Medicinal Uses of Cannabis: The Current Status

Cathy Davies, PhD
Postdoctoral Research Associate
Department of Psychosis Studies
Institute of Psychiatry, Psychology & Neuroscience
King’s College London

Presenting on behalf of Dr Sagnik Bhattacharyya
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
Cannabinoids: THC & CBD
History of Cannabis as medicine in the UK

• 1842 – William O’Shaughnessy “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

- Psychoactive
- Anxiogenic
- Psychotomimetic
- Amnestic

Delta-9-tetrahydrocannabinol (THC)

Not psychoactive
Potentially:
- Anxiolytic
- Antipsychotic

Cannabidiol (CBD)
Opposite neural effects of THC & CBD

Memory

Go/No-Go (response inhibition)

Anxiety
Cannabis type & potency

Potter et al 2008
CBD+THC vs pure THC

Nicky Taylor gets injections of both pure THC and pure cannabinoid in order to experience the differences between these two compounds.

This is an extract from the BBC documentary “Should I Smoke Dope” filmed in 2008.

(www.InterCannabis.com)

Morrison et al 2010

NB: “Cannabinoid” here is referring to CBD
What are the outcomes in healthy recreational cannabis users?
Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

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


<table>
<thead>
<tr>
<th>Study (use)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHDS (daily)</td>
<td>1.56 (1.20–2.03)</td>
</tr>
<tr>
<td>ECA (daily)</td>
<td>2.00 (1.27–3.16)</td>
</tr>
<tr>
<td>EDSP (daily)*</td>
<td>2.23 (1.30–3.83)</td>
</tr>
<tr>
<td>NEMESIS (weekly)*</td>
<td>6.81 (1.79–25.91)</td>
</tr>
<tr>
<td>NPMS (dependence)*</td>
<td>1.47 (0.55–3.93)</td>
</tr>
<tr>
<td>Swedish (&gt;50 times)</td>
<td>3.10 (1.72–5.58)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.09 (1.54–2.84)</td>
</tr>
</tbody>
</table>
Psychosis

“Ever used”
OR = 1.97

“Most severe users”
OR = 3.90

Psychosis risk distribution

Tien 1990
Degenhardt 2001
Zammit 2002
Arseneault 2002
Henquet 2005
Wiles 2006
Miettunen 2008
McGrath 2010
Zammit 2011
GAP data 2012

Cannabis Exposure
Depression

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

Tabea Schoeler1,*, Delphine Theobald2,*, Jean-Baptiste Pingault1, David P. Farrington3, Jeremy W. Coid4 and Sagnik Bhattacharyya5

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. Schoeler4†, D. Theobald1,2†, J.-B. Pingault3, D. P. Farrington4, W. G. Jennings5, A. R. Piquero6, J. W. Coid7 and S. Bhattacharyya4*

OR = 7.08 (2.19 – 23.59)
What are the outcomes in patients with psychosis using cannabis?
Relapse in psychosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negrete et al (1986)</td>
<td>0.80 (0.32 to 1.28)</td>
</tr>
<tr>
<td>Peralta and Cuesta (1992)</td>
<td>-0.14 (-0.61 to 0.33)</td>
</tr>
<tr>
<td>Martinez-Arevalo et al (1994)</td>
<td>0.46 (-0.21 to 1.12)</td>
</tr>
<tr>
<td>Linszen et al (1994)</td>
<td>0.45 (0.03 to 0.87)</td>
</tr>
<tr>
<td>Caspari (1999)</td>
<td>1.04 (0.57 to 1.52)</td>
</tr>
<tr>
<td>Salyers and Mueser (2001)</td>
<td>0.37 (0.05 to 0.69)</td>
</tr>
<tr>
<td>Bersani et al (2002)</td>
<td>-0.07 (-0.43 to 0.28)</td>
</tr>
<tr>
<td>Sorbaro et al (2003)</td>
<td>0.62 (0.02 to 1.22)</td>
</tr>
<tr>
<td>Maremmani et al (2004)</td>
<td>-0.08 (-0.50 to 0.34)</td>
</tr>
<tr>
<td>Isaac et al (2005)</td>
<td>0.62 (0.24 to 1.01)</td>
</tr>
<tr>
<td>Wade et al (2006)</td>
<td>0.87 (0.41 to 1.33)</td>
</tr>
<tr>
<td>Jockers-Scheruebl et al (2007)</td>
<td>-0.40 (-1.03 to 0.24)</td>
</tr>
<tr>
<td>Rehman and Farooq (2007)</td>
<td>0.40 (0.00 to 0.79)</td>
</tr>
<tr>
<td>Beaza et al (2009)</td>
<td>0.00 (-0.56 to 0.56)</td>
</tr>
<tr>
<td>Ringen et al (2010)</td>
<td>0.20 (-0.13 to 0.53)</td>
</tr>
<tr>
<td>Rentzsch et al (2011)</td>
<td>0.25 (-0.29 to 0.79)</td>
</tr>
<tr>
<td>González-Pinto et al (2009)</td>
<td>0.58 (0.07 to 1.09)</td>
</tr>
<tr>
<td>van Dijk et al (2012)</td>
<td>0.38 (0.05 to 0.71)</td>
</tr>
<tr>
<td>San et al (2012)</td>
<td>0.25 (0.13 to 0.36)</td>
</tr>
<tr>
<td>Faridi et al (2012)</td>
<td>0.04 (-0.53 to 0.61)</td>
</tr>
<tr>
<td>Barrowclough et al (2013)</td>
<td>0.33 (0.11 to 0.55)</td>
</tr>
<tr>
<td>Sara et al (2014)</td>
<td>0.92 (0.88 to 0.96)</td>
</tr>
<tr>
<td>Koenders et al (2014)</td>
<td>0.20 (-0.18 to 0.57)</td>
</tr>
<tr>
<td>van der Meer and Velthorst (2015)</td>
<td>0.23 (0.03 to 0.43)</td>
</tr>
</tbody>
</table>

Random effects model continued use versus non-use (n=16157)

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

- More relapses
- More severe relapses
- Shorter times to relapse
- Longer durations of hospital stay

![Graph showing the proportion of relapsed patients over months following the onset of psychosis for different cannabis use categories. The x-axis represents months following the onset, ranging from 0 to 24, and the y-axis represents the proportion of relapsed patients, ranging from 0 to 100. The graph includes lines for never (regular) user, intermittent user, continued user (Hash-type), continued user (Skunk-like/low-frequency), continued user (Skunk-like/high-frequency), and former (regular) user. Each category has a p-value indicating statistical significance.]

29 additional days in hospital
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

Leweke et al 2012

Similar efficacy
Side-effects

CBD displayed a markedly superior side-effect profile

---

**Figure a:**
- Change in EPS over time on treatment.
- CBD and AMI comparisons.
- Significant differences indicated with symbols: 
  - **#** p < 0.05
  - **##** p < 0.01
  - **###** p < 0.001

**Figure b:**
- Weight gain over time on treatment.
- CBD and AMI comparisons.
- Significant differences indicated with symbols: 
  - **##** p < 0.001

**Figure c:**
- Change in prolactin over time on treatment.
- CBD and AMI comparisons.
- Significant differences indicated with symbols: 
  - **+++** p < 0.001

Leweke et al 2012
Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial


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

p=.019

p=.018
Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial

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)

<table>
<thead>
<tr>
<th>System Organ Class and Preferred Terma</th>
<th>All Causes</th>
<th>Treatment Related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cannabidiol Group (N=43)</td>
<td>Placebo Group (N=45)</td>
</tr>
<tr>
<td>At least one event</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>9</td>
<td>20.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>7.0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3</td>
<td>7.0</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>7.0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3</td>
<td>7.0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration</td>
<td>2</td>
<td>4.7</td>
</tr>
<tr>
<td>site conditionsb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigationsc</td>
<td>2</td>
<td>4.7</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2</td>
<td>4.7</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>2</td>
<td>4.7</td>
</tr>
</tbody>
</table>

McGuire et al 2017
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
Can we start prescribing CBD?

- 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
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>
<thead>
<tr>
<th>Example</th>
<th>Bedroc</th>
<th>Tilray</th>
<th>Sativex</th>
<th>Epidiolex</th>
<th>Dronabinol</th>
<th>Nabilone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoid profile</td>
<td>THC +/-CBD</td>
<td>THC +/-CBD</td>
<td>THC:CBD ratio 1:1</td>
<td>CBD</td>
<td>THC</td>
<td>THC</td>
</tr>
<tr>
<td>Formulation</td>
<td>Herbal cannabis</td>
<td>Oil</td>
<td>Oromucosal spray</td>
<td>Oral solution</td>
<td>Capsule or liquid</td>
<td>Capsule</td>
</tr>
<tr>
<td></td>
<td>Variied; capsule and oil</td>
<td>Varied; herbal cannabis</td>
<td>Herbal, liquid, or powder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed indications (UK)</td>
<td>None</td>
<td>None</td>
<td>Multiple sclerosis</td>
<td>None</td>
<td>None</td>
<td>Chemotherapy induced nausea and vomiting</td>
</tr>
<tr>
<td>Quality standards</td>
<td>Good manufacturing practice</td>
<td>Good manufacturing practice</td>
<td>Good manufacturing practice</td>
<td>Good manufacturing practice</td>
<td>Good manufacturing practice</td>
<td>Good manufacturing practice</td>
</tr>
<tr>
<td>Affected by rescheduling (UK) on 1 November 2018?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pre-amendment Schedule (UK)</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>Not scheduled</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Post-amendment Schedule (UK)</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>Not scheduled</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Can be prescribed in the UK?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Issues to consider...

✓ 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)

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

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?
What if patients are taking cannabis products from health-food shops?
CBD products bought online / from high-street shops

- 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

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

Freeman et al 2019
Summary

- 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
Contact: Dr Cathy Davies
cathy.davies@kcl.ac.uk

Principal Investigator: Dr Sagnik Bhattacharyya
sagnik.2.bhattacharyya@kcl.ac.uk

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

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

PARKINSON’S UK
CHANGE ATTITUDES. FIND A CURE. JOIN US.
CAN-PDP – Cannabidiol for Parkinson’s Disease Psychosis

NIHR | National Institute for Health Research

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