Effects and Cost-Effectiveness of Pharmacogenetic Screening among Elderly Starters with Antidepressants: A Pragmatic Randomized Controlled Trial

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Primary Objective: * To determine the effects of pharmacogenetic screening for CYP2D6 on the time to reach adequate serum drug levels according to the guidelines.Secondary Objective(s): * To determine the effects of pharmacogenetic screening for...

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

Summary

ID

NL-OMON40010

Source
ToetsingOnline

Brief title
Cytochrome P450-2D6 screening in elderly using antidepressants

Condition

- Mood disorders and disturbances NEC

Synonym
depression

Research involving
Human

Sponsors and support

Primary sponsor: Rijksuniversiteit Groningen

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: CYP2D6, nortriptyline, pharmacogenetics, venlafaxine

Outcome measures

Primary outcome

Main study parameter/endpoint

Time to reach adequate serum drug levels according to the guidelines

(nortriptyline

50- 150 µg/L; venlafaxine + desmethylvenlafaxine: 250- 750 µg/L).

Secondary outcome

Secondary study parameters/endpoints

o Adverse events by using an abbreviated self-reported Antidepressant Side

Effect Checklist (ASEC), self-reported functional health status and

general and disease-specific quality of life by means of EQ5D (including

VAS).

o Incremental cost-effectiveness ratio for intervention versus control strategy

from a societal perspective including uncertainty analysis (bootstrapping,

Fieller*s estimates), discounting, scenario analysis, (probabilistic)

sensitivity analysis and presentation in cost-effectiveness acceptability

curves.

Other study parameters

At each visit to the physician, data on health care associated resource use

will be collected (e.g. visits to the specific specialists including diagnoses; drug use including exact dosing and durations of prescriptions; hospitalizations, inclusive exact intensities of care; and lab values if relevant) and effects on productivity will be investigated. To control for the influence of severity of depression on primary and secondary parameters, severity of depression will be measured by means of the QIDS-SR

Study description

Background summary

Depression is common among elderly with an estimated prevalence of 5% and due to ageing the national burden will double in the coming decade. Antidepressants as TCAs and SSRIs are effective in reducing symptoms, particularly if the symptoms are more serious as in psychiatric settings (Arroll B, 2009, Nelson et al, 2008, Tedeschini et al, 2011)). In the Netherlands in 2009, already more than 12,000 and 20,000 elderly patients aged 65 years or older were using nortriptyline and venlafaxine, respectively, the current first choice drugs according to the Dutch Guideline Depression (Addendum Elderly). Also the American Geriatrics Society mentions these drugs in their Geriatrics At Your Fingertips (Reuben et al, 2011). However, dose-finding in elderly is still too slow. Although there are indications for applicability of CYP2D6 genotyping in dose finding for nortriptyline and venlafaxine (Kootstra-Ros et al, 2006, Vandel et al, 2007, Whyte et al, 2006), the evidence base for adequate tailor made dosing and tolerability of antidepressant drugs is lacking (Pollock et al, 2009). Especially in this more seriously ill population, in initiating treatment with antidepressants it is important to increase the dose as fast as possible to the desired effective dose. This will increase adherence and enhance drug efficacy. A too fast dose escalation may lead to strong adverse effects and discontinuation of therapy.

In advanced age, the enzyme activity of hepatic enzymes involved in drug metabolism is decreased (Bebia et al, 2004; Jin et al, 2010) as well as delivery of medication from the blood to the hepatocytes as well as liver size (Lotrich and Pollock, 2005). Additionally, CYP2D6 and CYP2C19 show pharmacogenetic differences relevant to different drugs resulting in poor (PM), intermediate(IM), extensive(EM) and ultrarapid metabolisers(UM). In antidepressant therapy, genotyping for CYP2D6 only, allows the prediction of a major proportion of the intra-individual variation of plasma levels of most

antidepressants (Kirchheiner 2004; Maier et al.2008) and genotyping for other potential polymorphisms has not yet demonstrated an important role. The Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association developed guidelines for dose-adaptation for drugs predominantly metabolised by CYP2D6 and CYP2C19 based on the genotype of these enzymes (Swen et al, 2008 and 2011). In this guideline dose-interventions based on all deviating genotypes(PM, IM, UM) for CYP2D6 are advised for nortriptyline and venlafaxine accompanied by Therapeutic Drug Monitoring. However, data to support the guideline for elderly are lacking. In general most TCAs are relatively contraindicated in older persons (Beers criteria(American Geriatrics Society 2012) and STOPP/START criteria(Gallagher et al, 2008)). Although in the guideline nortriptyline is a first choice drug within the tricyclic antidepressants (TCA), serious side effects because of anticholinergic and anti-*-adrenergic effects should be considered. Venlafaxine is first choice if a TCA is contraindicated according to the Dutch Guideline Depression-addendum Elderly. Additionally in this guideline application of Therapeutic Drug Monotoring is emphasized, which is also corroborated for these drugs by Mitchell (2004), Sjöqvist and Eliasson (2007), Wille et al (2008), Hiemke (2008) and Preskorn (2010). Intermediate metabolisers are sensitive to minor decrease in enzyme activity induced by enzyme inhibition by interacting co-medication. Although speculative, our hypothesis is that the inhibitory effect of older age on enzyme activity has a comparable effect on intermediate metabolisers as interacting co-medication in the younger population.

As mentioned above depression is common among elderly and increasing in the population due to aging. There is a lack of data on the impact of pharmacogenetics on tailormade therapy with the guideline based antidepressants nortriptyline and venlafaxine with respect to efficacy and tolerability in elderly. It is however well documented that in the general population both nortriptyline and venlafaxine are sensitive to polymorphism of CYP2D6 resulting in dose changes up to 60% (Kirchheiner 2004; Maier et al. 2008; Swen et al. 2008 and 2009 and references mentioned therein). However, since a longer duration of depression enhances the duration of an increased suicide-risk and often results in a worse prognosis increasing the dose as fast as possible in the more seriously ill population as adressed in this study is of major clinical importance.
Also the role of polymorphisms in the multi-drug resistance gene ABCB1 which encodes P-glycoprotein, a critical component of the Blood-Brain Barrier seems to be implicated via the drug availability in the central nervous system in the central actions of nortriptyline and venlafaxine (Roberts et al. 2002; Perroud et al. 2011), but there are no data available in elderly.
This clinical trial will advance scientific knowledge on the added value of pharmacogenetics to treatment of the elderly with nortriptyline or venlafaxine with serum drug levels as a proxy for efficacy as often required by drug registration authorities for special populations and emphasized in the Dutch guidelines. From a patient and societal perspective we will also record adverse events and non-adherence, quality of life and cost-effectiveness from a

societal perspective.

Study objective

Primary Objective:
* To determine the effects of pharmacogenetic screening for CYP2D6 on the time to reach adequate serum drug levels according to the guidelines.

Secondary Objective(s):
* To determine the effects of pharmacogenetic screening for CYP2D6 on the adverse events by using an abbreviated self-reported Antidepressant Side Effect Checklist (ASEC), self-reported functional health status and general and disease-specific quality of life by means of EQ5D (including VAS).
* To determine the incremental cost-effectiveness ratio for intervention versus control strategy from a societal perspective including uncertainty analysis (bootstrapping, Fieller*s estimates), discounting, scenario analysis, (probabilistic) sensitivity analysis and presentation in cost-effectiveness acceptability curves.
* To determine the effects of the genotype for ABCB1 alone or in combination with CYP2D6 on the serum drug levels.
* To determine the effects of the genotype for ABCB1 alone or in combination with CYP2D6 on the adverse events by using an abbreviated self-reported Antidepressant Side Effect Checklist (ASEC), self-reported functional health status and general and disease-specific quality of life by means of EQ5D (including VAS).

Study design

Design: To determine the value of pharmacogenetic screening when starting anti-depressants among the elderly in a real world setting, we propose the conduct of a pragmatic randomized controlled trial. The trial is designed according to the CONSORT guidelines (Begg et al, 1996).

Setting and study population: All patients aged 60 years and older with a depression in whom drug treatment with either nortriptyline or venlafaxine is started in any of the participating psychiatric clinics in the Netherlands are eligible for first screening to be included into the trial. Use of clinically relevant CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, quinidine, ritonavir, efavirenz) or inducers (e.g. dexamethasone, rifampicine) or other drugs that affect plasma levels as co-medication is an exclusion criterion, since dosing schedules need to be adapted differently.

First pharmacogenetic screening: After informed consent has been given in writing for pharmacogenetic screening, blood will be drawn from eligible participants by use of a minimal invasive, but clinically validated Dry Blood Spot Method (drop of blood from finger on filtration paper; De Boer et al, 2011, Edelbroek et al, 2009, Wijnen et al, 2008). Based on their genetic information on CYP2D6, patients will then be classified as poor, intermediate, extensive (normal) or ultrarapid metaboliser. Then, after randomization (see below) informed consent will be asked in writing for participation in the part of the trial in which an intervention based on genotype is applied.

Randomization and intervention: Patients with a deviant polymorphism for which the guideline advices to adapt the standard dosing schedule (nortriptyline: PM, IM, UM; venlafaxine: PM, IM, UM), will be randomly allocated by computer to an intervention or control strategy according to daily practice. Based on extensive literature (Tamminga et al, 1999 and 2000, Raimundo et al, 2000, Sachse et al 1997, Bradford 2002, Zanger et al, 2004, Van Schaik et al, 2006) we expect that about 20 to 30% within this group of starters will be eligible for randomization. In the intervention group, an advice for dose adaptation based on blood level of the drug and/or the genotype will be communicated by a dedicated research team to the treating physician. In the control group, an advice for dose adaptation based on blood level of the drug only will be given to the physician according to current daily practice. Therefore the additional burden for the patients caused by participating in this trial will be restricted to the fact of the randomization, but will be alleviated in comparison to standard care by taking blood by a fingerprick instead of intravenously.

External control study group: From the first screened study population we will randomly sample 75 extensive metabolisers for CYP2D6 and follow them up similarly as those within the trial. This group will provide reference data on outcomes for the deviant patient groups.

Clinical follow-up: At the second scheduled visit a blood spot will be taken for assessment of the serum drug level. Thereafter, blood spots will be taken at the next visits by the treating physician for assessment of the serum drug level according to daily practice. Such sampling will start at least one week after dose adaptation and will be repeated until an adequate drug serum level is reached. Normally it takes approximately two weeks to reach such levels. It is expected that in these deviant patients the time doubles to 4 weeks. Our hypothesis is that by giving dose adaptation based on genotypes, the time to reach adequate drug levels will be halved to be comparable with controls without deviant genotypes.

Duration: 2- 4 weeks for individual patients

Study burden and risks

The risk of participation in the first part of the study is limited to a finger prick to obtain blood for pharmacogenetic screening.
The patients who will participate in the second/main part of the study will be alleviated in comparison to standard care by taking blood for the assessment of the serum drug level according to daily practice by a finger prick instead of intravenously. Furthermore the following data are collected extra for the study: self-reported functional health status and general and disease-specific quality of life by means of EQ5D (including VAS), data on health care associated resource use (e.g. visits to the specific specialists including diagnoses; drug use including exact dosing and durations of prescriptions; hospitalizations, inclusive exact intensities of care; and lab values if relevant).

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

*Age 60 years or older
*Major depression according to DSM-IV criteria for which the treating psychiatrist decided to start drug treatment with either nortriptyline or venlafaxine
*Competent to understand the informed consent procedure

Exclusion criteria

*Use of clinically relevant CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, quinidine, ritonavir, efavirenz)
*Use of clinically relevant CYP2D6 inducers (e.g. dexamethasone, rifampicine)
*Use of other drugs that affect plasma levels as co-medication
*Serious hepatic failure (ASAT/ALAT or gamma-GT * twice the maximal reference value)
*Patients for which drug treatment with venlafaxine is started and a GFR < 30 ml/min.
*Patienst with the very rare genotype: Intermediate Metabolizer with duplications (IMDUP).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-02-2013
Enrollment:	750
Type:	Actual

Ethics review

Approved WMO Date:	10-07-2012
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	24-01-2013
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	16-09-2013
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	14-08-2014
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	NL40925.099.12