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Medicinal Uses of Cannabis: The Current Status

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Presenting on behalf of
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1. Cannabinoids: THC & CBD
2. Outcomes in healthy recreational cannabis users
3. Outcomes in patients with psychosis using cannabis
4. Cannabinoid medications in psychiatry?
5. Legal status & prescribing
6. CBD from health-food shops

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1

Cannabinoids: THC & CBD

History of Cannabis as medicine in the UK

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- 1842 – William O'Shaugnessy "tetanus & other convulsive disorders"
- 1890 – JR Reynolds (Lancet) asthma, cough, migraine, childbirth, menstrual cramps
- 1971 – Cannabis left British pharmacopoeia

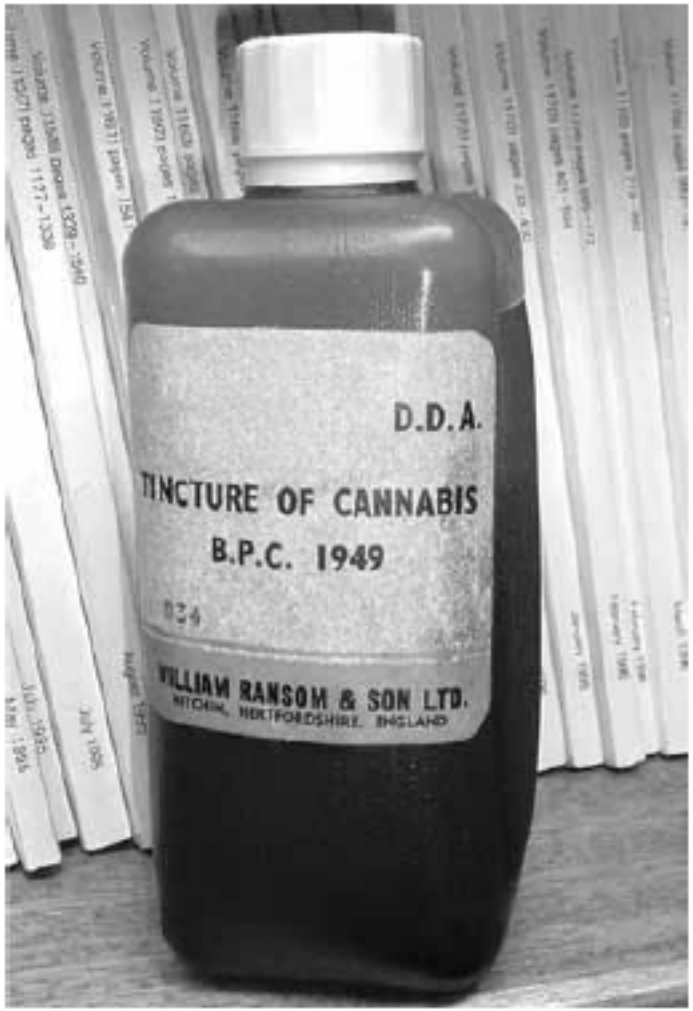

Image courtesy of Wellcome Trust Centre for the History of Medicine

Cannabis sativa

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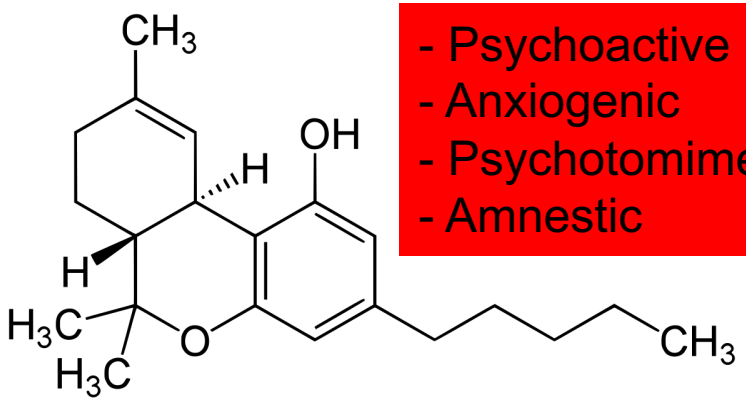
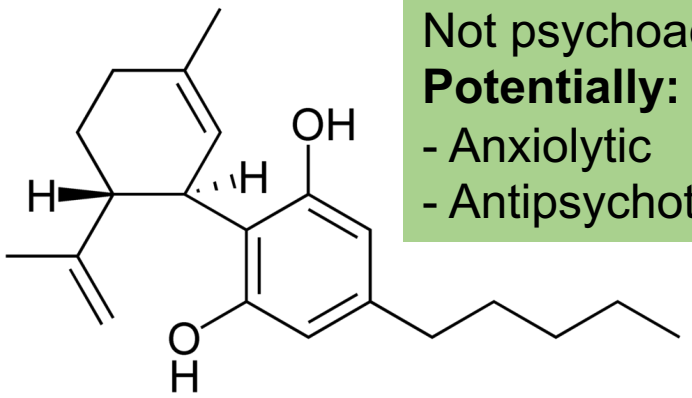


- Psychoactive
- Anxiogenic
- Psychotomimetic
- Amnestic

Delta-9-tetrahydrocannabinol (THC)



Not psychoactive

Potentially:

- Anxiolytic
- Antipsychotic

Cannabidiol (CBD)

Opposite neural effects of THC & CBD

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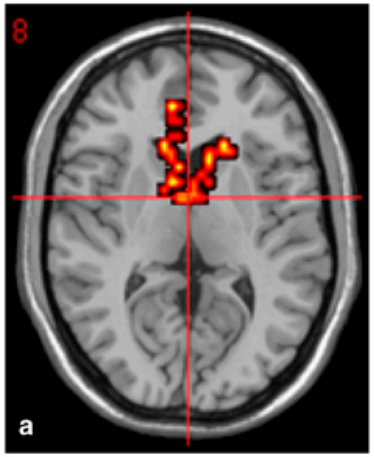
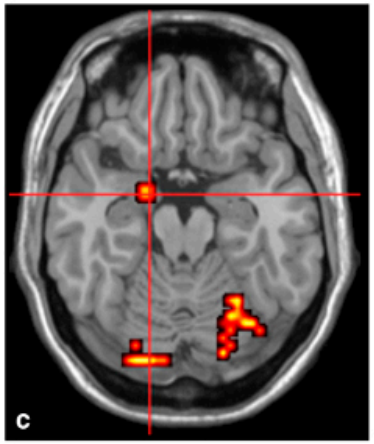
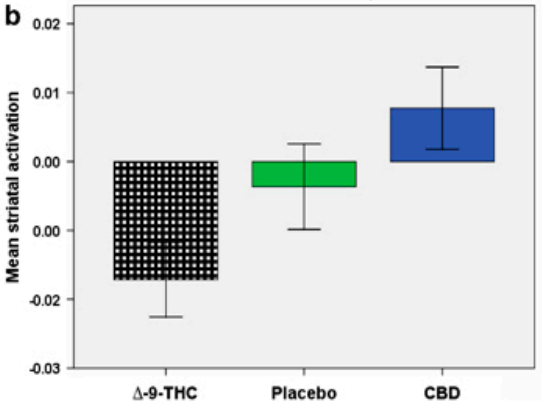
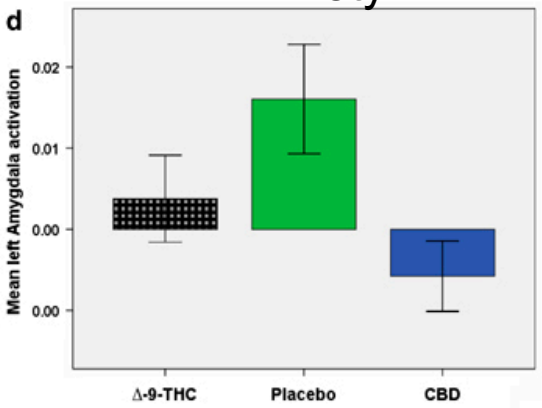


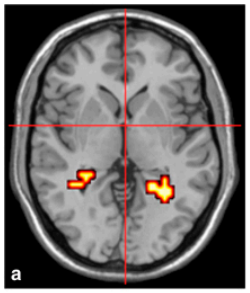


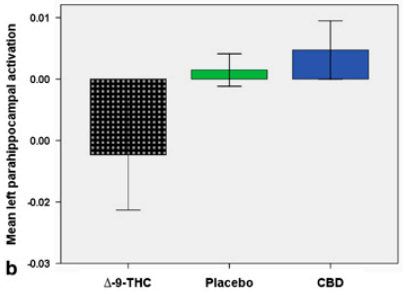
Memory



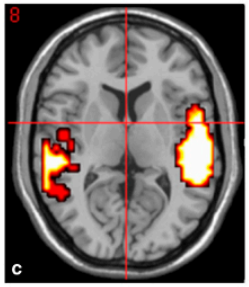
Anxiety

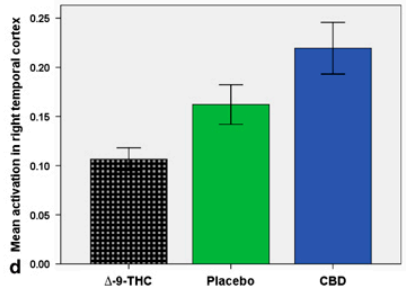


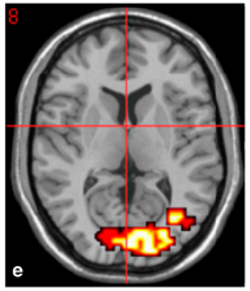


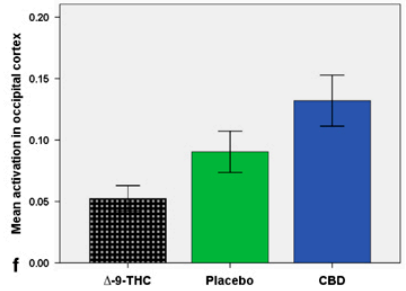


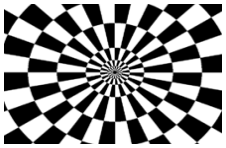
Go/No-Go (response inhibition)











Cannabis type & potency

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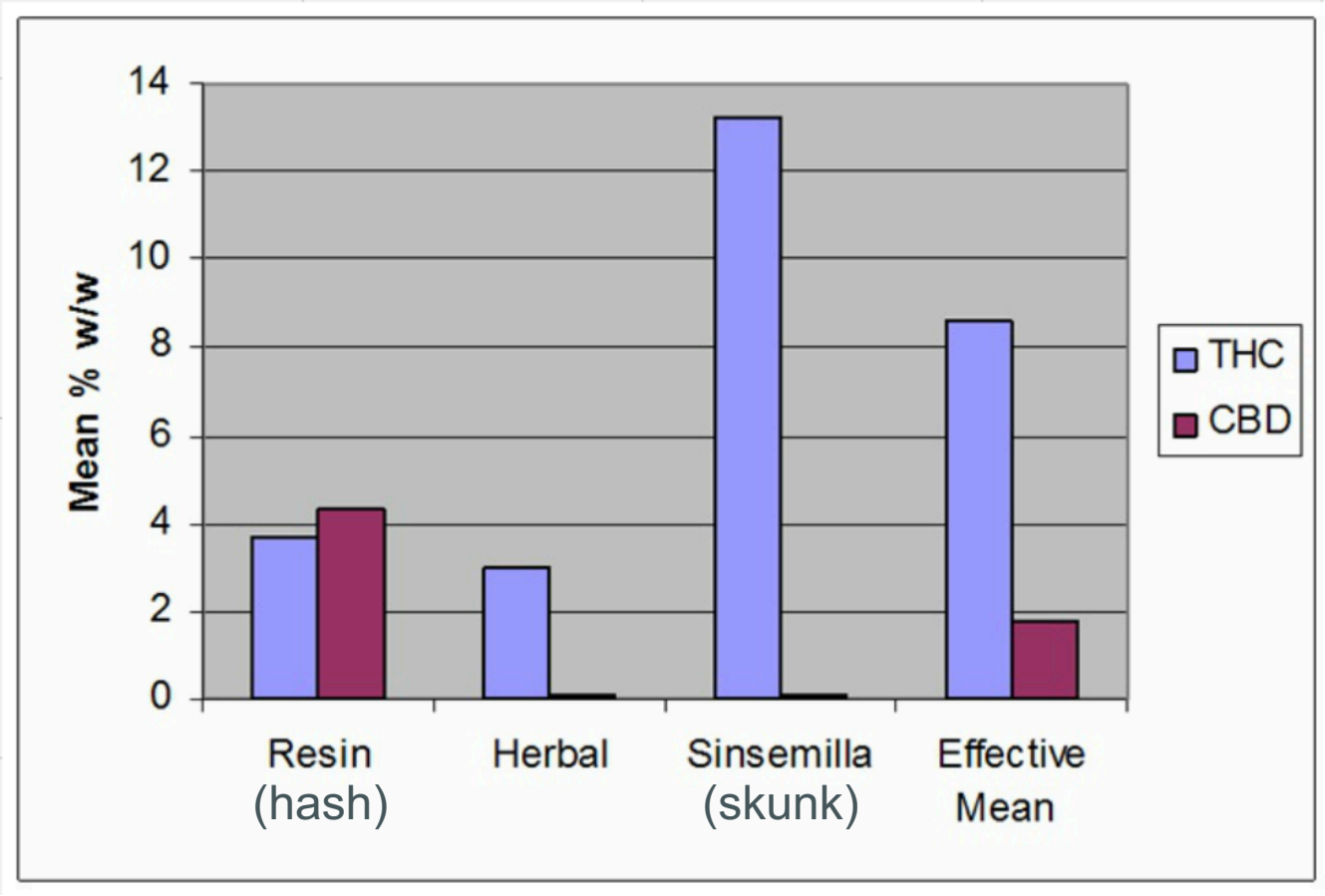

Potter et al 2008

CBD+THC vs pure THC

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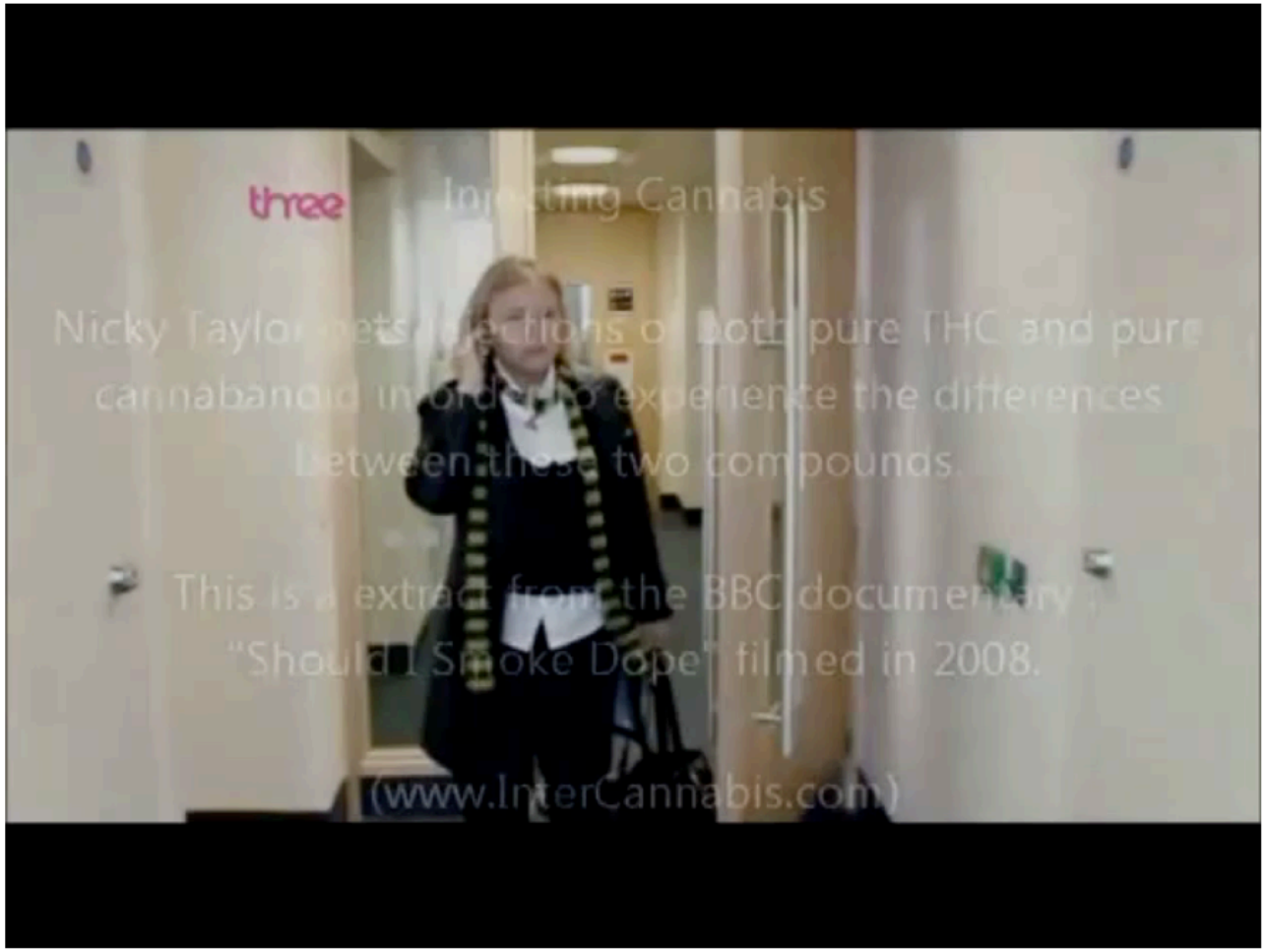

NB:
"Cannabinoid" here is referring to **CBD**

Morrison et al 2010

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2

What are the outcomes in healthy recreational cannabis users?

Psychosis

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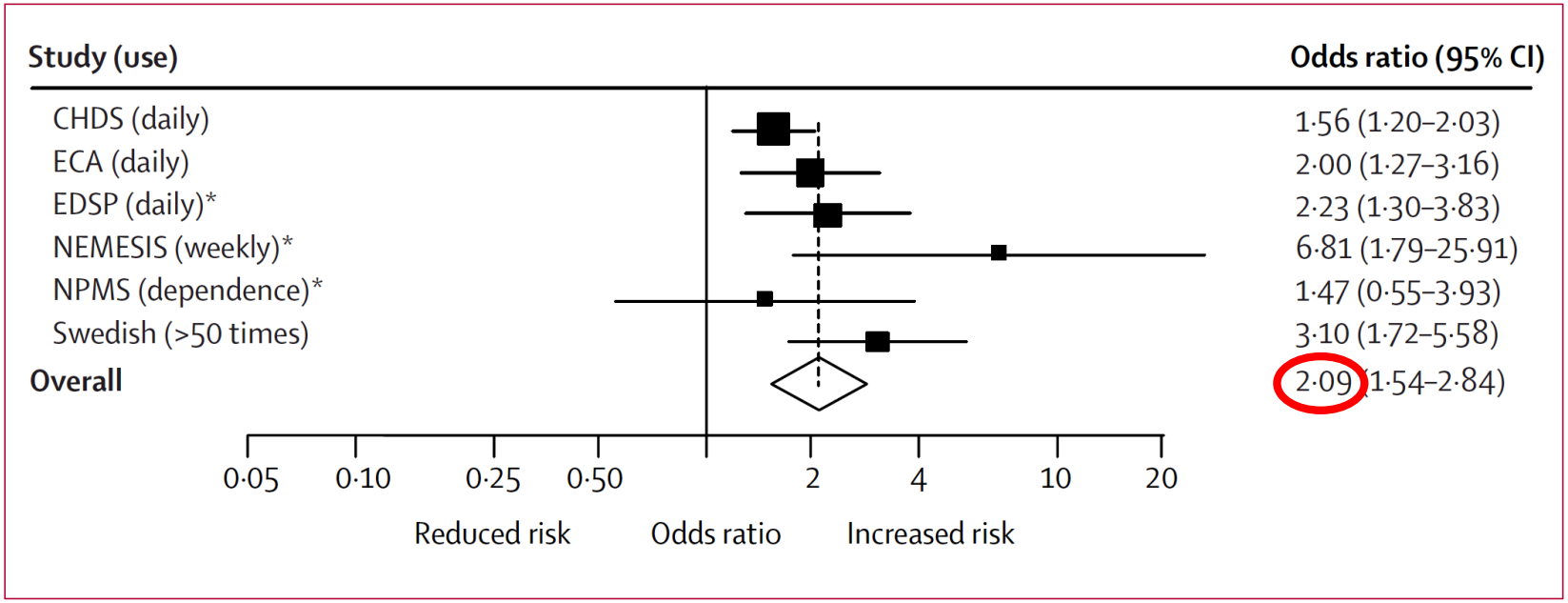
Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Lancet 2007; 370: 319–28

Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis



Psychosis

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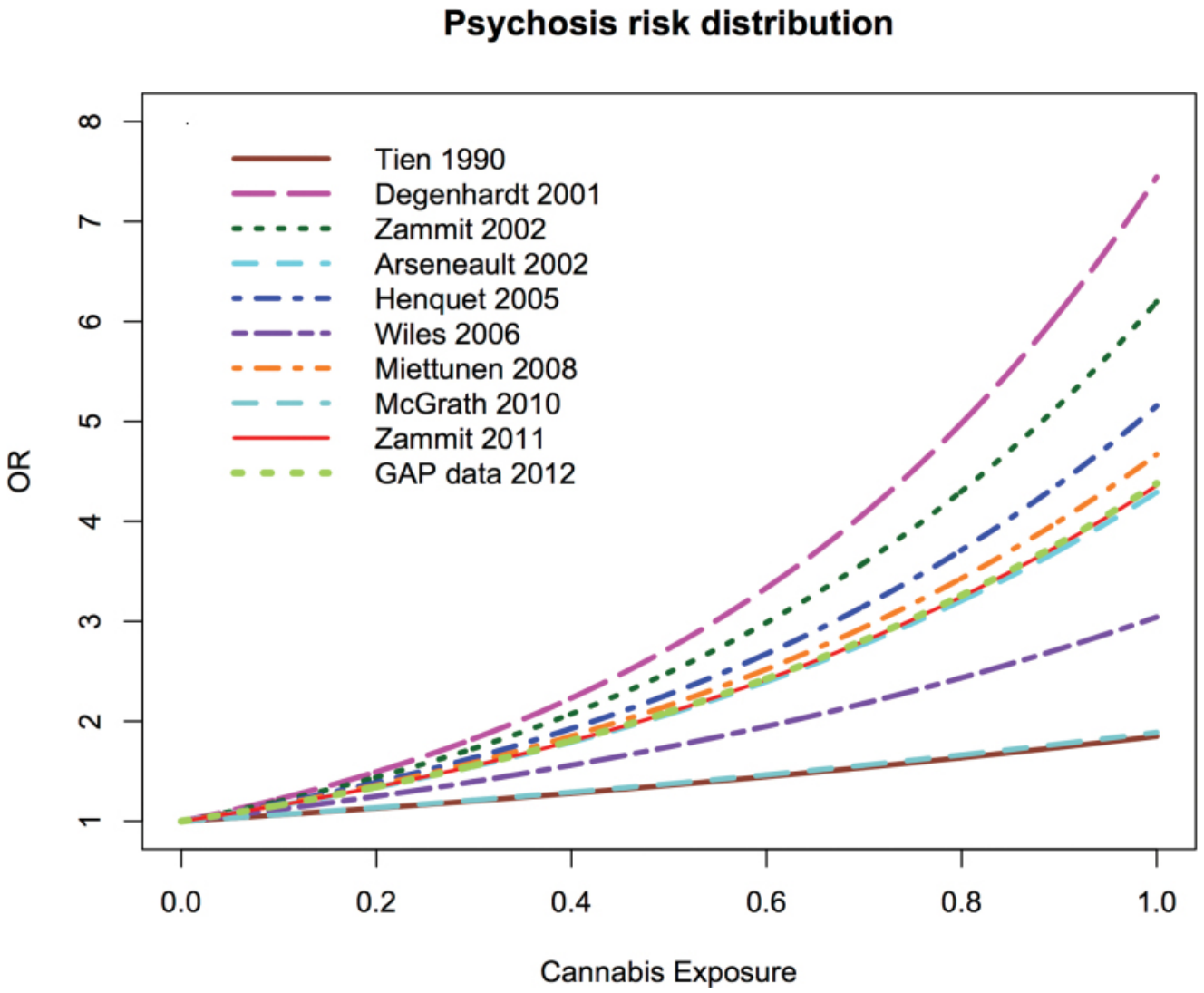
"Ever used"
OR = 1.97

"Most severe users"
OR = 3.90



SCHIZOPHRENIA BULLETIN
The Journal of Psychoses and Related Disorders

Marconi et al 2016

Depression

Developmental sensitivity to cannabis use patterns and risk for major depressive disorder in mid-life: findings from 40 years of follow-up

Tabea Schoeler[1,*], Delphine Theobald[2,*], Jean-Baptiste Pingault[1], David P. Farrington[3], Jeremy W. Coid[4] and Sagnik Bhattacharyya[5]

implicates cannabis use **during adolescence** as a risk factor for later life **depression**

Cannabis early onset – low frequency: OR = 2.41 (1.22 – 4.76)

Cannabis early onset – high frequency: OR = 8.83 (1.29 – 70.79)

Violence

Continuity of cannabis use and violent offending over the life course

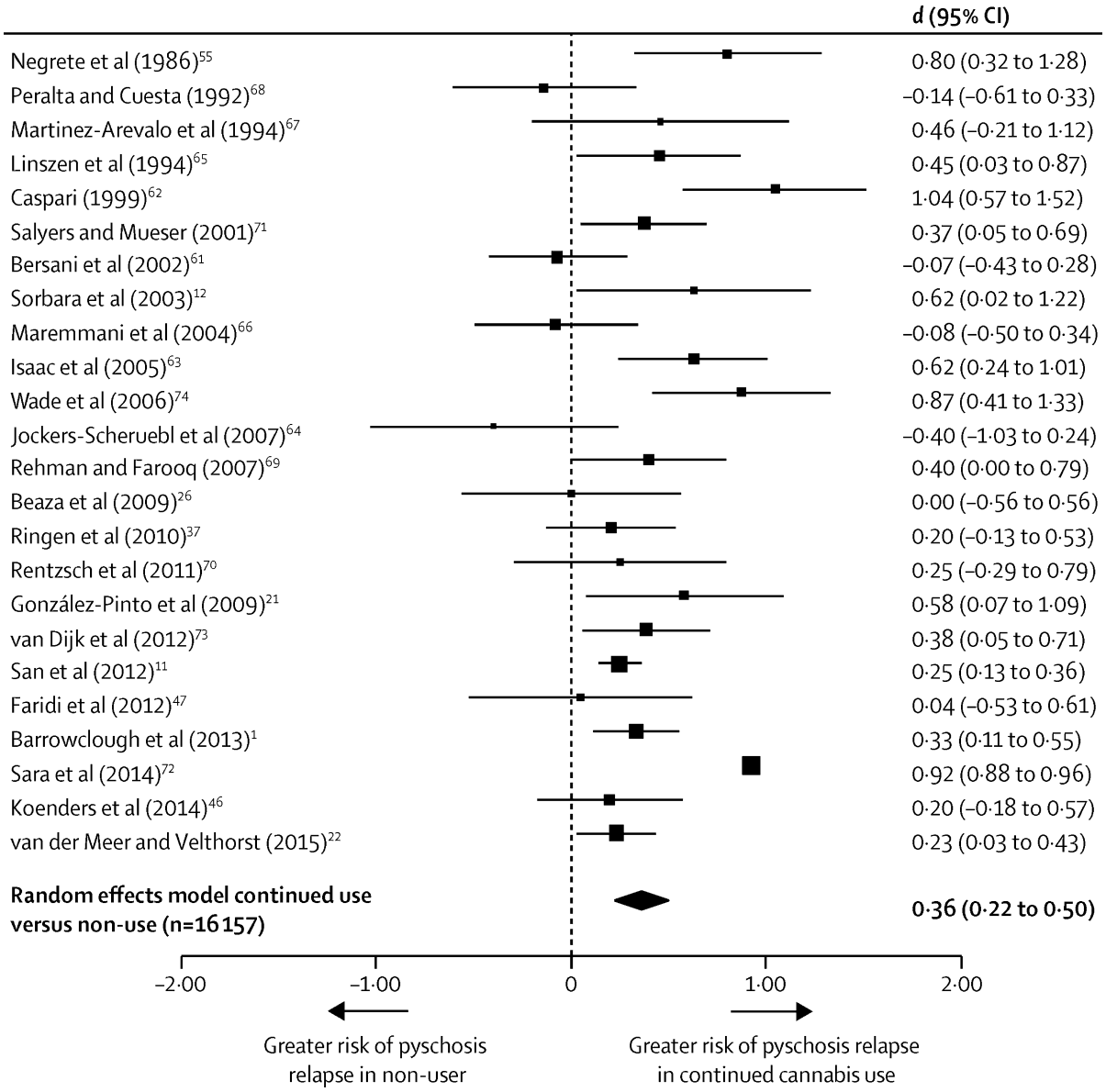
T. Schoeler[1]†, D. Theobald[1,2]†, J.-B. Pingault[3], D. P. Farrington[4], W. G. Jennings[5], A. R. Piquero[6], J. W. Coid[7] and S. Bhattacharyya[1]*

OR = 7.08 (2.19 – 23.59)

3

What are the outcomes in patients with psychosis using cannabis?

Relapse in psychosis



across more than 16,000 patients - greater risk of psychosis relapse in continued users

Schoeler et al, Lancet Psych 2016

Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study

Tabea Schoeler, Natalia Petros, Marta Di Forti, Ewa Klamerus, Enrico Foglia, Olesya Ajnakina, Charlotte Gayer-Anderson, Marco Colizzi, Diego Quattrone, Irena Behlke, Sachin Shetty, Philip McGuire, Anthony S David, Robin Murray, Sagnik Bhattacharyya

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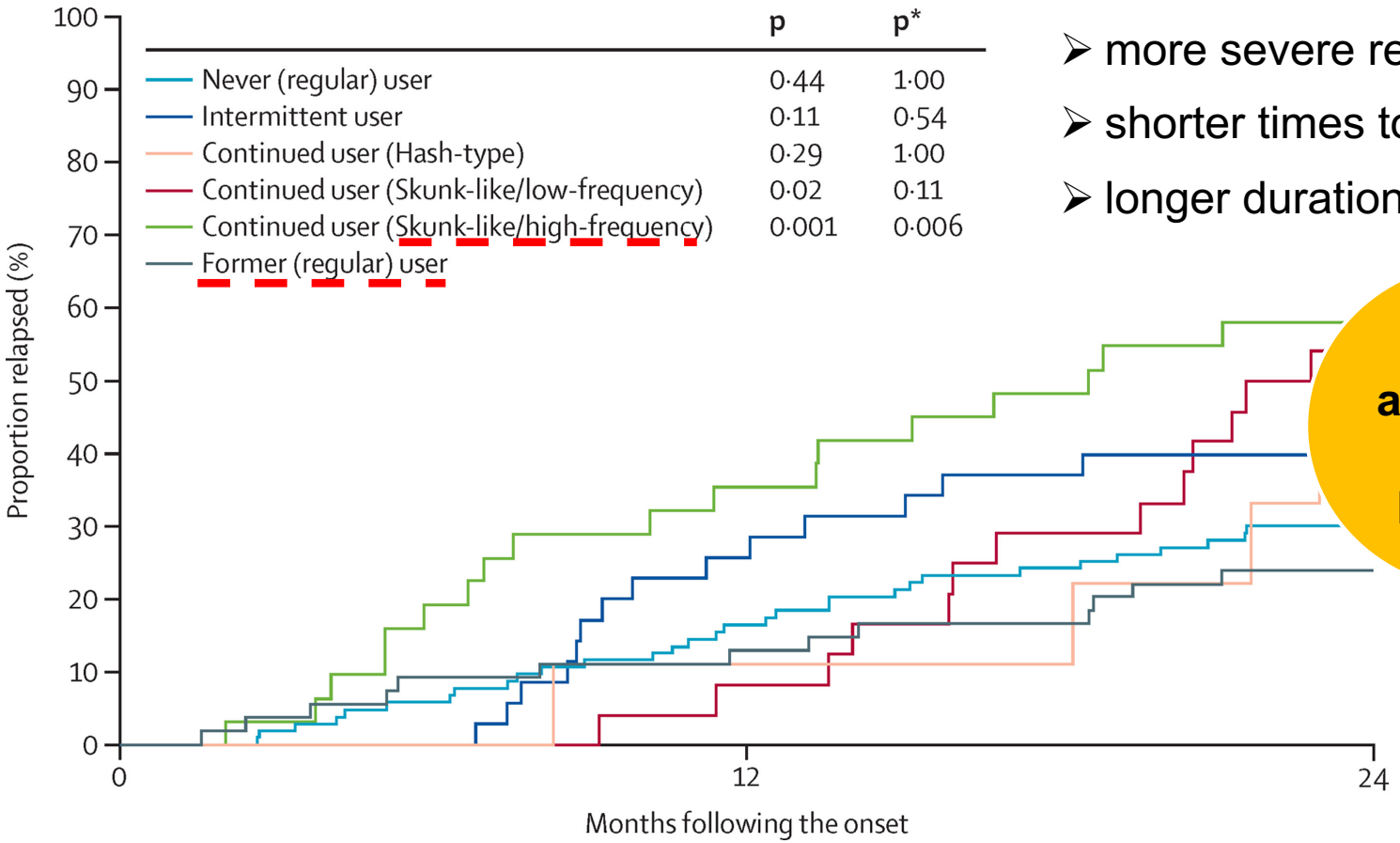

- more relapses
- more severe relapses
- shorter times to relapse
- longer durations of hospital stay

29 additional days in hospital

Lancet Psych 2016

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4 cannabinoid medications in psychiatry?

Efficacy

RCT of patients with schizophrenia, treated with 800mg/day of either Amisulpride (N=19) or CBD (N=20) for 28 days

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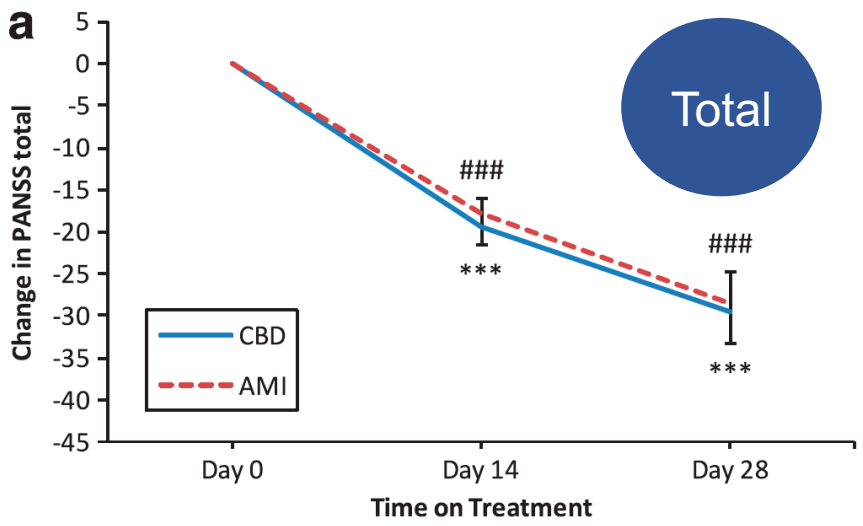
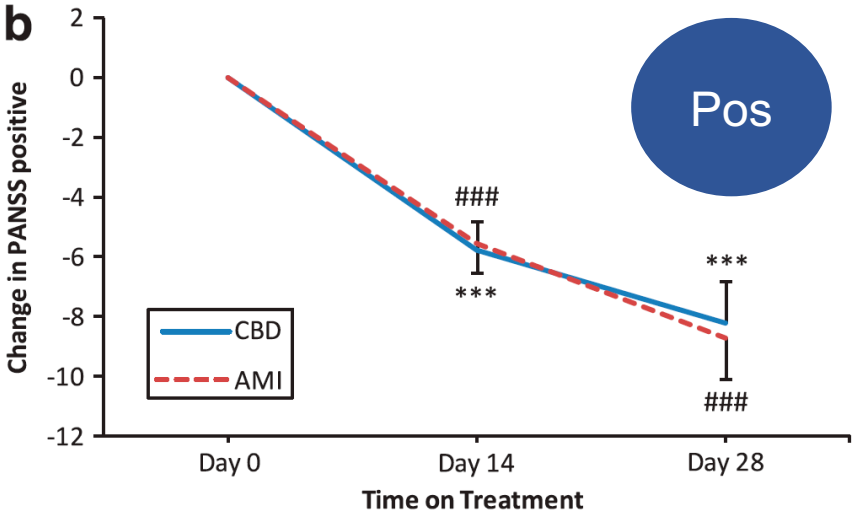
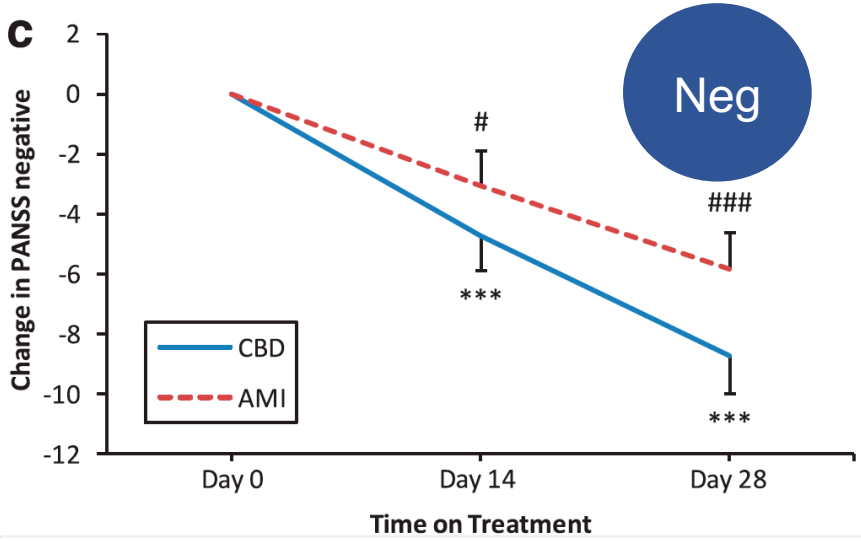
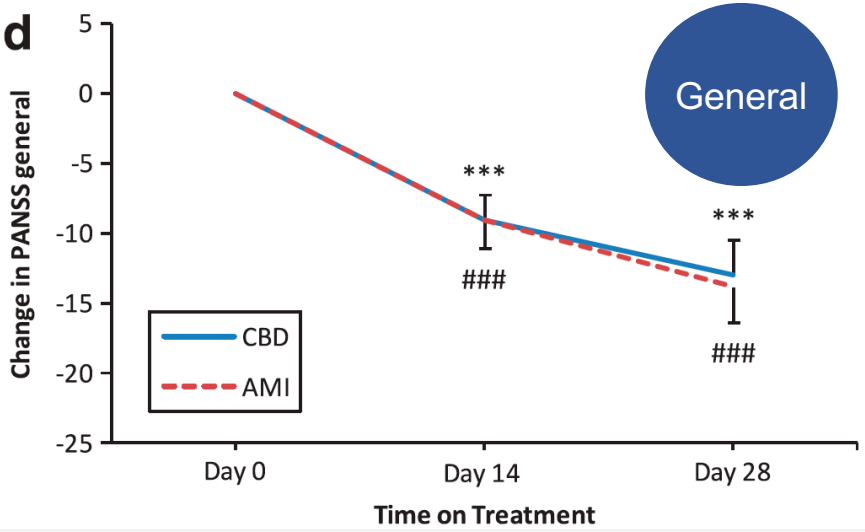
Leweke et al 2012

Similar efficacy









Side-effects

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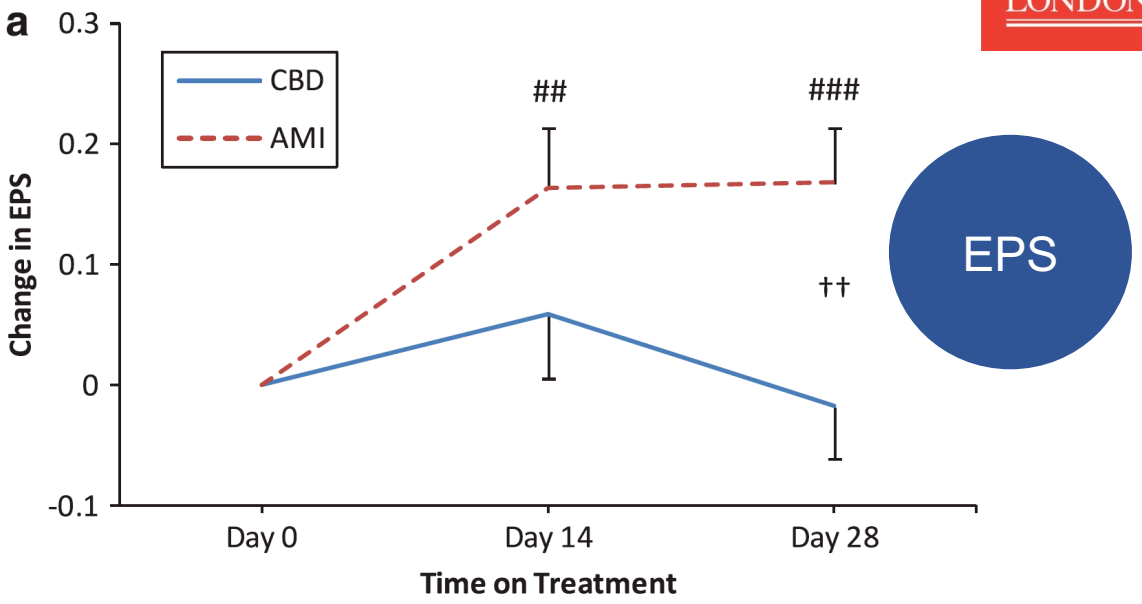
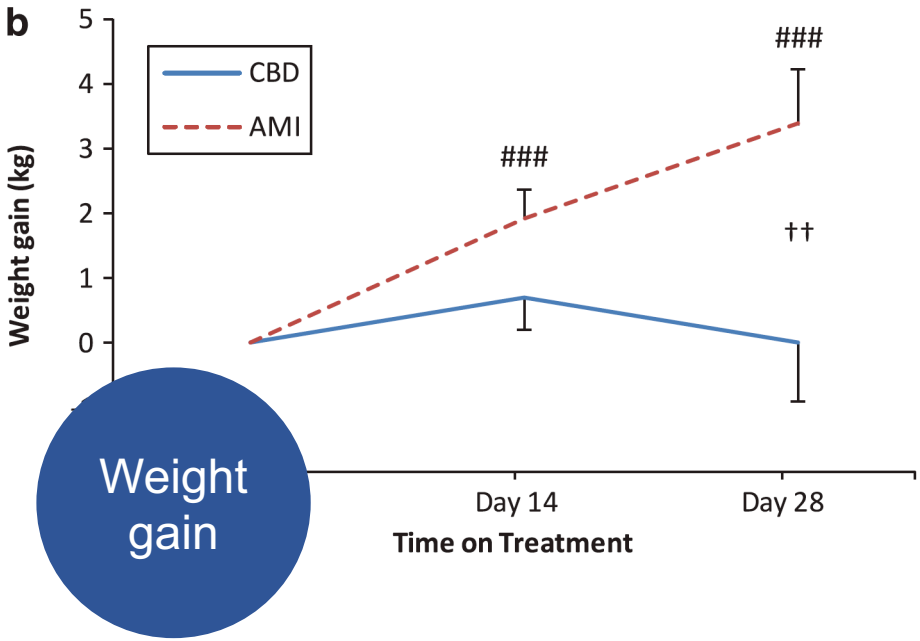
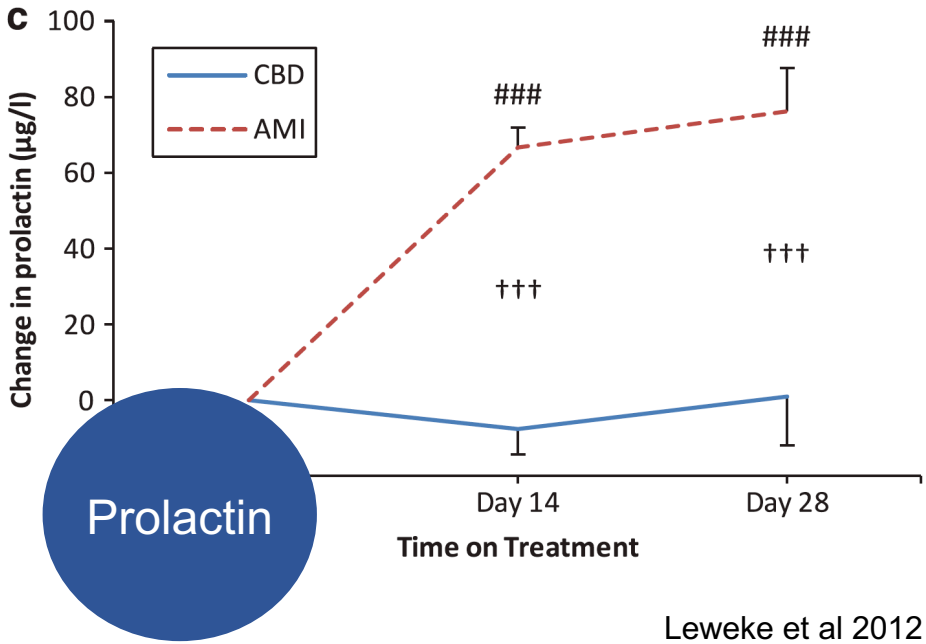
CBD displayed a markedly superior side-effect profile







Leweke et al 2012

Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial

Philip McGuire, F.R.C.Psych., F.Med.Sci., Philip Robson, M.R.C.P., F.R.C.Psych., Wieslaw Jerzy Cubala, M.D., Ph.D., et al.

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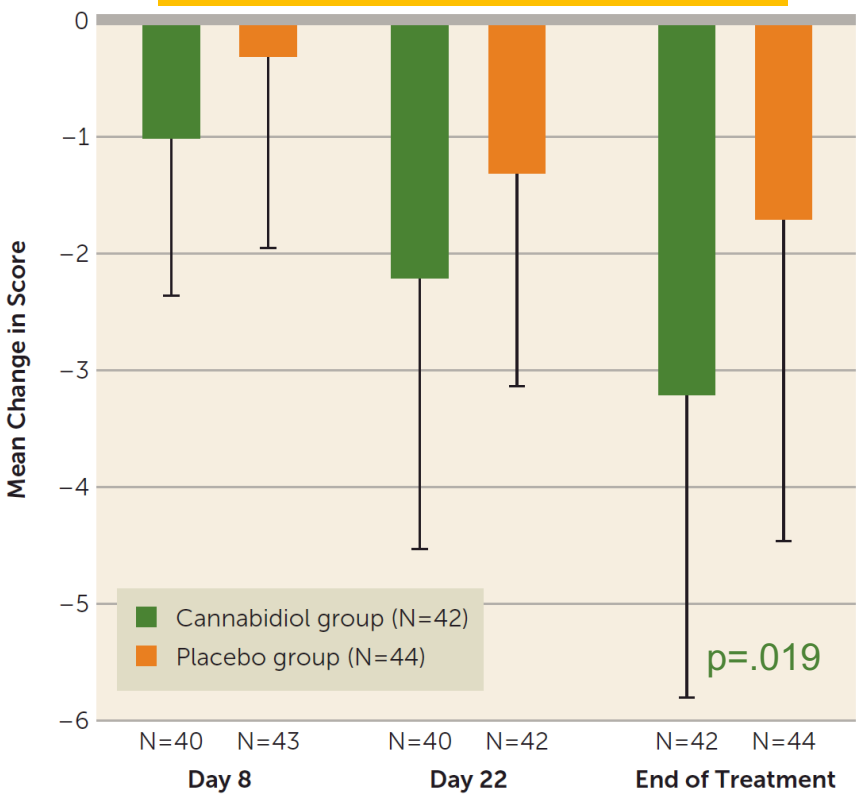
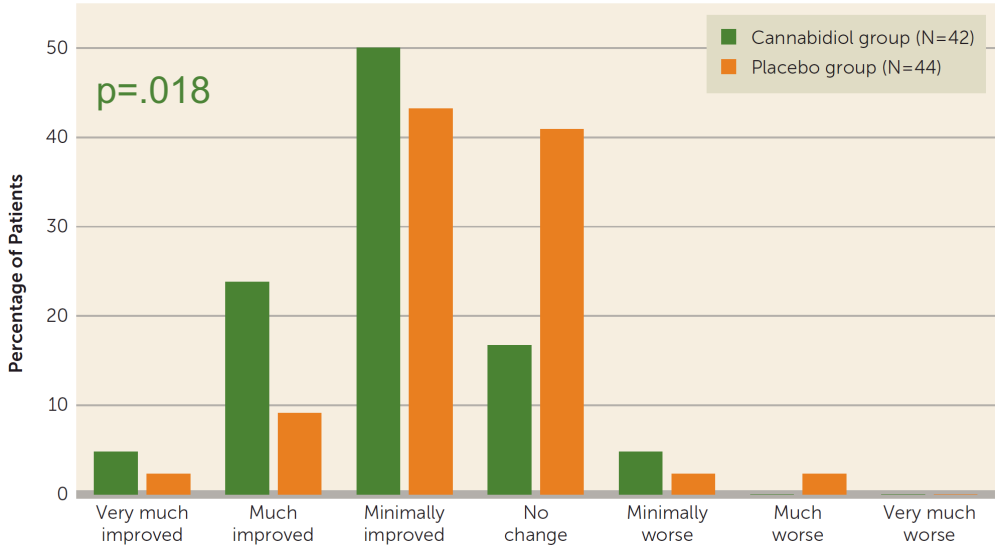
The American Journal of Psychiatry

6-week RCT (N=88) of **1000mg/day CBD** or **placebo** alongside existing antipsychotics

CBD group had lower levels of positive symptoms



CBD group more likely to have been rated as improved and not as severely unwell by the treating clinician



Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial

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Across studies:
- Diarrhoea
- Sedation

TABLE 3. Most Common Adverse Events (Incidence ≥4%), by Causality, in a Study of Adjunctive Cannabidiol in Schizophrenia (Safety Analysis Set)

System Organ Class and Preferred Term[a]	All Causes				Treatment Related			
	Cannabidiol Group (N=43)		Placebo Group (N=45)		Cannabidiol Group (N=43)		Placebo Group (N=45)	
	N	%	N	%	N	%	N	%
At least one event	15	34.9	16	35.6	10	23.3	10	22.2
Gastrointestinal disorders	9	20.9	3	6.7	8	18.6	3	6.7
Diarrhea	4	9.3	2	4.4	4	9.3	2	4.4
Nausea	3	7.0	0		3	7.0	0	
Nervous system disorders	3	7.0	6	13.3	2	4.7	4	8.9
Headache	3	7.0	4	8.9	2	4.7	2	4.4
Somnolence	0		3	6.7	0		3	6.7
Infections and infestations	3	7.0	3	6.7	0		0	
Psychiatric disorders	1	2.3	4	8.9	1	2.3	3	6.7
Insomnia	0		2	4.4	0		1	2.2
General disorders and administration site conditions[b]	2	4.7	1	2.2	1	2.3	0	
Investigations[c]	2	4.7	1	2.2	1	2.3	1	2.2
Metabolism and nutrition disorders	2	4.7	1	2.2	2	4.7	1	2.2
Skin and subcutaneous tissue disorders	2	4.7	1	2.2	2	4.7	1	2.2

McGuire et al 2017

JAMA Psychiatry | Original Investigation

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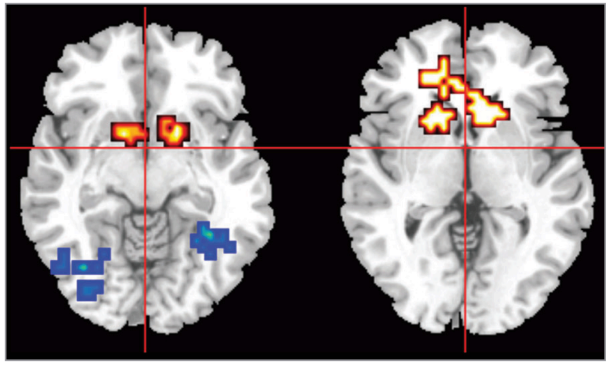
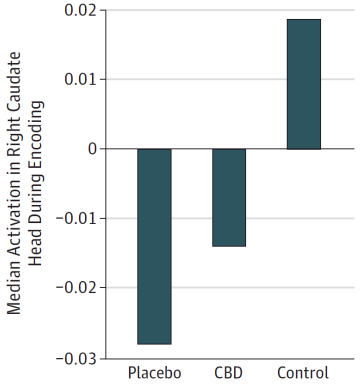
Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis
A Randomized Clinical Trial

Sagnik Bhattacharyya, MBBS, MD, PhD; Robin Wilson, MBBS, MRCPsych; Elizabeth Appiah-Kusi, MSc; Aisling O'Neill, MSc; Michael Brammer, PhD; Jesus Perez, MBBS, MD, PhD; Robin Murray, DSc, FRCPsych, FRS; Paul Allen, PhD; Matthijs G. Bossong, PhD; Philip McGuire, MD, PhD, FRCPsych

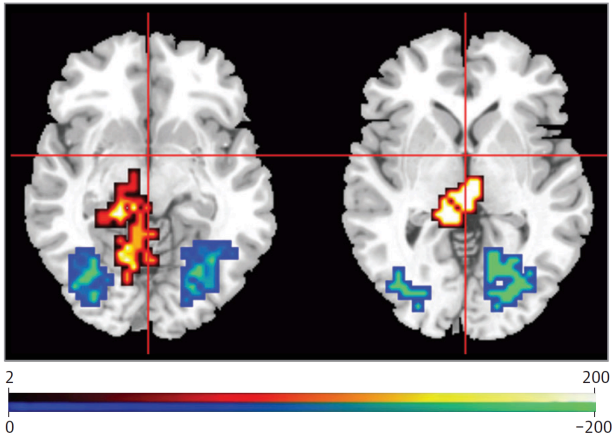
A Activation during encoding



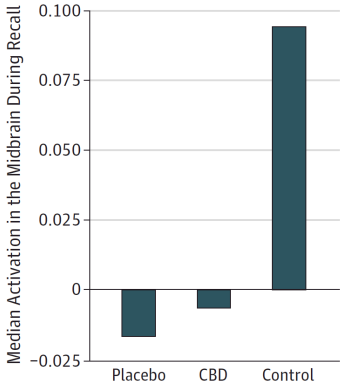
B Activation during encoding by group



C Activation during recall



D Activation during recall by group



Can we start prescribing CBD?

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- Initial evidence **suggests potential** antipsychotic effects across different stages of psychosis (CHR > FEP > chronic)
- However, before it can be licensed there is a need for **large and definitive trials**
- **We are NOT there yet**
- We will run first efficacy RCT in CHR patients in 2020
- Further studies in pipeline

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5 legal status & prescribing

UK legal status

- Cannabis products previously in schedule 1 were rescheduled in 2018 (to schedule 2)
- Can now be prescribed by doctors on GMC specialist register
- Named-patient basis
- Not licensed for specific (psychiatric) indications
- Can be prescribed as a “special”
- Quality certified (good manufacturing practice; GMP)

Table 1| **An overview of cann**

Not NICE-recommended (cost)

FDA-approved; under EMA review

	Canna				inoids for use		Non-medicinal products		
							Non-medicinal CBD products	Non-medicinal cannabis	Non-medicinal synthetic cannabinoids
Example	**Bedrocan**	**Tilray**	**Sativex**	**Epidiolex**	**Dronabinol**	**Nabilone**	**CBD oil[2]**	**White Widow[3]**	**Spice[4]**
Cannabinoid profile	THC +/–CBD	THC +/–CBD	THC:CBD ratio 1:1	CBD	THC	THC	High CBD, low THC	High THC, low CBD	Synthetic cannabinoid receptor agonists
Formulation	Herbal cannabis	Oil	Oromucosal spray	Oral solution	Capsule or liquid	Capsule	Varied; capsule and oil	Varied; herbal cannabis	Herbal, liquid, or powder
Licensed indications (UK)	None	None	Multiple sclerosis	None	None	Chemotherapy induced nausea and vomiting	Not medicinal products		
Quality standards	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	No quality assurance		
Affected by rescheduling (UK) on 1 November 2018?	Yes	Yes	No	No	No	No	No	No	No
Pre-amendment Schedule (UK)	1	1	4	Not scheduled	2	2	Not scheduled (if THC does not exceed 0.2%)	1	1
Post-amendment Schedule (UK)	2	2	4	Not scheduled	2	2	Not scheduled (if THC does not exceed 0.2%)	1	1
Can be prescribed in the UK?	Doctors on General Medical Council specialist register; named patient basis	Doctors on General Medical Council specialist register; named patient basis	Specialist doctors with expertise in treating multiple sclerosis	No restrictions on prescribing; named patient basis. Likely to be a specialist prescribing due to the proposed indications	No restrictions on prescribing; named patient basis	No restrictions on prescribing. Preferably administered in a hospital setting. GPs may prescribe once treatment initiated	No	No	No

Freeman et al 2019

Issues to consider...

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- ✓ Doctors on specialist register
- ✓ Not licensed for any psychiatric indication in UK
- ✓ Provide full info to patient
- ✓ Explain clearly that drug not yet licensed for the condition, no definitive evidence for efficacy, potential side-effects (ideally with care coordinator/others/family present)
- ✓ Document this discussion
- ✓ Don't take decision in first consultation
- ✓ Seek out specialists with experience

Medicinal use of cannabis based products and cannabinoids (in general medicine)

OPEN ACCESS

Tom P Freeman *senior lecturer*[1 2 3 4], Chandni Hindocha *research fellow*[3 4 5], Sebastian F Green *academic foundation doctor*[4], Michael A P Bloomfield *UCL excellence fellow and consultant psychiatrist*[3 4 5 6 7]

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thebmj

Box 2: Managing requests for cannabis based products and cannabinoids

Consider

- Is this indication supported by evidence from randomised clinical trials? (table 2)
- What is the cannabinoid profile of the medicinal product being requested (THC, CBD, THC+CBD?)
- Is this medicinal product available, and who can prescribe it? (table 1)
- Might this medicinal product interact with other prescribed drugs?
- Are specific considerations necessary for young people, children and babies, older people, people with mental health problems, people with a learning disability, pregnant women, and women who are breastfeeding?
- If a prescription is not offered, might this patient seek or use a non-medicinal product lacking safety and quality assurance?

6 What if patients are taking cannabis products from health-food shops?

CBD products bought online / from high-street shops

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- CBD sold as nutraceuticals:
  - not pharmaceutical grade / tested
  - not prepared under GMP conditions

- Unknown **ingredients** / **dose:**
  - 43% contained **more** CBD than labelled
  - 26% contained **less** CBD than labelled

- **THC/other cannabinoids likely present:**
  - THC detected in 21% of CBD samples
  - THC levels sufficient to induce intoxication/impairment

Example H&B CBD oil dose = **20 mg/day**

Freeman et al 2019

clinical CBD dose = **600 to 1000 mg/day**

cannot be sure that over-the-counter products will not be harmful

Bonn-Miller et al 2017

Summary

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- CBD may have beneficial effects in certain psychiatric conditions **– evidence is not yet definitive**
- THC and other cannabinoids in medicinal/recreational cannabis may have harmful effects on mental health
- Risk-benefit analysis on individual case-by-case basis
- Over-the-counter CBD is not regulated, not quality assured and should not be used for medicinal purposes

If you have patients who you would like to refer to take part in our RCTs, please contact us

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Thanks

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Cantop RCT

CANTOP-RCT – Cannabidiol as a Treatment for **Psychosis Clinical High Risk** State – A Randomised Clinical Trial

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CAN-PDP – Cannabidiol for **Parkinson's** Disease Psychosis

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CANBiSAD – A Pilot Trial of Cannabidiol for Behavioural Symptoms in **Alzheimer's** Disease