# The value of Real World Evidence in Cannabis Medicine

Anne Katrin Schlag PhD

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Drug Science

# Conflict of interests

*Drug Science receives an unrestricted educational grant from a consortium of medical cannabis companies to further its mission, that is the pursuit of an unbiased and scientific assessment of drugs regardless of their regulatory class.*

# Presentation outline

*Why do we* need *real world evidence  in cannabis medicine?*

Focus on two types of RWE:

Selected findings from T21 (focusing on psychiatric disorders): large scale patient registry

Case series paediatric epilepsy: individual in depth case studies

- Different RWD collections offering evidence that RCTs cannot…

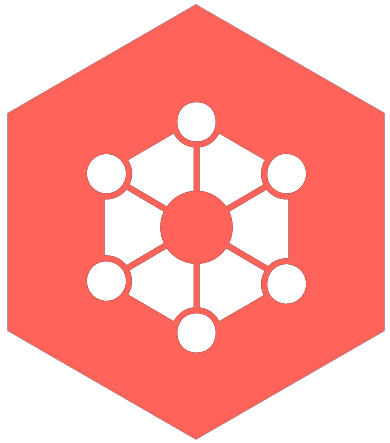
# Background: Medical Cannabis in the UK

- In the UK, medical cannabis has been made legal since November 1st 2018
- NICE (2019) recommends the use of (a limited range of) cannabis-based medicinal products (CBMPs) for three main conditions: chemotherapy induced nausea and vomiting, spasticity from MS, severe treatment-resistant epilepsy
- After over 7(!) years, only a handful of full spectrum NHS prescriptions have been written to date- more private prescriptions but at high cost
- Barriers to prescribing remain, incl. lack of randomized controlled trial (RCT) evidence

- If there is a lack of RCTs, what can we do?
- Real world evidence

# Project Twenty21- quick summary

UKs biggest non profit national medical cannabis real-world registry



Multi-stakeholder partnership with academia, industry, clinicians and patients

Largest body of evidence for the effectiveness and tolerability of medical cannabis

Publication of data, regardless of whether favourable or not

Over 4500 patients accessed medical cannabis through project

# Indications Covered

| Participation is not limited by primary condition |
| --- |
| Condition specific self report measures for 'target' conditions: |
| **Chronic pain** – Brief pain inventory short form. |
| **Anxiety disorder** – Generalized Anxiety Disorder 7-Item Scale |
| **PTSD** - Posttraumatic Stress Disorder Checklist for DSM-5. |
| **Tourette's syndrome** - Tourette's syndrome is the Yale Global Tic Severity Scale. |
| **MS** - Expanded Disability Status Scale. |
| **Substance use disorder** – Severity of Dependence Scale. |
| **Epilepsy** - Patient Weighted Quality of Life in Epilepsy + number of seizures. |

Measures assessed on all patients include sleep quality, quality of life (EQ-5D), and *depression/mood (PHQ-9).*

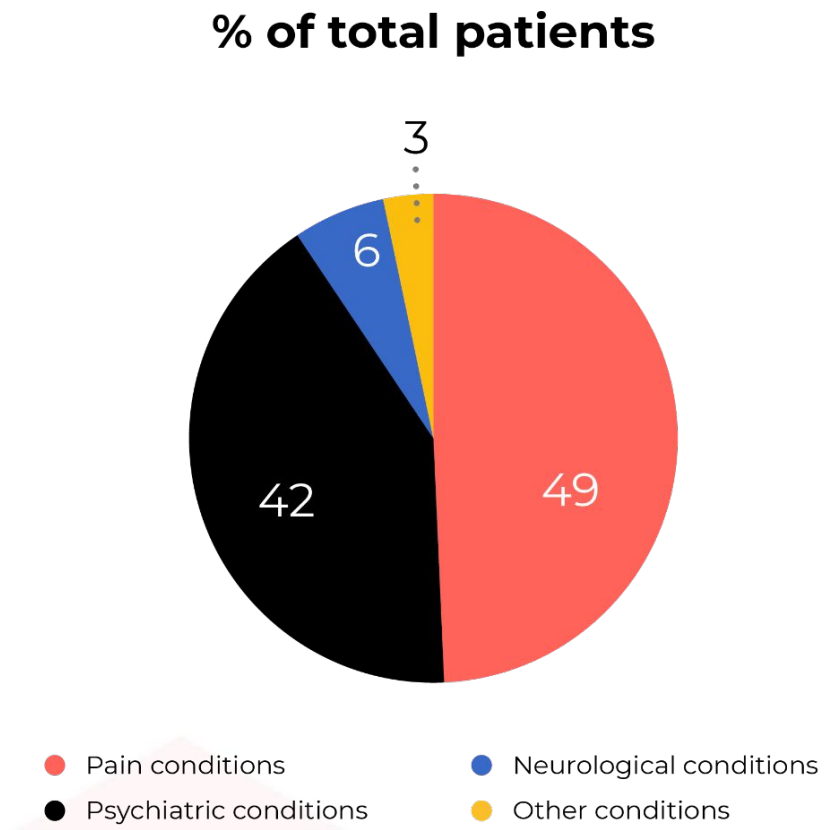
Demographics, diagnosis (and comorbid conditions), medication and previous failed treatments, cannabis product and dosing, adverse events, and primary self-report outcome measure for each.

# Products prescribed

- THC-dominant flower (64.0% of all prescriptions),
- THC-dominant oil (17.8%)
- Balanced oil (11.8%)
- CBD dominant oil (4.5%)
- Balanced flower (1.4%)
- CBD dominant flower (0.5%)

- Participants reported receiving an average of 2.01 (range = 1-7) prescriptions

| Total no. of patients | 4546 |
|---|---|
| Completed 1+ follow-ups | 3164 |
| 3 month follow-up completed | 2682 |
| 6 month follow-up completed | 2132 |
| 9 month follow-up completed | 1822 |
| 12 month follow-up completed | 1520 |
| 15 month follow-up completed | 1297 |
| 18 month follow-up completed | 10091 |
| 21 month follow-up completed | 882 |
| 24 month follow-up completed | 674 |
| 27+ month follow-up completed | 539 |



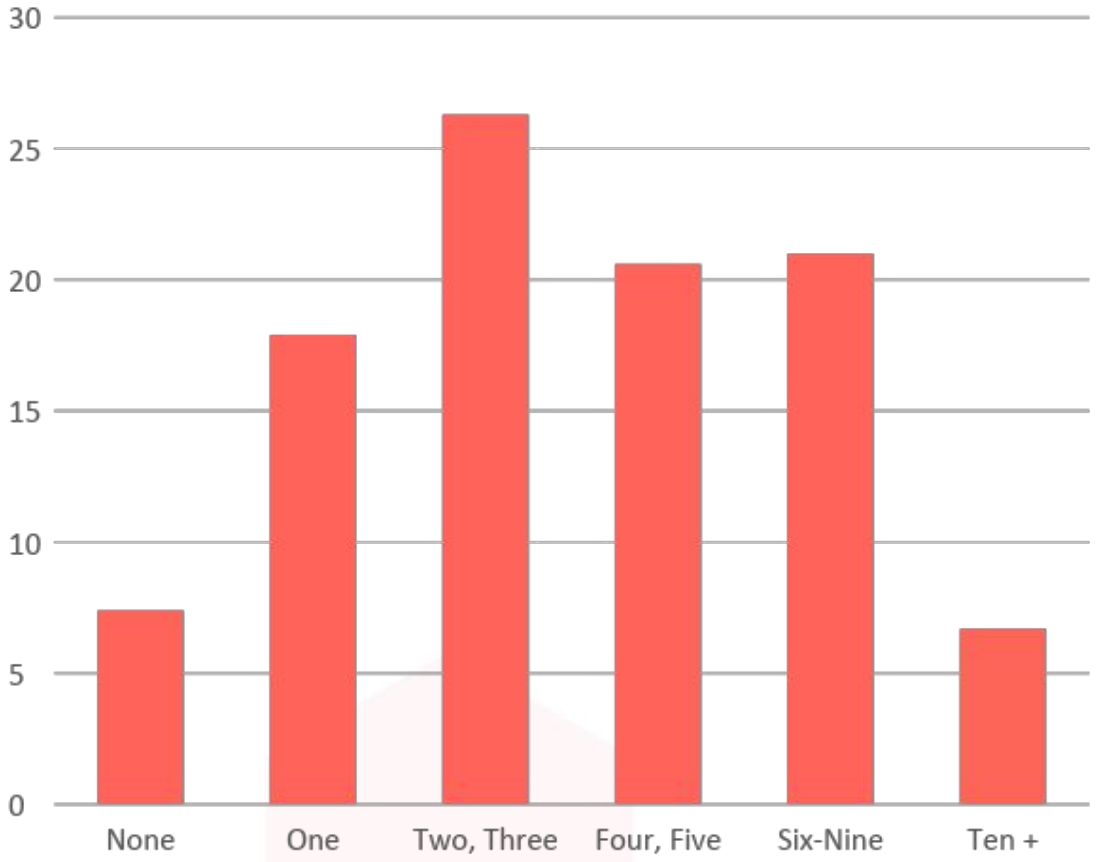
# Multi-morbidity common

Participants are asked whether they had been diagnosed with any other physical or mental health problems.

Most common:

- **Stress (33.0%)**
- **Insomnia (31.0%)**
- **Depression (48.1%)**
- **Back & neck probs (34.2%)**
- **Anxiety (31.8%)**

- The patients would be excluded from RCTs...



# Cannabis and psychiatric disorders

- Past discussions centred around the potential harms of cannabis use
- Concerns about e.g., dependence and psychosis based on recreational use

- Our understanding of potential benefits of CBMPs to treat psychiatric conditions is still developing- CBMPs in psychiatric disorders is an emergent field

- Limited  randomised controlled trials examined the role of CBMPs to treat psychiatric conditions
- But patients in the real world are being prescribed CBMPs for psychiatric conditions…

Schlag AK, Hindocha C, Zafar R, Nutt DJ, Curran HV. Cannabis based medicines and cannabis dependence: A critical review of issues and evidence. J Psychopharmacol. 2021 Jul;35(7):773-785. doi: 10.1177/0269881120986393. Epub 2021 Feb 17. PMID: 33593117; PMCID: PMC8278552.

# Cannabis and psychiatric disorders: Systematic reviews

- Black et al (2019): evidence of CBMPs to treat psychiatric disorders is mixed/low quality
- Sarris et al (2020): encouraging, albeit embryonic, evidence for CBMPs in the treatment of psychiatric disorders. Supportive findings emerging for some key isolates- however, clinicians need to be mindful of a range of prescriptive and occupational safety considerations, especially if initiating higher dose THC formulas.
- McKee et al (2021): limited evidence for the effectiveness of CBMPs to acutely treat a narrow range of psychiatric symptoms. No evidence supporting the mid- to long-range effectiveness of any currently available CBMP. Quality of evidence assessed as low- to moderate. Importantly, none of the studies discussed in this review presently endorse the use of cannabis flower as a method of treatment for any recognized psychiatric disorder.

Sarris, J., Sinclair, J., Karamacoska, D. *et al.* Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. *BMC Psychiatry* **20**, 24 (2020). https://doi.org/10.1186/s12888-019-2409-8

McKee KA, Hmidan A, Crocker CE, Lam RW, Meyer JH, Crockford D, Trépanier A, Aitchison KJ, Tibbo PG. Potential therapeutic benefits of cannabinoid products in adult psychiatric disorders: A systematic review and meta-analysis of randomised controlled trials. J Psychiatr Res. 2021 Aug;140:267-281. doi: 10.1016/j.jpsychires.2021.05.044. Epub 2021 Jun 1. PMID: 34119912.

Black, Nicola et al. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. The Lancet Psychiatry, Volume 6, Issue 12, 995 - 1010

# Psychiatric disorders in T21

Agoraphobia
Attention Deficit Hyperactivity Disorder (ADHD)
Cancer Related Anxiety
Eating Disorders
Generalized Anxiety Disorder
Insomnia
Major Depressive Disorder
Obsessive Compulsive Disorder
Other condition that causes Anxiety
Palliative Care Anxiety
Panic Disorder
Post Traumatic Stress Disorder
Social Anxiety Disorder
Substance Use Disorder

BJPsych Open

BJPsych Open (2024)
10, e62, 1–7. doi: 10.1192/bjo.2024.13

# Medicinal cannabis for treating post-traumatic stress disorder and comorbid depression: real-world evidence

Michael T. Lynskey, Alkyoni Athanasiou-Fragkouli, Hannah Thurgur, Anne Katrin Schlag and David J. Nutt

# Background: PTSD and comorbid depression

- CBMPs are increasingly being used to treat post-traumatic stress disorder (PTSD), despite limited RCT evidence of their efficacy.

- PTSD is often comorbid with major depression, and little is known about whether comorbid depression alters the effectiveness of CBMPs.

- In T21 – and in other RWE studies PTSD is one of the most common conditions among people seeking medicinal cannabis

 Our aim: to document the prevalence of depression among individuals seeking CBMPs to treat PTSD and to examine whether the effectiveness of CBMPs varies by depression status.

  *Does comorbid depressed mood alter effectiveness of cannabis for PTSD?*

## Participants

Of 3557 patients (May 2023): 221 (6.2%) reported PTSD as primary condition; 3 months follow up data for 105 patients

Depression data available for 209 (94.6%) of PTSD sample

High prevalence of depression: 77% of PTSD patients meet screening criteria for major depression

## Results

PTSD patients with comorbid depression reported substantially higher levels of PTSD symptomatology (mean = 67.8 vs 47.9; $F(1,205)=116.3$, $p<.001$).

They also reported lower well-being across three indicators: quality of life ($F_{(1,207)}=26.1$, $p<.001$), general health ($F_{(1,205)}=19.9$, $p<.001$) and sleep ($F_{(1,207)}=86.3$, $p<.001$).

Prevalence of depression higher among female PTSD patients (86.3% vs 13.8%; $\chi^2$, 1df = 6.5, $p<.05$) but no age differences between the two groups.

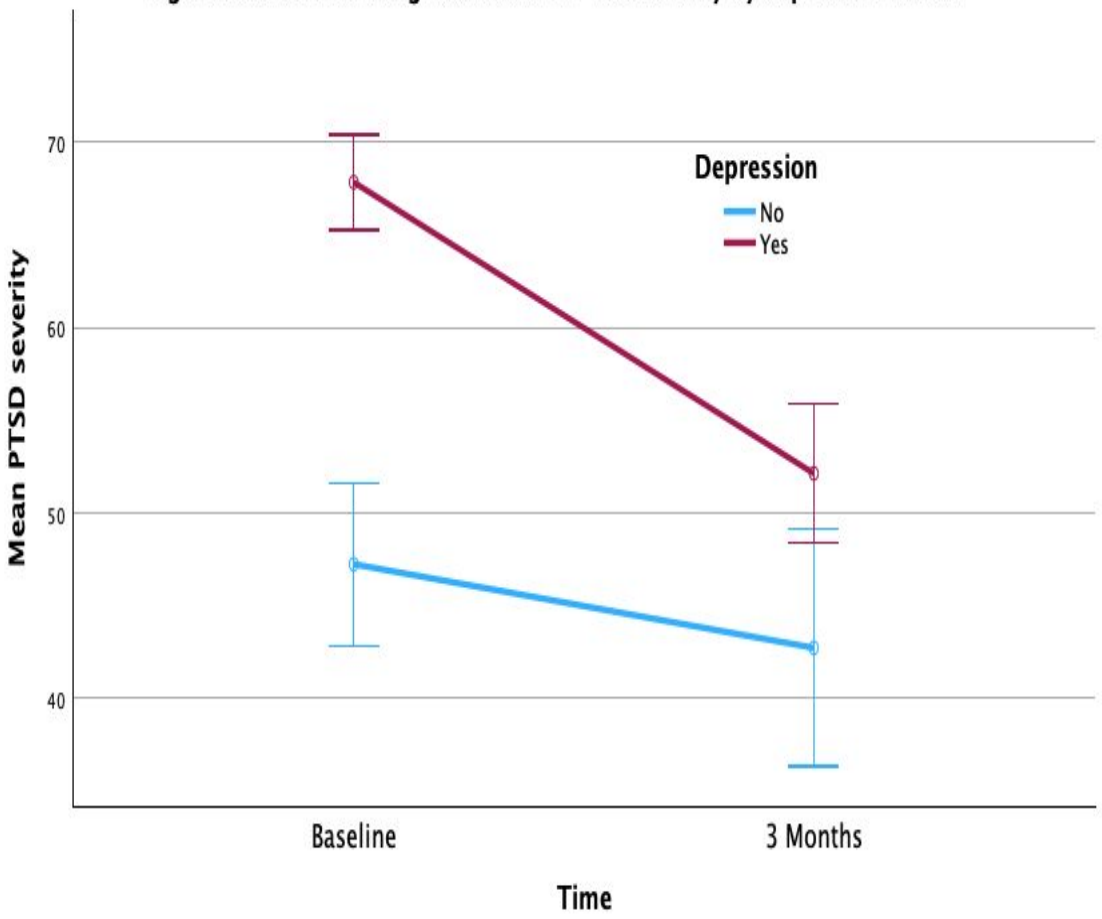
No differences between types of CBMPs used- preference for THC dominant flower

# PTSD comorbid with depression

Significant interaction indicating that *reductions in PTSD at 3 months were HIGHER* in those with comorbid depressed mood at entry to treatment

Concurrent depressed mood should *not* be used to exclude PTSD patients from treatment – or from future trials

Figure 1: Estimated Marginal Means of PTSD severity by depression status



# Implications of our results

1

Treatment with CBMPs associated with substantial reductions in severity of PTSD symptomatology with these improvements being *more* marked in individuals with depression.

2

Findings parallel recent RWE studies of CBMPs for the treatment of PTSD which have indicated benefits of these treatments- CBMPs may have role in addressing this *unmet* need .

3

Results add to emerging literature indicating that the presence of comorbid depression is associated with a *greater* reduction in PTSD symptomatology.

4

Design of future clinical trials: excluding comorbid patients may risk recruiting unrepresentative sample and exclude patients who would most benefit.

# Real world evidence: pediatric epilepsy

Alfie had his first seizure at 8 months and continued to suffer clusters of seizures.

At 5 years old, these clusters came every week. Diagnosed with a rare form of epilepsy called PCDH19, Alfie only responded to intravenous steroids. However, he needed up to five doses every week - a treatment that could eventually kill him.

In 2017, Alfie and his family moved to the Netherlands so they could access medicinal cannabis in an attempt to save his life.

Full extract CBD oil reduced Alfie's seizures, and after adding THC, he went without a seizure for 42 days.

**After a long and hard-fought campaign, Alfie's mother Hannah Deacon secured the first UK licence for medical cannabis products for Alfie.**

On 7 Nov 2018, Alfie received the first NHS prescription for medical cannabis, supervised by Professor Mike Barnes.

# Real world data on prescribed cannabis use: Evidence from Project: T21

Project Twenty21

Drug Science

Drug Science, Policy and Law
Volume 6, December 2020

https://doi.org/10.1177/2050324520974487

SAGE journals

*Article*

## Ending the pain of children with severe epilepsy? An audit of the impact of medical cannabis in 10 patients

**RR Zafar, AK Schlag, and DJ Nutt**

**Background** Scientific and anecdotal evidence suggest that whole plant cannabis extracts are effective in reducing seizure frequency in individuals with a range of epileptic etiologies. We report a case series of 10 individuals using CBMPs in the UK to treat their conditions.

**Methods** In this retrospective study, we report on patients (aged 2-48) with severe, intractable, childhood onset epilepsies using combined cannabinoid therapy. Carers of patients provided details through the charity 'End our Pain' and these data were subsequently analysed. Our primary objective was to assess changes in monthly seizure frequency pre and post initiation of CBMPs. We also report on previous and current AED, CBD:THC daily dose, quality of life and financial costs associated with CBMP private prescription. Change in monthly seizure frequency were assessed using a Wilcoxon Signed-ranks test.

**Results** Of the 10 patients enrolled in the study there was an 97% mean reduction in monthly seizure frequency post initiation of CBMPs which was statistically significant ($Z = 0$, $p < 0{\cdot}01$). We showed a reduction in AED use following initiation of CBMPs from a mean of 8 (±5·98) to 1 (±1·05). All patients were using either Bedrolite or Bedica (Bedrocan International) as their CBMP. Individual daily doses of THC ranged from 6·6mg – 26·5mg and for CBD, 200 mg – 550 mg. Average monthly cost of CBMP was £1816·20.

**Interpretation** Our findings suggest a combination of CBD and THC based products are effective in reducing seizure frequency in a range of epileptic conditions. We highlight the inefficacy of the healthcare system in supporting these patients who bare great personal and financial burdens. We encourage specialist physicians and relevant bodies to permit greater ease of access of these medications to those patients where efficacy has been shown.

**Keywords**
CBD, CBMPs, epilepsy, medical cannabis, pediatric, THC

Imperial College London, UK

**Corresponding author(s):**
David J Nutt, Centre for Psychedelic Research & Neuropsychopharmacology, Division of Psychiatry, Department of Brain Sciences, Imperial College London, Burlington Danes Building, Du Cane Road, London W12 0NN, UK. Email: d.nutt@imperial.ac.uk

Open access Original research

BMJ Paediatrics Open

## Medical cannabis for severe treatment resistant epilepsy in children: a case-series of 10 patients

Rayyan Zafar [1,2], Anne Schlag,[1,2] Lawrence Phillips,[1,3] David J Nutt[1,2]

*Article*

Independent Scientific Committee on Drugs

Drug Science, Policy and Law
Volume 7: 1–10

DOI: 10.1177/2050324521034930
journals.sagepub.com/home/dsp
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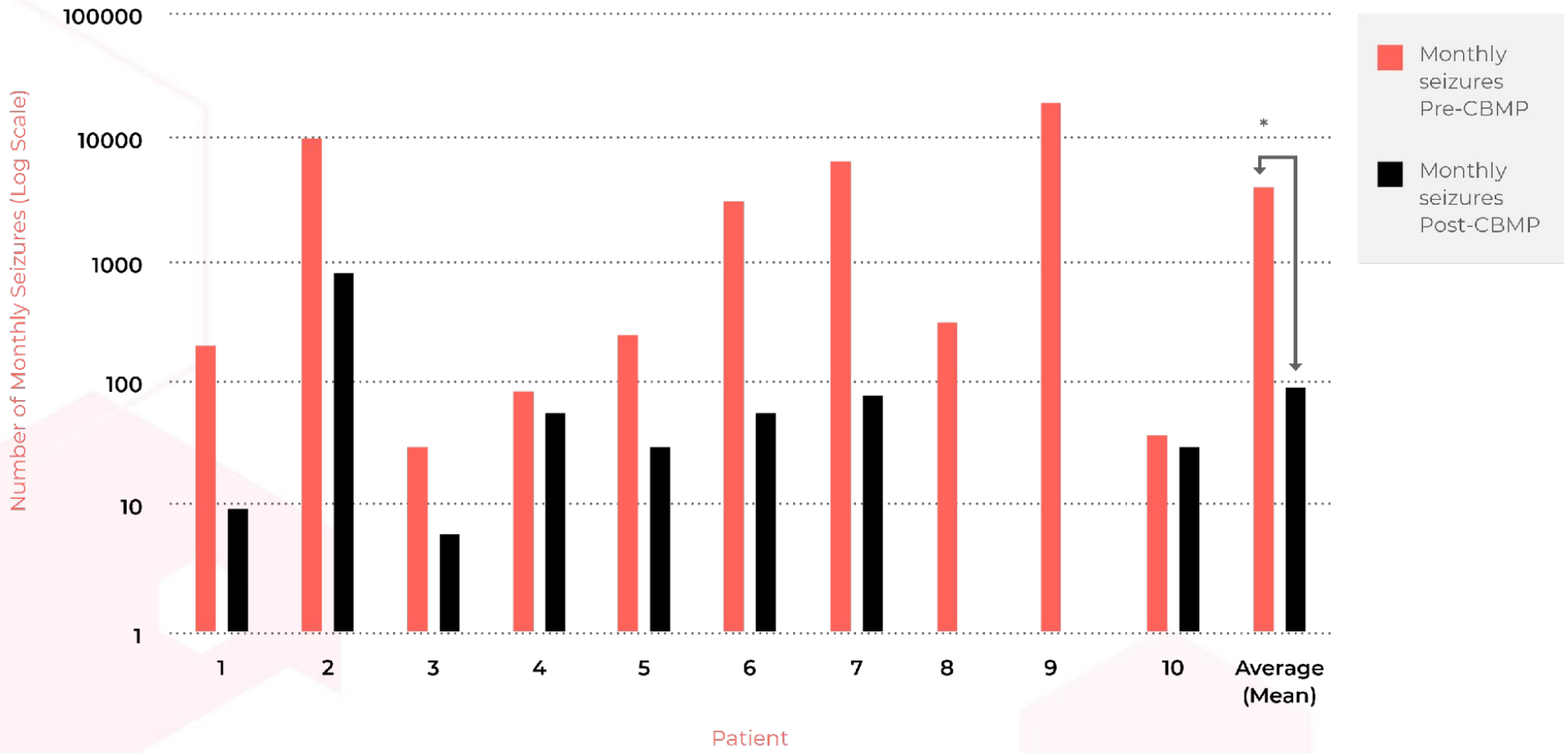
## Medical cannabis and epilepsy in the UK – A qualitative analysis of the carers' perspective: "We're asking for quality of life for our children"

**Anne Katrin Schlag, Rayyan Zafar and David Nutt**

## Log scale of monthly seizure frequency pre & post initiation of Cannabis Based Medicinal Products



# Benefits (and limitations) of RWE...

- **RWE advantages vs clinical trials:** larger patient groups, broader range and ratio of components of CBMPs, inclusion of more and rarer medical conditions, patients with comorbidities and from a wider demographic profile, higher ecological validity, significant cost savings, long-term follow-up...
- **Identifying research areas:** RWE contributes to the development of a pattern of evidence and highlights specific areas for further research
- **Growing Recognition:** Increased interest and acknowledgment of the value of Real-World Evidence (RWE) by regulatory bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA), and National Institute for Health and Care Excellence (NICE).

**Limitations**

- Lack of a placebo control
- Self reported data

# Conclusions

- Promising RWE findings about potential utility of CBMPs for various conditions despite a relative lack of high-quality RCTs testing their efficacy and effectiveness- need for more research, including both RCTs and real-world studies

- While RCTs are still considered the gold standard of medical evidence shortcomings are evident in relation to our findings- advances made in this area more likely to come from RWD collections which typically have more numerous and diverse patients rather than clinical trials

- Exclusion criteria in RCTs may mean that results may not be representative of treatment effects that would be obtained in the real world

- Real world evidence plays an essential role in understanding cannabis medicines

# We thank our T21 patients and partners:




# Thank you!

https://www.drugscience.org.uk

https://www.drugscience.org.uk/twenty21/

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