Selective D1 activation by addition of L-Dopa to antipsychotic treatment in patients with schizophrenia

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To examine the effect of L-dopa addition to optimal D2-blocking antipsychotic treatment on positive symptoms, negative symptoms, cognitive symptoms and extrapyramidal symptoms in schizophrenia.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON36435

Source
ToetsingOnline

Brief title
ALOHA

Condition

- Schizophrenia and other psychotic disorders

Synonym
psychosis, schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cognition, L-dopa, negative symptoms, schizophrenia

Outcome measures

Primary outcome

- change in verbal learning as assessed by the Hopkins Verbal Learning Test Revised (HVLT-R), as compared between patients receiving L-dopa vs those receiving placebo

- change in working memory as assessed by the N-back task, as compared between patients receiving L-dopa vs those receiving placebo

- change in the severity of negative symptoms, as assessed by the PANSS negative symptoms subscale, as compared between patients receiving L-dopa vs those receiving placebo

Secondary outcome

- change in the severity of positive symptoms, as assessed by the PANSS positive symptoms subscale, as compared between patients receiving L-dopa vs those receiving placebo

- change in cognitive functions other than working memory and verbal memory, as tested by the MATRICS, as compared between patients receiving L-dopa vs those receiving placebo

- change in frontal functions as assessed by the FAB (Frontal Assessment Battery), as compared between patients receiving L-dopa vs those receiving placebo

- change in extrapyramidal symptoms, as scored by the ESRS, as compared between patients receiving L-dopa vs those receiving placebo

- change in general functioning as scored by the HoNOS (Health of the Nations Outcome Scale) and CGI (Clinical Global Impression - severity scale), as compared between patients receiving L-dopa vs those receiving placebo

- change in subjective well-being, as assessed by the SWN (Subjective Well-being under Neuroleptics), as compared between patients receiving L-dopa vs those receiving placebo

Study description

Background summary

Schizophrenia is the psychiatric disorder with the worst prognosis. Its lifetime prevalence is about 1%, the disorder starts at an early age and has a chronic course. The symptoms of schizophrenia can be divided into positive symptoms (hallucinations, delusion, formal thought disorder, catatonic symptoms), negative symptoms (affect flattening, loss of interest, social withdrawal) and decline in cognitive functions. Although the exact neurobiological substrates for schizophrenia remain unclear, it is widely accepted that a disbalance in dopaminergic neurotransmission plays a key role in psychosis. The classic dopamine (DA) hypothesis proposes that increased striatal DA transmission mediates positive psychotic symptoms in schizophrenia. While positive symptoms generally respond rather well to antipsychotic treatment, negative symptoms are only minimally affected or even exacerbated. Hence, even patients with schizophrenia in which antipsychotic (D2-blocking) treatment has been optimized, often suffer from debilitating long-term negative symptoms, leading to a serious decline in quality of life. Another point of interest is the fact that antidopaminergic antipsychotic treatment can have extrapyramidal side effects, such as acute dystonia (sustained, often painful muscular spasms, producing twisting abnormal postures), parkinsonism, akathisia (feeling of inner restlessness and a compelling need to be in constant motion) and in the long term irreversible tardive dyskinesia (involuntary, repetitive movements), which have been reported to ameliorate after addition of L-dopa. In contrast to positive psychotic symptoms, cognitive dysfunction and negative psychotic symptoms have been related to a reduction of DA activity in other areas of the brain, especially the prefrontal cortex (PFC). Increase of cortical DA type 1 (D1) receptor activity has been proposed to correlate with amelioration of cognitive dysfunction and negative symptoms in schizophrenia. Until now, no selective D1 agonists are available for human use. Attempts to activate cortical dopamine transmission by adding L-dopa to conventional

(D2-blocking) antipsychotic treatment have reported promising results. However, these studies show several inconsistencies, which can largely be attributed to methodological differences, small sample size, and flawed study design.

Study objective

To examine the effect of L-dopa addition to optimal D2-blocking antipsychotic treatment on positive symptoms, negative symptoms, cognitive symptoms and extrapyramidal symptoms in schizophrenia.

Study design

double-blind, randomized, placebo-controlled

Intervention

25 patients receive Sinemet in a build-up dosing schedule:
days 1-4: 4 dd 50 mg
days 5-8: 2 dd 100 mg, 2 dd 50 mg
days 9-12: 4 dd 100 mg
days 13-16: 2 dd 150 mg, 2 dd 100 mg
days 17-20: 4 dd 150 mg
days 21-24: 2 dd 200 mg, 2 dd 150 mg
days 25-42: 4 dd 200 mg

25 patients receive a placebo

Study burden and risks

The burden for participants is small. The side effects of Sinemet (involuntary movements, sleepiness, dizziness, mood changes, raised blood pressure and nausea, (re)occurrence or worsening of positive psychotic symptoms) are generally mild and the change of the occurrence of side effects is further decreased by simultaneous use of haloperidol or risperidone.
Substantial parts of the examinations (PANSS) are routine diagnostics and are standard procedure for patients admitted to the psychosis ward of the Erasmus MC. The other examinations will ask time from the participants, but are not invasive or tiring.
There are no risks associated with the tests and questionnaires used.

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

All patients will be recruited from the Psychiatry ward of the Erasmus Medical Center, Rotterdam, and diagnosed according to DSM-IV criteria by a senior psychiatrist Patients will be included if they meet the criteria for schizophrenia. Further inclusion criteria inpatients aged 18-40 years with a diagnosis of schizophrenia, stable under haloperidol or risperidone treatment (<=20 points, or >3 points on no more than three items on PANSS positive symptom scale), with significant negative symptoms (total of >20 points, or >3 points on two items on PANSS negative symptom scale) are eligible for the study.

Exclusion criteria

pregnancy,use of psychotropic medication other than benzodiazepines serious neurological disorders. Subjects will also be excluded when they cannot understand Dutch language sufficiently to understand the purposes and implications of the experiment.

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:	Will not start
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Sinemet
Generic name:	L-dopa/Carbidopa
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-09-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	14-04-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	20-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-019897-33-NL
CCMO	NL32185.078.10