Phenomics and Genomics of Clozapine Pharmacotherapy

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Primary:-To assess whether the genetic architecture of this severe SCZ phenotype differs from the broad DSM-based SCZ phenotypeSecondary:-To detect genetic associations with the current severe SCZ phenotype (case-control comparison)-To unravel...

Ethical review	Not approved
Status	Will not start
Health condition type	Schizophrenia and other psychotic disorders
Study type	Observational non invasive

Summary

ID

NL-OMON42072

Source
ToetsingOnline

Brief title
CLOZ-NL

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

In a discovery cohort a case-control genome-wide association study (GWAS) will be performed on 2000 clozapine using subjects (cases) and >30,000 already available SCZ patients (controls, drawn from the most recent Psychiatric Genomics Consortium analysis, http://www.med.unc.edu/pgc/downloads). We hereby aim to reveal potential differences in the genetic architecture between the severe CLZ-SCZ phenotype and the broad SCZ phenotype. This analysis will be compounded by polygenic risk score analyses determining explained variances by risk loci at predefined p-value association cut-offs of 10-7, 10-6, 10-5, 10-4, 10-3, 10-2, 0.05, 0.1 and 0.5 between the CLZ-SCZ phenotype and the broad SCZ phenotype.

Secondary outcome

Second, by running a case-control GWAS for the CLZ-SCZ phenotype as cases and healthy subjects as controls (13,000 already available healthy individuals who will be age and sex-matched, i.e. a group of healthy controls drawn from a genetic study of amyotrophic lateral sclerosis) we test our hypothesis that stronger genetic associations may be detected when using this homogeneous, severe psychiatric phenotype compared with broad behavioral phenotypes. This analysis will be compounded by polygenic risk score analyses determining explained variances by risk loci at predefined p-value association cut-offs of 10-7, 10-6, 10-5, 10-4, 10-3, 10-2, 0.05, 0.1 and 0.5 between the CLZ-SCZ

phenotype and the healthy controls. Third, a replication cohort of the same size as the discovery cohort (N=2000 clozapine using subjects and the same number of healthy controls) will be used to replicate any positive associations for each of the two GWAS analyses. Fourth, positive associations in or near genes will be followed up by targeted sequencing of one or more of these genes using the Illumina MiSeq next-generation sequencing machine available at our facility or a different next-generation sequencing (NGS) machine. Fifth, we will additionally perform whole-exome sequencing on the subjects who suffered from any of the aforementioned serious ADRs during clozapine use and compare these results to patients who have used clozapine for over 4 years and have been free of this ADR. Sixth, in subjects who start clozapine quantitative changes in methylation patterns across the genome will be correlated with response to clozapine and the occurrence of the abovementioned three adverse drug reactions. Seventh, to dissect the phenotypic characteristics determining response to clozapine and the occurrence of adverse drug reactions we will collect a range of continuous and categorical data before treatment initiation and also after treatment initiation for state-dependent information. These may be divided into epidemiological, illness-related, pharmacotherapeutic, and other parameters (see under *Study parameters*). These data will be collected in a subset of the study population (N=200): only patients who are about to initiate clozapine treatment will be followed up. The collected data will be used to try and predict which patients are more likely to benefit from clozapine and which patients are more likely to suffer from adverse drug reactions. A final aim of the current project is to store participants* DNA and

blood for biobanking so that their DNA and blood may be used for future research questions, e.g. by the integration of data collected by international consortia that collect SCZ samples for GWAS and next-generation sequencing (such as the Psychiatric Genomics Consortium, http://www.med.unc.edu/pgc) and immunology measurements in blood 39. For both GWAS and NGS, limited sample sizes have precluded drawing definite conclusions regarding the neurobiological pathways involved in SCZ and the variance explained by genetic risk loci 1, 4, 5. Considering the increase in genetic knowledge leveraged by increases in sample sizes of SCZ GWASs 1-3 it is likely that international collaborations will yield increased understanding of both endpoints during the course and after termination of the CLOZ-NL study. For this purpose, DNA will be stored at the central biobank of the UMCU only of those participants who specifically consent to have their DNA and blood stored for such possible future analyses.

Study description

Background summary

Clozapine (CLZ) is generally prescribed if at least two trials of antipsychotic agents have not led to satisfactory clinical improvement, thereby implying that patients on clozapine generally suffer from more severe and/or persistent symptoms than SCZ patients on other antipsychotic agents. Unraveling the (functional) genetic variation underlying this severe SCZ phenotype therefore has the potential to deepen our understanding of the biological underpinnings of SCZ beyond the boundaries of DSM-based consensus criteria. Such knowledge in turn has the potential to shape future pharmacotherapeutic research. We here hypothesize that targeting this phenotype in genome-wide association studies and next-generation sequencing studies will signal genetic risk loci implicated in this severe SCZ phenotype. Moreover, it is currently impossible to predict who will respond to clozapine treatment. Genetic data may help prognosticate which patients will benefit from clozapine treatment. Besides genotypic data, a range of epidemiological, illness-related, pharmacotherapeutic and other

parameters may determine treatment outcome in those patients who use clozapine. This has not been systematically investigated in prospective designs. In addition, adverse drug reactions (ADRs) to clozapine carry a high burden of disease and sometimes prompt non-compliance. The underpinnings of these ADRs are poorly understood. Elucidating both the genetic and phenotypic determinants underlying the occurrence of clozapine*s ADRs may be of direct benefit to clinical practice because such knowledge may in the future enable tailoring of antipsychotic treatment choices to the individual patient.

Study objective

Primary:
-To assess whether the genetic architecture of this severe SCZ phenotype differs from the broad DSM-based SCZ phenotype

Secondary:
-To detect genetic associations with the current severe SCZ phenotype (case-control comparison)
-To unravel genetic determinants of both response and adverse reactions to clozapine
-To design a model that comprehensively dissects the phenotypic characteristics predicting response and adverse drug reactions to clozapine
-To discover changes in methylation after instatement of clozapine

Study design

This is a partly cross-sectional, partly prospective study in which both phenotypic and genotypic data are gathered from this study population that uses clozapine. A genome-wide association study (GWAS) will be performed to reveal possible differences in genetic architecture between patients on clozapine and the broad schizophrenia phenotype on the one hand and between those on clozapine and healthy controls on the other. Targeted next-generation sequencing may be used to follow-up possible positive associations. Changes in methylation before and after the start of clozapine will be assessed. Finally, a range of epidemiological, illness-related, pharmacotherapeutic and other phenotypic data will be collected before treatment initiation for a subset of the study population. These phenotypic data will be used to try and predict treatment outcome following clozapine initiation.

Study burden and risks

Almost all patients on clozapine regularly have their blood drawn for routine white blood cell counts and/or clozapine blood level assessments. We anticipate that the majority of the study population will consist of such patients as white blood cell monitoring is strictly enforced in clinical practice for this patient group. For these patients, no 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. In addition, time investment for these participants will be negligible as only three brief questions will be asked during a routine visit with their in or outpatient treating physician. Patients about to initiate clozapine treatment will also undergo routine venipunctures for the purpose of the same assessments as mentioned above. They will additionally be asked to fill out questionnaires and allow for a brief interview to obtain epidemiological, illness-related and pharmacotherapeutic phenotypic data. Although the time investment of this latter group may thus be substantial, no invasive procedures will be applied here either and we will give every participant the possibility to opt out of these phenotypic assessments at any moment.
A minority of patients on clozapine doesn*t have their blood routinely monitored. These subjects will be asked to allow a single blood draw. A venipuncture entails the risk of a hematoma (blood leaving the vessel). We aim to minimize this risk by only allowing experienced personnel to draw blood and in the event of deeply located or thin veins request central lab personnel to perform the venipuncture. Although a hematoma resulting from a traumatic puncture imposes an esthetical burden on the subject, no serious health risks are involved. Should the venipuncture be traumatic and insufficient blood is obtained, we will give the participant the option to terminate his/her participation.

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 currently uses clozapine or is about to initiate a treatment of clozapine
-he/she has received a diagnosis of schizophrenia or schizoaffective disorder, either clinician-rated based on DSM-IV or 5 criteria or according to a (semi-)structured interview
-his/her age must be >=18 years old
-he/she must be able to speak and read the Dutch language
-he/she must understand the information provided about the study and express a willingness to participate

Exclusion criteria

- admission to a psychiatric unit involuntarily in the context of an *inbewaringstelling* (IBS) or *rechterlijke machtiging* (RM)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4000
Type:	Anticipated

Ethics review

Not approved

Date:	19-02-2015
Application type:	First submission
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
CCMO	NL52215.041.15