Phenomics and Genomics of Clozapine Pharmacotherapy - New Clozapine Users

Published: 23-09-2015
Last updated: 13-01-2025

To investigate whether methylation patterns/levels and gene expression profiles predict treatment outcome after initiating CLZ.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Schizophrenia and other psychotic disorders
Study type	Observational non invasive

Summary

ID

NL-OMON50475

Source
ToetsingOnline

Brief title
CLOZIN New Users

Condition

- Schizophrenia and other psychotic disorders

Synonym
Psychosis, psychotic disorders

Research involving
Human

Sponsors and support

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

Intervention

Keyword: adverse reactions, clozapine, efficacy, genetics

Outcome measures

Primary outcome

Response to CLZ is measured using the Positive and Negative Syndrome Scale (PANSS) and the first two questions of the Clinical Global Impression (CGI).
The results will be linked to changes in targeted methylation and gene expression. Furthermore, the presence of several Adverse Drug Reactions are assessed.

Secondary outcome

Secondary:

1. To identify non-genetic predicting factors for treatment outcome after initiation of CLZ.

2. To predict reponse and side effects

3. To assess whether the genetic architecture of this severe SCZ phenotype differs from the broad DSM-based SCZ phenotype. *

4. To detect genetic associations within the current severe SCZ phenotype by performing a case control comparison with healthy participants. *

5. To investigate whether CLZ use increases or decreases the risk of cardiovascular disease and early death. *

* These goals are the main objectives in our other protocol entitled *Phenomics and genomics of CLZ pharmacotherapy - current users*. To make optimal use of patients* DNA and to increase power for that other study we will ask participants in the current study for informed consent to use their DNA for

these objectives.

Study description

Background summary

Clozapine (CLZ) is one of the most effective antipsychotic medications, but with life-threatening adverse drug reactions (ADRs), such as agranulocytosis, diabetic ketoacidosis and gastrointestinal hypomotility and insidious adverse reactions such as metabolic syndrome (MetS). For many patients with schizophrenia spectrum disorders (SCZ), CLZ is the last resort when other antipsychotics have not resulted in sufficient clinical improvements. Prescribing CLZ in clinical practice therefore requires balancing ADR risk profile likelihoods with clinical response probabilities. This need highly contrasts with the current state of knowledge as it is unknown who will respond to CLZ and to what degree a specific patient may develop ADRs. Based on preclinical studies, we hypothesize that epigenetic and gene expression mechanisms influence treatment outcome (here defined as response and development of ADRs) after CLZ initiation. We will therefore investigate methylation patterns and gene expression profiles before and after initiation of CLZ pharmacotherapy. Furthermore, we will try and identify other predictive factors for treatment outcome following CLZ pharmacotherapy initiation.
Since, patient on clozapine have their leukocytes checked regularly, we can collect the blood for DNA analyses non-invasively and ask them questions before the initiation (max. 10 days after initiation) of clozapine and 4-12 and 28 weeks after the initiation.
At last, because considerable debate exists as to whether clozapine use increases or decreases risk of cardiovascular disease and early death, we would like to ask patient for consent to follow them up on long term.

Study objective

To investigate whether methylation patterns/levels and gene expression profiles predict treatment outcome after initiating CLZ.

Study design

This is a prospective study in which both phenotypic and (epi)genotypic data are extracted from this study population starting on clozapine.
We will include 300 patients who are about to initiate clozapine treatment may be included during the study duration of six years.

Study burden and risks

All patients starting with CLZ regularly have their blood drawn for routine white blood cell counts and/or CLZ blood level assessments. No additional risks will be attached to the study as the blood necessary for DNA extraction for the current study will be drawn from these routinely performed venipunctures. Time investment is three times about 1 hour and 20 minutes.

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

-he/she is about to initiate clozapine
-he/she has received a diagnosis of schizophrenia, schizophreniform, schizoaffective disorder or psychosis not otherwise specified (DSM-IV)/(un)specified other schizospectrum psychotic disorder
-he/she must be able to speak and read the Dutch language

- he/she must be 18 years or older
-he/she must understand the information provided about the study and understand the consequences of participating and express a willingness to participate.
This estimation is done by the treating physician during the informed consent procedure.

Exclusion criteria

- admission to a psychiatric unit involuntarily in the context of an *inbewaringstelling* (IBS)
- when the treating physician doubts if the patient understands the information/consequences of participation or the willingness to participate
- Patients with Parkinson*s disease

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-03-2016
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	23-09-2015
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	20-01-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-12-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC NedMec

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: 20290
Source: NTR
Title:

In other registers

Register	ID
Other	5257
CCMO	NL52728.041.15
OMON	NL-OMON20290