This house believes that cannabis is an efficacious and safe analgesic for neuropathic pain

Against: Andrew SC Rice
Conflict of Interest Declaration

• ASCR is a member of the European Commission funded collaboration “NEUROPAIN” which includes as a partner GW Pharma

• ASCR is co-inventor on patent Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain. WO 2005/079771

• In the last 24 months ASCR has received consultancy fees and associated expenses (contracted via Imperial College Consultants) from: Astellas, Relmada, Medivir, Asahi Kasei Pharma and Spinifex

• ASCR is owner of share options in Spinifex

• ASCR is a member of the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) Innovative Medicines Initiative collaboration: EUROPAIN. This includes direct research funding from Pfizer and Astellas and collaborative relationships with other companies in the consortium

• ASCR also has current/recent grant funding from: European Union, Wellcome Trust, Medical Research Council, NC3Rs, Dunhill Medical Trust and the International Association for the Study of Pain

• ASCR is currently Chair of NeuPSIG
• Medicinal cannabis use is illegal in nearly all jurisdictions.

• Doctors cannot legally prescribe cannabis in any jurisdiction because it has not received regulatory approval, although in a small number of jurisdictions (eg in some US states) doctors may “recommend” its use. (Farrell et al 2014)

• Although sativex/naxibimols has been granted regulatory approval for the relief of MS spasticity in several countries, only in Canada and Israel is it approved for the relief of neuropathic pain in MS.

• Unaware of any cannabinoid which has been approved for more general use in neuropathic pain.
This house believes that cannabis is an efficacious and safe analgesic for neuropathic pain.
FDA Has Not Approved Smoked Marijuana For Any Condition Or Disease Indication

- …no animal or human data supported the safety or efficacy of marijuana for general medical use.
- …There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana.
- …Marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision.

- FDA is the sole Federal agency that approves drug products as safe and effective for intended indications. … requires new drugs be shown to be safe and effective for their intended use before being marketed in this country.
- Efforts that seek to bypass the FDA drug approval process would not serve the interests of public health because they might expose patients to unsafe and ineffective drug products.
- A growing number of states have passed voter referenda … making smoked marijuana available for a variety of medical conditions upon a doctor's recommendation. These measures are inconsistent with efforts to ensure that medications undergo the rigorous scientific scrutiny of the FDA approval process and are proven safe and effective ….

- …Accordingly, FDA, DEA and the Office of National Drug Control Policy, do not support the use of smoked marijuana for medical purposes.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108643.htm; reaffirmed Apr. 9, 2014 email to ProCon.org from the FDA

Map-of-US-state-cannabis-laws
- States with medical cannabis laws only
- States with marijuana decriminalization laws only
- States with both decriminalization and medical cannabis laws
- States with both medical marijuana laws and legalized recreational cannabis
Against: This house believes that cannabis is an efficacious and safe analgesic for neuropathic pain

- There are strong pre-clinical data supporting the concept of cannabinoid mediated analgesia

- Selected clinical trials support or refute the concept of efficacy of cannabinoids in selected clinical pain states. However, this evidence is currently insufficient to recommend the use of cannabinoids in neuropathic pain.

- Is cannabis safe, especially given literature on long-term psychiatric and cognitive adverse effects?

- Do therapeutic preparations of cannabis have mis-use potential, including “diversion” to street use?

- Strategies are being pursued for development of cannabinoid-related therapeutics, that have the potential to avoid the above limitations and have an acceptable therapeutic index.
Clinical Evidence of Efficacy
In patients with neuropathic pain, is treatment with a cannabinoid for at least three weeks more likely to result in reduction in pain intensity than treatment with placebo?

**GRADE recommendation:**

• Weak recommendation against use of cannabinoids in NP on grounds of generally negative results and potential safety concerns.
The effectiveness of cannabinoids for the treatment of muscle spasticity or neuropathic pain in multiple sclerosis is unclear and any benefit is likely to be modest, while mild to moderate adverse events are common and long term safety has not been established.

The effectiveness of cannabinoids for the treatment of other neuropathic pain has not been proved.
Harm
Harm

• Minor adverse events are frequent in cannabinoid trials (NNT~NNH)

• But serious adverse event sufficient to cause patient withdrawal from trial are rare
Short Term Adverse Events in RCTs
Wang et al *CMAJ* 2008;178:1669-1678

- Systematic review of 23 short term RCTs for adverse events
- Median duration of treatment 2 weeks [8 hrs - 12 months]
- IHC definition of adverse event
- 1932 people exposed to cannabinoid (1121 placebo)
- No evidence of higher rate for serious adverse events (rate ratio 1.04)
- Most frequent minor AEs:
  - 37% Nervous system
  - 16% Gastrointestinal
  - 11% Psychiatric
Long Term Adverse Events: 
Association Between Cannabis Use and Psychosis

Case-crossover analysis.
**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Cannabis use is associated with increased risk for psychotic disorder

The temporal association between cannabis use and the onset of psychotic symptoms, as well as the mechanism by which cannabis use leads to psychotic disorder, remain unknown

**WHAT THIS STUDY ADDS**

Cannabis use precedes the onset of psychotic symptoms in individuals with no history of psychotic experiences; incident cannabis use was associated with incident psychotic experiences four years later

Continued use of cannabis might increase the risk for psychotic disorder by impacting on persistence of (normally transitory) psychotic experiences in young people
Influence of Frequency of Exposure to Cannabis on Development of Cannabis-Associated Psychosis

Cannabis use and incidence of schizophrenia in 42,360 military conscripts followed for 26 years
Zammit et al BMJ 2002;325:1199

Cannabis use and incidence of > 2 psychosis symptoms in 2437 adolescents followed for 4 years
Henquet et al BMJ 2005;330:11-16
**Cannabis Dose & Psychosis Risk**


- **Resin (hashish)**
  - 2000: 70% of abuse market
  - 2–4% $\Delta 9$-THC
- **Sinsemilla (skunk)**
  - 2008: >70% of abuse market
  - 12–18% $\Delta 9$-THC with virtually no cannabidiol

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### Table 3 Patterns of cannabis use

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Cases, n = 159</th>
<th>Controls, n = 109</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>0-5 years</td>
<td>65 (40.8)</td>
<td>68 (62.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Over 5 years</td>
<td>94 (59.2)</td>
<td>41 (37.5)</td>
<td>2.4 (1.2–4.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of use</th>
<th>Cases, n = 159</th>
<th>Controls, n = 109</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than every day</td>
<td>37 (23.1)</td>
<td>73 (66.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Every day</td>
<td>122 (76.9)</td>
<td>36 (33.3)</td>
<td>6.7 (2.0–11.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type used</th>
<th>Cases, n = 159</th>
<th>Controls, n = 109</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resin (hashish)</td>
<td>34 (21.6)</td>
<td>68 (62.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sinsemilla (skunk)</td>
<td>125 (78.4)</td>
<td>41 (37.4)</td>
<td>8.1 (4.6–13.5)</td>
</tr>
</tbody>
</table>

CBD, cannabidiol; $\Delta 9$-THC, $\Delta 9$-tetrahydrocannabinol

* Adjusted for age, gender, ethnicity, other stimulant use, level of education achieved and employment status.

*P* < 0.05.
Baseline Psychosis Predisposition & Risk of Cannabis-Associated Psychosis

2436 Adolescents Followed for 4 Years

Henquet et al BMJ 2005;330:11-16

Table 4 Interactions between any cannabis use and predisposition for psychosis

<table>
<thead>
<tr>
<th>Cannabis use at baseline</th>
<th>No with psychosis outcome*</th>
<th>No without psychosis outcome*</th>
<th>Risk of psychotic symptoms at follow up</th>
<th>Difference in risk Unadjusted</th>
<th>Difference in risk Adjusted† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No predisposition for psychosis at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>294</td>
<td>1042</td>
<td>15%</td>
<td>6%</td>
<td>5.6% (0.4 to 10.8) P=0.033</td>
</tr>
<tr>
<td>Any (≥5 times)</td>
<td>59</td>
<td>216</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predisposition for psychosis at baseline‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>47</td>
<td>133</td>
<td>26%</td>
<td>25%</td>
<td>23.3% (7.9 to 39.7) P=0.003</td>
</tr>
<tr>
<td>Any (≥5 times)</td>
<td>23</td>
<td>22</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*DNumbers total 2436 because of one missing value on predisposition for psychosis at baseline.
†Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at follow up. Test for additive interaction 18.2% adjusted difference in risk (95% confidence interval 1.6 to 34.6), P=0.032 (tests whether risk difference in “predisposition” group is significantly greater than risk difference in “no predisposition” group).

Nb. predisposition to psychosis at baseline does not predict cannabis use, thus refuting self-medication hypothesis
Influence Of Genetic Polymorphism On Cannabis-Associated Psychosis Risk

Dunedin cohort (n=1,037) followed from birth (1972/1973) to age 38

Cannabis use ascertained by interview at 5 points ages 18-38

Neuropsychological testing conducted at:
  - 13 yr before initiation of cannabis use
  - 38 yr after a pattern of persistent cannabis use had developed
Persistent cannabis users show neuropsychological decline from childhood to midlife


- Persistent cannabis use associated with broad neuropsychological decline across domains, even after controlling for years of education
- Informants also reported noticing more cognitive problems for persistent cannabis users
- Persistent cannabis use associated with greater decline
- Impairment concentrated among adolescent-onset cannabis users
- Cessation of cannabis use did not fully restore neuropsychological function in adolescent-onset cannabis users
Lessons from Rimonabant (SR141617a)

- CB₁ antagonist (inverse agonist)
- Developed for obesity & smoking cessation
- EMEA & FDA approval for obesity 2006
- Withdrawn 2009
  - Suicidality, depression and other psychiatric AEs

Christensen et al Lancet 2007;370:1706
Implications of Adverse Effects of Cannabis Mis-use For Therapeutic Use of Cannabis
Rice ASC Nature Clinical Practice Neurology 2008;4:654-655

- There is a dose-dependant risk of psychotic illness associated with cannabis abuse and risk factors have been identified.

- Cannabis use is associated with risk of long term decline in cognitive function, especially in adolescent-onset users.

- The relevance of this risk for long term regular therapeutic users of cannabinoids at doses required for analgesic efficacy is unknown.

- For RCTS of cannabinoids:
  - Informed consent for RCT subjects should be explicit on mental health risks
  - Subjects with psychosis risk factors should be excluded from RCTs
  - RCTs should focus on analgesic efficacy of non-psychoactive/non brain penetrant cannabinoids and be of sufficient power and duration to detect such AEs
  - Long term follow up of subjects required
Abuse/Diversion Potential Of Potent Brain Penetrant Cannabinoids Oro-Mucosal Spray?
Policy analysis

Prescription opioid misuse in the United States and the United Kingdom: Cautionary lessons

Daniel F. Weisberg\textsuperscript{a,1}, William C. Becker\textsuperscript{b,a}, David A. Fiellin\textsuperscript{a}, Cathy Stannard\textsuperscript{c,*}

\textsuperscript{a} Yale University School of Medicine, Department of Internal Medicine, New Haven, CT, United States
\textsuperscript{b} VA Connecticut Healthcare System, West Haven, CT, United States
\textsuperscript{c} Macmillan Centre Frenchay Hospital, Bristol, UK
The Future: Improving Therapeutic Index Of Cannabinoids

Divorcing Analgesia From Psychoactive Properties

- CB₁
  - Brain
  - Spinal Cord
  - Peripheral

- CB₂
  - Peripheral immune cells
  - Keratinocytes

- Non-psychotropic “cannabinomimetics”
  - Palmitoylethanolamide & analogues

- FAAH or MGL inhibitors
PEA Analogue Palmitoylallylamide (L-29) Attenuates Hypersensitivity and Thigmotaxis in Models of Traumatic, Varicella & Antiretroviral Neuropathy


Mechanical

Heat

Cold

Time spent in inner zone

Total distance moved

Vehicle

L 29
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Hippocratic Oath

• I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone.

• I will give no deadly medicine to any one if asked, nor suggest any such counsel.
A Framework for Cannabinoid Analgesia

- Brain
- Spinal Cord
- Periphery
Multiple Physiological Roles of Endocannabinoids

The “Cannabinoid Tetrad”

- Hypothermia
- Hypolocomotion
- Catalepsy
- Analgesia

• For example:
  - Memory
  - Analgesia
  - Locomotion
  - Thermoregulation
  - Appetite control
  - Immune response