Treatment Response in Non-Affective Psychosis.

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1) To compare between treatment responders, treatment non-responders, and healthy controls: sDSC and GABA in the ACC;2) To assess, in psychotic patients and healthy controls, whether AEA and 2-AG plasma levels are associated with sDSC, and…

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

Summary

ID

NL-OMON54876

Source
ToetsingOnline

Brief title
TRIP

Condition

- Schizophrenia and other psychotic disorders

Synonym
mental illness, psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Rivierduinen
Source(s) of monetary or material Support: Stichting GGZ Rivierduinen en Stichting J.M.C.Kaptein Fonds

Intervention

Keyword: Neurobiology, Psychosis, Schizophrenia, Treatment-resistance

Outcome measures

Primary outcome

- Striatal [18F]-DOPA influx (Ki) values.

- 1H-MRS glutamate and GABA levels in the ACC.

- AEA and 2-AG plasma levels.

- Responders: much or very much improved with regard to positive symptoms on the Degree of Change subscale of the Clinical Global Impression scale - Schizophrenia Version (CGI-SCH) at the first follow-up compared to the start of medication (for the common timeline, see section 3.1) or compared to the baseline assessment (for the ideal timeline, see section 3.1).

- Non-Responders: minimally improved, not improved or worse with regard to positive symptoms on the CGI-SCH Degree of Change subscale at the first follow-up compared to the start of medication or compared to the baseline assessment.

Secondary outcome

- Neuromelanin contrast ratio on NM-MRI.

- Percentage change of positive symptoms between the baseline assessment and the first follow-up (after 4-6 weeks of non-clozapine treatment at adequate dose).

- Percentage change of total PANSS score on the PANSS between the baseline assessment and the first follow-up.

Tertairy study parameters/outcome:

- Responders: much or very much improved with regard to positive symptoms on the Degree of Change subscale of the Clinical Global Impression scale - Schizophrenia Version (CGI-SCH) at the second follow-up compared to the start of medication (for the common timeline, see section 3.1) or compared to the baseline assessment (for the ideal timeline, see section 3.1).
- Non-Responders: minimally improved, not improved or worse with regard to positive symptoms on the CGI-SCH Degree of Change subscale at the second follow-up compared to the start of medication or compared to the baseline assessment.
- Percentage change of positive symptoms between the baseline assessment and the second follow-up (6 months after the start of antipsychotic medication).
- Percentage change of total PANSS score on the PANSS between the baseline assessment and the second follow-up.
- Striatal connectivity.

Study description

Background summary

Approximately 30% of patients with non-affective psychotic disorder show insufficient response to non-clozapine antipsychotic treatment. Therefore, it is desirable to identify these patients early on by use of a clinical algorithm. This algorithm is likely to be based on a number of biomarkers. Potential biomarkers are striatal dopamine synthesis capacity (sDSC), glutamate and gamma aminobutyric acid (GABA) concentrations in the anterior cingulate cortex (ACC). sDSC can be measured by use of [18F]-DOPA Positron Emission Tomography (PET). Glutamate and GABA concentrations in the ACC can be measured by use of proton Magnetic Resonance Imaging (1H-MRI).

Using resting-state functional MRI Sarpal et al (Am J Psychiatry; 2016, volume 173, pp. 69-77) examined the relationship between (i) striatal connectivity with other brain areas and (ii) response to antipsychotic drug. The results showed that a greater connectivity between posterior regions and striatal subdivisions is associated with a better response to antipsychotics, whereas,a greater connectivity between frontal regions and striatal subregions was associated with a worse response.

Interestingly, cannabis use is associated with an increased risk of psychosis. The main constituent of cannabis, delta-9-tetrahydrocannabinol (THC), exerts its psychotropic effect by binding to receptors of the endocannabinoid system (ECS), and influences dopamine release. The evidence in support of sensitisation of the mesolimbic dopamine system in the pathogenesis of non-affective psychotic disorder is large. However, the relationships between sDSC, glutamate and GABA concentrations in the ACC and blood levels of the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) have never been examined.

A drawback of PET imaging is the use of radiotracers. Preferably, treatment-resistant patients should be identified without using radioactivity. One promising tool to do this, without inducing a radiation burden, is by use of a neuromelanin-MRI (NM-MRI) sequence. However, it is unknown whether an association exists between NM-MRI signal and sDSC. Therefore, validation of NM-MRI as an indirect measurement of striatal functioning in schizophrenic patients is necessary to develop a non-invasive algorithm to predict treatment-response.
Understanding the relationships between the activity of various neurotransmitter systems and treatment response is an important step in the development of personalized treatment.

Study objective

1) To compare between treatment responders, treatment non-responders, and healthy controls: sDSC and GABA in the ACC;
2) To assess, in psychotic patients and healthy controls, whether AEA and 2-AG plasma levels are associated with sDSC, and concentrations of glutamate and GABA in the ACC;
3) To exploratory investigate, whether, NM-MRI signal is associated with treatment response to non-clozapine antipsychotics (in patients) and with sDSC (in patients and healthy controls).
4) Replicating Sarpal et al. (2017). Hypotheses: Greater connectivity between posterior regions and striatal subdivisions is associated with a better response to antipsychotics. Whereas, greater connectivity between frontal regions and striatal subregions is associated with a worse response.

Study design

Prospective study

Study burden and risks

Participants will be assessed on four separate occasions:
- Baseline assessment (before or within 6 weeks after the start of non-clozapine antipsychotic medication; total duration: 2h): evaluatin of competence, screening for inclusion/exclusion criteria, informed consent, urine drug test, and assessment of symptoms;
- Test day (before or within 9 weeks after the start of non-clozapine antipsychotic medication; total duration: 2h): MRI scan, urine drug test, determination of endocannabinoid plasma concentrations, fatty acid patterns, TG, CRP and antipsychotic plasma concentrations. Furthermore, depressive symptoms and factors that may influence the endocannabinoids will be assessed. In a subgroup of 26 psychotic patients, an additional [18F]-DOPA PET scan will be acquired. The PET scan will occur on the same day as the MRI scan, if possible with the scanning facilities of the UMC Amsterdam. This will add three hours to the visit. Otherwise, an additional visit will be scheduled;
- First follow-up (after 4-6 weeks of non-clozapine antipsychotic treatment at adequate dose; total duration: 2h): diagnostic interview and assessment of symptoms and determination of antipsychotic plasma concentration;
- Second follow-up (6 months after the start of non-clozapine antipsychotic treatment; total duration: 1h): assessment of symptoms and substance use.
If applicable, treatment compliance will be evaluated together with the patient during each occasion. The test day will take place at the UMC Amsterdam (location AMC). The other assessments will take place at the mental healthcare centre where the patient is under treatment. Total amount of time consuming for the individual patient: 10 hours (in case of MRI and PET scans) or 7 hours (in case of MRI scan only). Total duration of the study for the individual patient: 6 months.

Twenty healthy controls will be assessed on two separate occasions: (T1) informed consent, screening, psychiatric interview, urine drug test, and assessment of anxiety symptoms and medication use (total duration: 2h); (T2) PET and MRI scans, urine drug test, evaluation of depressive symptoms and blood sampling (total duration: 5h). Total amount of time consuming for the individual subject: 7 hours. Total duration of the study for the individual subject: 1 month.

Risks: The radiation dose is 4.1 mSv and falls within category IIb (minor to intermediate). Benefits of the study: patients and healthy controls will not benefit from participation. However, the obtained knowledge will contribute to the development of a non-invasive algorithm to predict treatment-response and may offer new starting points for the development of alternative treatments for non-affective psychotic disorders.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patients:
- First or later episode of psychosis, provided that the patient has not used antipsychotics for at least one year and that lifetime use of antipsychotics does not exceed 6 months.
- A rating of at least 4, corresponding to moderately ill, on the positive symptoms item of the severity of illness part of the CGI-SCH at T0 (in case of the common timeline, see study protocol C1 section 3.1) or T1 (in case of the ideal timeline, see study protocol C1 section 3.1).
- Age: 18-35 years.
- Within the first 5 years after onset of the first psychotic episode.

Healthy controls:

- Age: 18-35 years.

Exclusion criteria

General exclusion criteria patients:
- Antipsychotic use longer than 9 weeks at the moment of the PET scan.
- Current neurological disorder or history of neurological disorder (e.g. epilepsy) or history of severe head trauma (contusio cerebri).
- Incompetent to participate in research.
- Patients who resist or oppose antipsychotic mediation.
- Primary diagnosis of bipolar disorder with psychotic features or major depressive disorder with psychotic features at the start of non-clozapine antipsychotic medication.
- Psychotic disorder due to another medical condition or substance/medication-induced psychotic disorder.

General exclusion criteria healthy controls:
- Current neurological disorder or history of neurological disorder (e.g. epilepsy) or history of severe head trauma (contusio cerebri).
- Current psychiatric disorder or history of any psychiatric disorder (DSM-5).
- First-degree relative with schizophrenia spectrum disorder (DSM-5).
- Incompetent to participate in research.

Exclusion criteria related to alcohol, soft/hard-drugs, and medicinal drugs (patients and healthy controls):
- Lifetime history of DSM-5 diagnosis of any Substance Use Disorder (except cannabis use disorder in sustained remission (12 months), tobacco use disorder and alcohol use disorder).
- Participants who used cannabis on a daily basis for a period of at least two weeks in the year before the first contact with the researcher.
- Current use of substances other than tobacco, cannabis or alcohol, such as XTC, cocaine, amphetamine, opioids or GHB.
- Subjects with a disorder in the use of cannabis in the year before the baseline assessment.
- Positive urine drug screen on the day of the MRI/PET scan (cannabis, cocaine, XTC, opioids, amphetamines).
- Current or recent (less than 1 month ago) use of sleep medication (controls only).
- Current or recent (less than 3 months ago) use of psychotropic drugs that may influence the dopamine system (e.g. lithium, sodium valproate, and methylphenidate) or anti-epileptic drugs that may influence the GABAergic and/or glutamatergic systems.
The use of benzodiazepines, hypnotics and antidepressants in amounts within the therapeutic range is allowed (patients only).

Exclusion criteria directly related to MRI and PET/CT scanning (patients and healthy controls):
- Participation in a scientific examination where radiation was used, in the last year.
- Contra-indications for MRI (e.g. pacemaker, claustrophobia, pregnancy).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-12-2020
Enrollment:	63
Type:	Actual

Ethics review

Approved WMO

Date:	03-11-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	25-01-2021
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	04-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-08-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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: 28864
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL72218.058.20
Other	NL8338

Study results

Date completed: 28-11-2022

Summary results
Trial ended prematurely