

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



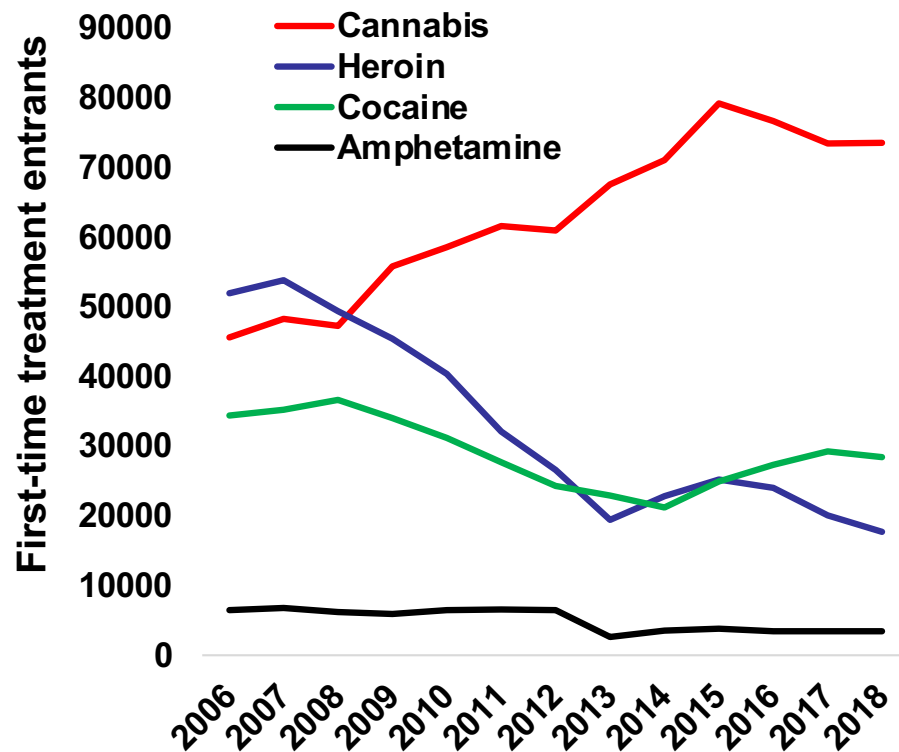
**Tom Freeman, PhD**  
**Addiction and Mental Health Group**  
**University of Bath, UK**



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# Cannabis use disorder

## Health burden in Europe



EMCDDA (2020)

**No pharmacotherapies**  
*Need treatments*

**~95% do not seek treatment**  
*Need harm reduction*

# Cannabis plant

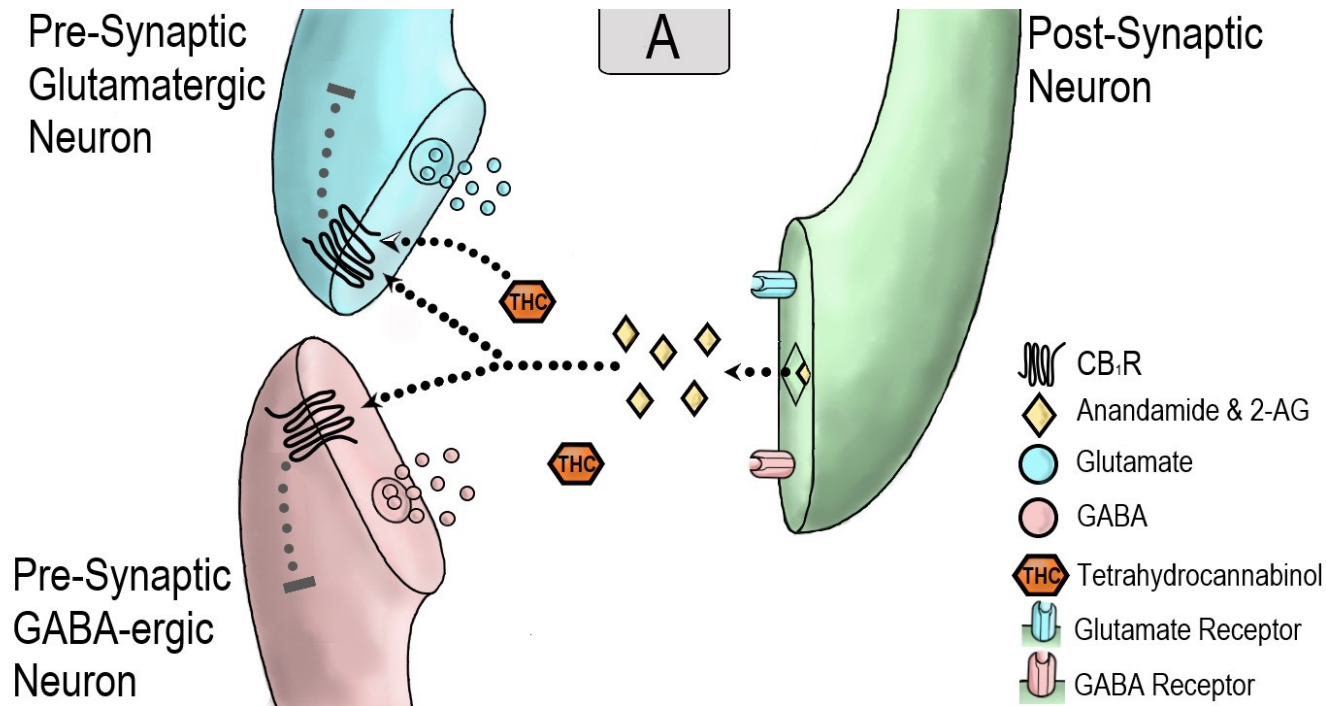


**At least 144 (phyto)cannabinoids**  
Act on endocannabinoid system

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



# Effects of THC

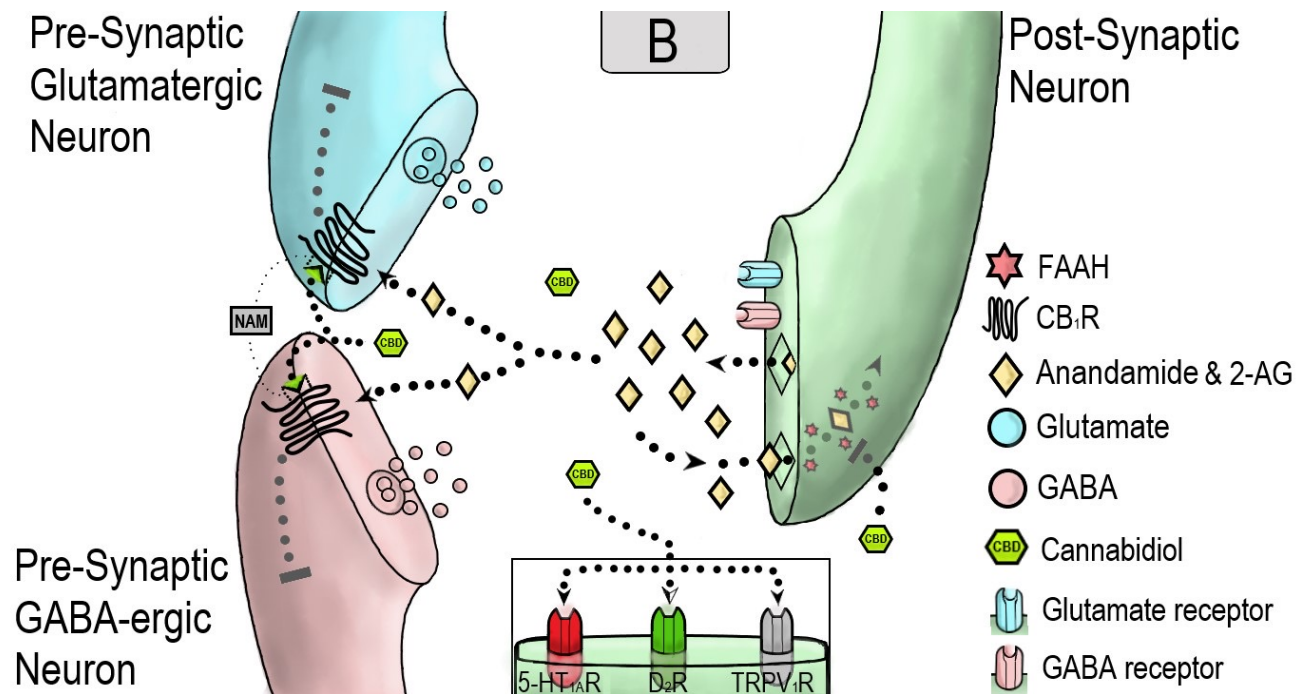


Partial agonist at CB1Rs

Inhibits release of excitatory (glutamate) and inhibitory (GABA) neurotransmitters



# Effects of CBD



Minimal direct action at CB1Rs

Prevents other agonists binding to CB1Rs (Negative Allosteric Modulation)

Inhibits FAAH (which breaks down endocannabinoids)

# Effects of THC and CBD

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

- Intoxicating
- ↑Anxiety & psychotic-like symptoms
- Cognitive impairment
- Addiction

## CBD (cannabidiol)

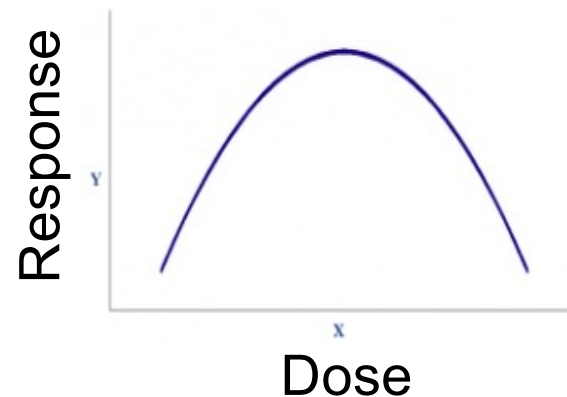
- Non-intoxicating
- ↓Anxiety & psychotic-like symptoms
- Pro-cognitive effects
- Anti-addictive effects



# CBD for treatment of cannabis use disorder

**Novel treatment strategy**; no previous evidence on efficacy/safety; optimal doses (if any) unclear

CBD and anxiety: inverted-U

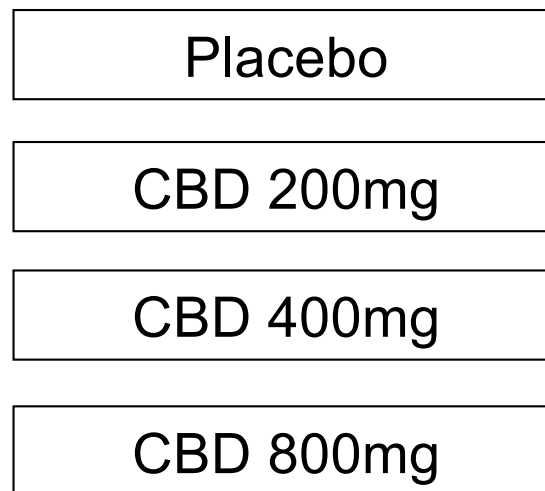


# CBD for treatment of cannabis use disorder

*Adaptive Bayesian phase 2a trial*

**Eliminate inefficacious doses/retain efficacious doses**

DSM-5  
Cannabis Use  
Disorder,  
want to quit



24 week  
follow up

*4 weeks*

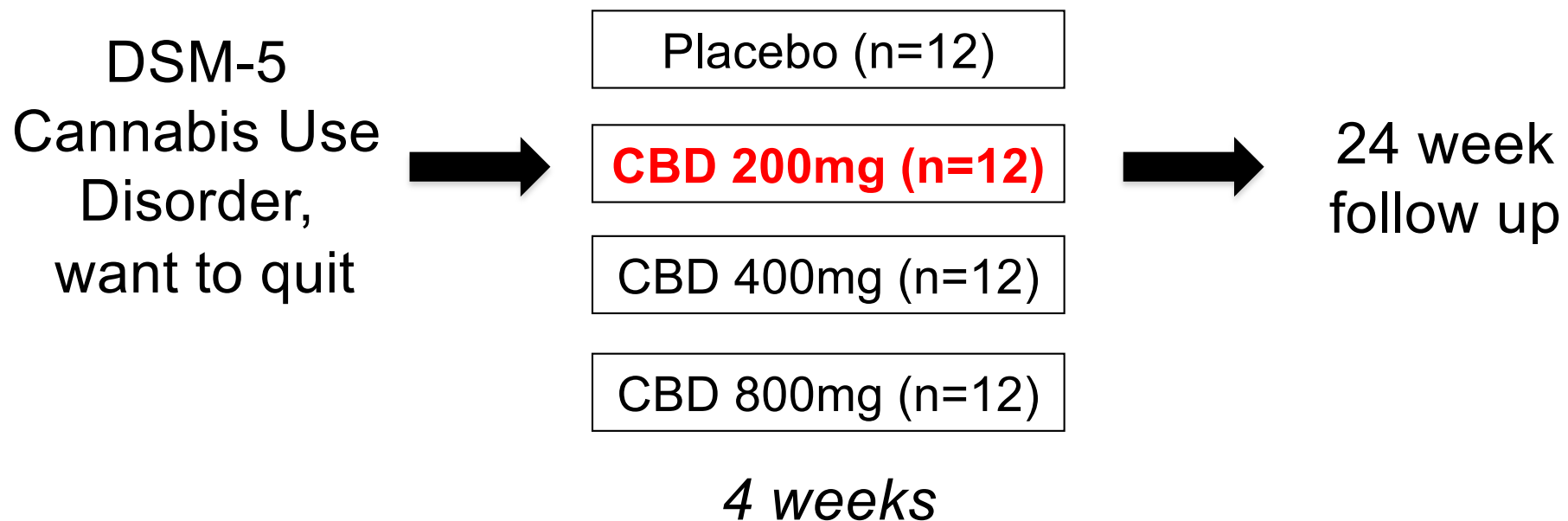


# CBD for treatment of cannabis use disorder

## *Interim analysis*

### *Adaptive Bayesian phase 2a trial*

**Eliminate inefficacious doses/retain efficacious doses**

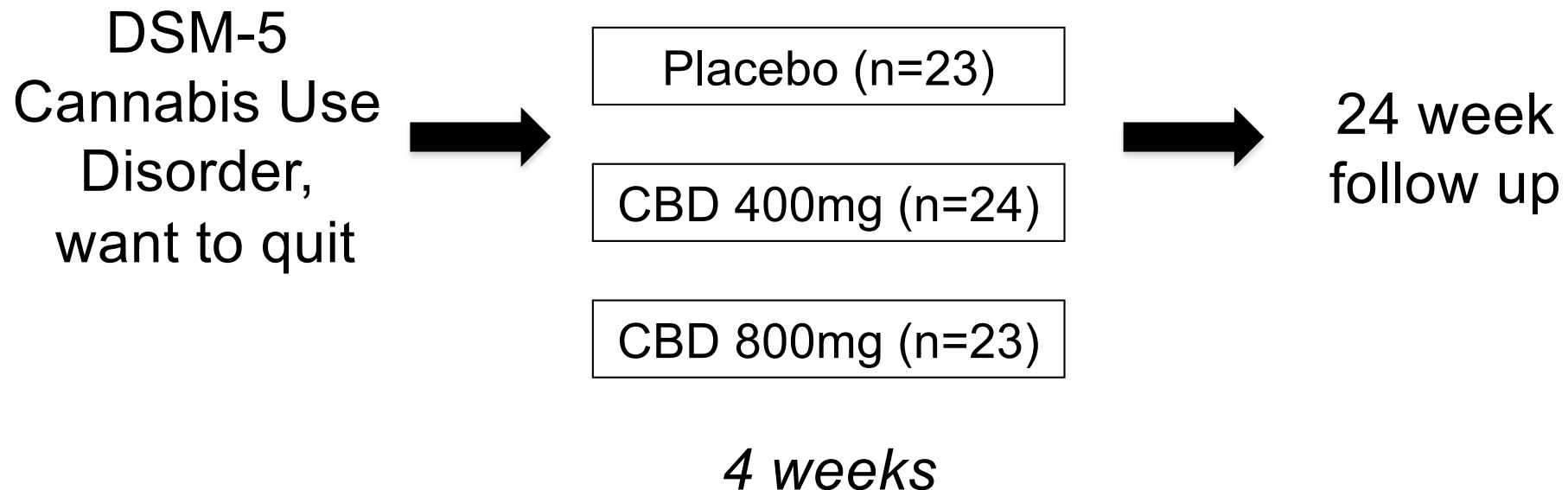


# CBD for treatment of cannabis use disorder

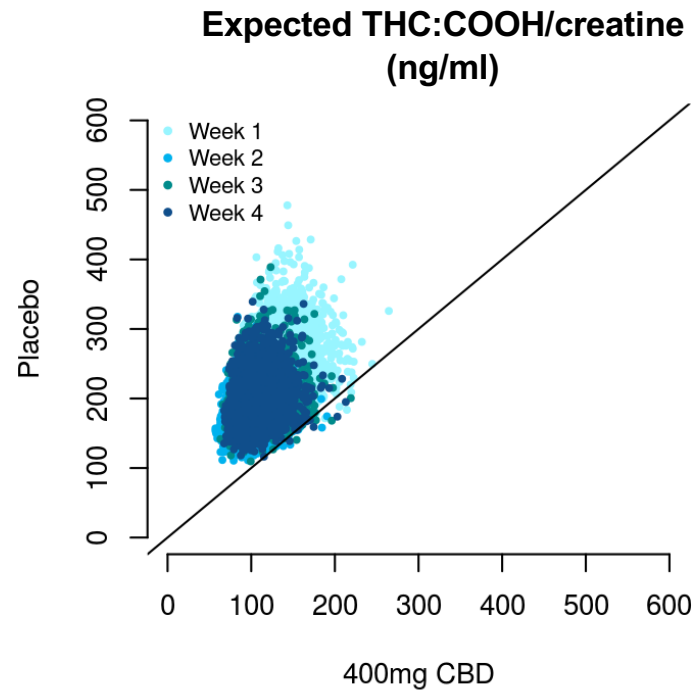
## *Final analysis*

### *Adaptive Bayesian phase 2a trial*

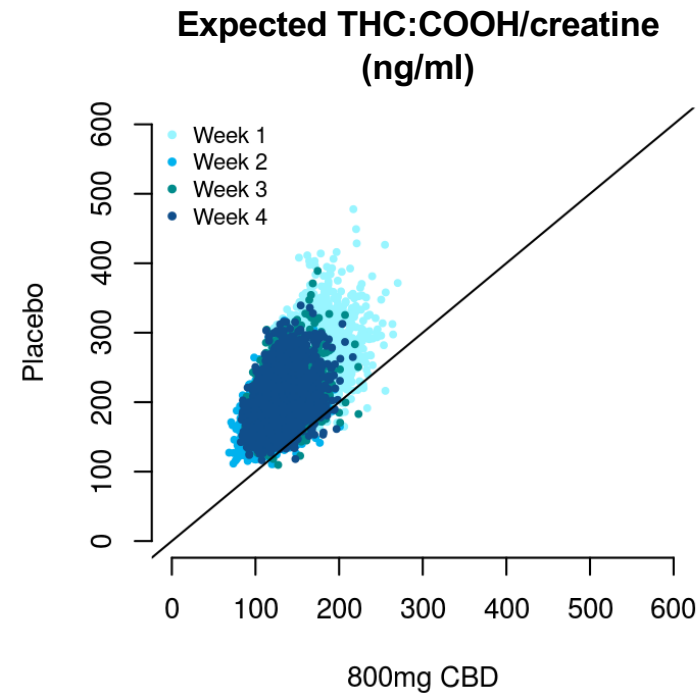
**Eliminate inefficacious doses/retain efficacious doses**



# Primary endpoint 1: urinary THC metabolites



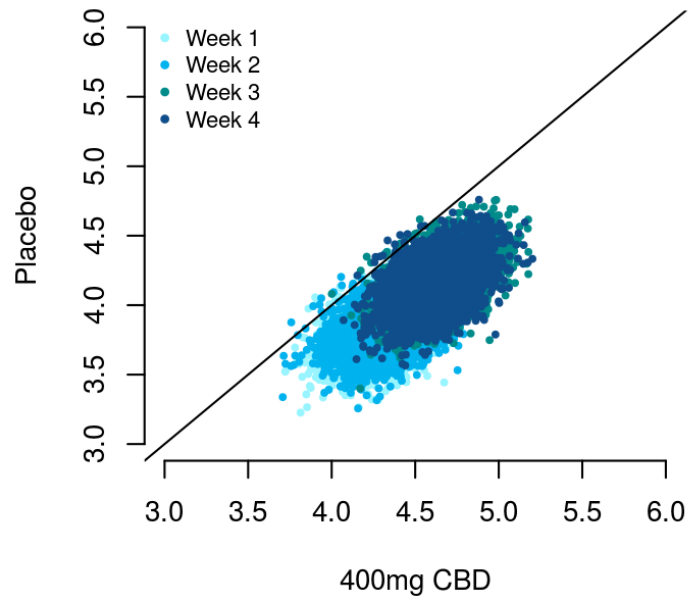
400mg CBD more efficacious than placebo **P = 0.9995**



800mg CBD more efficacious than placebo **P = 0.9965**

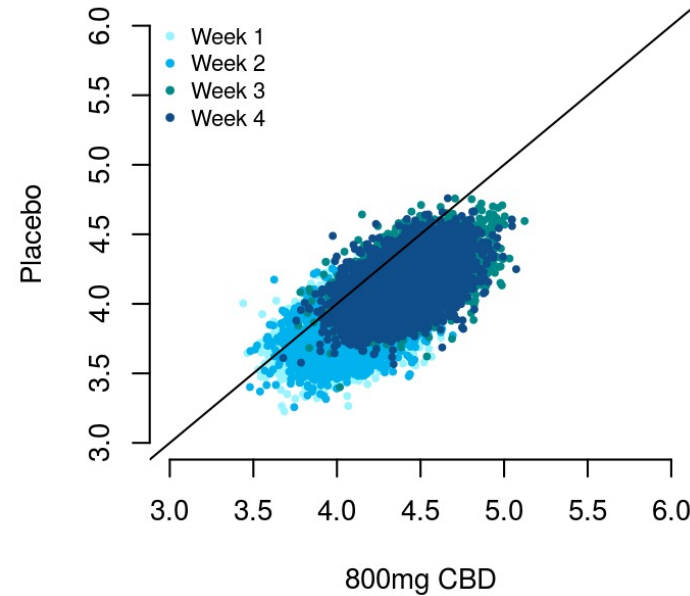
# Primary endpoint 2: days abstinent

Expected number of days abstinent



400mg CBD more efficacious  
than placebo **P = 0.9966**

Expected number of days abstinent



800mg CBD more efficacious  
than placebo **P = 0.9247**



# CBD for treatment of cannabis use disorder

**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*

Phase 2a, single site, 4-week treatment

400mg and 800mg safe and more efficacious than placebo  
for both primary endpoints of cannabis use

# CBD for treatment of cannabis use disorder



Translational Psychiatry

[www.nature.com/tp](http://www.nature.com/tp)

ARTICLE **OPEN**

 Check for updates

Effects of cannabidiol on anandamide levels in individuals with cannabis use disorder: findings from a randomised clinical trial for the treatment of cannabis use disorder

Daniel Ying-Heng Hua <sup>1</sup>, Chandni Hindocha<sup>2</sup>, Gianluca Baio<sup>3</sup>, Rachel Lees<sup>1</sup>, Natacha Shaban<sup>4</sup>, Celia J. Morgan<sup>5</sup>, Ali Mofeez<sup>6</sup>, H. Valerie Curran<sup>2</sup> and Tom P. Freeman <sup>1</sup>✉

CBD increased anandamide levels compared to placebo



# CBD for treatment of cannabis use disorder

**STUDY PROTOCOL**

**Open Access**

A phase III multisite randomised controlled trial to compare the efficacy of cannabidiol to placebo in the treatment of cannabis use disorder: the CBD-CUD study protocol



Anjali K. Bhardwaj<sup>1,2\*</sup>, Llew Mills<sup>1,2</sup>, Michael Doyle<sup>1</sup>, Arshman Sahid<sup>1,2</sup>, Mark Montebello<sup>1,3</sup>, Lauren Monds<sup>1,3</sup>, Shalini Arunogiri<sup>4</sup>, Paul Haber<sup>1,5</sup>, Valentina Lorenzetti<sup>6</sup>, Dan I. Lubman<sup>4</sup>, Peter Malouf<sup>7</sup>, Mary E. Harrod<sup>8</sup>, Adrian Dunlop<sup>9</sup>, Tom Freeman<sup>10</sup> and Nicholas Lintzeris<sup>1,2</sup>

Ongoing: multisite phase 3 trial

N=250, 12-week treatment, 400mg CBD versus placebo

# CBD and harm reduction

95% don't seek treatment; CBD to reduce harms?



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 <sup>a</sup> ✉, Katherine Petrilli <sup>a</sup>, Rachel Lees <sup>a, b</sup>, Chandni Hindocha <sup>a, d</sup>, Claire Mokrysz <sup>a</sup>, H. Valerie Curran <sup>a</sup>, Rob Saunders <sup>a</sup>, Tom P. Freeman <sup>a, b, c</sup>

- The most common finding was that CBD reduced the acute effects of THC, however, results were mixed.





# CBD and harm reduction

ARTICLE **OPEN**



Does cannabidiol make cannabis safer? A randomised, double-blind, cross-over trial of cannabis with four different CBD:THC ratios

Amir Englund <sup>1,2</sup>✉, Dominic Oliver <sup>2</sup>, Edward Chesney <sup>2</sup>, Lucy Chester<sup>2</sup>, Jack Wilson <sup>3</sup>, Simina Sovi<sup>2</sup>, Andrea De Micheli<sup>2</sup>, John Hodson<sup>4</sup>, Paolo Fusar-Poli<sup>2,5</sup>, John Strang<sup>1,6</sup>, Robin M. Murray <sup>2</sup>, Tom P. Freeman<sup>7</sup> and Philip McGuire <sup>2</sup>

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No effect of CBD at four different CBD:THC ratios

Doses of CBD **very low** in natural cannabis

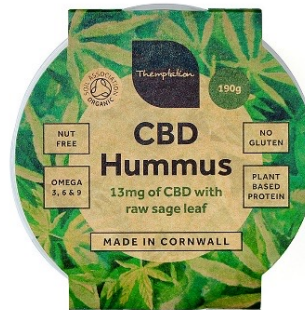
## Consumer CBD products



'Cannabis light'



CBD oil



CBD hummus



CBD dog treats

- Daily doses ~25mg CBD/day; clinical trials: 200-1500mg
- ~Half of contain traces of THC (making them illegal)

# THC and harm reduction



Comparing today's cannabis to 60's/70's:  
*"Like comparing the buckshot in a shotgun shell to a laser-guided missile - they're different"*

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REVIEW

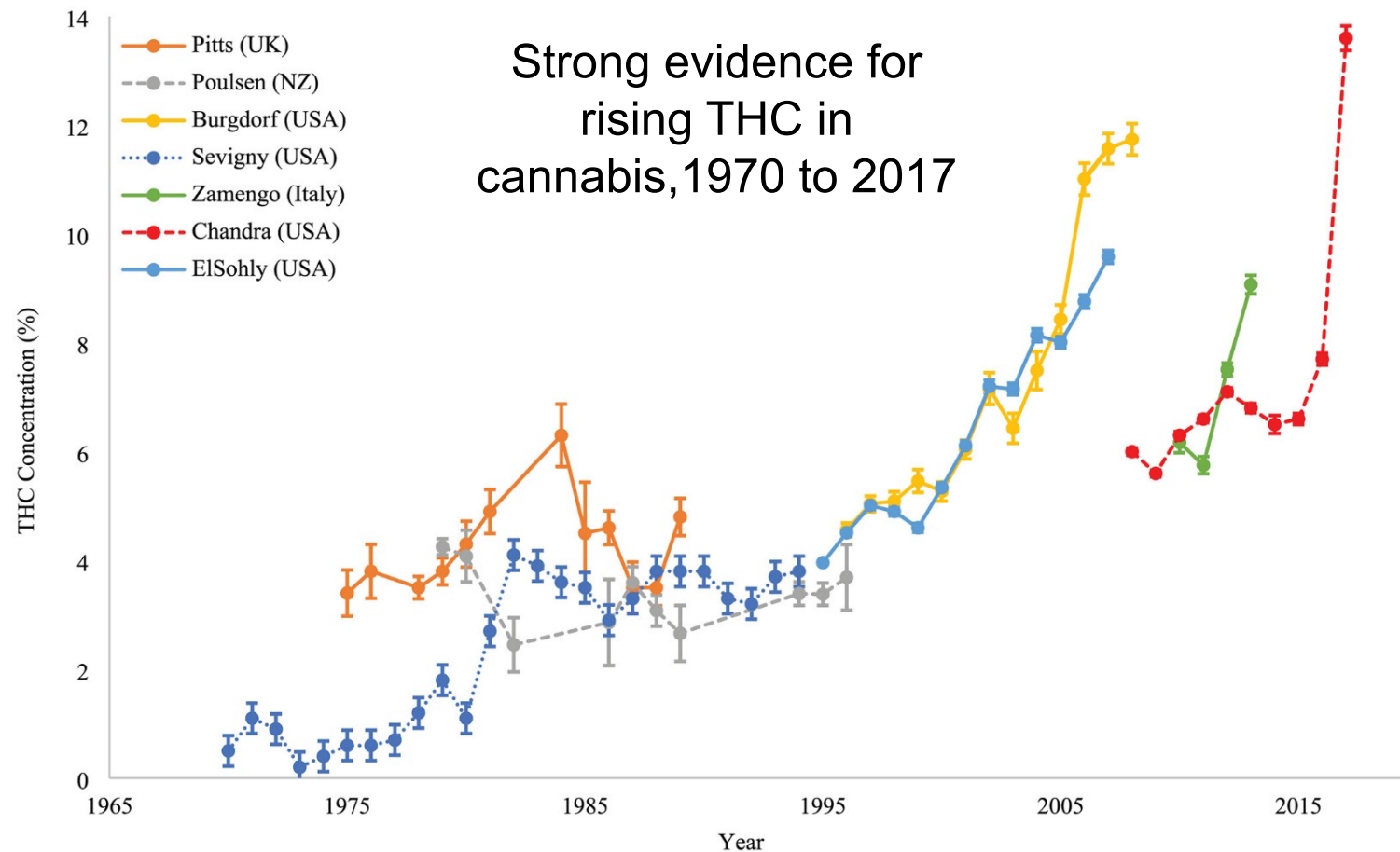
doi:10.1111/add.15253

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

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

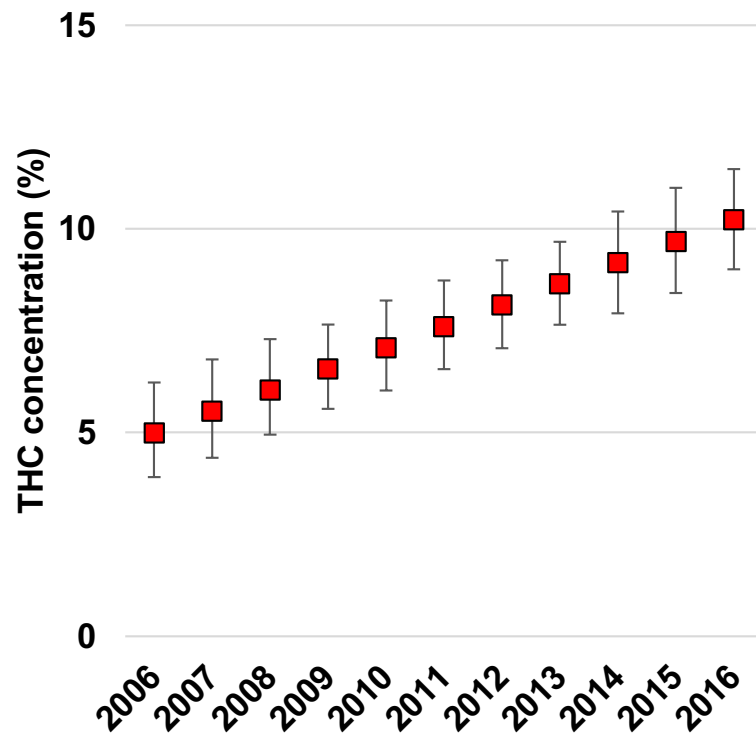


# THC and harm reduction



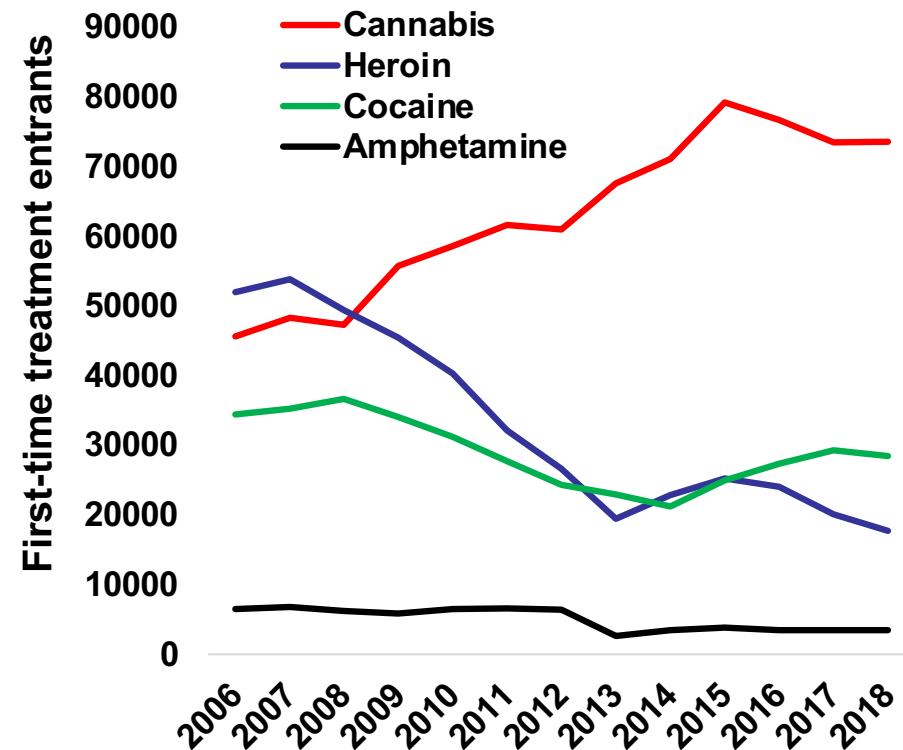
# THC and harm reduction

## Cannabis potency in Europe



Freeman et al. (2019) *Addiction*

## Treatment in Europe



EMCDDA (2020)

# THC and harm reduction

## Cannabis potency (THC%)



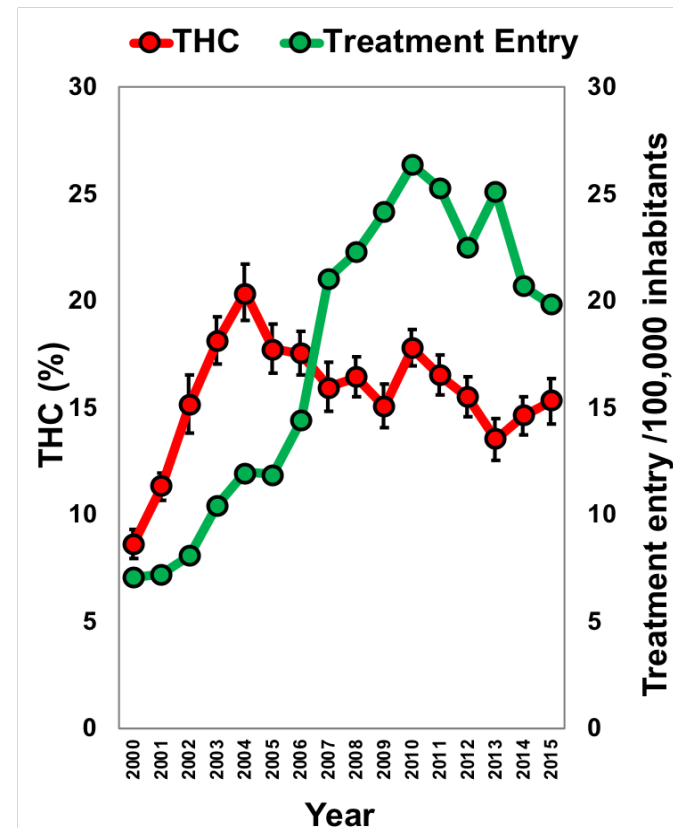
Randomized sampling from  
'coffee shops'

## Cannabis treatment



First-time clients presenting with  
cannabis problems

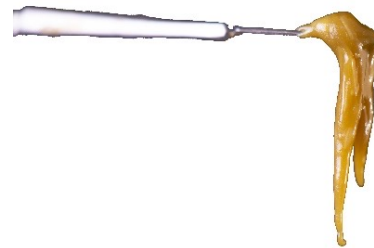
## THC and treatment



# THC and harm reduction

## Association of cannabis potency with mental ill health and addiction: a systematic review

*Kat Petrilli, Shelan Ofori, Lindsey Hines, Gemma Taylor, Sally Adams, Tom P Freeman*



Lower potency products: reduce risks of cannabis use disorder

Potency a “proxy” measure for THC dose

Precise measure of THC dose could improve harm reduction

# How should we measure dose of THC?

## Alcohol

Un verre standard =



**1 unit = 10g alcohol**



# How should we measure dose of THC?

## Novel strategy – the “standard THC unit”

*1. Should reflect dose of primary pharmacological constituent (i.e., THC, in milligrams)*


*2. Should apply to all products and methods of administration*



# The standard THC unit

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Addiction Opinion and Debate |  Full Access

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

Tom P. Freeman  Valentina Lorenzetti

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Commentary |  Open Access | 

### Importance of a standard unit dose for cannabis research

Nora D. Volkow  Susan R.B. Weiss

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Commentary |  Free Access

### Standard tetrahydrocannabinol units: an idea whose time has come

David Hammond 

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### The viability of a standard THC unit

Francesca M. Filbey 

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Commentary |  Free Access

### How experimental cannabinoid studies will inform the standardized THC unit

Lucy Chester  Edward Chesney, Dominic Oliver, Jack Wilson, Amir Englund

# The standard THC unit

## Reporting requirement for US National Institutes of Health



College on Problems of Drug Dependence








# The standard THC unit

METHODS AND TECHNIQUES

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SSA

**Enhanced cannabis timeline followback (EC-TLFB):  
Comprehensive assessment of cannabis use including standard  
THC units and validation through biological measures**

Kat Petrilli<sup>1</sup>  | Will Lawn<sup>2,3,4</sup>  | Rachel Lees<sup>1</sup>  | Claire Mokrysz<sup>4</sup> |  
Anya Borissova<sup>5,6</sup> | Shelan Ofori<sup>4</sup> | Katie Trinci<sup>4</sup> | Renato dos Santos<sup>7</sup> |  
Harry Leitch<sup>4</sup> | Shilpa Soni<sup>4</sup> | Lindsey A. Hines<sup>1,8</sup>  | Valentina Lorenzetti<sup>9</sup>  |  
H. Valerie Curran<sup>4</sup> | Tom P. Freeman<sup>1</sup>

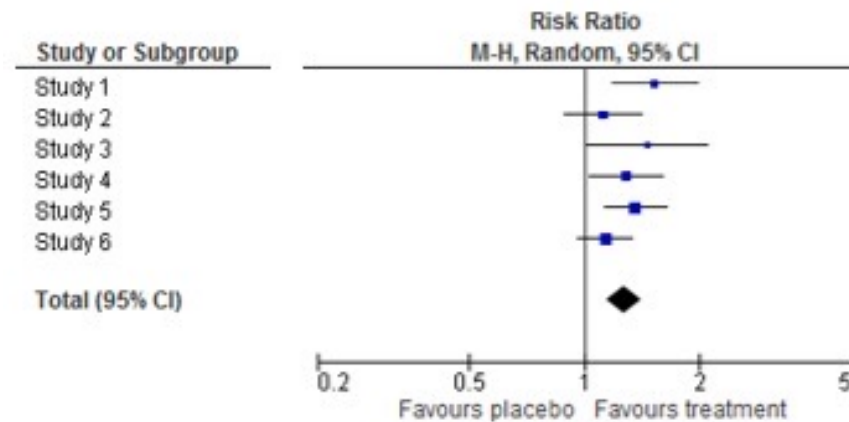
Can be measured using enhanced timeline followback (EC-TLFB)

Highest validity of all cannabis use measures



# The standard THC unit

- Precision of dose
- Quality of evidence
- Product labelling
- Harm reduction



## Conclusions

- Significant health burden of cannabis use disorder
- CBD potential treatment; further evidence needed
- Cannabis potency for harm reduction (proxy for dose)
- Standard THC unit: precise measure of dose for harm reduction (like alcohol unit)





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## Thanks to colleagues and funders

Val Curran

Valentina Lorenzetti

Michael Lynskey

Celia Morgan

Sam Craft

Marta Di Forti

Nick Lintzeris

Chandni Hindocha

Gianluca Baio

Ali Mofeez

Peggy van der Pol

Michael Bloomfield

