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

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Summary

Background A substantial and unmet clinical need exists for pharmacological treatment of cannabis use disorders. Cannabidiol could offer a novel treatment, but it is unclear which doses might be efficacious or safe. Therefore, we aimed to identify efficacious doses and eliminate inefficacious doses in a phase 2a trial using an adaptive Bayesian design.

Methods We did a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial at the Clinical Psychopharmacology Unit (University College London, London, UK). We used an adaptive Bayesian dose-finding design to identify efficacious or inefficacious doses at a-priori interim and final analysis stages. Participants meeting cannabis use disorder criteria from DSM-5 were randomly assigned (1:1:1:1) in the first stage of the trial to 4-week treatment with three different doses of oral cannabidiol (200 mg, 400 mg, or 800 mg) or with matched placebo during a cessation attempt by use of a double-blinded block randomisation sequence. All participants received a brief psychological intervention of motivational interviewing. For the second stage of the trial, new participants were randomly assigned to placebo or doses deemed efficacious in the interim analysis. The primary objective was to identify the most efficacious dose of cannabidiol for reducing cannabis use. The primary endpoints were lower urinary 11-nor-9-carboxy-δ-9-tetrahydrocannabinol (THC-COOH):creatinine ratio, increased days per week with abstinence from cannabis during treatment, or both, evidenced by posterior probabilities that cannabidiol is better than placebo exceeding 0·9. All analyses were done on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov (NCT02044809) and the EU Clinical Trials Register (2013-000361-36).

Findings Between May 28, 2014, and Aug 12, 2015 (first stage), 48 participants were randomly assigned to placebo (n=12) and to cannabidiol 200 mg (n=12), 400 mg (n=12), and 800 mg (n=12). At interim analysis, cannabidiol 200 mg was eliminated from the trial as an inefficacious dose. Between May 24, 2016, and Jan 12, 2017 (second stage), randomisation continued and an additional 34 participants were allocated (1:1:1) to cannabidiol 400 mg (n=12), cannabidiol 800 mg (n=11), and placebo (n=11). At final analysis, cannabidiol 400 mg and 800 mg exceeded primary endpoint criteria (0·9) for both primary outcomes. For urinary THC-COOH:creatinine ratio, the probability of being the most efficacious dose compared with placebo given the observed data was 0·9995 for cannabidiol 400 mg and 0·9965 for cannabidiol 800 mg. For days with abstinence from cannabis, the probability of being the most efficacious dose compared with placebo given the observed data was 0·9966 for cannabidiol 400 mg and 0·9247 for cannabidiol 800 mg. Compared with placebo, cannabidiol 400 mg decreased THC-COOH:creatinine ratio by –94·21 ng/mL (95% interval estimate –161·83 to –35·56) and increased abstinence from cannabis by 0·48 days per week (0·15 to 0·82). Compared with placebo, cannabidiol 800 mg decreased THC-COOH:creatinine ratio by –72·02 ng/mL (–135·47 to –19·52) and increased abstinence from cannabis by 0·27 days per week (–0·09 to 0·64). Cannabidiol was well tolerated, with no severe adverse events recorded, and 77 (94%) of 82 participants completed treatment.

Interpretation In the first randomised clinical trial of cannabidiol for cannabis use disorder, cannabidiol 400 mg and 800 mg were safe and more efficacious than placebo at reducing cannabis use.

Funding Medical Research Council.

Introduction

Cannabis is increasingly being legalised for medicinal and recreational use. The long-term effects of these policy reforms are unclear, but might include substantial changes to the types of cannabis products sold and their availability to millions of people worldwide.[1] When considering the potential health effects of cannabis use, its largest contribution to the global burden of disease is the impact of cannabis use disorders, which affect an estimated 22 million people worldwide—similar to the prevalence of opioid use disorders.[2]

Δ-9-tetrahydrocannabinol (THC), a partial cannabinoid receptor agonist, is the primary cannabinoid in cannabis products and causes dose-dependent intoxicating and

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Research in context

Evidence before the study

We searched the Cochrane database and peer-reviewed journal articles in Google Scholar with no language restrictions up to March 12, 2020, using the terms "CBD", "cannabis", and "marijuana". A Cochrane review on pharmacotherapies for cannabis use disorders published in 2019 did not recommend any pharmacotherapies for reducing cannabis use in clinical settings. We found no randomised trials testing cannabidiol as a treatment for cannabis use disorder.

Added value of this study

To our knowledge, this was the first randomised clinical trial of cannabidiol for the treatment of cannabis use disorder. Using an adaptive Bayesian dose-finding design, we showed that at daily oral doses of 400 mg and 800 mg, cannabidiol was a safe and efficacious treatment for reducing cannabis use in people with a cannabis use disorder, assessed by both biological and self-reported measures.

Implications of all the available evidence

Cannabidiol at daily oral doses of 400 mg and 800 mg has potential to address the substantial and currently unmet clinical need for a pharmacological treatment of cannabis use disorders.

reinforcing effects.[1] Studies in Europe[3] and the USA[4] reported a doubling in THC concentrations in cannabis during the past decade. Use of products with higher THC concentrations has been associated with a greater severity of cannabis use disorder[5,6] and increases in the incidence of treated cannabis use disorders.[7] In the past two decades, the proportion of people seeking treatment for cannabis use disorders has risen in all world regions apart from Africa.[8] Cannabis is now the primary drug cited by first-time clients presenting at addiction services across Europe, having increased by 76% in the past decade.[9] Daily use of cannabis with high THC concentrations is associated with a five-times increased risk of psychosis.[10] Despite the substantial and increasing demand for treatment, no pharmacotherapies are recommended for the treatment of cannabis use disorders.[11]

Cannabidiol is another cannabinoid found in many cannabis products.[4] Cannabidiol has minimal direct action at cannabinoid receptors but it has broad pharmacological actions, including inhibiting the hydrolysis and reuptake of endocannabinoids[12] and negative allosteric modulation of cannabinoid receptors.[13] Cannabidiol has generated substantial interest because of its potential medicinal uses[14] and ability to interact with the effects of THC.[15] Cannabidiol has shown therapeutic effects in humans and preclinical models of addiction by reducing the effect of drug-related cues in attentional bias,[16,17] cue-induced craving,[18] and cue-induced reinstatement[19] paradigms. Collectively, these studies suggest that cannabidiol has potential for treating a range of substance use disorders including cannabis,[16] opioids,[18,19] and tobacco.[17,20] A meta-analysis of randomised clinical trials found that cannabidiol was safe and well tolerated with few adverse effects, but interactions with other medications should be monitored carefully because cannabidiol can inhibit cytochrome P450 enzymes.[21]

To our knowledge, no randomised trials have investigated cannabidiol as a potential treatment for cannabis use disorder. Open-label case studies have reported that the use of cannabidiol products was associated with reduced cannabis withdrawal symptoms during cannabis abstinence.[22,23] A 10-week open-label trial found that cannabidiol administration was associated with improvements in psychological wellbeing and cognition in regular users of cannabis who were not engaged in a cessation attempt.[24] A combination of THC and cannabidiol at 1:1 ratio (nabiximols) has been found to reduce cannabis withdrawal symptoms, cannabis use, or both in some randomised, double-blind, placebo-controlled trials.[25–27] However, the causal role of cannabidiol in these studies is unclear because they either used an open-label design[22–24] or co-administered THC with cannabidiol.[25–27]

Studies in humans[28] and in rat[29] models of anxiety have reported inverted-U shaped dose-response effects of cannabidiol. These findings highlight the importance of doing an initial dose-finding trial when investigating a novel indication for cannabidiol. Trials testing a single dose against placebo might not select the most efficacious dose for that indication. Therefore, we did a phase 2a trial to identify potentially efficacious doses and eliminate inefficacious doses using an adaptive Bayesian design. Bayesian methods are advantageous for adaptive clinical trials because of their efficiency, flexibility, and ability to make use of all available evidence in a formal and principled way. As a result, they can reduce the amount of resources and participant burden required when doing clinical trials. Additionally, Bayesian analyses provide direct probabilistic measures of the likelihood of a hypothesis (ie, that a treatment is more efficacious than placebo) given the observed data. As such, they provide results that can be more clinically meaningful than frequentist analyses, which test the likelihood of the observed data given the null hypothesis being true (ie, that a treatment does not differ from placebo). We selected a dose range informed by previous clinical trials of oral cannabidiol[30,31] of 200 mg, 400 mg, and 800 mg daily for 4 weeks. Our primary objective was to identify which (if any) dose of cannabidiol was most efficacious at reducing cannabis use compared with placebo.

Methods

Study design and participants

We did a phase 2a, randomised, double-blind, placebo-controlled, parallel group clinical trial to investigate cannabidiol as a pharmacological treatment for cannabis use disorder. The trial was done at the Clinical Psychopharmacology Unit (University College London, London, UK) and was approved by the UK Health Research Authority (13/EE/0303) and the UK Medicines and Healthcare Regulatory Agency (20363/0325/001–0001). We did the trial according to Good Clinical Practice and reported according to the CONSORT checklist (appendix pp 1–3; the protocol is available online).

Participants were recruited through advertisements on websites, forums, and flyers in the local community. We initially intended to restrict eligibility to individuals aged 16–26 years with vital signs in normal limits, but we removed these criteria early in the first stage of the trial to increase the generalisability of our findings to a wider population who might stand to benefit from this treatment. Participants were included if they were aged 16–60 years, met DSM-5 criteria for a cannabis use disorder (of at least moderate severity), and expressed a desire to stop using cannabis and intended to do so in the next month, based on an adapted Motivation To Stop Scale.[32] Participants were additionally required to report one or more unsuccessful quit attempts for their cannabis use; report co-administering their cannabis together with tobacco, which is the most common method of using cannabis in Europe,[33] provide a urine sample positive for 11-nor-9-carboxy-THC (THC-COOH; urine cup 10A, assessing methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbiturates, phencyclidine, amphetamines, morphine, and methadone; Alere Toxicology, Abingdon, UK); and have capacity to give written informed consent as defined by Good Clinical Practice guidelines.

Women of childbearing potential were required to have a negative pregnancy test within 7 days of starting treatment. An additional inclusion criterion for women of childbearing potential and all men was to use an effective method of contraception including oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine system or device; a barrier method of contraception; or true abstinence from the time consent was signed until 6 weeks after treatment discontinuation.

Exclusion criteria were current breastfeeding or pregnancy; allergies to cannabidiol, microcrystalline cellulose or gelatine; prescribed psychotropic drug use at screening assessments or during treatment weeks; use of other illicit drugs more than twice per month at screening; evidence of inaccurate self-reported drug use due to a positive urine test for a drug that was not reported during screening assessment; current or previous self-reported diagnosis of a psychotic disorder; any physical health problem deemed clinically significant by the investigator team; and not speaking English (because of verbal assessments). All data were collected at the Clinical Psychopharmacology Unit (University College London, London, UK).

Randomisation and masking

For the first stage of the trial, participants were randomly assigned (1:1:1:1) to parallel treatment groups receiving either cannabidiol in three different daily doses (200 mg, 400 mg, or 800 mg) or matched placebo. For the second stage of the trial, new participants were randomly assigned to placebo or doses deemed efficacious in the interim analysis. The randomisation sequence was generated by the trial statistician (GB) by use of block randomisation (R command blockrand) with a block size equivalent to the number of treatment groups in the randomisation code. The randomisation code was held by the emergency unblinding service (Sealed Envelope, London, UK) and the drug manufacturer for labelling before shipping to the trial site. Medication packages were labelled by the manufacturer and sent to the trial site with anonymous participant numbers. All investigators and participants remained masked throughout the duration of the trial. Only masked investigators enrolled participants, assigned participants to interventions, did assessments, and entered data. Unmasking did not occur until after the database had been locked by the trial statistician.

See Online for appendix

For the **protocol** see https://osf.io/3cbef/

Procedures

Synthetic cannabidiol (99·9% purity) was obtained from STI Pharmaceuticals (Brentwood, UK) and manufactured by Nova Laboratories (Leicester, UK). The trial drug was administered in identical size two gelatine capsules containing microcrystalline cellulose filler and cannabidiol (50 mg, 100 mg, or 200 mg) or no cannabidiol (placebo). After a telephone screening and a screening visit to determine eligibility, participants engaged in a cannabis cessation attempt scheduled to begin at their baseline visit (week 0). At the end of their baseline visit, participants were randomly assigned to treatment groups and instructed to take two capsules twice daily to achieve the daily doses of placebo (capsules with no cannabidiol) and of cannabidiol 200 mg (50 mg capsules), 400 mg (100 mg capsules), and 800 mg (200 mg capsules) for 4 weeks. The bioavailability of oral cannabidiol is increased by food, and twice-daily administration is recommended on the basis of pharmacokinetic and safety data.[34] Participants attended site visits weekly during treatment (weeks 1–4), arranged at a time that was most convenient for each participant. Follow-up occurred at weeks 6 (site visit), 8 (telephone), 12 (site visit), 16 (site visit), 20 (telephone), and 24 (telephone).

Participants received scheduled text messages twice daily reminding them to take their medication, spaced 12 h apart. Dosette boxes were provided for each week of treatment to aid adherence. Adherence was assessed by self-report at weekly assessments as well as by return

of capsules that were not used. If participants did not show adequate adherence on any treatment week (either ≥30% capsules returned, or ≥30% self-reported doses missed), if they did not attend a site visit within 2 days of the scheduled appointment during treatment, or if any concomitant psychotropic medication was taken during treatment, they were not provided with additional medication for the duration of the trial but continued all other aspects of the protocol.

All participants received a brief psychological intervention of motivational interviewing.[35] Motivational interviewing is widely used in health-care settings and has been found to reduce cannabis use in randomised trials of cannabis use disorder.[36] Six 30-min individual sessions of motivational interviewing were delivered by trained psychologists (TPF, CH, NDCS, EMT, DA, and AMF) at the screening visit, baseline visit, and treatment weeks 1–4. During the first motivational interviewing session, a target quit date was planned to coincide with the baseline visit. All sessions were audio recorded for clinical supervision. Training and supervision were provided by a lead clinical psychologist (DO) based in specialist National Health Service drug services throughout the duration of the trial.

Urine samples were collected at site visits using temperature monitored cups to ensure adherence (Galle pot, Synergy Health, Abergavenny, UK). Samples were stored in 10 mL polypropylene tubes at –80°C before analysis using liquid chromatography-tandem mass spectrometry by ABS Laboratories (Hertford, UK) with a lower limit of THC-COOH quantification of 1 ng/mL. Blood samples were collected at site visits; samples were drawn into a 6 mL lithium heparin vacutainer and centrifuged immediately at 2800 rpm for 5 min. Plasma samples were stored in 2 mL cryotubes at –80 °C before analysis with gas chromatography-mass spectrometry (ABS Laboratories) with a lower limit of quantification of 0·1 ng/mL.

Outcomes

Primary outcomes were cannabis use, as measured in urine (THC-COOH:creatinine ratio) and by self-report (days per week with abstinence from cannabis). These were the two variables that were most strongly associated with cannabis use disorder severity in a study testing 15 different biological and self-reported measures of cannabis use.[37] Self-reported days with abstinence from cannabis were assessed weekly by use of the timeline follow-back method.[38] The primary endpoints were a reduction in urinary THC-COOH:creatinine ratio, an increase in days per week with abstinence from cannabis, or both for cannabidiol versus placebo during treatment, evidenced by posterior probabilities exceeding 0·9. All primary endpoint data were double entered independently by two researchers (TPF and NDCS for the first stage and EMT and DA for the second stage of the trial) and were 100% verified against source data by an independent clinical trial monitor. Reductions in cannabis use up to the final follow-up were analysed as a secondary endpoint.

For secondary outcomes, we assessed the total score of the Cannabis Withdrawal Scale[39] and tobacco use, assessed in urine (cotinine:creatinine ratio, lower limit of cotinine quantification 1 ng/mL; ABS Laboratories) and by self-report (number of cigarettes smoked using the timeline follow-back method).[38] We assessed alcohol consumption using a timeline follow-back[38] of each beverage consumed and its alcohol by volume, which was converted to the number of standard UK alcohol units (8 g alcohol). Sleep quality was assessed by use of the total score on the Pittsburgh Sleep Quality Index.[40] Depression and anxiety were assessed by use of total scores on the Beck Depression Inventory[41] and Beck Anxiety Inventory.[42] Secondary endpoints were reduced cannabis withdrawal symptoms, cigarette and alcohol consumption, urinary cotinine:creatinine ratio, depression and anxiety symptoms, and improved sleep quality, assessed during the treatment weeks and up to the final follow-up assessment. Additional secondary outcomes included cognitive, biological, and physiological measures that will be reported elsewhere.

Participants were asked about possible adverse events at each assessment from week 1 to week 16. Adverse events were categorised as mild (does not interfere with the participant's daily routine and does not require intervention; it causes slight discomfort), moderate (interferes with some aspects of daily routine, or requires intervention, but is not damaging to health; it causes moderate discomfort) or severe (results in alteration, discomfort, or disability that is clearly damaging to health). All adverse events were verified with a medical supervisor and an independent trial monitor throughout the trial on an ongoing basis.

Statistical analysis

Because no previous trials investigating cannabidiol as a treatment for cannabis use disorder were available, our effect size estimates were informed by a pilot study testing the effects of 1-week treatment with cannabidiol on cigarette consumption in tobacco smokers who intended to quit.[20] On the basis of these data, we estimated that a sample size of 12 participants per group would provide 80% power to detect a similar effect of cannabidiol in this study (Cohen's d 1·21). Because of uncertainty in these estimates, we planned analyses with 12 (interim analysis) and 24 participants per group (final analysis) in a two-stage adaptive design.

All analyses were done on an intention-to-treat basis. Missing data were handled using Bayesian multiple imputation under the assumption of missing at random. The missing outcomes were automatically simulated from the Bayesian procedure, in accordance with the modelling and distributional assumptions. The same primary endpoints were analysed at interim analysis and final analysis. To test our primary endpoints, we analysed

THC-COOH:creatinine ratio and days per week with abstinence from cannabis during treatment weeks 1–4. We ran a Bayesian model for each dose of cannabidiol compared with placebo to compute the predictive distribution of the outcome given the evidence that had become available up to that point. On the basis of these joint posterior distributions (obtained using Markov chain Monte Carlo algorithms, with model convergence assessed using the Gelman-Rubin statistic), we computed the probability that each dose of cannabidiol was the most efficacious dose compared with placebo. This posterior probability was used to determine which doses were dropped or continued at the interim analysis, and which doses were most efficacious at final analysis. If this probability was lower than a prespecified lower threshold of 0·1, the dose was dropped. Similarly, if the probability was higher than a prespecified upper threshold of 0·9, then the dose was considered the most efficacious dose.[43] All analyses included time as a fixed effect (treatment weeks 1–4) and were adjusted for

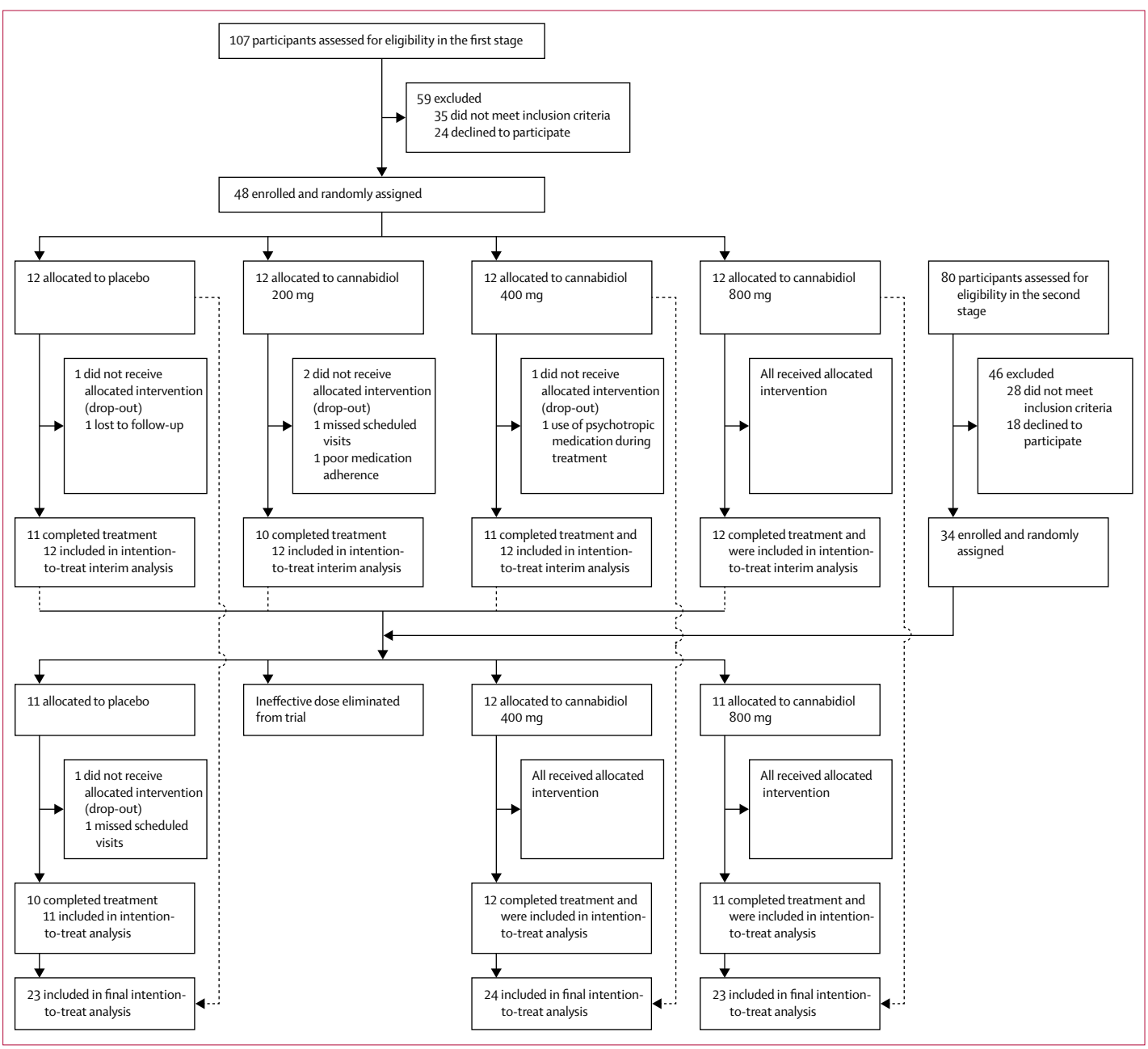

Figure 1: **Trial profile**
CONSORT diagram showing enrolment, allocation, and the analysis populations at the interim and final stages of the trial.

	Placebo (n=23)	Cannabidiol 200 mg (n=12)	Cannabidiol 400 mg (n=24)	Cannabidiol 800 mg (n=23)
Age, years	24·87 (18·55–43·35)	27·33 (19·28–39·08)	26·58 (19·15–41·25)	27·43 (19·00–36·90)
Sex				
Men	17 (74%)	9 (75%)	17 (71%)	16 (70%)
Women	6 (26%)	3 (25%)	7 (29%)	7 (30%)
DSM-5 cannabis use disorder symptoms at screening assessment*	8·61 (7·63–9·58)	8·67 (7·63–9·70)	9·00 (8·29–9·71)	8·48 (7·39–9·57)

Data are n(%) or mean (95% interval estimates). *Data show the mean number of DSM-5 symptoms out of 11: 2–3 indicate mild cannabis use disorder, 4–5 moderate cannabis use disorder, and 6–11 severe cannabis use disorder.

Table 1: **Characteristics of participants included in both interim and final analysis stages of the trial**

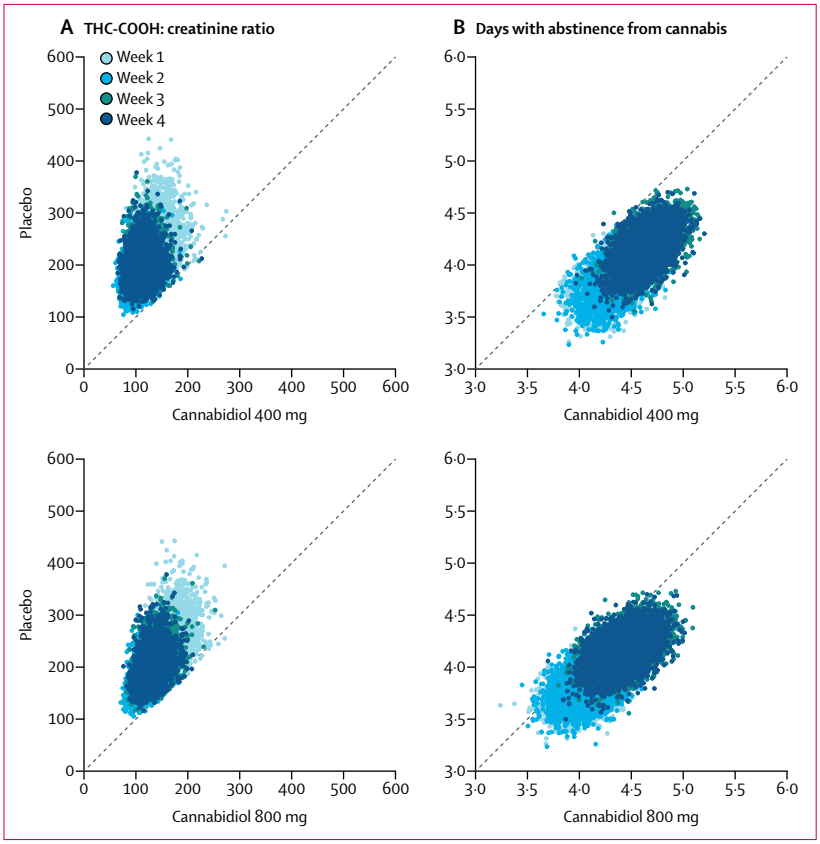

Figure 2: **Final analysis of primary endpoints THC-COOH:creatinine ratio (A) and days with abstinence from cannabis (B)**

Each cloud of points represents the expected value of the primary outcome for each of the 4 weeks of treatment for participants randomly assigned to cannabidiol 400 mg, cannabidiol 800 mg, or placebo, simulated from the joint posterior distribution of treatment groups. THC-COOH=11-nor-9-carboxy-δ-9-tetrahydrocannabinol. Cannabidiol 400 mg and 800 mg exceeded the upper threshold for primary endpoint criteria (posterior probability 0·9), showing reduced THC-COOH:creatinine ratio (left panel) and increased days per week abstinent from cannabis (right panel) compared with placebo.

baseline scores at week 0. Participant was fitted as a random intercept. For continuous, positive, and skewed outcomes (eg, THC-COOH:creatinine ratio), we used generalised linear regression models assuming a gamma distribution. We used logistic regression models for binomial count outcomes (eg, the number of days with abstinence from cannabis in a week). We did post-hoc sensitivity analyses adding age and sex to primary endpoint models. Secondary endpoints were analysed at the final analysis only. We analysed cannabis use (urinary THC-COOH:creatinine and days per week with abstinence) up to the final follow-up as secondary endpoints. Secondary outcomes were analysed separately for treatment week data (weeks 1–4) and for all data (all treatment weeks and follow up data combined) as additional secondary endpoints. Models were selected assuming gamma, binomial, or Poisson distributions as appropriate. We used absolute differences between cannabidiol and placebo to estimate treatment effects for all primary and secondary endpoints. These were obtained from statistical models including fixed effects of time, adjusted for baseline scores at week 0, and with a random intercept of participant. Summary statistics stratified by treatment group and timepoint were obtained from raw data. All analyses were done in R. The Bayesian models were done using JAGS as interfaced with R using the package R2jags. This trial was prospectively registered before data collection began with ClinicalTrials.gov (NCT02044809) and the EU Clinical Trials Register (2013-000361-36).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 28, 2014, and Aug 12, 2015 (first stage), and between May 24, 2016, and Jan 12, 2017 (second stage), 82 participants were randomly assigned across both stages of the trial (figure 1, table 1). Across the trial, 77 (94%) of 82 participants completed treatment as evidenced by medication adherence at each treatment week (for both self-reported and returned medication) and attending all treatment week visits within 2 days of the scheduled appointment. Comparisons at both the interim analysis (appendix, p 4) and the final analysis (appendix, p 5) stages of the adaptive trial showed that cannabidiol and placebo groups were similar for demographics and drug use at baseline.

In the first stage, 48 participants were randomly assigned (1:1:1:1) to placebo (n=12) and to cannabidiol 200 mg (n=12), 400 mg (n=12), and 800 mg (n=12; figure 1). At interim analysis, cannabidiol was more efficacious than placebo at reducing cannabis use at doses of 400 mg and 800 mg, but not at 200 mg. For urinary THC-COOH:creatinine, cannabidiol 400 mg and 800 mg exceeded the primary endpoint criterion of 0·9. The probability of being the most efficacious dose compared with placebo given the observed data was 0·4191 for cannabidiol 200 mg, 0·9827 for cannabidiol 400 mg and 0·9488 for cannabidiol 800 mg. For days per

	Placebo (n=23)		Cannabidiol 400 mg (n=24)		Cannabidiol 800 mg (n=23)	
	Urinary THC-COOH: creatinine ratio (ng/mL)	Days with abstinence from cannabis	Urinary THC-COOH: creatinine ratio (ng/mL)	Days with abstinence from cannabis	Urinary THC-COOH: creatinine ratio (ng/mL)	Days with abstinence from cannabis
Baseline	343·09 (188·41–497·78)	1·17 (0·48–1·87)	521·00 (316·55–725·44)	0·79 (0·34–1·24)	315·31 (150·00–480·61)	1·65 (0·68–2·62)
Week 1	202·99 (68·59–337·38)	4·17 (3·29–5·05)	267·60 (71·61–463·60)	4·25 (3·40–5·10)	142·27 (70·65–213·90)	4·04 (3·07–5·01)
Week 2	187·53 (89·46–285·60)	3·83 (2·77–4·88)	227·17 (77·62–376·72)	4·17 (3·26–5·07)	98·04 (53·89–142·20)	4·43 (3·55–5·32)
Week 3	185·53 (88·22–282·84)	4·36 (3·26–5·46)	272·31 (62·70–481·92)	4·67 (3·75–5·58)	125·73 (60·51–190·94)	4·52 (3·63–5·41)
Week 4	195·00 (92·08–297·92)	4·14 (3·20–5·08)	251·24 (95·38–407·11)	4·38 (3·39–5·36)	144·07 (48·53–239·62)	4·91 (4·05–5·78)

Data are mean (95% interval estimates). THC-COOH=11-nor-9-carboxy-delta-9-tetrahydrocannabinol.

Table 2: **Primary endpoint data stratified by group and timepoint at final analysis for placebo, cannabidiol 400 mg, and cannabidiol 800 mg groups**

	Treatment weeks		Up to final follow-up	
	Cannabidiol 400 mg *vs* placebo	Cannabidiol 800 mg *vs* placebo	Cannabidiol 400 mg *vs* placebo	Cannabidiol 800 mg *vs* placebo
THC-COOH:creatinine ratio (ng/mL)	−94·21 (−161·83 to −35·56)*	−72·02 (−135·47 to −19·52)*	−29·18 (−52·08 to −7·25)	−13·20 (−37·58 to 12·10)
Days with abstinence from cannabis	0·48 (0·15 to 0·82)*	0·27 (−0·09 to 0·64)*	0·03 (0·00 to 0·07)	−0·02 (−0·06 to 0·03)
Cannabis Withdrawal Scale	−0·34 (−1·14 to 0·50)	−1·26 (−2·13 to −0·39)	−1·32 (−1·89 to −0·60)	−2·50 (−3·08 to −1·93)
Urinary cotinine:creatinine ratio (ng/nL)	−72·31 (−194·35 to 36·57)	−36·08 (−163·46 to 104·28)	−66·52 (−157·06 to 13·10)	−56·60 (−145·36 to 35·19)
Number of cigarettes smoked	−5·04 (−6·57 to −3·47)	8·66 (6·89 to 10·26)	−1·32 (−1·89 to −0·60)	−2·50 (−3·08 to −1·93)
Alcohol units consumed	15·32 (−3·60 to 49·27)	−8·49 (−17·27 to 0·44)	0·86 (−2·82 to 3·84)	−1·50 (−4·83 to 1·04)
Pittsburgh Sleep Quality Index	0·84 (0·15 to 1·57)	0·16 (−0·57 to 0·81)	0·55 (0·21 to 0·92)	0·46 (0·08 to 0·82)
Beck Depression Inventory	0·34 (−0·47 to 1·17)	0·14 (−0·70 to 1·00)	−0·48 (−0·76 to −0·21)	−0·21 (−0·49 to 0·07)
Beck Anxiety Inventory	1·41 (0·65 to 2·17)	−1·29 (−1·97 to −0·62)	0·01 (−0·25 to 0·34)	−0·52 (−0·82 to −0·27)

Data are absolute difference (95% interval estimate) between cannabidiol 400 mg (n=24) and placebo (n=23) or between cannabidiol 800 mg (n=23) and placebo. Separate analyses are presented for treatment weeks only and up to the final follow-up. THC-COOH=11-nor-9-carboxy-δ-9-tetrahydrocannabinol. *Primary endpoint.

Table 3: **Final analysis of primary and secondary endpoints**

week with abstinence from cannabis, the group receiving cannabidiol 400 mg exceeded the primary endpoint criteria of 0·9, whereas the cannabidiol 200 mg group was below the lower threshold criterion of 0·1, indicating that this group should be dropped. The probability of being the most efficacious dose compared with placebo given the observed data was 0·0082 for cannabidiol 200 mg, 0·9354 for cannabidiol 400 mg, and 0·8660 for cannabidiol 800 mg (appendix p 6). Therefore, the cannabidiol 200 mg group was eliminated from the trial after the first stage and no additional participants were assigned to this group. Post-hoc sensitivity analyses including age and sex did not change the pattern of results.

In the second stage of the trial, an additional 34 participants were randomly assigned (1:1:1) to the remaining groups of placebo (n=11), cannabidiol 400 mg (n=12), and cannabidiol 800 mg (n=11). At final analysis, cannabidiol 400 mg and 800 mg exceeded the primary endpoint criterion of 0·9 for both primary outcomes of urinary THC-COOH:creatinine and days per week with abstinence from cannabis. For urinary THC-COOH:creatinine ratio, the probability of being the most efficacious dose compared with placebo given the observed data was 0·9995 for cannabidiol 400 mg and 0·9965 for cannabidiol 800 mg. For days with abstinence from cannabis, the probability of being the most efficacious dose compared with placebo given the observed data was 0·9966 for cannabidiol 400 mg and 0·9247 for cannabidiol 800 mg (figure 2, table 2). Compared with placebo, cannabidiol 400 mg decreased THC-COOH:creatinine ratio by 94·21 ng/mL (95% interval estimate [IE] −161·83 to −35·56) and increased abstinence from cannabis by 0·48 days per week (0·15 to 0·82; table 3). Compared with placebo, cannabidiol 800 mg decreased THC-COOH:creatinine ratio by 72·02 ng/mL (95% IE −135·47 to −19·52) and increased abstinence from cannabis by 0·27 days per week (−0·09 to 0·64). Post-hoc sensitivity analyses including age and sex did not change the pattern of results.

At final analysis, we assessed secondary endpoints for cannabidiol 400 mg versus placebo and cannabidiol 800 mg versus placebo (table 3, appendix pp 7–15). Analysis of cannabis use up to the final follow-up showed that cannabidiol 400 mg reduced urinary THC-COOH: creatinine and increased abstinence from cannabis compared with placebo (table 3). However, results from the cannabidiol 800 mg group were similar to those of placebo up to the final follow-up (table 3). The results of other secondary endpoints were mixed, but some findings were consistent across analyses of treatment and

	Placebo (n=23)	Cannabidiol 200 mg (n=12)	Cannabidiol 400 mg (n=24)	Cannabidiol 800 mg (n=23)
Week 0	0·12 (–0·01 to 0·24)	0·02 (–0·01 to 0·06)	0·15 (–0·06 to 0·36)	0·02 (–0·02 to 0·07)
Week 2	0·06 (–0·03 to 0·15)	10·28 (4·20 to 16·36)	40·42 (19·12 to 61·72)	59·31 (17·95 to 100·67)
Week 4	0·07 (0·00 to 0·13)	10·24 (2·65 to 17·83)	21·63 (11·06 to 32·20)	63·33 (30·09 to 96·57)
Week 6	0·09 (–0·04 to 0·21)	0·49 (0·32 to 0·66)	4·14 (0·12 to 8·16)	3·91 (2·42 to 5·41)
Week 12	0·02 (–0·03 to 0·08)	0·00 (0·00 to 0·00)	0·19 (0·06 to 0·32)	0·34 (0·14 to 0·55)

Data are mean (95% interval estimate) concentrations of cannabidiol in ng/mL.

Table 4: **Mean plasma concentrations of cannabidiol stratified by treatment group and timepoint**

follow-up. Compared with placebo, cannabidiol 400 mg decreased the number of cigarettes smoked per week during treatment and up to the final follow-up (table 3). However, compared with placebo, cannabidiol 400 mg increased Pittsburgh Sleep Quality Index scores during treatment and follow-up, indicating poorer sleep quality in participants receiving cannabidiol (table 3). Compared with placebo, cannabidiol 800 mg reduced Cannabis Withdrawal Scale scores during treatment and follow-up, indicating a reduction in cannabis withdrawal symptoms with cannabidiol. Compared with placebo, cannabidiol 800 mg also reduced Beck Anxiety Inventory scores during treatment and follow-up, indicating a reduction in anxiety symptoms with cannabidiol (table 3).

We observed dose-response increases in plasma cannabidiol concentrations during treatment (table 4). Compared with placebo, plasma cannabidiol concentrations increased by 9·37 ng/mL (95% IE 5·80–14·66) with cannabidiol 200 mg, by 29·90 ng/mL (19·62–49·44) with cannabidiol 400 mg, and by 46·30 ng/mL (33·90–63·13) with cannabidiol 800 mg.

We recorded 65 mild adverse events and nine moderate adverse events in the placebo group (n=23), 42 mild adverse events and four moderate adverse events in the cannabidiol 200 mg group (n=12), 96 mild adverse events and eight moderate adverse events in the cannabidiol 400 mg group (n=24), and 78 mild adverse events and eight moderate adverse events in the cannabidiol 800 mg group (n=23). The number of mild adverse events did not differ between placebo and cannabidiol 200 mg (relative risk 1·24, 95% IE 0·73–2·09), 400 mg (1·39, 0·91–2·14), and 800 mg (1·19, 0·77–1·86; appendix p 16). The number of moderate adverse events did not differ between placebo and cannabidiol 200 mg (0·85, 0·26–2·58), 400 mg (0·84, 0·35–2·24), and 800 mg (0·89, 0·40–2·45; appendix p 17). No severe adverse events were recorded and no participants dropped out because of treatment.

The final follow-up assessment was done on June 5, 2017. Because of lack of funding, a subsequent phase 2b stage was not initiated and the trial ended on May 30, 2018.

Discussion

To our knowledge, we did the first randomised clinical trial of cannabidiol for the treatment of cannabis use disorder, in which we used an adaptive Bayesian design to establish which (if any) dose of cannabidiol was more efficacious than placebo at reducing cannabis use. We eliminated cannabidiol 200 mg at the first stage and continued randomisation to cannabidiol 400 mg, cannabidiol 800 mg, and placebo treatment groups. At final analysis of the primary endpoints, cannabidiol 400 mg and 800 mg were more efficacious than placebo at reducing cannabis use. These treatment effects were found over and above a brief psychological intervention typically delivered in drug treatment settings.

All participants in this trial met a DSM-5 diagnosis of cannabis use disorder. Participants expressed a desire to quit using cannabis in the next month, smoked tobacco with their cannabis, and had not succeeded in quitting cannabis use on at least one previous cessation attempt. This is an important population for whom substantial and rising need for treatment exists[8,9] and for whom no pharmacotherapies are recommended at present.[11] Cannabidiol did not differ from placebo in the number of mild or moderate adverse events at 200 mg, 400 mg, or 800 mg doses. No severe adverse events were recorded, and no participants dropped out because of treatment. The excellent safety and tolerability data and exceptionally high retention rates in our trial suggest that these doses of cannabidiol offer a safe and acceptable treatment for this population.

To our knowledge, this is the first adaptive Bayesian dose-finding trial of cannabidiol for a new medical indication. The primary objective of this phase 2a trial was to establish which (if any) dose of cannabidiol was more efficacious than placebo at reducing cannabis use. Cannabidiol 400 mg and 800 mg exceeded the primary endpoint criterion (posterior probability 0·9) for reducing cannabis use during treatment, with converging evidence from biological and self-reported primary outcomes. Our estimates showed that cannabidiol 400 mg and 800 mg both decreased THC-COOH:creatinine ratio and increased abstinence from cannabis.

The effects of the cannabidiol doses tested are suggestive of an inverted-U dose-response curve. The 200 mg group was eliminated as an inefficacious dose, and we found some indication that cannabidiol 400 mg was marginally more efficacious than cannabidiol 800 mg. Secondary endpoints showed that the reductions in cannabis use were maintained up to the final follow-up in the cannabidiol 400 mg group but not in the cannabidiol 800 mg group. From a treatment perspective, our findings indicate that cannabidiol doses ranging from 400 mg to 800 mg have the potential to reduce cannabis use in clinical settings, and that additional benefit is unlikely to be gained from doses exceeding 800 mg. It is important to be aware that this dose range (400 mg to 800 mg) is considerably higher than concentrations found in cannabidiol products widely available without a prescription (eg, 25 mg per day).[14] These products have inadequate quality assurance and should not be used for medicinal purposes.

We observed mixed results for several secondary endpoints, but some findings were consistent across treatment weeks and follow-up. Compared with placebo, cannabidiol 400 mg decreased the number of cigarettes smoked, in line with previous studies of cannabidiol in tobacco smokers.[17,20] However, sleep quality was lower in the cannabidiol 400 mg group compared with placebo, which might be interpreted in the context of greater reductions in cannabis use in this group. Compared with placebo, cannabidiol 800 mg reduced cannabis withdrawal symptoms, consistent with previous case reports,[22,23] and reduced anxiety symptoms, in line with experimental studies in humans[28] and rats.[29]

The key strengths of this study include its novel indication, for which substantial clinical need exists, and its adaptive Bayesian dose-finding design. This design enabled us to test a range of doses in an efficient manner, which would have required considerably greater resources and participant burden when using a typical trial design. In terms of limitations, this phase 2a dose-finding trial was not designed to provide robust estimates of the magnitude of efficacy. Additional evidence is needed to improve the precision of the estimates obtained in this study. Although we found strong evidence for dose-response effects of cannabidiol on plasma cannabidiol concentrations, factors such as food consumption could have contributed to variation in the bioavailability of cannabidiol. This trial used a 4-week treatment period, consistent with a previous clinical trial for psychosis.[30] Additional studies are needed to investigate the extent to which these findings translate to different durations of treatment. Additional research is needed to investigate whether cannabidiol reduces cannabis use independently or through mechanisms shared with other mental health symptoms such as anxiety.

In conclusion, our trial provides the first causal evidence supporting cannabidiol as a treatment for cannabis use disorders. These findings are important in light of major policy changes surrounding the production and sale of cannabis products, increases in the number of people entering treatment for cannabis use disorders worldwide,[8,9] and the absence of recommended pharmacotherapies at present.[11]

Contributors

TPF, CH, GB, JK, CJAM, and HVC designed the study. TPF and CH coordinated the trial. HVC supervised the trial, and MAPB and AM were responsible for medical supervision of the trial. JK was responsible for project management. DO was responsible for training and supervision of motivational interviewing. TPF, CH, NDCS, EMT, DA, and AMF did assessments and delivered motivational interviewing. NDCS, EMT, DA, RL, TPF, and SC handled database management. GB did statistical analyses. TPF wrote the first draft of the manuscript, and all authors critically revised the manuscript.

Declaration of interests

MAPB reports personal fees from Spectrum Therapeutics, outside the submitted work. All other authors declare no competing interests.

Data sharing

We are unable to share data because participants did not provide consent for data sharing.

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