LEOPARD: Longitudinal Evaluation Of a Predictive Algorithm for Response in Depression

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON27632

Source
NTR

Brief title
LEOPARD

Health condition

Major Depressive Disorder

Sponsors and support

Primary sponsor: EUROSTARS
Source(s) of monetary or material Support: EUROSTARS

Intervention

Outcome measures

Primary outcome

Response or non-response defined as a greater than 50% reduction in MADRS score at week 8 when compared to baseline.

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

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 medication or treatment should be started, after reconsidering the diagnosis. In summary, ineffective 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 reduces treatment adherence. Meanwhile, patients suffer from MDD and might experience serious 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 determination 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 contrast 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 biology 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 towards translation of the DEPREDICT algorithm and put this into psychiatric practice is to demonstrate reproducibility. Therefore, LEOPARD aims to establish and repli-cate predictive accuracy of putative biomarkers. The purpose of the LEOPARD study is to test the effectiveness of the DEPREDICT radiomics algorithm. That is, to determine how success-ful the algorithm is at predicting who will not, and who will respond to AD he / she is being treated with, based on quantitative MRI features prior to, and at week 2 of treatment.

Results of LEOPARD will be crucial in defining the strategy of the further development of the DEPREDICT algorithm for clinical practice. If the algorithm holds sufficient predictive power, LEOPARD could pave the way for a randomized clinical trial (RCT) aiming to test the benefit of

applying the algorithm (i.e. change medication faster based on DEPREDICT-results) versus treatment as usual; a final step towards real-world deployment. If proven ef-fective, deployment of the algorithm could hold for major health and economic benefits.

Study objective

Week 8 clinical outcome can be predicted using baseline and week 2 clinical and medical imaging data

Study design

Clinical Assessment:
On baseline, week 2 and 8, clinical assessment will be conducted prior to scanning that takes about one hour maximum. The assessment consists of:
- MADRS questionnaire
- DM-TRD to assess the level of treatment resistance for the current depressive episode

Self-assessment:
Initially, for the first 2 weeks, depression severity and medication adherence will be weekly checked with participants through a Castor-survey. After week 2 these surveys will be sent out every second week (week 4, 6 8).
- IDS-SR questionnaire for depressive symptomatology
- Morisky questionnaire for medication adherence

MRI Scanning:
The radiomics algorithm/tool requires several non-invasive MRI scans to predict non-response regarding treatment outcome. At baseline and week 2, patients will participate in an MRI scan session consisting of the following sequences: Anatomical 3D T1-weighted scan, Whole-brain DTI, Resting-state fMRI, Arterial Spin Labeling, B0 scan.

Intervention

Questionnaires and non-invasive MRI scanning.

Contacts

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Eligibility criteria

Inclusion criteria

Moderate or severe diagnosis of MDD based on a structured clinical interview (MINI)
Score of >20 on the MADRS.
Age 18-6

Exclusion criteria

IQ of less than 70 as assessed by the Dutch national adult reading test (Nederlandse Leest-est voor Volwassenen (NLV)).
Alcohol and/or drug dependence according to DSM-5 criteria.
A history of skull fracture or a severe or disabling medical condition.
Contraindications to MRI scanning
Neurological comorbidity or major residual structural differences due to prior neurological pathology

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Single blinded (masking used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2020
Enrollment:	80

Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion Date:	08-09-2020
Application type:	First submission

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	NL8978
Other	METC AMC : 2020_102#B2020445

Study results