CANNABIS AND PSYCHOSIS:
THE ROLE OF HIGH POTENCY CANNABIS

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1985 Skunk (High Potency cannabis) arrives in Europe

T. Leggett UNODC Bulletin on Narcotics Volume LVIII, Nos. 1 and 2, 2006

Around 1985, during the era when then President Ronald Reagan began a crackdown on illegal drugs in the United States, the Skunkman brought the best in American cannabis breeding to a location where he could experiment with his plants a little more openly: Amsterdam.

The Skunkman is said to be the father of “skunk”—a smelly hybrid of three distinct and previously uncrossed cannabis genetic lines.

At the time, indoor cultivation of cannabis was just starting to take off in the Netherlands, so he joined up with a number of local cannabis experts and the “breeding revolution” in Amsterdam began.
Skunk Sam (David Watson)
UK Sensimilla=SKUNK

Female plant with no seeds as crops are grown not exposed to pollens

Glandular Trichomes which contain the cannabinoids
Organoleptic properties:
Very smelly=SKUNK
Skunk=Sinsemilla is the female plant with no seeds as crops are grown not exposed to pollens

Effect of ‘skunk’ genetics on UK cannabis sativa

Wispy plant from seed in imported herbal: 6% THC

High yielding potent skunk plant of a modern variety made in UK: 18% THC
Preparing for use!

To prepare sinsemilla/Skunk herbal cannabis for smoking:
1. Grinders for the trichomes to produce the powders: this increases the THC % up to 3 fold.

2. Trichome separation and collection can also be performed in water; the Trichome’s contents harden and separation of the resin heads is facilitated (Jansen and Terris, 2002). By using high-THC sinsemilla cannabis, the resin material produced is high in THC. Cannabidiol is almost totally absent. This can reach up to 60% THC and it is known as “modern hashis”
Skunk - Made in England

MY NEIGHBOUR IS REALLY INTO THIS HIGH-TECH THING. FOR DAYS HE'S BEEN BRINGING IN WIRES, CABLES, LIGHTS AND FANS. HE'S SUCH A HARD WORKER, TOO.

... THE LIGHTS ARE ON ALL NIGHT.
### Table 2: Cannabis use

<table>
<thead>
<tr>
<th></th>
<th>First-episode psychosis group (n=410)</th>
<th>Control group (n=370)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime history of cannabis use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>275 (67%)</td>
<td>232 (63%)</td>
<td>0.277</td>
</tr>
<tr>
<td>No (never used)</td>
<td>135 (33%)</td>
<td>138 (37%)</td>
<td></td>
</tr>
<tr>
<td>Frequency of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once per week</td>
<td>68 (17%)</td>
<td>128 (35%)</td>
<td></td>
</tr>
<tr>
<td>At weekends</td>
<td>84 (20%)</td>
<td>83 (15%)</td>
<td></td>
</tr>
<tr>
<td>Every day</td>
<td>123 (30%)</td>
<td>41 (11%)</td>
<td></td>
</tr>
<tr>
<td>Most used type of cannabis</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never used</td>
<td>135 (33%)</td>
<td>138 (37%)</td>
<td></td>
</tr>
<tr>
<td>Hash-like</td>
<td>57 (14%)</td>
<td>162 (44%)</td>
<td></td>
</tr>
<tr>
<td>Skunk-like</td>
<td>218 (53%)</td>
<td>70 (19%)</td>
<td></td>
</tr>
<tr>
<td>Cannabis users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of use (years)</td>
<td>9.7 (7.4)</td>
<td>9.1 (7.8)</td>
<td>0.635</td>
</tr>
<tr>
<td>No details</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age at first cannabis use (years)</td>
<td>16.1 (4.2)</td>
<td>16.6 (3.2)</td>
<td>0.146</td>
</tr>
<tr>
<td>No details</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age at first use ≥15 years</td>
<td></td>
<td></td>
<td>0.028</td>
</tr>
<tr>
<td>No</td>
<td>172 (63%)</td>
<td>178 (77%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100 (36%)</td>
<td>53 (23%)</td>
<td></td>
</tr>
<tr>
<td>No details</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD) unless stated otherwise.

**SLAM**: South London and Maudsley Mental Health NHS Trust

THC: tetrahydrocannabinol
Skunk and its frequency of use

First episode Psychosis Patients=410
Controls=370

Di Forti et al. Lancet Psychiatry 2015

Figure 2: Probability of individuals having a psychotic disorder by pattern of cannabis use
OR adjusted for age, gender, ethnic origin, education, employment status, and tobacco use. OR=odds ratio.
*p<0.05.
Daily skunk users experience their onset 6 years earlier than never users.
Two of the 100 active ingredients of cannabis

- **Tetrahydrocannabinol (THC)** – partial agonist at CB1
  - Impairment of attention, memory and learning
  - Hallucinations and paranoid ideas

- **Cannabidiol (CBD)**
  - Is not hallucinogenic
  - Has anxiety relieving properties
  - Antipsychotic actions?
  - Antagonise effects of THC?
The ingredients of cannabis

- THC causes
  - Impairment of attention, memory and learning
  - Hallucinations and paranoid ideas

- Cannabidiol (CBD)
  - Is not hallucinogenic
  - Has anxiety relieving properties
  - No adverse effect on cognition

THC: tetrahydrocannabinol.
Psychotogenic effect of acute administration of 2.5 mg of IV tetrahydrocannabinol (THC)

THC induces transient psychotic symptoms

Cannabidiol (CBD) blocks the effects of THC

Paul Morrison et al. 2009; Bhattacharyya et al. 2010.
If the type of cannabis consumed differentially affects individual risk to develop psychosis, does it also have an effect at a population level?
Population Attributable Fraction (PAF)

1. The PAF measures the population effect of an exposure by providing an estimate of the proportion of disorder that would be prevented if the exposure were removed.

1. Causality does not have to be proven before the PAF can be estimated, and this causation is not usually established when PAFs are estimated (indeed no single study could ever prove causation).

1. Because the same proportion of disorder attributable to a specific risk factor can also be attributable to other factors with which the specific risk factor might interact, PAFs for multiple risk factors can add up to more than 100%.

2. Furthermore, the PAF depends on both the prevalence of exposure (ie, measures of cannabis use) in cases and the odds ratio (OR) for the exposure, such that a risk factor with a modest OR can have a major population effect if the factor is common.
Cannabis causing a quarter of psychosis

NEW YORK BOWS TO BECKHAM

Labour may ban private government contracts

Population attributable fraction (95% CI)
0% (13.1–27.0)
0% (17.4–30.6)
0% (14.0–20.3)
Because, the strongest evidence for an effect of cannabis use on risk of clinical psychosis derives from populations where most cannabis use would have been either resin cannabis or relatively low-potency herbal strains (Moore et al., 2007)

An alternative explanation:

Could it be that when skunk became available, a sub-group already at high risk of psychosis may have selected to use this form of cannabis. Therefore, while it is certainly plausible that use of skunk could be causally associated with psychosis, it is important to consider alternative explanations for the associations observed ???
Imported herbal cannabis and Hash

Moroccan Hash = 0.9%-10% THC
Pakistani = 2.4%-15% THC
India = 10-26% THC
Netherland up to 59% THC
Are skunk users genetically different from hash users? Polygenic Risk Score quartiles for p value threshold= 0.05

<table>
<thead>
<tr>
<th>4PRS_{T=0.05} quartiles</th>
<th>OR for psychosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRS0</td>
<td>1</td>
</tr>
<tr>
<td>PRS1</td>
<td>1.9 (0.964- 3.79)</td>
</tr>
<tr>
<td>PRS2</td>
<td>3.0 (1.49- 5.96)</td>
</tr>
<tr>
<td>PRS3</td>
<td>7.0 (3.46-14.25)</td>
</tr>
</tbody>
</table>

There is no correlation between Polygenic Risk Score and type of cannabis used

\[ Pearson \, chi^2(3) = 1.0317 \quad Pr = 0.794 \, (controls) \]
\[ Pearson \, chi^2(3) = 5.6001 \quad Pr = 0.133 \, (whole \, sample) \]
Are skunk users less intelligent than hash users?

- No difference in premorbid IQ, NART
  \[ t = -0.7376; p=0.4639 \]
  Hash users mean Premorbid IQ= 95.6
  Skunk users Premorbid IQ=97.2
- Incidence Psychoses cases across 5 EU site N=1010
  61.4% males; mean age 30.7 (10.9)

Ethnic breakdown
- White 66.7%
- Black 11.5%
- Others* 21.8%

* Asian/North African/Mixed

- Population Controls across the same 5 sites N=1383
  46.3% males; mean age 36.1 (13.3)

Ethnic breakdown
- white 79.6%
- Black 6%
- Others 14.4%
Population Attributable Fraction (PAF) for daily cannabis use and Incidence for Schizophrenia and other Psychosis

C-Incidence=18.9
L-Incidence=63.9
Incidence-NL=40
F-Incidence=26
SP-Incidence=21.8
I-Incidence=24.4
P-Incidence=12.8
Does cannabis use contribute to such differences?

![Bar chart showing lifetime cannabis use percentage in different locations: London (85%, case), Cambridge (63%, case), NL (80%, case), Spain (65%, case), France (55%, case), Italy (53%, case), Palermo (62%, case).]
....Does cannabis use contribute to such differences?

**Y= Incidence rates**

Lifetime cannabis use % in controls across the different countries
Use of High Potency Cannabis: TCH>10%

- **p<0.001
- *p<0.05

OR Adj for age, gender, ethnicity

Use of High Potency Cannabis

- London: 39%
- Cambridge: 12%
- NL: 53%
- Spain: 29%
- France: 27%
- Italy: 21%
- Palermo: 28%

Use of High Potency Cannabis Adj-OR

- London: 8.6
- Cambridge: 4.3
- NL: 7.2
- Spain: 1.7
- France: 2.9
- Italy: 0.8
- Palermo: 0.9

**L-PAF=34%**

**NL-PAF=45%**

**F-PAF=18%**
What do we need?

1. Public education

2. Improve training of primary care and secondary care staff

3. Appropriate integrated services for dual diagnosis patients. More collaboration with Addiction colleagues

4. Better understanding of the underlying biology to optimise pharmacological treatment
Last but not least

My gratitude to:
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patients