Cannabis use and psychotic disorders: "The chicken or the egg?"

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1

What do you know about Psychosis

Psychotic Disorders such as Schizophrenia cost over 12 billion pounds each year

Self-portrait (11-16 April)
Bryan Charnley

2

Beliefs: that are developed and held "against the evidence of the contrary" and outside the person background
Unshakable ideas, worries that others around us find bizarre or unsubstantiated
We become very suspicious and fear we are under threat or the target of a conspiracy
We fear that others can read our own thoughts and that our thoughts are no longer private

3

Behaviour:

Getting worried about others spying on us. Perhaps our phone is bugged?

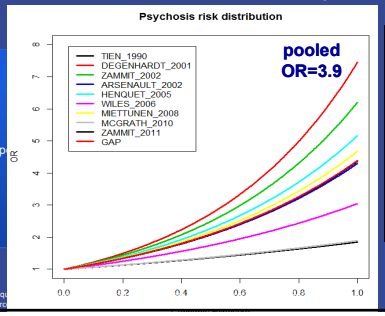
These worries become so intense that can affect our ability to carry on with life, interact with others, trust those around, concentrate on work or learning even enjoy and feel happiness!

We forget to care for ourselves

Abnormal perceptions: See (people, animals, shapes, demons) hear (clear voices, sounds) and more rarely feel (touch), smell taste things that nobody else can perceive

4

Cannabis use and Psychotic Disorders



5

My two clinical & research questions:

1. Who are the cannabis users at risk of developing psychosis?

2. Is there a relationship between prevalence of cannabis use in the population and the incidence rates of psychosis?

6

London and *Cannabis Sativa*

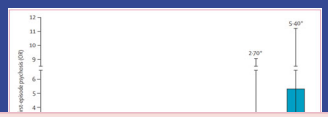
UK Sensimilla = SKUNK: female plant with no seeds as crops are grown not pollinated

Skunk – on average THC=16%
Imported Herbal THC=5–6%
Hash THC=4–5% (THC/CBD=1)

THC, Tetrahydrocannabinol; CBD, cannabidiol.
Potter DJ, *et al. J Forensic Sci* 2008;**53**:90–4; Hardwick & King. Home Office Potency Study 2008.

7

Does cannabis type matter in South London?



	Odds ratio* (95% CI)	Prevalence of exposure in patients with first-episode psychosis	Population attributable fraction (95% CI)
Daily cannabis use	3·04 (1·91–7·76)	123/410 (30%)	19·3% (13·1–27·0)
Skunk use	2·91 (1·52–3·60)	218/410 (53%)	24·0% (17·4–30·6)
Skunk use every day	5·40 (2·80–11·30)	103/410 (25%)	16·0% (14·0–20·3)

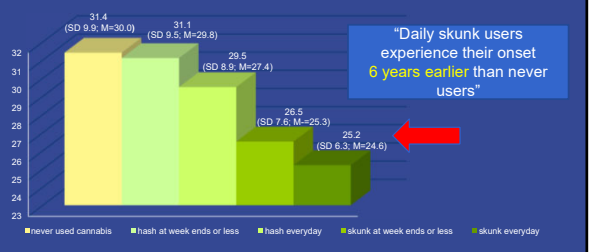
*Adjusted for age, gender, ethnic origin, number of cigarettes, alcohol units, other drugs used, level of education, and employment status.

Table 4: **Population attributable fraction for daily use of cannabis, skunk use, and skunk use every day**

Di Forti M, *et al. Br J Psychiatry* 2009;**195**:488–91;
Di Forti M, *et al. Lancet Psychiatry* 2015;**2**:233–38.

8

Mean age (yrs) of onset of psychosis by degree of exposure to cannabis



"Daily skunk users experience their onset 6 years earlier than never users"

Di Forti, *et al. Schizophr Bull* 2014;**40**:1509–17.

9

What about outcome in those who continue using drugs after psychosis onset?

10

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

Summary

Background Although the link between cannabis use and development of psychosis is well established, less is known about the effect of continued versus discontinued cannabis use after the onset of psychosis. We aimed to summarise available evidence focusing on the relationship between continued and discontinued cannabis use after onset of psychosis and its relapse.

Lancet Psychiatry 2016
Published Online January 14, 2016
http://dx.doi.org/10.1016/S2215-0366(15)00363-6

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.

Schoeler T, *et al. Lancet Psychiatry* 2016;3:215–25.

11

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

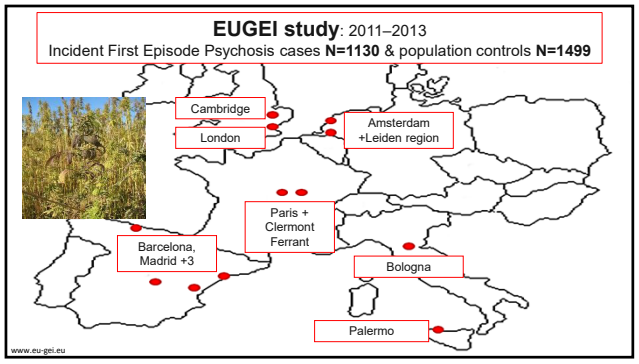
Tabea Schoeler, Natalia Petros, Marta Di Forti, Ewa Klamerus, Enrico Foglia, Olesya Ajnakina, Charlotte Gayer-Anderson, Marco Colizzi, Diego Quattrone, Irena Behlke, Sachin Shetty, Philip McGuire, Anthony S David, Robin Murray, Sagnik Bhattacharyya

Findings Between April 12, 2002, and July 26, 2013, 256 patients presented with a first episode of psychosis. We did follow-up assessments for these patients until September, 2015. Simple analyses showed that former regular users of cannabis who stopped after the onset of psychosis had the most favourable illness course with regards to relapse. In multiple analysis, continued high-frequency users (ie, daily use in all 24 months) of high-potency (skunk-like) cannabis had the worst outcome, indexed as an increased risk for a subsequent relapse (odds ratio [OR] 3·28; 95% CI 1·22–9·18), more relapses (incidence rate ratio 1·77; 95% CI 0·96–3·25), fewer months until a relapse occurred (*b* –0·22; 95% CI –0·40 to –0·04), and more intense psychiatric care (OR 3·16; 95% CI 1·26–8·09) after the onset of psychosis.

Schoeler T, et al. *Lancet Psychiatry* 2016;3:947–53.

12

13


EUGEI study: 2011–2013
Incident First Episode Psychosis cases N=1130 & population controls N=1499
Cambridge
London
Amsterdam +Leiden region
Paris + Clermont Ferrant
Barcelona, Madrid +3
Bologna
Palermo
www.eu-gei.eu

14


Working out cannabis potency (THC %)…starting from London

15

2016 Report:
European Monitoring Centre for Drugs and Drug Addiction

High potency=THC≥10%

Low potency=THC<10%

http://www.emcdda.europa.eu

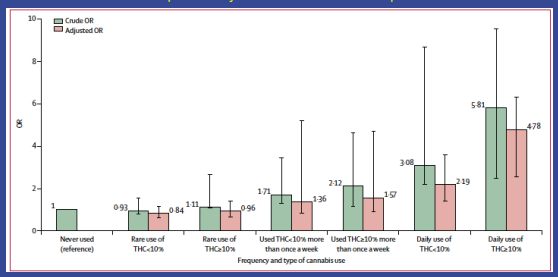
16

TCH on average <10%

- UK hash (*not the one imported from Marocco*)
- UK imported herbal cannabis
- Italian hash
- Italian imported herbal cannabis
- *Holland Geimporteerde Wiet*
- Spain imported herbal cannabis
- France imported herbal cannabis

17

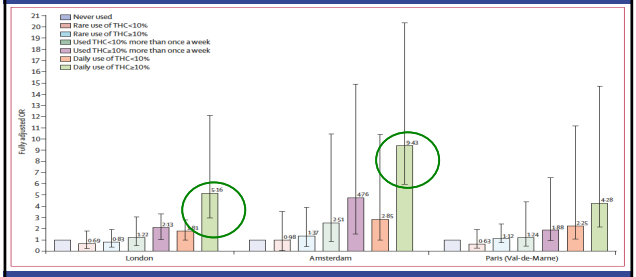
Combined measure of Frequency-Type of cannabis use crude ORs (*adjusted only for age, gender and ethnicity*) and fully Adj ORs* for Psychotic disorders in the whole sample
N=901 First Episode Psychosis Case N=1237 Population controls



*Adjusted for age, gender, ethnicity, level of Ed, employment status and other drugs (tobacco, alcohol, stimulants, Ketamine, Legal highs, Hallucinogenics)
Di Forti et al, Lancet Psych, online 2019

18

The effect of daily use of high-potency cannabis on the odds for psychotic was particularly visible in **London and Amsterdam**



*Adjusted for age, gender, ethnicity, level of Ed, employment status and other drugs (tobacco, alcohol, stimulants, Ketamine, Legal highs, Hallucinogenics).
Di Forti et al, Lancet Psych, online 2019

19

Is there a relationship between prevalence of cannabis use in the population and the incidence rates of psychosis?

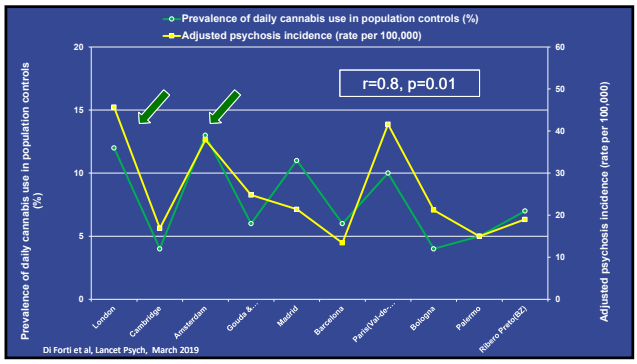
20

Trans-European (plus Brazil)

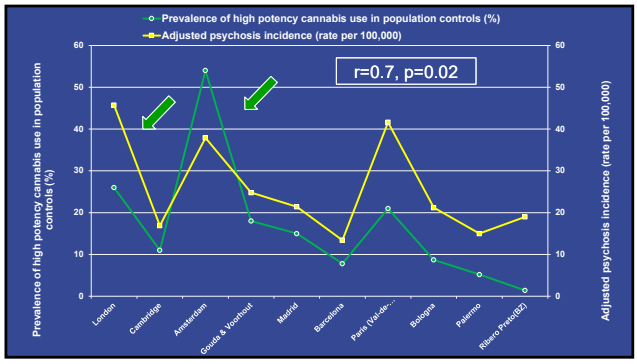
Adjusted (age, gender, minority status) psychosis incidence (rate per 100,000)

Jongsma HE, *et al. JAMA Psychiatry* 2018;75:36–46.

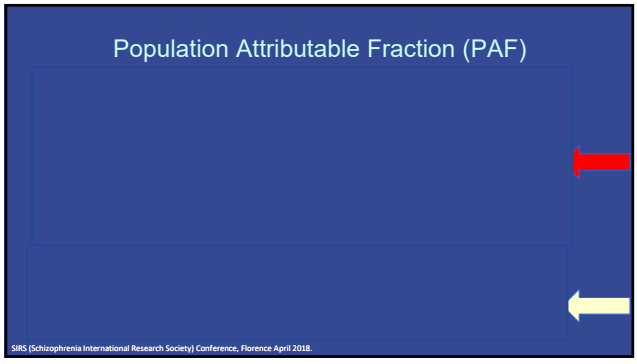
21


Prevalence of daily cannabis use in population controls (%)
Adjusted psychosis incidence (rate per 100,000)
r=0.8, p=0.01
Prevalence of daily cannabis use in population controls (%)
Adjusted psychosis incidence (rate per 100,000)
London
Cambridge
Amsterdam
Gouda &...
Madrid
Barcelona
Paris(Val-de-...
Bologna
Palermo
Ribeiro Preto(BZ)
Di Forti et al, Lancet Psych, March 2019

22


Prevalence of high potency cannabis use in population controls (%)
Adjusted psychosis incidence (rate per 100,000)
r=0.7, p=0.02
Prevalence of high potency cannabis use in population controls (%)
Adjusted psychosis incidence (rate per 100,000)
London
Cambridge
Amsterdam
Gouda & Voorhout
Madrid
Barcelona
Paris (Val-de-...
Bologna
Palermo
Ribeiro Preto(BZ)

23


Population Attributable Fraction (PAF)
SIRS (Schizophrenia International Research Society) Conference, Florence April 2018.

24

From this pre-Brexit EU journey the message is:

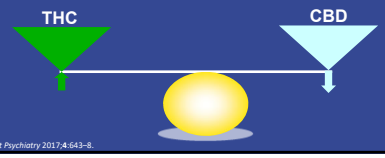
- The Patterns of Cannabis Use vary widely across European countries, but its effect on the OR of Psychotic Disorder is consistent
- Daily use and use of high potency types have the greatest effect on individual risk across sites
- Differences in the frequency of use and the availability of high potency cannabis explain part of the differences in the proportion of new cases of Psychosis attributable (PAFs) to daily use and use of high potency across the study sites

25

Two key 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?



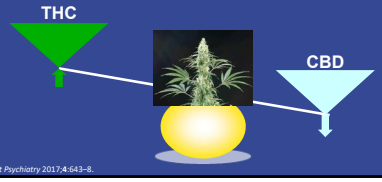
Englund A, *et al. Lancet Psychiatry* 2017;4:643–8.

26

The ingredients of cannabis

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

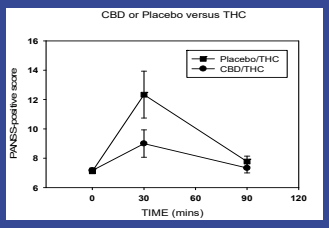
Cannabidiol (CBD)
- Is not hallucinogenic
- Has anxiety relieving properties
- No adverse effect on cognition



Englund A, *et al. Lancet Psychiatry* 2017;4:643–8.

27

Psychotogenic effect of acute administration of 2.5 mg of IV Tetrahydrocannabinol (THC)



Cannabidiol (CBD) blocks the effects of THC

Morrison PD, *et al. Psychol Med* 2009;**39**:1607–16; Englund A, *et al. J Psychopharmacol* 2013;**27**:19–27.

28

Cannabis use and risk of Psychosis: is it all explained by schizophrenia genes?

A recent large Mendelian Randomization (MR) study claims that is the genetics of Schizophrenia that causes cannabis use (Pasman J et al 2018) but few months later…..

https://targ.blogs.bristol.ac.uk/2019/01/07/does-schizophrenia-influence-cannabis-use-how-to-report-the-influence-of-disease-liability-on-outcomes-in-mendelian-randomization-studies/

29

We decided to:

- Test :

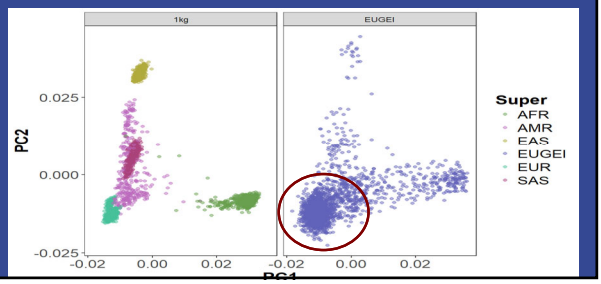
1) for differences in Schizophrenia Polygenic Risk Score (SZ PRS) between cannabis-users and never users in controls

2) if SZ PRS predicts different patterns of cannabis use

3) If we can use SZ PRS to predict who are the cannabis users at risk to develop a Psychotic Disorder

30

EUGEI-white EUR only
FEP=492; Controls=787

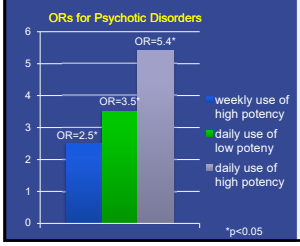


31

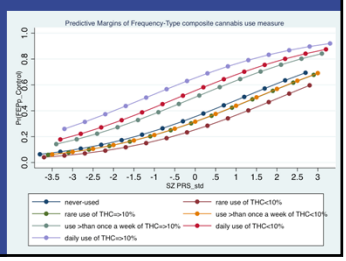
Do Cannabis users in the general population have a higher SCZ PRS than never users?

32

- Even after controlling for the effect of Schizophrenia genes (SZ Polygenic risk scores) the following patterns of cannabis use increased the risk (OR) for Psychotic disorder:



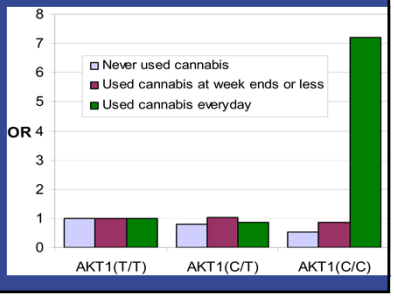
- Combined effect of SZ Genes (PRS) and Cannabis use



33

Dopamine Candidate genes previous work:

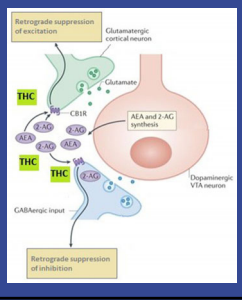
- COMT Val-Met (+/--)
- AKT1 rs2494732 (+++)
- AKT1+DRD2 (+)



Caspi et al, 2005; van Winkel et al 2011; Di Forti et al, Biological Psych, 2012
Colizzi et al ,Nature SCZ, 2015

34

The Endocannabinoid (eC)system and Psychosis: what is the link?



1. The eC system modulates Dopamine transmission
2. Excess Dopamine synthesis underlies psychotic symptoms
3. THC disrupts the eC system

35

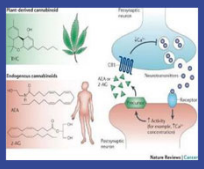
How does cannabis have any effect on the rest of our physiology?

36

A report from the International Cannabinoid Research Society (ICRS) published in *Nature* 2015 reminds us about …A PERSONABLE SYSTEM

Endocannabinoids *(1st described 10 years ago)* ***are everywhere***

The Endocannabinoid system on demand (CB1-CB2 Receptors) is the pathway by which tetrahydrocannabinol (THC) exerts its effects on:



- Appetite, memory, alertness, pain, inflammation and bone health, and stimulation of the endocannabinoid system is associated with the protection of healthy cells
- "The endocannabinoid system helps us eat, sleep, relax, forget and protect our neurons"
- Endocannabinoid receptors are spread throughout the body…this could explain why the compounds found in cannabis seem to have no end of potential medical uses

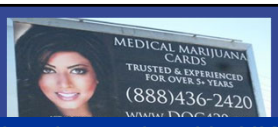
Owens B. *Nature* 2015;**525**:S6–8.

37

The Endocannabinoid system: our CNS safety helmet and more

Regulates Glutamate and GABA transmission

38



Medicinal Cannabis has is now legal in UK from the1st of November 2019

39

Aspirin (acetylsalicylic acid)

Indications:

- Fever
- Inflammation
- Pain
- Rheumatic fever
- Blood clots
- Ischaemic Stroke

Adverse effect:

- Gastric bleeding
- Intra-cerebral haemorrhage
- Skin Swelling
- Reye's Disease *(do not give to children or adolescents to control fever!!!)*

Dose: 300 or 325 mgs tbs
75 or 81 mgs tbs
Interaction: e.g. NSAID

BNF, 2018.

40

Medicinal cannabis

(THC,CBD and plus hundred more cannabinoids):

Adverse effect:

- Transient Psychosis
- Psychotic Disorders (high THC)…*daily use; adolescent use…*
- Impaired Cognition (high THC)
- Reduced driving ability

Indications:

- Pain (Dronabinol synthetic THC)
- Intractable Nausea (Nabilone synthetic THC)
- Spasticity (Sativex THC-CBD…)
- Epilepsy (CBD)
- Inflammation (THC & ?)
- Schizophrenia/Psychosis (CBD)

Medicinal Cannabis Dose: ???????
Exact active Ingredients proportion ?????
Interactions ?????

Whiting PF, *et al. JAMA* 2015;**313**:2456–73.

41

What next?

Biological pathways that might underlie individual susceptibility

Set up a Cannabis Clinic to develop and implement *Psychological* and *Pharmacological* intervention for:

1. Harm Reduction
2. Cessation

42

Thanks to the:
In June 2019 the
Cannabis Clinic for Patients with Psychosis
(CCP) was born!

Maudsley Charity
Health in Mind


43

Our newly developed Service

44

Last but not least

My gratitude to:
Firstly to all our wonderful first episode psychosis patients and controls

All the EUGEI teams
Diego Quattrone, Professor Craig Morgan
Professor Sir Robin Murray
And my CCP team


45