RELATE and PREDICT TRD.

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27079

Source
Nationaal Trial Register

Brief title
RELATE-TRD

Health condition

Major Depressive Disorder

Sponsors and support

Primary sponsor: UMCG
Source(s) of monetary or material Support: ZonMW
Unrestricted Investigator Initiated Trial grant from Lundbeck (supplying study-medication)

Intervention

Outcome measures

Primary outcome

Clinical:

1. Decrease in HDRS17-score (continuous scores);

2. Response and remission (defined as >=50% decrease in HDRS17 and a HDRS17<=7, respectively);

3. Early improvement in week 2 will be defined as >=20% decrease in HDRS.

Neuroimaging:

1. Pavlovian learning paradigm: BOLD response of prediction errors in VTA/ventral striatum/habenula;

2. PET: amphetamine challenged decrease in [11C]Raclopride binding in the striatum.

Secondary outcome

Clinical:

1. Decreases in IDS-SR30;

2. Early improvement (>=20% decrease);

3. Response (>=50% decrease) and remission (IDS-SR30<=14);

4. Total patient-drop-out and specified as due to inefficacy or adverse effects);

5. Changes in SHAPS, SRRS, CORE and RRS-NL.

Neuroimaging:

1. Voxel-based morphometry (VBM) based volumes of the pgACC, sgACC, dorsal ACC, amygdala, hippocampus and DLPFC;

2. 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;

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

Neurocognitive:

1. 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;

2. 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);

3. Emotional Categorization: the percentage correct responses and response times to self-referent items, stratified for positive/negative adjectives.

Study description

Background summary

Background 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). 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 (¡Ý20% decrease in HDRS), neuropsychological tests that measure changes in facial recognition within 1 week are likely able to predict response to an antidepressant.

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:

Eight weeks randomized, double blind placebo-controlled trial comparing escitalopram and nortriptyline (dosed on blood-levels) versus placebo.

Study population:

See in- and exclusion criteria above.

Outcomes:

See primary and secondary outcomes above.

Nature and extent of the burden and risks associated with participation:

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 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.

Study objective

1. Treatment resistant depression (TRD) is characterized by dopaminergic dysfunction as assessed with a fMRI Pavlovian learning task and [11C]Raclopride PET with amphetamine challenge;

2. Relative to placebo, current serotonergic and noradrenergic antidepressants (escitalopram and nortriptyline, respectively) do not change this dopaminergic dysfunction, especially in non-reponders to treatment.

Study design

1. Baseline: Clinical assessment, neurocognitive tests, fMRI and when possible PET scanning;

2. T0: Randomisation;

3. Week 1-Week 6: Clinical visits: assessment of clinical response, adverse effects and adjustment of study drug dosages based on blood levels;

4. T3 (week 8): Clinical assessment, neurocognitive tests, fMRI and when possible PET scanning.

Intervention

1. Escitalopram 5 mg capsules orally dosages adjusted based on blood-levels;

2. Nortriptyline 35 mg capsules orally dosages adjusted based on blood-levels;

3. Placebo capsules orally dosages adjusted based on fake blood-levels.

All interventions will be given for a duration of 8 weeks.

Contacts

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Eligibility criteria

Inclusion criteria

Patients:

1. Male or female, age: 20 - 60 years;

2. DSM-IV diagnosis of MDD (ascertained by structured interview for DSM-IV (SCID));

3. Hamilton Depression Rating Scale (HDRS17)>18;

4. Without or with resistance to previous antidepressant treatment; described as Group I, non-TRD [who used >=1 antidepressant for the current MDD-episode and are currently drug-free] and Group II TRD [who were nonresponsive to >=2 antidepressants (SSRIs and/or SNRIs) during the current MDD-episode].

Controls:

1. Male or female, age: 20 - 60 years;

2. No DSM-IV diagnosis/abuse/dependence (SCID);

3. Inventory for Depressive Symptomatology (IDS-SR) <=14;

4. 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:

1. Psychotic or Bipolar depression;

2. Comorbid current (primary) anxiety disorder;

3. Comorbid current abuse/dependence of alcohol, cannabis, cocaine, amphetamine;

4. Neurologic or auto-immune disease, hypothyroidism;

5. Contra-indications for escitalopram or nortriptyline like earlier non-response (in the current

episode);

6. Contra-indications for fMRI-scanning (metal objects in the body, claustrophobia).

Controls:

1. First degree family history of psychiatric illnesses;

2. Contra-indications for fMRI-scanning;

3. Neurologic or auto-immune diseases, hypo-/hyperthyroidism.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2013
Enrollment:	105
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL3796
NTR-old	NTR3969
Other	EudraCT : 2013-001818-14
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A