Uncovering Pathophysiologic Mechanisms of Treatment Resistant Depression: A comparison with non-TRD patients

Published: 25-04-2022
Last updated: 05-04-2024

To determine if dopaminergic dysfunction and neuroinflammation is increased in patients with TRD compared to patients who respond to antidepressant medication

Ethical review	Approved WMO
Status	Pending
Health condition type	Mood disorders and disturbances NEC
Study type	Observational invasive

Summary

ID

NL-OMON54371

Source
ToetsingOnline

Brief title
UNCOVER-TRD

Condition

- Mood disorders and disturbances NEC

Synonym
Major Depressive Disorder, Treatment Resistant Depression

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Dopaminergic dysfunction, Neuroinflammation, Treatment Resistant Depression

Outcome measures

Primary outcome

- VTA-related BOLD-signals and habenula-VTA connectivity coding for Temporal Difference Errors in reward/punishment-related learning

- [18F]DPA-714 binding potential in the brain

Secondary outcome

- Changes in VTA-related BOLD-signals and habenula-VTA connectivity coding for Temporal Difference Errors in reward/punishment-related learning after treatments (SSRI/SNRI in non-TRD group; and ECT in TRD-group; distinction of responders and non-responders)

- Serum markers indicative of inflammation and changes thereof after treatment

- Clinical symptoms (HDRS-17, IDS-SR, RRS, SHAPS and TEPS) and changes thereof after treatment

- Additional MRI-scans (T1 structural, DTI, and resting state) and changes thereof after treatment

Study description

Background summary

Major Depressive Disorder (MDD) is a highly prevalent psychiatric disorder with a lifetime prevalence of 18.7% in the Dutch adult population. Approximately 35% of MDD patients still do not achieve a response after two courses of adequate treatment with antidepressant medication. MDD which does not respond to at least two trials of antidepressant medication is referred to as Treatment Resistant Depression (TRD). With this study we will investigate two

pathophysiologic mechanisms that could underly MDD and lead to TRD: dysfunction of the dopaminergic system and neuroinflammation. Both dopaminergic and anti-inflammatory medication (for example Pramipexole and Celecoxib) show promising results in trials investigating efficacy of these medication in the treatment of depressive symptoms. However, it is unknown which MDD patients suffer from dopaminergic dysfunction and/or neuroinflammation and therefore it is unknown which patients could benefit from these potential new treatments. We will investigate dopamine dysfunction via dopamine neuron activity in the habenula-Ventral Tegmental Area (VTA) network during a pavlovian reward/punishment-related learning task before and after treatment in MDD patient with and without TRD. In addition, we will investigate baseline microglial activation (indicating neuroinflammation) by measuring [18F]DPA-714 binding, and pro- and anti-inflammatory cytokines in peripheral blood before and after treatment.

Study objective

To determine if dopaminergic dysfunction and neuroinflammation is increased in patients with TRD compared to patients who respond to antidepressant medication

Study design

A longitudinal case-control study comparing two cohorts: TRD patients versus non-TRD MDD patients. Patients will receive treatment as usual during the whole duration of the study. Patients will undergo (f)MRI before the start of treatment and after discontinuation of ECT (TRD group) or after six weeks of antidepressant medication (non-TRD MDD group). Both TRD as well as non-TRD patients will additionally undergo a [18F]DPA-714 PET-scan (as an opt-in) at baseline and two vena punctures. TRD-patients will be recruited for MRI-assessments according to a previously approved protocol (NL 48067.901.14) and are asked to participate with the additional measures of this study ([18F]DPA-714 PET-scan and assessment of inflammation markers)

Study burden and risks

The (f)MRI measurements will require approximately 60 minutes of the patients time at two time points. The [18F]DPA-714 tracer used for PET/CT-scan has a favourable safety profile and no observational pharmacological effect due to the small dosage used in this study. Radiation during PET-scan is within safety limits. The entire PET-scan procedure including preparation will take approximately 120-150 minutes. At last blood samples will be drawn at two timepoints. Risks associated with these measurements are negligible.

Contacts

Public
Radboud Universitair Medisch Centrum

Reinier Postlaan 4
Nijmegen 6525GC
NL
Scientific
Radboud Universitair Medisch Centrum

Reinier Postlaan 4
Nijmegen 6525GC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Males and females between 18-70 years of age
- First or recurrent episode of unipolar major depressive disorder
- Treatment resistance for at least two antidepressants for the TRD group
- Never or only once being treated with antidepressants without effect for the non-TRD group

Exclusion criteria

- ECT within one year prior to the current course
- Current use of antidepressants, antipsychotics and mood stabilizers
- Use of benzodiazepines within 24 hours before ECT

- Use of anti-inflammatory drugs for more than a week in the past month (for patients included for PET-scan only)
- Use of immune suppressants (for patients included for PET-scan only)
- Presence of current or past relevant somatic disorder
- Presence of comorbid bipolar disorder, schizophrenia or substance abuse disorder
- MRI- or PET-related exclusion criteria
- ECT-related exclusion criteria(for TRD group only)
- Low-affinity binder for TSPO (for patients included for PET-scan only)

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:	Pending
Start date (anticipated):	01-06-2023
Enrollment:	83
Type:	Anticipated

Ethics review

Approved WMO Date:	25-04-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-12-2022

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL78514.091.21