# Novel strategies for treatment and harm reduction in cannabis use disorder


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# Outline of talk

1) Scale of the problem

2) Cannabinoids: THC and CBD

3) Treatments for cannabis use disorder

4) Harm reduction

# Scale of the problem

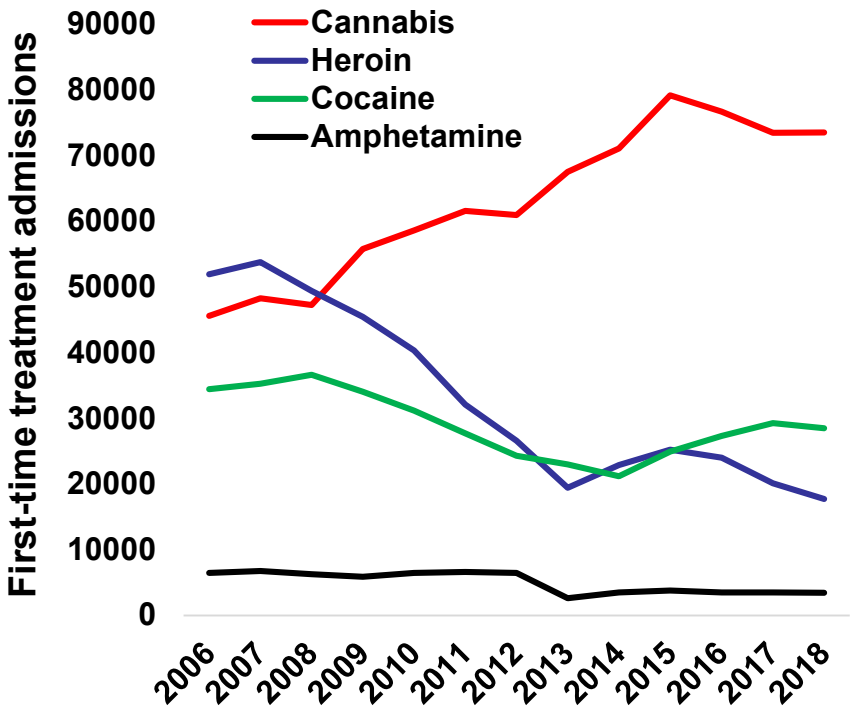
**Is cannabis addictive?**

- 31% past year cannabis users meet criteria for cannabis use disorder: representative USA household study
- 22 million with a cannabis use disorder worldwide – similar to number with opioid use disorder (27 million)

Hasan et al. (2015) *JAMA Psychiatry;* Degenhardt et al. (2016) *Lancet Psychiatry*

# Scale of the problem

## Addiction treatment in Europe




**More first-time admissions for cannabis than any other drug**

emcdda

Lees et al. (2021) *Psychological Medicine*

# Scale of the problem

- Cannabis withdrawal: similar time course and severity to tobacco

# Outline of talk

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2) Cannabinoids: THC and CBD

3) Treatments for cannabis use disorder

4) Harm reduction

# Cannabinoids: THC and CBD

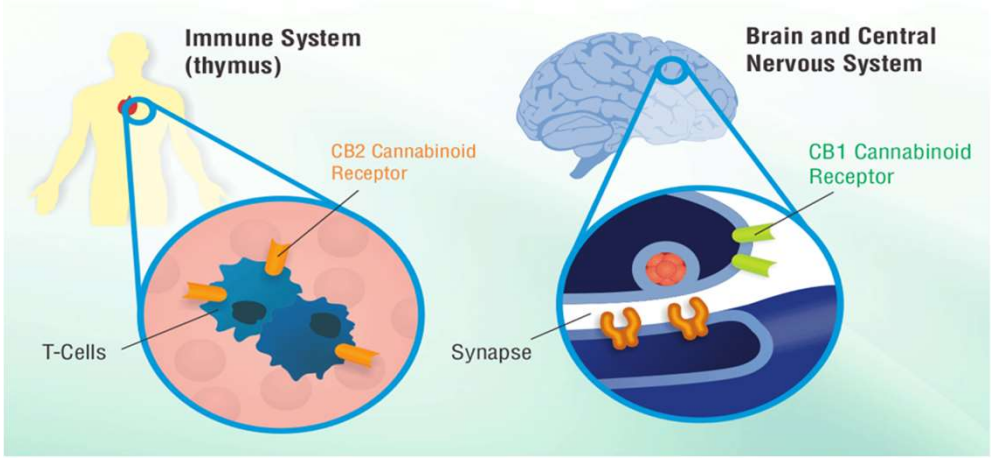
**Cannabis plant produces at least 144 “cannabinoids”**

**THC ($\Delta^9$-tetrahydrocannabinol)**
**CBD (Cannabidiol)**

# Cannabinoids: THC and CBD

THC and CBD act on *endocannabinoid system* – found in all mammals

Includes cannabinoid receptors (e.g. CB1 and CB2), and endocannabinoids (e.g. anandamide, 2-AG) that bind to them



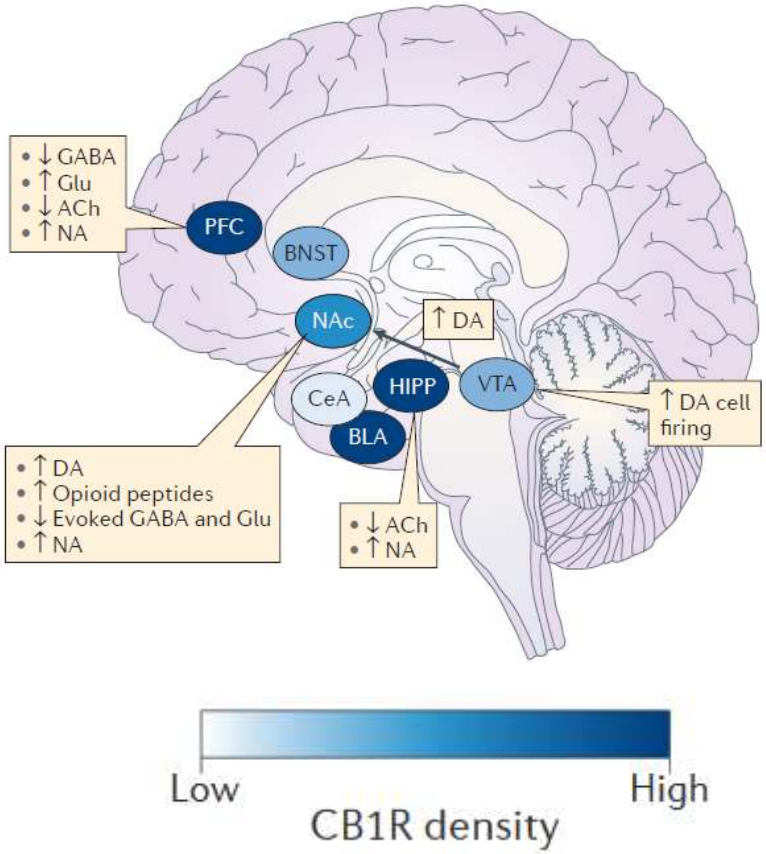
# Cannabinoids: THC and CBD

**THC ($\Delta^9$-tetrahydrocannabinol)**

- Intoxicating
- Impairs memory
- Addictive

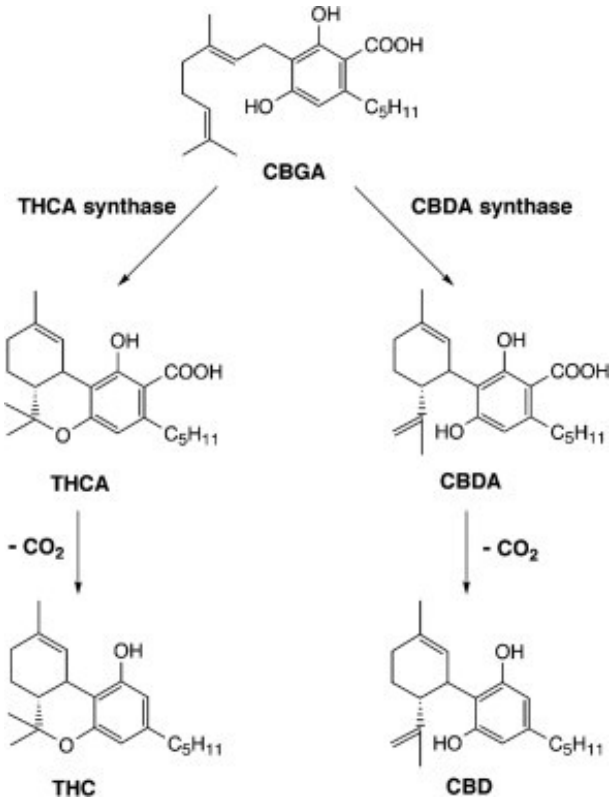
**CBD (cannabidiol)**

- Non-intoxicating
- Pro-cognitive
- Anti-addictive




Curran et al. (2016) *Nature Reviews Neuroscience*

# Cannabinoids: THC and CBD

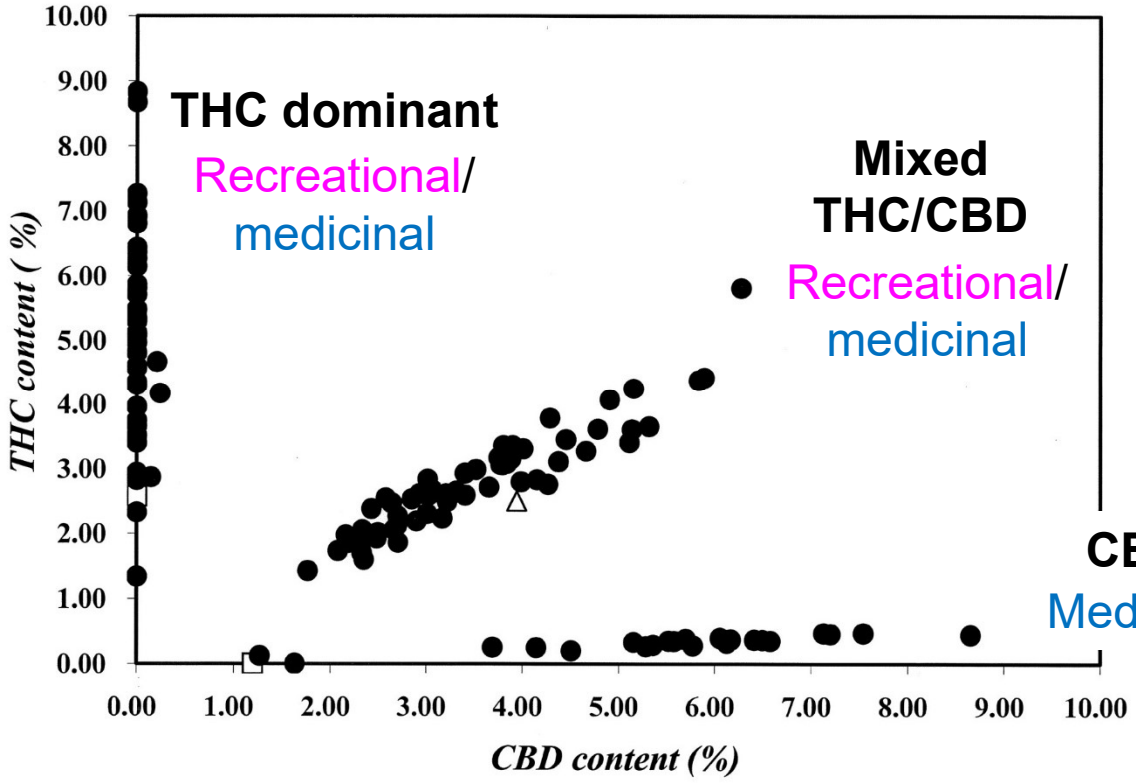



Taura et al. (2007) *FEBS Letters*

THC and CBD
produced in 'trichomes'

More THC production = less CBD
(and vice versa)

# THC and CBD





de Meijer et al. (2003) *Genetics*

# THC and CBD: medicinal use

Table 2| **Summary of evidence for medicinal use of cannabis based products and cannabinoids.**

| Indication | Number of studies (participants) | Primary products tested | Comparator | Outcome | Summary estimate (95% confidence interval) | GRADE certainty rating |
|---|---|---|---|---|---|---|
| Chronic pain[23] | 9 (1734) | Sativex (THC+CBD) | Placebo | 30% reduction in pain | Odds ratio: 1.46 (1.16 to 1.84). More effective than placebo | ⊕⊕⊕◯ Moderate |
| Multiple sclerosis[11] | 5 (1244) | Sativex (THC+CBD) | Placebo | Ashworth spasticity scale | Weighted mean difference: −0.12 (−0.24 to 0.01). Not more effective than placebo | ⊕⊕⊕◯ Moderate |
| Treatment resistant epilepsy[24] | 2 (291) | Epidiolex (CBD) | Placebo | 50% reduction in seizure frequency | Relative risk: 1.74 (1.24 to 2.43). More effective than placebo | ⊕⊕◯◯ Low |
| Nausea and vomiting due to chemotherapy[11] | 3 (102) | Dronabinol (THC) | Placebo | Complete response in nausea and vomiting | Odds ratio: 3.82 (1.55 to 9.42). More effective than placebo | ⊕⊕◯◯ Low |

Grading of recommendations, assessment, development, and evaluations (GRADE)[25]

⊕⊕⊕⊕ High, the authors have a lot of confidence that the true effect is similar to the estimated effect

⊕⊕⊕◯ Moderate, the authors believe that the true effect is probably close to the estimated effect

⊕⊕◯◯ Low, the true effect might be markedly different from the estimated effect

⊕◯◯◯ Very low, the true effect is probably markedly different from the estimated effect

Freeman et al. (2019) *BMJ*

# THC and CBD: recreational use

ELSEVIER

Neuroscience & Biobehavioral Reviews
Volume 107, December 2019, Pages 696-712

## How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review

Abigail M. Freeman [a], Katherine Petrilli [a], Rachel Lees [a, b], Chandni Hindocha [a, d], Claire Mokrysz [a], H. Valerie Curran [a], Rob Saunders [a], Tom P. Freeman [a, b, c]

- The most common finding was that CBD reduced the acute effects of THC, however, results were mixed.
- CBD may reduce intense experiences of anxiety or psychosis-like effects of THC but this was not seen in all studies.
- CBD may blunt effects of THC on emotion and reward processing.

# Changes in cannabis potency

Joe Biden

Comparing today's cannabis to the 60's/70's:

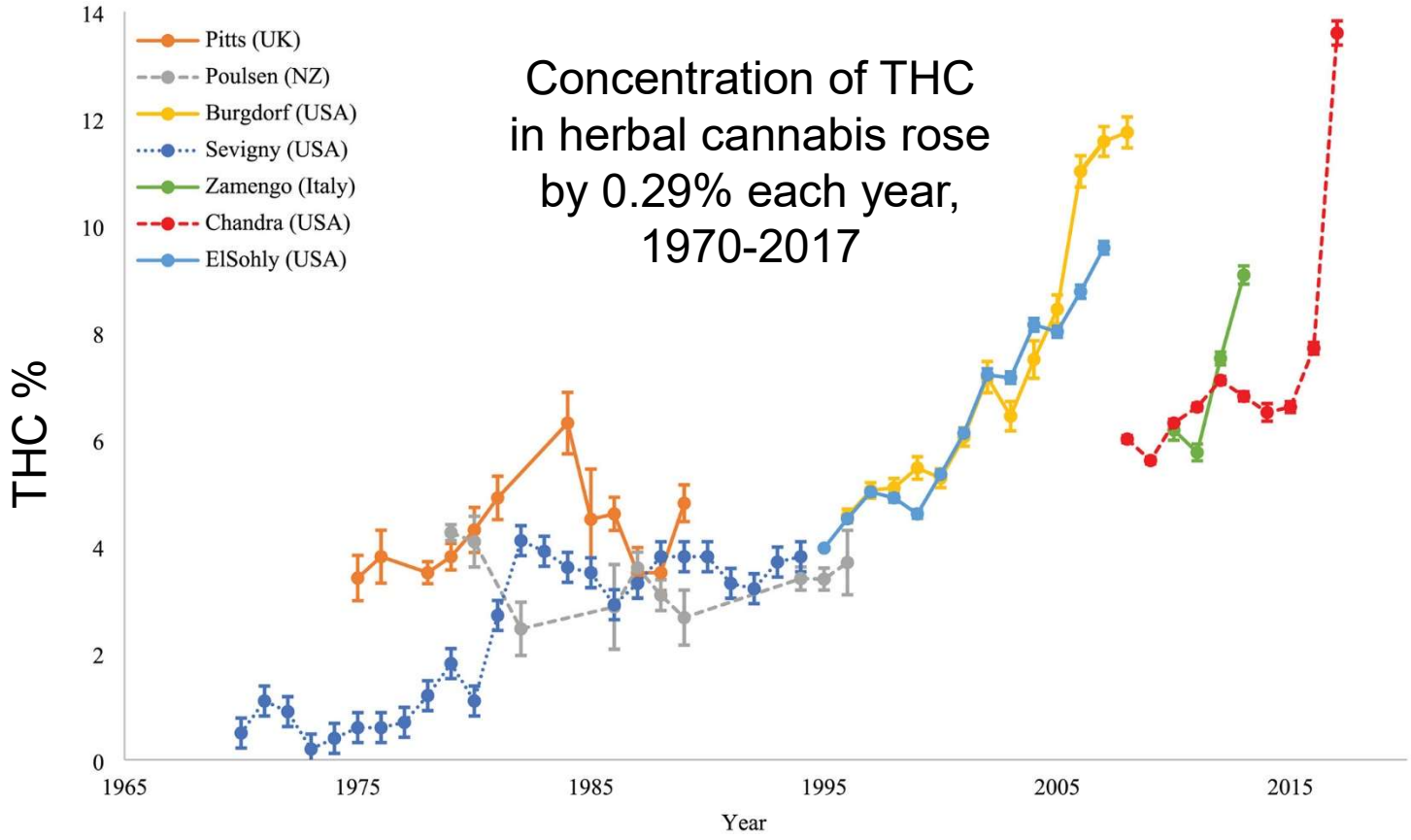
"*It's like comparing the buckshot in a shotgun shell to a laser-guided missile - they're different*"

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION
REVIEW doi:10.1111/add.15253

**Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis**

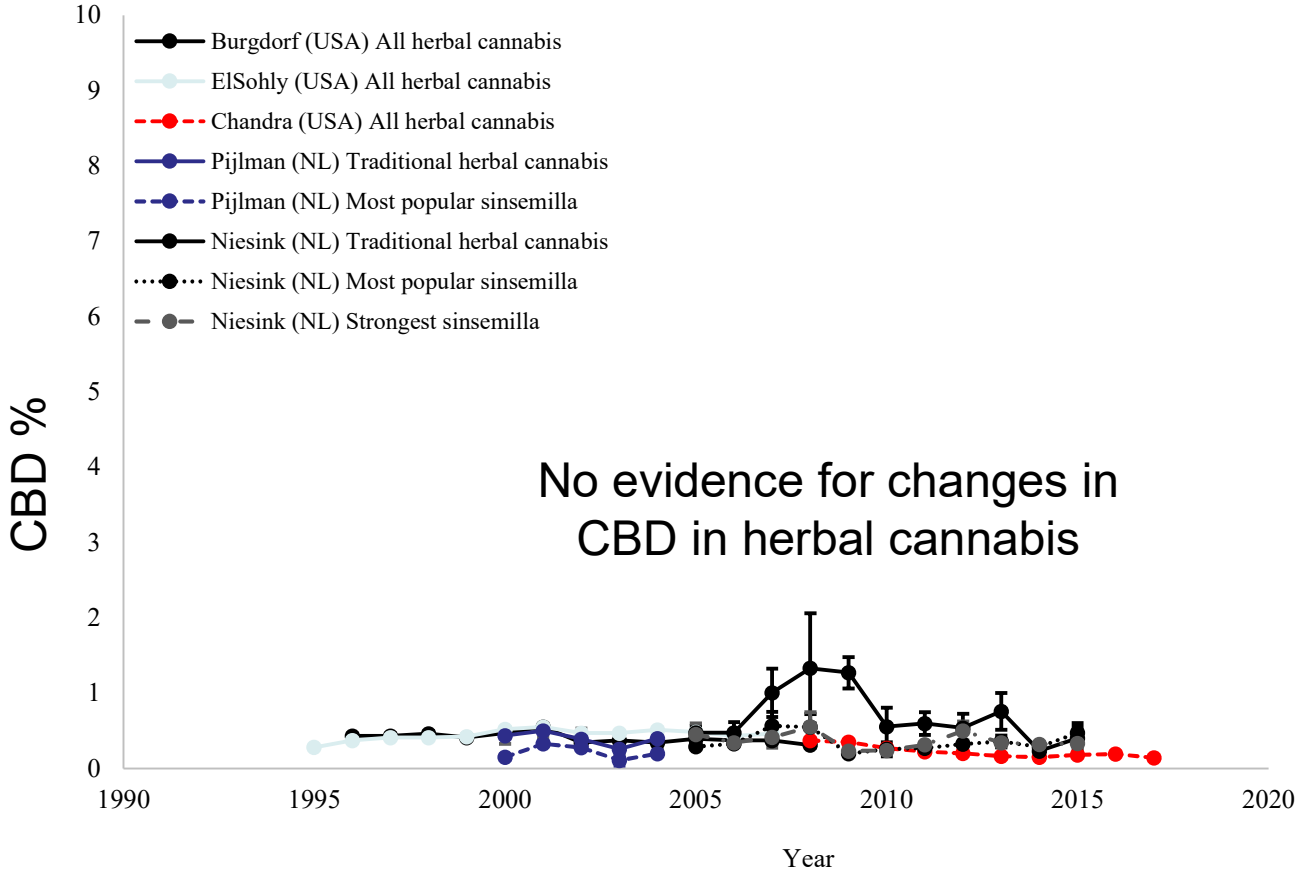
Tom P. Freeman[1,2], Sam Craft[1,2], Jack Wilson[3], Stephan Stylianou[2], Mahmoud ElSohly[4,5], Marta Di Forti[6] & Michael T. Lynskey[2]

# Changes in herbal cannabis




Freeman et al. (2020) *Addiction*

# Changes in herbal cannabis




Freeman et al. (2020) *Addiction*

# Changes in herbal cannabis

**Seeded herbal cannabis**

Females fertilized by males, seeded, grown outdoors:

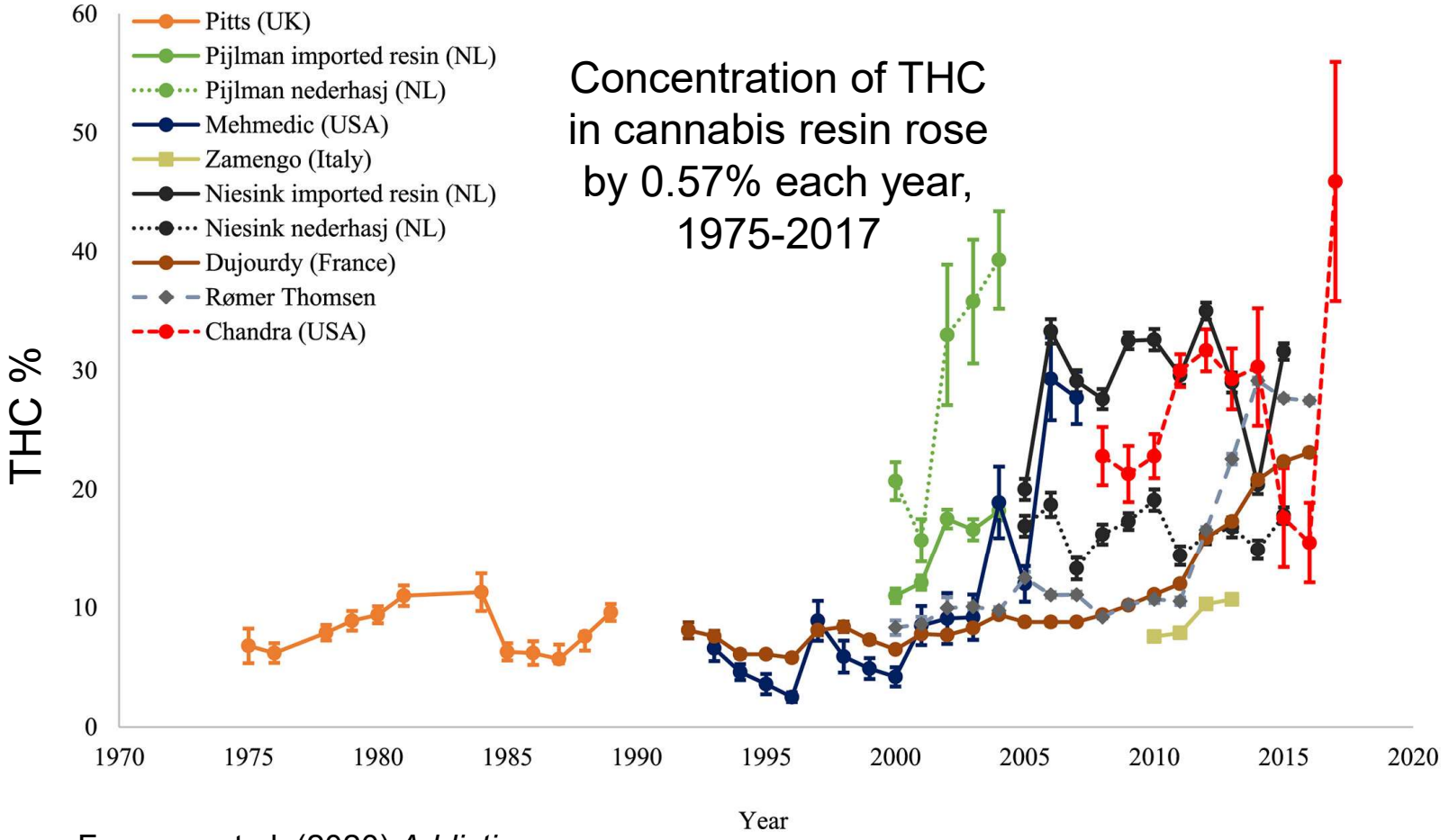
~6% THC

**Sinsemilla**

Females separated from males, indoor grown, UV light:

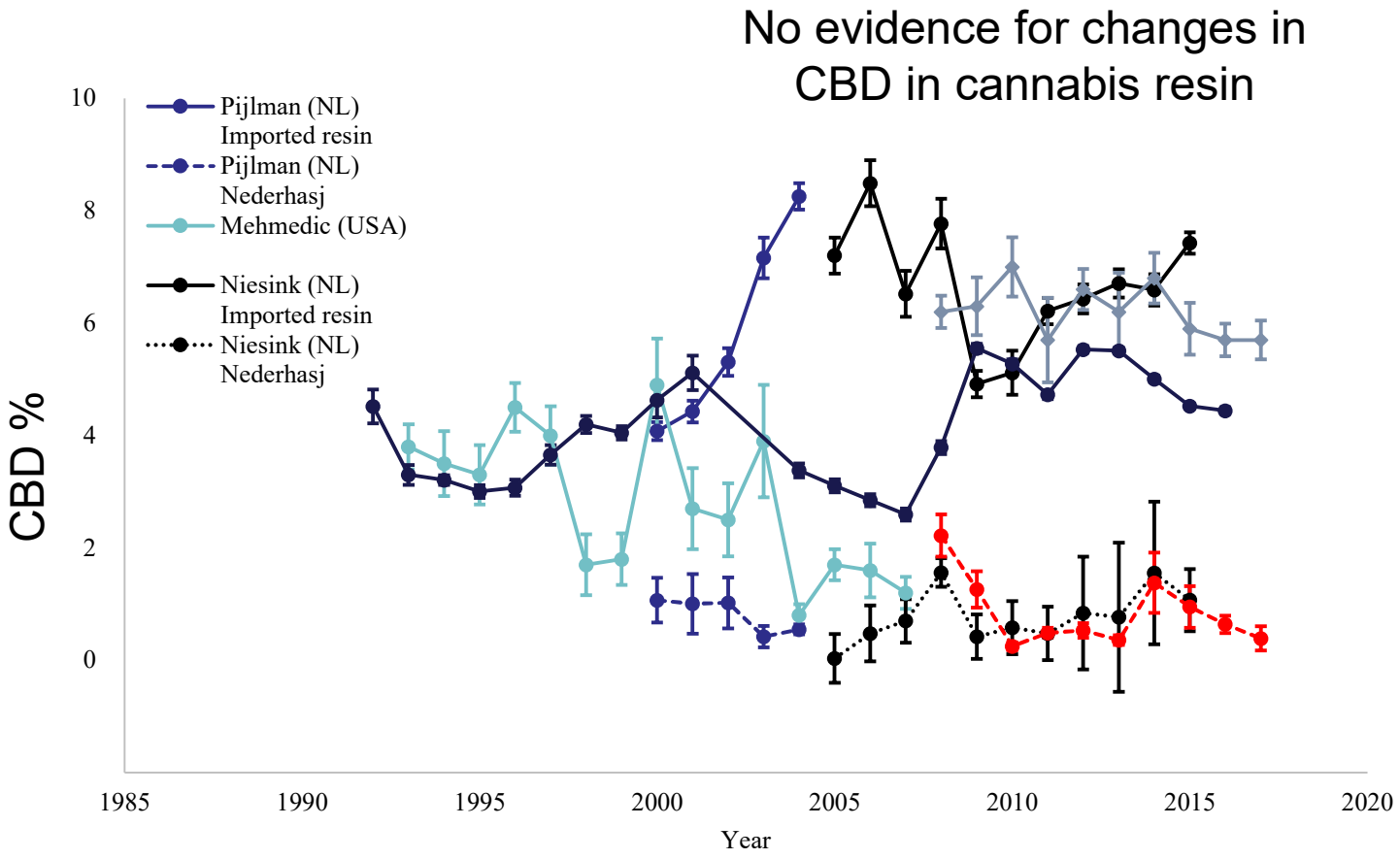
~15% THC

# Changes in cannabis resin




Freeman et al. (2020) *Addiction*

# Changes in cannabis resin




Freeman et al. (2020) *Addiction*

# Changes in cannabis resin

Cannabis material rubbed over screen

**Sieving**

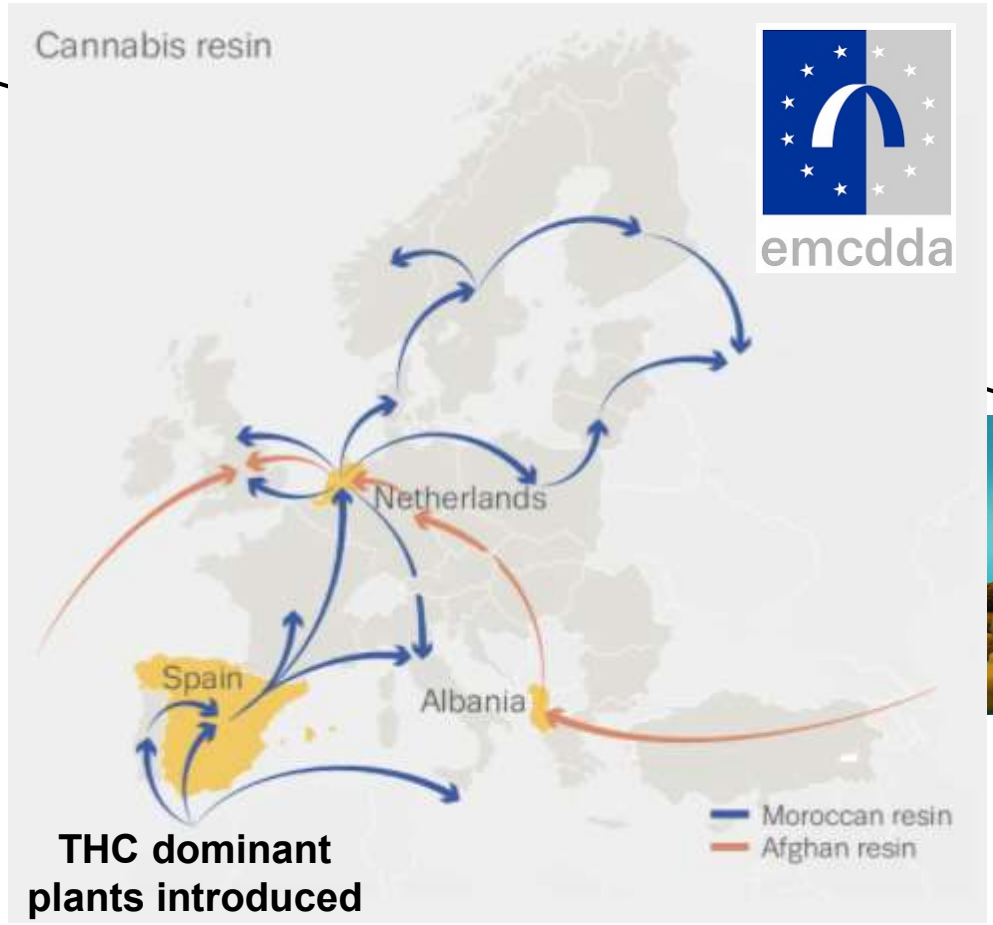
Trichome heads detach, fall through screen

Loose trichomes: “kief”

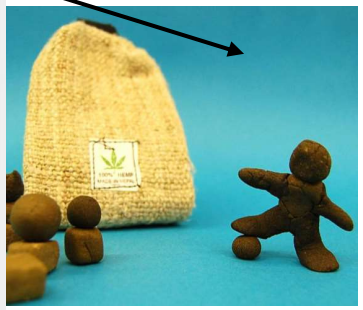
Compressed into “resin” or “hashish” ~15% THC

# Changes in cannabis resin

**Icy water (cold) and agitation removes trichomes**




**THC dominant plants introduced to Morocco**



**Resin: ~30% THC**

# Cannabis potency and addiction

*Psychological Medicine* (2015), **45**, 3181–3189. © Cambridge University Press 2015
doi:10.1017/S0033291715001178

ORIGINAL ARTICLE

## Examining the profile of high-potency cannabis and its association with severity of cannabis dependence

T. P. Freeman[1]* and A. R. Winstock[2]

[1] *Clinical Psychopharmacology Unit, University College London, London, UK*
[2] *Institute of Psychiatry, King's College London, Camberwell, UK*

GLOBAL DRUG SURVEY

UK (n=929)

**High potency cannabis: greater severity of dependence**

## Characterising heterogeneity in the use of different cannabis products: latent class analysis with 55 000 people who use cannabis and associations with severity of cannabis dependence

Sam Craft[1], Adam Winstock[2,3], Jason Ferris[4], Clare Mackie[1], Michael T. Lynskey[1] and Tom P. Freeman[1,2,5]

International (n=55,000)

GLOBAL DRUG SURVEY

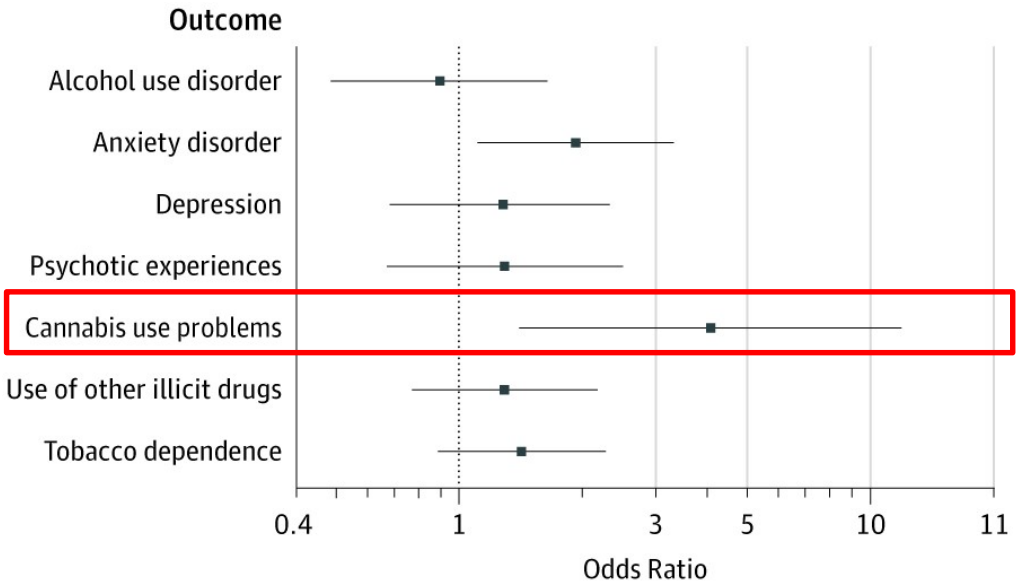
# Cannabis potency and addiction

JAMA Psychiatry | Original Investigation

## Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence

Lindsey A. Hines, PhD; Tom P. Freeman, PhD; Suzanne H. Gage, PhD; Stanley Zammit, PhD; Matthew Hickman, PhD; Mary Cannon, PhD; Marcus Munafo, PhD; John MacLeod, PhD; Jon Heron, PhD

ALSPAC, N=1087




High versus low potency cannabis use

Adjusted for demographics, longitudinal mental health, frequency of use

# Cannabis potency and addiction

**Cannabis potency (THC)**

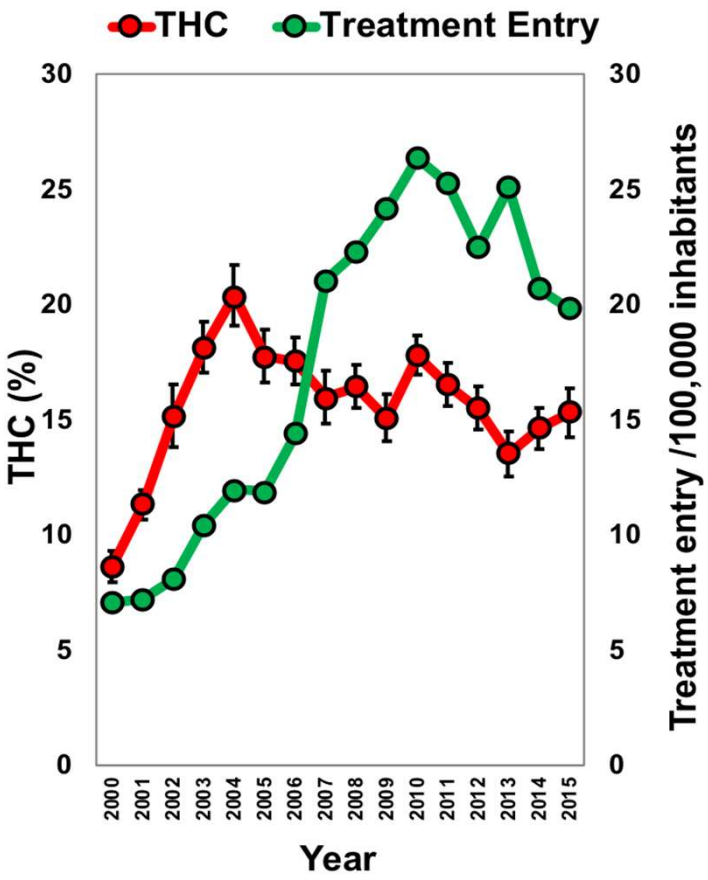
Trimbos instituut
Netherlands Institute of Mental Health and Addiction

Randomized sampling from ‘coffee shops’ in the Netherlands, 2000-2015

**Cannabis treatment**

IVZ
zicht op zorg

All first-time clients presenting with cannabis problems to addiction services in the Netherlands, 2000-2015




Freeman et al. (2018) *Psychological Medicine*

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# Treatment for cannabis use disorders

## Pharmacotherapies

None recommended

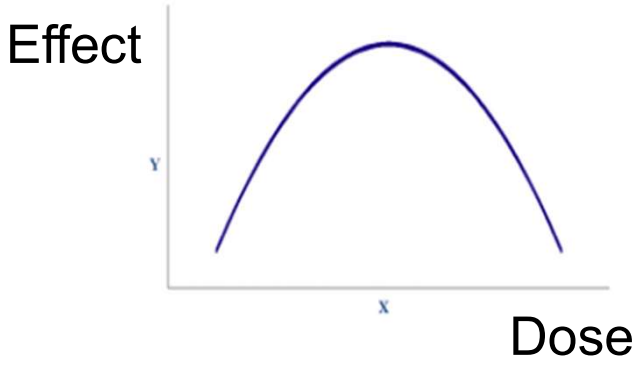

**THC preparations: abstinence no more likely compared to placebo** (moderate-quality evidence).

**SSRIs, mixed action antidepressants, anticonvulsants and mood stabilisers, buspirone and N-acetylcysteine: abstinence no more likely compared to placebo** (low- to very low-quality evidence).

# Cannabidiol as a novel treatment for CUD

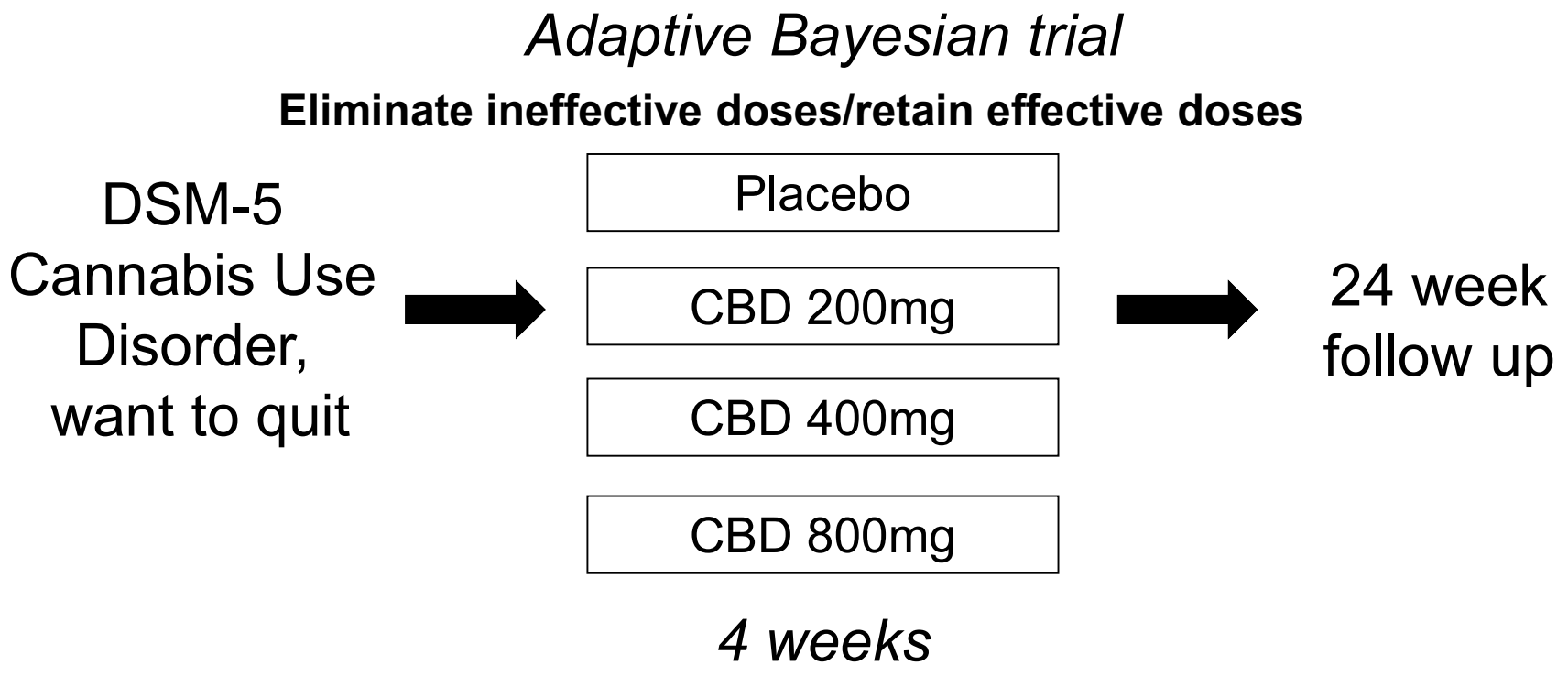
## Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial

*Tom P Freeman, Chandni Hindocha, Gianluca Baio, Natacha D C Shaban, Emily M Thomas, Danica Astbury, Abigail M Freeman, Rachel Lees, Sam Craft, Paul D Morrison, Michael A P Bloomfield, Dominic O'Ryan, Jane Kinghorn, Celia J A Morgan, Ali Mofeez, H Valerie Curran*

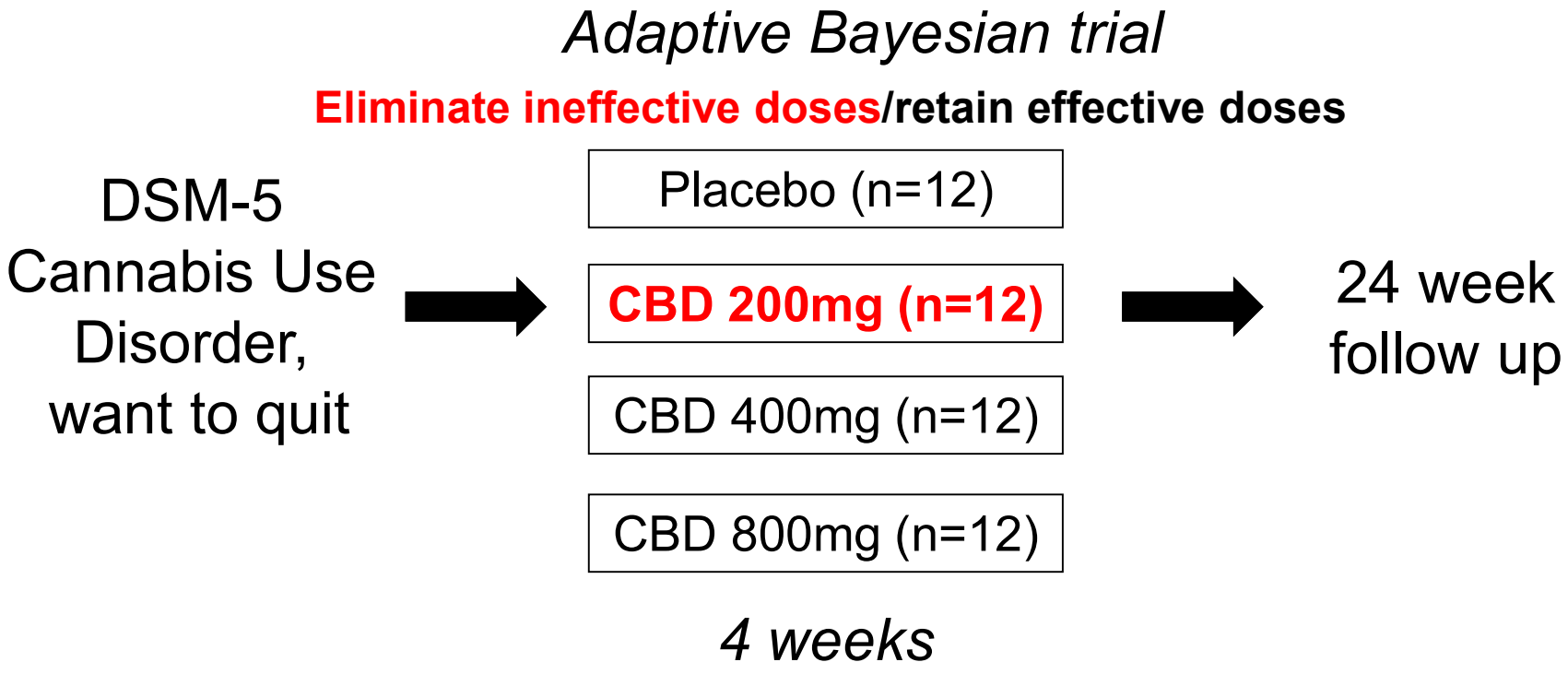



Doses ranging from 200mg - 800mg CBD?

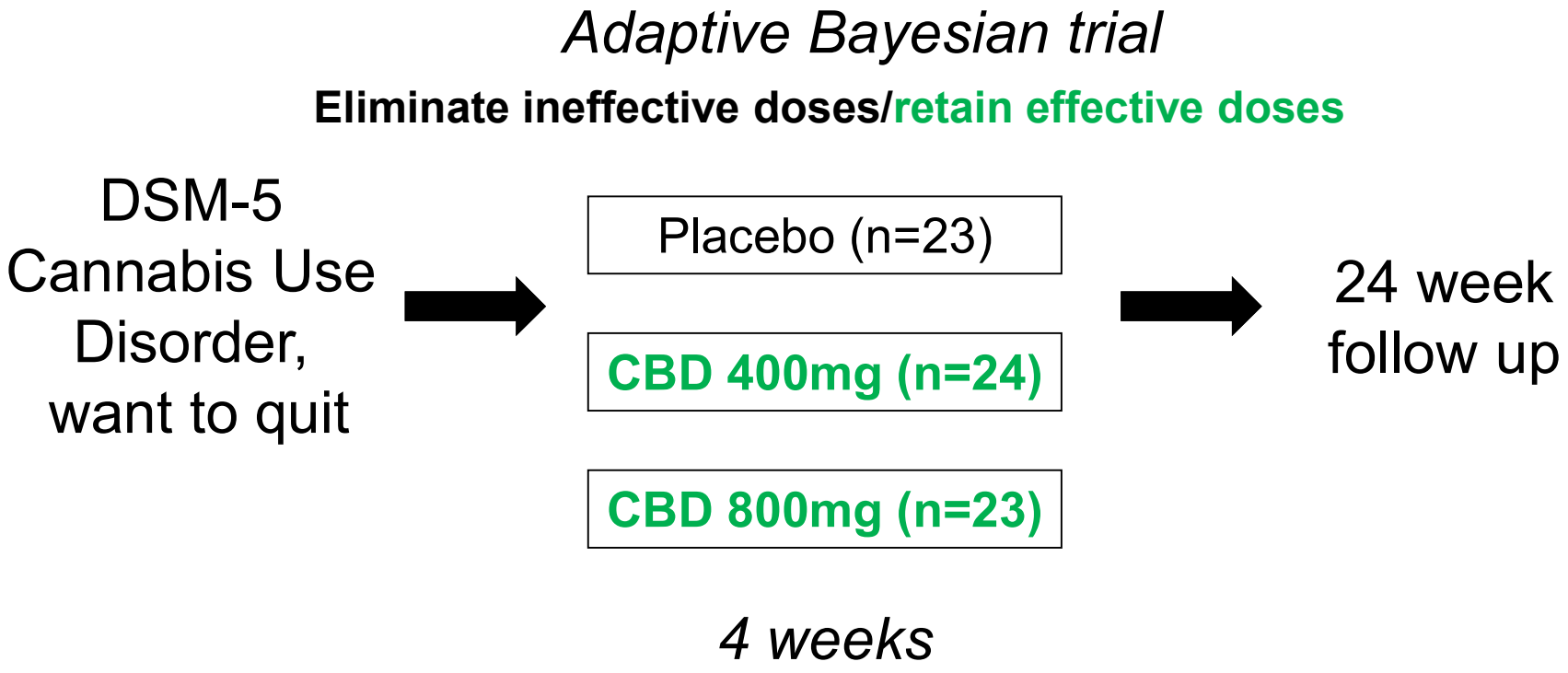
# Cannabidiol as a novel treatment for CUD



# Interim analysis



# Final analysis



# Cannabidiol as a novel treatment for CUD

Frequentist statistics: probability of observed *data* given null hypothesis being true

**Bayesian statistics: probability of *hypothesis* being true given the observed data**

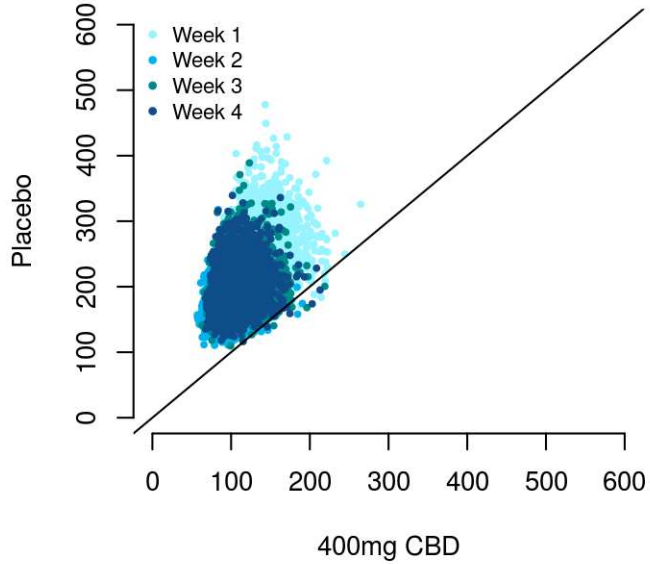
Upper/lower thresholds: **0.9 (effective)**; **0.1 (ineffective)**

**Primary endpoints: reduced cannabis use**

1. Biological (THC metabolites in urine)
2. Self-report (days abstinent from cannabis)

# Primary endpoint 1: urinary THC

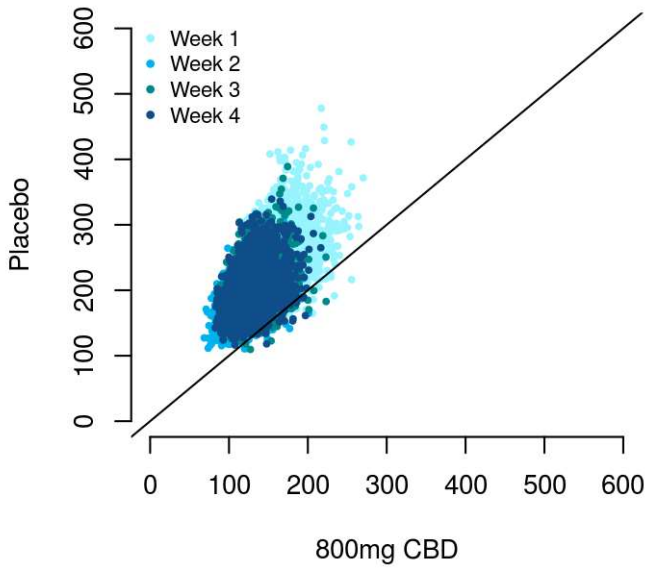
**Expected THC-COOH/creatinine (ng/ml)**




Probability 400mg CBD more effective than placebo given the data = **0.9995**

−94·21 ng/ml (−161·83 to −35·56)

**Expected THC-COOH/creatinine (ng/ml)**



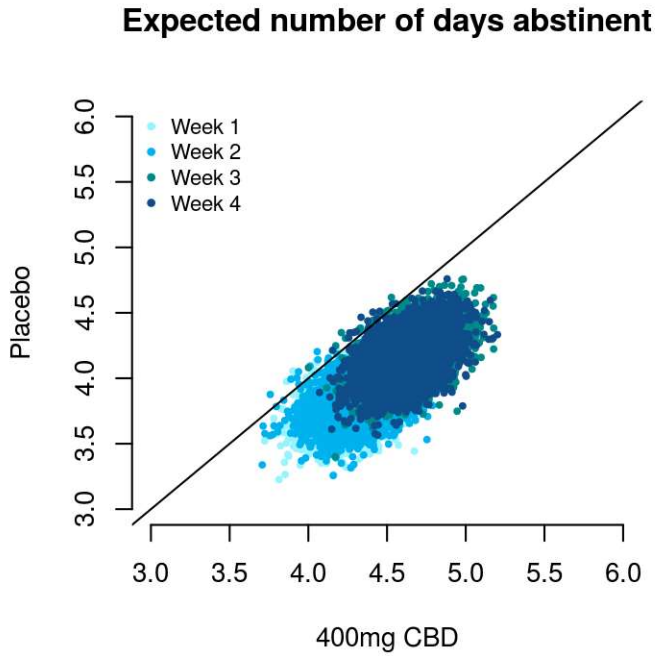

Probability 800mg CBD more effective than placebo given the data = **0.9965**

−72·02ng/ml (−135·47 to −19·52)

Freeman et al. (2020) *Lancet Psychiatry*

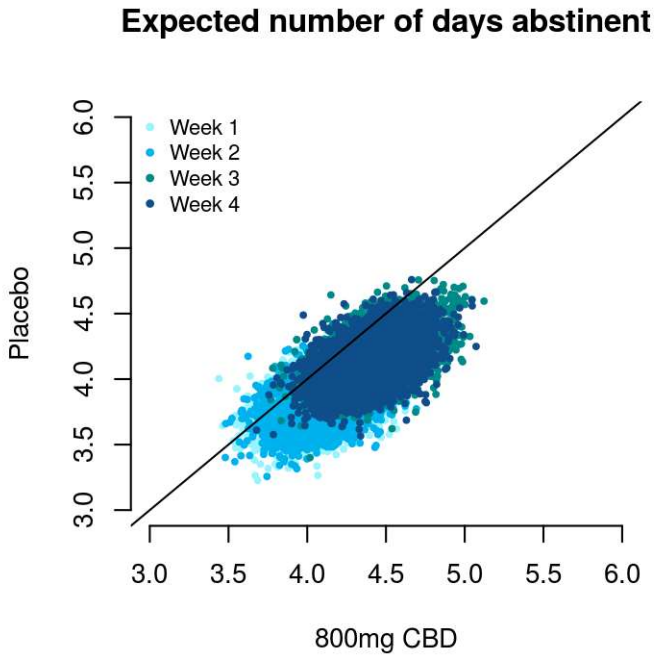
**P*u* = 0.9 (effective), P*l* = 0.1 (ineffective)**

# Primary endpoint 2: days abstinent




Probability 400mg CBD more effective than placebo given the data = **0.9966**

0·48 (0·15 to 0·82)




Probability 800mg CBD more effective than placebo given the data = **0.9247**

0·27 (−0·09 to 0·64)

Freeman et al. (2020) *Lancet Psychiatry*

**P*u* = 0.9 (effective), P*l* = 0.1 (ineffective)**

# Outline of talk

1) Scale of the problem

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4) Harm reduction

# Harm reduction


No recommendations based on ***quantity*** of use

Fischer et al. (2017) *American Journal of Public Health*

Government of Canada / Gouvernement du Canada

# Harm reduction

Lower risk alcohol use: core recommendations based on ***quantity*** of use

Finland: 1 standard drink (dose) = 12g alcohol

**Table 2.** Task Force Recommendation on Risk Levels for Alcohol Use

| |
|---|
| **The high risk** level is 23 to 24 doses per week for men and 12 to 16 doses per week for women. This can be considered as an alert threshold at which alcohol consumption should be addressed at the latest. Rationale: These doses increase morbidity and significantly increase the risk of mortality [2]. |
| **The** level of **moderate risk** is 14 doses per week for men and 7 doses per week for women. Justification: These dose levels increase the GT values [15]. |
| Alcohol use, which **is unlikely to pose a risk to a healthy person of working age**, is 0-1 doses per day for women and 0-2 doses per day for men. Basis: Finnish and Nordic nutrition recommendation [21]. |

# Standard THC units

1. Should reflect quantity of key pharmacological constituent (THC)

2. Should apply to all cannabis products

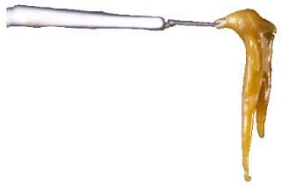
A

B

C

**Standard THC Units = *milligrams* of THC**

D



E

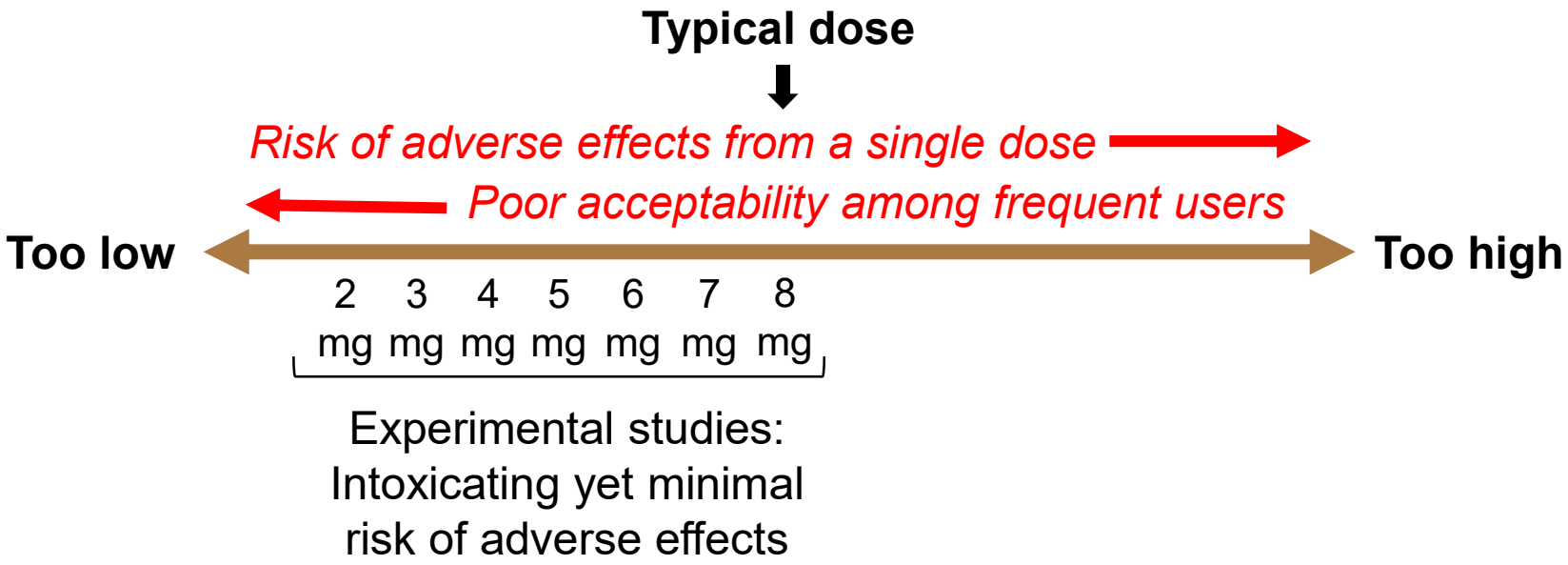
F

(similar to *grams* of alcohol)

Freeman & Lorenzetti (2019) *Addiction*

# Standard THC Units

**How many milligrams of THC should form one standard unit?**




Freeman & Lorenzetti (2019) *Addiction*

# Standard THC Units

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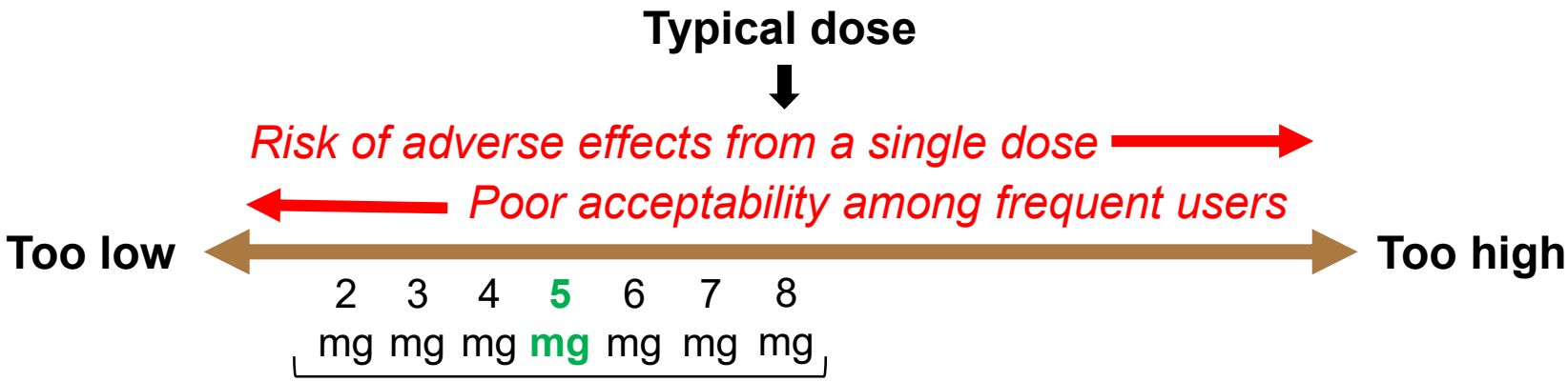



Experimental studies:
Intoxicating yet minimal
risk of adverse effects

**5mg** compatible with existing
legislation in Canada and USA
(limits of 5mg or 10mg per serving)

Freeman & Lorenzetti (2019) *Addiction*

# Standard THC Units

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION

Addiction Opinion and Debate | Full Access

## 'Standard THC Units': a proposal to standardise dose across all cannabis products and methods of administration

Tom P. Freeman, Valentina Lorenzetti

First published: 12 October 2019 | https://doi.org/10.1111/add.14842

Nora Volkow
National Institute on Drug Abuse

March 23, 2020 *By Dr. Nora Volkow*

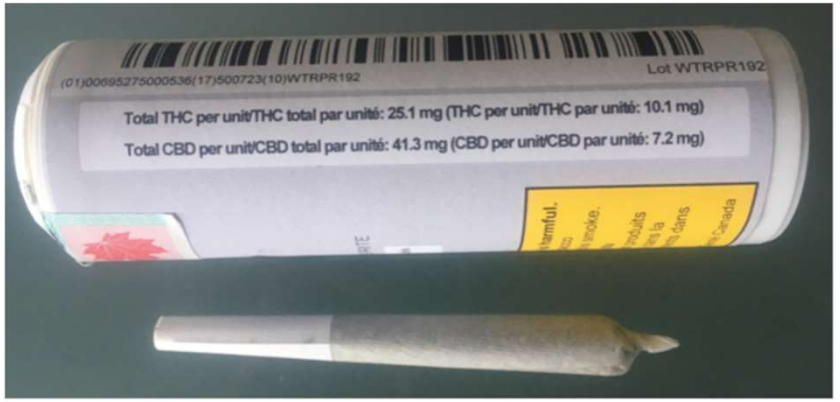
### *Input Invited on the Establishment and Implementation of a Standard Unit Dose of Δ-9-tetrahydrocannabinol (THC) for Cannabis Research*

If a standard unit dose can be established, for it to be maximally useful for research and public health, the research community will need to incorporate it in their measures of use, industry will need to adopt it for labeling, and consumers will need to be educated about what the standard dose means. Indeed, establishment of such a standard would have the greatest impact if universally adopted for commercial product labeling

# Standard THC Units


Package of cannabis flower containing 54mg THC
"*This package contains 10.8 standard doses of THC*"

Pre-rolled joints, 25mg THC
"*Each joint contains 5.0 standard doses of THC*"



# Conclusions

- THC and CBD: contrasting effects
- THC increased in cannabis over time, CBD stable
- High THC products = greater severity of cannabis use disorder; increased incidence of treatment
- Novel treatment: CBD more efficacious than placebo at daily doses of 400mg and 800mg
- Novel harm reduction approach: Standard THC unit - improve understanding of dose; guidelines for safer use

# Thanks to colleagues and funders

Val Curran

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Chandni Hindocha

Gianluca Baio

Ali Mofeez

Adam Winstock

Lindsey Hines

Michael Lynskey