RELATE and PREDICT TRD;A pharmacological and neuroimaging study investigating neurobiological effects of Selective Serotonin Reuptake Inhibitors and Norepinephrine Reuptake inhibitors on dopaminergic reward-learning signals and prediction of clinical (non-) response in Major Depressive Disorder

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The proposed study aims to examine: I. whether MDD-patients with a high TRD-level have diminished reward/reinforcement learning, dysfunctional dopaminergic, glutamatergic and/or GABA-ergic neurotransmission (relative to no-TRD patients/controls) II…

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

Summary

ID

NL-OMON38845

Source
ToetsingOnline

Brief title
RELATE & PREDICT TRD

Condition

- Mood disorders and disturbances NEC

Synonym
Chronic Depression, Treatment Refractory Depression, Treatment Resistant Depression

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMW (VENI-subsidie)

Intervention

Keyword: Dopamine, Neuroimaging, Reinforcement learning, Treatment Resistant Depression

Outcome measures

Primary outcome

Clinical:

- decrease in HDRS-17-score

- response and remission (defined as >=50% decrease in HDRS-17 and a

HDRS-17<=7, respectively)

- early improvement in week 2 will be defined as >=20% decrease in HDRS-17

Neuroimaging:

- Pavlovian learning paradigm: BOLD response of prediction errors in

VTA/ventral striatum/habenula

- PET: amphetamine challenged decrease in [11C]Raclopride binding in the

striatum

Secondary outcome

Clinical:

- decreases in IDS-SR-30

- early improvement (>=20% decrease in IDS-SR-30)

- response (>=50% decrease in IDS-SR-30) and remission (IDS-SR-30<=14)

- total patient-drop-out and specified as due to inefficacy or adverse effects

- changes in SHAPS, SRRS, CORE and RRS-NL

Neuroimaging:

- voxel-based morphometry (VBM) based volumes of the pgACC, sgACC, dorsal ACC, amygdala, hippocampus and DLPFC

- resting state scans: group maps of the DMN as determined with an independent component analysis. Seed-region based functional connectivity from a priori RoIs in the amygdala, pgACC, sgACC, ventral striatum/Nucleus accumbens, VTA and habenula

- MRS-measurements: GABA and glutamate in basal ganglia and pgACC

Neurocognitive:

- Exogenous Cueing Task: The 'benefit' ratio of response times on valid emotional trials versus valid neutral trials and the 'delay' ratio of response times on invalid emotional trials compared to the neutral trials

- Faces Emotional Recognition Task: the percentage of recognition of different facial expressions and the recognition threshold (level of emotional intensity at which participants correctly identify >=75% of the facial expressions of emotion for four consecutive intensities)

- Emotional Categorization: the percentage correct responses and response times

to self-referent items, stratified for positive/negative adjectives

Study description

Background summary

Major depressive disorder (MDD) is a major burden for society. The pathophysiology of MDD remains, however, an enigma. Usually MDD is treated with serotonergic/noradrenergic antidepressants. Non-response (<50% improvement of symptom-severity) occurs frequently and causes prolonged hospitalizations and suicides. Non-response to more classes of antidepressants represents increasing levels of treatment resistant depression (TRD). Previous research addressed pharmacological strategies for non-response to antidepressants but could not resolve why symptoms do not improve in ~35% of patients. It has been suggested that in TRD non-serotonergic/non-noradrenergic subtypes of MDD are over-represented. Recent cross-sectional studies in MDD indeed suggest dysfunctions in dopamine and/or glutamate/GABA systems and diminished reward/reinforcement learning. However, over-representation of non-serotonergic/non-noradrenergic subtypes as putative mechanisms for TRD remains to be demonstrated. Furthermore, to what extent contemporary serotonergic/noradrenergic antidepressants already influence these putative underlying mechanisms in humans remains unexplored.
Whether depression (MDD) patients with a high TRD-level have dysfunctional dopamine and/or glutamate/GABA systems can be demonstrated with novel multimodality neuroimaging techniques like functional Magnetic Resonance Imaging (fMRI) and [11C]Raclopride Positron Emission Tomography (PET).
Besides early improvement within the first 2 weeks (>=20% decrease in HDRS), neuropsychological tests that measure changes in facial recognition within 1 week are likely able to predict response to an antidepressant.

Study objective

The proposed study aims to examine:
I. whether MDD-patients with a high TRD-level have diminished reward/reinforcement learning, dysfunctional dopaminergic, glutamatergic and/or GABA-ergic neurotransmission (relative to no-TRD patients/controls)
II. how treatment with the contemporary antidepressants escitalopram and nortriptyline affect these dysfunctions in no-TRD and high-TRD patients.
III. prediction of treatment-outcomes within the first weeks of antidepressant treatment

Study design

Randomized, double-blind, placebo-controlled study comparing escitalopram and

nortriptyline (dosed on blood-levels) versus placebo.

Study burden and risks

Subjects will be requested to participate in MRI and PET-scanning, the latter will use a minor-moderate dose of radioactivity. There are no direct benefits for subjects to participate. General benefit will be the better understanding of the involvement of the dopamine system in TRD. When TRD is indeed characterized by diminished reward/reinforcement learning, dysfunctions in dopamine and/or glutamate/GABA systems, in the future MRI-scans and/or [11C]Raclopride PET-scans might enable us to subtype MDD-patients and predict treatment-outcomes, which ultimately may prevent the development of TRD. Furthermore, developing treatment strategies targeting these dysfunctions is desirable.

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

Patients:
- Male or female, age: 20 - 60 years
- Signed informed consent
- DSM-IV diagnosis of MDD (ascertained by structured interview for DSM-IV (SCID))
- Hamilton Depression Rating Scale (HDRS17)>18
- Group I, non-TRD [who used <=1 antidepressant for the current MDD-episode and are currently drug-free]
- Group II TRD [who were nonresponsive to >=2 antidepressants (SSRIs and/or SNRIs) during the current MDD-episode].;Controls:
- Male or female, age: 20 - 60 years
- Signed informed consent
- No DSM-IV diagnosis/abuse/dependence (SCID)
- Inventory for Depressive Symptomatology (IDS-SR) <=14
- Controls will be matched with participating patients on age (<=3 years), sex and estimated intelligence with the Dutch adult reading test (DART).

Exclusion criteria

Patients:
- Psychotic or Bipolar depression
- Comorbid current (primary) anxiety disorder
- Comorbid current abuse/dependence of alcohol, cannabis, cocaine, amphetamine
- Neurologic or auto-immune disease, hypothyroidism
- Contra-indications for escitalopram or nortriptyline like earlier non-response (in the current episode)
- Contra-indications for fMRI-scanning (metal objects in the body, claustrophobia)
For blood-measurements regarding research questions 4.1-4.3
- Use of aspirin and psychopharmaca other than used in study setting
- Alcohol abuse (8 weeks prior to participation: for women >14 consumptions/week, and for men >21 consumptions/week).
- Consumption of bananas and walnuts 48 hours prior to blood withdrawal.;Controls:
- First degree family history of psychiatric illnesses
- Contra-indications for fMRI-scanning (for neuroimaging participants)
- Neurologic or auto-immune diseases, hypo-/hyperthyroidism

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-11-2014
Enrollment:	165
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	escitalopram
Generic name:	escitalopram
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nortriptyline
Generic name:	nortriptyline
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-08-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2013

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-001818-14-NL
CCMO	NL43584.042.13
Other	NTR TC 3969