Longitudinal evaluation of an MRI-based predictive algorithm for early assessment of treatment response in depression (LEOPARD study)

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To replicate the DEPREDICT algorithm (formed from external cohorts/datasets) as a valid tool for prediction of AD treatment non-response, we aim to recruit 80 patients who are treat-ed with an SSRI or SNRI and are eligible and willing to have an MRI...

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

Summary

ID

NL-OMON55321

Source
ToetsingOnline

Brief title
LEOPARD

Condition

- Mood disorders and disturbances NEC

Synonym
depression, Major Depressive Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Eurostars;public-private partnership. Eurostars is een subsidie ten behoeve van internationaal marktgericht onderzoek van de Rijksdienst voor Ondernemend Nederland in opdracht van de Europese Commissie en het ministerie van Economische Zaken en Klimaat. Eurostars is geen (commerciële) partij. Er is geen onderzoekscontract gesloten.

Intervention

Keyword: Deep Learning, Imaging biomarkers, Major Depressive Disorder, Radiomics

Outcome measures

Primary outcome

Response or non-response. In accordance with the CAN-BIND study7, response is defined as a greater than 50% reduction in MADRS score8 at week 8 when compared to baseline. Success of the DEPREDICT algorithm to predict treatment response will be judged based on the calculated sensitivity/specificity of the algorithm (which is based on both baseline-, and/or the 2 week MRI scan, as well as clinical variables and information on sleep and activity) to predict clinical outcome (MADRS-non-response).

Secondary outcome

- Response to treatment as a score of 1 or 2 on the Clinical Global Impression Scale (CGI) improvement item (indicating *very much improved *or *much improved*) at week 8. Partial response is defined as a score of 3 on the improvement item. Worsening of depression is defined as a CGI improvement item score of 5, 6, or 7 at week 8.
- Inventory of Depressive Symptomatology - Self Rated (IDS-SR)
- Morisky questionnaire for medication adherence
- Self-reported anhedonia using the Dimensional Anhedonia Rating Scale (DARS)

Study description

Background summary

Major depressive disorder (MDD) is a highly prevalent condition worldwide. It is associated with increased morbidity and mortality. Symptoms include depressed mood lasting more than 2 weeks, emotional distress, functional impairment, health problems, and suicide. MDD is the leading cause of disability10 resulting in a high socioeconomic burden.

Although MDD typically has a relatively good response to antidepressants (ADs), only about one third of the patients show significant symptom relief in response to the initial treatment4 and 50% have not found an efficacious AD after 1 year. Clinical guidelines recommend 4-8 weeks of treatment before considering an alternate medication in nonresponding patients14. The guidelines recommend that, if the treatment is ineffective after 1-2 months, a new medi-cation or treatment should be started, after reconsidering the diagnosis. In summary, ineffec-tive pharmacotherapy may cause delay in adequate treatment, persistence of depressive symp-toms and functional impairment, which could be shortened by better prediction of therapeutic response. In general guidelines recommend to use a Selective Serotonin Reuptake Inhibitor (SSRI) as a first step treatment while for a second step treatment a second SSRI or a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) is often used.

This lengthy process can negatively impact patients* confidence in pharmacotherapy and re-duces treatment adherence. Meanwhile, patients suffer from MDD and might experience seri-ous adverse effects of different drugs without effectively resolving symptoms. adverse effects include weight gain and insomnia. Thus, a solution is urgently needed that allows faster de-termination of AD non-response in MDD.

There is growing interest in the development of precision medicine algorithms with the aim of tailoring treatment strategies to individual patients according to unique biological signatures. This biomarker-based approach to precision prescribing has the potential to improve therapeu-tic response, minimize adverse reactions, and by stopping ineffective drugs as early as possi-ble reduce time to symptomatic relief. Personalized medicine is already revolutionizing can-cer treatment, in which treatments are tailored to a tumor*s genomic profile.

The application of personalized medicine to psychiatry, however, is more challenging. In con-trast to cancer, there is no biological or histological test for definitive psychiatric diagnoses, because of the inaccessibility of the human brain and the complexity of the link between biol-ogy and psychiatric symptoms. For example, the diagnosis of MDD is based on a combination of

symptoms alone, by standard nosology, as reflected in diagnostic manuals, such as the DSM or the International Classification of Diseases, which does not incorporate any biologi-cal dimension, nor can guide any treatment selection.

The National Institute of Mental Health (NIMH)*s Research Domain Criteria emphasize bi-omarker discovery as a clinical research priority by articulating an approach to the integration of biological and clinical data. The emerging field of psychoradiology, pioneered by Gong and colleagues17 aims to provide biomarkers based on objective tests in support of the diag-nostic classifications, as in other parts of medicine. Biomarkers derived from neuroimaging data are potentially important contributors to the goal of guiding treatment selection using clinical and biotyping data. Because of its non-invasive nature, it has great potential to revolu-tionize clinical psychiatry. Information on brain structure and function may be used to predict non-response versus response to various treatments. Properties predictive of treatment re-sponse presented in literature include pre-treatment brain volumes, post-treatment chang-es in regional morphology, gray and white matter patterns at baseline, presence of increase of subcortical white matter hyperdensities (WMH), lowered DTI measures of fractional anisotropy (FA) and mean diffusivity (MD)9, and baseline and regional changes in resting-state functional connectivity (RSFC). Reviews on this topic are available by Fonseka and colleagues and recently by us.

In DEPREDICT, we will develop a radiomics-based algorithm that allows early (within 2 weeks after first administration) prediction and / or assessment of the later (non-)response to AD in patients with MDD. Radiomics is the high-throughput extraction of quantitative fea-tures that result in the conversion of images into mineable data and the subsequent analysis of these data for decision support. This is in contrast to the traditional practice of treating medi-cal images as pictures intended solely for visual interpretation. Radiomic data contain first-, second-, and higher-order statistics. These data are combined with other patient data and are mined with sophisticated bioinformatics tools to develop models that may potentially improve diagnostic, prognostic, and predictive accuracy.

We will first develop the radiomics algorithm based on existing MRI datasets of the brains of patients with MDD. Whereas existing literature predominantly compares pre-treatment data between responders and non-responders retrospectively, using a single outcome measure, DEPREDICT aims to employ advanced radiomics analysis of MRI measurements of the brain as predictive biomarker in a multivariate predictive solution. There are good indications that this approach may offer improvement.

The first step for DEPREDICT towards clinical implementation is to demonstrate reproducibility. Therefore, this study -LEOPARD- aims to determine the predictive value of this algorithm by means of a longitudinal study. It will test the algorithm's ability to predict week 8 response based on baseline and

week 8 clinical information, MRI scans, and activity and sleep information obtained with a wrist-worn accelerometer. The results of LEOPARD will be essential for the strategy of the development of the DEPREDICT algorithm towards clinical implementation. A positive result of this study (being: strong predictive properties of the algorithm) will enable the next step, a randomized blind study. If the DEPREDICT algorithm turns out to be effective in this, it will be a major step towards becoming a valuable objective tool to support clinical decision making, with great health and economic impact.

Study objective

To replicate the DEPREDICT algorithm (formed from external cohorts/datasets) as a valid tool for prediction of AD treatment non-response, we aim to recruit 80 patients who are treat-ed with an SSRI or SNRI and are eligible and willing to have an MRI-scan session before initiation of treatment and 2 weeks thereafter.

Study design

An 8-week non-randomized, longitudinal brain imaging study for assessment of open label antidepressant (SSRI/SNRI) treatment response in the brain of adult subjects suffering from MDD and in need of pharmacological treatment with AD but free of psychotropic medications for at least 5 half-lives at baseline. The effect of DEPREDICT algorithm is tested by predicting week 8 AD treatment response from baseline and week 2 clinical data, MRI scans, and information regarding activity and sleep collected using a wrist-worn accelerometer

Study burden and risks

Risks:
There are no risks associated with assessment of other MRI sequences at 3T, clinical interviews, nor with the wrist-worn accelerometer.

Benefit:
Our hypothesis is that our DEPREDICT can sufficiently predict treatment outcome at week 2. This would reduce the time to selection of an AD by 75%. If LEOPARD confirms this, this algo-rithm could hold for major health and economic benefits. It will not only reduce the lengthy *tri-al-and error* process of finding the right drug, but also increase treatment adherence, and re-duce time patients suffer from side effects of ineffective medication. In doing so, this study will validate a novel tool in personalizing AD treatment, furthering its way towards clinical deployment.

Although the patients participating in this study will not have direct benefits themselves in participating, their fellow and future MDD patient-peers could benefit, if our study is successful. The overall nature and extent of the added risk associated with participation in the current study is to be classified as

negligible and the burden can be considered minimal.

Conclusion:
The overall nature and extent of the burden associated with participation in the current study are to be classified as minimal and the risk negligible. There is a group benefit associated with study participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Moderate or severe diagnosis of MDD - based on a structured clinical interview (MINI) - score of >20 on the MADRS score, and in need of pharmacological treatment with AD according to their physician and existing guide-lines.
- Free of psychotropic medications for at least 5 half-lives (e.g. 1 week for

most antidepressants, 5 weeks for fluoxetine) at baseline.
- Fluency in Dutch, sufficient to complete the interviews and self-report questionnaires.

Exclusion criteria

- IQ < 70 based on national adult reading test (Nederlandse Leestest voor Volwassenen)
- Contraindications to MRI scanning
- Neurological comorbidities

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-06-2021
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	07-08-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-11-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL74000.018.20