Effect of different antipsychotic medications on craving and craving related brain activity in patients with schizophrenia and cannabis abuse or dependence:
a randomized controlled study comparing clozapine and risperidone

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Objective: To test the hypothesis that clozapine treatment compared to risperidone treatment is associated with a significant reduction in subjective craving and in a lower activity of the different functional craving pathways and their associated...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON32193

Source
ToetsingOnline

Brief title
fmri.clo.ris.can

Condition

- Other condition
- Schizophrenia and other psychotic disorders

Synonym

psychotic disorders, schizophrenia

Health condition

verslaving

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Clozapine, Craving, fMRI, Randomized, Risperidone

Outcome measures

Primary outcome

Differences between the treatment conditions in pre-post treatment changes in

craving related brain activity are the primary outcome measure.

Secondary outcome

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Study description

Background summary

Cannabis abuse and dependence in patients with schizophrenia occurs frequently and is associated with adverse outcomes. Craving is regarded as a central phenomenon that contributes to the continuation of cannabis use and to relapse in cannabis use after a period of abstinence. Three partly overlapping functional craving pathways, associated with dopaminergic neurotransmission, are: (1) *chronic craving or anhedonia*, referring to the relative insensitivity to non-drug rewards; (2) *attentional bias*, referring to the underlying attentional focusing on drug cues as a prerequisite for motivational behaviour; and (3) *cue elicited physiological reactivity and craving*, referring to the high motivation to use cannabis elicited by drug-related stimuli. Antipsychotic medications with high affinity for the dopamine D2

receptor have been found to increase craving. Clozapine, with its low affinity for the dopamine D2 receptor, is associated with reduced substance use. However, firm evidence for clozapine*s superiority is lacking (Lange et al., 2005). Randomized controlled trials to study efficacy of clozapine on reducing cannabis abuse are difficult to conduct and pharmaceutical companies do not support these studies since clozapine is off patent. We hypothesize that abovementioned pathways will be differentially modified by different antipsychotic medications dependent on their differences in affinity for the dopamine D1 and D2 receptor.

Study objective

Objective: To test the hypothesis that clozapine treatment compared to risperidone treatment is associated with a significant reduction in subjective craving and in a lower activity of the different functional craving pathways and their associated brain activity patterns.

Study design

A randomized controlled trial comparing the effect of clozapine and risperidone on cannabis craving in cannabis abusing or dependent patients with schizophrenia. Specific cognitive tasks will be used to test craving pathways and associated brain activities are assessed with functional MRI.

Intervention

Patients will be randomly allocated to receive clozapine or risperidone. Dose titration scheme of clozapine depends on smoking status of patients: - smokers: 12,5 mg day 1, 25mg day 2, 50 mg day 3, 100 mg day 4, 150 mg day 5, 200 mg day 6, 250 mg day 7, 300 mg day 8, and thereafter adjustment of dose to obtain a blood level of clozapine of about 350 ng/ml. This dose will be continued till day 28; - non smokers: 12,5 mg day 1, 25 mg day 2, 50 mg day 3, 75 mg day 4, 100 mg day 5, 125 mg day 6, 150 mg day 7, 200 mg day 8, and thereafter thereafter adjustment of dose to obtain a blood level of clozapine of about 350 ng/ml. This dose will be continued till day 28.
Dose titration scheme risperidone: during 6 days with daily steps of 0.5 mg to a dose of 3,5 mg per day, and thereafter continuation of this dose till day 28.
Concomitant psychotropic medications are restricted to oxazepam up to 50 mg if sedation is necessary and biperiden 2 mg if extrapyramidal symptoms occur. Biperiden and oxazepam co-medication will be discontinued as soon as possible and biperiden as a prophylaxis is prohibited. In case of lack of antipsychotic efficacy resulting in dangerous or disturbing behaviour, dosage of clozapine or risperidone can be increased if clinically applicable. In case of dose related side effects dosage of clozapine or risperidone can be decreased or dose titration scheme can be slowed down if clinically applicable. Clinician or

patient decision can be a reason for discontinuation of the study medication.

Study burden and risks

Burden: Patients will be randomly allocated to receive clozapine or risperidone. One extra session is needed to inform patients on the study design and procedure. Two extra sessions are needed to assess baseline and outcome data. Two fMRI scanning sessions are needed during which specific tests will be administered. Duration of first fMRI scanning session is 38 minutes. Duration of second fMRI session is 32 minutes. Task difficulty of these tests will be set such that each participant will succeed on approximately 66% of his or her target responses. Scanning procedures may induce some burden because participants need to refrain from movements. To diminish the burden from the noise from the scanner, earplugs are used. Use of cannabis is prohibited in the three days before scanning. Three hours before scanning participants are not allowed to smoke cigarettes. One cup of coffee is allowed in the morning before scanning. Urine drug screen will be taken. Before the second fMRI scan blood level of risperidone or clozapine will be taken.
The healthy controls will follow the same protocol but they will only have one baseline fMRI scan.
Risk: There is a risk on adverse effects related to the treatment with clozapine or risperidone. Careful clinical procedures will be performed to detect adverse effects and respond to them as needed. There are no known risks related to fMRI scanning.
Benefit: no direct benefits for participants are predicted, although study medication may be associated with favourable effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligible for the study are male in- and outpatients age 18 to 30 (extremes included), of diverse ethnicity, meeting DSM-IV criteria for schizophrenia, schizoaffective - or schizophreniform disorder and cannabis abuse or dependence based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID-P).
Women will not be included because co-morbid cannabis abuse or dependence occurs more frequent in men and the expected number of included subjects, therefore, would not allow separate analysis.
We will also include schizophrenia patients without cannabis abuse or dependence and compare their outcomes with those of patients with co-occurring cannabis abuse or dependence.
A group of healthy, matched controls will be included to get information on brain activation patterns associated with specific cognitive tasks in antipsychotic-naïve healthy controls. These controls are included to make a comparison with patients with schizophrenia who have been treated with antipsychotics for 4 weeks.
All patients need to be abstinent for cannabis use minimally three days before assessment of functional craving pathways

Exclusion criteria

Exclusion criteria are
(1) known hypersensitivity to any ingredient of clozapine or risperidone,
(2) concomitant use of any antipsychotic drug other than clozapine or risperidone,
(3) use of depot antipsychotics in the three months prior to inclusion,
(4) use of psychotropic medications other than oxazepam or biperiden,
(5) narrow angle glaucoma,
(6) known neurological or endocrine disease,
(7) presence of non-removable metal objects

(8) myeloproliferative disorders,
(9) unstable epilepsy,
(10) agranulocytosis or leucopenia in the past
(11) Current leukocyte level is lower than 3.5 x 109/l, current neutrophilic granulocyte level is lower than 2.0x 109/l

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2008
Enrollment:	70
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	clozapine
Generic name:	Clozapine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Risperidone
Generic name:	Risperidone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 21257
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2008-003623-23-NL
CCMO	NL22828.018.08
OMON	NL-OMON21257