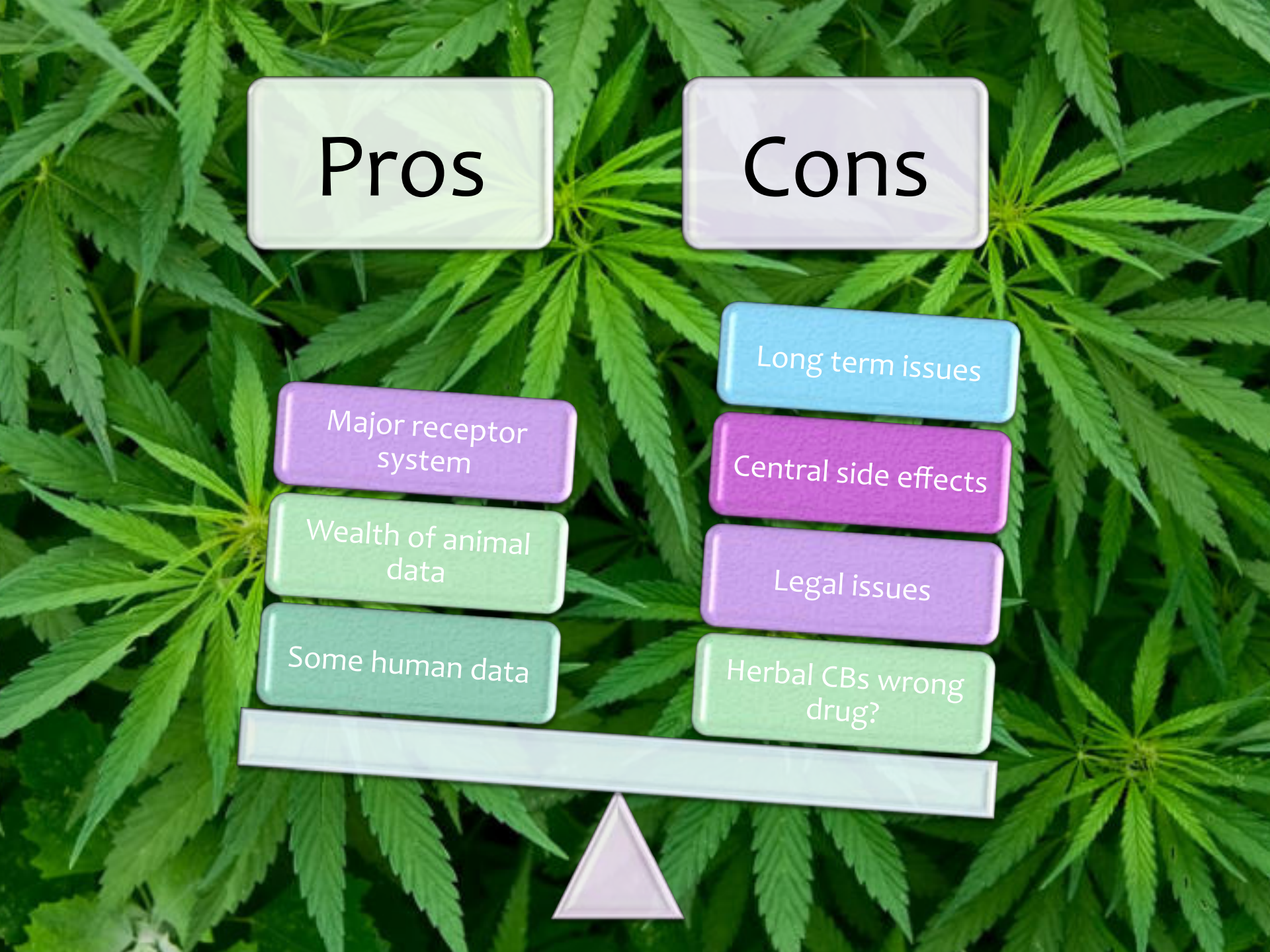
- Historical cohort study 1969-70 Swedish conscripts
- n=50,087 (97% of Swedish 18-20 yr. olds)
- Questionnaire of drug use
- National register of psychiatric admissions 1970-1996
- Dose dependent increase risk of developing schizophrenia with cannabis use (30% increased risk of schizophrenia [OR: 6.7(2.1-21.7)]

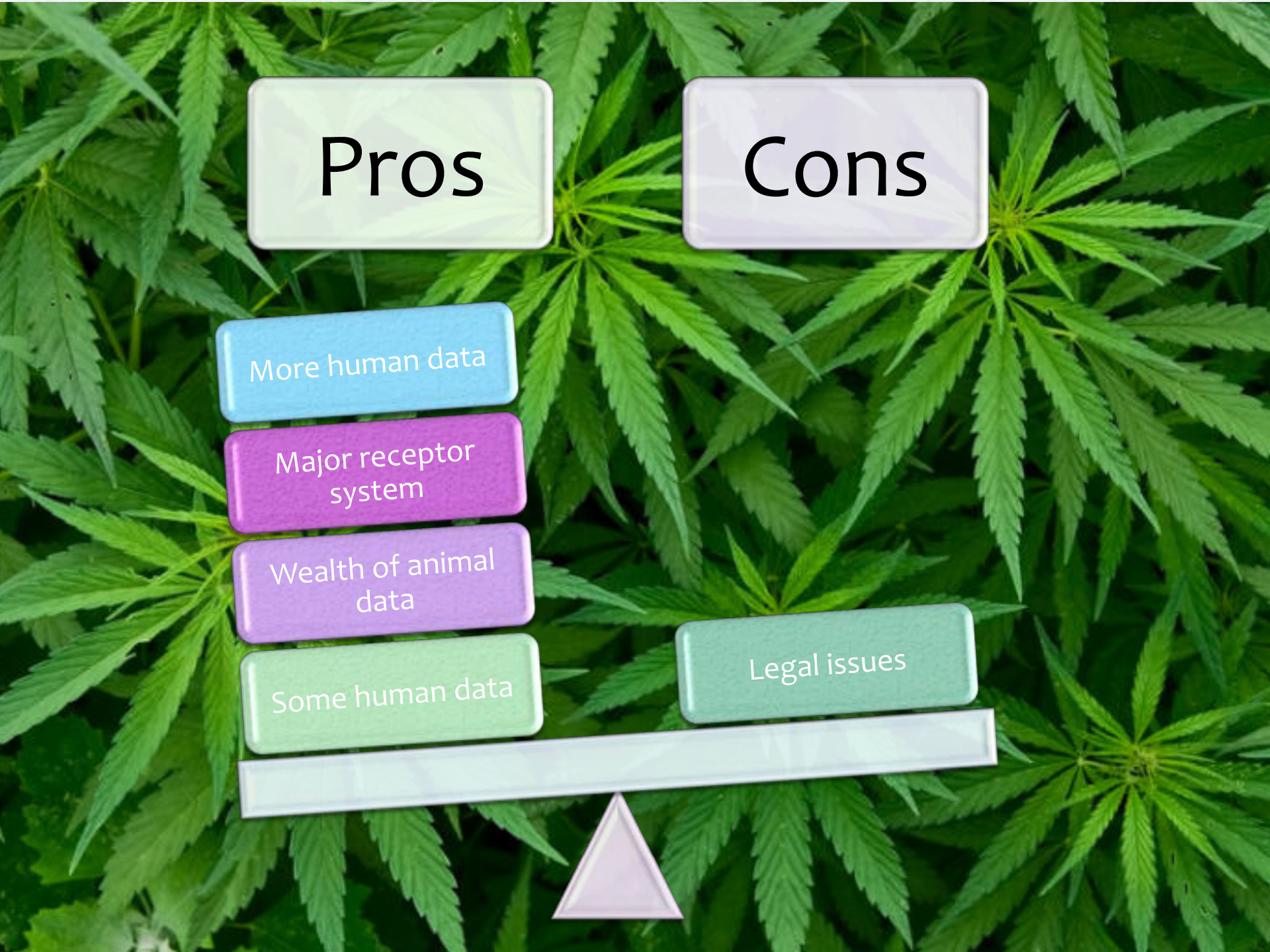
Zammit et al 2002 BMJ

The bottom line

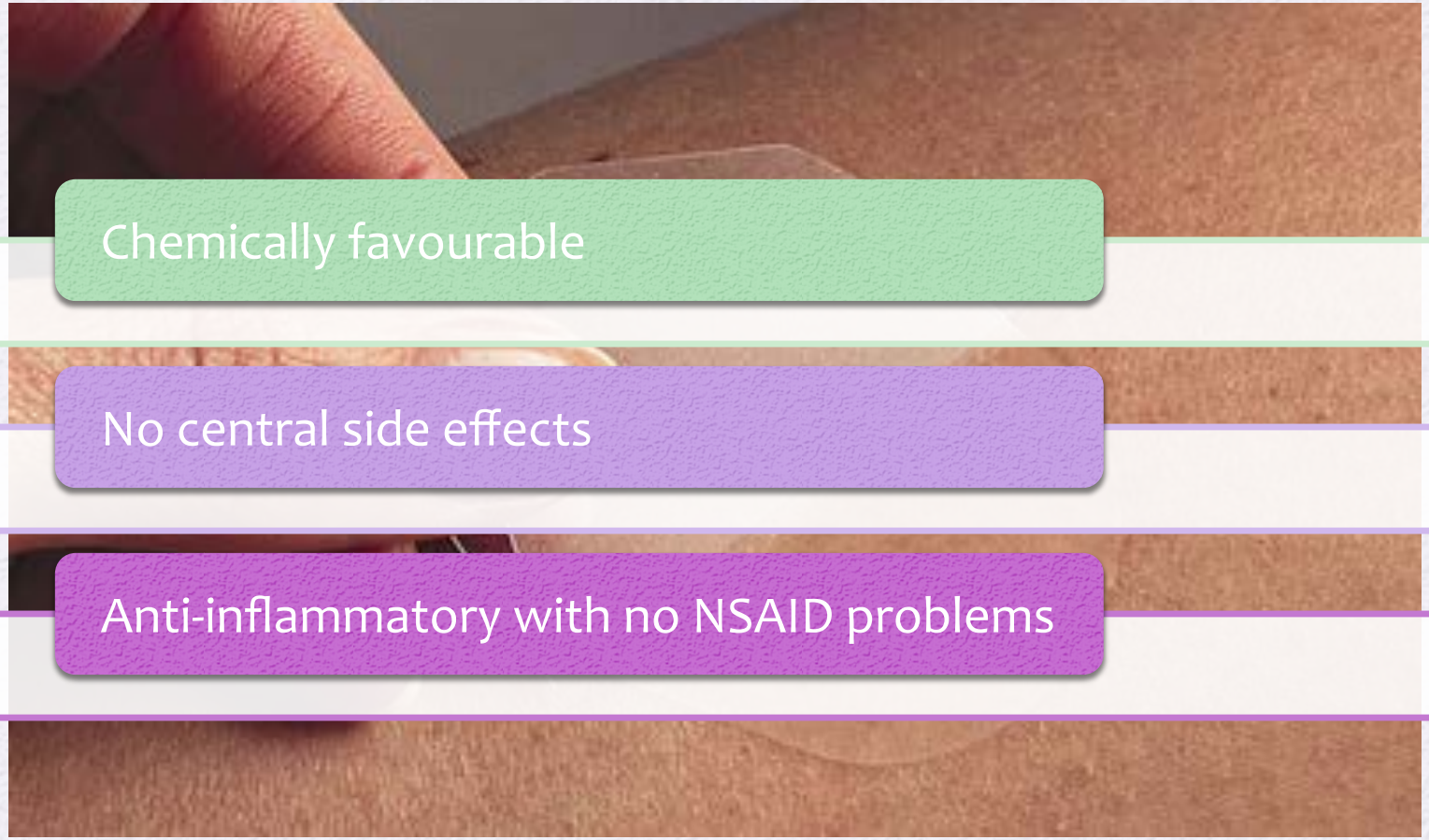
‘*May be beneficial*’
(but potential of side effects)

The future?


Pros
Cons
Major receptor system
Wealth of animal data
Some human data
Long term issues
Central side effects
Legal issues
Herbal CBs wrong drug?


Pros
Cons
More human data
Major receptor system
Wealth of animal data
Some human data
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?