CANGLIA: Endocannabinoid control of microglia activation as a new therapeutic target in the treatment of schizophrenia

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Ethical review	Approved WMO
Status	Completed
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON47069

Source
ToetsingOnline

Brief title
CANGLIA

Condition

- Schizophrenia and other psychotic disorders

Synonym
psychotic disorder, schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Psychiatrie
Source(s) of monetary or material Support: NWO

Intervention

Keyword: cannabidiol, Magnetic Resonance Spectroscopy (MRS), microglia, schizophrenia

Outcome measures

Primary outcome

The main study parameter is the concentration of prefrontal metabolites as measured with 1H-MRS, with the level of myo-inositol being regarded as a marker of glia function.

Secondary outcome

In addition, symptomatology will be examined using semi-structured interviews and questionnaires including the Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning scale (GAF), Clinical Global Impression Scale (CGI) and Hamilton Depression Rating Scale (HAM-D). Cognition will be assessed using the Brief Assessment of Cognition in Schizophrenia (BACS), which is a validated battery of neuropsychological tests that capture key deficits associated with psychosis, such as attention, memory, verbal fluency and executive function. Blood samples will be drawn to assess CBD plasma concentrations and immune and haematological parameters. Finally, brain structure and function are measured using MRI techniques.

Study description

Background summary

Schizophrenia is a chronic and severe mental disorder with an urgent need for new and more effective treatments. A promising novel pharmacological target in this respect is the endocannabinoid system. In particular the cannabinoid compound cannabidiol (CBD) displays a highly favourable profile for development

as a new antipsychotic agent. Increasing evidence indicates a significant role for neuroinflammation in the pathophysiology of schizophrenia, especially for activation of resident macrophages of the brain: microglia. Interestingly, converging preclinical evidence suggests that microglia activation is under control of the endocannabinoid system. However, how manipulation of the endocannabinoid system affects microglia activation in humans has not been established, but it is presumably related to clinical improvement of schizophrenia patients.

Study objective

The primary objective of this study is to compare microglia activation as measured with proton Magnetic Resonance Spectroscopy (1H-MRS) between recent-onset schizophrenia patients who are randomised to CBD and those randomised to placebo. Secondary objectives include comparisons between the two treatment arms regarding symptomatology, inflammatory and haematological blood markers, cognitive function, and brain structure and function. Third, it will be examined how microglia activation and inflammatory markers before treatment predict the clinical response to CBD, and correlations between study parameters are assessed.

Study design

A randomised, double-blind, placebo-controlled between-subjects intervention study.

Intervention

Schizophrenia patients are randomised to daily treatment with either 600 mg CBD or placebo for four weeks, in addition to their regular antipsychotic medication.

Study burden and risks

This study includes three site visits. The first visit is the screening visit, which consists of screening for in- and exclusion criteria. Blood will be drawn for routine laboratory tests. At both visits 2 and 3, which is before and after four weeks of daily CBD or placebo treatment, patients will undergo an MRI session of at maximum sixty minutes, consisting of 1H-MRS, structural MRI, and functional MRI at rest and during reward processing. Both visits include examination of symptomatology, psychosocial and cognitive function, and drug use. Venous blood samples are drawn to assess immune markers, haematological parameters and CBD plasma concentrations. Both blood sampling and MRI are safe procedures; standard procedures are followed, which will be performed by appropriately trained staff to minimise risks. Participation in this study may be of therapeutic benefit to patients since treatment with CBD has been

associated with both clinical and functional improvement. Previous studies have shown the potential of CBD as an effective, safe and well-tolerated antipsychotic compound.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* A DSM-IV diagnosis of 295.x (schizophrenia, schizophreniform disorder or schizoaffective disorder) or 298.9 (psychosis NOS). Diagnosis must be confirmed in writing by the treating psychiatrist.
* Age 16 - 40
* Onset of first psychosis no longer than five years ago

* Written informed consent of the subject

Exclusion criteria

* Any clinically significant medical condition that may influence the results of the trial or affect the ability to take part in a trial
* Routine laboratory screening values considered an impediment for participation by a medical doctor (see Appendix 1)
* Positive urine test on any drug of abuse, except cannabis
* Treatment with more than one antipsychotic agent or with an unstable dose of one type of antipsychotic medication in the month prior to study inclusion
* Use of glucocorticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) within two weeks prior to study inclusion
* Use of co-medication other than antipsychotics that has a clinically relevant interaction with the cytochrome P450 (CYP) 2C19 or CYP3A classes of liver enzymes within two weeks prior to study inclusion (because CBD may be an inhibitor of these classes of liver enzymes; see paragraph 6.3)
* Intake of investigational drug within one month prior to study inclusion
* Daily use of alcohol or drugs of abuse (including cannabis) in the three months prior to study inclusion
* Any current or previous neurological disorder, including epilepsy
* History of head injury resulting in unconsciousness lasting at least 1 hour
* IQ < 70, as measured with Dutch version of the National Adult Reading Test (DART)
* Breastfeeding, pregnancy or attempting to conceive
* MRI contraindications, e.g. claustrophobia or metal objects in or around the body

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-11-2017
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	cannabidiol

Ethics review

Approved WMO Date:	02-02-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-02-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-01-2020
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	EUCTR2016-003529-41-NL
ClinicalTrials.gov	NCT02932605
CCMO	NL58805.041.16

Study results

Date completed:	31-01-2020
Results posted:	29-07-2021
Actual enrolment:	20

First publication
23-07-2021