Dose-escalation in the picture: pharmacological and imaging studies in depression
Ruhé, H.G.

Citation for published version (APA):
DESIGN AND METHODS OF THE DELPHI-STUDY
The DELPHI-study

DELPHI is an acronym for Dose-Escalation Legitimate? Pharmacology and Imaging studies in depression. The DELPHI-study is the backbone of the studies described in Part IV of this thesis. Because the DELPHI study in fact comprised three research projects, with slightly different patient populations and different numbers of participants, this chapter will describe the design of the DELPHI-study and indicate how the nested sub-studies relate to the major DELPHI-study. Furthermore the patient disposition over these projects will be given.

Objectives, rationale and research questions

The major aims of the DELPHI-study were to investigate the clinical efficacy of and the neurobiological mechanism behind dose-escalation. In order to determine the neurobiological effects of dose-escalation, we intended to study different biological measures during treatment: paroxetine serum concentrations (PSC), serotonin transporter (SERT) occupancy, functional activations in the cortico-limbic-network, awakening cortisol changes and changes in ω-3/ω-6 poly unsaturated fatty acids (PUFAs). Furthermore, we planned to study the effects of genetic polymorphisms on outcomes (i.e. the serotonin transporter gene promoter region (5-HTTLPR)). Results related to some of these neurobiological measures are described in this thesis.

As a study drug, we chose paroxetine for three reasons. First, paroxetine is the selective serotonin reuptake inhibitor (SSRI) which is prescribed most frequently in the Netherlands. Second, paroxetine is a potent inhibitor of the cytochrome P450 2D6 sub-enzyme, which also is the enzyme that is responsible for its metabolism. Therefore paroxetine inhibits its own metabolism, which causes an exponential rise in blood serum concentrations after dose-escalation. Third, when we initiated this study, Gilmor et al. reported noradrenergic reuptake inhibition by paroxetine, suggesting that paroxetine, like venlafaxine and duloxetine, in fact was a ‘dual action’ antidepressant, especially at higher doses.

Our main research-questions were:
1. Is a 6-week true dose-escalation of paroxetine (up to 30-50 mg/day) in patients non-responsive to a 6-week trial with standard dose (20 mg/day) more effective than placebo dose-escalation?
2. Does a 6 week true dose-escalation of paroxetine increase SERT occupancy more than a placebo dose-escalation?
3. What is the relation between SERT occupancy and clinical response to paroxetine (either at a standard dose or after dose-escalation)? Is this relation modified by other neurobiological parameters (i.e. genetic polymorphisms)?
4. Which changes in the functional activation of the cortico-limbic brain regions correlate with clinical response to paroxetine? Is there a common and/or differential effect of paroxetine exposure and/or clinical response?
5. Does a 6 week true dose-escalation of paroxetine generate additional changes (e.g. in noradrenergic reuptake inhibition, cortisol awakening responses, or ω-3/ω-6 PUFAs) compared to a placebo dose-escalation, and are these changes related to clinical response?

Only questions 1-4 will be discussed in this thesis, and the methods used for these questions will briefly be discussed. However, for specific technical we refer to the method-sections in the relevant chapters.

Design and interventions

The DELPHI-study was set up as a randomized clinical trial (ISRCTN register nr. ISRCTN44111488; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=193). The study was approved by the Academic Medical Center (AMC) medical ethical committee (03/120, 03/287 and addendum to 03/120), and all participants provided written informed consent.
Between October 2003 and February 2007 patients were recruited from primary care, our AMC Program for Mood Disorders, and public psychiatric settings. Patients were treated by their referring physician or were referred to our outpatient department. In DELPHI two nested sub-studies were embedded, the DELPHI-SPECT and the DELPHI-fMRI (Figure 2.1). These sub-studies had slightly different in- and exclusion criteria (see below).

Figure 2.1. Design of the DELPHI-study.

All eligible patients were treated open-label with paroxetine 20 mg/day for 6 weeks. When severe adverse effects occurred, dosages were reduced to 10 mg/day and again increased to 20 mg/day after one week. After 6 weeks of treatment, patients who responded (defined as ≥50% reduction of the pretreatment Hamilton depression rating scale (HDRS)) continued paroxetine 20 mg/day. Treatment non-responders were randomized to a true dose-escalation or a placebo dose-escalation, added to paroxetine 20 mg/day in a double blind design. Dose-escalation was provided in blue capsules containing 10 mg paroxetine or placebo. Randomization was stratified for treatment setting (SPECT/fMRI-group, outpatient department AMC, primary care, and public psychiatry), gender and age. Within strata, we applied a minimization method to achieve a balanced distribution. We concealed allocation by using an independently operated computer program.

Dose-escalation consisted of incremental steps of one capsule every 5 days towards a maximum of 50 mg/day (20 mg + 3 capsules). Patients were allowed to increase at a slower pace (e.g. by 7 days) or stop further escalation (e.g. 20 mg + 2 capsules) according to adverse effects. No dosage adjustments were allowed during the last 3 weeks of the study. We checked adherence by pill-counts and anamnesis.
Patients

Figure 2.2 summarizes patient disposition in the DELPHI-study and the DELPHI-SPECT/fMRI neuroimaging sub-study.

Figure 2.2. Patient enrolment and disposition over sub-studies.

The patients in DELPHI-SPECT and DELPHI-fMRI sub-studies are combined (left). For disposition of patients randomized see chapter 9.

**General in- and exclusion criteria**

Eligible patients met the following inclusion criteria: Age between 18 and 70 years, major depressive disorder (MDD) determined by the structured clinical interview for DSM-IV (SCID), and a HDRS (17 items) score above 18. All participants were either drug-free and/or had undergone no more than one antidepressant treatment (other than paroxetine) at an effective dose for ≥ 6 weeks for the present MDD-episode. By the latter criterion, we avoided treatment resistance as potential bias for inefficacy of dose-escalation. Exclusion criteria, apart from pregnancy (or wish to become pregnant), were bipolar disorder, psychotic features, neurological cognitive impairments (i.e. dementia), primary anxiety and/or substance abuse disorders and acute, severe suicidal ideation. Contrary, we allowed secondary co-morbid anxiety and/or substance abuse to increase applicability of our findings. In total, 278 patients were referred, of whom 107 patients started treatment with paroxetine 20 mg/day. Twenty patients withdrew from the study before week 6, and 27 patients were responder by then. Sixty non-responders were randomized.
DELPHI-SPECT and fMRI
Patients who were drug-free (for >4 weeks and ≥5 half-lives of a previous antidepressant) were asked to additionally participate in the neuroimaging sub-studies. Patients were initially asked to participate in DELPHI-SPECT only, but from August 2005 onwards, when DELPHI-fMRI was approved, we asked them for both DELPHI-SPECT and DELPHI fMRI. Participation in only one of the neuroimaging studies was also possible. We limited age to 25-55 years to reduce variability in SERT-measurements by age. For participation in the fMRI's, patients had to be free of metal objects in their body. None of the included patients reported past or present use of 3,4-methylenedioxymethamphetamine. We treated DELPHI-SPECT and DELPHI-fMRI patients at the outpatient department of the Program for Mood Disorders. We supplied medication in pillboxes.

We included 51 patients in the DELPHI-SPECT study, of whom 33 non-responders were randomized. For DELPHI-fMRI we included 22 patients, of whom 16 were randomized. Twenty patients participated both in the DELPHI-SPECT and DELPHI-fMRI. Unfortunately not all (repeated) scans were analyzable adequately, the reason why in chapters 8-10 different numbers of patients are described.

Healthy controls
We recruited 53 healthy controls as reference for the study-entry scans. We individually matched each patient in DELPHI-SPECT and DELPHI-fMRI by gender and age (±2.5 years). Healthy controls were in good physical health, and had never used psychotropic medication. Exclusion criteria were current or lifetime psychiatric disorder(s) according to the SCID (including abuse or addiction disorders), a Beck Depression Inventory (BDI) score >9, alcohol use >4 units per day (last month) or a 1st-degree relative with psychiatric disorder(s). We allowed healthy controls to have incidentally used illicit drugs, unless criteria for a DSM-IV disorder was met, but we prohibited illicit drug use the month prior to scanning. Twenty healthy controls also participated both in the DELPHI-SPECT and DELPHI-fMRI.

Measurements

Time points and questionnaires
We administered the HDRS17,7 Inventory for depressive symptoms (IDS-SR 30),9 the occurrence of adverse effects and health-related quality of life (MOS-SF36)10 at study-entry, randomization (T0), and 6 weeks after randomization (T1). Adverse effects and depressive symptoms were also monitored in the weeks 1, 2 and 4 after the initial start of treatment, and after randomization, using the Maier and Bech subscales11 and IDS-SR 309 (Figure 2.1). Three trained investigators administered clinician-rated questionnaires. Agreement between raters was good (intraclass correlation coefficient = 0.98). Raters and patients were blinded for treatment.

Definition of primary and secondary outcomes
Primary clinical outcomes were HDRS17-scores and the proportion of patients achieving response (≥50% decrease in HDRS17) or remission (HDRS17 ≤7). Secondary outcomes were total and specific (adverse effects / inefficacy) dropout rates, the Maier and Bech subscales and IDS-SR 30-scores, the occurrence of adverse effects and health-related quality of life.

Neurobiological measurements
Paroxetine serum concentrations: See chapters 8 and 9 for details.
SERT-gene promoter polymorphism: See chapters 8 and 11 for details.
Saliva and additional blood specimens
At study-entry, at T0, and T1, we collected two saliva specimens at awakening and 30 minutes thereafter, to determine salivary cortisol, dehydroepiandrosterone-sulphate, and α-amylase.12-15 Furthermore, we collected blood-specimens to quantify [H]Noradrenaline and [H]Serotonin uptake in ex-vivo models.3;16;17 Finally we collected blood-specimens to determine levels of platelet and plasma ω-3/ω-6 PUFAs.18 These neurobiological measurements remain to be analysed in different papers not in this thesis.
Neuroimaging

Measurement of SERT occupancy

We performed SPECT imaging at study-entry, T0 and T1 (Figure 2.1), between 2 to 10 pm according to previously described procedures.\(^1\)\(^9\) We made all scans 230 ±18 (SD) minutes after intravenous injection of approximately 100 MBq \(^{[123]I}\)β-CIT, when the radioligand is at equilibrium for SERT binding in brain areas expressing high densities of SERTs.\(^2\)\(^0\) We performed SPECT imaging using a 12-detector single slice brain-dedicated scanner (Neurofocus 810, Strichmann Medical Equipment; Cleveland, OH). After attenuation correction and reconstruction in 3D mode (http://www.neurophysics.com), we defined regions of interest (RoIs) for midbrain, diencephalon (regions rich of SERT) and cerebellum (as a reference) by using validated templates (Figure 2.3).\(^1\)\(^9\) For further details of SPECT-procedures see chapters 7-10.

Figure 2.3. Regions of Interest (RoI) for Midbrain, Cerebellum and Diencephalon.

Magnetic resonance imaging of functional activation of the cortico-limbic-network

We acquired fMRI scans at study-entry, T0 and T1 (Figure 2.1), between 2 to 10 pm. FMRI-sessions lasted 50-60 minutes, each including a cognitive task (Tower of London),\(^2\)\(^1\)\(^2\)\(^3\) a structural scan and a facial expression task, reported in this thesis.\(^2\)\(^2\)\(^2\)\(^3\) We used a 3Tesla Intera MRI scanner (Philips, Eindhoven, NL), with a 6 channel head-coil for radiofrequency reception. Two magnet compatible response boxes were used to record subject’s performance and reaction times. For further details of fMRI-settings and the parameters of the faces paradigm: see chapter 10.

Power and interim analysis

For the randomization-phase of the total DELPHI-study, we performed a-priori power-calculations for two co-primary endpoints. We planned an interim analysis after SPECT data had been collected on at least 30 patients. Stopping criteria were predetermined using the O’Brien and Fleming\(^2\)\(^4\) approach, and were p<0.0026 in case of superiority and p>0.50 for futility. See chapter 9 for further details.
References