Pharmacogenetics to improve personalized antidepressant dosing in patients with severe depression; a randomized controlled trial using Tricyclic Antidepressants

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Primary Objective: To assess whether CYP450 genotype guided dosing of TCAs results in faster attainment of therapeutic plasma concentrations compared to dosing as usual. . Secondary Objectives: * To assess whether genotype guided dosing results in...

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

Summary

ID

NL-OMON49004

Source
ToetsingOnline

Brief title
Dosing of Tricyclic Antidepressants using Pharmacogenetics.

Condition

- Mood disorders and disturbances NEC

Synonym
major depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Cytochrome P450 system, Major Depressive Disorder, Pharmacogenetics, Tricyclic Antidepressants

Outcome measures

Primary outcome

Primary outcome measure: Time to TCA plasma concentration in the therapeutic range (primary outcome measure). Blood for plasma concentration measurements will be taken in the morning, at 12 (+/-) 1 hours after the last evening dose. When a patient attains a plasma level within the therapeutic range at steady state, the primary endpoint has been reached (for nortriptyline 0.05*0.15 mg/l; for clomipramine: 0.15*0.30 mg/l (clomipramine plus desmethylclomipramine) and for imipramine 0.15-0.25 mg/l (imipramine plus desipramine).

Secondary outcome

a. Reduction of depressive symptoms after 7 weeks of treatment (defined as the baseline HDRS score minus the HDRS score at the 7 weeks assessment.) rated by a blinded investigator.

b. Highest level of side effects based on the Antidepressant Side Effect Checklist (ASE, Uher et al. 2009) and the FIBSER (Frequency, Intensity, and Burden of Side Effects Rating FIBSER (Wisniewski et al. 2006)) rated by the patient.

c. Economic Evaluation:

The impact of the intervention on the quality of life of patients will be

assessed both by the EuroQol 5 dimensions with 5 levels (EQ5D5L) and the The Short Form (36) Health Survey (SF36) at weeks 0, 2,4,6,13 and 26 following randomization.

Cost analysis: The cost analysis consists of two main parts. First, at patient level, volumes of care related to MDD and TCA therapy will be measured by means of the iMTA Medical Consumption Questionnaire. This questionnaire measures all relevant health care related costs like outpatient visits at any medical specialist and hospitalizations. In addition the medication use will be derived from the electronic patient records. Loss of productivity due to illness or recovery, will be estimated based on patient reported absences from paid (or unpaid) labour measured with the Productivity Cost Questionnaire. The second part of the cost analysis consists of determining the cost prices for each volume of consumption. The standard cost prices from the 'Dutch Guidelines for Cost Analyses* and www.medicijnkosten.nl will be used. For units of care where no standard prices are available real costs prices will be determined on the basis of full cost pricing. Productivity losses will be valued by means of the friction cost method. In the end volumes of care will be multiplied with the cost prices for each volume of care to calculate costs.

Study description

Background summary

Tricyclic Antidepressants (TCA*s) are the cornerstone of treatment for patients with severe Major Depressive Disorder (sMDD). Current dosing is guided by

repeated measurements of blood levels. Compared to patients with a normal metabolization function, for those with increased cytochrome P450 (CYP450) enzyme activity it takes longer to reach a therapeutic drug level. As a consequence patients have a prolonged treatment period, increased risk of suicidal behaviour and eventually lower remission rates. For those with reduced CYP450 activity higher rates of side effects are expected. An innovative TCA dosing strategy, taking the genetic variants of the CYP2D6 and CYP2C19 genes into account may help to reduce the above mentioned problems. Up till now, the current guidelines for CYP450 pharmacogenetics based TCA dosing have not been systematically evaluated for effectiveness and cost-effectiveness in larger groups of patients. Such evaluation is necessary before broad implementation of these guidelines can be advocated. We hypothesize that for patients with genotypes reflecting deviant CYP450 enzyme activity, genotype informed dosing results in faster attainment of therapeutic drug levels, lower rates of side effects, earlier symptom relief and lower levels of health- and working related costs

Study objective

Primary Objective:
To assess whether CYP450 genotype guided dosing of TCAs results in faster attainment of therapeutic plasma concentrations compared to dosing as usual. .
Secondary Objectives:
* To assess whether genotype guided dosing results in lower rates of adverse effects compared to dosing as usual.
* To assess whether genotype guided dosing results in earlier reductions of depressive symptoms compared to dosing as usual.
* To assess the value of an early TCA blood level (12 hours after the first dose) as a potential predictor of time to therapeutic plasma concentration, treatment response and side effects.
* To explore the contribution of other clinical (psychomotor retardation) and biological factors (measures of metabolomics) and the changes within these factors during treatment as predictors of time to therapeutic plasma concentration, treatment response and side effects.
* To compare the healthcare costs and work related costs of genotype based dosing to dosing as usual.

Study design

This study is a randomized controlled clinical trial. As we aim to approach actual clinical practice (which is important for generalisation and implementation of the results), prescribing physicians will be unblinded for the CYP2C9 and CYP2D6 genotype and the resulting metabolization phenotype.

Intervention

Using a genetic test, genetic variants that have an impact on the metabolizing capacity of CYP2D6 and CYP2C19 will be determined. These variants explain 90-95% of the cases with changes in CYP2D6 and CYP2C19 enzyme activity. Dedicated genotyping assays or copy number variant methods will be used to detect the genetic variants.
Based on the drug choice (imipramine, nortriptyline or clomipramine) and based on the latest allele definition tables (see KNMP kennisbank achtergrondteksten) patients in the intervention group will be classified into a metabolic phenotype category (PM,IM,EM or UM). Initial TCA dosing of 100 patients will take place according to the dosing guidelines by the KNMP (https://kennisbank.knmp.nl). These patients will be compared to 100 matched patients who will be dosed based on the conventional dosing guideline (farmacotherapeutisch kompas).

Study burden and risks

There is a low burden for participating patients: 4 extra samples of blood will be drawn: one for genotyping, two for storage and one for an extra TCA level determination (12 hrs after the first dose). Extra questionnaires will be adminisered for cost effectivity analyses. We expect an extra time investment of about 330 minutes per patient. Risks are minimal. We expect a lower risk for side effects for participants in the intervention group as the dose will be adapted to the individual's metabolising capacity. The extra monitoring in all groups also will increase safety compared to standard psychiatric care.

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 are in- and outpatients, having a primary diagnosis of severe major depressive disorder (SCID-I diagnosis in agreement with DSM-5 criteria and a Hamilton Rating Scale for Depression score * 19 (HRSD-17-item version), aged 18-65 years, who, according to their physician, are eligible for treatment with a TCA (Nortriptyline (NOR), Clomipramine (CLOMI) or Imipramine (IMI)). The choice of the specific TCA is at the discretion of the physician in attendance.

Exclusion criteria

(1) Psychotic depression (2) Bipolar I or II disorder. (3) Schizophrenia or other primary psychotic disorder.(4) Drug or alcohol dependence in the past 3 months. (5) Mental Retardation (IQ < 80). (6) For women: pregnancy or possibility for pregnancy without adequate contraceptive measures. (7) Breast-feeding. (8) Serious medical illness affecting the CNS, including but not restricted to M Parkinson, SLE, brain tumour, CVA. (9) Relevant medical illness as contra-indication for TCA use, such as recent myocardial infarction. (10) Other drugs influencing the pharmacokinetics of the TCAs as based on a list of interacting drugs. In case of psychotropic co-medication only a benzodiazepine in a dose equivalent up to 4 mg lorazepam will be allowed.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-05-2018
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	07-02-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2019

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCT03548675
CCMO	NL63514.091.17