Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON44760

Source
ToetsingOnline

Brief title
Cannabidiol in the treatment of phobic anxiety disorders

Condition

- Anxiety disorders and symptoms

Synonym
Phobic anxiety disorders

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Utrecht
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: cannabidiol, Cognitive Behavioral Therapy (CBT), exposure with response prevention, phobic anxiety disorders

Outcome measures

Primary outcome

Main parameter regarding treatment effects on anxiety symptoms are measured at baseline, after every ERP-session, in the week after session 4 (at mid-treatment), in the week after session 8 (at post treatment) and at 3, and 6 months follow up. Secondary parameters (effects on other symptom questionnaires, on fear extinction in a laboratory assessment, learning and habituation and effects on health care use, costs, quality of life and loss of work productivity) are measured at baseline, and directly post treatment (one week after 8 exposure sessions), and a part of these are also monitored at 3, and 6 months follow-up. Further, 10 ml of blood to extract DNA will be drawn through venapuncture twice, before the first and the eight treatment session, in order to determine CBD-related genetic polymorphisms, to establish blood cannabidiol levels, and to perform epigenetic analyses.

Secondary outcome

n.a.

Study description

Background summary

Phobic disorders (e.g., social anxiety, panic disorder with agoraphobia) have an estimated lifetime prevalence of 19% (de Graaf et al. 2012), and are among the most prevalent disorders according to the WHO (2003). The estimated annual

health care costs in the USA due to anxiety disorders are $42 billion, and these disorders are burdensome in terms of loss of quality of life and loss of work productivity. Standard treatments (exposure with response prevention therapy (ERP), and/or serotonin reuptake inhibitors (SSRI)) are relatively successful, with improvement in up to 60% of patients, but only 30% to 50% phobic patients achieve full remission (Gloster et al. 2013). Therefore, there is still substantial room for improvement, especially in treatment resistant patients. Preclinical research has yielded solid evidence that the cannabinoid system is involved in the extinction of fear, presumed to underlie the beneficial effects of exposure therapy with response prevention in anxiety disorders (Hofmann 2008). A recent study from our experimental psychology group (Heitland et al. 2012) uncovered a genetic variant in the cannabinoid system that is associated with little to no spontaneous extinction of fear in a large group of healthy controls. Together, these findings suggest that: 1) the endocannabinoid system may form a novel target for the facilitation of extinction of pathological anxiety in general; 2) those individuals who have a high risk genetic profile within the endocannabinoid system, with the consequence of reduced efficacy of fear extinction mechanisms, may be particularly enhanced by administration of cannabidiol preceding exposure therapy. Cannabidiol functions through inhibition of the FAAH enzyme that degrades endogenously released cannabinoid neurotransmitters (Leweke et al. 2012), thereby enhancing endogenous endocannabinoid signalling. As opposed to tetra hydrocannabinol (THC), the psychoactive compound in cannabis that produces "high" feelings, cannabidiol does not produce any of these effects, nor other significant side effects (see Chapter 6 and the Investigational Brochure, IB), which makes it relatively safe to use.

Study objective

The aim of this research project is to investigate cannabidiol as a new medicine to target the cannabinoid system in the reduction of anxiety disorder symptoms. The research question is whether cannabidiol, as an augmentation strategy of exposure therapy in patients with phobic disorders (panic disorder with agoraphobia and social phobia), can speed up and/or increase the magnitude of change due to treatment. We specifically want to target those subjects in whom previous treatment as usual (with serotonergic antidepressants and/or psychotherapy) has not yielded in sufficient response to treatment, since it is this group that needs treatment enhancement most and therefore may benefit most from treatment enhancement with cannabidiol.
A subsidiary aim of this project is to explore determinants of the expected treatment-enhancing effect of cannabidiol; specifically, we are interested in exploring which combination of clinical, behavioural and genetic profiles of patients are related to treatment response. Preclinical studies have confirmed that pharmacological or genetic blockade of the CB1 receptor blocks extinction of fear (Marsicano et al. 2002). Our study in healthy volunteers translated these findings by demonstrating that a polymorphism in the cannabinoid receptor 1 (CB1) affects spontaneous extinction of fear (Heitland et al. 2012). Based on

the analogy with the preclinical findings, we expect the group with the profile associated with markedly reduced spontaneous fear extinction to have relatively poor endocannabinoid signalling. We will explore whether augmentation of exposure therapy (which is based on extinction learning) with cannabidiol will facilitate favourable therapy outcome especially in this particular group.

Study design

Seventy-two patients with phobic disorders with incomplete response to earlier treatment will be included. Incomplete response is defined as insufficient improvement, i.e. still fulfilling the criteria of a phobic disorder (according to the SCID) after pharmacotherapy with an serotonergic antidepressant or golden standard psychotherapy. Patients are randomly assigned to the placebo or 300 mg cannabidiol group. The study medication is administered orally, preceding 8 sessions of exposure with response prevention. If necessary (which is to be agreed upon between patient and therapist) regular treatment with ERP will be given after the research phase. This flexible dosage of ERP will improve sensitivity to pick up (cost-)effectiveness due to treatment augmentation. Direct response will be assessed at baseline, at each individual session throughout treatment, at mid-treatment, post-treament and at 3 and 6 months follow-up. Outcome will be measured using both symptom-specific measures and quality of life measures. For patient recruitment and inclusion, departments will collaborate with the anxiety outpatient clinic of GGZinGeest Amsterdam, the Altrecht Academic Anxiety center Utrecht, and University Center Psychiatry Groningen.

Intervention

All patients receive exposure therapy following the treatment protocol. One group will additional receive 300 mg cannabidiol before ERP, and one group placebo.

Study burden and risks

This study can make a contribution to a better understanding of how and with what kind of treatment phobic anxiety disorders (more specifically social phobia and panic disorder with agoraphobia) could be treated better. It is expected that this study brings little harm to the patients. The only burden is that patients will be requested to invest some time for extra measurements. Risk for adverse effects of cannabidiol are low. Research to date has reported no side-effects at this dosage, as no significant side-effects have been reported to date (Bergamaschi, 2011). However, occurrence of possible side-effects will be closely monitored.

Contacts

Public
Universiteit Utrecht

Martinus J. Langeveldgebouw Heidelberglaan 1
Utrecht 3584 CS
NL
Scientific
Universiteit Utrecht

Martinus J. Langeveldgebouw Heidelberglaan 1
Utrecht 3584 CS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients will be invited to participate when they fulfill the DSM IV criteria for a diagnosis of either generalized social phobia or panic disorder with agoraphobia, and provided that they have not or only partially responded to treatment in the year preceding referral to the outpatient clinics. We will use the following definition of patients who only partially responded to treatment:
a) having been treated in the past year for the same symptoms (psycho- or pharmacotherapy) and/or
b) specifically referred to second-line treatment

Exclusion criteria

Patients with co-morbid severe psychiatric disorders (severe major depressive or bipolar disorder, psychosis, dependence of alcohol and drugs), with mental deficiency (IQ<80), autism (AQ>32) or inability to adequately read or speak Dutch will be excluded, as well as persons with (a history of) epilepsy, cardiovascular disease or brain damage, renal or liver abnormalities, and a history of allergies on medication (adverse reactions or rash).
Regular use of benzodiazepines and of antipsychotics will be an exclusion criterion, since benzodiazepine use might hamper the ERP effect. Use of serotonergic antidepressants will be permitted, provided that dosages are kept constant during the study. Use of drugs (among others THC, XTC, cocaine) of is not permitted from 2 months before the start of the treatment until the end of the study.
Lastly pregnant or breastfeeding women will be excluded from the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-02-2016
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cannabidiol

Generic name:	cannabidiol

Ethics review

Approved WMO Date:	08-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-11-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004094-17-NL
CCMO	NL50898.041.15