Tailored treatment of functional dyspepsia with nortriptyline: a multi-center double-blind placebo-controlled trial (TENDER)

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Aim: To investigate the efficacy of nortriptyline in FD patients with a predicted CYP2D6 extensive metabolizer phenotype. Nortriptyline is a second generation TCA with significantly fewer anticholinergic side effects compared to the first generation…

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal signs and symptoms
Study type	Interventional

Summary

ID

NL-OMON52924

Source
ToetsingOnline

Brief title
TENDER

Condition

- Gastrointestinal signs and symptoms

Synonym
Functional Dyspepsia / indigestion

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: CYP genotyping, Functional Dyspepsia, Nortriptyline, Tricyclic Antidepressants

Outcome measures

Primary outcome

Response to therapy, as defined by a 30% reduction from baseline (i.e. the run-in period) in the weekly average of daily symptom scores, during at least 50% of weeks 3-12 of treatment. This is in line with the FDA guidelines on IBS treatment studies. Recorded symptoms include the five core symptoms of FD: epigastric pain, epigastric burning, postprandial fullness, early satiety and upper abdominal bloating.

Self-reported weekly global adequate relief of symptoms (defined as a "yes" in at least 50% of weeks 3-12 of the treatment), collected electronically. Weeks 1 and 2 are excluded in order to allow for establishment of steady-state drug levels

Secondary outcome

- Self-reported weekly global adequate relief of symptoms (defined as a "yes" in at least 50% of weeks 3-12 of the treatment), collected electronically. Weeks 1 and 2 are excluded in order to allow for establishment of steady-state drug levels
- Quality of life, assessed with the use of the EQ-5D-5L (change from baseline).
- Dyspepsia-specific quality of life, assessed with the use of the Nepean Dyspepsia Index (change from baseline).

- Cost-utility, as determined by calculations incorporating total treatment costs and changes in EQ-5D-5L (QALYs gained) and MCQ/PCQ results (savings from reduced medical resource use and increased work productivity respectively).

- Use of rescue medication.

- Number and severity of side effects

- Responder rates following discontinuation of treatment at 6 months follow-up, as defined by a *Yes* to the query regarding adequate relief from baseline symptoms.

- Worst-case-analysis: imputing a non-response day for each day on which the electronic diary entry was missing (due to non-reporting of the patient) in patients assigned to nortriptyline; in patients assigned to placebo, a response day will be imputed for each day the electronic diary entry was missing.

Study description

Background summary

Dyspeptic symptoms, including upper abdominal pain and symptoms of meal-related fullness, occur often in the general population in Western countries with an estimated incidence of up to 40%. Over 70% of patients presenting with dyspepsia do not have an identifiable cause of their symptoms such as peptic ulcer disease or Helicobacter gastritis and are therefore referred to as having functional dyspepsia (FD). As no biomarkers for FD are known, the diagnosis is made on the basis of symptoms. The current standard for the diagnosis of FD are the Rome criteria, developed by the Rome Committee. According to the most recent criteria (Rome IV), issued in May 2016, FD is defined as having bothersome postprandial fullness, early satiety or epigastric pain/burning, in the absence of evidence fur structural disease.

The global prevalence of the condition is estimated to be 5-11%, based on Rome III criteria. However, large regional differences have been reported, with the prevalence being highest in Western populations, an estimated 10-20%. Unfortunately, there is currently no definitive therapy that is beneficial for

all FD patients. This is mainly due to the fact that the disorder is quite heterogeneous and the pathogenesis remains unclear. Several mechanisms have been suggested to play a role in the pathogenesis including visceral hypersensitivity, impaired gastric accommodation, delayed gastric emptying and low-grade duodenal inflammation (increased permeability and mucosal eosinophilia). According to the Rome criteria, FD is subdivided into epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). This subdivision is based on the assumption that different pathophysiological mechanisms underlie different dyspeptic symptoms (predominantly sensory abnormalities in EPS vs. motoric disturbances of gastric physiology in PDS). The rationale for assigning patients into these two syndrome subtypes in clinical practice is that the classification may help guide therapy; anti-secretory and analgesic therapy for EPS and prokinetics for PDS. However, there is significant overlap between EPS and PDS. In addition, very recently, Vanheel et al. reported on a comprehensively analysis of 560 patients with FD and provided novel data on gastric physiological disturbances in PDS and EPS compared with an overlap group. Interestingly, no differences mbetween the Rome subgroups in the prevalence of gastric hypersensitivity, impaired gastricaccommodation, and delayed gastric emptying were found. Furthermore, an association of gastric hypersensitivity was found with the severity of both PDS symptoms, EPS symptoms, and the cumulative symptom score, supporting the hypothesis that this mechanism plays an important role in the pathogenesis of FD symptoms, regardless of the FD subtype.

Treatment entities for FD include dietary modifications, anti-emetics, gastric acid inhibitors, prokinetics, psychological interventions and analgesics. Options cover a wide range and are applied based on predominant symptom and patient preference. Generally, all patients with dyspepsia are treated with antisecretory drugs. However, in the absence of gastrointestinal reflux disease and/or peptic ulcer disease, literature points to a number needed to treat of 14.6 using proton pump inhibitors (PPI) in dyspepsia. Overall, the effectiveness of PPI treatment in FD appears modest with a therapeutic gain of approximately 7-10%. Therefore, the implementation of an effective alternative (and inexpensive) medicinal therapy has the potential to reduce unnecessary PPI use and has added potential with regards to cost-saving. Accumulating evidence suggests efficacy for low-dose tricyclic antidepressants (TCAs) in FD. TCAs were approved in the 1960s and are widely used *off-label* as non-narcotic analgesics. TCAs are believed to act via noradrenergic and serotonergic descending inhibitory perceptive pathways and have extensively been used as neuromodulators in patients with chronic pain.Earlier studies however were of small size and have not been compelling enough to routinely advocate antidepressants for FD. Widespread use of TCAs, an otherwise relatively inexpensive drug group, is further hampered by the fact that these are traditionally considered antidepressants. There is therefore considerable reluctance for from both patients and heath care providers to initiate a therapy with TCAs, especially in the absence of evident psychiatric comorbidity. In addition, TCAs are often associated with side effects,

including constipation, drowsiness, dry mouth (due to anticholinergic and antihistaminergic effects), which appear to be dose dependent and occur early after initiation of therapy preceding the therapeutic effect. This often results in discontinuation of an otherwise potentially effective therapy. On the other hand, previous studies have shown that the clinical response is independent of the total dose of TCAs, supporting the concept of titration of low dosages in FD (10-50 mg/day) - as opposed to the higher dosages traditionally used for psychiatric indications (150-300 mg/day). Furthermore, side effects appear to be dependable on drug metabolism. Fortunately, CYP genotyping can predict drug metabolism. A pre-treatment assessment of CYP2D6 genotype is used in the present study to exclude abnormal metabolizers, who are potentially at risk of side-effects and treatment failure. By including only CYP2D6 extensive metabolizers, we expect to reduce associated side effects, which often result in discontinuation of TCA therapy. On a group level, this may increase compliance and ultimately efficacy.

Study objective

Aim: To investigate the efficacy of nortriptyline in FD patients with a predicted CYP2D6 extensive metabolizer phenotype. Nortriptyline is a second generation TCA with significantly fewer anticholinergic side effects compared to the first generation TCA amitriptyline. In addition, its metabolism only involves one enzymatic step, which makes clinical response based on polymorphisms more predictable. Prior to initiation of the drug therapy, genotyping of the cytochrome P450 enzyme CYP2D6 - the primary enzyme involved in nortriptyline metabolism - will be performed. CYP2D6 poor, intermediate and ultrarapid metabolizers are excluded from the current study.

Primary objectives:
1. To assess the efficacy of an escalating dose regimen of nortriptyline as compared to placebo in FD patients without evidence of significant psychiatric disease, that have been identified as extensive metabolizers based on their CYP2D6 genotype.

Secondary objectives:
1. To evaluate the effect of treatment on quality of life, as compared to placebo.
2. To evaluate the cost-effectiveness of treatment, as compared to placebo.
3. To evaluate the effect of treatment after discontinuation, as compared to placebo.
4. To evaluate the occurrence of side-effects of nortriptyline as compared to placebo.

Addendum (open label extension):
Primary objective:
1. To explore the efficacy of low dose (10 mg) nortriptyline in FD patients

without evidence of significant psychiatric disease, that have been identified as poor or intermediate metabolizers based on their CYP2D6 genotype.

Secondary objectives:
In addition to the objectives described in section 2, we aim to explore the relationship between CYP2D6 genotype and nortriptyline plasma levels at week 1 of treatment, when dosages are similar in all nortriptyline regimens (i.e. 10mg)

Study design

This study is a double-blind placebo-controlled clinical trial in FD patients. Patients will be randomized into one of three arms:
1. Placebo,
2. Nortriptyline in an escalating dose regimen (see intervention)

The treatment period will be 12 weeks and patients will be followed up for 6 months after discontinuation of the therapy. Patients in each treatment arm will also receive standard care, including diet and lifestyle coaching.

Following inclusion, patients will be randomly assigned in equal proportions to one of three groups. Randomization will be performed centrally by the Department of Pharmacy of the Maastricht University Medical Center (MUMC) by means of a computer-generated schedule based on the minimization method. Treatment allocation will be balanced according to inclusion center, gender and age (18-30; 31-50; 51-65). Site-stratified blocks will be created and balanced dynamically within each inclusion center using balancing constraint to ensure overall study balance. The patients, the primary physician of the patient, the coordinating physician-investigator and study nurse will be blinded to the treatment assigned.

Addendum:
CYP2D6 genotyping results in four categories:
- Poor metabolizers
- Intermediate metabolizers
- Extensive (normal) metabolizers
- Ultrarapid metabolizers

As described above, only patients that (by genotype) are predicted to being extensive metabolizers, can be eligible for randomization in this study. Patients that are excluded on the basis of their genotype however, might still benefit from nortriptyline. We therefore aim to offer open label nortriptyline treatment to FD patients recognized as poor or intermediate metabolizer. Ultrarapid metabolizers will not be eligible for this open label extension.

Intervention

Nortrilen (nortriptyline)
Week 1-2: 10mg per day
Week 3-4: 25mg per day
Week 5-12: 50gm per day

Placebo treatment will be performed using identical capsules.

Addendum:
poor and intermediate metabolizers will receive 10mg nortriptyline (open label), without dose escalation.

Study burden and risks

Subjects may experience minor burden from (digital) visits and study questionnaires and diaries. There are 3 (digital) visits, including the first visit in which eligible subjects will be screened before participation. The screening will take up to 1 hour and will consist of a simple questionnaire, a general physical exam performed by the physician- investigator and a standard pregnancy test (in women of fertile age, <55 year only). If deemed suitable by the investigator, subjects will enter the run-in period. During this period, patients are asked to report their daily symptom scores to an electronic diary. If after the run-in period, patients meet the in- and exclusion criteria, they will enter the treatment period. During the treatment period, subjects are again asked to complete a (short) diary (8 weeks). Additional questionnaires are completed in week 4, 8 and 12 and 6 months after treatment.

Only one blood sample is part of the standard procedures in the current study. The burden of these samples however is kept minimal with the application of a dried blood spot, which only involves drawing a few drops of blood from the finger.
On indication (when a patient has significant side effects), a venepuncture will be performed by either a local study nurse of the coordinating investigator. This may cause transient mild discomfort. In rare cases, it may cause a hematoma, which usually is resorbed in several days. During this time, the arm may feel stiff.

Subjects randomized to placebo may experience small burden due to not receiving any treatment (although dietary and lifestyle advice continue as usual). Low dose and personalized regimens used in this study may reduce side effects of nortriptyline treatment. Nonetheless, side effects can occur. The most frequent side effects of nortriptyline include dry mouth, headache, nausea, palpitations, weight gain and blurred vision (due to accommodative dysfunction). ECG changes can occur, but are most often harmless. An ECG will be performed prior to the start of treatment in selected patients to ensure that study medication (nortriptyline) can be started safely. Patients that require baseline ECG are those with cardiac comorbity (myocardial infarction, significant arrhythmias or cardiomyopathy), or patients using medication that

can prolong QT time.

Subjects may or may not benefit directly from participating in this study. There is evidence that TCAs cause relief of FD symptoms. We have reasons to believe that treatment with nortriptyline on the basis of CYP genotyping will result in fewer side effects than empirical treatment. Therefore, it is expected that at least a part of patients randomized nortriptyline treatment will have some sort of benefit from participating in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Patients with functional dyspepsia (FD), diagnosed according to the Rome IV criteria
- Age 18-65 years

- Predicted CYP2D6 extensive metabolizer phenotype on the basis of CYP genotyping
- In the presence of alarm symptoms, patients are required to have undergone a upper gastrointestinal endoscopy (without evidence of organic disease), and have tested negative for Helicobacter pylori 2 years prior to inclusion.
- Insufficient effect of first line treatment with proton pump inhibitors or prokinetics.
- Women in their fertile age (<55 years old) must use contraception or be postmenopausal for at least two years., Patients are recruited in primary and secondary/tertiary healthcare settings.

Exclusion criteria

- History of gastric ulcer;
- Evidence of current anxiety and/or depression disorder as defined by a score >= 10 on the GAD-7 and/or PHQ-9 questionnaire, supported by a detailed interview by the investigator (i.e. the investigator is required to confirm suspicion of anxiety or depressive disorder);
- Predicted CYP2D6 poor, intermediate or ultrarapid metabolizer phenotype on the basis of CYP genotyping
- Current use or any previous use of psychotropic medication in the last 3 months prior to inclusion;
- Inability to discontinue prokinetics*, NSAIDs or opioids;
- Excessive alcohol consumption, defined as > 2 of 3 units per day (females and males
respectively)
- Using drugs of abuse;
- Previous major abdominal surgery or radiotherapy interfering with gastrointestinal function:
a. Uncomplicated appendectomy, cholecystectomy and hysterectomy allowed unless within the past 6 months;
b. Other surgery upon judgment of the principle investigator;
- History of liver disease, cholangitis, achlorhydria, gallstones or other diseases of the gallbladder/biliary system;
- Pregnancy or lactation.
- History of glaucoma, * Patients still using prokinetics at the time of inclusion will be asked to discontinue treatment. A wash-out period of 2 weeks before the run-in period is required. Patients that cannot discontinue prokinetic therapy will be excluded. Patients on proton pump inhibitors should continue these without altering dosage, given that rebound symptoms can occur with discontinuation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-10-2018
Enrollment:	154
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nortrilen
Generic name:	nortriptyline
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-12-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-05-2018
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-05-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-09-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	11-09-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-02-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-01-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	clinical trials.gov registratie under review
EudraCT	EUCTR2017-003307-21-NL
CCMO	NL62932.068.17

Study results

Date completed: 24-07-2024

Summary results
Trial ended prematurely