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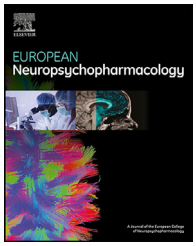

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Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: A randomised controlled trial

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Abstract
Preclinical research suggests that enhancing CB1 receptor agonism may improve fear extinction. In order to translate this knowledge into a clinical application we examined whether cannabidiol (CBD), a hydrolysis inhibitor of the endogenous CB1 receptor agonist anandamide (AEA), would enhance the effects of exposure therapy in treatment refractory patients with

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anxiety disorders. Patients with panic disorder with agoraphobia or social anxiety disorder were recruited for a double-blind parallel randomised controlled trial at three mental health care centres in the Netherlands. Eight therapist-assisted exposure in vivo sessions (weekly, outpatient) were augmented with 300 mg oral CBD ($n = 39$) or placebo ($n = 41$). The Fear Questionnaire (FQ) was assessed at baseline, mid- and post-treatment, and at 3 and 6 months follow-up. Primary analyses were on an intent-to-treat basis. No differences were found in treatment outcome over time between CBD and placebo on FQ scores, neither across ($\beta = 0.32$, 95% CI [-0.60; 1.25]) nor within diagnosis groups ($\beta = -0.11$, 95% CI [-1.62; 1.40]). In contrast to our hypotheses, CBD augmentation did not enhance early treatment response, within-session fear extinction or extinction learning. Incidence of adverse effects was equal in the CBD ($n = 4$, 10.3%) and placebo condition ($n = 6$, 15.4%). In this first clinical trial examining CBD as an adjunctive therapy in anxiety disorders, CBD did not improve treatment outcome. Future clinical trials may investigate different dosage regimens.

1. Introduction

Cognitive behavioural therapy including exposure therapy is the first line evidence based treatment for anxiety disorders (Van Dis et al., 2020). Effect sizes are small to medium at six to twelve months of follow-up for panic disorder and social anxiety disorder. Notwithstanding its effectiveness at a group level, around one third of patients are non-responders (Taylor et al., 2012). In addition, relapse rates in anxiety disorders are high, with recurrence rates up to 23.5% in patients with a remitted anxiety disorder within two years (Scholten et al., 2012).

Fear extinction, which occurs when a conditioned stimulus is repeatedly presented in the absence of the associated aversive event, is presumed to underlie the effect of exposure therapy (Craske et al., 2014). Marsicano et al. (2002) were the first to show the central function of cannabinoid type 1 (CB1) receptors in fear extinction in rodents. They demonstrated that fear extinction was impaired after genetically or pharmacologically blocking of CB1 receptors (Marsicano et al., 2002), which are expressed in the prefrontal cortex, hippocampus, and amygdala (Herkenham et al., 1991; Moldrich and Wenger, 2000).

Direct evidence of involvement of the human endogenous cannabinoid system in fear extinction stems from a study in healthy human subjects ($n = 150$) who underwent a fear conditioning and extinction procedure in a virtual reality environment (Heitland et al., 2012). Participants were genotyped for two polymorphisms located within the promoter (rs2180619) and coding region (rs1049353) of the CB1 receptor. Whereas both homozygote (G/G, $n = 23$) and heterozygote (A/G, $n = 68$) G-allele carriers of rs2180619 displayed robust extinction of fear, extinction of fear-potentiated startle was absent in A/A homozygotes ($n = 51$). This resistance to extinguish fear resulted in increased levels of fear-potentiated startle at the end of the extinction training within the group of A/A carriers (Heitland et al., 2012).

Human studies have investigated exocannabinoids in relation to fear extinction. Of these, Δ^9-tetrahydrocannabinol (THC) may be less suitable for clinical applications given the induction of psychotic and anxiety symptoms in some individuals (Bhattacharyya et al., 2010). In contrast, cannabidiol (CBD) seems to exert an anxiolytic effect in animal experimental (Almeida et al., 2013; Campos et al., 2012; Moreira et al., 2006) and human studies (Crippa et al., 2011, 2004; Fusar-Poli et al., 2009; Zuardi et al., 2017) without these psychotropic effects, coupled with a favourable safety profile (Bergamaschi et al., 2011a) and low abuse potential (Parker et al., 2004). Contrary to direct CB1 receptor agonists (like THC), CBD does not induce psychomotor impairment and does not lead to feelings of "high" (Dalton et al., 1976). CBD increases availability of the endogenous cannabinoid anandamide (AEA; Kano et al., 2009), which binds to CB1 receptors (Devane et al., 1992). The main metabolic enzyme of AEA, fatty acid amide hydrolase (FAAH), catalyses its' hydrolysis (Ueda et al., 2000).

The role of AEA signalling in anxiety has been underpinned by genetic data. Non-patient carriers ($n = 31$) of the FAAH polymorphism C385A (rs324420), which has been associated with low expression of FAAH in human blood T-lymphocytes (Chiang et al., 2004) and elevated plasma AEA levels (Sipe et al., 2010), exhibited greater amygdala-habituation during repeated viewing of threatening faces compared to other genotypes ($n = 50$; Gunduz-Cinar et al., 2013). In addition, homozygous C385A carriers ($n = 48$) had lower trait stress reactivity scores than other genotypes ($n = 833$; Gunduz-Cinar et al., 2013). These findings suggest that pharmacological augmentation of AEA signalling may be a promising avenue for reducing anxiety. Here, CBD, an AEA reuptake and hydrolysis inhibitor (Bisogno et al., 2001), comes into play.

There is substantial -although not entirely unambiguous- evidence from animal studies that CBD may be used as an adjunct to exposure therapy and help to alleviate anxiety through enhancement of fear memory extinction learning (Bitencourt et al., 2008; Do Monte et al., 2013; Lemos et al., 2010; Resstel et al., 2006; Song et al., 2016). In addition, CBD may also exert more global anxiolytic effects apart from extinction learning, which may not in all experiments be distinguishable from effects on fear extinction (Lemos et al., 2010; Resstel et al., 2006).

Two studies demonstrated lower freezing during context re-exposure in fear conditioned rats treated intraperitoneally with 10 mg/kg CBD, compared to vehicle-treated animals. In non-conditioned rats, CBD had no effects on freezing (Lemos et al., 2010; Resstel et al., 2006). In another study, freezing during context re-exposure was

lower in rats who received CBD prior to extinction training than in rats who received vehicle (Song et al., 2016). This effect was reversed when rats were conditioned with two foot shocks (Song et al., 2016).

Further, rats treated with high dosages of 2 μg intracerebroventricular CBD prior to extinction training displayed lower freezing time compared to the vehicle-treated group (Bitencourt et al., 2008). This effect, which only occurred at this high dose, persisted after one day of CBD washout, which suggests long-term facilitation of extinction (Bitencourt et al., 2008). Another study with a similar set-up found effects during extinction training with their highest dose of 0.4 μg CBD injected into each side of the infralimbic cortex, that persisted until the drug-free test (Do Monte et al., 2013). These effects were blocked by administering a CB1 receptor antagonist, which suggests mediation of extinction learning by CB1 receptor activation (Do Monte et al., 2013).

The effect on extinction learning of 32 mg vaporized CBD or placebo before or after extinction training was studied in healthy human volunteers ($n = 48$; Das et al., 2013). Administration after extinction training led to lower shock expectancy upon presentation of the conditioned stimulus 24 h after conditioning compared to placebo. Null effects were found when CBD was administered prior to extinction training. The authors argued that ceiling-level extinction might have obscured potential differences between drug conditions (Das et al., 2013). More room for improvement would be expected in patients than in healthy subjects (Duits et al., 2015).

There is a paucity of clinical studies with CBD in patients with anxiety disorders. We identified three studies with a randomised controlled design in patients with social anxiety disorder (Bergamaschi et al., 2011b; Crippa et al., 2011; Masataka, 2019). In the first single dosage study, 24 participants were subjected to a simulated public speaking task 80 min after ingesting 600 mg oral CBD dissolved in corn oil, or placebo (Bergamaschi et al., 2011b). In the second single dosage study, 10 subjects ingested 400 mg CBD or placebo 110 min before SPECT neuroimaging (Crippa et al., 2011). Subjective state anxiety and functional activity of temporolimbic and paralimbic regions were measured (Crippa et al., 2011). In these works, CBD exerted beneficial effects on measures of subjective anxiety (Bergamaschi et al., 2011b; Crippa et al., 2011), and led to functional activity changes that were in line with these effects (Crippa et al., 2011). In a third randomised controlled trial 300 mg CBD ingested daily for four weeks ($n = 17$) by teenagers decreased severity of social anxiety disorder compared to placebo ($n = 20$; Masataka, 2019). In this study no exposure-based CBT was added during the study period.

In conclusion, preclinical animal and human research suggests a critical role of the endocannabinoid system in fear extinction and, possibly, extinction consolidation. In addition, evidence exists for a general anxiolytic effect of CBD. In order to bridge the gap between these promising results and application in the clinic we conducted a randomised controlled trial in patients with panic disorder with agoraphobia or social anxiety disorder. Our main research question was whether augmentation of exposure therapy with 300 mg oral CBD would lead to stronger or faster improvement of anxiety symptoms. In addition, we explored whether CBD would enhance extinction within treatment sessions and/or would reduce fear acutely. Furthermore, considering potential effects on extinction consolidation, we tested whether an effect of CBD on symptom severity would be moderated by within-session extinction learning. Assuming that CBD would enhance the consolidation of adaptive learning during treatment sessions, we expected a beneficial effect from CBD on symptom severity only when fear and/or credibility of the feared outcome at the end of the treatment session were low.

2. Experimental procedures

2.1. Study design

Patients with treatment refractory social anxiety disorder or panic disorder with agoraphobia participated in this randomised, double-blinded, parallel, placebo-controlled fixed dose clinical multicentre trial. Patients were considered to be treatment refractory when they either had not profited from at least one previous state of the art pharmacological and/or psychological treatment, or when they experienced a relapse after previous successful treatment. The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht (protocol number 40-41,200-98-9269). The study protocol has been published (https://link.springer.com/article/10.1186/s12888-019-2022-x), and the trial is registered on EU Clinical Trials Register (2014-004094-17).

2.2. Participants

At one of the three participating mental health care centres, participants received an explanation of study procedures and were given the opportunity to ask questions before providing written informed consent. A screening interview and Structured Clinical Interview on DSM-IV disorders (SCID; First et al., 2002) was conducted to check in- and exclusion criteria (full criteria in study protocol; Van der Flier et al., 2019):

Inclusion criteria.

- Patients between 18 and 65 years with a primary diagnosis of social anxiety disorder or panic disorder with agoraphobia according to DSM-IV criteria.

Exclusion criteria.

- Co-morbid psychiatric disorders, i.e. current severe major depressive (BDI $>$ 40) or bipolar disorder, psychosis, dependence of alcohol and drugs;
- Use of antipsychotic medication;
- Regular daytime use of benzodiazepines;
- Changes in dosing regimen of serotonergic antidepressants $<$ 4 weeks prior to study entry;
- Use of recreational drugs $<$ 2 months preceding study entry (alcohol and tobacco were permitted);
- Pregnancy or breastfeeding.

2.3. Randomisation and masking

The randomisation (CBD or placebo with a 1:1 allocation ratio) was conducted by an independent data manager using block randomisation, stratifying for study centre and primary diagnosis. Patients were allocated to one of the medication groups after enrolment according to the order in the stratum. The capsules containing CBD and placebo were identical in appearance.

Investigators, research assistants, therapists, and participants were blinded with respect to randomisation. For one patient the randomisation code was broken and participation discontinued because of an unplanned pregnancy. Data for the remaining patients were unblinded after the last post-treatment measurement (December 3, 2019) to allow timely reporting to the trial funder. Research assistants who remained blinded collected remaining follow-up measurements. Patients were unblinded after the last follow up measurement. In the eighth treatment session and at post-treatment, therapists and patients were asked to speculate whether the patient had received CBD or placebo. Judgements of therapists and patients were mostly based on expected and observed adverse or anxiolytic effects, and independent of actual drug conditions (for therapists $p = 0.851$; for patients, $p = 0.110$), indicating that blinding was successful.

2.4. Procedures

Eight 90-min therapist-assisted augmented exposure *in vivo* sessions were delivered by psychologists trained in cognitive behavioural therapy (CBT) and in the standardised protocols for exposure therapy in the current study.

In the introductory session patients received the treatment rationale and -explanations, and baseline assessments. Synthetic CBD in powder form (purity > 99.9%) was manufactured by STI pharmaceuticals (UK) and THC Pharm (Germany) and encapsuled by ACE Pharmaceuticals in compliance with Good Manufacturing Practice (GMP). Approximately 2 h before exposure treatment sessions 1 to 8 patients ingested 300 mg CBD or placebo (lactose). Timing of administration was aimed at achieving peak plasma levels during the treatment session (Englund et al., 2013). In order to ensure dosage in the effective and safe range we employed dosages of 300 mg, in line with previous work (Zuardi et al., 2017, 1993).

Outcome measures were assessed at baseline (T0), at mid-treatment (T1), post-treatment (T2) and at 3 and 6 month follow-up (T3 and T4). During treatment, a short assessment including the primary outcome measure was done at each therapy session (S0 to S8). In order to check compliance, blood samples to assess CBD plasma levels were collected preceding the first (S1) and last (S8) treatment session, 2 h after medication administration.

2.5. Outcomes

The primary outcome measure comprised the Fear Questionnaire (FQ; Marks and Mathews, 1979), which measures level of avoidance as a result of the anxiety disorder. Overall severity of anxiety, as measured by the Beck Anxiety Inventory (BAI; Beck et al., 1988), was our most important secondary outcome measure (for all clinical outcome measures, see Table S1). The primary endpoint of this study was the clinical change until post-treatment (at assessment T2) measured with the FQ. Therapists asked their patients in each treatment session (S0 to S8) whether any negative effect had occurred that could be related to the study medication. In addition, patients' spontaneous reports of adverse events were collected. Grouping of adverse events into the categories "none", "potential", "probable", and "definite" related to the study medication was based on therapists' and researchers' judgement .

2.6. Statistical analysis

Sample size calculation, based on a repeated measures design for two groups with two measurements, and an envisioned effect size of 0.6 Cohen's *d* yielded groups sized of 36 patients per treatment arm for a power of 0.8, with $\alpha = 0.05$.

We used multilevel regression analyses with factors time (linear and quadratic trends), drug, and diagnosis to investigate (1) whether CBD augmentation would be associated with better clinical outcome at post-treatment (T2) and a more favourable time course of the treatment effect. Further, we assessed (2) whether clinical improvement in the CBD condition was more enduring (from post-treatment (T2) to follow-up at 6 months (T4) and (3) whether improvement occurred faster (from the introductory (S0) to the last drug augmented treatment session S8) compared to the placebo condition. In order to reduce unexplained error variance, the following covariates were investigated (and discarded from the final models if they did not significantly affect outcome): Use of antidepressant medication, stability or change in medication dosing regimen during the follow-up period, and number of treatment sessions until the last follow-up assessment.

With ancillary multilevel discrete-time (since treatment response was measured per session rather than continuously) survival analyses (Hox et al., 2018) we investigated (4) early treatment response by CBD, defined as a 25% or greater symptom reduction (Taylor et al., 2012; Hofmeijer-Sevink et al., 2017) on FQ and BAI from the introductory session to session 8.

We also examined (5) direct CBD effects on extinction learning or anxiolysis occurring within treatment sessions, as measured with subjective units of distress (SUDs) scores prior and directly after exposure exercises. Finally, to explore whether CBD may enhance consolidation of (mal)adaptive learning during exposure therapy sessions we tested, in line with a previous method (Hofmeijer-Sevink et al., 2017; Smits et al., 2013) whether (6) low SUDs scores at the end of treatment sessions moderated effects of CBD on FQ, BAI, CGI, LSAS, or MI "alone" score at the next session.

In the analyses on assessments from baseline to second follow-up (T0-T4), full information maximum likelihood (FIML) estimates for model parameters were calculated using all available data of 78 patients. Two patients failed to fill in any of the questionnaires, so they were not included in these analyses. Missing values in the per session assessments were handled by multiple imputation.

Elaborate report of methodology in Supplemental experimental procedures, Table S1.

3. Results

3.1. Study population

Patients were randomly assigned between June 2016 and August 2019. The last follow-up assessment took place in May 2020. Treatment discontinuation rates did not differ significantly between the CBD ($n = 7$, 17.9%) and placebo condition ($n = 12$, 29.3%), $\chi^2 = 1.41$, $p = 0.23$. The flow of participants through the study is displayed in a CONSORT diagram (Fig. S1). Participants' baseline characteristics are provided in Table 1.

3.2. Intent-to-treat analysis

The multilevel analyses to answer objectives (1), (2), and (3) described under 'Statistical analysis' were performed on the intent-to-treat sample. Results from the analyses on assessments from baseline (T0) to follow-up (T4) to assess clinical change until post-treatment (T0 to T2; objective 1) and long-term treatment effect (T2 to T4; objective 2) are summarized in Tables 2 and 3. As shown in Table 2, a two-level regression analysis with factors time (linear and quadratic trends), drug, and diagnosis revealed main effects of time on level of avoid-

Table 1 Sociodemographic and clinical characteristics at baseline, split by drug condition.

	Total sample ($n = 80$)	Placebo ($n = 41$)	Cannabidiol ($n = 39$)
Sociodemographics			
Age at study entry	36.7 (10.5)	38.3 (11.3)	34.9 (9.3)
Female sex	32 (40.0)	15 (36.6)	17 (43.6)
Double nationality	4 (7.7)	2 (7.7)	2 (7.7)
Married or cohabiting	27 (50.9)	15 (55.6)	12 (46.2)
Post-high school education	35 (68.6)	17 (65.4)	18 (72.0)
Currently employed	43 (65.2)	19 (59.4)	24 (70.6)
Clinical variables			
Having received previous treatment	49 (65.3)	26 (66.7)	23 (63.9)
Use of antidepressant medication	34 (42.5)	16 (39.0)	18 (46.2)
Primary diagnosis social anxiety disorder	37 (46.3)	19 (46.3)	18 (46.2)
Primary diagnosis panic disorder with agoraphobia	43 (53.8)	22 (53.7)	21 (53.8)
FQ, mean	51.9 (19.8)	54.2 (19.4)	49.5 (20.2)
BAI, mean	27.9 (10.0)	29.3 (9.1)	26.4 (10.8)
CGI severity, mean	4.8 (1.0)	4.7 (1.0)	4.9 (1.1)
BDI-II	22.9 (12.1)	22.1 (12.3)	23.6 (12.0)
SPAI-18 Social phobia subscale	60.2 (21.2)	61.8 (20.9)	58•7 (21•6)
BSQ	2.3 (0.7)	2.4 (0.8)	2.2 (0.7)
Panic disorder specific questionnaires ($n = 43$)			
ACQ	2.2 (0.6)	2.1 (0.6)	2.2 (0.7)
MI "alone"	3.1 (0.9)	3.3 (0.9)	2.9 (1.0)
MI "accompanied"	2.4 (0.9)	2.4 (0.9)	2.4 (0.9)
PDSS	15.5 (5.0)	15.5 (5.3)	15.5 (4.7)
Social anxiety disorder specific questionnaires ($n = 37$)			
LSAS	78.7 (29.8)	84.3 (27.4)	74.1 (32.1)

Note: Data are mean (SD) or n (%).

ance, measured by the FQ, with patients showing on average a decrease in avoidance over time. Most importantly, the linear and quadratic time by drug and linear and quadratic time by drug by diagnosis interactions were not significant. This indicates that there were no significant differences between placebo and CBD condition in FQ scores over the course of the study, in both diagnostic groups. Numerically, it seemed that the placebo condition unexpectedly improved more than the CBD condition (Fig. S2), suggesting that lack of power was not the reason for these non-significant results.

On overall severity of anxiety, measured by the BAI, the multilevel analysis yielded main linear and quadratic time effects (Table 2). Time by drug and time by drug by diagnosis interactions were not significant. This indicates that there were no significant between-group differences: both groups improved, but CBD did not lead to stronger or more enduring effects compared to placebo, regardless of diagnosis (objectives 1 and 2). Again, the fact that the placebo condition seemingly improved more than the CBD condition (Fig. S3) suggests that lack of power was not the reason for these non-significant results.

Further, multilevel regression analyses on the assessments taken in every treatment session (S0 to S8) yielded no significant time by drug or time by drug by diagnosis interactions, indicating that CBD did not lead to faster improvement compared to placebo, irrespective of diagnosis (objective 3).

3.3. Secondary outcomes and completers analysis

The multilevel analyses to answer objectives (1), (2), and (3) described under 'Statistical analysis' were also performed with secondary outcomes and on the completers sample. Overall, secondary outcomes (see Tables 2 and 3) and results of completers analyses (see Tables S4, S5, and Fig. S4) corroborated the primary outcomes. That is, CBD did not lead to stronger, faster, and/or more enduring clinical improvement on these outcome measures, neither in patients with panic disorder with agoraphobia nor in those with social anxiety disorder.

3.4. Exploratory analysis

Additional exploratory analyses to answer objectives (4), (5), and (6) described under 'Statistical analysis' did not yield significant effects of CBD either. This included multilevel discrete-time survival analyses with response defined as 25% reduction in FQ and BAI scores (objective 4). This implies that probability of response was equal for the CBD and placebo condition in each treatment session, *p*s $\geq$ 0.089 (Figures S5-S6). Further, analyses of within session improvement using within session SUD scores (objective 5) showed no significant enhancement of within-session extinction learning (Supplemental results Section 2.1, Table S8, Figures S7-S8) nor enhancement of SUDS within session

Table 2 Predictors of primary and secondary outcomes in multilevel regression analyses on assessments from baseline to second follow-up (T0-T4) in the intent-to-treat sample (placebo $n = 39$; cannabidiol $n = 39$).

	FQ (primary outcome)		BAI		BDI-II		BSQ		SPAI-18	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Time level										
Time	−1.82*	(−2.51; −1.14)	−0.65*	(−1.07; −0.22)	−0.44*	(−0.73; −0.15)	−0.056*	(−0.084; −0.029)	−0.52*	(−0.74; −0.30)
Time^2	0.027*	(−0.13; 0.042)	0.0098	(−0.00040; 0.020)	0.0069	(0.00010; 0.014)	0.00089*	(0.00036; 0.0014)	NA	NA
Patient level										
Intercept	55.59*	(46.49; 64.69)	22.86*	(18.52; 27.19)	22.32*	(17.26; 27.39)	2.38*	(2.05; 2.71)	51.79*	(41.31; 62.26)
Drug (PLB; CBD)	−8.88	(−22.42; 4.66)	5.25	(−0.99; 11.48)	1.53	(−4.61; 7.68)	0.027	(−0.38; 0.43)	−5.48	(−18.91; 7.95)
Diagnosis (PD; SOC)	−11.20	(−23.38; 0.98)	−3.97	(−11.04; 3.09)	1.08	(−6.55; 8.71)	−0.17	(−0.66; 0.32)	13.95*	(1.81; 26.09)
Drug x diagnosis	9.57	(−9.12; 28.26)	−5.73	−15.13; 3.67)	−0.53	(−10.54; 9.48)	−0.26	(−0.86; 0.34)	5.52	(−11.20; 22.25)
Antidep (no; yes)	NA	NA	NA	NA	−4.77*	(−8.74; −0.80)	NA	NA	NA	NA
Time interaction variables										
Time x drug	0.32	(−0.60; 1.25)	−0.32	(−0.87; 0.23)	−0.11	(−0.48; 0.26)	0.013	(−0.022; 0.048)	0.22	(−0.047; 0.50)
Time x diagnosis	0.26	(−0.66; 1.18)	0.053	(−0.51; 0.61)	0.0042	(−0.50; 0.49)	0.011	(−0.032; 0.055)	0.088	(−0.21; 0.38)
Time x drug x diagnosis	−0.11	(−1.62; 1.40)	0.56	(−0.20; 1.33)	0.065	(−0.54; 0.67)	0.0074	(−0.045; 0.060)	0.017	(−0.35; 0.39)
Time^2 x drug	−0.00067	(−0.021; 0.020)	0.0095	(−0.0044; 0.023)	0.0037	(−0.0055; 0.013)	−0.00023	(−0.00096; 0.00050)	NA	NA
Time^2 x diagnosis	0.00092	(−0.019; 0.021)	0.0016	(−0.012; 0.015)	−0.0018	(−0•013; 0•0092)	−0.000074	(−0.00098; 0.00083)	NA	NA
Time^2 x drug x diagnosis	0.0026	(−0.033; 0.038)	−0.013	(−0.033; 0.0072)	0.0038	(−0.011; 0.018)	−0.000054	(−0.0013; 0.0011)	NA	NA

Note: FQ=Fear Questionnaire; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory-II; BSQ=Bodily Sensations Questionnaire; SPAI-18=Social Phobia and Anxiety Inventory-18; PLB=placebo; CBD=cannabidiol; PD=panic disorder with agoraphobia; SOC=social anxiety disorder; Antidep=antidepressant; CI=confidence interval; NA=not applicable: Covariates which did not significantly predict outcome were omitted from the final models. Confidence intervals based on robust standard errors.

* $p < 0.05$.

fear or credibility scores at the end of treatment sessions by CBD augmentation (objective 6, Figures S7-S8).

3.5. Compliance check

Overall, significant, albeit variable CBD plasma concentrations were measured for participants in the CBD condition preceding the first (S1) (mean = 19.23 ng/ml; SD = 24.28; $n = 38$) and the last (S8) treatment session (mean = 21.44 ng/ml; SD = 32.19; $n = 30$). Thus, CBD ingestion resulted in marked increases in plasma concentrations of CBD on at least one measurement occasion. For all participants in the placebo condition CBD concentrations were below the detection threshold of the assay (<0.10 ng/ml) preceding S1 ($n = 36$) and S8 ($n = 28$). For four participants in the CBD condition, CBD concentrations were below the detection threshold at S1, when drug intake was monitored by a research assistant ($n = 3$), and at S8 ($n = 1$). Taken together, these results suggest that overall, trial participants adhered to the assigned drug treatments.

3.6. Adverse events

No serious adverse events occurred. Adverse events were judged by blinded therapists and researchers as 'not related' or 'possibly related' to the study medication. After unblinding they appeared evenly distributed between the CBD ($n = 4$) and the placebo condition ($n = 6$), $p = 0.40$ (see Table 4). Suicidal thoughts occurred in one patient in the placebo condition, leading to treatment discontinuation. The patient stabilized after a period of crisis intervention.

3.7. Sensitivity analysis

Outcomes of sensitivity analyses, in which we excluded patients in treatment trajectories with low protocol adherence (including one patient who displayed an undetectable CBD level despite allocation to the CBD condition) and excluding patients who needed intensive treatment programs

Table 3 Predictors of primary and secondary disorder-specific outcomes in multilevel regression analyses on assessments from baseline to second follow-up (T0-T4) in the intent-to-treat sample.

	LSAS		MI "alone"		MI "accompanied"		ACQ		PDSS	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Time level										
Time	−2.48*	(−3.86; −1.10)	−0.035*	(−0.071; 0.0019)	−0.020*	(−0.029; −0.011)	−0.039*	(−0.068; -0.010)	−0.41*	(−0.61; -0.21)
Time^2	0.052*	(0.022; 0.083)	0.00047	(−0.00031; 0.0013)	NA	NA	0.00057	(−0.000024; 0.0012)	0.0053*	(0.0015; 0.0090)
Session	NA	NA	−0.016*	(−0.018; −0.014)	NA	NA	NA	NA	−0.037*	(−0.059; −0.014)
Patient level										
Intercept	71.99*	(56.40; 87.58)	3.20*	(2.82; 3.58)	2.34*	(1.97; 2.72)	2.12*	(1.83; 2.40)	15.42*	(13.31; 17.52)
Drug (PLB; CBD)	0.40	(−20.69; 21.49)	−0.32	(−0.84; 0.20)	−0.11	(−0.59; 0.37)	0.062	(−0.32; 0.44)	0.65	(−2.28; 3.57)
Time interaction variables										
Time x drug	1.40	(−0.76; 3.56)	−0.0053	(−0.051; 0.040)	0.0072	(−0.0038; 0.018)	0.0059	(−0.028; 0.039)	−0.082	(−0.37; 0.20)

Note: LSAS=Liebowitz Social Anxiety Scale; MI=Mobility Inventory; ACQ=Agoraphobic Cognitions Questionnaire; PDSS=Panic Disorder Severity Scale; PLB=placebo; CBD=cannabidiol; CI=confidence interval; NA=not applicable: Covariates which did not significantly predict outcome were omitted from the final models. LSAS was filled in by 37 patients with social anxiety disorder (placebo $n = 19$; cannabidiol $n = 18$), MI, ACQ and PDSS by 41 patients with panic disorder with agoraphobia (placebo $n = 20$; cannabidiol $n = 21$). Confidence intervals based on robust standard errors. Time2 x drug interactions were not significant and are not displayed in the table.

* $p < 0.05$.

Table 4 Adverse events.

	Placebo ($n = 39$)	Cannabidiol ($n = 39$)
Isolated	sweating, hot flushes, nausea, blurred vision, and a bad taste in the mouth ($n = 1$)	dizziness ($n = 1$)
	the flu and gout attacks ($n = 1$)	drowsiness ($n = 1$)
	suicidal thoughts ($n = 1$)	
Recurrent	tiredness ($n = 1$)	tiredness ($n = 1$)
	drowsiness ($n = 1$)	feeling of a strong blood flow ($n = 1$)
	headaches ($n = 1$)	

after the per-protocol sessions, corroborated the outcomes of primary analyses.

Detailed results are provided in Supplemental results, Tables S2−S17, Figs. S2−S8.

4. Discussion

In this clinical trial we examined whether the AEA hydrolysis inhibitor CBD would improve exposure-based in vivo treatment outcome in social anxiety and panic disorder patients with agoraphobia. Results indicated that 300 mg CBD prior to 8 exposure in vivo treatment sessions did not lead to stronger, more enduring, or faster symptom improvement compared to placebo, nor did cannabidiol augmentation increase the probability of early treatment response. In addition, CBD did not improve within-session fear extinction, nor did it affect extinction learning consolidation. These negative findings applied to patients with panic disorder with agoraphobia and those with social anxiety disorder. Although we found no benefits of CBD as an adjunctive therapy, no side effects were detected either.

With respect to representativeness of our sample, on average, patients in the current study presented with severe symptoms, characteristic for a population in need of an adjunctive therapy. Recruitment at multiple treatment centres and with two different diagnoses increased generalizability of findings. The gender distribution in our study sample, with somewhat more men (60%) than women, was somewhat deviant from anxiety disordered populations in general, as anxiety disorders occur more frequently in women. However, the gender imbalance is smaller for social anxiety compared to panic disorder with agoraphobia (Wittchen et al., 2011). Moreover, our results were not affected by participants' gender.

The present findings contrast with earlier research that suggested acute fear extinction enhancement by CBD in rodents (Bitencourt et al., 2008; Do Monte et al., 2013; Lemos et al., 2010; Resstel et al., 2006; Song et al., 2016) and extinction learning consolidation in humans

(Das et al., 2013), with lasting effects (Bitencourt et al., 2008; Do Monte et al., 2013). Absence of CBD effects on fear extinction, however, has also been reported in experimental rodent studies. Intraperitoneal administration of CBD (5, 10 or 20 mg/kg) prior to extinction training had no effect on time freezing upon re-exposure to the conditioned cue (Jurkus et al., 2016). When tested in stress-susceptible rats exposed to predator odour, CBD (5 mg/kg) administered prior to extinction training had no effect on contextual conditioned fear (Shallcross et al., 2019).

The strengths of this study include the use of both patient and clinician rated outcome measures, and both disorder specific and generic outcome measures. We included a six month follow-up and accounted for (changes in) antidepressant treatment and /or number of treatment sessions. Within the active treatment phase, per session measures allowed to investigate drug induced acceleration of treatment response. Notwithstanding the richness of our dataset, multiple analyses on these data increased the probability of incorrectly rejecting the null hypothesis. However, none of our analyses indicated superiority of CBD to placebo.

Some limitations deserve discussion. First, although we opted for a 300 mg dose, which exerted anxiolytic effects without being sedative in healthy human subjects (Zuardi et al., 2017, 1993), patients may have received a suboptimal dose. In rats, an effect during extinction training was observed with 20 mg/kg intraperitoneally administered CBD, but not with any lower dosages (Jurkus et al., 2016). Further, dose-dependant effects have been reported with respect to within-session extinction (Do Monte et al., 2013; Lemos et al., 2010) and extinction retention (Do Monte et al., 2013) following intracerebral CBD administration in rats (Do Monte et al., 2013; Lemos et al., 2010). Beneficial effects were found only with a dose of 0.4 μg/side of the infralimbic cortex, but not with a lower dose (Do Monte et al., 2013). Further, there are some indications for an inverted U-shaped dose-response curve of CBD in anxiety. In an intermediate dose of 30 nmol, CBD enhanced extinction in rats, whereas lower and higher doses sorted no effects (Lemos et al., 2010). In healthy humans subjected to a public speaking task, only an intermediate dose of 300 mg oral CBD elicited anxiolytic effects, but lower and higher doses did not (Linares et al., 2019; Zuardi et al., 2017).

These findings from the only two studies that compared multiple doses in humans so far corroborate our choice for 300 mg. Nevertheless, the lack of clarity regarding the therapeutic window of oral CBD is an impediment to the advancement of the field. We are currently integrating data from (pre)clinical research to estimate the effective dose ranges in humans (Van Gerven and Cohen, 2018). This knowledge will be imperative for future studies of the effects of CBD in anxiety.

A second limitation is that we focused on the partly theoretical potential of CBD to enhance extinction learning. By exclusively dosing preceding exposure treatment sessions, and not also during homework assignments, we may have missed the potential of a general anxiolytic effect of CBD in anxiety disordered patients. Recently, general anxiolytic effects of CBD in a continuous dosing scheme (300 mg CBD ingested daily for four weeks) were reported by patients with social anxiety disorder (Masataka, 2019) and frontline health care professionals working with patients with COVID-19 (Crippa et al., 2021). This is supported by preclinical research in rats, in which differences between CBD and vehicle groups occurred only preceding, and in the first block of extinction training, but not in subsequent blocks (Jurkus et al., 2016).

In the present study, significant CBD plasma levels were observed in the CBD treated versus the placebo treated group, which are comparable to those previously reported (Fusar-Poli et al., 2009). However, our timing of administration, which was based on time to reach peak plasma levels in a published study (Englund et al., 2013), may have been suboptimal. The time course of plasma levels heavily depends on (the absence/presence of) the dissolving vehicle (Izgelov et al., 2020). Additionally, in line with previous pharmacokinetic results (Fusar-Poli et al., 2009; Izgelov et al., 2020) inter-subject variability of the CBD plasma levels was high. Future work might consider using a dissolving vehicle rather than administering CBD in powder form, in order to minimize this variability (Izgelov et al., 2020).

Although our study was adequately powered for our main analyses, sample sizes were still relatively small for analyses on secondary disorder specific outcome measures and survival analyses, with the risk of type II error. Furthermore, results with respect to a lack of within-session extinction learning enhancement should be replicated in future research.

In conclusion, augmentation of therapist-assisted exposure in vivo treatment with CBD administered preceding exposure therapy sessions did not have added value in a relatively large group of anxiety disordered patients. Overall, studies directly examining efficacy of CBD in patients are scarce. Whether the combination of continuous administration of CBD with exposure therapy may elicit better effects, is as of yet unknown. Future work may expand on the effects of CBD using continuous administration, and examine its added effect when combined with exposure therapy. Further, different dosing regimens should be explored.

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Contributors

JB (PI), DC, AvB, LG and NB obtained funding for this study. All authors contributed to the design of the study. FvdF and CK coordinated the recruitment of patients and the data collection. CK, JB, and ME have accessed and verified the data. CK and MM did the statistical analyses. JB, DC, AvB and NB are responsible for the overall design and supervision. CK

wrote the manuscript. All authors (FvdF, JB, DC, PD, DvdV, AvB, LG, NB, CK, MM, ME) read, contributed to and approved the final manuscript.

Declaration of Competing Interest

All authors report no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.04.003.

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