Exploring the Pharmacomicrobiomics of Depression

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This study has been transitioned to CTIS with ID 2024-518101-18-02 check the CTIS register for the current data. The main objective of this project is to associate the gut microbial community with treatment efficacy (i.e., relieve in symptoms and...

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

Summary

ID

NL-OMON50688

Source
ToetsingOnline

Brief title
Pharma-biome

Condition

- Mood disorders and disturbances NEC

Synonym
Depression, Major Depressive Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: European Union Horizon 2020 Program

Intervention

Keyword: Antidepressants, Depression, Microbiome

Outcome measures

Primary outcome

Treatment efficacy, defined as:

The change in depression score from baseline to follow-up, measured using the

Hamilton Rating Scale for Depression

The experienced side effects at follow-up, measured using the Antidepressant

Side-Effect Checklist (ASEC)

Gut-microbiota community:

Gut microbial profiling through 16s rRNA sequencing of the faecal samples. From

this data the following parameters will be derived:

o Global community measures: Alpha and Beta diversity (difference between

baseline and follow-up)

o Compositional measures: Relative abundance (difference between baseline and

follow-up)

Secondary outcome

Therapeutic medication levels measured from blood plasma

Study description

Background summary

The high prevalence of psychiatric disorders puts a burden on the society. A disorder that greatly contributes to this burden is depression, with a

life-time prevalence of 16-20%. Beyond the societal impact, depression can have a tremendous impact on the individual, as it affects, amongst others, cognitive abilities, independency, and general well-being. If persistent, depression is commonly treated with anti-depressant medication. Unfortunately, the treatment efficacy for drug treatments is limited. Anti-depressants are prescribed in a trial-and-error fashion, and patients* treatment response is highly variable, with overall one-third of patients not responding to medication. Furthermore, patients commonly experience debilitating side effects such as weight increase, metabolic dysfunction, and gastrointestinal complaints. Ineffective treatment and medication-induced health risks add significantly to the patients* as well as to the societal disease burden. Therefore, to improve treatment efficacy, a personalized treatment approach is desirable.

A promising but highly overlooked candidate contributing to variation in treatment efficacy are the gut microbiota, residing in the human intestinal tract in trillions. The gut microbiota are involved in myriad functions, including digestion and absorption of nutrients. Preliminary evidence suggested a modulating role for the gut microbiota in treatment response and side-effects of anti-depressant medication. Several studies describe a reduction in overall bacterial diversity and altered abundance of specific bacteria as a result of anti-depressant medication, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and Tricyclic Compounds (TCAs). Moreover, a recent study reports differences in the gut microbial composition between treated and untreated patients with depression, but also between treatment-resistant and -responding patients, suggesting a role of the gut microbiota in the treatment efficacy.

Several mechanisms could underly such a modulating effect of the gut microbiota on treatment efficacy. In terms of medication, the gut microbiota process oral medication before uptake in circulation, potentially modulating drug metabolism and absorption, and thereby to the treatment effect. A specific mechanism originates from the observed reduction in the abundance of spore-forming taxa such as T. sanguinis in animal and in-vitro studies. These are bacteria regulating serotonin metabolism, one of the main neurotransmitters involved in major depressive disorder. Interestingly, the majority of serotonin is produced in the gut where it affects gut immunity and gut motility, processes related to gastrointestinal side effects of SSRIs/SNRIs and TCAs. Hence, alterations in the guts* serotonin metabolism may affect treatment efficacy, both in terms of experienced symptoms and (gastrointestinal) side-effects.

Putting this all together, the gut microbiota are a plausible modulator for treatment efficacy in patients with depression. Possibly, medication-induced changes in the microbial community can explain part of the variability in the antidepressant treatment efficacy between patients. Although preliminary evidence is promising, longitudinal clinical data linking medication-induced gut microbial effects to treatment success in patients with depression is

currently lacking, stressing the need for further research.

Study objective

This study has been transitioned to CTIS with ID 2024-518101-18-02 check the CTIS register for the current data.

The main objective of this project is to associate the gut microbial community with treatment efficacy (i.e., relieve in symptoms and side effects) in patients with suspected treatment-resistant depression.
The secondary objective of this project is to clarify the role of drug metabolism and absorption in the association between the gut microbial community and treatment efficacy.

Study design

This is an observational, longitudinal study. Patients will come in for three visits as a part of their regular treatment. During the first visit the intake takes place. In between the first and second visit the current medication is phased out, and the second visit takes place about seven days (~ 5 times the half-life of the current medication) after stopping the current medication treatment. The third visit takes place approximately six to eight weeks after initiating the new medication treatment. All visits take place on site.

Intervention

Patients have a prescription for an antidepressant in the class SSRI/SNRI or TCA, prescribed as a part of regular care. Patients will start the treatment after the second (baseline) visit, after the previous antidepressant has completely phased out. The choice of antidepressant is determined using national guidelines (farmacotherapeutisch kompas).

Study burden and risks

The burden for the participating patients consists of providing two stool samples at home, six to eight weeks apart. Optionally, patients can consent to an additional blood draw by venipuncture apart from their standard care (10ml; six to eight weeks after starting a new medication). The risks, and physical and psychological discomfort associated with participating in this study are negligible. All other procedures are part of their regular treatment program.

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

Aged >= 18
Main diagnosis of unipolar depression
Indication for the prescription of an antidepressant
Starting a new SSRI/SNRI or TCA antidepressant treatment
Having already used one or more antidepressants without effect and/or with side-effects

Exclusion criteria

Use of antibiotics in a period of three months prior to the baseline visit
Currently pregnant or breastfeeding

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	12-12-2021
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Antidepressants
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-12-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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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
EU-CTR	CTIS2024-518101-18-02
EudraCT	EUCTR2021-006510-36-NL
CCMO	NL79264.091.21