Marijuana, high potency cannabis, and synthetic cannabinoids: increasing risk for psychosis?

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Callaghan et al followed up methamphetamine abusers admitted to hospital in California and showed that they had a ninefold increase of subsequent schizophrenia.

American Journal of Psychiatry, 2012
Psychopathology of individuals with methamphetamine psychosis

Patients 100
(\%)

0  20  40  60  80  100

Chen et al 2003

Auditory hallucinations
Delusions of persecution
Delusions of reference
Visual hallucinations
Reading their minds
Thought insertion
Odd speech

Patients (%)

n=163

Chen et al 2003
Other stimulants which increase risk of psychosis

Methylmethylcathinone (MMCat or miew-miew)

Khat - Cathinone

Methylmethylcathinone (MMCat or miew-miew)
Which drug do you have to use to become President?
Swedish Army Study of Andréasson et al 1987

Risk of psychosis in relation to extent of cannabis use

\[ \text{OR} = 3.9 \]

Marconi et al Schiz Bull 2016

### Cohort Studies

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>FU</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>50,053</td>
<td>25 yrs</td>
<td>3.1</td>
</tr>
<tr>
<td>NL</td>
<td>4,045</td>
<td>3 yrs</td>
<td>2.8</td>
</tr>
<tr>
<td>NL</td>
<td>4,045</td>
<td>3 yrs</td>
<td>12.0</td>
</tr>
<tr>
<td>NL</td>
<td>18,000</td>
<td>Retro</td>
<td>3.2</td>
</tr>
<tr>
<td>NZ (Chr)</td>
<td>1,265</td>
<td>3 yrs</td>
<td>1.8</td>
</tr>
<tr>
<td>NZ (Dun)</td>
<td>1,253</td>
<td>15 yrs</td>
<td>3.1</td>
</tr>
<tr>
<td>Germany</td>
<td>2,436</td>
<td>4 yrs</td>
<td>1.7</td>
</tr>
<tr>
<td>UK</td>
<td>8,500</td>
<td>18 mths</td>
<td>1.5</td>
</tr>
<tr>
<td>Australia</td>
<td>3,800</td>
<td>14 yrs</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Risk of schizophreniform psychosis at age 26 years

Arseneault et al BMJ 2002
IV administration of 2.5 mg of Tetrahydrocannabinol (THC) induces transient psychotic symptoms.

Morrison et al, 2009
121 schizotypal individuals were randomised to receive THC or placebo

Mean (S.D.) Paranoia Score
after Placebo  6.8 (9.8)
after THC 15.6 (17.3)

Dan Freeman et al, Schiz Bull, 2014
The 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?
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

Cannabidiol as an Antipsychotic?

Present:

1. Sativex for MS
2. Dronabinol (synthetic version of THC) for appetite loss and to relieve nausea,
3. Nabilone for nausea

Future:

CBD-based drug called Epidiolex (cannabidiol) is in phase III trials for two rare forms of epilepsy.

Several other drugs are in phase II trials: THC and CBD to treat glioma brain cancer, THCV for type 2 diabetes and CBD for schizophrenia.

GW Pharmaceuticals Announces Positive Proof of Concept Data in Schizophrenia
15 September 2015

Placebo-controlled trial of addition of Cannabidiol (CBD) to standard antipsychotic in 88 patients with schizophrenia who had previously failed to respond adequately.

CBD was consistently superior to placebo, with the most notable differences being in the PANSS positive sub-scale (p=0.018).
Increase in the potency of cannabis – the development of skunk!

When Ronald Reagan began a crackdown on illegal drugs, Tom Watson (the Skunkman) fled the USA in 1985 and brought his seeds to Amsterdam where he could experiment with his plants more openly.

Indoor cultivation of cannabis was just starting to take off in the Netherlands, so he joined up with local cannabis experts to “breed” more potent plants.

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

T. Leggett UNODC Bulletin on Narcotics Volume LVIII, Nos. 1 and 2, 2006
Cannabis potency in England


THC content (%)

0 2 4 6 8 10 12 14


- Skunk
- Imported Herbal
- Resin

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
Case-control study of cannabis and psychosis

- 410 patients in their 1st episode of psychosis.
- 370 population-based healthy controls (screened for psychosis)

All interviewed using the cannabis experience questionnaire

Di Forti et al, BJPsych 2009; Schiz Bull 2013
Patterns of Cannabis Use

<table>
<thead>
<tr>
<th></th>
<th>Ever used (%)</th>
<th>Daily (%) users</th>
<th>Skunk (%) users</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode Psychosis (n=410)</td>
<td>63.3</td>
<td>46.1</td>
<td>80.9</td>
</tr>
<tr>
<td>Controls (n=370)</td>
<td>63.4</td>
<td>18.7</td>
<td>42.6</td>
</tr>
<tr>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</table>
Skunk and its frequency of use

![Graph showing the risk of first-episode psychosis by pattern of cannabis use.](image)

**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.

Di Forti et al. Lancet Psychiatry 2015
Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study
Are cannabis using schizophrenics different from non using schizophrenics?

Users have an earlier onset
Users have a higher IQ
Users have better pre-morbid social functioning
If cannabis using psychotic patients are a discrete group, they should be different from non-using psychotic patients.

Users had an earlier onset of psychosis.

Users had a higher pre-morbid IQ and better pre-morbid social function.

Continued users had a worse outcome.

Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users

Marta Di Forti, Hannah Sallis, Fabio Allegri, Antonella Trotta, Laura Ferraro, Simona A. Stilo, Arianna Marconi, Caterina La Cascia, Tiago Reis Marques, Carmine Pariante, Paola Dazzan, Valeria Mondelli, Alessandra Paparelli, Anna Kolliakou, Diana Prata, Fiona Gaughran, Anthony S. David, Craig Morgan, Daniel Sthal, Mizanur Khondoker, James H. MacCabe, and Robin M. Murray
Cannabis Use and Earlier Onset of Psychosis

A Systematic Meta-analysis

Matthew Large, BSc(Med), MBBS, FRANZCP; Swapnil Sharma, MBBS, FRANZCP; Michael T. Compton, MD, MPH; Tim Slade, PhD; Olav Nielssen, MBBS, MCrIIM, FRANZCP

Context: A number of studies have found that the use of cannabis and other psychoactive substances is associated with an earlier onset of psychotic illness.

Data Synthesis: Meta-analysis found that the age at onset of psychosis for cannabis users was 2.70 years younger (standardized mean difference = −0.414) than for nonusers for those with broadly defined substance use. The age

Daily use and skunk use bring onset further
Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Tabea Schoeler, Anna Monk, Musa B Sami, Ewa Klamerus, Enrico Foglia, Ruth Brown, Giulia Camuri, A Carlo Altamura, Robin Murray, Sagnik Bhattacharyya

Interpretation Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.
Incidence of First Episode Psychosis across 16 sites - ranged from 12.0 per 100,000 person years in Palermo to 63.9 per 100,000 in London.

- Cambridge: 19
- London: 64.9
- Netherlands: 40
- France: 26
- Spain: 21.8
- Bologna-Verona: 20
- Palermo: 12.8
Use of High Potency Cannabis (TCH>10%) in 1600 Cases of First Episode Psychosis and 1383 Populations Controls

**p<0.001*p<0.05 OR Adj for age, gender, ethnicity, other drugs

**p<0.001**

**p<0.05**

Use of High Potency Cannabis Adj-OR

<table>
<thead>
<tr>
<th>City</th>
<th>Use of High Potency Cannabis Adj-OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>8.6</td>
</tr>
<tr>
<td>Cambridge</td>
<td>4.3</td>
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<tr>
<td>NL</td>
<td>7.2</td>
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<tr>
<td>Spain</td>
<td>1.7</td>
</tr>
<tr>
<td>France</td>
<td>2.9</td>
</tr>
<tr>
<td>Italy</td>
<td>0.8</td>
</tr>
<tr>
<td>Palermo</td>
<td>0.9</td>
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</table>
Gene-Environment Interaction

Environmental risk factor → Gene(s) → Psychosis
Gene-Environment Interaction

Cannabis use

Polygenic risk score

correlation or interaction?

Psychosis

AKT1

DRD2
Figure 1a. Interaction between *DRD2* rs1076560/*AKT1* rs2494732 and lifetime cannabis use on psychosis risk

<table>
<thead>
<tr>
<th></th>
<th>No cannabis use</th>
<th>Cannabis use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRD2rs1076560/AKT1 rs2494732</strong></td>
<td>Adj OR *</td>
<td>95% CI</td>
</tr>
<tr>
<td>No “risk” alleles</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>One “risk” allele</td>
<td>0.29</td>
<td>0.09, 0.88</td>
</tr>
<tr>
<td>Two “risk” alleles</td>
<td>0.14</td>
<td>0.03, 0.63</td>
</tr>
</tbody>
</table>
The arrival of synthetic cannabinoids puts the psychotogenic effect beyond doubt.
Spicing things up: synthetic cannabinoids

Max Spaderna · Peter H. Addy · Deepak Cyril D’Souza

While THC is a partial agonist at the CB1 Receptor, synthetic Cannabinoids are full agonists. Therefore they have much more powerful effects.

Users are 30 times more likely to seek emergency treatment than users of regular cannabis

Winstock A, Global Drug Survey 2014

"Spiceophrenia": a systematic overview of "Spice"-related psychopathological issues and a case report

Duccio Papanti¹², Fabrizio Schifano³, Giulia Botteon¹², Francesca Bertossi³, Jason Mannix⁴, Daniela Vidoni³, Matteo Impagnatiello³, Elisabetta Pascolo-Fabri³ and Tommaso Bonavigo¹⁴
Strange fame for an Academic

In 1984 Professor JW Huffman in Clemson Univ, USA began developing cannabinoid compounds to aid in research into multiple sclerosis, AIDS, and chemotherapy. Over twenty years, Huffman and his team developed 450 synthetic cannabinoid compounds.

In the late 2000s, Huffman's cannabinoid compounds began being sold in Germany as marijuana alternatives known as K2 and Spice …..JWH-018 etc.

“It bothers me that people are so stupid as to use this stuff".
CAUTION:
For fragrance purposes only.
Not for consumption.
Keep out of reach of children and pets.
Never leave burning incense unattended
and make sure all ashes fall in ashtrays
or burners.

Burn in a well-ventilated area.
Smoke inhalation may cause
light-headedness and be harmful
to your health.
Excess Synthesis of Striatal Dopamine

Psychosis

Dopamine

Striatal dopamine neuron

DRD2

Post-synaptic receptor
Excess Synthesis of Striatal Dopamine → Psychosis

AKT1 is a Kinase Protein involved in the transmission of the DRD2 signaling
Effect of chronic THC on DA transmission in rats

DA neuron

Only a little DA is released

+++DRD2

NAc

Presynaptic hypo-activity

Postsynaptic supersensitivity

Nathalie Ginovart et al. Neuropsychopharmacology 2012

DA: dopamine; DRD2: dopamine receptor D2; NAc: nucleus accumbens; THC: tetrahydrocannabinol.
Striatal dopamine synthesis capacity in regular cannabis users vs. nonusers

Abi-Dhargum group showed that in cannabis-induced psychosis, striatal DA was low but even a small increase precipitated psychotic symptoms.

Chronic cannabis use induces low striatal dopamine – similar to other drug dependencies, but also the concurrent development of post-synaptic super-sensitivity.

DA: dopamine.
Conclusions

1) Administering THC can induce an acute psychosis; this effect is moderated by CBD.

2) Heavy use of cannabis, especially high potency varieties, is associated with greater later risk of psychosis.

3) Cannabis-using psychotic patients have an earlier onset, and better premorbid function than non-using psychotic patients; they have a worse outcome if they continue to use cannabis.

4) There is preliminary evidence that some people are genetically vulnerable.
Thanks to:
The GAP and EU-GEI Teams, and especially
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Amir Englund
Marco Colizzi
Evangelos Vassos
Jim Van Os

and all our patients