Cannabidiol for Treatment Resistant Anxiety Disorders in Young People: An Open-Label Trial

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Funding source: The study was funded by a grant from the Lambert Initiative for Cannabinoid Therapeutics (Sydney, NSW, Australia). MB was supported by a Rapid Applied Research Translation Fellowship awarded by the Medical Research Future Fund (Canberra, ACT, Australia). GPA was supported by an NHMRC Senior Research Fellowship (1080963).

Previous presentation: An interim analysis of this trial was presented at the Annual Conference of the Society for Mental Health Research (SMHR); Melbourne, 27-29 November 2019

Abstract

Background Treatment resistance is a significant problem among young people experiencing moderate to severe anxiety, affecting nearly half of all patients. We investigated the safety and efficacy of cannabidiol (CBD), a non-intoxicating component of *Cannabis sativa*, for anxiety disorders in young people who previously failed to respond to standard treatment.

Methods In this open-label trial, n=31 young people aged 12-25 years with a DSM-5 anxiety disorder and no clinical improvement despite treatment with cognitive-behavioural therapy and/or antidepressant medication were enrolled between May 16, 2018, and June 28, 2019. All participants received add-on CBD for 12 weeks on a fixed-flexible schedule titrated up to 800mg per day. The primary outcome was improvement in anxiety severity, measured with the Overall Anxiety Severity and Impairment Scale (OASIS), at Week 12. Secondary outcomes included comorbid depressive symptoms, clinical global impression and social and occupational functioning.

Results OASIS scores decreased from 10.8 (SD 3.8) at baseline to 6.3 (SD 4.5) at Week 12, corresponding to a -42.6% reduction ($p<0.001$). Depressive symptoms, clinical global impression and functioning improved significantly. Adverse events were reported in 25 of 31 (80.6%) participants and included fatigue, low mood, and hot flushes or cold chills. There were no serious and/or unexpected adverse events.

Conclusion Our findings suggest that CBD can reduce anxiety severity and has an adequate safety profile in young people with treatment-resistant anxiety disorders. Randomised-controlled trials are needed to confirm the efficacy and longer-term safety of this compound.

Key words: anxiety disorders, cannabidiol, endocannabinoids, clinical trial, open-label, young person,

Introduction

Anxiety disorders are among the most common mental disorders affecting young people globally, with a lifetime prevalence of 15-20% in children and adolescents 1. They typically have their onset early in life and are leading causes of disability 2-4. Current treatment guidelines typically recommend cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRI) as first line treatments for anxiety disorders. However, while these treatments are effective for many patients 5, only 55-60% of adolescents with anxiety disorders achieve remission 6-9.

Cannabidiol (CBD), a cannabinoid found in the plant *Cannabis sativa*, has received significant attention in recent years due to its emerging putative physical and mental health benefits. Unlike tetrahydrocannabinol (THC), CBD is devoid of pro-psychotic effects 10, 11. Reductions in anxiety severity after administration of CBD have been observed in animal studies 11, case reports 12-14 as well as in small human studies 15-17. A recent small randomised-controlled trial in 37 adolescents with social anxiety disorder demonstrated that a 4-week intervention with 300mg CBD per day led to modest but significant reductions in anxiety severity 17. The mechanisms of action whereby CBD reduces anxiety are not fully understood but likely involve a modulatory effect of CBD at the CB1 cannabinoid, serotonin 5-HT1A, and transient receptor potential vanilloid type 1 (TRPV1) receptors, upregulation of endocannabinoid tone via inhibition of anandamide metabolism, as well as anti-inflammatory and anti-oxidative effects 11, 18-21. While the anxiolytic effects of CBD appear promising, its acceptability and safety for young patients with anxiety disorders is unclear, as are the duration of treatment and the optimum dose needed to achieve clinical response and the efficacy of CBD for patients who have previously not responded to established treatments. Therefore, the aim of this trial was to test the safety and the efficacy of CBD as an adjunctive treatment for anxiety disorders in young people aged 12-25 years with anxiety disorders who do not respond to standard treatment.

Patients and Methods

Study design and patients

The present study was an open-label single-arm Phase II trial in patients with anxiety disorders who previously did not respond to standard treatment with CBT and/or antidepressant medication. There was no control group. Patients, investigators and clinicians were not blind to the intervention. All participants received the study intervention. Study participants were recruited from all patients with anxiety disorders who attended a primary mental health care service in Melbourne (headspace) 22 between May 2018 and July 2019. To be eligible, participants had to be aged between 12 and 25 years (inclusive), diagnosed with a DSM-5 anxiety disorder (ascertained with the SCID-5), and experienced no improvement in anxiety severity in the current episode of care despite standard treatment with CBT and/or antidepressant medication (operationalised as a score of 3 or higher on the Clinical Global Impression- Improvement [CGI-I] subscale). The participants were also required to be able to provide informed consent and have sufficient fluency in English. Exclusion criteria were a DSM-5 schizophrenia spectrum disorder, delusional disorder, bipolar I disorder, substance/medication induced psychotic disorder; prior sensitivity or allergy to CBD or any cannabis-derived product; current treatment with antipsychotic medication, anxiolytic medication or mood stabiliser; or any medication that either interacts with the metabolism of CBD or is affected by CBD and in the view of the study doctor cannot be co-administered safely; pregnancy, lactation, or if sexually active, no effective contraception; haematological findings that indicate a medically significant liver, thyroid or other conditions; acute or unstable systemic medical disorder; psychiatric condition due to a medical condition; acute suicidality; previous or current severe drug or severe alcohol dependence; severe disturbance, such that the person is unable to comply with either the requirements of informed consent or the treatment protocol. Antidepressant medication was permitted if the participant had been on a stable dose for a minimum of 6 weeks prior to enrolment The number of participants screened, excluded and enrolled is shown in Figure S1.

The trial was sponsored by Orygen and reviewed and approved by an independent human research ethics committee (Bellberry Ltd.; HREC2017-02-107). The study was approved under the Clinical Trial

Notification Scheme by the Therapeutic Goods Administration (TGA) and registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR) on 06/06/2017 with the registration identifier ACTRN12617000825358.

Procedures and intervention

Written informed consent was obtained from all participants prior to commencing study related procedures. Parent or legal guardian consent was obtained in addition to participant assent for participants aged 17 years or younger. All participants were invited to attend a screening interview with a researcher where the presence of all inclusion and absence of all exclusion criteria were established. The participant's treating psychologist, who was not part of the study team, provided a CGI-I rating to determine clinical improvement. After enrolment, participants received the study medication and attended study visits at weeks 4, 8, 12 and 26. In addition, blood draws were completed every 4 weeks and participants were seen by a study physician at 4-weekly intervals up until week 12 to monitor the safety of the study drug. All participants continued treatment as usual throughout the trial, consisting of fortnightly CBT sessions in addition to antidepressant treatment and/or psychosocial care as determined by their psychiatrist.

All participants received CBD for 12 weeks, followed by gradual weaning for one week. CBD was administered in the form of oral capsules each containing 200mg high-purity (>99.9%) CBD and the inactive ingredient Softisan 379 (Trigal Pharma GmbH, Vienna, Austria). Dosing followed a fixed-flexible schedule, starting with 200mg per day for all participants. Doses were subsequently increased in 200mg increments if participants did not show clinically meaningful improvement (operationalised as a score of 3 or higher on the CGI-I). The maximum doses were 400mg per day at Week 1, 600mg per day at Week 4 and 800mg at Week 8. Treatment adherence was confirmed by pill count.

Biomarker analysis

Routine clinical safety blood tests and additional research blood draws to measure the plasma levels of CBD and antidepressants were completed every 4 weeks throughout the trial.

Outcome measures

The primary endpoint was improvement in anxiety severity at week 12, measured on the Overall Anxiety Severity and Impairment Scale (OASIS). The OASIS is a 5-item trans-diagnostic self-report measure that can be used to assess severity and impairment associated with any anxiety disorder. It has excellent test–retest reliability, good convergent and discriminant validity,23, 24 and strong sensitivity to change 25. Secondary outcomes were safety and tolerability of CBD, assessed as the frequencies of adverse events, serious adverse events and withdrawals and discontinuations due to adverse events, study completion rate and routine clinical blood tests completed in 4-weekly intervals. Secondary outcomes also included absence of a diagnosis of an anxiety disorder, as diagnosed by the Structured Clinical Interview for DSM-5; the Clinical Global Impression–Improvement (CGI-I) scale; the Hamilton Anxiety Rating Scale (HAM-A); the Quick Inventory Depression Symptomatology (QIDS); the Social and Occupational Functional Assessment Scale (SOFAS); and the Cannabis Withdrawal Scale (CWS) to assess symptoms of withdrawal once the study medication was ceased. Research assessments were completed by trained research assistants who were not involved in the clinical care of research participants.

Statistical analysis

The sample size for this pilot trial was pre-determined based on feasibility and anticipated attrition rather than statistical power. Safety analyses were carried out on all enrolled participants (n=31). Efficacy analyses were carried out on an intention-to-treat basis, restricted to all participants who completed baseline and at least one post-baseline observation (n=30). Raw scores of outcome measures were calculated, including change in scores from baseline to Week 12 and from baseline to the 26-week follow-up. Effect sizes were calculated using the formula $(Mean_{post} - Mean_{pre})/ SD_{diff.,}$. For change in symptom and functioning scores, we used linear mixed effects models with restricted maximum likelihood estimator and unstructured covariance matrix. All models included random intercepts for participants and fixed effects for time, age and gender. Clinical global improvement and changes in clinical global severity ratings were compared with the Wilcoxon signed-rank test. In a

post-hoc analysis, non-parametric correlation coefficients and linear and logistic regression models were used to examine the effect of antidepressant medication, maximum daily dose of CBD and CBD plasma levels on adverse events and on the efficacy of CBD. A p-value below 0.05 was considered significant. All analyses were performed in Stata 15.1 (Stata Corp, College Station, TX, USA).

Results

Patient characteristics

A total of 31 participants were enrolled between 16 May 2018 and 28 June 2019 (Figure S1). Of 70 patients initially approached, 37 provided informed consent and 31 were eligible for the trial following a screening interview and blood test. All 31 participants were included in the safety analysis and 30 of 31 (96.8%) participants were included in the efficacy analysis. One participant withdrew prior to the first post-baseline study visit and another participant withdrew prior to the primary endpoint. Reasons for withdrawal included skin rash deemed possibly related to the study medication (n=1) and inability to meet the time commitment required for the study (n=1). Anxiety disorder diagnoses at baseline included social anxiety disorder, generalized anxiety disorder, panic disorder and specific phobias. The median duration of prior treatment as usual for anxiety disorders was 25.5 months. Twenty-one participants were prescribed antidepressants in addition to CBT with a median duration of 19 months and a median number of medication changes due to lack of efficacy or side effects of two. Participant characteristics for the safety and efficacy analysis group are reported in Table 1.

Efficacy analysis

Nineteen participants were titrated to the maximum dose of 800mg CBD per day. Ten participants received a lower maximum dose of 600mg per day (n=9) or 400mg per day (n=1) at Week 12 based on treatment response and/or adverse events. Two participants who withdrew prior to Week 12 received lower maximum doses of 200mg per day.

In the intention-to-treat analysis, anxiety severity decreased significantly from Baseline to Week 12 (Table 2). The mean change in OASIS score was -4.6 (SD 4.2) points or -42.6% from baseline (Cohen's

d = -1.07). Twelve of 30 (40%) participants had a reduction of at least 50% in OASIS scores by Week 12, and 18 of 30 participants had a reduction of at least 33% (Figure 1). Analysis of the secondary endpoints showed that HAM-A scores similarly decreased from Baseline (-11.1 (SD 10.6) points or 50.2% (Cohen's d = -1.00; Table 2, Figure 2b). We also observed a reduction in depressive symptom severity of -3.5 (SD 4.2) points or 29.9% on the QIDS-A17 (Cohen's d = -0.83; Table 2, Figure 2c). Social and occupational functioning improved by 6.4 (SD 8.9) points or 11.3% on the SOFAS (Cohen's d = 0.69; Table 2, Figure 2d). Improvements in anxiety and depressive symptoms and social and occupational functioning were not sustained after 6 months (n=13), which included a 14-week follow-up phase during which treatment was not controlled.

Analysis of CGI ratings showed that 26 (86.7%) of 30 participants had improved and 16 (55.2%) of 30 participants had substantially improved by Week 12. By the end of treatment, the number of participants rated as markedly or severely ill had decreased from 17 (56.7%) to 5 (17.2%) (Table 3).

At baseline, CBD was not detectable in plasma in any of the participants. Mean CBD plasma concentrations increased to 43.5ng/mL (SD 5.7) at Week 4, 74.1ng/mL (SD 7.7) at Week 8 and 68.7ng/mL (SD 8.4) at Week 12. Results of the post-hoc analysis examining the relationship between plasma concentrations of CBD and outcome showed that CBD plasma concentrations at Week 12 ($r=-0.14$, $p=0.46$) and the maximum CBD plasma concentrations during the treatment period ($r=-0.004$, $p=0.83$) were not correlated with the mean reduction in OASIS scores. We further examined whether the observed reduction in anxiety severity was dependent on antidepressant medication and found a significant interaction between antidepressant medication and change in OASIS score with participants not prescribed antidepressant medication having greater reductions ($p=0.02$). However, the improvement in OASIS scores from baseline to week 12 was significant in participants who were prescribed antidepressants (-3.5 (SD 5.3), $p=0.003$) as well as those not taking antidepressant (-5.6 (SD 2.8), $p<0.001$).

Safety analysis

Adverse events were reported by 25 of 31 (80.6%) participants included in the safety analysis (Table S1). Adverse events deemed related or possibly related to the study drug by the study physician were reported by 19 of 31 (61.3%) participants and included fatigue, low mood, increased or decreased appetite, drowsiness, nausea, diarrhea, dry mouth, insomnia and hot flushes or cold chills. All adverse events were mild or moderate in severity and most were transient and resolved spontaneously during the study. No serious adverse events or suspected unexpected serious adverse reactions were observed. There were no clinically significant changes to red or white blood cell counts, renal function or liver function. One request for withdrawal was due to an adverse event (skin rash deemed possibly related to CBD).

A post-hoc analysis showed that the number of adverse events was unrelated to the maximum CBD dose achieved during the trial (Spearman's rho=-0.03, p=0.88), plasma concentrations of CBD at Week 12 (Spearman's rho=-0.26, p=0.17), or the maximum plasma concentrations of CBD during the trial (Spearman's rho=-0.09, p=0.63). Patients who were prescribed antidepressants were more likely to experience at least one adverse event (OR=6.4 (95CI 1.16 – 35.44), p=0.03). While CBD plasma concentrations were unrelated to the risk of experiencing adverse events among all participants who were prescribed antidepressants (OR=1.01 (95%CI 0.97 – 1.05), p=0.62), 5 of 6 participants taking citalopram or escitalopram showed increases in the plasma concentrations of the two drugs after 12 weeks' treatment with CBD.

Discussion

The aim of this open-label trial was to test the safety and efficacy of CBD for treatment resistant anxiety disorders in people aged 12-25 years. In the intention-to-treat analysis we observed a statistically significant reduction in anxiety severity after 12 weeks of treatment with CBD. The mean reduction in OASIS score at Week 12 of 4.6 points (42.6%) corresponds to a clinically meaningful effect in this group of young people who have previously not responded to standard treatment for anxiety disorders. Approximately 40% of all participants experienced a 50% reduction in OASIS score and

two thirds experienced a 33% reduction. The improvement in anxiety severity was confirmed by secondary outcome measures (HAM-A) and supported by the CGI-I rating, which showed that clinically significant improvement was evident to the clinicians in 26 of 30 participants. CBD has previously been found to reduce anxiety symptoms in case reports of patients with anxiety disorders 12-14, observational studies in patients with primary anxiety, or anxiety related to other illnesses 26 and experimental studies in patients 15, 16, healthy volunteers 11 and adolescents with social anxiety 17. Given that the patients included in our trial were some of the most severe and treatment resistant and had significant functional impairment and multiple failed treatment attempts, the reduction in anxiety severity observed here suggests that CBD has clinically meaningful anxiolytic effects.

The mechanisms by which CBD may exert beneficial effects on anxiety are not completely understood but likely include effects on the CB1 and 5-HT1A receptor, TRPV1, anti-inflammatory and antioxidant effects, and increases in endocannabinoid tone 11, 18. In imaging studies, CBD reduced activation of limbic and paralimbic brain areas during anxiety in patients with social anxiety disorder.15 With a mechanism of action that is apparently different to that of SSRIs commonly used to treat anxiety disorders, CBD may represent a new class of drug for anxiety disorders. Future studies should further explore the mechanism of action of CBD, its interactions with psychotropic medication and potential synergistic effects with psychological therapies.

CBD demonstrated an acceptable safety profile in our trial, with no serious adverse events reported and no clinically significant deviations to blood cell counts. While a majority of participants reported some adverse events deemed possibly related to the intervention, the majority of these were mild and resolved spontaneously. The most common adverse events were fatigue, low mood, hot flushes or cold chills. One of two withdrawals in this trial were due an adverse event (skin rash). Overall, the adverse events observed in our trial are similar to those in other trials of CBD in different populations 27, 28. A noteworthy finding from this trial was that adverse events were more common in participants who were concurrently taking antidepressants. CBD is an inhibitor of the CYP3A4,

CYP2C19 and other cytochrome P450 enzymes involved in the metabolism of psychotropic drugs 29. Several antidepressants including fluoxetine, venlafaxine and escitalopram are substrates of these enzyme 30. To test the hypothesis that CBD increases plasma levels of antidepressants, we examined whether plasma levels changed during the trial. Among 5 of 6 participants taking escitalopram, plasma levels were increased throughout the trial relative to baseline. This may reflect the particular reliance of escitalopram, relative to other antidepressants, on metabolism via CYP2C19, which is strongly inhibited by CBD 31. Of note, participants were required to remain on a stable dose of antidepressant medication for 6 weeks before enrolment and throughout the trial. There was no evidence for a relationship between CBD plasma levels and the frequency of adverse events. Overall, results from this trial confirm the notion that CBD has a favourable safety profile and demonstrate that CBD is generally well tolerated in a population of young people with anxiety disorders.

Our trial has several limitations that need to be considered when interpreting these findings. Firstly, our trial was open-label and uncontrolled. Therefore, causal inferences about the efficacy of CBD relative to other influences cannot be made. Secondly, the prominent role of CBD in the media and the fact that we included a treatment resistant population increase the risk of expectancy bias in our trial. To reduce this risk, the trial only accepted referrals from clinicians (and not self-referrals). Moreover, failed treatment attempts in the past may reduce expectancy bias in this population. Strengths of the trial include the use of high-purity (>99.5%) CBD, the stringent eligibility criteria, the dose-escalation protocol and the analysis of CBD plasma levels.

Since our trial included the titration period and because the strongest effects were observed in the last 4 weeks of treatment, it is possible that longer treatment at an effective dose or more rapid titration would have led to even greater improvements. Based on our criteria to increase the dose until efficacy was noted in the CGI, the majority of participants were titrated to the maximum dose of 800mg per and a smaller proportion to 600mg and 400mg per day. Because our trial also included a

background intervention of CBT and/or antidepressant medication and close monitoring by researchers and study doctors, the relative contribution of these components needs to be determined in future trials with appropriate control conditions. However, we found no evidence that the reduction in anxiety severity was dependent on antidepressant medication use in this trial. The observation that there were no sustained benefits of CBD three months after the end of the intervention further supports the notion that treatment as usual did not explain the observed benefits during the 12-week intervention. While concomitant recreational cannabis use might complicate the therapeutic actions of CBD on anxiety and depression, only two of the 30 participants displayed detectable concentrations of THC or THC-COOH in their plasma during the trial. It is therefore unlikely that cannabis use contributed to or diminished the observed effect.

To our knowledge, this is the first clinical trial of CBD in young people with anxiety disorders for whom established treatments are not effective. The findings of this trial suggest that further investigation of CBD for anxiety in conjunction with usual care is warranted.

Disclosures

The authors declare that there is no biomedical or financial conflict of interest.

Acknowledgements

We would like to thank the participants and their families. We would also like to acknowledge the technical assistance of Rebecca Vogel and Dr Melissa Benson and the contributions of the late Associate Professor David Allsop to this trial. The study was funded by a grant from the Lambert Initiative for Cannabinoid Therapeutics. MB was supported by a MRFF Rapid Applied Research Translation Fellowship. GPA was supported by an NHMRC Senior Research Fellowship (1080963).

Contributors

GPA, PMG and MB were responsible for the study design, obtaining funding and for drafting the study protocol. As Principal Investigator, GPA had overall responsibility for the implementation of the study. EL and MB were responsible for project management and data collection. GPA oversaw

the medical management of the study participants. RK and IMG analysed cannabinoid and antidepressant plasma concentrations. GPA and MB developed the statistical analysis plan and MB analysed the data. MB wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

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Figure legends:

Figure 1 Percentage change in OASIS score of patients included in the efficacy analysis (n=30) from baseline to week 12. Percentage change are shown for each patient, ordered from greatest increase to greatest decrease.

Figure 2 Primary and secondary outcome measures of patients included in the efficacy analysis (n=30) at baseline, week 4, week 8, week 12 and 3 months post-CBD. Monthly changes in (A) OASIS scores, (B) HAM-A scores, (C) QIDS-A17 scores and (D) SOFAS scores. Boxplots show median values, 25^{th} and 75^{th} percentiles. Whiskers represent the 25^{th} percentile – 1.5 × IQR and the 75^{th} percentile + 1.5 × IQR.

Figure S1 CONSORT diagram.